Indications to Liver Transplantation for Liver Cirrhosis

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Martina Gambato and Alberto Ferrarese

Abbreviations

AAH	Acute alcoholic hepatitis
ACLF	Acute-on-chronic liver failure
ARLD	Alcohol-related liver disease
DAA	Direct-acting antiviral
ESLD	End-stage liver disease
HCC	Hepatocellular carcinoma
HE	Hepatic encephalopathy
HPS	Hepatopulmonary syndrome
HRS	Hepatorenal syndrome
LT	Liver transplantation
MELD	Model for end-stage liver disease
POPH	Portopulmonary syndrome
QoL	Quality of life

Overview
Liver transplantation (LT) is considered the best therapeutic option for patients with end-stage liver disease (ESLD), hepatobiliary malignancies, and acute liver failure worldwide. Since 1967, when the first successful liver transplantation was performed, there has been a progressive evolution on the indications for LT, according to changes in epidemiology and in ethical and cultural issues. This chapter will describe the indications for LT in patients with liver cirrhosis.

M. Gambato (✉) · A. Ferrarese
Multivisceral Transplant Unit and Gastroenterology, Padua University Hospital, Padua, Italy

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2.1 Introduction

Liver cirrhosis determines more than one million deaths per year in the World [1, 2], with an increasing trend [3]. Liver transplantation (LT) has been considered an excellent therapeutic option for patients with cirrhosis and its complications, producing a significant increase in life expectancy and improvement in quality of life (QoL) [4]. After refinements of surgical technique, intensive care, diagnosis, and immunosuppression with excellent survival results, liver transplant programs have spread worldwide [5, 6]. Patients should be selected for LT if expected survival in the absence of LT is 1 year or less, or if the patient has an unacceptable QoL due to liver disease. In the United States, the total number of LT candidates continues to rise (11,340 candidates in 2016 compared to 10,636 in 2015), with simultaneous increase in transplants per year (+10% in 2016 vs. 2015) [7]. Nevertheless, several issues, such as limited organ availability, longer waiting times, and thus morbidity and mortality challenges, remain to be solved yet [8–10].

2.2 Liver Transplantation for Complications of End-Stage Liver Disease

Liver cirrhosis represents the most common indication for LT (52% of all indications), followed by cholestatic diseases (11%), metabolic diseases (6%), and acute liver failure (5%). In Europe, primary liver tumors represented the 14% of indications for LT between 1999 and 2009, more than 90% occurring on cirrhosis [11]. The main indications for LT in patients with cirrhosis, according to etiology of liver disease and liver-related complications, are shown in Table 2.1.

Compared to the 1990s, end-stage liver disease (ESLD) is facing a proportionally decreasing trend as indication for LT, mainly due to the contemporary increase in malignancies [7, 11]. Patients transplanted for ESLD displayed a 1- and 5-year post-LT survival of 85% and 73%, with variations due to underlying etiologies and transplantation date.

Since 2002, the model for end-stage liver disease (MELD) score [12] has been adopted in most allocation systems worldwide. Given that patients with MELD $\leq$14 had a 1-year survival lower with LT rather than without transplantation [13–15], a MELD score $\geq$ 15 is recommended for listing patients with ESLD [4, 16]. Nevertheless, MELD score does not reflect the impact of complications of liver cirrhosis such as refractory ascites and recurrent encephalopathy in the risk of mortality without transplantation. Thus, in the last decades, several attempts have been made to improve its prognostic accuracy [17, 18], being the addition of serum sodium to the MELD equation the most relevant [19–21]. However, other prioritization rules tailored to specific characteristics of waitlisted patients—including extra points for complications of portal hypertension, waiting time, hepatocellular carcinoma—have been proposed [22–27]. Among complications of portal hypertension, refractory ascites is one of the most prevalent (20% cumulative incidence within 5 years) [28] and associated with a poor prognosis (median survival of about

Table 2.1 Indications to liver transplantation according etiology of liver disease

By etiology
• Viral
◦ Hepatitis C
◦ Hepatitis B
◦ Hepatitis B/D coinfection
◦ Hepatitis BC/BCD coinfection
◦ Hepatitis due to HIV coinfection
• Alcohol
• Metabolic diseases
◦ NAFLD
◦ Wilson disease
◦ Hemochromatosis
◦ Alpha-1 antitrypsin deficiency
• Miscellaneous liver diseases
◦ Budd–Chiari syndrome
◦ Familial amyloidosis
◦ Cystic fibrosis
◦ Hereditary hemorrhagic telangiectasia
◦ Polycystic liver disease
◦ Primary hyperoxaluria
• Cryptogenic
• Autoimmune
• Drug related
• Cholestatic diseases
◦ Primary biliary cholangitis
◦ Primary sclerosing cholangitis
◦ Secondary sclerosing cholangitis
By indication
• End-stage liver disease
• Isolated complications of portal hypertension
◦ Hepatic encephalopathy
◦ Refractory ascites
◦ Hepatorenal syndrome
◦ Gastrointestinal (variceal) bleeding
◦ Portopulmonary hypertension
◦ Hepatopulmonary syndrome
• Acute-on-chronic liver disease
• Miscellaneous
◦ Recurrent bacterial infection/cholangitis
◦ Significant impairment of QoL (i.e., intractable pruritus, repeated hospitalizations)
• Hepatobiliary malignancies
◦ Hepatocellular carcinoma
◦ Cholangiocarcinoma

6 months) [29]. Even if several therapeutic options (e.g., transjugular intrahepatic portosystemic shunt, intra-abdominal devices) have been recently proposed [30, 31], LT is associated with a net benefit in survival and with a gain in QoL and costs for patients with refractory ascites [32].

When associated with poor liver function, refractory and recurrent hepatic encephalopathy (HE) is a widely accepted indication for liver transplantation, given

the poor prognosis related to this complication (20% of 5-year survival) [33], the impairment of QoL, the high rate of hospitalization, and the increase of healthcare costs [34, 35]. Furthermore, several studies showed that HE has been associated with increased mortality while in the waiting list (WL) [34, 36], suggesting the need for prioritization. Complete post-LT recovery from severe forms of recurrent/persistent HE remains still a matter of debate [37].

Hepatorenal syndrome (HRS) represents another indication for LT, given the worse prognosis [38] and the high probability of recurrence (about 20%), regardless of the use of specific medical therapy [32, 39]. There are still conflicting data about the role of HRS in the posttransplant renal function. If the net benefit provided by LT in renal function has been widely established [40], some data suggested a post-LT creatinine impairment in patients with episodes of HRS before LT, compared to those without [41–43].

Hepatopulmonary syndrome (HPS) is present in 10–15% of patients with portal hypertension, being caused by reversible intrapulmonary vascular dilatations [44]. HPS has been associated with a twofold risk in mortality and a significant impairment in QoL without LT [44, 45]. In the last decade, there has been a modest expansion of criteria for LT in patients with HPS [4, 32, 44]. Even if only patients with moderate stages of HPS – defined according to a PaO_2 (partial arterial oxygen tension) between 50 and 59 mmHg – have been considered suitable for LT in the past, recent studies showed excellent outcomes also for patients with more advanced stages, defined by a pre-LT PaO_2 between 45 and 50 mmHg [46, 47].

Conversely, portopulmonary hypertension (POPH) (caused by the imbalance between vasodilating and vasoconstrictive agents and a misguided angiogenesis [48]) remains a controversial indication for LT, due to the absence of effective pre-transplant treatments, high intra- and perioperative risks and the absence of complete posttransplant recovery [44, 49].

In summary, end-stage liver disease and the complications of portal hypertension represent well-known indications for liver transplantation, with excellent posttransplant outcomes, both in terms of survival and quality of life. In the next years, we will expect a modest expansion for some of these indications.

2.3 Liver Transplantation for ACLF

Acute-on-Chronic Liver Failure (ACLF) has been defined by both hepatic and extrahepatic organ failures [50] and recognized as a life-threatening condition in patients with cirrhosis. Criteria for definition of ACLF may vary worldwide, according to the epidemiology and clinical presentation [32, 51]. Moreover, ACLF is characterized by a dynamic course [52], with a detrimental short-term outcome, especially at worse stages (28-day transplant-free mortality 42–92% for ACLF 2–3 [52]), as demonstrated by specific prognostic scores [53–55]. Given these characteristics, the choice and timing to offer a graft to such patients are difficult. Levesque et al. [56] showed that ACLF—diagnosed using European Association for the Study of the Liver—Chronic Liver Failure (EASL-CLIF)

criteria – was associated with a five-fold higher risk in mortality within 90 days posttransplant. On the contrary, this could be balanced with the high prioritization granted by MELD score and with the net benefit provided by LT [57]. In a further multicenter French study [58] on 73 selected patients with ACLF-3 stage, LT was associated with a significantly higher survival than patients without transplant (1-year survival 83.9% vs. 7.9%), even postoperative complications occurred in 100% of patients. A larger report from the United Network for Organ Sharing (UNOS) database [59] confirmed the transplant benefit in ACLF-3 patients (30-day survival without LT 8% vs. 1-year post-LT survival 84%). Another retrospective study from Germany [60] demonstrated that patients with a clinical stabilization (defined by recovery of at least one previously failed organ system) before transplantation had posttransplant survival similar to that of patients without ACLF.

In summary, ACLF represents a growing indication for LT in the last few years; further refinement of selection criteria and definition of correct timing for LT are on ground, in order to provide a correct balance between post-LT survival and futility of transplantation [57].

2.4 Specific Indications for Liver Transplantation: Changing Trends in the Last Years

2.4.1 Hepatitis C

Cirrhosis due to hepatitis C (HCV) infection, with or without hepatocellular carcinoma (HCC), has been the leading indication for LT worldwide. Recurrent HCV infection of the allograft is universal if the virus is detectable at the time of transplant, with variable clinical course. In one third of liver recipients, recurrent HCV infection leads to cirrhosis in the graft within only 5 years after LT [61]. A small proportion of recipients can develop fibrosing cholestatic HCV, a severe form of recurrence carrying a poor prognosis [62, 63]. In the last years, the approval of interferon-free (IFN-free) regimens for the treatment of chronic HCV has been a major step forward in transplant hepatology. The safety and efficacy of direct-acting antivirals (DAAs) allow to treat patients awaiting LT as well as individuals with HCV recurrence after LT [64–66].

Consequently, the number of waiting list registrants as well as the number of liver transplants for HCV-related cirrhosis decreased dramatically in the last years. The US scenario showed a 32% decrease of waitlist registrations for HCV-related decompensated disease after DAA introduction [67]. Similarly, in Europe there was a significant decrease in the LT rates for HCV (from 21.1% in 2014 to 10.6% in 2017) [68], being the decline more evident in patients with decompensated disease. In Italy, where the prevalence of HCV as indication to LT is higher, the decrease was even more evident [69].

In the next future, HCV-related cirrhosis would not be an indication for LT anymore, as happened for HBV after the introduction of antivirals and vaccination.

2.4.2 Hepatitis B

In the past, chronic HBV infection was considered a relative contraindication to LT, except in experimental protocols. Following the advent of intravenous administration of anti-HBV immunoglobulins, LT became an accepted therapeutic option for HBV-infected patients [70]. Currently, with antiviral treatment before and after liver transplantation, the 1- and 5-year survival of patients transplanted for HBV equals that of patients transplanted for non-HBV disease [71].

Using the current antiviral strategies, patients can be transplanted with no detectable viremia. Data from several observations suggested that the rate of reinfection of the graft with HBV is higher in those recipients who are HBV-DNA positive at the time of LT [71, 72]. Suppression of viral replication also appears to decrease the necroinflammation in the liver related to HBV infection, leading to a decrease of fibrogenesis and carcinogenesis [73–75].

2.4.3 Alcohol-Related Liver Disease

Globally, alcohol use remains a leading cause of death (age-standardized deaths of 2.2% and 6.8% in females and males, respectively), even if epidemiology and modalities of assumption are rapidly changing [76, 77].

In the European scenario, alcohol-related liver disease (ARLD) accounted for 38% of indications for LT in patients with end-stage liver disease between 1999 and 2009, whereas In the US landscape [7], it rose from 21% to 26% of all indications between 2009 and 2016.

The increasing trend in LT for ALD has been mainly due to profound social, medical, and ethical evolution in the management of ALD candidates in the transplant setting. The need for abstinence of at least 6 months prior to LT ("six-month rule"), in order to evaluate a possible improvement in liver function without alcohol consumption and patients' adherence has been recently questioned in the last years [78, 79].

In this view, acute alcoholic hepatitis (AAH), a detrimental condition associated with high short-term mortality, previously considered a contraindication to LT, because of a too short period of abstinence, has been recently reconsidered in the field of transplantation. In the last decades, many efforts have been made to better refine the outcome of patients with severe AAH not responding to medical therapy. The pioneering study by Mathurin et al. [80] demonstrated both a dramatic improvement in survival for selected patients who underwent LT in comparison to their expected survival and a low rate of recidivism at 2 years. Thus, the option of transplantation has been considered for selected patients with AAH in many transplant programs worldwide, with excellent results [9, 81, 82].

2.4.4 NAFLD

Nonalcoholic fatty liver disease (NAFLD) is an emerging indication to LT worldwide [83–85]. This might be due to the epidemic increase in obesity (15% of women

and 11% of men are obese) and to profound changes in lifestyle [86]. The prevalence of NAFLD is 22% in Europe, 27.4% in Asian Countries, and 30% in the USA [87–89]. In the US scenario, this increased burden on the general population has also determined an increase in NAFLD-related cirrhosis and increased proportion of new wait-listings for liver transplant [90]. Notably, NAFLD has been considered the most rapidly growing indication to LT (+162% from 2003 to 2014) and the fastest growing case of hepatocellular carcinoma among candidates for LT [91]. However, it is possible that these data could be partly influenced by the misdiagnosis of NAFLD as "cryptogenic cirrhosis" in the past, who accounted for 4% of all indications to transplantation before 2009. Furthermore, NAFLD accounted for a significant increase in simultaneous liver-kidney transplantation, from 8.2% in 2002 to 22% in 2011, while the proportion of simultaneous liver-kidney transplantation performed for HCV or ALD decreased from 52% to 40% in the same period [92]. Patients with NAFLD have an excellent post-LT survival (5-year patient survival 77%) [93], even if they seemed at higher risk for cardiovascular complications and sepsis [94].

▶ Tip Acute-on-chronic liver failure is a dynamic syndrome characterized by worse outcome, especially at advanced stages.

New ethical, social, and cultural perspectives are changing the issue of liver transplantation for acute alcoholic hepatitis.

An epidemic increase in obesity and the profound changes in lifestyle would change the indications trend for LT in the next future.

Key Points

- Liver transplantation is an effective therapeutic option for patients with end-stage liver disease with two major aims: to prolong survival and to improve the quality of life.
- The presence of life-threatening complications of liver cirrhosis should be considered an indication for liver transplantation.
- Acute-on-chronic liver failure and acute alcoholic hepatitis are emerging indications to liver transplantation. Refinement of criteria for listing and individuation of an adequate window time are needed.
- Hepatitis C infection is no longer the leading indication for LT since the introduction of high effective and safe direct-acting antivirals. Conversely, alcoholic and nonalcoholic fatty liver diseases represent increasing indications in the Western Countries.

References

1. Mokdad AA, Lopez AD, Shahraz S, Lozano R, Mokdad AH, Stanaway J, et al. Liver cirrhosis mortality in 187 countries between 1980 and 2010: a systematic analysis. BMC Med. 2014;12:145.
2. Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. J Hepatol. 2019;70(1):151–71.

3. Organization WH. who.int/gho/data/view.main.53420.
4. EAftSotLEa. EASL clinical practice guidelines: liver transplantation. J Hepatol. 2016;64(2):433–85. easloffice@easloffice.eu
5. Observatory T. 2018. http://www.transplant-observatory.org/.
6. Lucey MR, Terrault N, Ojo L, Hay JE, Neuberger J, Blumberg E, et al. Long-term management of the successful adult liver transplant: 2012 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Liver Transpl. 2013;19(1):3–26.
7. Kim WR, Lake JR, Smith JM, Schladt DP, Skeans MA, Harper AM, et al. OPTN/SRTR 2016 annual data report: liver. Am J Transplant. 2018;18(Suppl 1):172–253.
8. Burra P, Belli LS, Ginanni Corradini S, Volpes R, Marzioni M, Giannini E, et al. Common issues in the management of patients in the waiting list and after liver transplantation. Dig Liver Dis. 2017;49(3):241–53.
9. Burra P, Giannini EG, Caraceni P, Ginanni Corradini S, Rendina M, Volpes R, et al. Specific issues concerning the management of patients on the waiting list and after liver transplantation. Liver Int. 2018.
10. Toniutto P, Zanetto A, Ferrarese A, Burra P. Current challenges and future directions for liver transplantation. Liver Int. 2017;37(3):317–27.
11. Adam R, Karam V, Delvart V, O'Grady J, Mirza D, Klempnauer J, et al. Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). J Hepatol. 2012;57(3):675–88.
12. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33(2):464–70.
13. Merion RM, Schaubel DE, Dykstra DM, Freeman RB, Port FK, Wolfe RA. The survival benefit of liver transplantation. Am J Transplant. 2005;5(2):307–13.
14. Schaubel DE, Sima CS, Goodrich NP, Feng S, Merion RM. The survival benefit of deceased donor liver transplantation as a function of candidate disease severity and donor quality. Am J Transplant. 2008;8(2):419–25.
15. Schaubel DE, Guidinger MK, Biggins SW, Kalbfleisch JD, Pomfret EA, Sharma P, et al. Survival benefit-based deceased-donor liver allocation. Am J Transplant. 2009;9(4 Pt 2):970–81.
16. Martin P, DiMartini A, Feng S, Brown R, Fallon M. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Hepatology. 2014;59(3):1144–65.
17. Freeman RB, Gish RG, Harper A, Davis GL, Vierling J, Lieblein L, et al. Model for end-stage liver disease (MELD) exception guidelines: results and recommendations from the MELD Exception Study Group and Conference (MESSAGE) for the approval of patients who need liver transplantation with diseases not considered by the standard MELD formula. Liver Transpl. 2006;12(12 Suppl 3):S128–36.
18. Cholongitas E, Marelli L, Shusang V, Senzolo M, Rolles K, Patch D, et al. A systematic review of the performance of the model for end-stage liver disease (MELD) in the setting of liver transplantation. Liver Transpl. 2006;12(7):1049–61.
19. Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med. 2008;359(10):1018–26.
20. Biggins SW, Kim WR, Terrault NA, Saab S, Balan V, Schiano T, et al. Evidence-based incorporation of serum sodium concentration into MELD. Gastroenterology. 2006;130(6):1652–60.
21. OPTN_Policies, https://optn.transplant.hrsa.gov/news/meld-serum-sodium-policy-changes.
22. Cillo U, Burra P, Mazzaferro V, Belli L, Pinna AD, Spada M, et al. A multistep, consensus-based approach to organ allocation in liver transplantation: toward a "Blended Principle Model". Am J Transplant. 2015;15(10):2552–61.
23. Cucchetti A, Ross LF, Thistlethwaite JR, Vitale A, Ravaioli M, Cescon M, et al. Age and equity in liver transplantation: an organ allocation model. Liver Transpl. 2015;21(10):1241–9.

24. Dutkowski P, Oberkofler CE, Slankamenac K, Puhan MA, Schadde E, Müllhaupt B, et al. Are there better guidelines for allocation in liver transplantation? A novel score targeting justice and utility in the model for end-stage liver disease era. Ann Surg. 2011;254(5):745–53. discussion 53
25. Francoz C, Belghiti J, Castaing D, Chazouillères O, Duclos-Vallée JC, Duvoux C, et al. Model for end-stage liver disease exceptions in the context of the French model for end-stage liver disease score-based liver allocation system. Liver Transpl. 2011;17(10):1137–51.
26. Dutkowski P, Clavien PA. Scorecard and insights from approaches to liver allocation around the world. Liver Transpl. 2016;22(S1):9–13.
27. Schrem H, Focken M, Gunson B, Reichert B, Mirza D, Kreipe HH, et al. The new liver allocation score for transplantation is validated and improved transplant survival benefit in Germany but not in the United Kingdom. Liver Transpl. 2016;22(6):743–56.
28. Planas R, Montoliu S, Ballesté B, Rivera M, Miquel M, Masnou H, et al. Natural history of patients hospitalized for management of cirrhotic ascites. Clin Gastroenterol Hepatol. 2006;4(11):1385–94.
29. Salerno F, Guevara M, Bernardi M, Moreau R, Wong F, Angeli P, et al. Refractory ascites: pathogenesis, definition and therapy of a severe complication in patients with cirrhosis. Liver Int. 2010;30(7):937–47.
30. Bureau C, Thabut D, Oberti F, Dharancy S, Carbonell N, Bouvier A, et al. Transjugular intrahepatic portosystemic shunts with covered stents increase transplant-free survival of patients with cirrhosis and recurrent ascites. Gastroenterology. 2017;152(1):157–63.
31. Bureau C, Adebayo D, Chalret de Rieu M, Elkrief L, Valla D, Peck-Radosavljevic M, et al. Alfapump® system vs. large volume paracentesis for refractory ascites: a multicenter randomized controlled study. J Hepatol. 2017;67(5):940–9.
32. EAftSotLEa, Liver EAftSot. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol. 2018; easloffice@easloffice.eu
33. Jepsen P, Ott P, Andersen PK, Sørensen HT, Vilstrup H. Clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. Hepatology. 2010;51(5):1675–82.
34. Wong RJ, Gish RG, Ahmed A. Hepatic encephalopathy is associated with significantly increased mortality among patients awaiting liver transplantation. Liver Transpl. 2014;20(12):1454–61.
35. Wong RJ, Aguilar M, Gish RG, Cheung R, Ahmed A. The impact of pretransplant hepatic encephalopathy on survival following liver transplantation. Liver Transpl. 2015;21(7):873–80.
36. Gadiparthi C, Cholankeril G, Yoo ER, Hu M, Wong RJ, Ahmed A. Waitlist outcomes in liver transplant candidates with high MELD and severe hepatic encephalopathy. Dig Dis Sci. 2018;63(6):1647–53.
37. Garcia-Martinez R, Rovira A, Alonso J, Jacas C, Simón-Talero M, Chavarria L, et al. Hepatic encephalopathy is associated with posttransplant cognitive function and brain volume. Liver Transpl. 2011;17(1):38–46.
38. Fede G, D'Amico G, Arvaniti V, Tsochatzis E, Germani G, Georgiadis D, et al. Renal failure and cirrhosis: a systematic review of mortality and prognosis. J Hepatol. 2012;56(4):810–8.
39. Ginès P, Solà E, Angeli P, Wong F, Nadim MK, Kamath PS. Hepatorenal syndrome. Nat Rev Dis Primers. 2018;4(1):23.
40. Boyer TD, Sanyal AJ, Garcia-Tsao G, Blei A, Carl D, Bexon AS, et al. Predictors of response to terlipressin plus albumin in hepatorenal syndrome (HRS) type 1: relationship of serum creatinine to hemodynamics. J Hepatol. 2011;55(2):315–21.
41. Angeli P, Gines P. Hepatorenal syndrome, MELD score and liver transplantation: an evolving issue with relevant implications for clinical practice. J Hepatol. 2012;57(5):1135–40.
42. Gonwa TA, Klintmalm GB, Levy M, Jennings LS, Goldstein RM, Husberg BS. Impact of pretransplant renal function on survival after liver transplantation. Transplantation. 1995;59(3):361–5.
43. Trawalé JM, Paradis V, Rautou PE, Francoz C, Escolano S, Sallée M, et al. The spectrum of renal lesions in patients with cirrhosis: a clinicopathological study. Liver Int. 2010;30(5):725–32.

44. Krowka MJ, Fallon MB, Kawut SM, Fuhrmann V, Heimbach JK, Ramsay MA, et al. International liver transplant society practice guidelines: diagnosis and management of hepatopulmonary syndrome and portopulmonary hypertension. Transplantation. 2016;100(7):1440–52.
45. Rodríguez-Roisin R, Krowka MJ. Hepatopulmonary syndrome—a liver-induced lung vascular disorder. N Engl J Med. 2008;358(22):2378–87.
46. Iyer VN, Swanson KL, Cartin-Ceba R, Dierkhising RA, Rosen CB, Heimbach JK, et al. Hepatopulmonary syndrome: favorable outcomes in the MELD exception era. Hepatology. 2013;57(6):2427–35.
47. Goldberg DS, Krok K, Batra S, Trotter JF, Kawut SM, Fallon MB. Impact of the hepatopulmonary syndrome MELD exception policy on outcomes of patients after liver transplantation: an analysis of the UNOS database. Gastroenterology. 2014;146(5):1256–65.e1
48. AbuHalimeh B, Krowka MJ, Tonelli AR. Treatment barriers in portopulmonary hypertension. Hepatology. 2018;
49. DuBrock HM, Goldberg DS, Sussman NL, Bartolome SD, Kadry Z, Salgia RJ, et al. Predictors of waitlist mortality in portopulmonary hypertension. Transplantation. 2017;101(7):1609–15.
50. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology. 2013;144(7):1426–37. 37.e1–9
51. Sarin SK, Kedarisetty CK, Abbas Z, Amarapurkar D, Bihari C, Chan AC, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL) 2014. Hepatol Int. 2014;8(4):453–71.
52. Gustot T, Fernandez J, Garcia E, Morando F, Caraceni P, Alessandria C, et al. Clinical course of acute-on-chronic liver failure syndrome and effects on prognosis. Hepatology. 2015;62(1):243–52.
53. Bajaj JS, O'Leary JG, Reddy KR, Wong F, Biggins SW, Patton H, et al. Survival in infection-related acute-on-chronic liver failure is defined by extrahepatic organ failures. Hepatology. 2014;60(1):250–6.
54. Duseja A, Choudhary NS, Gupta S, Dhiman RK, Chawla Y. APACHE II score is superior to SOFA, CTP and MELD in predicting the short-term mortality in patients with acute-on-chronic liver failure (ACLF). J Dig Dis. 2013;14(9):484–90.
55. Jalan R, Saliba F, Pavesi M, Amoros A, Moreau R, Ginès P, et al. Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. J Hepatol. 2014;61(5):1038–47.
56. Levesque E, Winter A, Noorah Z, Daurès JP, Landais P, Feray C, et al. Impact of acute-on-chronic liver failure on 90-day mortality following a first liver transplantation. Liver Int. 2017;37(5):684–93.
57. Linecker M, Krones T, Berg T, Niemann CU, Steadman RH, Dutkowski P, et al. Potentially inappropriate liver transplantation in the era of the "sickest first" policy—a search for the upper limits. J Hepatol. 2017;
58. Artru F, Louvet A, Ruiz I, Levesque E, Labreuche J, Ursic-Bedoya J, et al. Liver transplantation in the most severely ill cirrhotic patients: a multicenter study in acute-on-chronic liver failure grade 3. J Hepatol. 2017;67(4):708–15.
59. Thuluvath PJ, Thuluvath AJ, Hanish S, Savva Y. Liver transplantation in patients with multiple organ failures: feasibility and outcomes. J Hepatol. 2018;
60. Huebener P, Sterneck MR, Bangert K, Drolz A, Lohse AW, Kluge S, et al. Stabilisation of acute-on-chronic liver failure patients before liver transplantation predicts post-transplant survival. Aliment Pharmacol Ther. 2018;47(11):1502–10.
61. Coilly A, Roche B, Duclos-Vallée JC, Samuel D. News and challenges in the treatment of hepatitis C in liver transplantation. Liver Int. 2016;36(Suppl 1):34–42.
62. Verna EC, Abdelmessih R, Salomao MA, Lefkowitch J, Moreira RK, Brown RS. Cholestatic hepatitis C following liver transplantation: an outcome-based histological definition, clinical predictors, and prognosis. Liver Transpl. 2013;19(1):78–88.
63. Carrión JA, Navasa M, Forns X. Retransplantation in patients with hepatitis C recurrence after liver transplantation. J Hepatol. 2010;53(5):962–70.

64. Cheung MCM, Walker AJ, Hudson BE, Verma S, McLauchlan J, Mutimer DJ, et al. Outcomes after successful direct-acting antiviral therapy for patients with chronic hepatitis C and decompensated cirrhosis. J Hepatol. 2016;65(4):741–7.
65. Foster GR, Irving WL, Cheung MC, Walker AJ, Hudson BE, Verma S, et al. Impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. J Hepatol. 2016;64(6):1224–31.
66. Belli LS, Berenguer M, Cortesi PA, Strazzabosco M, Rockenschaub SR, Martini S, et al. Delisting of liver transplant candidates with chronic hepatitis C after viral eradication: a European study. J Hepatol. 2016;65(3):524–31.
67. Flemming JA, Kim WR, Brosgart CL, Terrault NA. Reduction in liver transplant wait-listing in the era of direct-acting antiviral therapy. Hepatology. 2017;65(3):804–12.
68. Belli LS, Perricone G, Adam R, Cortesi PA, Strazzabosco M, Facchetti R, et al. Impact of DAAs on liver transplantation: Major effects on the evolution of indications and results. An ELITA study based on the ELTR registry. J Hepatol. 2018;
69. Ferrarese A, Germani G, Gambato M, Russo FP, Senzolo M, Zanetto A, et al. Hepatitis C virus related cirrhosis decreased as indication to liver transplantation since the introduction of direct-acting antivirals: a single-center study. World J Gastroenterol. 2018;24(38):4403–11.
70. Samuel D, Muller R, Alexander G, Fassati L, Ducot B, Benhamou JP, et al. Liver transplantation in European patients with the hepatitis B surface antigen. N Engl J Med. 1993;329(25):1842–7.
71. Burra P, Germani G, Adam R, Karam V, Marzano A, Lampertico P, et al. Liver transplantation for HBV-related cirrhosis in Europe: an ELTR study on evolution and outcomes. J Hepatol. 2013;58(2):287–96.
72. EAftSotLEa, Liver EAftSot. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67(2):370–98. easloffice@easloffice.eu
73. Buti M, Fung S, Gane E, Afdhal NH, Flisiak R, Gurel S, et al. Long-term clinical outcomes in cirrhotic chronic hepatitis B patients treated with tenofovir disoproxil fumarate for up to 5 years. Hepatol Int. 2015;9(2):243–50.
74. Yao FY, Terrault NA, Freise C, Maslow L, Bass NM. Lamivudine treatment is beneficial in patients with severely decompensated cirrhosis and actively replicating hepatitis B infection awaiting liver transplantation: a comparative study using a matched, untreated cohort. Hepatology. 2001;34(2):411–6.
75. Yuen MF, Chen DS, Dusheiko GM, Janssen HLA, Lau DTY, Locarnini SA, et al. Hepatitis B virus infection. Nat Rev Dis Primers. 2018;4:18035.
76. Pimpin L, Cortez-Pinto H, Negro F, Corbould E, Lazarus JV, Webber L, et al. Burden of liver disease in Europe: epidemiology and analysis of risk factors to identify prevention policies. J Hepatol. 2018;69(3):718–35.
77. Collaborators GA. Alcohol use and burden for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2018;
78. Rice JP, Lucey MR. Should length of sobriety be a major determinant in liver transplant selection? Curr Opin Organ Transplant. 2013;18(3):259–64.
79. Donckier V, Lucidi V, Gustot T, Moreno C. Ethical considerations regarding early liver transplantation in patients with severe alcoholic hepatitis not responding to medical therapy. J Hepatol. 2014;60(4):866–71.
80. Mathurin P, Moreno C, Samuel D, Dumortier J, Salleron J, Durand F, et al. Early liver transplantation for severe alcoholic hepatitis. N Engl J Med. 2011;365(19):1790–800.
81. Lee BP, Mehta N, Platt L, Gurakar A, Rice JP, Lucey MR, et al. Outcomes of early liver transplantation for patients with severe alcoholic hepatitis. Gastroenterology. 2018;155(2):422–30.e1
82. Im GY, Kim-Schluger L, Shenoy A, Schubert E, Goel A, Friedman SL, et al. Early liver transplantation for severe alcoholic hepatitis in the United States—a single-Center Experience. Am J Transplant. 2016;16(3):841–9.
83. Pais R, Barritt AS, Calmus Y, Scatton O, Runge T, Lebray P, et al. NAFLD and liver transplantation: current burden and expected challenges. J Hepatol. 2016;65(6):1245–57.
84. Rinella ME. Nonalcoholic fatty liver disease: a systematic review. JAMA. 2015;313(22):2263–73.

85. (EASL) EAftSotL, (EASD) EAftSoD, (EASO) EAftSoO. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64(6):1388–402.
86. Estes C, Anstee QM, Teresa Arias-Loste M, Bantel H, Bellentani S, Caballeria J, et al. Modeling NAFLD Disease Burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016–2030. J Hepatol:2018.
87. Le MH, Devaki P, Ha NB, Jun DW, Te HS, Cheung RC, et al. Prevalence of non-alcoholic fatty liver disease and risk factors for advanced fibrosis and mortality in the United States. PLoS One. 2017;12(3):e0173499.
88. van den Berg EH, Amini M, Schreuder TC, Dullaart RP, Faber KN, Alizadeh BZ, et al. Prevalence and determinants of non-alcoholic fatty liver disease in lifelines: a large Dutch population cohort. PLoS One. 2017;12(2):e0171502.
89. Fan JG, Kim SU, Wong VW. New trends on obesity and NAFLD in Asia. J Hepatol. 2017;67(4):862–73.
90. Goldberg D, Ditah IC, Saeian K, Lalehzari M, Aronsohn A, Gorospe EC, et al. Changes in the prevalence of hepatitis C virus infection, nonalcoholic steatohepatitis, and alcoholic liver disease among patients with cirrhosis or liver failure on the waitlist for liver transplantation. Gastroenterology. 2017;152(5):1090–9.e1
91. Younossi Z, Stepanova M, Ong JP, Jacobson IM, Bugianesi E, Duseja A, et al. Non-alcoholic steatohepatitis is the fastest growing cause of hepatocellular carcinoma in liver transplant candidates. Clin Gastroenterol Hepatol. 2018;
92. Singal AK, Salameh H, Kuo YF, Wiesner RH. Evolving frequency and outcomes of simultaneous liver kidney transplants based on liver disease etiology. Transplantation. 2014;98(2):216–21.
93. Cholankeril G, Wong RJ, Hu M, Perumpail RB, Yoo ER, Puri P, et al. Liver transplantation for nonalcoholic steatohepatitis in the US: temporal trends and outcomes. Dig Dis Sci. 2017;62(10):2915–22.
94. Wang X, Li J, Riaz DR, Shi G, Liu C, Dai Y. Outcomes of liver transplantation for nonalcoholic steatohepatitis: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2014;12(3):394–402.e1