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MANAGEMENT OF CIRRHOTIC PATIENT (A CARDENAS AND P TANDON, SECTION EDITORS)

Portal Hypertension after Liver Transplantation—Causes and Management

Lukas W. Unger[1,2] · Mattias Mandorfer[2,3] · Thomas Reiberger[2,3]

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Abstract

Purpose of Review While portal hypertension (PHT) treatment strategies for patients with advanced chronic liver disease (ACLD) are well established, studies on the management of PHT after orthotopic liver transplantation (OLT) are limited. This is due to the heterogeneous causes of portal hypertension in the OLT setting.

Recent Findings Specific recommendations for the management of non-alcoholic steatohepatitis (NASH), including medical and surgical therapeutic options, and hepatitis C virus (HCV) infection after OLT, are available with most of them applying to transplanted patients. Important concepts to prevent and manage portal vein thrombosis (PVT)—including anticoagulation and TIPS implantation—have been developed. Surgical approaches to resolve PVT, when encountered intraoperatively, have been refined. Finally, interventional treatment options for PHT-related complications and hepatic venous outflow obstruction are available.

Summary NASH has a high recurrence rate and causes considerable postoperative morbidity. HCV can be successfully treated in most cases. Specific medical and interventional as well as surgical treatment options are available for PHT after OLT—including for PHT due to surgical complications.

Keywords Portal hypertension · Orthotopic liver transplantation · Portal vein thrombosis · Anticoagulation · Transjugular intrahepatic portosystemic shunt

Abbreviations

ACLD	Advanced chronic liver disease
CAP	Controlled attenuation parameters
CHC	Chronic hepatitis C
EASL	European Association for the Study of the Liver
ESLD	End-stage liver disease
HA	Hepatic artery
HCV	Hepatitis C virus
HVOO	Hepatic venous outflow obstruction
HVPG	Hepatic venous pressure gradient
IVC	Inferior vena cava
PHT	Portal hypertension
PV	Portal vein
SVR	Sustained virologic response
TIPS	Transjugular intrahepatic portosystemic shunt

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✉ Thomas Reiberger
thomas.reiberger@meduniwien.ac.at

[1] Division of Transplantation, Department of Surgery, Medical University of Vienna, Vienna, Austria

[2] Vienna Hepatic Hemodynamic Laboratory, Medical University of Vienna, Vienna, Austria

[3] Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Waehringer Gürtel 18-20, A-1090 Vienna, Austria

Introduction

Portal hypertension (PHT) defined as a hepatic venous pressure gradient (HVPG) of > 5 mmHg [1] can result from different causes. The most common etiology of PHT is cirrhosis as an intrahepatic cause of PHT. However, the causes of PHT after orthotopic liver transplantation (OLT) [2] are heterogeneous with specific pathophysiological mechanisms. While PHT treatment algorithms are well established for non-transplanted patients with cirrhosis [3, 4], our review will summarize the causes of post-OLT PHT and the limited data on specific treatment strategies.

Treatment of Chronic Hepatitis C (CHC) before and after OLT

In Western countries, CHC has been the most common indication for OLT for decades. However, using highly effective and well-tolerated interferon (IFN)-free regimens, sustained virologic response (SVR) is achieved in nearly all patients, even in difficult-to-cure subgroups such as patients with HIV-coinfection [5] or patients with advanced chronic liver disease (ACLD) [6].

Importantly, hepatitis C virus (HCV)-eradication pre-transplant improves portal hypertension [7–10], as assessed by HVPG. Since portal hypertension drives the development of the first [11••] and further [12] hepatic decompensation, the availability of highly effective IFN-free regimens has substantially changed the pre- and post-transplant landscape.

Firstly, the proportion of patients with HCV-induced ACLD listed for OLT is decreasing [13, 14••]. Further decreases are expected in the near future, as a consequence of the broad access to IFN-free regimens, even at early stages of liver disease. Moreover, selected patients can be delisted after achieving SVR on the waiting list [15], since these patients have a favorable prognosis without OLT [16]. Accordingly, the European Association for the Study of the Liver (EASL) recommends treatment up to a model for end-stage liver disease (MELD) score of 18–20 points. Recommended regimens are 12 weeks of sofosbuvir plus ledipasvir [17, 18]/velpatasvir [19] plus ribavirin, or in case of intolerance, 24 weeks without ribavirin [20]. Patients with a MELD score of more than 18–20 points should be preferably treated post-transplant. Importantly, despite initial concerns, SVR to IFN-free therapies does neither increase the risk of de novo hepatocellular carcinoma (HCC) development [21] nor recurrence of HCC after local ablative therapies [22].

In viremic patients at the time of OLT, HCV reinfection and recurrence of hepatitis C are nearly universal and associated with an accelerated progression of liver fibrosis [20]. Accordingly, about one-third of patients progress to cirrhosis within 5 years. Therefore, IFN-free treatment should be initiated as early as possible when the patient is stabilized, especially in conditions indicating a high risk of early graft loss such as fibrosing cholestatic hepatitis [20]. Transplanted patients without cirrhosis or compensated cirrhosis should be treated with 12 weeks of sofosbuvir plus ledipasvir/velpatasvir without the need for pre-treatment immunosuppressant drug dose adjustments. Decompensated patients should receive similar regimens as in the pre-transplant setting. Patients with an estimated glomerular filtration rate < 30 ml/min/1.73 m^2 should be treated with glecaprevir plus pibrentasvir. However, HCV protease inhibitors (e.g., glecaprevir) are contraindicated in decompensated patients, which still limits the treatment options for subjects who have both decompensated cirrhosis and severe renal impairment.

Information on the regression of portal hypertension after HCV eradication in patients with recurrent hepatitis C is limited. A recent study by Mauro et al. [23•] evaluated the course of liver fibrosis and HVPG in patients who achieved SVR to IFN-based or IFN-free therapies. One year after SVR, two-thirds of patients had liver fibrosis regression, as defined by a decrease of at least one METAVIR stage, with lower rates being observed in patients with pre-treatment cirrhosis. In line with this finding, patients with liver fibrosis regression had higher baseline HVPG values. Changes in HVPG seemed to be comparable to previous observations in the pre-transplant setting and were more consistent in patients with less pronounced portal hypertension. This highlights the importance of timely treatment initiation.

Finally, we would like to underline the importance of co-factors for the regression and/or the prevention of progression of portal hypertension after HCV eradication. Since persistent necroinflammatory activity was associated with hepatic steatosis and a numerically higher body mass index in our study, underlying metabolic liver disease might be of relevance [24]. Thus, weight loss should be recommended to obese patients and avoidance of significant alcohol intake should be recommended for all patients [25].

Post-Transplant Metabolic Liver Disease and Recurrence of NASH

In general, recurrence rates of post-transplant cirrhosis might change in the future due to the recent epidemiologic changes in the etiology of liver disease necessitating OLT with an increasing proportion of metabolically vulnerable patients with non-alcoholic steatohepatitis (NASH) [26, 27]. Although survival rates of patients transplanted due to NASH are, in general, comparable to other etiologies [28], NASH patients seem to be at increased risk for cardiovascular events post-OLT. Regarding short-term complications, however, a subgroup analysis published by Malik et al. showed that patients with an age ≥ 60 years, a body mass index ≥ 30 kg/m^2, and concomitant diabetes mellitus as well as arterial hypertension had a very high 1-year mortality rate (50%) after OLT, mostly due to septic complications [29•]. These findings highlight the importance of optimized management of metabolic comorbidities and require a thorough pre-listing risk-benefit evaluation. Interestingly, while the referenced studies investigated graft and patient survival (and cause of death), they do not present reliable data on the course of liver fibrosis or the incidence of portal hypertensive complications (i.e., occurrence of ascites and variceal bleeding). While liver fibrosis and cirrhosis might not be common in the first years after transplantation, de novo hepatic steatosis is highly prevalent with up to 67% in patients transplanted for other etiologies than NASH and 100% in patients transplanted for NASH after 1 year. Importantly, the progression to severe

fibrosis is far more common in the recurrent NASH group [30•]. Impact of steatosis itself, however, has to be further investigated, as hepatic steatosis (measured via controlled attenuation parameter, CAP) does not predict hepatic decompensation in the ACLD setting [12], while fibrosis/cirrhosis does [31]. In longitudinal studies investigating fibrosis progression in patients with NASH, however, older age and metabolic comorbidities increased the risk of fibrosis progression, highlighting strict post-transplant screening programs to detect fibrosis progression and initiating (lifestyle) interventions as early as possible [32–34]. As several serum markers are currently under investigation, it is a long road until reliable data will be available in the transplant setting [35]. Despite advances in the non-invasive diagnosis of NASH-associated fibrosis by liver stiffness measurements, NASH treatment is currently mostly limited to lifestyle intervention or bariatric surgery [36]. Regular exercise and long-term lifestyle intervention programs can improve NASH, even in non-obese patients but require a certain level of physical fitness [37].

This limitation remains crucial when it comes to the post-transplant patient population as sarcopenia is prevalent post-transplant (and in cirrhosis in general), and large prospective multicenter studies are lacking, in particular with regard to improvement of steatosis. Small intervention studies have proven beneficial effects before as well as post-transplant [38], and recommendations for sarcopenia treatment strategies for clinical practice have recently been published by Tandon et al. [39]. As persistent sarcopenia after liver transplantation leads to deterioration of graft and patient survival and a poor quality of life, interventions should be initiated. Nevertheless, despite the fact that malnutrition is less prevalent after liver transplantation, sarcopenia increases within the first post-transplant year [40••].

For obesity itself, as mentioned above, studies with small sample sizes have shown technical feasibility of minimally invasive bariatric surgery in combination with liver transplantation [41, 42] which might be performed in this high-risk population in the future. Nevertheless, it should be considered that bariatric surgery itself can lead to devastating liver-related morbidity [43•], and malabsorptive techniques probably alter immunosuppression trough levels postoperatively. Therefore, the role of bariatric surgery in the post-transplant setting should be evaluated in clinical trials before general recommendations can be made.

Importantly, optimized nutrition and diet together with exercise was able to reduce portal pressure in patients with cirrhosis not only due to NASH etiology. [44•] This "sport-diet" concept likely translates to beneficial effects on PHT in the post-OLT setting.

Certainly, patients after liver transplantation are metabolically fragile and thus, regular screening for NASH and associated fibrosis is necessary for early detection of NASH-associated PHT.

Surgical Complications Causing Portal Hypertension

Specific reasons for PHT in the post-transplant setting include surgical complications. While vascular complications other than portal vein thrombosis (PVT) are rare prior to OLT, anastomoses of the inferior vena cava (IVC), the portal vein (PV), and the hepatic artery (HA) need to be performed, all with potential incongruent lumen size and subsequent flow problems. Figure 1 illustrates a summary of potential surgical complications at the anastomotic sites leading to PHT. Hepatic artery thrombosis is a severe complication that may require immediate re-transplantation in many cases and often causes ischemic cholangiopathy, a potential cause for PHT and graft failure in the long term [45, 46]. However, hepatic artery thrombosis and associated biliary complications are not further discussed, as they do not directly lead to portal hypertension. PVT and hepatic venous outflow obstruction (HVOO) can lead to portal hypertension and thus, development of (refractory) ascites and varices.

Hepatic Venous Complications

In general, a diagnostic workup is often initiated due to persistence/occurrence of severe/refractory ascites or abnormal laboratory tests in the postoperative period. Radiological assessment by ultrasound and/or computer tomography is highly sensitive to diagnose stenosis, obstruction, or thrombosis of hepatic vessels [47]. For early detection before the occurrence of symptoms, many centers perform CT scans at predefined intervals (e.g., postoperative day 7) even in case of an uneventful postoperative course [48]. In our center, CT scans are only performed in case of abnormal or inconclusive ultrasound examination or in case of clinical suspicion of vascular complications.

Especially when the piggyback technique is used during OLT, drainage pattern of the hepatic veins should be assessed, and twisting of the anastomoses must be recognized [49]. Many different techniques of suturing have been proposed, and recently, non-penetrating vascular closure systems have been developed with similar efficacy for anastomosis of the IVC and the PV and with shorter anastomotic time [50]. Irrespective of the established technique, a sufficiently wide lumen is essential, although intervention is rarely necessary. In a recently published study, only approximately 1% of patients undergoing OLT required endovascular treatment of HVOO [51]. Treatment was successful in 9/10 patients and consisted of balloon dilation, stent implantation, or a combination of both. Although stent migration occurred in 2/10 patients and required a re-intervention, no additional procedure-related complications were observed, indicating a favorable safety profile compared to surgical revision. Due to the small sample

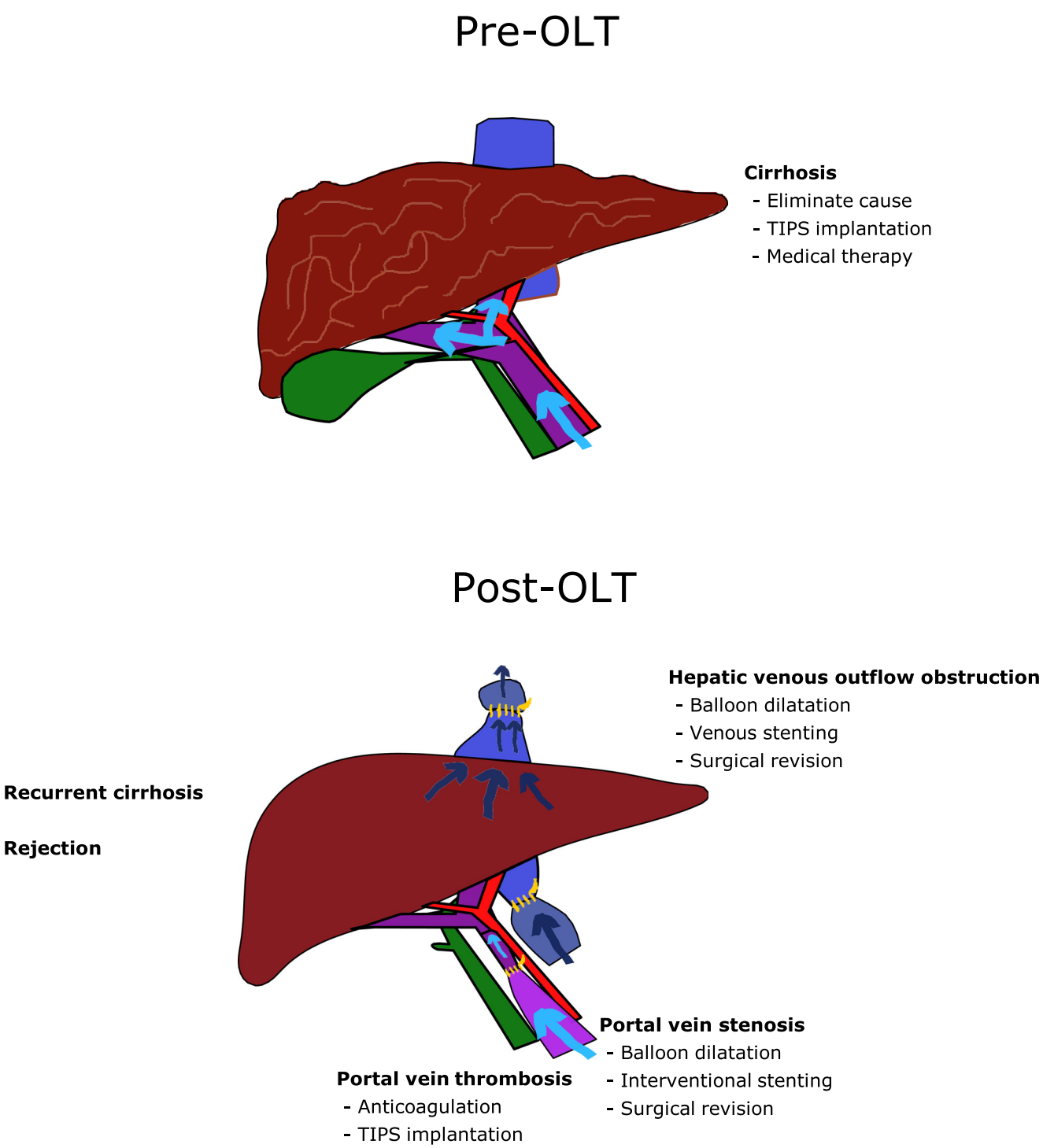

Fig. 1 Causes and treatment options of PHT before and after liver transplantation. Pre-OLT: On the waiting list, PHT is mostly caused by liver cirrhosis. Therefore, etiological treatment and medical therapy including betablocker therapy and TIPS implantation can improve survival. Post-OLT: After OLT, several pre- and posthepatic factors can lead to PHT, including hepatic venous outflow obstruction due to stenotic anastomoses or venous thrombosis, portal vein stenosis or portal vein thrombosis. In rare cases, disease recurrence or rejection can lead to PHT. Treatment strategies can include medical, interventional, and surgical therapies

size, no definitive treatment guidelines exist, and decision for the proper intervention should be performed in an interdisciplinary case discussion with transplant surgeons and interventional radiologists.

Portal Venous Complications

Several operative and medical factors influence the risk for portal hypertension, ranging from arterioportal fistulas to

PVT. While arterioportal fistulas are rare and can develop also late after transplantation due to diagnostic biopsies in the direct postoperative period, treatment usually consists of interventional coiling or plug insertion which leads to resolution of symptoms in most cases [52]. For portal vein thrombosis, several treatment options are available. In general, the importance of an adequate inflow to the graft has to be recognized and is clearly correlated with postoperative outcome [53••]. When stenosis cannot be prevented and PVT develops or is preexistent in OLT recipients, surgical reconstruction during OLT is required but might be difficult and associated with inferior outcomes. In a recently published study, 6.3% of all liver transplant recipients in the United Network for Organ Sharing database had PVT at the time of transplantation, while patients with underlying nonalcoholic steatohepatitis, as emerging indication, showed an even higher risk [54]. In a single-center analysis, rate of PVT was even as high as 12.6% at the time of transplantation, while 48% of these patients had complete and 52% had partial PVT [55••]. Due to the increased risk of 90-day mortality post-transplant (OR 1.7) and the increased risk of graft failure (OR 1.72) in case of PVT, it is of great importance to prevent or resolve PVT on the waiting list whenever possible [56]. When physiological portal venous flow is not successfully reestablished during transplantation (and e.g., cavoportal hemitransposition, renoportal anastomosis, or arterialization is necessary), long-term survival is significantly worse compared to physiological PV anastomosis techniques or as compared to patients without PVT at the time of transplantation [55••]. Due to the important impact of PVT on OLT surgery and post-OLT outcome, several trials on PVT prevention/treatment on the waiting list have been performed. In 2012, enoxaparin was shown to reduce the risk of PVT development and importantly, also reduced the risk of decompensation without increasing the risk of hemorrhagic events. Thus, low-molecular-weight heparin should be used for PVT treatment on the waiting list when no contraindications are present [57••]. These findings of PVT prevention have been validated by others [58•], and treatment algorithms, including TIPS implantation in patients with contraindication for anticoagulation or progression despite anticoagulation [58•], have been proposed. Finally, bleeding complications were not increased in patients with cirrhosis on low-molecular-weight heparin and variceal band ligation for esophageal varices compared to patients without [59•]. For oral anticoagulants/vitamin K antagonists, prospective controlled trials are not available to date, but retrospective data also suggests a beneficial effect [60] on (partial) recanalization. Notably, TIPS may be the treatment of choice in patients with increased risk of nonresponse to anticoagulation [61], especially as it does not lead to increased intraoperative complication rates, at least when conventional venous anastomoses are performed [62]. Importantly, anticoagulation after TIPS implantation seems to add no additional benefit on resolution of PVT, as shown by Wang et al., but larger multicenter trials are warranted [63].

Complete PVT, when recognized on the waiting list, is still considered a relative contraindication for liver transplantation. However, several recent advances have led to potential therapies to recanalization. In line with the above-mentioned highlighting of physiological reconstruction during OLT, a high portal venous blood flow was recently proven to be essential for graft survival after portal venous thrombectomy at the time of OLT [53••]. In this study, a portal venous blood flow of > 1300 mL/min was associated with significantly better postoperative outcome. However, no further analysis of recipients' BMI or graft-to-recipient body weight ratio was applied. In multivariate analysis, a low portal venous blood flow (and older age) was associated with worse survival, although postoperative portal vein thrombosis rates were not different between patients with high or low portal venous blood flow. These differences in survival are probably attributed to the significantly increased rate of biliary structures leading to cholangitis and sepsis, but final conclusions remain speculative. In addition to surgical approaches for portal vein recanalization, less invasive approaches have been shown to allow transplantation of potentially untransplantable patients (e.g., cavernous transformation of the portal vein). Thornburg et al. have recently published the final report of a cohort comprising 61 patients undergoing pre-transplant portal vein recanalization using transjugular intrahepatic portosystemic shunt (TIPS) and percutaneous transsplenic approach for splenic vein puncture. In their paper, 34 patients had complete thrombosis [64]. Nevertheless, recanalization was achieved in 55/61 patients and only 8% suffered from recurrent PVT. Twenty-four patients (39%) underwent subsequent OLT (mostly with end-to-end portal vein anastomosis) and none of the transplanted patients experienced recurrent PVT during follow-up.

In another study of "incidental PVT" found during OLT despite regular radiographic results in the pre-OLT workup, long-term outcomes did not differ between patients with and without PVT [65]. However, previous studies have found worse long-term outcomes in patients with PVT at OLT [66], which was confirmed by the most recent meta-analysis—especially for patients undergoing OLT with obstructive PVT [67]. These findings indicate that, as long as a proper portal venous inflow is established during OLT, recurrence of PVT and subsequent prehepatic portal hypertension seems to be rare.

Medical Therapy for Post-Transplant PHT

Despite the vast body of literature on technical finesse and short- to medium-term outcomes after liver transplantation, large randomized studies that evaluate established medical therapy such as non-selective beta-blockers (NSBB) after OLT are lacking. However, carvedilol, an NSBB and alpha1-blocker, should be favored [68••]—especially in case of arterial hypertension since carvedilol has a better efficacy than nifedipine [69], if tolerated. One study has shown a significant decrease

in portal pressure in patients with recurrent hepatitis C and HVPG ≥ 12 mmHg receiving propranolol [70]. Until further high-quality research is available, similar treatment algorithms as for cirrhotic PHT in the pre-transplant setting should be used. More evidence regarding the use of HVPG-guided therapy is needed with specific attention to the altered hemodynamic properties of transplanted patients, namely an increase in arterial pressure after propranolol administration, potentially due to more pronounced peripheral vasoconstriction [70].

Conclusion

PHT usually resolves after transplantation. To avoid pre- and perioperative complications, patients need optimal management of PHT on the waiting list. In NASH patients, aggressive medical therapy for comorbidities is required in order to reduce the risks associated with BMI > 35 kg/m^2, arterial hypertension, and diabetes mellitus. Nutrition and exercise programs may prevent and treat metabolic liver disease and NASH in the post-OLT period and thus, prevent NASH-associated PHT after OLT.

In case of PVT on the waiting list, anticoagulation and TIPS implantation should be considered as PVT at OLT surgery negatively impacts on post-OLT outcome. Surgical causes of PHT such as hepatic venous complications are rare; however, PVT is more common and may lead to severe PHT after OLT. In case of PVT at the time of OLT, physiological (anatomical) reconstruction should always be preferred with special attention to a sufficient portal venous blood flow towards the liver graft. While insufficient data are yet available on postoperative PHT, similar medical treatment strategies as for cirrhotic PHT should be applied.

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Compliance with Ethical Standards

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- •• Of major importance

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