GUIDELINES



Asian Pacific Association for the Study of the Liver clinical practice guidelines on liver transplantation

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Received: 15 May 2023 / Accepted: 18 December 2023 / Published online: 28 February 2024 © Asian Pacific Association for the Study of the Liver 2024

Abstract

Liver transplantation is a highly complex and challenging field of clinical practice. Although it was originally developed in western countries, it has been further advanced in Asian countries through the use of living donor liver transplantation. This method of transplantation is the only available option in many countries in the Asia-Pacific region due to the lack of deceased organ donation. As a result of this clinical situation, there is a growing need for guidelines that are specific to the Asia-Pacific region. These guidelines provide comprehensive recommendations for evidence-based management throughout the entire process of liver transplantation, covering both deceased and living donor liver transplantation. In addition, the development of these guidelines has been a collaborative effort between medical professionals from various countries in the region. This has allowed for the inclusion of diverse perspectives and experiences, leading to a more comprehensive and effective set of guidelines.

Keywords Living donor liver transplantation · Deceased donor liver transplantation · Multidisciplinary · Grade

Introduction

Liver transplantation (LT) has become the standard treatment for the acute and chronic liver failure of various etiologies as well as hepatocellular carcinoma (HCC) [1]. Advances in surgical techniques and perioperative care have made this radical surgical treatment much safer than before. Operative mortality and morbidity have improved significantly over the last several decades, and long-term survival with normal socioeconomic activity is achievable [2, 3].

However, the disparity between the demand and supply of graft livers from deceased donors has been significant globally and has made this effective treatment unavailable to many patients on the waiting list, especially in the Asia-Pacific region, which has led to the development of living donor liver transplantation (LDLT) [4]. The striking difference in the availability of liver grafts from deceased donors clearly distinguishes the practice pattern in the Asia-Pacific region from the pattern in other regions, which further highlights the necessity of clinical practice guidelines from the Asian Pacific Association for the Study of the Liver (APASL).

This clinical practice guideline has been developed to assist physicians, surgeons, and other healthcare providers throughout the process of LT, covering both deceased donor liver transplantation (DDLT) and LDLT.

The evidence and recommendations in the guideline have been graded according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (Table 1) [5, 6].

Extended author information available on the last page of the article

	Notes	Symbol
Grading of evidence		
High quality	Further research is very unlikely to change our confidence in the estimate of effect	А
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	В
Low or very low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is uncertain	С
Grading of recommendation		
Strong recommendation warranted	Factors influencing the strength of the recommendation included the quality of the evidence, presumed important patient outcomes, and cost	1
Weaker recommendation	Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted. Recommendation is made with less certainty; higher cost or resource consumption	2

Table 1 Grading of evidence and recommendations (adapted from the GRADE system [5, 6])

Evaluation and management of candidates

Indications

Non-malignant conditions

Acute liver failure (ALF) ALF refers to development of severe acute liver injury characterized by markers of liver damage and impaired liver function manifested by prolongation of international normalized ratio (INR), usually > 1.5 or a prolongation of prothrombin time (PT) which usually precedes hepatic encephalopathy appearing in patients without cirrhosis or pre-exiting liver disease [7, 8]. While the time course that differentiates acute liver failure varies between reports, a commonly used cutoff is an illness duration of < 26 weeks and disease duration greater than 28 weeks before the onset of encephalopathy is categorized as chronic liver disease [7, 8]. Considering jaundice as the first symptom, hyperacute liver failure indicates patients developing hepatic encephalopathy within 7 days after jaundice, acute liver failure when hepatic encephalopathy develops between 8 to 28 days of noting jaundice and subacute liver failure when hepatic encephalopathy occurs within 5-12 weeks of jaundice [8]. Hyperacute liver failure patients develop severe coagulopathy, markedly increased serum transaminases and initially only moderate increase in bilirubin, while subacute liver failure patients present with milder increase in serum transaminases, deep jaundice, and mild to moderate coagulopathy with often splenomegaly, ascites, and a shrinking liver volume [8, 9]. In general, patients with hyperacute liver injuries have better short-term survival than subacute liver failure patients [9].

The epidemiology and presentation of ALF in Asia differ significantly from those in the West. In Asia, viral hepatitis is the main cause of ALF, but recent data suggest that the incidence of ALF secondary to drugs and herbs is increasing in most countries, excluding Japan [10]. Unlike in the West, paracetamol-induced ALF is rare in Asia, as the most implicated drugs in cases of ALF are herbal and traditional medicines in China [11, 12] and anti-tuberculosis (TB) drugs in India [13]. In Asia, more than 50% of ALF cases are caused by viral hepatitis. The main virus responsible for ALF in East Asia is the hepatitis B virus, especially in Japan, South Korea, and Taiwan [14-16]. Hepatitis A virus (HAV) infection generally has a mild course and seldom causes ALF, which develops in less than 1% of HAV-infected patients [17]. The seroprevalence of the hepatitis E virus varies widely across countries, including India, Laos, Malaysia, Indonesia, China, and Pakistan, where the disease course tends to be more severe in pregnant female [18-21]. Acute hepatitis D may occasionally be diagnosed in hepatitis B virus-positive individuals. The prevalence of acute hepatitis D virus infection is highest in Mongolia, where 8% of the general population and 83.3% of hepatitis B surface antigen (HBsAg)-positive patients are infected [22, 23]. Other causes for ALF are pregnancy-related, autoimmune hepatitis (AIH), and Wilson's disease [24–27].

Indication of LT One of the important challenges in the management of ALF is determining the survival outcome after LT. Timing of LT is crucial, as ALF is frequently fatal due to cerebral edema and multisystem organ failure. Therefore, once ALF is diagnosed, referral of patients to transplantation centers should be considered. Table 2 outlines several prognostic scoring systems in ALF that correlate with poor outcomes [28–30], which mandate urgent evaluation for LT.

Although these criteria can be used to select LT candidates among patients with ALF, no system has been universally adopted or widely validated. These criteria may provide reasonable but imperfect predictive accuracy [31]; hence, relying entirely on these scores should be discouraged. Generally, the presence of hepatic encephalopathy (HE) is a key

Table 2 Criteria for liver transplantation in acute liver factors	ilure
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Factor	Kings college	ALFSG	ALFA
Age	±*	_	+
Gender	-	-	+
Etiology	+	+	_
Encephalopathy	+	+	+
Arterial pH	± [§]	_	_
Bilirubin	±*	+	+
Coagulopathy	+	+	+
Ammonia	_	_	+
Lactate	$\pm^{\$}$	_	_
Creatinine	_	_	+
Hemoglobin	_	_	+
Vasopressor use	_	+	-

ALF due to paracetamol	ALF not due to paracetamol
Arterial pH $<$ 7.30 after resuscitation and $>$ 24 h since ingestion	INR > 6.5 or
Lactate $> 3.5 \text{ mmol/L or}$	3 out of 5 following criteria:
The 3 following criteria:	Etiology: Indeterminate etiology of hepatitis, drug-induced hepatitis
Grade III or IV hepatic encephalopathy	Age < 10 years or > 40 years
Serum creatinine > 3.4 mg/dL	Interval jaundice-encephalopa- thy > 7 days
INR > 6.5	Bilirubin > 17.6 mg/dL
	INR > 3.5
ALFSG prediction model	

 $Logit for 21-day SS = 2.67-0.95 (HE^*) + 1.56 (Etiology^*) - 1.25 (Vasopressor Use^*) - 0.70 (In bilirubin) - 1.35 (In INR) - 1.25 (In INR)$

*Light HE 0, Deep HE 1, Unfavorable Etiology 0, Favorable Etiology (acetaminophen overdose, pregnancy, ischemia, or hepatitis A) 1, Absence of vasopressor use 0, Vasopressor use 1

ALFA score

Kings College Criteria

ALFA score = $0.024 \times age + 0.054 \times bilirubin + 1.551 \times (prothrombin time INR: 1 if > 3; 0 if <math>\leq 3$) + $0.003 \times ammonia + 0.495 \times (creatinine: 1 if > 1.1 for female or > 1.2 for male; 0 if <math>\leq 1.1$ for female or ≤ 1.2 for male; 0 if ≤ 1.1 for female or ≤ 1.2 for male; 0 if ≤ 1.1 for female or ≤ 1.2 for male; 0 if ≤ 1.1 for female or ≤ 1.2 for male; 0 if ≤ 1.1 for female or ≤ 1.2 for male; 0 if ≤ 1.1 for female or ≤ 1.2 for male; 0 if ≤ 1.1 for female or ≤ 1.2 for male; 0 if ≤ 1.1 for female or ≤ 1.2 for male; 0 if ≤ 1.1 for female or ≤ 1.2 for male; 0 if ≤ 1.2 for male; 0 if ≤ 1.1 for female or ≤ 1.2 for male; 0 if \leq

ALF, acute liver failure; ALFA, acute hepatitis A-related ALF; ALFSG, Acute Liver Failure Study Group; SS, spontaneous survival

*Not included in paracetamol use

[§]Not included in the non-paracetamol use

indicator of poor prognosis and indicates prompt evaluation for LT. When a liver graft becomes available, the patient should be reassessed before proceeding with LT. If there is evidence of irreversible brain injuries, such as the presence of bilateral non-reactive pupils with no spontaneous ventilation, loss of middle cerebral artery flow, loss of gray-white matter differentiation, or evidence of uncal herniation, LT is contraindicated [8]. Otherwise, the decision to proceed with LT should be individualized by a multidisciplinary team that includes a hepatologist, transplant surgeon, and intensive care unit (ICU) intensivist after considering the dynamic course of ALF during the waiting time. Futility also needs to be identified timely for better prognostication. However, determining the appropriate timing for LT in patients with ALF can be challenging. ALF is a dynamic state with patients' conditions potentially changing very rapidly [32]. Poor post-LT outcomes is observed in ALF patients with grade 4 HE unless LT was performed within 48 h of the onset of hepatic coma. The 3-year survival rate was only 50% in those LT performed after 48 h compared with 85% where LT was performed within 48 h [33]. In addition to recipient factors, donor factor such as cold ischemic time (CIT) has major effect in graft survival following LT [32]. Based on United Network for Organ Sharing (UNOS) database, longer CIT was significantly associated with increased risk for post-transplant prolonged length of stay [34], indicating that modes of transportation in larger geographical areas may affect graft survival. When compared to local

donor livers, airplane transported livers showed worse graft survival and patient survival [35].

Special consideration: LDLT in ALF In the West, LT from deceased donors is well established, and patients with ALF receive whole liver allografts, often with the highest priority on the waiting list. In contrast, access to deceased donor allografts is very low in Asia, which makes LDLT the most common form of transplantation even for ALF [36]. Based on the Organ and Procurement and Transplantation Network (OPTN) database assessing post-LT outcomes of adults with ALF undergoing LDLT and DDLT, the patient and graft survival rates for LDLT were similar to those for DDLT [37]. Living donor safety and recipient outcomes following LDLT for ALF were comparable in Asian transplantation centers [38–40]. The most common causes of mortality following LDLT are progressive cerebral edema and sepsis [40, 41].

The benefit of LDLT in patients with ALF lies in the possibility of providing rapid transplantation. If there is a willing liver donor, LDLT is an attractive option since liver donor evaluation can be expedited and LT can be performed within 24 h from the presentation [42]. A study comparing donor complication rates showed no difference in terms of donor safety between emergency and elective donors [40]. In Western countries, patients are listed on transplant waiting lists, which provides time to stabilize the patient before LT and to re-assess the patient until a deceased donor liver graft becomes available. In contrast, emergent LDLT has some disadvantages in the context of re-assessment. The clinical course during the waiting time provides valuable information on the prognosis of the patient, which can be useful in making decisions regarding whether to proceed with LT. However, when a willing living donor is available, decisions regarding whether to proceed with LT or to wait and observe spontaneous recovery are very challenging, as the patient may not survive when ALF progresses to a point where the patient's condition becomes too unstable for LT. Therefore, in this situation, the decision to proceed with LT heavily relies on the prognostic marker, which has reasonable but imperfect performance [31]. In addition, selection bias may exist as criteria to proceed with emergent LDLT differs in various institutions. The criteria for living donor graft quality for patients with ALF need to be determined as well. Optimal timing and criteria for emergent LDLT in ALF patients require further studies to ensure timely and safe LDLT in ALF patients.

[Recommendations]

• LT is a life-saving treatment option to improve the outcome of patients with ALF. (A1)

- LDLT can provide a comparable outcome as DDLT in ALF, but optimal timing and criteria need further evaluation. (B1)
- Several criteria or scoring systems that have been developed for ALF can be used to identify transplant candidates. (B2)

Acute on chronic liver failure (ACLF)

The APASL ACLF guideline defines ACLF as "an acute hepatic insult manifesting as jaundice and coagulopathy complicated within 4 weeks by clinical ascites and/or HE in a patient with previously diagnosed or undiagnosed chronic liver disease or cirrhosis and is associated with a high 28-day mortality" [43]. ACLF is defined differently by the European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) consortium and the North American Consortium for the Study of End-Stage Liver Disease (NACSELD) [44, 45]. Major differences include stages of liver diseases (chronic liver disease, compensated cirrhosis, and decompensated cirrhosis), precipitating events (intrahepatic, extrahepatic), and organ failure (hepatic, extrahepatic) to define ACLF [46]. Although varying definitions are used to define ACLF [47], common features in all definitions of ACLF include rapid worsening of chronic liver disease and a high risk of mortality with a potential for reversibility [48].

In studies that evaluate the role of LT in patients with ACLF, varying definitions of ACLF were used, and this makes it difficult to compare various studies; hence, careful interpretation is needed. Notably, when ACLF is defined by the EASL-CLIF or NACSELD definition, patients with cirrhosis with the previous decompensation are included [44, 45]. In patients with cirrhosis and previous decompensation, long-term outcomes are poor even if they recover from the episode of ACLF [49-51]. Additionally, the EASL-CLIF and NACSELD definitions of ACLF require the presence of organ failure [44, 45]. Organ failure (hepatic and extrahepatic) may occur in a late state and may be irreversible despite intensive therapy [48], leading to early post-LT mortality. Hence, in the decision to transplant a patient in the setting of ACLF as defined by the EASL-CLIF and NAC-SELD definitions, the futility of LT is of more concern than reversibility, as these are cirrhotic patients with and without previous decompensation and with organ failure that may be irreversible. In contrast, ACLF defined by the APASL criteria does not include cirrhosis patients with previous decompensation [43]. ACLF survivals, according to the APASL definition, can maintain recovered liver function and have good long-term outcomes [43]. For patients with chronic liver disease who experience ACLF, reversibility might be more important than futility in the decision to transplant such patients, as the long-term outcome can be favorable for ACLF survivors. The differences in ACLF definitions

should be carefully considered in interpreting studies on the role of LT in ACLF.

Indication and timing of LT in ACLF ACLF is characterized by a very high short-term mortality [43, 52]. An effective artificial liver support system capable of preserving liver function while awaiting LT or liver regeneration remains an unresolved clinical need. The molecular adsorbent recirculating system (MARS), and fractionated plasma separation and absorption failed to show improvement in survival in patients with ACLF, although they may temporarily improve systemic hemodynamics and the degree of encephalopathy [53]. The "transplantation window" can be very short in ACLF, and the decision to transplant a patient must be quick [54]. Emergent LT for patients with ACLF has been shown to have significant survival benefits when compared with the outcomes of patients without LT, even among patients with multiple organ failure [54-57]. The seminal research on emergent LT reported survival in 75% of patients with ACLF who underwent early LT (<28 days) [58]. Survival of patients with ACLF grades 2 and 3 (on days 3-7) undergoing LT within 28 days was 81% at 6 months compared to 10% in those who did not undergo LT. Mortality in those with \geq 4 organ failures and/or CLIF-C score > 64, and not undergoing LT was 100% at 90 days [58]. However, the indications to proceed with LT in patients with ACLF and multiple organ failure can differ according to transplantation centers, and selection bias is inevitable. In addition, ACLF is a potentially reversible condition, and some ACLF survivors can maintain recovered liver function without mortality for a prolonged period [43, 49, 50]. Furthermore, LT might be a futile exercise for a patient with ACLF who has a high probability of mortality early after LT, has an unacceptable quality of life, or multiple complications post-LT, and might be considered as a "potentially inappropriate candidate" [59]. Patients with ACLF may become too sick for LT, and identifying those who are inappropriate candidates is valuable. A post-LT survival of < 3 months (or in-hospital mortality) is considered as a futile LT [60], and some of futility indicators in ACLF are≥4 organ failures, respiratory failure, mechanical ventilation, development of hepatic encephalopathy, rise in creatinine and white cell counts, controlled sepsis for <24 h, and high vasopressor support [59, 61, 62]. Several predictive factors and scoring systems have been suggested to predict the outcome of patients with ACLF [63]. These predictive factors and scoring systems can be used to identify poor responders and may be used to select patients who may benefit from early LT. Nevertheless, to date, there are no reliable predictors of reversibility, and do not adequately predict patient outcome. Consequently, relying solely on predictors or scoring system in clinical decision-making is not advisable. In the ACLF cohort study, transplant eligibility of an ACLF candidate increased from 35 to 60% within seven days, and delay in LT up to 7 days led to a higher incidence of multiorgan failure [62]. Hence, emergent LT should be offered to a patient who will not recover by medical treatment, not too early, but also not too late, and not to a "potentially inappropriate candidate." The APASL ACLF guidelines suggest that patients with an APASL ACLF Research Consortium (AARC) score of 11 or more at the time of ACLF diagnosis need early consideration for LT, as their response is poor even with the best medical supportive care [43]. Otherwise, patients can be managed for 4-7 days with specific therapy and medical supportive care, and in the event of any deterioration or an AARC score of 11 or more, LT should be considered [43]. The AARC score is composed of total bilirubin, HE grades, PT-INR, serum lactate, and serum creatinine levels (Table 3). However, as the AARC model lacks robust validation for its reliability and accuracy, it requires prospective validation in large and varied population [43].

In studies that used ACLF according to the EASL-CLIF definition, improvement of ACLF grade at transplantation compared to ACLF grade at listing was associated with post-LT survival [64, 65]. Moreover, the progression of ACLF grade at transplantation compared to ACLF grade at listing was associated with poor post-LT survival [57]. Mechanical ventilation at LT and the use of marginal organs were associated with an increased risk of death [66]. Even if the decision is made to transplant a patient, the waiting time is inevitable. Hence, the dynamic change of ACLF during the waiting time can help in the decision of LT. Improvement or stabilization of ACLF may indicate a good post-LT outcome while worsening of ACLF may indicate a poor post-LT outcome, which may help in guiding the decision to proceed with or stop LT when a deceased donor's liver is allocated or when a living donor becomes available.

The high short-term mortality of ACLF and the favorable outcomes of LT in patients with ACLF suggest that LT should be considered for all patients with ACLF upon

Table 3	AARC score (adopted
from Al	PASL ACLF guidelines)

Points	Total bilirubin (mg/dl)	Hepatic encepha- lopathy grade	Prothrombin time (INR)	Lactate (mmol/l)	Creatinine (mg/dl)
1	<15	0	<1.8	<1.5	< 0.7
2	15–25	I–II	1.8-2.5	1.5-2.5	0.7-1.5
3	> 25	III–IV	>2.5	> 2.5	>1.5

diagnosis. However, studies on long-term LT survivals have found that ACLF LT survivals show strikingly low quality of life compared to non-ACLF LT survivors [67], and greater healthcare resource utilization after LT [68]. As LT may not provide full benefit of a LT in patients with ACLF compared to other indication, deciding on transplant eligibility and assessing the potential benefit for an ACLF patient can be challenging, particularly when facing limited graft availability. Ethical issues need to be considered as well. The decision to proceed with LT should be individualized and assessed daily, considering the potential for reversibility, availability of donors, and potential for futility assessment by a multidisciplinary team members including hepatologists, transplant surgeons, and ICU intensivists.

Special consideration: LDLT in ACLF In a study of 112 LDLT recipients with ACLF, defined by the APASL definition, post-LT outcomes were excellent (92.9% at 5 years) [69]. In a study on high-model end-stage liver disease (MELD) (score \geq 30) LDLT recipients with ACLF (*n*=190), defined by the World Congress of Gastroenterology [70], the 5-year survival rate was 72.1% [71]. In a study of 117 LDLT recipients who had ACLF, as defined by the EASL-CLIF definition, post-transplant survival after LDLT was 92.9%, 85.4%, and 75.6% at 1 year, while mortality rate without LT was 28.5%, 77.7%, and 93.4% at 90 days, for ACLF grades 1, 2, and 3, respectively [72]. These data indicate that LDLT can be a life-saving treatment option for patients with ACLF.

LDLT differs significantly from DDLT, as the timing of LDLT can be determined by the transplant team. There are advantages and disadvantages of LDLT in the setting of ACLF. The benefit of LDLT in patients with ACLF is its ability to provide rapid transplantation to critically ill patients [73], without waiting for deceased donor allocation. The ideal time for LT can be selected by transplant team when willing living donor is available. If ideal time for LT can be selected in the dynamic course of ACLF, this may improve post-LT outcome. The disadvantages of LDLT include the need for healthy, willing liver donor, and the use of partial grafts for critically ill patients. A graft-to-recipient weight ratio (GRWR) is a factor associated with post-LT outcomes in LDLT [74]. The donor risk index is a factor associated with post-LT outcomes for patients with ACLF who received DDLT [66, 75]. This indicates that DDLT, which uses whole liver grafts, might be a better compared to LDLT, which uses partial grafts, in ACLF. In addition, there are uncertainties regarding the criteria for living donor graft quality that is required for critically ill patients with ACLF. In studies that reported the outcome of LDLT for patients with ACLF using the new Japanese diagnostic criteria [76], the post-LT outcome was poor (33.3% at 5 years) for patients with ACLF with multiple organ failure, although the number of analyzed patients was small (n=9) [77]. Further studies are needed to fully understand potential advantage and disadvantage of LDLT and DDLT in patients with ACLF.

[Recommendations]

- LT is a life-saving treatment option that improves the survival of patients with ACLF, including those with multiple organ failure. (A1)
- LDLT can provide outcomes that are comparable to those of DDLT in cases of ACLF, but the optimal criteria of LT for ACLF need further evaluation. (B1)
- LDLT in ACLF is often an urgent or emergent indication depending upon the dynamic clinical course in the first week of presentation and changes in the AARC score (B2)

Decompensated cirrhosis

Decompensated cirrhosis is a symptomatic condition characterized clinically by the presence of jaundice, ascites, variceal hemorrhage, hepatorenal syndrome, and/or HE [78, 79]. In patients with decompensated or advanced cirrhosis, the patient's prognosis deteriorates rapidly, and the 1-year survival rate drops below 50% [80]. Furthermore, decompensation reduces the median survival from > 12 years to approximately 2 years [81–83]; moreover, the accumulation of multiple decompensations further decreases survival. In these patients, the indication for LT should be assessed independently of the etiology.

In a landmark study, the waiting list and post-transplant mortality were followed in a cohort of 12,996 patients with cirrhosis [84]. The hazard ratio (HR) for 1-year post-transplant mortality was higher than waiting list mortality in patients with a MELD score < 15 (HR = 1.76 for a MELD score of 12–14, p = 0.04). Generally, patients with MELD scores < 15 are not qualified for LT, as the operative risk exceeds their predicted mortality on the waiting list. However, several studies have shown that the stages of liver cirrhosis, which depend on variceal bleeding and ascites, are significant predictors in cirrhotic patients, particularly those with a MELD score of < 15 [85, 86]. Some patients with portal hypertension and a low MELD score may be candidates for LT. Therefore, irrespective of the MELD score, once complications of cirrhosis develop, the indication for LT should be made, and the patient should be evaluated for LT. It is generally accepted that LT is indicated in patients with (1) a complication of decompensated cirrhosis, such as ascites, variceal hemorrhage, HE, and jaundice, or (2) a MELD score of > 15 [87, 88].

It should be noted that, for some patients, recovery from decompensation may be potentially reversible. Stable recompensation has been reported after effective antiviral treatment in patients with hepatitis B virus (HBV) [89, 90] or hepatitis C virus (HCV) [91, 92]-related decompensated cirrhosis, and with abstinence in patients with alcohol-related cirrhosis [93]. In these limited circumstances, decompensation may be reversed with appropriate therapies, and the indication for LT may need to be reevaluated [83, 87, 94].

[Recommendations]

- Evaluation for LT should be considered in cases of irreversible hepatic failure regardless of the etiology and those with a complication of decompensated cirrhosis. (A1)
- The indication for LT may be reevaluated in patients who have recovered from decompensation with successful treatment of the underlying etiology. (B2)

Hepatic neoplasms

HCC

LT has been recognized as the best curative treatment for patients with cirrhosis and HCC as it can both remove the tumor and treat the underlying liver cirrhosis if a liver graft is available [95].

The Milan criteria (MC), proposed in 1996 [96], are the most widely accepted patient selection criteria for identifying candidates that are suitable for LT with low rates of HCC recurrence and acceptable post-LT survival [97–99]. On the other hand, there are concerns that the upper limit for tumor burden indicated by the MC may be too restrictive, as it may restrict access to LT for some patients who may benefit from the procedure. Recently, starting with the University of California San Francisco criteria described by Yao et al. [100], several centers worldwide have also proposed expanded criteria with acceptable outcomes [100–107].

In Asia, where LDLT is not restricted by the organ allocation system and is the mainstay for LT, many experienced centers have developed center-specific expanded criteria based on institutional and regional experience [101, 103–105, 107–111]. While the expanded criteria initially

proposed were based on the size and number of tumors, this was later shifted to a combination of parameters reflecting the biological behavior of tumors in addition to traditional morphological parameters [112]. In Korea, Kim et al. published their criteria that included both biological and morphological parameters using alpha-fetoprotein (AFP) levels [108]. Lee et al. proposed expanded criteria using the total tumor size and 18F-fluorodeoxyglucose positron emission tomography, rather than a tumor marker [110]. In Japan, both Kaido et al. and Uchiyama et al. have presented updated selection criteria, including pre-LT serum prothrombin induced by vitamin K absence or antagonist II (PIVKA-II) levels, while increasing the upper limit or removing the limitation of the number of tumors [103, 111]. In China, Zheng et al. suggested including the HCC biopsy result in the selection criteria and proposed criteria that included a total tumor diameter of ≤ 8 cm or total tumor diameter > 8 cm, with grade I or II at the histopathologic exam, and a pre-LT AFP level $\leq 400 \text{ ng/mL}$, simultaneously [104]. The Asian LT criteria for patients with HCC are described in Table 4.

Another way to expand the LT criteria to obtain improved post-LT outcomes relies on selecting a patient subgroup beyond the MC that has favorable biology and is responsive to locoregional and/or systemic treatments. This is called the "downstaging strategy" [113–115]. Downstaging combines the expanded criteria with a positive response to locoregional therapies rather than simply raising the upper limits in tumor burden, and has now moved to the paradigm of selecting suitable LT candidates with initial tumors exceeding the conventional criteria [115, 116]. In 2017, the United Network for Organ Sharing (UNOS) adopted the expanded inclusion criteria to facilitate the prioritization of HCC candidates with an initial tumor burden meeting UCSF/Region 5 inclusion criteria, who are successfully downstaged to fulfill the MC. The American Association for the Study of Liver Diseases (AASLD) guidelines for the treatment of HCC suggest that patients beyond the MC (\geq T3) should be considered for grafting after an effective downstaging of the disease. Moreover, the Barcelona Clinic Liver Cancer

 Table 4
 Asian Liver transplantation criteria for patients with hepatocellular carcinoma

Criteria	a Study group Year Eligibility criteria		Survival		
				OS	RFS
Asan	Lee et al	2008	Number of tumors ≤ 6 and size ≤ 5 cm	81.6% (5-year)	_
Kyoto	Kaido et al	2013	Number of tumors ≤ 10 , size ≤ 5 cm or DCP level ≤ 400 mAU/mL	82.0% (5-year)	_
Tokyo	Akamatsu et al	2014	Number of tumors ≤ 5 cm and size ≤ 5 cm	80% (5-year)	_
Samsung	Kim et al	2014	Number of tumors ≤ 7 , size of tumors ≤ 6 cm and AFP level ≤ 1000 ng/mL	_	89.6% (5-year)
NCCK	Lee et al	2016	Number of tumors ≤ 10 , negative PET	85.2% (5-year)	84.0% (5-year)
MoRAL	Lee et al	2016	Any number and size of tumors, $11 \times \sqrt{\text{PIVKA} + 2 \times \sqrt{\text{AFP}}}$	82.6% (5-year)	66.3% (5-year)
Kyushu	Uchiyama et al	2017	Any number of tumors, size < 5 cm or DCP < 300 mAU/mL	82.1% (5-year)	80.4% (5-year)

(BCLC) prognosis and treatment strategy, updated in 2022, stated that "effective downstaging may allow for LT in BCLC-B patients" after incorporating an expert clinical decision-making component [117].

This change was triggered by several single-center studies that showed similar post-LT outcomes in patients who were successfully downstaged compared to patients who were initially within the MC [113, 116, 118, 119]. The satisfactory results of the downstaging strategy observed in published retrospective and prospective multicenter studies, which have gained broad acceptance for the downstaging approach in clinical practice, have also provided the basis for changes in national policy and a single-center and global guideline [120–124]. Recently, Mazzaferro et al. reported the result of their randomized controlled trial that LT after effective and sustained downstaging of eligible HCC beyond the MC improved recurrence-free and overall survival compared to non-transplantation therapies [122]. This study provides strong evidence that supports a downstaging strategy for curative therapy with LT for HCC patients in the expanded criteria.

Despite the availability of published studies on satisfactory post-LT outcomes following downstaging of HCC candidates with an initial tumor burden meeting UCSF/ Region 5 inclusion criteria, there is currently no welldefined upper limit in terms of size or number for eligibility criteria. In contrast to the previous studies that have used the MC as the endpoint of downstaging [116, 119], Neil et al. from the International Liver Transplantation Society (ILTS) Transplant Oncology Consensus Conference suggested that the UCSF criteria may be a more achievable downstaging endpoint before LDLT [119]. Therefore, an international consensus is currently needed to define effective downstaging and its eligibility criteria.

Under the influence of the medical system or the accessibility of LT in the Asia-Pacific region, LT is frequently performed as a rescue procedure when patients become unresponsive to locoregional treatment as a first-line treatment without prior consideration of LT. The role of LT after downstaging has been verified to be satisfactory in HCC treatment. Therefore, through multidisciplinary treatment integrating hepatologists, surgeons, and radiologists, the opportunity for transplantation and cure should be provided to more patients by offering downstaging strategies as one of the treatment options for patients with HCC beyond the MC at the time of diagnosis. In addition, because standardized downstaging criteria are so important for consistent patient selection that ensures acceptable outcomes across centers, the challenge and ongoing effort to reach consensus on defining effective downstaging and eligibility criteria is essential.

[Recommendations]

- LT is a primary treatment for HCC patients with a single mass measuring ≤ 5 cm or ≤ 3 tumors with a size of ≤ 3 cm, as per Milan Criteria without radiological vascular invasion or remote metastasis which are unsuitable for liver resection (A1).
- LT is recommended when successful downstaging is achieved after locoregional treatment in patients with HCC beyond the Milan Criteria which deviate from the indication for LT (B1).
- Even in patients with HCC beyond the Milan Criteria, LDLT can be performed according to center-specific criteria (C1).

Cholangiocarcinoma (CCA)

In general, LT is contraindicated in cases of known CCA. For high-risk CCA, LT alone without adjunctive therapy showed a 5-year survival rate of only 30% [125, 126]. However, since the introduction of the Mayo Clinic protocol, which combines strict patient selection (a localized tumor (< 3 cm) without distant or lymph node metastases) with neoadjuvant chemoradiation treatment before LT [126-129], the 5-year survival rate ranges from 65 to 70%, showing significantly improved outcomes [130, 131]. According to previous studies, LT may be performed in patients with unresectable hilar CCA who fulfill the Mayo Clinic protocol [132–134]. However, there are no large-scale prospective study on the benefits of LT for CCA, and studies to date have many limitations in convincing the benefits of LT for CCA. Accordingly, locoregional interventions and many systemic chemotherapies, traditional chemotherapy and target therapies, are still prioritized for unresectable CCA rather than liver transplantation. For LT to be extended to more patients with CCA, indications and standardized protocols that provide maximal potential benefits should be established through prospective or randomized clinical trials.

Colorectal liver metastases (CRLM)

CRLM can be an indication for LT in select patients [135–139]. In the first secondary cancer (SECA) study, involving 21 patients at the Oslo University Hospital who underwent LT because of CRLM, the 5-year overall survival rate was 60% at a median follow-up duration of 27 months [136]. Using strict selection criteria, the 5-year overall survival rate increased to 83% in the SECA-2 study [138]. A recent systematic review of 18 studies and a pooled analysis of 110 patients undergoing LT for CRLM reported that the 1-, 3-, and 5-year overall survival rates were 88.1%, 58.4%, and 50.5%, respectively [140]. The ILTS Transplant Oncology Consensus Conference recommendations suggested

that LT could be implemented in patients with unresectable CRLM with only liver involvement and a maximum tumor diameter of ≤ 5.5 cm, pre-LT CEA $\leq 80 \ \mu$ g/L, response to pre-LT chemotherapy, and a time interval from the diagnosis to LT ≥ 1 year [141].

LT techniques for CRLM such as "Living Donor Auxiliary Partial Orthotopic Liver Transplantation in Combination With Two-stage Hepatectomy" have been introduced, and liver transplantation cases for CRLM are increasing recently [142]. However, the indications in ongoing clinical trials are very strict; therefore, the number of eligible patients is small. All previous studies were conducted in the West, and it is unreasonable to apply their indications and protocols to populations in the Asia-Pacific region. Welldesigned clinical trials suitable for the CRLM characteristics of the Asia-Pacific region should be conducted to develop precise selection criteria and identify the patients who will benefit from LT for unresectable CRLM. Currently, LT is performed only in well-designed clinical trials or after careful evaluation by a multidisciplinary team comprising oncologists, radiologists, and surgeons.

Liver metastasis of a neuroendocrine tumor (NETLM)

In highly selected patients, non-resectable NETLM resistant to medical treatment is an accepted indication for LT [143]. The most commonly used criteria for LT are the MC, LT criteria according to the European Neuroendocrine Tumor Society guidelines, and LT criteria according to the UNOS guidelines [144–146]. The study involving the largest number of patients ever published is a multicenter study of 213 patients with mixed NET, where the 5-year overall survival was 52% [147], and a recent systematic review of retrospective case series reported a 5-year overall survival rate of 47–71% [148]. However, since heterogeneous overall survival data have been published, controversies regarding NETLM as an indication for LT remain, and further welldesigned randomized control studies are required to elucidate the clinical impact of LT for NETLM.

Hepatic epithelioid hemangioendothelioma (HEHE)

HEHE is a rare vascular tumor with an aggressiveness that is between that of hepatic hemangiomas and hemangiosarcomas. HEHE was classified as a malignant vascular tumor in the 2020 World Health Organization classification of soft tissue tumors because of its 15% risk of metastasis [149]. Due to its rarity and volatile behavior, the best clinical approach for the management of HEHE has not yet been standardized. In a literature review of 434 patients with HEHE, 87% and 37% of patients had a multifocal tumor and extrahepatic disease [150].

LT has been successfully performed in cases with advanced liver involvement and/or extrahepatic disease [151–153]. In 2007, Lerut et al. published a retrospective review of 59 patients from the European Liver Transplant Registry (ELTR) who underwent LT between June 1989 and June 2004. HEHE recurrence occurred in 14 patients (23.7%) at a median follow-up of 78.5 months after LT. The 5- and 10-year overall survival rates after diagnosis were 83% and 74%, respectively [154]. In the recently updated long-term ELTR-European Liver and Intestinal Transplant Association (ELITA) HEHE study, pre-LT EHD is not a significant predictor of survival or recurrence [155]. Furthermore, this updated ELTR-ELITA HEHE study (the largest in the world) strengthens the position of the LT in HEHE's treatment algorithm. The 5- and 10-year overall survival rates after diagnosis were 80.8% and 77.1%, respectively. The mortality rate within 3 months after LT was 4.7% [155].

Generally, macrovascular invasion, short waiting time (< 120 days), and lymph node involvement are known risk factors for the recurrence of HEHE after LT. Conversely, EHD is not a contraindication to LT. Although there is an opinion that the use of antiangiogenic mammalian target of rapamycin (mTOR) inhibitors after transplantation may be helpful; however, the number of patients treated with mTOR inhibitors was too small to examine their role after LT.

[Recommendations]

• In the treatment of unresectable HEHE, LT is worth considering, and extrahepatic disease in HEHE is not a contraindication to LT. (C2)

Benign neoplasm

Benign liver tumors are often diagnosed incidentally. Generally, most benign liver tumors do not require treatment. Patients with symptomatic benign liver tumors and reduced quality of life may be referred for surgery. In some cases of benign liver tumors, LT may be considered a surgical treatment.

Polycystic liver disease (PCLD) The LT indication for PCLD is usually for symptomatic relief and to improve the patient's quality of life. LT is the definitive treatment for PCLD, with excellent patient survival rates when compared to patients who had transplantation for other reasons. According to a recent published study that included 51 patients (46 (90%) DDLT and 5 (10%) LDLT) who underwent LT for PCLD, although most PCLD LT recipients were female, both sexes had a 5-year survival rate of above 90% [156]. LT has become a life-saving procedure for patients with PCLD; however, this is limited by the shortage of organ donors [157].

Hepatic hemangioma In cases of symptomatic hepatic hemangiomas, surgery remains an important treatment option [158]. Out of 87,280 transplants, 25 were performed for hemangiomas, and the overall survival rates were 87.8%, 81.5%, and 74.8% at 1, 3, and 5 years, respectively [159]. Due to the postoperative morbidity of LT and the lack of a donor's liver, these active treatments are very limited, and the indications for them have not yet been defined. Therefore, LT for hemangiomas should be reserved for cases of unresectable giant hemangiomas that cause severe symptoms that have been unresponsive to previous interventions or life-threatening complications, such as Kasabach–Merritt syndrome [160].

Hepatocellular adenoma (HCA) It is very rare to perform LT for HCAs. According to the UNOS database (1987–2020), a total of 142 patients with HCA had undergone LT [161]. In the UNOS cohort, the patient survival rates at 1, 3, and 5 years were 94.2%, 89.7%, and 86.3%, respectively. Suspected malignancy (39.7%), unresectable HCA (31.7%), and increasing size (27.0%) were the most common indications for LT. Glycogen storage diseases were also present in 53.1% of cases. Likewise, LT may be considered in very few situations, including in male patients with unresectable multiple lesions, large HCA associated with intrahepatic venous shunts, and patients with glycogen storage disorders who do not respond to medical treatment [162].

[Recommendations]

• In special cases, LT can be considered for patients with benign liver tumors; however, the decision must be made carefully due to the limited supply of donor organs. (C2)

Organ allocation policy

Transplantation should be taken before life-threatening events occur. However, careful planning is required, as the advantage of a transplant might be outweighed by the risk of surgery and lifelong immunosuppression. The decision to proceed with LT should be individualized after the patient has been evaluated by a multidisciplinary transplantation team while considering prognosis and contraindications. The demand for LT is on the increase; however, organ availability is still limited. As a result, transplant waiting times have increased, and consequently, the morbidity and mortality rates for potential recipients on waiting lists have also increased. Optimal patient selection is necessary, and those that are likely to have the best outcomes should be prioritized on the waiting list. However, it is difficult to decide which recipients should be prioritized on the waiting list and which patients should undergo transplantation first. Therefore, organ allocation policies have evolved to optimize outcomes and ensure fairness. Although the organ allocation system remains imperfect, each policy change is designed to optimize organ donation, increasing equity in access to organ transplants, decreasing waitlist deaths, and improving the outcomes of transplant recipients.

Prioritization

The Child-Turcotte- Pugh (CTP) score was first used for organ allocation in patients who required LT because of the predictability of survival in patients with cirrhosis. However, it was never prospectively validated and had limitations due to the subjective interpretation of ascites and encephalopathy [163]. The MELD score, based on objective measures such as creatinine, bilirubin, and PT-INR, was originally developed to predict 3-month mortality after the transjugular intrahepatic portosystemic shunt (TIPS) procedure in patients with end-stage liver disease [164]. It reports a reliable disease severity index that can be used to determine organ allocation priorities in LT and has been implemented in most LT programs in many countries [165]. The MELD score implementation resulted in a 3.5% reduction in mortality on the liver transplant wait list, and the median time to transplantation was reduced by more than 200 days [166]. When candidates with a MELD score \geq 35 were given priority on the wait list, more transplants, fewer discards, and lower waitlist mortality were reported [167, 168]. Although the MELD score reflects dual organ function of the liver and kidneys, other important conditions, such as refractory ascites and recurrent encephalopathy in the risk of mortality and/or organ functions impacting the medical acuity of decompensated patients, are not captured by the score [59].

Hyponatremia is a common complication in patients with decompensated cirrhosis, and several studies have demonstrated that incorporating serum sodium into the MELD score provides a more accurate survival prediction [169, 170]. The new score (MELD-Na) was adopted in the wait list priority system, and it led to a reduction in wait list mortality in candidates with a serum sodium less than 137 mEq/L [171, 172]. However, the introduction of the MELD-Na score worsened the sex disparity. Female patients had a lower likelihood of LT compared to that of male patients at the same MELD-Na score and were more likely to be delisted due to death or becoming too sick, with higher hospitalization rates after listing. [173–175]. Compared with MELD-Na, the MELD 3.0 score is characterized by additional variables of female sex and serum albumin, an upper bound for creatinine at 3.0 mg/dL, and interactions between bilirubin and sodium and between albumin and creatinine. The MELD 3.0 score also showed more accurate mortality prediction than the current MELD model and decreased wait list mortality, including the sex disparity [176].

The MELD system does not reflect the mortality risk and needs for transplantation in all potential medical emergencies for LT. Therefore, transplant programs may apply for additional MELD points or exemptions to fairly prioritize waitlist candidates (Table 5). Patients with HCC commonly have relatively low MELD scores at the time of diagnosis, which often underestimates their urgency for transplantation before the tumor progresses beyond the level that is amenable to LT. The exceptional points have been added to the MELD score to reduce the disadvantage among patients with HCC. Additional points have been changed depending on the type of tumor (size, number of nodules, alpha-fetoprotein level, waiting time, and response to downstaging procedures) [96, 177, 178]. The MELD score does not fully reflect the risk of multiple organ failure and mortality in patients with ACLF [179, 180]. LT can significantly improve survival in patients with ACLF; therefore, it needs to be considered to incorporate the presence of extrahepatic organ failure into the organ allocation policy [54, 56]. However, LT can be a futile treatment when the post-transplant mortality risk is too high in critically ill patients [60, 181]. In prioritization, factors that predict futility should be considered to optimize patient survival after LT for ACLF. Severe alcoholic hepatitis that is unresponsive to steroid treatment is associated with high mortality rates; however, LT significantly increases survival rates in such cases [182, 183]. Patients with severe alcoholic hepatitis are likely to have high MELD scores and receive priority on the wait list. However, it is difficult to prioritize patients with alcoholic hepatitis because of the equity related to pre-transplant abstinence and the risk of post-transplant alcohol relapse [184]. Strict criteria for selecting patients with a low risk of sustained alcohol use after LT could help in deciding who should be allowed to receive LT [185]. Sarcopenia is a frequent finding and a negative predictor of survival in patients with cirrhosis. The MELD score does not include nutrition or parameters related to sarcopenia. However, sarcopenia is associated with wait list mortality in LT candidates with cirrhosis, especially if their MELD or MELD-Na scores are low. In the organ allocation process, nutritional assessment can be included to reduce wait list mortality and improve overall outcomes [186, 187].

[Recommendations]

- MELD-based scores can be used to determine organ allocation priorities. (B1)
- Patients whose disease severity is difficult to evaluate using a MELD-based score should be considered exceptions or additional points should be used for prioritization. (B1).

Oversight of process and outcomes

An optimal allocation system for scarce resources should ensure maximal utility as well as equity. Therefore, the most frequent principles for allocation policies in LT are criteria that rely on the sickest first policy (utility) or benefit, meaning pre-transplant survival, post-transplant survival, or a combination of these. The authorities should oversee multifaceted logistics-related activities during the entire organ donation procedure, such as identifying suitable donors, reporting, diagnosing, managing, documenting, and obtaining the required donors' consent [188, 189]. Additionally, continuous efforts are needed to increase public and medical community awareness of the importance of donation and transplantation of organs, to rise the count of transplantations [188, 189]. Guidelines regarding the diagnosis of brain death and, subsequently, the discontinuation of life support in such donors are required. Additionally, guidelines related to organ donation and increased public awareness about brain death are a priority and should be considered a medical condition [188, 189]. The guidelines for LT focused on pre-transplant and post-transplant survival as indicators of benefit. However, it is also worthwhile to consider quality of life and long-term outcomes including graft survival, probability of liver disease recurrence, and overall functional improvement after LT.

Malignancy	Specific situations	Other diseases
Hepatocellular carcinoma	Refractory ascites	Budd-Chiari syndrome
Cholangiocarcinoma	Recurrent gastrointestinal bleeding	Familial amyloidosis
	Recurrent encephalopathy	Cystic fibrosis
	Hepatopulmonary syndrome	Hereditary hemor- rhagic telangiectasia
	Portopulmonary hypertension	Polycystic liver disease
	Chronic intractable pruritus	Primary hyperoxaluria
	Acute on chronic liver failure	Recurrent cholangitis
	Severe alcoholic hepatitis	
	Sarcopenia	

Table 5Common conditionsthat need consideration ofexceptions to MELD score

The incredible success of LT in the Asia-Pacific region has resulted in a growing disparity between those with endstage liver disease in need of LT and the overall availability of donor organs. The decision to prioritize high-risk patients has resulted in lower post-LT survival, better resource utilization, and uneven transplantation rates for various indications. There is increasing recognition that allocation systems need to continuously evolve to account for changing indications for LT, improvements in alternative treatments, and novel technologies [190]. Continuous monitoring of outcomes categorized according to donor characteristics will allow for inevitable refinements to be made so that any objective inequity can be minimized. Strategies to improve organ allocation will continue to evolve and adapt to changes in the transplant population as long as there is a difference between demand and supply. Furthermore, comprehensive data collection is important. Regular review and refinement of these policies based on emerging evidence and the changing transplant landscape can improve the overall transplantation system.

It is important to carefully consider the prospect of producing a reasonably good outcome before any LDLT is undertaken for patients who would otherwise be declined on a waiting list. Each case involving LDLT for a patient who would otherwise be ineligible for a DDLT is likely to be heart-wrenching and involve its idiosyncrasies; therefore, it is important to develop a programmatic policy in advance to guide these difficult decisions and carefully consider the prospect of LDLT. Criteria that determine when the use of a living donor is reasonable should be clearly defined. Ideally, they should be endorsed by a consensus of the multidisciplinary team when there is no particular factor that could bias the team's judgment [191]. In addition to the well-accepted standards that focus on minimizing donor risks by excluding donors for medical reasons, the criteria for the acceptability of living donor transplantation should focus on the likelihood of both long-term and short-term recipient survival [191].

Ethical issue

Organ allocation and the decision to perform LT raise numerous ethical and moral issues, and the transplant community has discussed them [192]. A measure of consensus has been achieved on many issues, such as the acceptability of the brain death standard, the use of liver grafts from deceased donors, the allocation of liver grafts based on urgency and need rather than social factors, and the acceptability of living donor transplantation [193]. A wide variety of liver allocation ethical concerns are important, including equity, solidarity, fairness, efficiency, quality of life, maximum benefit, economical responsibility, informed consent, and minimum corruptibility [194]. Among them, a more specific list of ethical concerns involves four general principles: justice, utility, beneficence or nonmaleficence, and patient autonomy.

The public feels that post-transplant outcomes, citizenship or resident status, and functional status should be considered in allocation decisions, as should local allocation and cost. Current organ allocation almost exclusively prioritizes the risk of waiting list death without clear ethical justification. The ethical rules that underlie live donation are different from those that concern deceased donors. LDLT involves the harms of scarring, the loss of a partial liver graft, as well as the physical and psychological risks and burdens associated with the liver procurement surgery, and the physical and emotional aftermath for both the donor and the recipient. Subjecting a healthy person to such risks and burdens for the sake of another individual is remarkably unusual in medical practice. Organ donations within the circle of a family are very welcome and respected. Altruistic donations are also acceptable. However, an organ donation carried out with a financial motive is strictly unethical [195].

[Recommendations]

• High ethical standards should be maintained for organ allocation policies and decision to living donation (A1).

Evaluation process including comorbidities

Although liver disease severity is the initial concern in initiating LT evaluation, there are several other important considerations. All potential candidates for LT should undergo an extensive work-up before a final decision is made.

Age

Usually, there is no formal age limit for potential LT recipients and LT has been successfully performed even in patients older than 70 years. However, since such patients have an increased risk of cardiovascular complications [196, 197], patients over 65 years of age need to be evaluated by a multidisciplinary team to exclude comorbidities. In addition, physiological, not chronological, age should also be considered to determine whether an old patient can be accepted for LT.

[Recommendations]

• In the absence of significant comorbidities, older age (> 70 years) is not a contraindication to LT (B2).

Cardiovascular function

The purpose of cardiac evaluation before LT is to assess perioperative risk and exclude concomitant cardiopulmonary disorders that would preclude good long-term outcomes. The hemodynamic state typical of advanced liver disease results in a low prevalence of systemic hypertension, and the impaired hepatic production of lipids may reduce serum cholesterol levels. Nevertheless, increased cardiac output and/or latent cardiac dysfunction, which includes a combination of reduced cardiac contractility with systolic and diastolic dysfunction and electrophysiological abnormalities, might occur and are often referred to as cirrhotic cardiomyopathy [198]. Furthermore, coronary artery disease (CAD) is at least as frequent in LT candidates as in the general population and is influenced by typical cardiovascular risk factors [199]. Therefore, electrocardiography and transthoracic echocardiography should be performed in all LT candidates to rule out underlying heart diseases. LT candidates with \geq 3 traditional CAD risk factors are most likely to have obstructive CAD and cardiac events after LT [200-203]. Of note, non-alcoholic steatohepatitis (NASH), the fastestgrowing indication for LT, has been associated with adverse cardiac outcomes after LT [204, 205]. Hence, if clinically indicated, a non-invasive modality such as cardiac computed tomography (CT)-based tests, rather than cardiopulmonary exercise testing or myocardial perfusion scintigraphy, might be favored first [206]. If significant obstructive CAD is suspected during the evaluation in high-risk patients, coronary angiography should be performed, considering that patients with CAD treated effectively before LT have outcomes that are comparable to those of patients without CAD [207]. However, such approaches to CAD in LT candidates must be individualized according to CAD severity, degree of liver dysfunction, and local expertise.

[Recommendations]

- An electrocardiogram and transthoracic echocardiography should be performed in all LT candidates to rule out underlying heart diseases (B1).
- In patients with multiple cardiovascular risk factors, anatomical assessment of the coronary artery should be considered (B2).
- Cardiac revascularization before LT might be considered based upon the weighing of risk and benefit among LT candidates with significant coronary artery stenosis (C2).

Pulmonary function

To evaluate the respiratory function, lung function tests and a chest radiograph are recommended in all LT candidates. In addition, portopulmonary hypertension (POPH) should be screened using transthoracic echocardiography [208]. POPH should be suspected in patients with portal hypertension who present with symptoms such as leg edema, dyspnea on exertion, atypical chest pain, or elevated jugular venous pressure, which are suggestive of pulmonary hypertension [209, 210]. Although there is no agreement regarding the diagnostic criteria for POPH that should warrant right cardiac catheterization [211–213], those with moderate to high risk of pulmonary hypertension (i.e., peak tricuspid regurgitant velocity [TRV] > 2.8 m/s or peak TRV ≤ 2.8 m/s and other signs of pulmonary hypertension) should undergo a right cardiac catheterization to diagnose POPH. The moderate (mean pulmonary artery pressure $[mPAP] \ge 35 \text{ mmHg}$) and severe POPH (mPAP \geq 45 mmHg) are predictors of increased mortality following LT, with a mortality rate of > 50% [214]. Therefore, if indicated, pharmacological treatments before LT are required [215-218].

[Recommendations]

- Screening for POPH should be recommended using transthoracic echocardiography for LT candidates, and those with positive screening tests should receive right heart catheterization (B1).
- LT candidates with POPH should be managed by a pulmonary or cardiac specialist (B1).

Renal function

The recognition of renal dysfunction in a patient with cirrhosis has a dramatic effect on the prognosis, since cirrhotic patients with renal failure have a sevenfold increased risk of death, with 50% of these patients dying within 1 month [219]. Therefore, assessing renal function is essential when evaluating patients for LT. The differential diagnosis of renal failure in patients with cirrhosis is broad and includes intercurrent sepsis, hypovolemia, parenchymal renal disease, and most commonly, hepatorenal syndrome [220]. Hepatorenal syndrome can be an indication of LT; when renal replacement therapy is required for more than 8-12 weeks, simultaneous liver-kidney transplant should be also considered. In addition, patients with end-stage liver disease and with GFR less than 30 m/min or patients in whom renal biopsy reveals more than 30% fibrosis and glomerulosclerosis would benefit from receiving both simultaneous liver-kidney transplant [221].

Extrahepatic malignancy

In LT candidates with a preexisting malignancy, the treatment received should have been curative, and sufficient time should have elapsed to exclude recurrence. The interval from cancer diagnosis to treatment and subsequent presumed cure to transplant listing candidacy varies depending on the type of malignancy and the proposed evidence-based efficacy of the treatment received [www.ipittr.com]. Furthermore, all LT candidates should undergo age- and risk factor-appropriate cancer screening, including esophagogastroscopy, colonoscopy, mammography, and a Papanicolaou smear from an epidemiological viewpoint.

[Recommendations]

• LT candidates should undergo age- and risk factor-appropriate cancer screening (A1).

Nutrition

LT candidates experience a variety of nutritional challenges including the effects of catabolic chronic illness often accompanied by reduced appetite. In a similar context, liver cirrhosis is associated with malnutrition, and cachexia is present in nearly 70% of patients with end-stage liver disease [222]. Malnutrition is associated with a lower survival rate after LT, and patients with body mass index $(BMI) < 18.5 \text{ kg/m}^2$ have the highest risk of poor outcomes [223]. Therefore, malnutrition and/or sarcopenia should be treated with adequate nutritional support to improve LT survival. Conversely, outcomes after LT seem to be worse in patients with a BMI > 40 kg/m² compared with the outcomes of normal-weight patients. Furthermore, with the increasing prominence of non-alcoholic fatty liver disease (NAFLD) as an indication for LT, metabolic syndrome, potentially resulting in the development of post-transplant diabetes mellitus (PTDM), should also be managed.

[Recommendations]

• A nutritional assessment should be performed on every LT candidate (B1).

Bone disease

Osteoporosis is frequent (up to 55%) in patients with cirrhosis [224], primarily owing to various risk factors common in these patients, including inactivity, inadequate nutritional status, hypogonadism, chronic cholestasis, alcohol excess, and disease-specific medications (e.g., corticosteroids). Therefore, given the frequency of osteoporosis in patients with cirrhosis, the following initial evaluation is recommended during the pre-LT evaluation: (i) bone densitometry of the hip or spine; (ii) radiographs of the thoracolumbar spine to screen for vertebral fractures; and (iii) assessment of serum 25-hydroxyvitamin D levels. Furthermore, a treatment strategy can be established to manage bone diseases after LT.

[Recommendations]

 Prior to LT, bone densitometry of the hip or spine, spine radiographs of the thoracolumbar spines to screen for vertebral fractures, and assessment of serum levels of 25-hydroxyvitamin D are required (B1).

Psychosocial evaluation

Social workers and/or mental health professionals typically provide a psychosocial evaluation with input from psychiatrists or physicians from other specialties (e.g., addiction medicine). It includes evidence of compliance with medical directives, adequate support from able caregivers, especially during the perioperative period, and an absence of active psychiatric disorders as well as behaviors that are harmful to health (e.g., alcohol, tobacco, or illicit drug use). To date, some reports suggest that depressive symptoms, particularly in the early postoperative period, are associated with poorer outcomes after LT [225, 226]. However, no psychiatric disorder is an absolute contraindication to transplantation. With not only proper evaluation and preparation but also adequate social support, successful long-term outcomes could be achieved.

Stably abstinent, methadone-maintained, opiate-dependent patients are generally good candidates for LT [227]. Cigarette smoking is implicated in many adverse outcomes in LT recipients including cardiovascular mortality as well as hepatic artery thrombosis [228, 229]. Oropharyngeal and other neoplasms following LT are also linked to cigarette smoking and can result in significant, potentially avoidable long-term mortality [230–232]. Hence, there are compelling reasons to prohibit all tobacco use in LT candidates.

On the other hand, the evaluation process should also include an assessment of the patient's social support network. As the care of a transplant patient involves frequent visits to clinics, a caregiver should organize suitable transportation and other logistical tasks.

[Recommendations]

- Patients should be evaluated for reasonable expectations regarding adherence to medical directives and mental health stability (A1).
- Cessation of cigarette smoking should be mandatory in all transplant candidates (B1).
- Alcohol abstinence is better, but strict rule of 3 to 6 months abstinence needs center-specific approach (B2)

Infectious diseases

Patients with cirrhosis are prone to infections that could result in the development of multiple organ failure and death

[233]. The active infection needs to be adequately treated before LT can be attempted. In addition, screening for latent infections is required to treat potentially lethal infections and to prevent disease exacerbation after LT under immunosuppressive regimens. As part of the transplant evaluation, a candidate should be screened serologically for viral infections including HBV, HCV, and human immunodeficiency virus (HIV), as well as herpes simplex virus (HSV)-1, HSV-2, Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpes virus 8, and varicella zoster virus [234, 235]. Screening should also be performed for latent syphilis and TB infections. Screening for TB can be done by tuberculin skin testing or interferon (IFN)-c-release assays, such as QuantiFERON (QFT, Cellestis) or T-SPOT.TB (Oxford Immunotec), as well as performing a chest radiograph [236]. If latent TB is detected, antimicrobial therapy might be considered before LT, if the patient is clinically eligible. The 1st-line regimen might include isoniazid daily for 9 months, rifampin daily for 4 months, or a weekly isoniazid/ rifapentine for 12 weeks, alternatively, isoniazid daily for 6 months, rifabutin daily for 4 months, or isoniazid/rifampin daily for 3 months. Pyridoxine (vitamin B6) 25–50 mg daily should be administered concomitantly with isoniazid due to the increased risk of neurotoxicity [237]. If detected, syphilis screened by the venereal disease research laboratory (VDRL) needs to be treated before LT. As part of transplant evaluation, a programmatic pre-transplant vaccination should be considered for all LT candidates. For example, pneumococcal, influenza, and tetanus immunizations along with serology-based vaccine recommendations against measles, mumps, varicella/herpes zoster, HBV, and HAV are key targets, based upon the routine vaccination protocols [available from https://www.cdc.gov/vaccines/hcp/acip-recs/ index.html].

If live vaccines are indicated (mumps, measles, rubella, varicella, or herpes zoster), they should be administered as soon as possible to avoid their use within several weeks of transplantation and the associated introduction of therapeutic immunosuppression. Influenza vaccine and pneumococcal vaccine are generally recommended for re-immunization [238].

Coronavirus disease 2019 (COVID-19) vaccinations are also recommended within the scope of the Emergency Use Authorization or Biologics License Application for the particular vaccine (https://www.cdc.gov/vaccines/hcp/aciprecs/vacc-specific/covid-19.html) [239]. As, severe cases of COVID-19 have also been reported in solid organ transplant recipients who received two doses of the vaccine [239], three doses of an mRNA COVID-19 vaccine in LT recipients are recommended [240, 241]. Human papillomavirus vaccination is also recommended prior to LT.

If necessary, collaboration with an infectious disease specialist might help manage specific endemic infections.

For example, to detect such infections, serology for Strongyloides, Schistosoma, and Leishmania, and malaria blood test, might be required for patients residing in South Eastern Asia. Furthermore, considering the clinical history, comorbidities, endemic diseases, and local epidemiology, screening for vancomycin-resistant enterococcus (VRE) might be necessary, if clinically indicated.

[Recommendations]

- LT candidates should be screened for bacterial, viral, and fungal infections prior to LT (A1).
- Pre-transplant sepsis needs evaluation and controlled bacterial sepsis should be considered for LT (A1)
- Systemic or invasive fungal infection is a contraindication for LT (A1)
- Treatment for latent TB should be initiated pre-LT, if clinically eligible (B2).
- A programmatic vaccination should be considered for all LT candidates (A1).

Anatomical aspects

Preoperative radiologic evaluation is essential to determine abnormalities that preclude LT and abnormalities related to surgical procedures using ultrasonography, CT, and magnetic resonance imaging (MRI). The patency and size of the extrahepatic portal vein, hepatic vein, hepatic artery, and inferior vena cava (IVC) must be ascertained. Narrowing or occlusion of these vessels and diseases involving the bile duct can alter the surgical plan for the reconstruction of the vessels and the bile duct.

Portal vein thrombosis (PVT) is still a common problem in patients with cirrhosis, with an estimated prevalence of 2–26% in those awaiting LT [242, 243]. Adequate portal flow is critical for graft survival after LT, which is why PVT has long been regarded as a contraindication for LT [244].

According to PVT grade, many surgical techniques for PVT during LT have been used, including eversion thrombectomy (or thrombendvenectomy) combined with an end-to-end anastomosis, jump grafts from the superior mesenteric vein or collateral vein, renoportal or cavoportal bypass, portal arterialization, and multi-visceral transplantation [245–248]. Generally, when determining the PVT grade before LT, the Yerdel classification is used (Table 6) [249]. As a result of improvements in medical care and surgical techniques, PVT by itself is no longer a contraindication for LT.

However, the effect of PVT on morbidity and mortality after LT remains unclear. Patients with PVT confined to the portal vein (Yerdel grades I, II) can undergo LT with results that are comparable with those of patients without PVT [250–252]. There is also a report that the survival rates of patients with

Grade 1	Thrombus at main PV affecting less than 50% of the lumen with or without minimal extension into SMV
Grade 2	Thrombus at PV affecting more than 50%, including complete thrombosis with or without minimal extension into the SMV
Grade 3	Complete PVT plus thrombosis extending to the proximal SMV with patent distal SMV
Grade 4	Complete PVT plus complete thrombosis of the SMV (proximal and distal)

 Table 6
 Grade of portal vein thrombosis

PVT at 1 year and 5 years after LT are similar [253]. On the other hand, some studies have found a higher mortality rate after LT in patients with complete thrombosis of the main portal vein than in those without complete thrombosis. In a study on 21,673 LT recipients in the UNOS registry, PVT was an independent risk factor for mortality after transplantation [254]. In a recent meta-analysis, of seven studies that included 490 LT recipients, patients with PVT had a higher 30-day pooled mortality rate (13%) than did non-PVT patients (7%), and PVT was associated with a less pronounced but still significant increase in 1-year mortality (13.5% vs. 9.9%) [243]. The study showed that complete PVT was responsible for higher mortality. LT recipients with higher Yerdel grades, especially grades 3 or 4, have a higher morbidity and mortality rate after LT due to the complexity of the surgery. These operations often require difficult reconstructions that are nonphysiologic (renoportal bypass, arterialization, etc.).

Isolated thrombosis confined to the portal vein is not a surgical contraindication. Although innovations in medical care and surgical techniques have lowered the threshold for performing LT in candidates with PVT, these patients, especially those with PVT that are completely occluded and extend into the mesenteric vein, continue to have suboptimal outcomes after LT. Therefore, it is recommended that patients undergo appropriate screening for PVT while on the waiting list.

[Recommendations]

- Anatomical abnormalities should be ascertained by the preoperative images. (B1)
- The presence of PVT is not a contraindication to LT; if the thrombosis extends to the portomesenteric system, LT might not be feasible due to its suboptimal outcome. (C2)
- Pre-transplant anticoagulation for PVT is desirable if the thrombus is recent or progressive or symptomatic (B2)

Management of patients on the waiting list

Cerebral edema

Cerebral edema that induces elevation of intracranial pressure (ICP) is a perceived fatal complication of HE in patients with ALF. It is recommended that patients with ALF and progression to grade II HE, suggestive of impending cerebral edema, be intubated and managed in the ICU [255]. ICU management aims to support organ function with continuous monitoring of central hemodynamic parameters, but should also include neuroprotective treatments targeted to prevent the onset or reduce the severity of intracranial hypertension.

Invasive ICP monitoring is the most reliable method for the diagnosis and management of cerebral edema; however, it may lead to significant morbidity and mortality due to intracranial bleeding that may occur in 1–10% of patients. Moreover, the survival benefits of ICP monitoring are yet to be shown [256, 257]. Therefore, there are trends toward decreased use of ICP monitoring, and its placement should be reserved for a highly selected subgroup of patients. Several non-invasive approaches, including transcranial Doppler ultrasonography, continuous neurophysiological monitoring, near-infrared spectroscopy, optic nerve sonography, and pupillometry, have been developed for estimating ICP but have not been fully validated in patients with ALF [258].

General measures for intracranial hypertension include elevating the head by 30 degrees, preventing fever, hypoglycemia, and hyperglycemia, and clamping serum sodium at 140-145 mmol/L. The use of either hypertonic saline (200 mL, 2.7% or 30 mL, 30%) or mannitol (150 mL, 20%) given over 20 min as the first-line therapy in established cerebral edema is recommended [8, 259, 260]. The potential for hypertonic saline to produce brain dehydration owing to osmotic changes or severe hypernatremia is one of the concerns associated with its use in patients with ALF [261]. Serum sodium levels should be maintained at 160 mmol/L, but this threshold was derived from studies on mannitol [262]. Generally, a maximum serum osmolality of < 320 mOsm/L is recommended; however, this was established from insufficient data to avoid renal tubular injury, and exceeding this goal may not be harmful if the patient is not volume deprived. Repetitive use of mannitol may be particularly associated with undesirable consequences, such as intravascular volume depletion, rebound ICP increase, and renal failure due to mannitol accumulation [263]. Early implementation of renal replacement therapy with continuous veno-venous hemofiltration is an effective strategy for reducing circulating ammonia levels, with a clear association between ammonia clearance and creatinine clearance [264].

However, the initiation of renal replacement therapy primarily for hyperammonemia as opposed to acute kidney injury (AKI) has not been studied in a randomized controlled clinical trial (RCT) [8]. In the case of resistance, a brief period of hyperventilation may be necessary to reduce arterial $PaCO_2$ to 25–30 mmHg. The use of steroids is not advised [259]. High-volume plasmapheresis is not recommended since its use prior to transplantation does not improve survival outcomes compared with the use of standard medical therapy [265]. Standard-volume plasma exchanges increase transplant-free survival in patients with ALF waiting LT [266], but need further validation before implementation in clinical practice.

[Recommendations]

- Patients with ALF and impending cerebral edema should be intubated and managed in an ICU with regular evaluation for signs of intracranial hypertension (C1).
- Invasive ICP monitoring should not be *used* routinely for patients with ALF, but should be reserved for a highly selected subgroup of patients (B1).
- For ICP surges, hypertonic saline or mannitol should be administered, while considering short-term hyperventilation in refractory cases (B1).

Treatment of chronic hepatitis C virus infection pre-transplantation

Treatment of HCV infection in patients without HCC awaiting LT has two important goals: first, to improve liver function before transplantation, and second, to prevent liver graft infection after transplantation. Improvement in liver function after the administration of direct-acting antiviral agent (DAA) therapy in patients with decompensated cirrhosis pre-transplantation has been reported in several studies [92, 267-274]. In the SOLAR 1 study, a combination of ledipasvir/sofosbuvir + ribavirin was administered for 12 or 24 weeks to 108 patients with decompensated cirrhosis and with genotype 1 or 4 infections before LT [267]. Overall, 87% and 89% of patients with Child-Pugh B achieved sustained virological response (SVR) at 12 weeks after treatment (SVR12) among those who received 12 and 24 weeks of treatment, respectively. Among patients with Child-Pugh C decompensated disease, studies showed similar results, with SVR12 rates of 86% and 87% in patients who received 12 and 24 weeks of treatment, respectively. In most patients with Child-Pugh B and C disease, MELD, and Child-Pugh scores decreased between baseline and 4 weeks post-treatment. These findings were also confirmed by the SOLAR 2 study [268]. Ledipasvir/sofosbuvir + ribavirin pre-transplantation treatment resulted in high SVR12 rates in HCV patients with advanced liver disease (> 80% in patients with Child-Pugh B and C), and SVR12 was similar between the 12- and 24-week treatment groups in genotype 1. Improvements in MELD scores occurred in 72% of non-transplanted patients who achieved SVR12. Furthermore, 28% improved from Child-Pugh B at baseline to Child-Pugh A, and 68% improved from Child–Pugh C at baseline to Child–Pugh B cirrhosis at 12 weeks post-treatment. In the ASTRAL-4 study, patients with Child-Pugh B decompensated cirrhosis infected with genotypes 1-4 were randomized to receive sofosbuvir and velpatasvir for 12 weeks without ribavirin, for 12 weeks with weight-based dosed ribavirin, or 24 weeks without ribavirin [269]. The SVR12 rates with these three treatment groups were comparable, with a slightly higher rate in sofosbuvir and velpatasvir with ribavirin for 12 weeks, especially in genotype 3, confirming this as the standard regimen. In the ASTRAL-4 trial, of patients with a baseline MELD score < 15 treated with sofosbuvir and velpatasvir, with or without ribavirin, 51% (114/223) of patients had an improved MELD score at 12 weeks post-treatment. In a phase 3 study conducted in Japan, sofosbuvir and velpatasvir with or without ribavirin for 12 weeks in patients with decompensated cirrhosis were effective and tolerable, showing SVR12 rates of 92% in each group [271]. Among patients with SVR, 26% and 27% of patients had improved Child-Pugh class and MELD scores, respectively.

The baseline MELD score is an important factor in determining DAA treatment before LT to achieve clinical improvement and subsequent delisting. A European study promoted by ELITA reported that 21 of 103 (20.4%) patients with decompensated cirrhosis were delisted due to clinical improvement after a median of 60 weeks [275]. The probability of being delisted was very high (approximately 35%) in patients with a MELD score < 16), but minimal (about 5%) in those with a MELD score > 20. All delisted patients had either a complete regression or a dramatic improvement in signs of hepatic decompensation, such as ascites and/or HE. Improvement of the MELD score by at least three points and of albumin by at least 0.5 g/dL after 12 weeks of DAA are useful independent predictors of inactivation on the waiting list and subsequent delisting. In a United States modeling study using integrated data from recent trials, treating HCV before LT increased life expectancy only in patients with a MELD score of $\leq 23-27$, depending on the UNOS region [276]. In a retrospective analysis, five baseline factors (BMI, encephalopathy, ascites, serum levels of alanine aminotransferase [ALT], and albumin) were suggested as predictors of clinical improvement in HCV patients with decompensated cirrhosis receiving DAA treatment [270].

Despite the benefits of pre-transplantation antiviral treatment, caution is required in the following situations. In patients with low MELD scores (<16), clinical improvement after DAA treatment will favor delisting in some patients, while in patients with high MELD scores (>18-20), mild improvement in MELD scores after DAA may not be enough for delisting and may serve as a disadvantage to these patients who may lose priority on the waiting list (MELD purgatory) [273]. The effectiveness of DAA has not been proven in patients with high MELD scores; moreover, there are still concerns regarding the drug toxicity of DAA ± ribavirin treatment in these patients. HCV clearance can increase wait list time as these patients are no longer candidates for HCV-positive donor livers in most transplant centers, and should compete with other candidates for HCV-negative livers. Local supplies of HCV-positive donor livers should also be considered. Lastly, it is important to continue monitoring for future relisting for LT and long-term clinical outcomes, including the development of HCC, in patients who were removed from transplant waiting lists after HCV clearance. Although DAA treatment was associated with reduced mortality risk, it was not associated with liver-related death, decrease in HCC, or need for LT during a median follow-up period of 39.7 months [277]. HCC development, death, and relisting have been reported in delisted patients during 2 years of follow-up in a European study [278], and increased rates of liver refractory ascites and severe encephalopathy among delisted patients have been reported in another study [279].

IFN-free, DAA-based pangenotypic regimens are the most suitable options for patients with decompensated (Child-Pugh B or C) cirrhosis pre-transplantation. The use of protease inhibitors is contraindicated in patients with decompensated cirrhosis or with prior episodes of decompensation because of a substantially higher risk of toxicity [280]. In patients with any genotype of HCV (G1-6) infection, the combination of sofosbuvir 400 mg and velpatasvir 100 mg with weight-based ribavirin (1000 or 1200 mg in patients < 75 kg or \geq 75 kg, respectively) for 12 weeks is the treatment of choice for patients with decompensated (Child-Pugh B or C) cirrhosis. In patients with genotype 1 HCV infection, ledipasvir 100 mg and sofosbuvir 400 mg with weight-based ribavirin (1000 or 1200 mg in patients < 75 kg or ≥ 75 kg, respectively) for 12 weeks can be an alternative regimen. In patients with genotype 2 HCV infection, sofosbuvir 400 mg and weight-based ribavirin (1000 or 1200 mg in patients < 75 kg or ≥ 75 kg, respectively) for 16 weeks can be considered.

Treatment of HCV infection in patients with HCC awaiting LT—the optimal timing for antiviral therapy (before or after transplantation)—is still debated. Lower SVR rates have been reported with various DAA regimens in patients with active HCC compared to those without HCC [281, 282]. Post-transplantation treatment of HCV was reported to be cost effective in patients with HCC [283]. Meanwhile, a retrospective cohort study reported that HCV-infected patients with HCC treated with DAAs had lower risks for tumor progression or death compared to those of untreated patients [284]. Thus, for patients with HCC awaiting LT with an HCV infection, the optimal timing for antiviral therapy (before or after transplantation) should be decided on a caseby-case basis.

[Recommendations]

- Patients with chronic hepatitis C having decompensated (Child–Pugh B or C) cirrhosis without HCC, who are awaiting LT and having low MELD scores (<16) should be treated prior to LT (B1).
- Patients with chronic hepatitis C having decompensated (Child–Pugh B or C) cirrhosis without HCC, who are awaiting LT and having high MELD scores (>18–20) should be transplanted first without antiviral treatment, and HCV infection should be treated after LT (B1).

Gastroesophageal varices

Approximately 30–40% of patients with compensated cirrhosis and 80% of patients with decompensated cirrhosis have varices [285]; these numbers are similar to what is observed in cirrhotic patients on the waiting list [286]. Patients who are waiting for LT must undergo an endoscopy to rule out varices. Despite advances in treatment, the 6-week mortality rate for each episode of variceal hemorrhage remains between 15 and 25%. Without secondary prophylaxis, approximately 60–70% of patients may experience rebleeding, usually within 1–2 years of the initial hemorrhagic episode [287]. Patients on a liver transplant waiting list generally follow the recommendations for cirrhotic patients with gastroesophageal varices.

Esophageal varices Regarding primary prophylaxis of medium or large esophageal varices, either non-selective beta-blockers (NSBBs, such as propranolol and nadolol) or carvedilol or esophageal variceal ligation (EVL) is recommended for preventing the first variceal hemorrhage of medium or large esophageal varices in patients on a liver transplant waitlist [288–292]. Moreover, NSBBs or carvedilol is recommended for high-risk small varices (i.e., red wale markings on endoscopy and/or developed in a CTP-C patient) [293] since performing EVL in these varices and defining eradication may be difficult, although there is no study on this issue due to the rarity of high-risk small varices.

When choosing between EVL and NSBBs in patients on a liver transplant waiting list, several factors should be considered. The benefits of NSBBs and carvedilol include their low cost, ease of administration, and the fact that they do not require follow-up endoscopies. Additionally, the rate of decompensation and death is decreased in patients with hemodynamic responses to NSBBs and carvedilol [294]. In several studies of cirrhotic patients with ascites on a liver transplant waiting list, the use of NSBBs or carvedilol was associated with a lower risk of mortality [295, 296]. The use of NSBBs or carvedilol could also prevent bleeding from portal hypertensive gastropathy, which is not the case for EVL [297]. EVL can cause fatal iatrogenic bleeding. On the other hand, 15% of patients may have absolute or relative contraindications to therapy, and another 15% require dose reduction or discontinuation due to common side effects, such as fatigue, weakness, and shortness of breath. Moreover, NSBBs can lower arterial pressure, shorten survival time, and exacerbate paracentesis-induced circulatory dysfunction in cirrhotic patients with refractory ascites [298], resulting in increased waiting list mortality [299]. Since there is still insufficient data on the prognostic differences between the prophylactic methods in patients on a waiting list, local resources and expertise, patient characteristics, and waiting time till LT, adverse events and contraindications should be considered when deciding which treatment to apply among NSBBs, carvedilol, or EVL to prevent the first hemorrhage from esophageal varices. Discontinuation of NSBBs can increase the bleeding risk; therefore, if NSBBs is stopped due to contraindications, significant adverse effects, or poor compliance, EVL should be considered [79].

Several RCTs and meta-analyses that compared the combination of EVL and NSBBs against EVL alone or NSBBs alone have demonstrated that the combination treatment reduced overall rebleeding and variceal rebleeding [300, 301]. Carvedilol has only been compared with EVL alone [302] or with the combination of NSBB and isosorbide-5-mononitrate [303], but not with the standard of care consisting of NSBB and EVL combination therapy. In a recent retrospective study, carvedilol was associated with more marked reductions in the hepatic venous pressure gradient and lower rates of rebleeding, liver-related death, and nonbleeding decompensation than propranolol [304]. In line with this data, the Baveno VII consensus recommended both traditional NSBBs and carvedilol in combination with EVL for the prevention of recurrent variceal hemorrhage [79].

Pre-transplant TIPS is a safe and effective therapy for managing the complications of portal hypertension [305]. In a multicenter RCT comparing TIPS and EVL or glue injection plus NSBBs, a lower variceal rebleeding rate was observed, but the incidence of HE within 1 year was higher in the TIPS group. There was no difference in the mortality rate during the follow-up period [306]. Thus, TIPS should not be recommended as the primary treatment for the prevention of variceal rebleeding but should be recommended in patients on a transplant waiting list who have episodes of rebleeding despite NSBBs or carvedilol and EVL considering the favorable long-term results after LT [79]. TIPS as a bridge to LT can also be considered for patients with varices and other concomitant uncontrolled portal hypertension-related complications, such as refractory ascites [307].

Gastric varices Gastric varices are found in approximately 20% of cirrhotic patients, and the bleeding rate after 2 years is estimated to be 25% [308]. The incidence of gastric varices is lower than that of esophageal varices, but since they manifest with serious bleeding, their rebleeding rate and fatality rate are greater [308]. Regarding primary prevention of bleeding from gastric varices, a single randomized study revealed that endoscopic variceal obturation (EVO) may be more effective than NSBBs in preventing the first hemorrhage in patients with large cardiofundal varices, despite survival being comparable [309]. However, the last Baveno consensus recommended the use of NSBBs in this setting to prevent decompensation [79].

Regarding acute bleeding from isolated gastric varices type 1 and gastroesophageal varices type 2 that extend beyond the cardia, EVO is recommended for hemostasis [310]. EVL or tissue adhesive can be applied in cases of acute hemorrhage from gastroesophageal varices type 1 [311]. TIPS, with or without collateral embolization, is similarly efficacious for the treatment of acute bleeding events and the prevention of rebleeding in cases of both gastric and esophageal variceal hemorrhage [312]. In a meta-analysis, balloon-occluded retrograde transvenous obliteration (BRTO) and TIPS were shown to have comparable bleeding control rates (97.7% vs. 95.95%, p=0.84) with a similar technical success rate. However, BRTO is more effective in preventing rebleeding compared with TIPS [313].

Regarding secondary prophylaxis, in one RCT, repeated EVO was superior to NSBBs in preventing rebleeding from cardiofundal varices [314]. Another RCT comparing TIPS with EVO found that TIPS was more effective in avoiding rebleeding from gastric varices, with comparable survival and complication rates [315]. Given the significant rebleeding rate associated with cardiofundal varices, early TIPS should be highly considered, if the patient on a waiting list is a suitable candidate for the procedure. The alternative is BRTO, which allows for the treatment of fundal varices related to a spontaneous portosystemic shunt, and is theoretically more beneficial than TIPS as it does not divert portal blood flow from the liver. In a recent RCT, BRTO was shown to be more effective than EVO in preventing rebleeding from gastric varices with comparable survival and complication rates [316]. There are several variations of this procedure, including plug-assisted retrograde transvenous obliteration (PARTO) and coil-assisted retrograde transvenous obliteration (CARTO), which have a similar or higher success rate and do not require balloon indwelling times ranging from 3 h to overnight. However, given the grave prognosis after the procedure in patients with a high MELD score (> 15-18),

TIPS or BRTO should be performed only in the absence of other options, such as EVO.

[Recommendations]

- Patients with medium/large esophageal varices should be treated with either NSBBs such as carvedilol, or EVL in consideration of various factors, including waiting time until LT (A1).
- Patients with small esophageal varices with red color signs on endoscopy or Child–Pugh C, or those with gastroesophageal varices type 2 or isolated gastric varices type 1, should be treated with NSBBs such as carvedilol (C1).
- Combination therapy of NSBBs and EVL should be considered to prevent rebleeding from esophageal varices while waiting for LT (A1).
- TIPS as a bridge to LT should be considered for patients with varices who rebleed after NSBBs with EVL, or those with varices and refractory ascites (B1).
- Selective embolization (BRTO, PARTO, or CARTO) may be considered to control bleeding and prevent rebleeding from gastric varices with a portosystemic shunt (B2).

Portopulmonary hypertension

POPH refers to pulmonary arterial hypertension (PAH) linked with portal hypertension; it is a well-known consequence of portal hypertension owing to chronic liver disease or extrahepatic causes. The prevalence of POPH ranges from 2% in those with chronic liver disease to 16% in those with end-stage liver disease listed for LT. The prevalence does not seem to be affected by the severity of liver disease or portal hypertension [317, 318]. LT is not a treatment for POPH per se and should only be performed in patients with end-stage liver disease who meet the criteria for LT, and whose POPH is treated and responsive to PAH-specific therapy.

POPH is confirmed in the same manner as in patients with idiopathic PAH: (1) elevated mPAP > 20 mmHg at rest; (2) normal or low pulmonary capillary wedge pressure ≤ 15 mmHg at rest; and (3) elevated pulmonary vascular resistance (PVR; ≥ 2 Wood units [160 dynes/s/cm⁻⁵]) in patients with portal hypertension or a portosystemic shunt [319]. An elevated PVR is critical because it differentiates patients with precapillary disease from those with a passive elevation in the mPAP due to the hyperdynamic circulatory status associated with chronic liver disease. PVR, and not mPAP, is a strong predictor of wait list mortality in transplant candidates with POPH [320].

The evidence base for pharmacological therapy in POPH is lacking, as most data are drawn from studies on PAH. When possible, beta-blockers, which are commonly used for the treatment of varices, should be avoided in patients with POPH because they may exacerbate right heart failure owing to a decrease in right ventricular cardiac output and an increase in PVR [321]. TIPS may increase the preload on the right ventricle and aggravate heart failure [322], and is thus generally avoided in patients with POPH. BRTO can increase portal pressures, but the effect on pulmonary hemodynamic changes is unclear. In general, patients with a mPAP greater than 50 mmHg are ineligible for LT, based on the reports of a previous study, which showed that all patients with a mPAP of 50 mmHg or greater died after LT [323]. PAH-specific therapy is recommended for the treatment of POPH prior to LT in patients with a mPAP of between 35 and 50 mmHg [324]. PAH-specific therapy improves pulmonary hemodynamics and establishes transplant eligibility in up to 50% of LT candidates with PAH [325]. Patients are considered transplant candidates if, after receiving targeted therapy to reduce PAP, their mPAP and PVR have improved to less than 35 mmHg and 400 dynes/s/ cm⁻⁵, respectively. Favorable post-transplant outcomes for patients with an mPAP greater than 35 mmHg due to an increase in cardiac output associated with hyperdynamic circulation due to cirrhosis and a normal PVR have been reported [326, 327]. Based on these results, LT could be considered when mPAP is greater than or equal to 35 mmHg and less than 45 mmHg and PVR is less than 240 dynes/s/ cm⁻⁵. Generally, the principles of agent selection for POPH patients are similar to those for idiopathic PAH patients, with the following exceptions: (1) calcium channel blockers (CCBs) are contraindicated; (2) endothelin receptor antagonists should be avoided in patients with moderate to severe liver disease and patients with transaminase level greater than three times the upper limit of normal due to liver toxicity; and (3) phosphodiesterase-5 inhibitors, such as sildenafil and tadalafil, are routinely recommended since hepatic impairment does not impact their metabolism. In the only RCT, PORTICO, that included 85 patients with POPH, of whom two-thirds were already receiving medication for PAH, macitentan decreased PVR by 35% compared to placebo after 12 weeks without hepatic safety concerns. In the macitentan group, adverse outcomes, notably peripheral edema, were more prevalent [328].

[Recommendations]

- In patients with POPH, beta-blockers should be discontinued and varices should be treated with EVL (B1).
- TIPS should be avoided in patients with POPH (B1).
- A mPAP ≥ 50 mmHg should be regarded as an absolute contraindication to LT, regardless of the therapy applied (C1).
- Patients with mPAP of between 35 and 50 mmHg in whom targeted therapy lowers mPAP to < 35 mmHg and

PVR to < 400 dynes/s/cm⁻⁵ or mPAP to 35–45 mmHg and PVR to < 240 dynes/s/cm⁻⁵ could be considered for LT (B1).

Obesity

Due to concerns about more complex surgery, prolonged recovery, and post-transplant hospital stay, higher rates of wound complications, more frequent pulmonary complications, and an increased risk of major cardiovascular events [329, 330], obese patients were regarded as being suboptimal candidates for LT. There is no clear cutoff point for BMI when selecting the best transplant candidate with obesity. Recent data from European registries show that BMI > 40 kg/m² is linked with a 1.96-fold increased risk of post-transplant mortality as compared to normal-weight patients [331].

Lifestyle modification Malnutrition and sarcopenia are prevalent in patients with decompensated cirrhosis. Sarcopenia, which is frequent in patients with NASH cirrhosis and/or obesity, would likely lead to frailty in these patients. [332, 333]. Thus, efforts such as prehabilitation and exercise should be encouraged in an attempt to reduce the negative impact of frailty [334, 335]. Weight reduction in patients with decompensated cirrhosis should be done with caution since sarcopenia could be aggravated [336]. Currently, no specific recommendations exist for promoting weight reduction in patients with decompensated cirrhosis on a LT waitlist; however, limiting calorie intake and increasing protein intake are indicated [337]. Weight reduction by dietary modifications is safe for patients with compensated cirrhosis and may reduce the severity of portal hypertension [338].

Bariatric procedures Carefully chosen cirrhotic patients may receive bariatric surgery. Several retrospective cohort studies have demonstrated the cost-effectiveness as well as favorable outcomes of bariatric surgery (with most patients undergoing sleeve gastrectomy) in patients with Child-Pugh classes A and B cirrhosis [339, 340]. However, caution must be taken in patients with decompensated cirrhosis. A population-based study revealed that patients with decompensated cirrhosis had a higher postoperative mortality rate than those with compensated cirrhosis or those without cirrhosis (16.3% vs. 0.9% vs. 0.3%, respectively) [341]. In this select group of patients, simultaneous bariatric surgery and LT may be a viable option since this approach demonstrated more durable weight loss and fewer metabolic complications [342-344]. Bariatric endoscopy procedures like intra-gastric balloon placement in the absence of gastric varices or in small or obliterated esophageal varices is gaining acceptance, because of safety and outcomes particularly in compensated or decompensated (Child-B) cirrhosis [345, 346].

[Recommendations]

- Patients with a BMI ≥ 35 kg/m² are a relative contraindication to LT and should be thoroughly evaluated by a multidisciplinary team before LT (B2).
- Patients with a BMI≥35 kg/m² or≥30 kg/m² and comorbidities on the transplant waitlist require lifestyle intervention, including dietary changes and prehabilitation, prior to LT (C1).
- LT candidates with a BMI≥35 kg/m² or≥30 kg/m² and comorbidities can be considered for sleeve gastrectomy prior to LT for those with compensated cirrhosis and at the time of LT for those with decompensated cirrhosis (B2).

Donor evaluation and donation process

Deceased donor

Many Asia-Pacific countries have a severe shortage of deceased organs. Thus, LDLT has been commonly accepted as an alternative way to save the lives of patients who have end-stage liver disease or liver cancer [347].

Some European countries have "opt-out," i.e., presumed consent systems, in which no explicit consent is required for a person to become a potential donor [197]. However, most Asia-Pacific countries except Singapore have an "opt-in" policy that requires explicit consent from first-degree relatives of the potential donor [348].

As Asia is characterized by a huge diversity in social, economic, and cultural factors, each country has different policies and systems according to its circumstance for organ donation and allocation [347].

Donation after brain death (DBD)

According to the 2010 American Academy of Neurology guidelines, the determination of brain death in adults necessitates three clinical findings: an irreversible coma from a known cause, brainstem areflexia, and a conclusive apnea test (or one of several other ancillary tests) [349]. Brain-dead donor organs should be procured with the consent of donors and/or their relatives. After the determination of brain death, donors should be fully evaluated to check for transplantable organs.

For all deceased donors, biochemical evaluations should be normal, and there should be no known liver diseases and no acute active infections. All deceased donors should be evaluated for histories of malignancies, laboratory tests including complete blood cell count, coagulation, routine chemistry, urinalysis, a culture study, serologic markers for hepatitis, and imaging studies such as ultrasound. In addition, during procurement, a liver biopsy and frozen-section examination should be considered to check for chronic hepatitis, cirrhosis, severe hepatocellular injury, moderate diffuse hepatocellular ballooning, and severe macro-vesicular fatty changes [349, 350]. Hypernatremia, sepsis, extracranial malignancy, and high-dose vasopressor support have been associated with poor graft function [350–354].

Split LT is an important tool that can be used to reduce donor organ shortages and waitlist mortality, especially for pediatric patients and small adults [355]. Careful donor selection is necessary to perform a successful split LT. Although there is no definite algorithm for decision-making with regard to split liver transplants from deceased donors, in general, the split donor should be hemodynamically stable, using low-dose inotropic agents, relatively young, with well-preserved liver function, and with only mild fatty changes [356]. Additional criteria for donors of left lateral splitting include age < 55 years, intensive care stay < 5 days, fatty degeneration of the liver < 30%, gamma-glutamyl transpeptidase < 50U/L, serum glutamic pyruvic transaminase > 60U/L, and Na < 160mmol/L [357]. There are no definite selection criteria for recipient to receive split liver graft. However, depending on its relatively highly variable weight, the left lateral segment can be utilized for pediatric recipients up to 40 kg of body weight [357].

Surgical techniques for splitting a liver are almost the same as living donor hepatectomy. The most commonly employed parts of a graft used in children are segments 2 and 3 (left lateral segment). The other extended right lobe (ERL) graft with whole IVC is often matched to an adult recipient [358]. In situ split is currently the most common technique for separating the liver parenchyma. However, according to the donor hemodynamic instability or recipient matching circumstances, an ex situ split can be decided intraoperatively [359, 360]. Short- and long-term outcomes and survival after split LT can be similar to those of patients who receive whole organ LT if meticulous evaluations of donor organs and recipients are performed, and the logistics of organ allocation and splitting procedures are adapted [355].

[Recommendations]

- Brain-dead donors should be fully evaluated to determine whether they are suitable liver donors by taking a detailed medical history for malignancies and performing basic blood tests and imaging evaluations. (A1)
- When a donor is relatively young, hemodynamically stable, with well-preserved liver function, and with only mild fatty changes, split LT can be a good option to share

a liver graft for two recipients, commonly an adult and a child. (B1)

Donation after circulatory death (DCD)

Due to the lack of brain-dead organs, organ transplants using DCD are increasing, mainly in the United States and Europe. According to Maastricht's definition, DCD is categorized into four categories: category I (dead on arrival), category II (unsuccessful resuscitation), category III (awaiting cardiac arrest), and category IV (cardiac arrest in a brain-dead donor) [361]. Also, categories I and II are categorized to uncontrolled DCD, which refers donations from individuals who pass away after an unplanned, abrupt cardiac arrest for which resuscitation has failed, whereas categories III and IV are categorized to controlled DCD. Currently, the use of DCD liver grafts is based on only category III in most countries, but some countries implement category II [362]. Among Asian countries, such as China, India, Singapore, and Hong Kong, most DCDs are category III [363-366], except in Japan, where category IV and non-controlled DCDs are dominant because it is not recommended to end active treatment, such as respiratory withdrawal.

Extracorporeal membrane oxygenation could be used for organ perfusion throughout the needed observation time for DCD donors, increasing the utility of donated livers [367]. Furthermore, various organ perfusion strategies such as normothermic regional perfusion, hypothermic oxygenated perfusion, and normothermic machine perfusion could increase the quality of liver graft from DCD [368].

Extended criteria donors (ECD)

ECD grafts have been defined as organs with an increased risk of transplant degradation and/or disease (infection or malignancy) due to adverse donor characteristics. There is no exact definition of what constitutes ECDs, but the frequently cited characteristics are shown in Table 7.

Donor age Although there is heterogeneity in the cutoffs that define older donors (ages 60–80 years), many studies have shown that older donors are associated with increased mortality and graft loss [369]. Feng et al., who defined the donor risk index, found that the relative risk associated with every decade of increasing donor age from 40 years to over 60 years of age is the strongest risk factor for transplant failure [370]. Traditionally, older donors are linked to HCV recurrence and worse patient and graft survival [371–373]. However, as the introduction of DAA increased post-LT survival [374], the risk of using livers from older donors in HCV-positive recipients has decreased [375]. A study reported that livers from donors > 70 years of age could be safely used in patients

Idule / Deminion of ECL	Table 7	Definition	of ECD
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Advanced age (>65 years)
Macro-vesicular steatosis (>40%)
DCD
Organ dysfunction at procurement
ICU stay greater than 7 days
Hypernatremia greater than 165 mEq/L
Bilirubin greater than 3 mg/dL
Elevated transaminases (ALT > 105 U/L, AST > 90 U/L
Vasopressor use
Cause of death: anoxia, cerebrovascular accident
Disease transmission
HBcAb+
HBsAg+
HCV+
HIV positive
Extrahepatic malignancy
CIT greater than 12 h

with HCV with adequate DAA treatment during the preand post-transplant periods [376]. Despite evidences on the detrimental effect of old donor age, there were promising results of LT using older donors even after the age of 80 years [377]. There is no globally accepted limitation on the age of deceased donors. However, careful donor and recipient selection and minimizing cold ischemic time (CIT) are important strategies for improving the performance of grafts from older donors [377].

Donor liver steatosis The amount of steatosis can be classified as mild (30% below), moderate (30-60%), or severe (60% or more) depending on histological features. In macro-vesicular steatosis, hepatocytes contain a single fat vacuole that replaces the nucleus. In micro-vesicular steatosis, hepatocytes contain many small fatty interventions that do not cause nuclear replacement. The latter has a lower risk of reperfusion damage and is not associated with a decline in initial transplant function [378]. In a study, liver grafts with more than 30% steatosis were independent risk factors for graft survival, with an increased risk of 71% per year [379]. However, there has been much evidence that shows the eligibility of LT using livers with > 30% of steatosis when balancing other risk factors, such as a low MELD score, favorable donor and recipient ages, and a low CIT [380, 381]. The decision to use a steatotic liver should depend on the consideration of other risk factors for liver graft failure as well as the scarcity of deceased donors in the given area. Macro-vesicular steatosis of more than 60% should not be considered as an eligible donor organ due to the relatively higher risk of mortality and graft loss [382].

Donor with positive hepatitis B core antibody (anti-HBc) or HBsAg LT from anti-HBc-positive donors is common in places where HBV infection is prevalent, such as in Asia and Mediterranean countries. De novo HBV infection is reported to be lower in anti-HBc- and/or anti-HBs-positive individuals compared with HBV-naïve recipients (15% vs. 48%) [383]. Recurrent HBV infection is reported at 11% in HBsAg-positive recipients, while de novo HBV infection is reported at 19% in HBsAg-negative recipients [384]. Thus, anti-HBc-positive donors' livers are preferable for HBsAgpositive or anti-HBc/anti-HBs-positive recipients. However, it could be transplanted in HBV-naïve recipients with proper antiviral prophylaxis, such as hepatitis B immunoglobulin (HBIG), oral nucleos(t)ide analogs (NUCs), or a combination of both [385]. In contrast, recipients who are positive for anti-HBc and anti-HBsAb do not need anti-HBV prophylaxis [384]. Generally, LT from anti-HBc-positive donors has been shown to have good post-transplant survival rates [386].

LT from HBsAg-positive donors could also be a feasible option in cases of organ shortage. Recipients with previous HBV infections (anti-HBc or both anti-HBc/anti-HBs-positive individuals) seem to be suitable candidates to receive HBsAg-positive grafts owing to the superior mobilization of their immune response and more frequent anti-HBs production and HBsAg loss [387]. The largest study so far contained LT cases of livers from 42 HBsAg-positive donors with normal liver function, fibrosis Ishak score < 1, and mild inflammation (grade < 4) in the absence of positive tests for other viruses [388]. When compared with LT from 327 HBsAg-negative donors, LT from HBsAg-positive donors showed the same graft survival and no flare-up of HBV in patients who received 42 HBsAg-positive livers under antiviral therapy with oral NUCs, regardless of using the HBIG combination, implying that HBIG should be abandoned in recipients of HBsAg-positive liver grafts.

Donor with positive HCV Many previous studies have shown similar survival of LT from HCV-positive and -negative donors in HCV-positive recipients [389]. Especially, outcomes of LT using HCV-viremic livers could be considerably increased by DAA treatment before and after LT [374]. Although several studies showed liver grafts from HCV-positive donors could lead to more advanced fibrosis, this seems to be dependent on certain risk factors and could be attenuated by avoiding risk factors, such as donor age, steatosis, and a higher donor risk index [390, 391]. For HCV-negative recipients, utilizing the livers of HCV-positive donors has been regarded as a contraindication. However, recent single-center studies have shown that an acceptable outcome could be achieved in HCV-aviremic recipients using liver from HCV RNA-positive donors using adequate DAA after LT, unless there were unacceptable graft conditions, such as grossly abnormal appearance and more than a score of 2 in the histologic grade of fibrosis or inflammation [392, 393].

Other situations Donors who are positive for HIV could donate livers to HIV-positive patients only, which could result in a feasible outcome [394]. After LT, an undetectable HIV viral load could be maintained with adequate HIV medication [395].

Donors with previous or current common malignancy, such as colorectal and breast cancers, are considered as absolute contraindications for donation if in advanced stages. Glioblastoma multiforme, along with melanoma, choriocarcinoma, and lung cancer were also considered absolute contraindications to liver donation [396]. Other primary intracranial malignancies have a relatively low risk of transmission to transplant recipients [397].

[Recommendations]

- LT from older donors can have promising results with careful donor and recipient selection and by avoiding other risk factors such as minimizing CIT; however, donor age over 60 years is associated with increased mortality and graft loss rates (B2).
- Livers with > 30% of macrosteatosis can be used after balancing other risk factors, such as low MELD score, favorable donor and recipient ages, and a low CIT; however, livers with > 60% of macrosteatosis should not be considered as eligible donor livers (B2).
- Anti-HBc-positive donor liver is preferable for HBsAgpositive or anti-HBc/anti-HBs-positive recipients although it is eligible for HBsAg-negative recipients with proper antiviral prophylaxis (A2).
- LT from HBsAg-positive donors is acceptable for HBsAg-positive recipients with the administration of oral antiviral therapy after surgery, regardless of HBIG combination (B2).
- LT from HCV-viremic donors can be transplanted into HCV-viremic recipients, and DAA before and after LT could improve outcomes, although careful attention is required to avoid other risk factors, such as older age and steatosis (A2).

Living donor

In the early period of LDLT, donor surgery was primarily performed using the left lobe (LL) of the liver due to the importance of donor safety [398–403]. However, right lobe (RL) resection of the donor has become increasingly common due to the development of surgical techniques and the small-for-size syndrome (SFSS) in recipients [399, 400, 404–407]. A French group performed the first laparoscopic living donor left lateral sectionectomy in 2002 [408], and a United States (US) group performed a robot-assisted living donor RL resection in 2012 [409].

Donor selection

Prior to donor consent for surgery, prospective living liver donors (LLDs) should be informed in detail about all possible complications and risks, and psychiatric evaluations should be performed to determine if the donation was not coerced if there are any past or present psychiatric issues, and if there is a possibility of depression after surgery in the future [191, 410-412]. After obtaining consent and completing a psychiatric evaluation, a full assessment of the donor is necessary to ensure that there is no morbidity from the operation. Contraindications for LLD include transmissible infections, such as HBV, HCV, and HIV, a history of CAD, a history of cerebral vascular disease, and a history of treatment for extracranial malignancy besides skin cancer; if the donor has a history of alcohol or drug abuse, the donor should be selected with extra caution and should undergo a liver biopsy prior to surgery [412, 413].

Age In a previous study, the 20 s donor group had improved recipient survival compared to other age groups (40 s, 50 s, and 60 s) [414], and in the > 50 years donor group, the SFSS was increased and graft and overall survival were decreased [415–417]. Nonetheless, due to the unavailability of donors, the ages of LLD have also been rising. In many institutions, individuals aged 60-65 years or older are highly selective donors [413, 418], and it was found that there was no difference in the outcomes of donor and recipient outcomes when the two groups of donors older than and younger than 60 years were compared [418, 419]. However, the outcomes of recipients who received grafts from young-age donors are excellent. Donors aged between 18 and 60 years can be allowed [410, 412, 413], and donors older than 60 years can also donate selectively, depending on donor conditions, graft type, remnant liver volume (RLV), steatosis, GRWR, and recipient conditions.

BMI Until now, BMI above 35 kg/m² has been considered a contraindication for liver donation [410], and many institutions have advised that the BMI of donors should be less than 30–35 kg/m² [413]. The incidence of donor wound infection increased as BMI exceeded 30 kg/m²; however, it was not associated with significant morbidity [420]. A comparison of the outcomes of donors and recipients between the BMI less than 30 kg/m² group and the BMI above 30 kg/m² group without steatosis revealed no differences between both groups [421–423]. Obesity has been defined as a BMI > 30 kg/m² in the West, while a BMI > 25 kg/m² in the Asia-Pacific region is regarded

as obesity [424]. In summary, in the absence of steatosis, there is no significant difference in the safety of donors and the outcomes of recipients, in cases where the BMI of donors and recipients is < 30-35 kg/m².

Donor-recipient relationship The majority of LDLT occurs between relatives [413]. For many pediatric metabolic disorders, including Wilson's disease, most cases of LDLT are performed from parents to their children. Such transplants are possible as most parents of pediatric patients with metabolic diseases are heterozygous carriers, and these diseases are autosomal recessive diseases [425]. However, before donation, the parents should undergo close examinations, including liver biopsy and genetic analysis [425]. When it was difficult to perform LDLT between family members due to problems such as ABO incompatibility and graft volume, sometimes LDLT has been performed as paired exchange programs [426–428].

Steatosis of liver Donor and recipient outcomes are impacted by macro-vesicular steatosis [380, 429]. Although there are some differences depending on RLV, donor age, graft type, and recipient condition, if possible, macro-vesicular steatosis of less than 10-20% has been associated with favorable outcomes, but donor livers with macro-vesicular steatosis of greater than 30% are not recommended for LT [407, 412, 413]. If there was donor steatosis prior to surgery, it would be advisable to delay LDLT for at least 2 weeks for the steatosis to improve after exercise and diet therapy [413, 430, 431]. Recently, magnetic resonance (MR) spectroscopy has been utilized as a non-invasive approach that more precisely indicates liver steatosis than preoperative CT and US [432]. Donor liver biopsies are recommended for those with an abnormal liver function test (LFT), suspected steatosis and parenchymal disease on CT, US, and MRI, a BMI of 28 kg/m² or above, a history of alcohol abuse, and hereditary conditions, such as metabolic diseases in the recipient [433].

RLV Although it is dependent on donor age and steatosis, sufficient RLV is crucial because it is directly associated with donor morbidity and death [407, 412, 413]. According to previous studies, a RLV of 30% or more was safe; however, if the RLV was less than 30%, the donor LFT and morbidity increased [434, 435]. On the other hand, another study reported there was no difference in donor outcomes between those with RLV of 35% or more and those with RLV of 35% or less [436]. Cases of ERL grafts that include the middle hepatic vein (MHV) have been reported to be safe in at least 30% of cases [404]; however, in another study, at least 35% of cases were proven to be safe [399]. In summary, RLV \geq 30% for young individuals without steatosis, RLV \geq 35% for older individuals with

mild steatosis, and RLV \geq 35% for ERL including MHV are recommended.

GRWR Many studies have indicated that the SFSS was decreased at GRWR > 0.8% and that the outcomes were favorable [407, 410, 412, 437-439]. Recent reports suggested that grafts with a GRWR of 0.8% or less could be transplanted selectively after considering the donor age, steatosis, and recipient condition [440-442]. Several institutions recommended that LDLT could be performed with recipient GRWR between 0.5 and 0.7%; nevertheless, it tended to a GRWR of 0.8% or higher in high-volume centers and 0.8% or less in low-volume centers [413]. According to recent studies from Hong Kong [443] and Kyoto [444], the lower limit of a GRWR of 0.6% was acceptable if certain conditions were fulfilled. In summary, LDLT with a GRWR greater than 0.8% could be safely performed to prevent SFSS; however, it could also be allowed in cases with a GRWR of less than 0.8%, considering donor age, graft steatosis, recipient portal hypertension, recipient severity, reconstructed vascular patency, portal inflow modulation, and perioperative management.

[Recommendations]

- Prospectively, LLD should be informed in detail about all possible complications and risks of hepatectomy, and donors should undergo medical and psychiatric evaluation. (A1)
- The outcomes of recipients who receive grafts from young-age donors are excellent, and liver donation is possible from adults who are less than 60 years of age and who have the right to autonomy and self-determination. (B2)
- If the donor's BMI is less than 30–35 kg/m2 and there is no liver steatosis, comparable outcomes of the donor and recipient can be expected. (C2)
- Macro-vesicular steatosis of less than 10–20% is associated with favorable outcomes, but donors with steatosis greater than 30% are not suitable donors. (C2)
- RLV ≥ 30% for young donors without steatosis, RLV ≥ 35% for older donors with mild steatosis, and RLV ≥ 35% for ERL, including MHV, are recommended. (C2)
- LDLT with a GRWR ≥ 0.8% is recommended to prevent SFSS. (B2)

Anatomical consideration

An ideal liver graft will have the normal liver vascular and biliary anatomy with each large anastomosis site and appropriate graft volume for a recipient with sufficient remaining liver volume. Anatomical variations, which are thought to occur in nearly half of the population, can influence the resection plane and surgical outcomes as well as the graft type. In addition, partial liver allografts with unconventional anatomies, such as multiple accessory vessels or ducts, present unique challenges for reconstruction. It is essential to accurately identify the donor's anatomy and make a proper surgical plan to reduce morbidity [445]. The liver vascular and biliary anatomy can be evaluated using advanced image processing techniques including multiphase CT and gadolinium ethoxybenzyl-diethylenetriaminepentaacetic acid (Gd-EOB-DTPA) MRI. However, in some cases, intraoperative cholangiography may be necessary to further clarify the bile duct anatomy and determine the division point.

Hepatic artery Noussios et al. reported that normal hepatic anatomy was present in approximately 60–80% of cases, and the remaining cases had multiple variations, based on previous reports of the anatomy of 19,013 patients [446–448]. Aberrant RHAs and aberrant LHAs were observed in 15.63% (879 of 5625) and 16.32% (918 of 5625) of patients, respectively. In 4.53% (255 of 5625) of patients, both an aberrant RHA and an aberrant LHA were identified [446]. Identification of the segment IV artery is critical for living donor candidates. A variant segment IV hepatic artery can cross the transection plane when it arises from the right hepatic artery, and its prevalence is up to 10–35% in the general population [449, 450].

The presence of variant anatomy leads to an increased risk of hepatic arterial thrombus in the recipient. Furthermore, Lida et al. reported that extra-anatomical anastomosis was the only independent risk factor for hepatic arterial complications [451].

Portal vein Sureka reported that normal anatomy (Type I) was seen in 773 (79.94%) out of 967 patients. Trifurcation (Type II) anomaly was seen in 66 (6.83%) cases. The right posterior vein was the first branch of the main portal vein (Type III) in 48 (4.96%) patients. Other anomalies were seen in 42 (4.34%) patients [445, 452].

Over half of those patients with portal vein variants were also found to have anomalous biliary anatomy, which always involved the hepatic ducts of the right liver. In 407 living donors, the presence of a variant bile duct was more frequently associated with a variant portal vein than with a usual portal vein (61% vs. 20%, p < 0.0001). Moreover, an infra-portal right posterior bile duct was significantly more common in donors with a variant portal vein than in donors with a usual portal vein (30% vs. 10%, p = 0.0004) [453].

Hepatic vein The intrahepatic drainage territory of the individual hepatic veins and tributaries must be considered to

maintain venous drainage in both the graft and the residual liver during LDLT.

Hepatic venous variants occur in approximately 40% of living donor liver grafts [454]. The most common hepatic venous variant is the presence of an inferior right hepatic vein (IRHV). Therefore, all sizable inferior accessory veins must be implanted into the IVC of the recipient to avoid congestion of the posterior section. However, the smaller vessels can be ligated without the risk of congestion [445, 455].

Many centers prefer to preserve the MHV with the donor LL remnant for right liver grafts. MHV reconstruction using autologous veins or synthetic grafts ensures excellent outflow drainage and favorable recipient outcomes [456].

Bile duct Despite growing experience with LDLT, the incidence of biliary complications in recipients remains high. Advances in non-invasive technology for imaging the biliary pathways of donors have played a significant role in reducing biliary complications in both donors and recipients. The incidence of variants that could potentially lead to multiple bile duct anastomoses was 35.0%, and eventually, 39.2% of these grafts had multiple orifices [457].

The right bile duct variant was classified into six types, and the left hepatic duct was divided into six types according to segmental bile drainage and its respective frequencies (Fig. 1) [458].

Nevertheless, unanticipated biliary variations may be a source of post-transplant complications, such as biliary leakage, strictures, and graft failure. Apart from surgical techniques, bile duct reconstruction techniques, appropriate use of stents across ductal anastomoses, and safe isolation of the graft bile duct under the precise imaging of the biliary tree can reduce biliary complications in both donors and recipients.

[Recommendations]

 It is essential to evaluate anatomical variations in donors and make a proper surgical plan based on advanced dedicated images obtained using multiphase CT and Gd-EOB-DTPA MRI. (B1)

Donor surgery

Graft type Grafts such as RL, ERL, extended left lobe (ELL), ELL plus caudate lobe, left lateral section, and right posterior section (RPS) are available in adult LDLT. RL and ELL are the most commonly used types of grafts [399, 406]. However, it is essential to tailor the resected graft decision to the donor's vascular and biliary anatomy, age, steatosis, RLV, GRWR, and recipient's condition [399, 406, 412]. The left lateral section graft can be performed mostly on pediatric LT or dual LDLT, and the operation is





Type B4

Type B5

Type B6



Fig. 1 Variations in bile duct anatomy

relatively low risk; therefore, donor safety will be excellent, and laparoscopic left lateral sectionectomy is recommended [406, 412, 425, 459, 460]. The ELL graft includes MHV and is preferred over RL because of donor safety; if the graft volume is sufficient, it can be utilized without producing SFSS; nonetheless, venoplasty of MHV and left hepatic vein would be necessary to ensure excellent outflow [399, 401, 461]. Including the CL can enhance the graft volume by approximately 5–10% of the ELL; however, the patency of the bile duct and hepatic vein of the CL is important for the CL portion to function effectively [399, 403, 462]. The incidence of SFSS may be lower in RL grafts than in ELL grafts; nonetheless, the anterior section (segments 5 and 8) and right inferior hepatic veins, which are greater than 5 mm in diameter, should be meticulously reconstructed because the patency of outflow is crucial [401, 405, 407, 412]. ERL grafts are superior to RL grafts in terms of MHV outflow, and it is recommended to consider surgery with a RLV of more than 35% for donor safety [399, 404, 463, 464]. In RPS grafts, biliary complications, such as biliary leakage or strictures in recipients, are more frequent than in cases of RL or ELL; therefore, it is encouraged that anatomic variation of the portal vein, especially in cases of Nakamura type C or D [457], or that GRWR is superior to ELL [465-467]. In cases of a left-sided gallbladder, donor selection and surgical procedures should be performed with extreme caution due to the presence of vascular and biliary anomalies [468, 469].

Minimally invasive living donor hepatectomy Minimally invasive surgery for organ donors has been developed and is currently being performed by many expert surgeons. In a recent multicenter study, a laparoscopic living donor left lateral sectionectomy had fewer surgical complications than laparoscopic donor nephrectomy, and the short-term outcome was deemed to be safe [460]. Since then, many institutions, particularly in Asia, have reported excellent outcomes of laparoscopic living donor hepatectomy (LLDH), and some meta-analyses have reported that LLDH is as feasible as open donor hepatectomy [470-477]. Nevertheless, the vascular or biliary anatomic variation of the donor's livers should be taken into consideration, and expert hepatic surgeons should perform the procedure. Comparing the outcomes of PLDRH with those of open donor right hepatectomy showed an increased probability of sustaining multiple bile duct openings in the pure laparoscopic donor right hepatectomy group [478], leading to higher rates of biliary complication. The length of graft hepatic veins is shorter in PLDRH than in open donor hepatectomy. However, venoplasty, or elongation of the hepatic or portal vein, can be performed during bench surgery.

Few institutions have reported robotic living donor hepatectomy (RLDH) after the report of the first case in 2012 [409, 479]. In a study in Taiwan [480], 13 RLDH outcomes were comparable to those of open donor hepatectomy outcomes, and the Yonsei University group in Korea [481] recently reported that 52 RLDH had similar donor and recipient outcomes compared to the open or laparoscopic donor hepatectomy group. Furthermore, a study in Saudi Arabia [482, 483] reported that the outcomes of 318 patients in the RLDH group were better than those of patients in the LLDH group, and robotic donor surgery was feasible in 501 RLDH. Nevertheless, in a recent meta-analysis [484], there was still insufficient evidence to conclude that robotic surgery is preferable compared to laparoscopic or open surgery, and more studies are expected.

[Recommendations]

• Laparoscopic living donor hepatectomy can be a feasible technique for donor operations; however, anatomic variation in the liver should be taken into consideration, and the procedure should be performed by an expert hepatic surgeon. (B2)

Donor complication

"Do no harm" is a very critical issue for living donors, and minimizing donor complications has always been a priority in LDLT. In an analysis of 214 published studies of adult liver donors, Middleton et al. reported a donor mortality rate of 0.2% and a median donor morbidity rate of 16.1% [485]. Adcock et al. reported an overall complication rate of 41% among RL donors in a Canadian cohort [486]. Similarly, Lauterio et al. reported a morbidity rate of 33.3% and a major complication rate of 12.6% in an Italian cohort including 220 RL donors, 10 LL donors, and 15 left lateral section donors [487].

With advances in techniques of donor hepatectomy and an understanding of safe margins in donor selection criteria, the mortality rate among donors is nearly 0% in the Asia-Pacific region [488]. Data from the Korean Organ Transplantation Registry reported that the mortality rate was 0% and the prevalence of major complications was 1.9% (Clavien–Dindo classification grade III or more) among 839 living donors. They showed a similar severe complication rate between the right and left lobes (2.1% vs. 0%, p = 0.62); moreover, the biliary complication rate was 1.7%, and it was the most common complication after donor hepatectomy [488].

Regarding complications according to graft type, a recent meta-analysis has reported that RL donors were more likely to experience major complications (RR = 1.63; 95% CI 1.30–2.05; I^2 = 19%) than LL donors; however, no difference was observed in the risk of any biliary complication, bile leaks, biliary strictures, or postoperative death [489].

Recently, several multicenter retrospective studies showed no significant differences between minimally invasive surgery groups and conventional open surgery groups [480, 481, 490–492]. Minimally invasive donor hepatectomy is safe and has no major differences in terms of donor complication rates or non-inferior recipient outcomes once surgeons have overcome the learning curve.

Regarding long-term outcomes, two studies showed that the outcomes of the live liver donor group were worse than those of the matched healthy control group, despite the relatively low number of deaths and medical morbidities in this group [191, 411]. Hong et al. reported that the 10-year cumulative mortality of live liver donors was 0.9%. The most common cause of death was suicide (n=19), followed by cancer (n=9) and traffic accidents (n=7) among the 59 deaths [411]. Choi et al. also suggested that depression and lower income were risk factors for adjusted mortality, and careful donor evaluation and selection processes could improve donor safety and enable safe LDLT [191].

LT

DDLT

Standard LT (conventional vs. piggyback)

Conventionally, the whole liver graft, retrieved from the deceased donor (such as DBD or DCD), is implanted in the orthotopic site where the diseased liver was removed. In Europe and the US, this standard type of LT is the most common [197, 493]. Surgical techniques for standard LT can be classified into two representative types based on the removal or preservation of the native vena cava.

Caval replacement technique versus piggyback technique Conventional LT was first described using caval replacement technique. The recipient's retrohepatic IVC is removed along with the liver, and two end-to-end anastomoses are simply made to the suprahepatic and infrahepatic IVC of the graft [494, 495]. In this technique, the recipient's IVC is clamped with a long occlusion of venous return, inducing hemodynamic disturbance [496]. Thus, this technique may not be suitable in unstable patients without venovenous bypass. However, this technique can be helpful in cases of a big liver or an encircled caudate lobe, when it is difficult to preserve the native IVC. Recently, the piggyback technique has been frequently used in most Asian countries. It includes preservation of the recipient's IVC and creating a single anastomosis between the donor's IVC and the recipient's IVC or hepatic veins [497]. It does not require bloody dissection of the retrocaval space and allows for partial clamping of the IVC, which minimizes the recipient's hemodynamic instability [498]. Classically, the donor's suprahepatic IVC is anastomosed to the common orifice of the recipient's hepatic veins, which may be formed by joining two or three hepatic veins [497]. So far, many modifications have been introduced, and the most representative modified technique is the side-to-side cavocavostomy [499, 500]. This approach may be technically easy, facilitate caval venous flow, and avoid veno-venous bypass during anastomosis [499]. In the early period, the piggyback was reported to be associated with an increased risk of suprahepatic caval stenosis and post-transplant ascites; however, it could promote hemodynamic stability [501, 502]. According to recent reports and expert opinions, there is no definite evidence that indicates the superiority of one venous reconstruction technique over another [503]. Therefore, the type of venous reconstruction should be selected based on the surgeon's preference, the center's circumstances, and the patient's condition [503] (Fig. 2).

Veno-venous bypass grafting or portocaval shunting During LT, most venous flow is blocked, especially when the caval replacement technique is used, and this can decrease venous return to the heart, which could lead to a decrease in blood pressure (BP) and perfusion to vital organs [504]. A veno-venous bypass is used to ameliorate this transient hemodynamic instability by returning blood to the heart through an external circuit. In addition, a temporary portocaval shunt might be created to avoid splanchnic congestion during the anhepatic phase. Some centers prefer venovenous bypass and portocaval shunts due to the advantages of better hemodynamic stability, less bleeding, less bowel congestion, and better postoperative renal function [505, 506]. However, these techniques are associated with technical complexity, additional morbidity, and longer operating times. Thus, the routine use of veno-venous bypass and a temporary portocaval shunt is not recommended [503].

Portal reconstruction After the removal of the diseased liver, the portal flow should be assessed by temporarily unclamping the portal vein before reconstruction. If the portal flow is not adequate, collateral veins, including splenorenal shunts and the left gastric vein, need to be ligated. About a third of patients have PVT at the time of LT, which may be a challenging problem as it could impair adequate portal flow to the graft [507]. Most thrombi extending up to the level of the spleno-mesenteric junction are usually managed by eversion thrombectomy or resection of the portal vein with the thrombus [508, 509]. However, the removal of organized PVT extending beyond the spleno-mesenteric junction can be difficult and risky, and it may even be impossible to achieve safely in some cases. In those situations, a jump graft from the superior mesenteric vein or its major branches can be used. In more advanced cases, other irregu-





lar portal reconstructions should be considered. The renal vein, large collaterals, the IVC, and even arteries can be considered physiologic or non-physiologic sources of portal inflow [510–514]. However, surgeons should be aware that variceal veins might be too thin to be used for anastomoses [507] and that non-physiologic reconstruction is usually associated with intractable and serious complications [510].

[Recommendations]

- The piggyback technique can minimize hemodynamic disturbance in standard LT. (C1)
- Adequate portal inflow should be achieved through the best thrombectomy and ligation of collateral vessels. (B1)

Partial graft transplantation

Different types of LT involving the use of reduced or partial grafts have been introduced to solve the problem of organ shortage.

Reduced-size or split graft LT Because most deceased donors are adults, it is difficult to obtain a small liver graft for pediatric patients. Thus, reduced-size LT might be performed for small patients using only parts of an adult donor liver. The left liver or left lateral section grafts are mostly used for pediatric recipients. However, in reduced-size LT, the rest of the donor's liver is discarded. This type of LT wastes usable liver tissue and places adult recipients at a disadvantage [515]. The concept of split liver LT has emerged to maximize the efficacy of liver grafts. In this procedure, an adult donor liver is divided into two grafts. Splitting is based on the weight of the intended recipients. For an adult and a small child, the donor's liver is usually split into an extended right liver and a left lateral section graft, while for two adult recipients, including a big child, it may be split into right and left liver grafts [516, 517].

Auxiliary LT Auxiliary LT is performed to preserve part or all of the recipient's native liver. ALF and metabolic liver disease are two traditional indications for this type of LT. Because ALF is potentially reversible, an implanted liver graft may provide physiologic support until the patient's native liver function is restored [518]. Once the native liver recovers, the graft liver can be removed, and immunosuppression can also be withdrawn. The second indication is for patients with functional congenital or metabolic disorders that affect the normal liver. Implanting a partial graft while preserving the native liver allows correction of the metabolic disorder while avoiding a full LT. Auxiliary LT may be performed orthotopically or heterotopically.

LDLT

In countries where deceased donations are scarce, such as in Asian countries, most LTs are performed from living donors, although the practice is still limited in the US and Europe (Fig. 3).

Issues in implantation

Venous drainage reconstruction in LDLT In comparison with the procedure of standard LT using a whole liver graft, one of the most different technical points in LDLT is hepatic vein reconstruction. In LDLT using a partial liver graft, hepatic vein anastomosis usually includes some kind of venoplasty to avoid stenosis or angulation [519, 520]. Particularly, because the anatomy of the right liver is complex in the relationship between inflow and outflow, meticulous outflow reconstruction is just as important as perfect inflow formation for the integrity of graft function [521]. Most LDLT centers prefer to reconstruct tributary veins of the MHV at the back table. Various interpositional grafts have been introduced for these procedures, which include various autologous, homologous, and synthetic grafts [521]. Even if there may be controversy over the material of choice, it is **Fig. 3** Living donor liver transplantation (LDLT). **a** LDLT using the right liver graft. **b** LDLT using the left liver graft. For the integrity of graft function, segment 5/8 branches of the middle hepatic vein (V5/8) should be meticulously reconstructed



generally agreed that all drainage veins in segments 5 and 8 that are larger than 5 mm in diameter should be reconstructed [407]. Similarly, large inferior right hepatic veins that are larger than 5 mm in diameter should be connected to the IVC [521].

Portal vein reconstruction in LDLT The surgical technique of portal vein reconstruction in LDLT is similar to that of DDLT. However, because the portal vein stump of the living donor graft is very short, additional venoplasty techniques may be required in cases with an atretic portal vein, or PVT. A conduit formation or patch venoplasty method has been introduced to secure adequate inflow in such cases [522]. In addition, complex and extensive PVT can be considered contraindications for LDLT, even if Asian centers with large expertise in LDLT selectively accept those patients for LDLT [507]. A single portal vein reconstruction can be performed in many LDLT cases. However, two separate portal vein stumps can be encountered in some LDLTs involving the use of a right liver graft. Two-portal reconstruction is still a challenge during LDLT. A single portal orifice can be created by performing venoplasty on the anterior and posterior branches. However, when the anterior and posterior branches are too distantly located to allow for direct venoplasty, additional reconstruction methods, such as Y-shaped interposition or the conjoined unification method, may be required to make the portal vein optimal for anastomosis [523, 524].

SFSS and portal flow modulation Grafts with a GRWR of less than 0.8 or a GV/SLV of less than 40% are widely regarded as small-for-size grafts (SFSG) [525]. These grafts have a higher risk of early allograft dysfunction as compared to larger grafts. Coagulopathy, cholestasis, ascites,

and post-transplant encephalopathy can develop within the first 1–2 weeks after an SFSG transplantation in the absence of any other identifiable cause, including any surgical, infectious, or immunological complications. This phenomenon is referred to as an "SFSS." [526]. A key triggering factor for SFSS is postulated to be excessive portal flow into the graft, leading to sinusoidal congestion, hemorrhage, and responsive vasoconstriction of the hepatic artery [526, 527]. That phenomenon is not caused by an absolute graft volume but by the inability of a graft to meet the metabolic demands of the recipient [525, 528, 529].

To attenuate the deleterious effect of excessive portal flow, various surgical and pharmacological maneuvers have been attempted. The use of terlipressin and octreotide in LDLT is one of the most common pharmacological portal flow modulation methods. Based on some randomized clinical studies, these drugs might be beneficial in decreasing portal flow and improving renal function in the immediate post-LT setting [530, 531]. Although splenectomy has demonstrated a marked decrease in portal flow, it cannot be recommended as the first choice due to the higher morbidity related to the procedure [532–534]. To partially divert portal flow, various shunt techniques have been tried, which include hemiportocaval, mesocaval, and mesorenal shunts [535–538]. However, because these shunt techniques are adversely associated with the risk of portal hypoperfusion and the portal steal phenomenon, it is recommended to assess portal flow and calibrate the size of the shunt accordingly [526]. Consequently, portal flow modulation should be based on intraoperative liver hemodynamics. Although there is no exact marker and level as a trigger for performing portal flow modulation, there is general agreement that the portal pressure should be less than 20 mmHg, with pressures of less than 15 mmHg being favorable or a hepatic venous portal gradient of less than 10 mmHg [528, 529, 533, 539, 540].

Hepatic artery reconstruction in LDLT The techniques of arterial reconstruction in LDLT are delicately performed with caution, not only because the arterial inflow to the graft is critical for a successful LT but also because the graft artery is very thin and short. The anastomosis is generally performed in an interrupted fashion under high magnification with an operating microscope or surgical loupes. The selection of the recipient hepatic artery for reconstruction depends on the length, caliber, natural direction, and integrity of the arterial wall. Although anatomical anastomosis may be the first choice, when the hepatic arteries of the recipient are inappropriate for an anastomosis due to atherosclerosis, intimal wall dissection, or wall damage, several extra-anatomical reconstructions can be considered as alternatives. The right gastroepiploic artery of the recipient is considered the first alternative, even if the splenic, left gastric, or gastroduodenal arteries can be also used as the inflow source [541-543]. In some cases where arteries are unavailable for direct anastomosis, an arterial graft, as an interposition, may be necessary.

Biliary reconstruction in LDLT Compared to DDLT, biliary reconstruction is technically more demanding and is associated with more complications, such as leakage or stricture [544]. Although Roux-en-Y hepaticojejunostomy was once considered the standard biliary reconstruction method, recently, duct-to-duct anastomosis has become a more preferred technique owing to many advantages, which include technical ease, the unnecessariness of bowel manipulation, the functional preservation of the sphincter of Oddi, and a possible endoscopic approach to the anastomotic sites [544]. Multiple duct stumps of right liver grafts are commonly observed and occasionally require multiple anastomoses [545].

Some surgeons prefer to insert an internal or external stent across the biliary anastomosis, especially when dealing with very small ducts. It can keep the lumen of small ducts open in the early postoperative period. Recently, it was reported that external biliary drainage could prevent leakage by minimizing intraductal pressure at the anastomotic site [407]. However, the significance of the stent across the anastomotic site and external drainage remains a controversial issue that should be evaluated with well-designed studies.

[Recommendations]

• In LDLT, when implanting a right liver graft, tributary branches of the MHV should be reconstructed to prevent detrimental venous congestion of the right anterior section and to improve post-transplant outcomes. (B1)

- In LDLT with an SFSG, pharmacological or surgical portal flow modulation can help reduce the risk of graft dysfunction and improve post-transplant outcomes. (B1)
- In LDLT, arterial anastomosis should be performed under high magnification with an operating microscope or surgical loupes. (C1)
- In LDLT, duct-to-duct anastomosis is the preferred method of biliary reconstruction. (C2)

ABO-incompatible (ABOi) LDLT

Because of deceased donor shortage, cases of ABOi LDLT are unavoidable in many Asian countries [546-548]. Apheresis to reduce preformed anti-donor ABO antibodies plays a key role in ABOi LDLT. In the early period of ABOi LDLT, in addition to apheresis, splenectomy was performed to eliminate the large source of antibody production during the operation, and portal vein or hepatic artery infusion therapy was added to prevent intravascular thrombosis [549, 550]. After the introduction of rituximab, the most common desensitization protocol before ABOi LDLT consisted of rituximab and plasmapheresis without splenectomy and local infusion therapy [548, 549, 551, 552]. The long-term outcomes of ABOi LDLT are comparable with those of ABO-compatible LDLT. However, biliary complications, infectious complications, and antibody-mediated rejection remain concerns in the era of rituximab [549, 553, 554].

[Recommendations]

- ABOi LDLT can be a good option to overcome the donor shortage. (B2)
- The long-term outcomes of ABOi LDLT are acceptable; however, it could increase the risk of biliary complications, infection, or antibody-mediated rejection. (B2)

Complications

Surgical complications

Vascular complications commonly occur early in the posttransplant period, although significant complications may be clinically silent. Duplex ultrasound is the primary screening modality and can determine vascular integrity without the need for more invasive and expensive imaging. Angiography is the gold standard for diagnosing arterial complications; however, CT or MR angiography is increasingly being used in these circumstances [555].

Biliary complications are a significant cause of morbidity post-transplantation, and prompt recognition and treatment of biliary complications reduces morbidity and mortality and improves graft survival [556, 557]. **Hepatic artery complications** Historically, arterial complication rates have been reported to be between 15 and 25% after hepatic artery anastomosis [558]; however, recent reports have shown that the rates of thrombosis and stenosis were 0–9.4% and 0–9.7%, respectively [559–563].

Treatment of hepatic artery thrombosis is recommended according to the time between LT and the onset of complications. A study reported that hepatic artery thrombosis is defined according to the time of onset, with early hepatic artery thrombosis occurring 30 days or less after LT and late hepatic artery thrombosis occurring more than 1 month after LT [564]. Early hepatic artery thrombosis resulted in an overall re-transplantation rate of 53.1% (the rate in children was higher than the rate in adults, 62% vs. 50%) and an overall mortality rate of 33.3% (adult rates were higher than rates in children, 34.3% vs. 25%) [565]. It is generally thought that early hepatic artery thrombosis (especially within the first few days after transplantation) without urgent revascularization or re-transplantation almost always leads to mortality. Wakiya et al. suggested that endovascular treatments were feasible and produced good outcomes for early hepatic artery thrombosis in pediatric recipients [566]. Pereira et al. also suggested that an endovascular approach is now evolving as an alternative technique [567]. Hepatic artery thrombosis remains a major complication after liver transplant; furthermore, the management of hepatic artery thrombosis is complex and requires a multidisciplinary approach, including reconstructions of the hepatic artery, LT, and other interventions.

Portal vein and hepatic vein complications Portal vein obstruction is a significant vascular complication after LT in recipients, especially in pediatric patients and patients with pre-LT PVT [568]. The incidence of PVT and portal vein stenosis is 1–12.5% according to studies on preoperative [249, 569] and postoperative findings [570].

The duration and range of thrombosis affect the clinical manifestations of PVT. In the early stage, PVT may lead to impairment of liver function complicated by coagulopathy, portal hypertension, varix bleeding, intestinal edema, and massive ascites [571].

A recent systemic review and meta-analysis of 22 studies on PVT after pediatric LDLT showed trends in the choice of interventions. They showed a total of 213 percutaneous transluminal angioplasties, 74 stent placements, 48 surgical options such as Mesorex bypass or other surgical shunts, and 28 endovascular recanalizations [568].

Pre-transplant PVT (odds ratio [OR] = 15.20; 95% CI 3.70–62.40; p < 0.001) was the only independent risk factor for portal vein stenosis, while male sex (OR = 5.57; 95% CI 1.71–18.20; p = 0.004), pre-transplant PVT (OR = 4.79; 95% CI 1.64–14.00; p = 0.004), and splenectomy (OR = 3.24; 95% CI 1.23–8.57; p = 0.018) were

independent risk factors for PVT [572]. Early detection of vascular problems and a tailored approach according to the time of onset and deformity patterns of vascular complications are essential [572, 573].

Optimal hepatic venous outflow is key for a successful outcome [407, 574–577]. Furthermore, right hepatic vein stenosis has emerged as a common and important vascular complication of LDLT with RL grafts, with an approximate incidence of 5% [578]. When managing early venous outflow problems, especially with venous reconstructions of vessels from segments 5 and 8, interventional radiological techniques should be considered [579].

Biliary complications Biliary complications are an Achilles' heel and an important source of morbidity after LT, with an estimated incidence of 5–32%. Post-LT biliary complications include strictures (anastomotic and non-anastomotic), bile leaks, stones, and sphincter of Oddi dysfunction [580].

Post-LT bile leaks can be divided into early (within 4 weeks post-LT) and late. Bile leaks are further subclassified into anastomotic and non-anastomotic leaks [581, 582]. Early bile leaks most commonly occur at the anastomotic site, with ischemia being an important mechanism. An important risk factor is hepatic artery thrombosis, which can cause necrosis of the anastomosis, leading to strictures or leaks. LDLT requires dissection of the donor hilum and dissection of the recipient bile duct. These maneuvers can result in biliary devascularization and increased ischemic time [583].

Anastomotic biliary strictures are more common than non-anastomotic biliary strictures and constitute up to 86% of all biliary strictures post-LT [584]. The majority of anastomotic strictures are diagnosed within 1 year following LT [585]. The cumulative risk of anastomotic stricture increases with time, 6.6% at 1 year and 12.3% at 10 years [586]. The pathophysiology for the development of anastomotic stricture is believed to be ischemia or fibrosis of the bile duct following a suboptimal surgical technique or a bile leak in the early postoperative period [587]. Small caliber of the bile ducts, size mismatch between donor and recipient ducts, postoperative bile leak, inappropriate suture material, tension at the anastomosis, and excessive use of cauterization to control bleeding were risk factors for anastomotic strictures [587–590].

Therapeutic options include endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic biliary drainage (PTBD), and surgery. While ERCP represents the first-line treatment in most cases, PTBD is usually performed in patients with a Roux-en-Y hepaticojejunostomy, a kind of biliodigestive anastomosis that makes ERCP technically difficult. Surgery is reserved for patients in whom endoscopic or percutaneous approaches have failed [591].

[Recommendations]

- Follow-up using postoperative imaging studies is required and plays a vital role by facilitating early detection of postoperative complications and enabling prompt treatment. (B1)
- Management of hepatic artery complications is based on the clinical presentation and onset of symptoms and may require revascularization through surgery or other interventions. (B2)
- Pre-transplant PVT is one of the major risk factors for PVT and stenosis after LT. (B2)
- When managing early venous outflow problems, interventional radiological techniques should be considered. (B2)
- Anastomotic biliary strictures are successfully managed with endoscopic or percutaneous balloon dilation and stenting or operative revision. (B1)

Perioperative infection prevention

The development of immunosuppressive agents has decreased the possibility of graft rejection; however, their use may increase the risk of opportunistic infections. Furthermore, LT recipients are susceptible to various infections in the process of recovery or post-transplant life and have risk factors. It is important to screen for the risk factors in these patients and prevent them using appropriate principles. In this guideline, we would like to introduce methods to prevent bacterial, CMV, and fungal infections that can threaten the viability of patients immediately after LT.

The most commonly used infection prevention protocols for LT recipients in South Korean hospitals are presented in Table 8. This was written based on a recent publication in the Korean Journal of Transplantation [592].

Bacterial infection The most common bacterial pathogens in LT patients are enteric gram-negative organisms (e.g., Enterobacteriaceae, Acinetobacter species, Enterococcus, etc.) and skin pathogens (e.g., staphylococci and streptococci) [593]. To prevent surgical site infections (SSI), prophylactic antibiotics that target these bacteria are essential. Traditional prophylactic regimens consist of a third-generation cephalosporin (usually cefotaxime, because of its antistaphylococcal activity) with ampicillin [594, 595]. The risk of SSI associated with different antibiotics ranged from 1.7% for a combination of glycopeptide and aztreonam to 17.1% for cefazolin alone. Asensio et al. suggested that amoxicillin and clavulanate or the combination of a 3rd-generation cephalosporin with amoxicillin could serve as a reasonable antibiotic prophylactic regimen after LT [596]. Similarly, the Infectious Diseases Society of America (IDSA), the Surgical Infection Society (SIS), etc., introduced the Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery [597]. Based on this, for LT recipients, it is recommended to administer third-generation cephalosporins in combination with ampicillin-sulbactam or piperacillintazobactam alone within 60 min before making any surgical incision. For patients who are allergic to β-lactam antimicrobials, clindamycin or vancomycin given in combination with gentamicin, aztreonam, or fluoroquinolone is suitable alternative. Intraoperative redosing is needed to ensure adequate serum and tissue concentrations of antimicrobial if the duration of the procedure exceeds two half-lives of the drug or there is excessive blood loss during the procedure. However, it is not recommended to maintain prophylactic antibiotics for several days after surgery. According to a recent

Table 8 Antimicrobial prevention protocols for LT patients from multicenters in South Korea

Target pathogen	Antimicrobial agent	Duration of medication or preemp- tive monitoring (median range)	Percentage of Korean 25 centers adopting the relevant regimen (%)
Prophylactic antibac- terial agent (SSI)	Cefotaxime + ampicillin/sulbactam	5 days (2–14)	24
	Piperacillin/tazobactam	5 days (2–14)	20
CMV			
D+R-	Valganciclovir or IV ganciclovir (preemptive strategy)	3 months for preemptive monitoring	36
	Valganciclovir (Universal Prophylaxis)	3 months (1–3)	28
R+	Valganciclovir or IV ganciclovir (Preemptive strategy)	3 months for preemptive monitoring	64
Fungus	Fluconazole	1 months (0.13–3)	40
	Itraconazole	1 months (0.13–3)	20
	Amphotericin B	1 months (0.13–3)	12
	No prevention		24
Pneumocystis jirovecii	Trimethoprim/sulfamethoxazole	6 months (2–12)	96

randomized controlled trial in 120 LT recipients studied by Berry et al., prolonged administration of antibiotics during LT after more than 72 h did not reduce the incidence of SSI or nosocomial infections. Rather, it may increase the length of hospitalization and the possibility of infections [598, 599].

Recently, the prevalence of multidrug-resistant bacterial infections, such as VRE, Extended-Spectrum Beta-Lactamases (ESBL) Enterobacteriaceae, and Carbapenem-Resistant Enterobacteriaceae (CRE), is on the increase. To prevent SSI in this situation, it is necessary to choose appropriate prophylactic antibiotics after careful consultations with infectious disease specialists.

[Recommendations]

• Administer prophylactic antibiotics (3rd-generation cephalosporin combined with ampicillin–sulbactam or piperacillin–tazobactam alone) within 1 h before LT incision, and re-administer according to their half-life and should not exceed 72 h. (A1)

CMV infection CMV is the most common opportunistic infection following solid organ transplantation. The pattern of infection may be CMV syndrome (fever, malaise, increased hepatic aminotransferase, leukopenia, and/or lymphocytosis in the absence of end-organ disease) or end-organ CMV disease (gastrointestinal disease, pneumonia, retinitis, etc.) [600–604]. Especially, there is a high probability of infection within 3 months after LT, during this period, it is important to prevent it certainly. Primary CMV infection may be asymptomatic or manifest as a self-limiting febrile illness in immunocompetent individuals. However, it persists in a latent state, which can be reactivated if immunity is weakened, such as in cases where immunosuppressants are used, and it can also be transmitted from donors to recipients. Therefore, one of the most important risk factors for CMV infection after LT is the donor and recipient's CMVspecific immunity. Hence, it is essential to check for CMV IgG and IgM in both donors and recipients before LT. CMV seronegative recipients transplanted from CMV seropositive donors (D + / R -) are at increased risk of infection [601, 605]. CMV prevention is essential in these high-risk groups. Other risk factors include severe immunosuppression, rejection, and coinfection with other infections.

There are two mainstream strategies for the prevention of CMV infection, namely, the use of universal antiviral prophylaxis and preemptive therapy: 1) Universal prophylaxis is a strategy that involves the administration of antiviral drugs to all patients at risk of developing CMV disease immediately after LT; 2) Preemptive therapy is a strategy of periodically measuring the viral load and administering antiviral drugs to patients with significant viremia [606]. Universal prophylaxis has been proven to be easier to coordinate for patient management and to have a positive impact on graft loss, mortality, and opportunistic infections. However, it may result in high drug costs and issues related to drug side effects. On the other hand, preemptive therapy is not easy to coordinate as patients need to have their viral load checked regularly. However, because the prevention period is relatively short, it is associated with lower costs and fewer side effects of antiviral agents [602, 607]. Moreover, the probability of delayed-onset CMV infection is minimal. A recent large, randomized clinical trial of 205 D+/R- from six centers compared a group that received universal prophylaxis for 3-6 months with a group that received preemptive therapy and concluded that the incidence of CMV disease was significantly lower in the preemptive group than in the universal prophylaxis group for 12 months after transplantation [608]. However, as mentioned earlier, each prevention strategy has its advantages and disadvantages; therefore, it is better to apply it depending on the prevailing situation in each center or country [609]. Table 9 shows each strategy according to the risk factors for individual CMV immunity.

CMV monitoring is important when performing preemptive therapy. There are two commonly used methods [610, 611]. The first is the use of molecular analysis to detect CMV DNA. Quantitative nucleic acid amplification testing (QNAT) is mainly used because it is very efficient in determining the viral load. It is also the preferred method for detecting CMV replication and is very helpful in determining the initiation, response, and termination of treatment. In the second method, in patients with CMV antigenemia, a semi-quantitative assay that detects the pp65 antigen in CMV-infected peripheral blood leukocytes is performed. Recently, this is being replaced by molecular analysis in many centers and countries.

[Recommendations]

- To assess the risk factors for CMV infection, both donors and recipients should be checked for CMV IgG and IgM antibodies prior to transplantation. (A1)
- In strategy of universal prophylaxis, it is recommended to administer oral valganciclovir or IV ganciclovir in D+/R- (high-risk group) for 3-6 months and R + for 3 months. (A1)
- In strategy of preemptive treatment, viral replication should be monitored weekly at 3 months or more by CMV QNAT (or pp65 antigenemia), and if positive, the patients should be treated with oral valganciclovir or IV ganciclovir until 2 consecutive negative weekly CMV test. (A1)

 Table 9
 Preventive strategies for CMV infection

Risk factor	Preventive strategy	Target patient	Drug/Dosage	Duration
D +/R –	Universal prophylaxis	All patients within 3 months after LT	Valganciclovir 900 mg daily or IV ganci- clovir 5 mg/kg daily	3–6 months
	Preemptive therapy	Weekly CMV QNAT (or pp65 anti- genemia) for 3 months after LT, if positive, start to treatment	Valganciclovir 900 mg every 12 h or IV ganciclovir 5 mg/kg every 12 h	Until 2 consecutive negative weekly CMV QNAT (or pp65 antigenemia)
R+	Universal prophylaxis	All patients within 3 months after LT	Valganciclovir 900 mg daily or IV ganci- clovir 5 mg/kg daily	3 months
	Preemptive therapy	Weekly CMV QNAT (or pp65 anti- genemia) for 3 months after LT, if positive, start to treatment	Valganciclovir 900 mg every 12 h or IV ganciclovir 5 mg/kg every 12 h	Until 2 consecutive negative weekly CMV QNAT (or pp65 antigenemia)

Fungal infections LT patients have a higher incidence of fungal infections than other solid organ transplant recipients. Invasive fungal infections occur in 7–42% of LT patients [612, 613]. They are mostly caused by Candida and Aspergillus species. Despite advances in antifungal agents and prophylactic strategies, IFI is still associated with poor outcomes, with a mortality rate of approximately 30–50% due to invasive candidiasis and 65–90% due to invasive aspergillosis in post-transplant patients [614, 615]. Therefore, it is very important to establish and implement an appropriate preventive strategy for IFI.

Targeted prophylaxis using selective antifungal therapy for IFI in high-risk patients is recommended. Risk factors include re-transplantation, re-operation, renal failure requiring hemodialysis, the transfusion of ≥ 40 units of cellular blood products, including platelets, packed red blood cells, and autotransfusion, MELD > 30, choledochojejunostomy, and candida colonization in the perioperative period. Moreover, it is also known that patients with two or more risk factors have a high incidence of IFI [614, 616, 617]. Many randomized clinical studies and comparative studies in adult LT patients [612, 618-620] have demonstrated the benefit of antifungal prophylaxis in high-risk patients, and these therapies were mostly based on fluconazole or liposomal amphotericin B. Recently, various comparative studies have been conducted on the prophylactic effect of traditional antifungal drugs and echinocandin. Echinocandin has antifungal prophylaxis like the effects of the above two drugs. It has fewer drug interactions with immunosuppressants; therefore, it can be administered easily in transplant recipients, can be used without restriction in patients with renal impairment, and significantly reduces fungal colonization and IFI rates. Supplementary Table S1 shows recently conducted echinocandin-related comparative studies [621, 622]. There is no comparative study on the prevention period of targeted antifungal prophylaxis. The duration of administration in previous studies varied widely, ranging from 5 days to 10 weeks. However, in most cases, prevention stopped within 2–4 weeks. Therefore, this period seems reasonable [617, 623–625].

Universal prophylaxis is the administration of an antifungal agent to prevent IFI in all LT patients, including those in the low-risk group. In particular, 28–33% of transplant centers in the US or Europe have adopted this strategy, and fluconazole (100–400 mg/day) is used [626, 627]. However, in several studies, the incidence of IFI in low-risk patients is very low, which suggests that universal prophylaxis in these patients is not justified [628–631]. Accordingly, it is important to focus on targeted prophylaxis in high-risk groups rather than on universal prevention.

Another pathogen that requires essential antifungal prophylaxis is *Pneumocystis jirovecii*. This is a ubiquitous organism and common fungus that manifests as pneumocystis jirovecii pneumonia (PCP) in immunocompromised hosts. The risk of PCP is greatest between the second and sixth months after LT, during periods of prolonged neutropenia and/or strong immunosuppression [632, 633]. Due to its evidence-based efficacy, low cost, protective effect for additional infections (Toxoplasma and Listeria), and ease of taking, oral trimethoprim-sulfamethoxazole is preferred for universal prophylaxis 6-12 months after LT. In the era of routine prophylaxis where late-onset PCP occurs, additional conditions to prolong or re-initiate prophylaxis have been suggested, including age \geq 65 years, lymphocytopenia, CMV coinfection, steroid pulse therapy, or recurrence of HCC in HCC-related LT [634-636].

[Recommendations]

- Patients with a high risk of invasive fungal infection should receive antifungal prophylaxis (targeted prophylaxis) with drugs such as fluconazole, amphotericin, or echinocandin for 2–4 weeks. (A1)
- Universal prophylaxis for low-risk patients is not strongly recommended. (B2)
• Oral trimethoprim–sulfamethoxazole is recommended for 6–12 months to prevent PCP in liver transplant patients. (A1)

Immunosuppression

Induction

Induction agents are increasingly being used to reduce the requirement for maintenance of immunosuppressants, especially calcineurin inhibitors (CNIs), in the early period to minimize their toxicity. Currently, interleukin-2 receptor (IL-2R) monoclonal antibodies are the most commonly used agents for induction. Among IL-2R antibodies, daclizumab and basiliximab have been investigated for their clinical efficacy. However, daclizumab is currently not available in the market. The RCTs published for using basiliximab as an induction agent showed consistently better outcomes in terms of rejection, graft loss, and death, as well as renal preservation, when combined with reduced and delayed CNIs [637–641].

Studies published on antithymocyte globulin (ATG) as an induction agent showed a high degree of heterogeneity in study designs [642–646]. These high degrees of heterogeneity in design as well as results limit the interpretations of the use of ATG in LT according to the original studies' purposes. Nevertheless, using ATG at a standard dose for 3 days along with reduced CNIs combined with mycophenolate mofetil (MMF) and steroids seems reasonable in an attempt to lower the toxicity of CNIs.

[Recommendations]

- IL-2 receptor antibody as an induction agent can improve clinical outcomes, especially regarding rejection compared to a placebo. (B1)
- ATG can be used as an induction agent to reduce the dosage of CNI. (B2)

Standard regimen

CNI

Currently, CNIs are the mainstay of the standard regimen after LT globally, and nearly 97% of LT recipients are prescribed CNIs as their initial maintenance regimen [647, 648]. As cyclosporine (CsA) and tacrolimus (Tac) share similar modes of action, RCTs comparing the two CNIs were mostly investigated in the 1990s and 2000s and were systematically reviewed by a meta-analysis that included a total of 3813 patients [649–665]. In general, Tac showed better clinical efficacy regarding mortality, graft loss, rejection, and steroid-resistant rejection compared to CsA. A prolongedrelease formulation of Tac that enables a once-daily dose has been developed and validated for its efficacy in LT recipients in relation to a twice-daily dose of Tac [666–669].

Besides the clinical importance of CNIs in maintaining graft function in LT recipients, the toxicity of CNIs, such as nephrotoxicity, neurotoxicity, metabolic derangements, and oncogenic potentials, has led to various strategies to reduce the use of CNIs by combining them with other immunosuppressants [670, 671]. Nephrotoxicity of CNIs is the main concern, and nearly 18% of LT recipients reportedly experience chronic renal dysfunction within 5 years post-transplant [672, 673]. However, cessation of CNIs can increase the risk of rejection and adversely affect graft and patient survival. As a solution, combining other immunosuppressants with a reduced dose of CNI has been evaluated in several studies. Increased risk of cancer with immunosuppression is another concern in LT recipients especially those with HCC. In retrospective studies, the risk of HCC recurrence showed a dose-dependent relationship with the dosage of CNIs [674–676]. These findings have led to several reviews and trials that aimed to investigate the impact of reducing CNIs while adding other immunosuppressants, such as mTOR inhibitors, which are expected to have anticancer effects.

While concerns about the occurrence of de novo malignancy (DNM) after using CNIs were raised, there is only limited published evidence regarding the increased risk in CsA-treated patients compared to the risk in patients treated with Tac [677]. However, more evidence is needed to make a solid conclusion on the cause of DNM in relation to CNIs.

[Recommendations]

- CNI-based immunosuppression is currently the cornerstone of immunosuppressive regimens in patients with LT. (A1)
- Tac has better long-term graft and patient survival compared to CsA; therefore, it should be considered the primary CNI. (A1)
- A combination of other immunosuppressants for the reduction of CNI is recommended for LT recipients with other comorbidities due to drug-related toxicities. (A1)

Antimetabolite

Antimetabolites, such as azathioprine (AZA) and MMF, are increasingly being used to reduce the dosage of CNIs, and currently, MMF is the most commonly used antimetabolite for this purpose [678, 679]. AZA was used in LT earlier than CNIs since the 1960s and was used in combination with CNIs after the introduction of CsA. Eventually, MMF substituted AZA and has been generally used in combination with Tac. However, comparing data between AZA and MMF showed that there were no significant differences in graft survival among LT recipients. Only two published randomized trials reported a marginal improvement in rejection episodes in patients who received MMF compared to those who received AZA when combined with CsA; however, no differences in graft or patient survival were demonstrated [680–682]. Moreover, the trial that showed better rejection rates in patients treated with MMF used a dose of 3 g/day, while the study that used a dose of 2 g/day failed to show statistically significant differences. Therefore, although MMF is predominantly used in conjunction with CNIs rather than AZA, no solid evidence of the superiority of MMF over AZA has been provided.

[Recommendations]

• MMF can be used as a maintenance immunosuppressant in combination with CNI. (B2)

Steroids

Steroids have been one of the main immunosuppressants since the beginning of transplantation. However, due to its side effects regarding increased susceptibility to infections and metabolic dysfunction, efforts to minimize exposure to steroids have always been of key interest to transplant clinicians. So far, five RCTs have been published, starting in 2004 [683-688]. The first RCT was designed to withdraw steroid therapy at 14 days post-LT but showed higher biopsy-confirmed rejection compared to the placebo group (p=0.03) [688]. However, the study published in 2007 that was designed to discontinue steroid therapy 2 weeks post-LT showed no difference in survival outcomes, while PTDM was higher in the steroid group [687]. The steroid-free group was related to higher steroid-resistant rejection in the RCT published in 2008 and showed a higher re-transplantation rate in the study published in 2013 [685, 686]. These results show that not administering steroids or an early withdrawal from steroid therapy can lead to increased rates of rejection.

[Recommendations]

- Steroids can be used as the main immunosuppressant in combination with other immunosuppressants, especially during the initial period post-transplant. (B1)
- Steroids are undoubtedly related to metabolic syndrome; therefore, a tapering strategy is recommended based on each patient's clinical course. (A1)

mTOR inhibitor

Sirolimus (SRL) and everolimus (EVR) inhibit mTOR. Initially, when mTOR inhibitors were used for LT, SRL was related to early hepatic artery thrombosis and poor outcomes in terms of graft and patient survival [689]. However, subsequent studies showed that mTOR inhibitors did not increase the risk of hepatic artery thrombosis [690–692]. Due to the theoretical anticancer effect and not being related to nephrotoxicity or diabetogenesis, mTOR inhibitors have been investigated as maintenance immunosuppressants in combination with CNI after LT.

[Recommendations]

- mTOR inhibitors can be used as maintenance immunosuppressants in combination with CNIs. (B2)
- Currently, mTOR inhibitors are not recommended in the immediate post-transplant period due to concerns regarding hepatic artery thrombosis and incisional hernias. (B1)

Special considerations

Renal impairment

The most important risk factor for the development of renal insufficiency after LT is the use of CNIs. Therefore, strategies used for renal protection focus on reducing exposure to CNIs while increasing other immunosuppressants.

To reduce the dose of CNI, antimetabolite can offer some room for minimization. Studies that evaluated MMF for CNI dose reduction were published in the 2000s [693–697]. These studies demonstrated improved serum creatinine and glomerular filtration rate with CNI dose reduction. However, most studies included only a small number of patients, and the study designs were heterogeneous.

mTOR inhibitors have been the subject of interest for CNI sparing over the last decades. Two recently published RCTs demonstrated solid evidence regarding a renal protective regimen. The study that combined two global RCTs concluded that renal function was particularly improved in chronic kidney disease (CKD) stage 1/2 in the reduced Tac with EVR group [698]. The time point for Tac reduction and mTOR inhibitor conversion is also important for successful renal protection. In the study, early reduction of the dose of Tac with the introduction of mTOR inhibitors showed significant renal protection with no significant increase in graft survival [698-700]. However, an observational study based on a multicenter registry of LT recipients with EVR showed that late conversion was related to poor prognosis [701]. Therefore, the time point for conversion is recommended to be earlier rather than later. Among these studies on Tac reduction and replacement with an mTOR inhibitor, most studies focused on the reduction but not the total elimination of Tac. The study that was initially designed as a three-arm randomization study included a Tac elimination group (H2304); however, high levels of biopsy-proven acute rejection were observed in the Tac elimination arm, resulting in the early termination of the study group [700]. Therefore, Tac elimination is not recommended, especially in the early period, while elimination in the long term requires more evidence.

One of the strategies was to use IL-2R antibodies to delay the introduction of CNI. Four published RCTs compared the clinical impact of IL-2R antibodies with groups without induction therapy [640, 702–704]. Based on the results of the studies, using IL-2R antibody as an induction agent seemed to be beneficial for the early period when CNI initiation can be both delayed and reduced. However, in the long term, the impact seems to be mild. A recent RCT on the use of polyclonal antibodies such as ATG showed that the ATG group with delayed Tac initiation had better delta creatinine levels at 9 months post-LT [645]. However, ATG as an induction agent needs more evidence to be used for renal preservation, while IL-2R antibody is mostly used as an induction agent.

[Recommendations]

- For renal preservation in patients with CNI-induced renal dysfunction, MMF can be considered for the reduction of CNI. (B2)
- Early EVR with a reduced CNI regimen improves renal function after LT without increasing the risk of rejection or graft loss for LT recipients. (B2)
- IL-2R antibodies combined with delayed and reduced Tac, MMF, and steroids can be used to reduce the risk of renal toxicity after LT, especially in the early period. (B1)

HCC

Although the introduction of CNIs to the immunosuppressive regimen led to increased survival rates for LT recipients, there were still concerns regarding the possibility of an increased risk of tumors such as HCC [674, 705]. In studies that analyzed HCC recurrence, MMF did not show any impact on recurrence [674, 675]. While other retrospective studies have reported conflicting results; some of these studies showed that mTOR inhibitors demonstrated lower HCC recurrence and lower overall mortality (Supplementary Table S2) [706–711]. These findings increased the need for well-designed RCTs, and two studies have been published on the topic [698, 712]. The SiLVER trial directly compared an mTOR inhibitor-free group to an mTOR inhibitor group and demonstrated better recurrence-free survival and overall survival in the first 3–5 years, especially in low-risk patients [712]. However, the result was not consistent beyond 5 years; therefore, the survival curves did not show a significant difference during the entire follow-up period. Further analysis published with the same trial demonstrated that more than 3 months of administering sirolimus (HR = 0.70; 95% CI 0.52-0.96; p=0.024) was a significant factor for better survival based on multivariable analysis [713]. Another RCT published in 2021 failed to draw a conclusive result that the efficacy of EVR in preventing HCC recurrence [698]. The study was not designed only for HCC; therefore, only 36.5% of patients were diagnosed with HCC. These results show that EVR with a reduced Tac can be considered to reduce the risk of HCC recurrence, while additional RCTs focusing on HCC recurrence are still necessary to arrive at definitive conclusions. The impact of EVR on HCC recurrence has also been investigated in retrospective studies. A study from two centers that included HCC patients with recurrence after LT demonstrated better survival among patients who were administered an mTOR inhibitor and sorafenib compared to those who were administered sorafenib alone only in univariate analysis [714]. A single-center retrospective study that analyzed HCC patients with recurrence after LT showed that early initiation of EVR within 3 months after recurrence improved survival outcomes (HR = 0.354; 95% CI 0.141–0.88; p = 0.027) [708].

[Recommendations]

- mTOR inhibitors can be considered along with a combination of immunosuppressants, including CNIs, for LT recipients with HCC to reduce the recurrence of HCC after transplantation. (B2)
- EVR can be used to improve the survival outcomes of patients with HCC recurrence after LT. (C2)

Long-term management

Prophylaxis for HBV recurrence

Transplanted patients without any prophylaxis may have HBV recurrence in up to 80% of cases [715]. HBIG represents an efficient passive immune agent against HBV, and long-term passive immunoprophylaxis after LT results in a 60–80% reduction in HBV recurrence [716]. Unfortunately, long-term HBIG usage presents some drawbacks, such as relevant costs and the need to repeatedly monitor hepatitis B surface antibody levels [717].

In the late 1990s, lamivudine (LAM) was introduced as a pre- and post-LT treatment, further improving the outcomes of HBV transplant recipients [718]. However, longterm LAM therapy was associated with the emergence of HBV resistance related to YMDD mutations [719]. Later on, the introduction of adefovir (ADV) offered a useful temporary option for patients in the pre- or post-transplant period, particularly those who develop LAM resistance [720]. Nevertheless, ADV also has some limitations, including a moderate genetic barrier to HBV resistance and the risk of nephrotoxicity. Over the last 12–15 years, oral NUCs with a high genetic barrier to resistance, such as entecavir (ETV) and tenofovir disoproxil fumarate (TDF), have been used for LT candidates and recipients [721]. In the last few years, tenofovir alafenamide (TAF) has also been introduced in the management of patients with HBV infection and offers similar efficacy compared to TDF, but has lower risks of adverse events related to renal function and bone mineral density (BMD), which are particularly important in transplant settings [722].

Recent systemic review and meta-analysis showed a reduced risk with the combination of HBIG and NUC versus NUC alone for HBV recurrence in 2093 patients in 27 studies (OR = 0.22; 95% CI 0.16–0.30; p < 0.0001) [723]. This study also showed a reduced risk with the use of HBIG alone versus NUC alone for HBV recurrence (OR = 0.20; 95% CI 0.09–0.44; p < 0.0001).

The current first-line NUCs (ETV, TDF, and TAF), usually in combination with HBIG, appear to be the best option for the prevention of post-LT HBV recurrence [724]. However, controversy remains regarding the optimal prophylactic protocol, particularly regarding the duration, dosage, and route of HBIG administration [721].

Several studies have shown that LT recipients who were switched to ETV or TDF monoprophylaxis 6–12 months after commencing a combination of HBIG and ETV or TDF therapy had low rates of detectable HBV DNA levels [721, 725–728]. However, for LT recipients with a higher risk of HBV recurrences, such as patients with HBV DNA positivity at LT or HCC pre-LT, a decision for HBIG discontinuation should be taken with great caution and after ensuring close monitoring, while further studies are needed for the evaluation of the safety of HBIG discontinuation in such patients [729].

[Recommendations]

- In HBV-related LT recipients, a prophylactic combination of HBIG and a potent NUC post-transplantation is recommended for the prevention of HBV recurrence. (A1)
 - Patients with a low risk of recurrence (HBV DNA negative at LT) can receive a short course or HBIG-free regimens but need continued monoprophylaxis with a potent NUC. (B1)
 - Patients with a high risk of recurrence (HBV DNA positive at LT, HDV coinfection, or poor adherence to NUC therapy) should receive a lifelong combination of HBIG and a potent NA. (B1)

 HBsAg-negative patients receiving anti-HBc-positive liver grafts have variations in HBV reactivation rates depending on the recipient's immunization status against HBV and should receive NUC therapy accordingly (B1).

Treatment of HCV recurrence

Recurrence of HCV infection occurs within a few hours after transplantation in patients with detectable HCV RNA at the time of LT [730]. Without antiviral treatment, HCV-related liver disease accelerates after LT, which may progress to cirrhosis in 20-30% of patients within 5 years following transplantation [731-733]. Therefore, the cure of HCV infection following LT is essential because it will significantly improve the rate of graft loss and post-transplant survival [734, 735]. Fibrosing cholestatic hepatitis is an extensive form of hepatitis accompanying moderate to severe fibrosis and portal hypertension, which are major causes of graft loss and patient mortality and require urgent antiviral treatment [736]. Considering that patients with early recurrent hepatitis are more likely to achieve a higher SVR rate than those who have progressed to cirrhosis, and treating such patients before progression to cirrhosis has clear clinical benefit; hence, early DAA treatment after the detection of HCV RNA is recommended [737–739].

Several reasons justify the use of antiviral treatment post-transplantation rather than pre-transplantation. DAAs are less effective in patients with advanced liver cirrhosis (Child-Pugh B or C) with lower SVR rates compared to non-cirrhotic patients, and the SVR rate reaches 90-100% when treated with DAA in the early stage of relapse after transplantation [267, 268]. In addition, many patients being treated in a pre-transplantation setting go on to undergo LT prior to completion of the DAA course (partial treatment), and additional courses may be required in a post-transplantation setting where post-transplantation immunosuppressive agents could hamper a complete virologic response, leading to the need for further treatment. Finally, pre-transplantation DAA treatment was reported to be cost-effective in patients without HCC with a MELD score of ≤ 20 , while DAA treatment after LT was cost-effective in patients with a MELD score of > 20 [283]. Some reports indicate that DAAs are extremely successful in post-transplantation viral clearance and can be utilized even in cases of rapidly progressing fibrosing cholestatic hepatitis [267, 268].

In patients with post-transplantation HCV recurrence without cirrhosis or with compensated (Child–Pugh A) cirrhosis of any genotype of HCV (G1-6) infection should be treated with either a combination of sofosbuvir 400 mg and velpatasvir 100 mg for 12 weeks or a combination of glecaprevir 300 mg and pibrentasvir 120 mg for 12 weeks. Considering the possible drug–drug interaction between the protease inhibitor, glecaprevir, and immunosuppressants, careful monitoring, and drug dose adjustment is required if needed. In patients with genotype 1 HCV infection, the combination of ledipasvir 100 mg and sofosbuvir 400 mg for 12 weeks can be an alternative regimen. In patients with genotype 2 HCV infection, sofosbuvir 400 mg and weight-based ribavirin (1000 or 1200 mg in patients <75 kg or \geq 75 kg, respectively) for 12 weeks can be considered. In any genotype of HCV (G1–6) infection with prior DAA failure, the combination of sofosbuvir 400 mg, velpatasvir 100 mg, and voxilaprevir 100 mg for 12 weeks is recommended.

In patients with post-transplant HCV recurrence with decompensated (Child–Pugh B or C) cirrhosis of any genotype of HCV (G1-6) infection should be treated with a combination of sofosbuvir 400 mg and velpatasvir 100 mg with weight-based ribavirin (1000 or 1200 mg in patients < 75 kg or \geq 75 kg, respectively) for 12 weeks. In patients with genotype 1 HCV infection, ledipasvir 100 mg and sofosbuvir 400 mg with weight-based ribavirin (1000 or 1200 mg in patients < 75 kg or \geq 75 kg, respectively) for 12 weeks can be an alternative regimen. In patients with genotype 2 HCV infection, sofosbuvir 400 mg and weight-based ribavirin (1000 or 1200 mg in patients < 75 kg or \geq 75 kg, respectively) for 16 weeks can be considered.

[Recommendations]

- All patients with post-transplant recurrence of HCV infection must be treated (A1), and treatment should be initiated as early as possible after LT (B1).
- Fibrosing cholestatic hepatitis or the presence of moderate to extensive fibrosis or portal hypertension necessitates urgent antiviral treatment (A1).

Recurrence of original disease

Autoimmune liver disease

Primary biliary cholangitis (PBC) A multicenter cohort study of 571 patients with PBC who underwent LT reported that the rates of PBC recurrence at 5 and 10 years were 18% and 31%, respectively [740]. Another multicenter study that analyzed 785 patients reported that the rates of PBC recurrence at 5 and 10 years were 22% and 36%, respectively [741].

Younger age at diagnosis of PBC or LT elevated alkaline phosphatase levels at 6 and 12 months after LT, and the use of Tac, sirolimus, or MMF increase the risk of recurrence of PBC after LT [741–743].

Strategies for the prevention of recurrence involve the use of ursodeoxycholic acid (UDCA 10-15 mg/ kg/day in two divided doses) following LT and an immunosuppressive regimen containing CsA (rather than Tac) [740, 742, 744]. A cohort study that analyzed 780 patients suggested that UDCA combined with CsA was associated with a lower risk of PBC recurrence compared to using either agent alone (adjusted HR = 0.47) [740]. A recent meta-analysis that evaluated 15 studies also showed that prophylactic UDCA reduced the recurrence rate of PBC. (OR = 0.7, p = 0.01) [745].

The diagnosis of recurrent PBC is based more on histologic rather than serologic findings. Persistent antimitochondrial antibody positivity and liver histology showing the characteristic portal tract lesions, including mononuclear inflammatory infiltrate, formation of lymphoid aggregates, epithelioid granulomas, and bile duct damage, are essential for the diagnosis of recurrent PBC.

There are limited data regarding the treatment of recurrent PBC, although treatment with UDCA is recommended [746]. Recurrent PBC in patients following LT is not an indication for treatment with obsticholic acid.

[Recommendation]

• To prevent PBC recurrence after LT, prophylactic administration of UDCA is recommended (B2).

Primary sclerosing cholangitis (PSC) PSC has excellent outcomes after LT, although disease recurrence may occur [747, 748]. The diagnosis of recurrence is based on the consistent findings of liver biopsy and cholangiography. Risk factors for PSC recurrence include inflammatory bowel disease (IBD) in patients with an intact colon, prolonged ischemic time, recurrent acute cellular rejection, CMV infection, prolonged use of glucocorticoids, and lymphocytotoxic cross-match. One study reported that colectomy before and during LT for PSC was protective against recurrent PSC [749].

The natural history of IBD, especially ulcerative colitis, following LT is variable. A retrospective cohort study that included 303 patients with IBD who underwent LT found that the only two independent risk factors for IBD progression were age > 30 years at the time of LT (HR = 1.5) and LT itself (HR = 3.1). The incidence rates for colectomy ranged from 0.007 per year before LT to 0.025 per year after LT [750]. In another longitudinal multicenter study that included 353 patients with IBD who underwent LT, IBD activity decreased in 17% of patients, remained unchanged in 43%, and increased in 40% of patients after LT [751]. The use of Tac plus MMF significantly increased the risk of worsening IBD activity (HR = 3.9), whereas the use of cyclosporin and AZA was associated with a decreased risk of worsening IBD (HR = 0.4). • For patients grafted for PSC and IBD, regular colonoscopies are recommended (B2).

AlH The 5-year patient and graft survival rates for AIH are reported to be 80–90% and 72–74%, respectively [752]. The frequency of acute and chronic rejection after LT for AIH is higher compared to other etiologies [753]. Long-term use of glucocorticoid therapy after LT has been suggested to protect against rejection and recurrence of AIH [754]; however, the increased risk of infection and adverse events of steroid therapy limit its long-term use.

Among patients who undergo LT, 17–42% have AIH recurrence [755–758]. Recurrent AIH is a major cause of allograft failure and reduced patient survival. A recent multicenter study that included 736 patients from 33 centers reported that younger age at LT, use of MMF post-LT, sex mismatch, and high IgG pre-LT were risk factors for recurrent AIH [759]. Furthermore, 5-year long-term steroid use was not a significant factor for AIH recurrence in this study. However, another study reported that maintenance of glucocorticoid therapy can lower the recurrence of AIH in patients who have undergone LT due to AIH [760]. Therefore, further studies on steroid treatment for patients with AIH who underwent LT are needed.

Since it is often difficult to differentiate between graft rejection and AIH recurrence after LT, clinicians should be cautious in interpreting clinical findings [761]. The diagnostic criteria for recurrent AIH are the same as those of the original disease. Laboratory profiles (increased serum aspartate aminotransferase, ALT, and IgG levels) and histological findings (lobular hepatitis, focal necrosis, pseudorosettes, interface hepatitis, and lymphoplasmacytic infiltration) are required for the diagnosis of recurrent AIH. Histological findings, including endothelialitis and bile duct damage, which are classically seen in cases of rejection, are usually absent in cases of recurrent AIH. Standard glucocorticoid-based therapy is used to treat recurrent AIH, along with the addition of AZA or MMF [762, 763]. Predniso(lo)ne 0.5–1.0 mg/kg or 40–60 mg/ day is the recommended dose for steroid monotherapy. Predniso(lo)ne < 0.5 mg/kg or 20-40 mg/day in combination with AZA 50 mg/day is the recommended dose for steroid and AZA combination therapy (reference: KASL 2022 AIH practice guideline).

Meanwhile, in patients whose pre-transplant chronic liver disease was not AIH but AIH was newly diagnosed after LT, which is often defined as "de novo" AIH [764, 765], the use of glucocorticoids in addition to CNI is the treatment of choice [762]; however, the optimal strategy has not been fully investigated, and future studies are needed.

[Recommendations]

• Standard glucocorticoid-based therapy along with the addition of immunosuppressive agents is recommended to treat recurrent AIH after LT (B1).

Alcohol-related liver disease (ALD)

Short-term patient and graft survival rates following LT for ALD are similar to the rates following LT for other etiologies; however, the 10-year patient and graft survival rates are lower for patients with ALD [766, 767]. In a cohort study of the United Network of Organ Sharing database, patients' 1- and 5-year survival rates were similar among patients with ALD and those with other chronic liver diseases after LT (1 year: 91% vs. 90%; 5 years: 79% vs. 80%) [768]. However, the 10-year survival rates were lower for patients with ALD compared with those of non-ALD patients (63% vs. 68%) after LT [768].

Despite comprehensive pre-LT evaluation and adherence to the 6-months of abstinence, some recipients resume alcohol abuse after LT. Rejection, graft loss, recurrent ALD, and fatal alcoholic steatohepatitis are the potential complications of relapsed alcohol abuse after LT [769]. In a study of 300 patients with ALD who underwent LT, recipients with a history of alcohol abuse after LT were more likely to develop alcoholic steatohepatitis (OR 6.2) and advanced fibrosis (OR 23.2) compared with those who maintained abstinence [770]. Another study also reported impaired 10-year survival rates in recipients who resumed alcohol abuse, possibly because of an increased mortality rate from cancer and cardiovascular events [771].

In a study of 103 patients with ALD who underwent LT, an alcohol treatment program resulted in lower rates of alcohol abuse during a 4-year follow-up period (22% vs. 48%) [772]. In the United Kingdom, all LT recipients with ALD were followed up by a psychiatrist for addiction treatment [773].

[Recommendations]

- All LT recipients with ALD should remain abstinent from alcohol (A1).
- LT recipients with ALD are encouraged to undergo addiction treatment if they relapse into alcohol use (B2).

NASH/NAFLD/obesity

Post-LT outcomes for patients with NAFLD in a metaanalysis that examined 1-, 3-, and 5-year survival outcomes were comparable to those of other etiologies, whereas the risk of graft failure was lower [774]. Notably, the graft outcomes from the United Network for Sharing Organs database reported that the 10-year graft survival rate for NASH LT recipients was 61%, which is like that for ALD LT recipients at 59% [775].

Maintaining a healthy weight and diet are important, especially given that weight gain is common following LT. Most body weight gain occurs within the first year after LT, with studies reporting a median body weight gain of 5.1–9.8 kg 1 year after LT [776]. Therefore, awareness about controlling body weight needs to be raised early in the post-LT period. A randomized trial of exercise and dietary counseling after LT reported that recipients who received exercise and dietary counseling had a similar increase in body weight and fat mass compared with the control group [777]. However, only 37% of recipients were completely adherent to the intervention. If interventions for lifestyle modification fail, medical or surgical treatment should be considered. No pharmacological agent has been studied in LT recipients so far. Regarding obesity, corticosteroids are potently adipogenic and could lead to weight gain. Therefore, minimizing corticosteroid use should be considered. The dose of prednisone is an independent predictor of the development of obesity [778]. However, once obesity is established, decreasing the dose of prednisone may not result in weight loss [778]. In addition, CsA-treated patients are more likely to gain weight than Tac-treated patients [779].

Steatosis in the graft liver makes it vulnerable to hepatic injury, resulting in a higher rate of early allograft dysfunction and post-LT vascular and biliary complications. Weight loss is the most effective treatment, and dietary and lifestyle modifications should be first recommended. A previous study has suggested an intense protocol for 2–8 weeks to reduce hepatic steatosis, which involves the use of an exercise program that burns 600 kcal per day, a protein-rich diet with 1000 kcal per day, and fibrate medication [780]. No single pharmacologic treatment has been recommended specifically for patients with recurrence or de novo NAFLD after LT.

[Recommendations]

- Prevention or treatment of NAFLD after LT should be performed to avoid excessive weight gain for all LT recipients (B1).
- The LT recipients should get assessment of liver fibrosis and fat through transient elastography, at least once a year (B2).

HCC recurrence

Despite the selection of HCC patients for LT using morphological criteria, such as MC, 15-20% of cases still have tumor recurrence, which is associated with a poor prognosis [781–784]. Therefore, it is important to identify risk factors influencing tumor recurrence after LT to refine patient selection and improve the outcomes of LT in patients with HCC. Commonly known risk factors for HCC recurrence can be classified in association with the tumor, patient, or treatment (Table 10) [785]. A high initial trough level of CNIs, such as CsA and Tac, may contribute to an increased risk of HCC recurrence after LT [674]. There is no consensus on a protocol to determine the modality of exams to be performed or the frequency or duration of follow-up for monitoring HCC recurrence after LT. In most cases, for the first 2-3 years post-transplant, chest and abdominal CT and tumor marker (AFP, PIVKA-II) levels should be monitored at 3- to 6-month intervals, after which the examination interval can be increased. There is no set time limit for monitoring recurrence after LT. Consensus conferences issued vague recommendations for monitoring HCC recurrence with the combination of imaging tests (CT or MRI) and AFP every 6–12 months [786].

Generally, HCC recurrence after LT usually occurs in the early period, with a median recurrence-free survival (RFS) of 12–16 months. In most cases, the median survival after recurrence is 7–16 months, with a poor prognosis. In a recent analysis of 857 patients with HCC who underwent

Table 10Factors possiblyassociated with the recurrenceof hepatocellular carcinomaafter liver transplantation

Related to the tumor	Related to the patient	Related to the treatment
Tumor staging	Obesity	Pre-transplantation
Vascular invasion	Viral etiology	Percutaneous tumor biopsy
Differentiation's grade	HCV treatment	Waiting time
Tumor marker (AFP, PIVKA-II)	NAFLD	Bridging therapy
Neutrophil–lymphocyte ratio		Peri-transplantation
Enhanced uptake in PET scan		Donor's age
MRI findings with gadoxetic acid		Ischemic time
Response to locoregional treatment		Surgical technique
		Post-transplantation
		Immunosuppression

LT [781], recurrence occurred in 106 patients (12.4%) with a median follow-up duration of 15.8 months after transplantation; furthermore, the median survival after recurrence was 10.6 months. About 75% of cases of HCC recurrence occur during the first 2 years after LT, and only 10% are detected after 4 years. The sites of recurrence include the lungs (55.7%), liver (37.8%), abdominal cavity (37.7%), and bones (25.5%) in that order. As such, the clinical course of HCC recurrence after LT tends to be dramatic due to tumor spread in immunosuppressed patients. HCC recurrence after LT should be considered a systemic event, as it is limited to the graft in only 30% of cases [787]. In more than 50% of cases, one or more organs are involved [781]. A Euro-American study [784] showed the following were the three poor prognostic factors in patients with HCC recurrence: HCC recurrence during the first year after LT (HR = 1.6), AFP levels greater than 100 ng/mL at HCC recurrence (HR = 2.1), and recurrent tumors that are unsuitable for surgical resection or local ablation (HR = 4.7). The 5-year survival rate for patients without these negative prognostic factors was 50%. These poor prognostic factors have recently been validated in another multicenter study [788].

There are currently no consensus guidelines for the management of HCC recurrence after LT. There are many treatment options for HCC recurrence, such as surgical resection, local ablation, intraarterial therapy (TACE, TARE), and systemic therapy. Therefore, individualized management of HCC recurrence is required. This is often accompanied by a multidisciplinary team approach that includes hepatology, transplant surgery, diagnostic and interventional radiology, and oncology [789].

Surgical resection should be considered first for the management of recurrent HCC. Although HCC recurs after LT, the survival rate can be increased if surgical resection is possible. A study that included 121 patients with HCC who relapsed after LT found that patients who were able to undergo surgical resection had a significantly longer median survival than those who received other treatments [784]. In a Japanese study of 17 patients who relapsed after LT, the 1-, 3-, and 5-year survival rates for patients who underwent surgical resection were 100%, 87.5%, and 87.5%, respectively, whereas, in those who received non-surgical treatments, significant differences were observed at 50%, 12.5%, and 0%, respectively [790]. When recurrent HCC is confined within the liver and surgical resection is difficult, local ablation can also be considered. Generally, the use of surgical resection or local ablation is usually possible in patients with HCC recurrence and less aggressive behavior, as represented by late recurrence, lower levels of tumor markers, and a lower number and size of tumor nodules [791]. However, even if surgical resection or local ablation is performed for recurrent HCC after LT, the recurrence rate is high, and repeated treatments may be required [792].

In patients with unresectable multifocal liver recurrence, intraarterial therapy with chemoembolization (TACE) or radioembolization with yttrium-90 (TARE) may be considered. Although studies on the efficacy and safety of TACE for HCC recurrence after LT are limited, a higher TACE-related complication rate for HCC recurrence after LT has not been reported in the literature [793]. In a report of 14 patients with HCC recurrence after LT, partial response after TACE was 57%, stable disease was 28%, and disease progression was 14%. This study shows that the 12- and 24-month survival rates after recurrence in patients who received TACE were 50% and 22.2%, respectively, and the survival rates in patients with systemic chemotherapy were 21.4% and 10.7%, respectively (p=0.034) [793]. It has also been reported that TARE using yttrium-90 was performed in patients with recurrent HCC without adverse events [794]. Combinations of locoregional therapies, such as local ablation and TACE, may be performed after individualized assessment by a multidisciplinary team.

Most patients, especially those with an early recurrence of HCC, have extensive metastatic disease that requires the use of systemic chemotherapy. Sorafenib can be used as a systemic therapy for HCC recurrence after LT. However, there are no well-designed RCT to validate the effectiveness and safety of sorafenib for HCC recurrence after LT. In a case-control study of 39 patients with recurrent HCC, the sorafenib-treated group had better outcomes compared to those of patients managed with only the best supportive care [795]. Second-line therapy with regorafenib after sorafenib failure in patients with a recurrence has also been published in a multicenter retrospective study [796]. Of the 132 patients treated with sorafenib after posttransplant recurrence, patients who were administered regorafenib as second-line treatment had significantly higher survival rates than did patients who received supportive care alone after sorafenib failure. Other tyrosine kinase inhibitors, such as lenvatinib and cabozantinib, and the use of monoclonal antibodies, such as ramucirumab, may be considered, but the safety and efficacy of using these agents after LT are still controversial. The use of sorafenib and mTOR inhibitors with potential synergistic effects has been suggested in HCC-relapsed patients, but there is currently insufficient evidence to recommend it.

Although immunotherapy is now accepted as the firstline treatment for HCC, significant concerns remain regarding the use of immunotherapy in post-transplant settings, with respect to the risk of promoting rejection through immune activation. In a recent study, since rejection by these checkpoint inhibitors can occur in up to 50% of cases, the use of immune checkpoint inhibitors after LT requires great concern [797].

[Recommendations]

- In case of recurrence of HCC after LT, surgical resection or local ablation is recommended as much as possible. (C1)
- It is necessary to take a multidisciplinary team approach in consideration of the time of recurrence, recurrence site, and graft function. (B1)
- Current first-line tyrosine kinase inhibitors are recommended for managing recurrence of HCC (B1).

Systemic disease

CKD

Among patients who are maintained on Tac, 36% experienced a decline in estimated glomerular filtration rate (eGFR) by more than 30% after LT during a mean duration of 3.7 years [798]. The decrease in eGFR occurs mainly in the first 6 months after LT and then remains stable. A cohort study that includes approximately 37,000 LT recipients reported that 14% and 18% of LT recipients have CKD with a moderately to severely decreased eGFR (<30 mL/min/1.73 m²) at 3 and 5 years post-LT, respectively [799]. The incidence of end-stage renal disease that requires dialysis or kidney transplantation is 5–8% during the first 10 years after LT [800, 801]. CKD is also associated with a 4.55-fold higher 1-year mortality [799].

The contributing factors of post-LT CKD include preexisting CKD, peri-LT AKI, persistent exposure to CNIs, older age, female sex, hypertension, diabetes mellitus (DM), dyslipidemia, obesity, and chronic HCV infection [799]. Cases of AKI caused by CNIs are due to renal vasoconstriction and improve with dose reduction.

An elevated serum creatinine level is a late and insensitive indicator of CKD. However, in estimating renal function, eGFR calculated using the CKD Epidemiology Collaboration formula with or without cystatin C is superior to serum creatinine alone and 24-h urine creatinine clearance [802]. Urinary protein quantification using the concentration ratio of protein to creatinine in a spot urine sample should be assessed at least annually [803].

Aggressive BP control and the use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are expected to have beneficial effects in LT recipients as well as in the non-transplant population. A reduction in the dose of CNI does not typically improve kidney function, but the renal function is more likely to be preserved if CNI is withdrawn earlier when an eGFR is 40–50 mL/min/1.73 m² [804]. However, substitution with MMF or an mTOR inhibitor in patients without proteinuria is an option [656, 657, 805].

[Recommendations]

• Reduction in the dose of CNIs should be considered to preserve renal function in LT recipients (A1).

DM

Patients with DM who require insulin or oral antidiabetic drug treatment prior to LT may frequently require insulin therapy after LT. The incidence of de novo PTDM at year 1 ranges from 10.8 to 33% [806]. Glucocorticoids, CNIs (Tac more than CsA), weight gain, and HCV infection are risk factors for the development of PTDM.

PTDM tends to resolve over time, particularly if corticosteroids are withdrawn and the Tac dosage is decreased. PTDM is not associated with short-term 1-year survival after LT; however, it is associated with shorter 5- to 10-year survival [807, 808].

The oral glucose tolerance test (OGTT) is the optimal screening tool for PTDM [809]. HbA1c is not indicated as a first-line diagnostic test for PTDM. A fasting plasma glucose level of < 100 mg/dL is considered normal, 100-125 mg/dL is considered impaired fasting glucose, and ≥ 126 mg/dL constitutes diabetes. A 2-h post-OGTT plasma glucose level of < 140 mg/dL is considered normal, 140–199 mg/dL is considered to be impaired glucose tolerance, and ≥ 200 mg/dL constitutes DM. If HbA1c is greater than 7%, pharmacological therapy is required [803].

The long-term goals of diabetes management do not significantly differ from those of non-transplant patients. Adjusting immunosuppression by decreasing or discontinuing glucocorticoid therapy may be advantageous. In patients with difficult-to-control DM, switching CNIs from Tac to CsA is another treatment option.

Traditional pharmacological treatments include metformin and sulfonylureas (e.g., glipizide and glimepiride), both of which are indicated for LT recipients with normal renal function. However, sulfonylureas are preferred if renal function has deteriorated. Meglitinides (e.g., repaglinide and nateglinide), thiazolidinediones (peroxisome proliferatoractivated receptor-y agonists, e.g., pioglitazone) are also utilized. In addition, interest in dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g., linagliptin, vildagliptin, and sitagliptin) for the treatment of PTDM has increased in recent years since incretins (glucagon-like peptide-1 [GLP-1] and glucosedependent insulinotropic peptide), of which the half-life is prolonged by DPP-4 inhibitors, counteract the diabetogenic actions of immune suppressants [810]. Recent introductions include GLP-1 analogs (e.g., liraglutide) and sodium-glucose cotransporter type 2 inhibitors; nevertheless, clinical data on PTDM are scarce.

[Recommendations]

• The management of DM after LT should aim for a target HbA1c below 7.0% with a combination of lifestyle modifications and pharmacological agents as appropriate (B1).

Hypertension

Approximately 65–70% of LT recipients develop hypertension [811]. The causes of post-LT hypertension are multifactorial, but CNIs and glucocorticoids play the most significant roles [812]. Hypertension increases the risk of cardiovascular events and CKD in LT recipients [813].

A target BP of < 130/80 mmHg is reasonable for liver transplant recipients since most of these patients have multiple risk factors for cardiovascular diseases (CVD), such as diabetes, obesity, and dyslipidemia [814].

If lifestyle modification and a reduction in immunosuppression fail to reduce a patient's BP to the desired level, antihypertensive medicines should be administered. CCBs, such as amlodipine, may be more effective in LT recipients because they counteract the vasoconstrictive effect of CNIs [815]. First-generation CCBs, such as nifedipine and verapamil, should be used with caution as they may inhibit cytochrome P450 and consequently increase serum CNI levels. Beta-blockers are equally effective as CCBs in the treatment of hypertension among LT recipients [815]. As non-selective beta-blockers may decrease portal blood flow, a cardio-selective beta-blocker such as metoprolol or atenolol might be preferred. ACEIs and ARBs are preferred in LT recipients with DM, CKD, and/or significant proteinuria [803]. Potassium levels must be monitored when ACEIs/ ARBs are used in combination with CNIs (particularly Tac). Generally, diuretics are not used as primary therapy for hypertension due to concerns regarding their potential to worsen electrolyte imbalances and dyslipidemias induced by CNIs, but they are sometimes used in conjunction with other agents.

[Recommendations]

• The treatment of hypertension should aim for a target BP of < 130/80 mmHg with a combination of lifestyle modifications and pharmacological agents as appropriate (A1).

Dyslipidemia

Dyslipidemia develops in up to 70% of LT recipients [816, 817]. Hypercholesterolemia develops in 16–43% of patients, and hypertriglyceridemia in 40–47% of patients [813]. Typically, hypertriglyceridemia occurs within the first month after LT and then plateaus throughout the first year of life. In

contrast, serum cholesterol levels rise gradually and remain stable after 6 months. Patients with elevated pre-LT cholesterol levels are most likely to develop hypercholesterolemia following LT.

Although age, body weight, and genetics have some influence, dyslipidemia observed in LT recipients mostly results from the side effects of medications, such as CNIs (CsA > Tac), mTOR inhibitors, and glucocorticoids.

Generally, the time to recommend medical treatment for dyslipidemia is guided by a patient's low-density lipoprotein cholesterol (LDL-C) levels and CVD risk. In LT recipients with elevated LDL-C levels of > 100 mg/dL with or without hypertriglyceridemia, treatment is indicated [803]. When glucocorticoids are withdrawn and maintenance levels of Tac (4-5 ng/mL) or CsA (100-120 ng/mL) are reached, dyslipidemia improves in many patients over time. Consequently, medical therapy is rarely recommended in the early post-LT period. If dyslipidemia persists after the early transplant period, treatment is like treatment in non-transplant patients. However, drug-drug interactions between statins and CNIs could complicate treatment. Most patients are treated with statins. Pravastatin and fluvastatin are favored over other statins due to their fewer interactions with immunosuppressants. Ezetimibe has also been shown to lower LDL-C levels with generally stable levels of immunosuppression and a low risk of severe side effects. Proprotein convertase subtilisin kexin-9 inhibitors have not been adequately evaluated in organ transplant recipients. Changes in immunosuppression, including conversion of CsA to Tac, reduction of CNIs by adding MMF, and withdrawal of sirolimus, should be addressed when dyslipidemia is resistant to pharmacotherapy.

Isolated hypertriglyceridemia is initially treated with omega-3 fatty acids (up to 4 g daily if tolerated). If this is not adequate for control, gemfibrozil or fenofibrate can be added, although patients must be closely monitored for side effects of fibrates, especially when statins and CNIs are used concurrently [803].

[Recommendations]

• In LT recipients with an elevated LDL-C level > 100 mg/ dL, treatment is indicated. If therapeutic lifestyle and dietary changes are not enough, statin therapy should be introduced (B1).

Bone disease

A decrease in BMD is an important cause of morbidity in LT recipients.

Most cases of bone loss and fractures occur within the first 4–6 months after LT [818]. Almost all LT recipients experience accelerated bone loss in the first 4 months due

to the effects of corticosteroids and possibly CNIs, regardless of their pre-LT BMD [819]. In cases of normal graft function for up to 4 months, bone metabolism improves. After the initial 6–12 months, the rate of bone loss reduces or reverses. In patients with osteopenia, BMD gradually increases; thus, the incidence of fractures reduces gradually [820].

Despite the lack of consensus on the ideal monitoring strategy, BMD measurement 1 year after LT may be recommended at a minimum, considering the typical BMD change following LT. Afterward, BMD monitoring is recommended to be performed annually for LT recipients with osteopenia or osteoporosis and every 2–3 years for those with normal BMD [197, 803].

Regardless of pre-LT BMD, the same procedures used to prevent or treat osteopenia (T-score between -1.0 and -2.5) and osteoporosis (T-score \leq -2.5) for the general population need to be applied to LT recipients. Recipients should be advised to engage in early mobilization following LT and to prevent falls. From the pre-LT period, patients need to intake calcium (1000–1200 mg/day from food and supplements) and vitamin D (800–1000 IU/day or 20–25 µg/day) [821]. The lower dose of prednisone that can ensure graft survival may be advantageous to bone health. Regular 30-min, three-times-weekly weight-bearing exercise is beneficial for restoring BMD to pre-LT levels.

All osteopenic patients who receive LT may be candidates for preventive medical therapy, as fractures occur most frequently during the first year post-LT, even in recipients without pre-LT osteoporosis, and recipients receive glucocorticoid doses that might cause bone loss.

Bisphosphonates are regarded as the medical therapy of choice for the prevention of post-LT bone loss, as bisphosphonates reduce steroid-induced bone loss, to which post-LT bone loss is highly related. Either oral alendronate or intravenous bisphosphonates (zoledronate or ibandronate) can be used. Bisphosphonates should be used with caution in premenopausal female due to insufficient information on their potentially harmful effects on the fetus.

Alternatives to bisphosphonates include calcitriol. A meta-analysis demonstrated that calcitriol is beneficial in reducing bone loss after solid organ transplantation, including LT [822]. Serum calcium levels should be monitored, and in the event of hypercalcemia, calcium supplementation should be discontinued.

Estradiol/progesterone therapy is another option for the prevention of post-LT bone loss in female with hypogonadism. Male patients with symptoms of hypogonadism should receive testosterone replacement therapy if it is not contraindicated. Estradiol/progesterone replacement in female patients and testosterone replacement in male patients after transplantation have been shown to reduce the rate of bone loss [823, 824]. However, estrogen/progesterone therapy is no longer a first-line treatment for osteoporosis in postmenopausal female because of the increased risk of breast cancer, stroke, and venous thromboembolism.

Denosumab, a monoclonal antibody against receptor activator of nuclear factor- κ B ligand, is a potent inhibitor of bone resorption that has been approved for the treatment of postmenopausal osteoporosis. In a recent RCT, twice-yearly administration of denosumab improved BMD 1 year after kidney transplantation compared to no treatment except for calcium and vitamin D [825]. Denosumab should not be used in patients with preexisting hypocalcemia until it is corrected. If denosumab is discontinued, alternative therapies, such as bisphosphonates, to prevent rapid bone loss and fracture are necessary.

Medical therapy to prevent post-LT osteoporosis can be discontinued at 1 year after LT if BMD is stable during the first year after transplantation, and if glucocorticoids have been withdrawn completely or reduced to doses of < 5 mg/ day. Considering that BMD begins to improve in the majority of recipients within 12 months of transplantation, long-term management may not be necessary, and 12 months of therapy may be adequate [826].

The treatment for patients diagnosed with osteoporosis prior to LT is similar to the treatment of osteoporosis in patients who did not undergo organ transplantation. Bisphosphonates are effective for patients with persistent osteoporosis years after solid organ transplantation, including LT [827–829]. Denosumab has also been associated with an increase in BMD among post-organ transplant osteoporosis patients in a small study [830].

[Recommendations]

- Osteopenic LT recipients should receive calcium and vitamin D supplements and perform regular weightbearing exercises (B1).
- Bisphosphonates are recommended for the prevention and treatment of post-LT bone loss and fractures (A1). If bisphosphonates are contraindicated or not tolerated, alternative treatments, including calcitriol (A1), denosumab (A1), and hormonal replacement therapies (A2) can be commenced. For preventive purposes, treatment for 12 months after LT is recommended if an LT recipient has osteopenia (A1).

Surveillance of DNM

DNMs represent a leading cause of late mortality in LT recipients, and they are reported to be the most common cause of death 10 years after LT [831]. The standardized incidence ratio (SIR) for individual malignancies has been estimated to range from 2.2 to 4.9 and includes the total risk of non-solid-organ cancers [832]. The risk of cancer

can vary significantly between different regions worldwide. The most common DNM reported in Western countries, predominantly in Caucasian populations, is non-melanoma skin cancer [833]. Moreover, other researchers have found that stomach cancer accounts for 25% of post-transplant DNMs in Korea [834, 835]. Despite having a greater cancer incidence, LT recipients have shorter life expectancies than those of the general population [836, 837].

Risk factors and surveillance strategies

General risk factors The following factors all influence individual risk factors for DNM in LT recipients: the underlying cause of the chronic liver disease (PSC and ALD), alcoholism, tobacco use, a history of pre-transplant malignancy, the type or duration or intensity of immunosuppressive medications taken, and viral infections [197, 833]. For post-LT patients, many screening criteria for DNM have been extrapolated from recommendations for the general population, although there are no studies on the cost-effectiveness of surveillance strategies post-LT.

Gastric cancer Patients who abuse alcohol have a 15-fold greater incidence of upper aerodigestive tract cancers [838]; therefore, in areas where the incidence of gastric cancer is high, such as in South Korea, annual screening for gastric cancer after LT may be needed [835]. To detect gastric cancer earlier, the EASL presently recommends an aggressive surveillance program [197].

Colorectal cancer (CRC) PSC patients with IBD are at a higher risk of CRC (up to 15% at 5 years) [197, 833]. LT recipients who have IBD should undergo a colonoscopy annually, accompanied by random biopsies [197, 803, 833]. Moreover, LT recipients without PSC may also have a higher incidence of CRC than the general population, according to some studies from both Eastern and Western countries [803, 839, 840]. According to a recent study, liver cancer patients with NASH who are older than 50 years may have an increased risk of CRC and may need earlier and more frequent screenings [840].

Skin cancer Skin cancers are the most prevalent forms of DNM post-LT in Western countries [197, 833]. Most of these malignancies are basal cell and squamous cell carcinomas, which are known to have little impact on survival [197, 833]. Skin type and prior sun exposure both affect skin cancer risk, with Caucasian transplant recipients having the highest risks [839]. Therefore, the AASLD, EASL, and ILTS guidelines recommend that patients who undergo LT stay out of direct sunlight and be screened by dermatologists [197, 803, 833].

Lung cancer Lung cancer is a common DNM. Low-dose CT (LDCT) enables early detection of lung cancer and reduces lung cancer mortality. Moreover, an intensive screening program for tobacco-related cancers in LT patients (particularly smokers) with LDCT has yielded promising results [841]. Therefore, LDCT screening should be implemented in high-risk patients after LT.

Head and neck or oropharyngeal, and esophageal Cancer The most common risk factors associated with head and neck, oropharyngeal, and esophageal cancers are smoking and alcohol abuse [841, 842]. Thus, many liver transplant hospitals now carry out screenings for head, neck, oropharyngeal, and esophageal cancers in patients with a history of cigarette smoking, especially those with a history of high-risk alcohol consumption [841].

Post-transplant lymphoproliferative disorder (PTLD) PTLD is one of the most serious complications of transplantation and is a consequence of therapeutic immunosuppression. With a SIR of 3.9-21, the general incidence of PTLD varies between 1.0 and 5.5% after LT [843]. Early-onset PTLD is defined as the development of PTLD within 2 years after LT, whereas all other cases are classified as late-onset PTLD [844]. Patients with early-onset PTLD are more likely to have EBV infection, while late-onset patients are more likely to be immunosuppressed [844]; moreover, recipient EBV seronegativity and the intensity of immunosuppression are among the key risk factors [845]. Monitoring EBV DNA levels in these high-risk recipients may be advantageous in the first year [833, 846]. Patients with rapidly rising EBV DNA levels may benefit from reduced immunosuppression and/or antiviral treatment [843]. However, most of these results have been obtained from studies that examined pediatric transplant recipients [847].

[Recommendations]

- All LT recipients must be informed that they have a higher risk of developing skin cancer compared with the risk in the general population and should be educated about skin protection and the need for regular examinations by a dermatologist (B1).
- All LT patients who are at risk of developing lung cancer must undergo LDCT chest imaging annually (B1).
- LT patients who have IBD should undergo colonoscopy annually, accompanied by random biopsies (B2).

General treatment strategies for DNM After LT

Lowering CNI in patients with DNMs following LT has been shown to lead to better outcomes. In LT patients with DNMs, mTOR inhibitors may be alternative agents for immunosuppression that has potential anticancer advantages [197, 803, 833, 848]. However, it is important to note that very few studies have examined the impact of switching to or introducing mTOR inhibitor-based immunosuppression on the prognosis of LT recipients with DNMs [849].

The surgical treatment of DNM should follow the general practice guidelines while considering the possible complexity of surgery in liver transplant recipients and the control of immunosuppression. Regarding patients with immunosuppression after LT, personalized optimization of systemic and radiation therapy should be designed to minimize expected toxicities. Additionally, the administration of immune checkpoint inhibitor therapy in LT recipients is related to an increased risk of graft rejection, graft loss, and mortality [850].

[Recommendations]

- It is advised that the doses of CNI be kept as low as possible in patients recovering from LT in order to reduce the risk of developing DNM (B1).
- mTOR inhibitors do not appear to increase the risk of cancer, and thus, these drugs can be used in CNI sparing or to minimize the dose of CNI regimens to prevent or treat DNMs following LT (C1).

Infection

Mycobacteria

Active TB in LT recipients usually occurs during the first year after LT and often results from the reactivation of LTBI [851]. Only less than 5% are donor-derived cases. LT recipients have an 18-fold increase in the prevalence of active TB compared with the general population [852]. Characteristically, approximately one-third to one-half of active TB cases after transplantation are cases of disseminated or extra-pulmonary TB, compared to only about 15% of cases in the general population [237].

Prior infection with TB, intense immunosuppression (especially T-cell depleting agents), DM, and coinfections with CMV, mycoses, *Pneumocystis jirovecii*, and Nocardia are well-known risk factors for the development of symptomatic TB after LT [853, 854].

The clinical manifestations of TB in LT recipients can differ from those in the general population [855, 856]. Fever is almost always present, particularly among those with disseminated disease, and constitutional symptoms (e.g., night sweats and weight loss) are also frequently observed. The lung is the most frequently involved site with varying radiographic findings, including focal or diffuse interstitial, infiltrates, nodules, pleural effusions, or cavitary lesions [855]. It is important to note that TB infection can involve diverse, unsuspected, and elusive sites and have various clinical symptoms and signs [857]. Therefore, a high index of suspicion is required for the timely diagnosis and treatment of active cases of TB after LT [858].

The standard treatment for active TB is a 4-drug combination of isoniazid, rifampin, pyrazinamide, and ethambutol for the first 2 months, followed by isoniazid and rifampin for an additional 4 months. If the identified mycobacterium TB is susceptible to other anti-TB agents, ethambutol can be discontinued. Fluoroquinolones are useful alternatives for LT recipients with hepatic dysfunction. Treatment regimen for TB should be selected considering the hepatic reserve of the recipient, after consultations with infectious disease specialists. Although its drug-drug interactions with CNIs, a rifamycin-containing regimen, is strongly recommended given its potent efficacy; moreover, rifabutin, which is known to have fewer drug-drug interactions can replace rifampin [851]. Approximately 50% of LT recipients may develop drug-induced hepatotoxicity with anti-TB agents; hence, careful monitoring is needed [857]. LT recipients with active TB have a fourfold increase in mortality rate compared with that of the general population [857]. The increased risk of mortality in active TB after LT was observed in patients who have disseminated disease or those who have had prior rejection or received OKT3 or anti-T-cell antibodies [855, 856].

The incidence of non-tuberculous mycobacteria (NTM) infections is uncertain, although it is estimated to be 0.04% in LT recipients [859]. The most common pathogens in NTM are *Mycobacterium abscessus* and *Mycobacterium avium complex*. NTM infection in the form of the pleuropulmonary disease is most prevalent, followed by disseminated disease; skin, soft tissue, musculoskeletal, catheter-associated, and lymphadenitis infections have been also reported [860–862].

A multidrug regimen is preferred for 3 months to 2 years to treat NTM infections in LT recipients. Secondary prophylaxis after NTM treatment is not routinely recommended due to the limited availability of data [859].

[Recommendations]

• Close monitoring for drug-drug interaction, druginduced hepatotoxicity, and graft rejection is important during anti-TB treatment in LT recipients (B1).

HIV

A study of LT recipients (2008–2018) from UNOS/OPTN reported that 0.6% of HIV-infected patients required LT, and this proportion has significantly increased over time [863]. Recently, non-viral liver disease, predominantly NASH and ALD, became the leading indication among HIV-infected LT recipients. This shift signifies the tremendous impact of DAAs,

increasing metabolic conditions, and the metabolic effects of ARTs, corticosteroids, and CNIs [864].

HIV-infected LT recipients treated with highly active antiretroviral therapy (ART) have no increase in the risk of opportunistic infections [865]. In general, ARTs used at pre-LT are maintained after LT, because they were effective in controlling viral replication [866]. No progression of HIV to AIDS after LT has been observed in previous experiences of liver and kidney transplantation in HIV-infected LT recipients [866]. LT in HIV-infected patients has complexities related to management of acute rejection and drug-drug interaction [867]. In particular, PIs, non-nucleoside reverse transcriptase inhibitors (NNRTIs), and pharmacokinetic enhancer such as cobicistat are affected CsA, Tac, and mTOR inhibitors. The use of once-daily single tablet combination regimens should be used with caution as many contain the pharmacokinetic booster cobicistat. If ART regimen in the HIV-infected LT recipient is not able to be modified to remove the PIs, NNRTIs, or cobicistat, dose adjustments of CNIs and mTOR inhibitors will be necessary [868].

HIV-infected LT recipients receiving ART should undergo regular assessment for viral loads of HIV and T lymphocyte subset counts [865]. In HIV-infected LT recipients, prophylaxis directed against Mycobacterium avium complex (MAC) is required when the CD4+T-cell count decreases to <75 cells per cubic millimeter [866].

Special consideration must be given to HIV/HCV coinfected LT recipients. First-generation DAA treatment became available in 2008; however, protease inhibitors require combination treatment with IFN and ribavirin, which have complex interactions in LT recipients, particularly with HIV [864]. In 2013, IFN-free DAAs were discovered, with cure rates approaching 100%, including in HIV-infected LT recipients. Moreover, advanced NS5A inhibitors enabled the combination treatment of DAA, ART, and immunosuppressants, resulting in fewer drug–drug interactions [864].

In the post-combination ART era, success in LT in HIVinfected patients with well-controlled infections has been reported in several studies [869–871]. LT recipients with HCV coinfection had significantly worse survival than those without HCV, and aggressive HCV recurrence has also been observed [870, 872–874]. Post-transplant HCV recurrence and fibrosing cholestatic hepatitis are significant issues in both the HCV mono-infected and HCV/HIV coinfected populations [875, 876]. However, the introduction of DAAs turned the almost inevitable fatal course into a curative outcome [877–879].

[Recommendations]

• HIV-infected LT recipients receiving ART need close monitoring of CNI levels, especially on regimens that include PIs (A1).

 Regular assessment for HIV viral loads and T lymphocyte subset counts is required in HIV-infected LT recipients receiving ART (A1).

COVID-19

The incidence and risk of infection with SARS-CoV-2 in LT recipients remain unclear [880]. A prospective study in a Spanish cohort of LT recipients reported that 111 LT recipients were diagnosed with COVID-19 during the Spanish outbreak from February 28 to April 7, 2020 [881]. Furthermore, 31.5% of patients met the criteria for severe COVID-19. The University of Washington registry of SOT recipients with COVID-19 showed a comparable risk of SARS-CoV-2 infection in LT recipients compared to that of the general population [882].

In the aforementioned prospective study in a Spanish cohort of LT recipients, the Charlson comorbidity index (RR = 1.28; 95% CI 1.05–1.56), male gender (RR = 2.49; 95% CI 1.14–5.41), dyspnea at diagnosis (RR = 7.25; 95% CI 2.95–17.82), and baseline immunosuppression containing MMF (RR = 3.94; 95% CI 1.59–9.74) were significant risk factors for severe COVID-19, particularly at doses higher than 1000 mg/day (p = 0.003).

Generally, fever is the first symptom in most patients; however, there may be only low-grade or no fever in LT recipients [883]. Dry cough, loss of olfactory and gustatory senses, fatigue, anorexia, nausea, nasal congestion, sore throat, myalgia, and diarrhea are other common symptoms [884]. COVID-19 may progress rapidly to acute respiratory distress syndrome in LT recipients because of their immunosuppressed status.

The imaging findings of COVID-19 have features that are like those of other viral pneumonia, including multiple ground-glass opacities, infiltrates, and lung consolidation. Compared with the general population, liver transplant recipients have more extensive, multiple, and lower lung lobes involvement [885].

The aforementioned study showed that LT patients were more likely to have significantly higher mean levels of creatinine, total bilirubin, and alkaline phosphatase compared to those of the general population [886].

Potential donors should be tested for the presence of the virus with a nasopharyngeal swab, and those who are positive should be deemed ineligible to donate [883]. Donors with a history of resolved COVID-19 or no known history of previous infection and a positive SARS-CoV-2 PCR should have consultations with infectious disease specialists [887, 888]. Recipients should be screened for SARS-CoV-2 using rapid PCR testing, and if found to be positive, transplantation may be delayed until after recovery from SARS-CoV-2 infection.

Scant data are available on the use and safety of medical therapy in COVID-19 [885]. When considering medical therapy in patients with COVID-19, LT recipients are at high risk of adverse events from drug–drug interactions, especially in patients receiving CNIs or mTOR inhibitors that require close monitoring [883]. Recent studies suggested the early administration of remdesivir significantly decreased hospitalization in organ transplant recipients without deleterious effect on allograft function or renal dysfunction [889–892].

Paxlovid is a promising agent in the fight against COVID-19; however, it can cause significant risks related to drug interactions in transplant patients, owing to the ritonavir component of paxlovid [893]. Therefore, the use of paxlovid should be avoided when close monitoring of CNI concentrations is not feasible (FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR PAXLOVID). If paxlovid and CNIs are co-administered, dose adjustment and monitoring for concentrations and adverse reactions are recommended. Concomitant use of EVR, sirolimus, and paxlovid should also be avoided.

In LT recipients without COVID-19, prophylactic reduction in immunosuppression is not recommended [894]. If LT recipients are infected with severe or rapidly progressing COVID-19, reducing the overall level of immunosuppression should be considered, particularly antimetabolite dosages [882, 885].

Generally, patients with transplants have a high risk of COVID-19 morbidity due to immunosuppression, a lack of response to vaccination, and comorbid conditions [893]. A retrospective, multicenter study demonstrated a significantly higher risk of hospitalization in LT recipients compared to the risk in the controls [886]. However, the risk of mortality, thrombosis, and ICU requirement were comparable between the two groups. In the aforementioned prospective study, the mortality rate in LT recipients was 18% (standardized mortality ratio = 95.5%; 95% CI 94.2–96.8), which was lower than the rate in the matched general population.

[Recommendations]

- All recipients and donors should be screened for SARS-CoV-2 using rapid PCR testing, and if found positive, transplantation may be delayed until after recovery from SARS-CoV-2 infection. (B1)
- In post-transplant patients with COVID-19, consider lowering the overall level of immunosuppression. (C1)
- Closely monitor the drug levels of immunosuppressants when administered together with COVID-19. (B1)

Immunization

Infection in LT recipients results in markedly increased morbidity and mortality, and antimicrobial therapy is often less effective than in the immunocompetent host [895]. There are some concerns that vaccination might trigger rejection; however, many studies have shown no causal association between vaccination and organ rejection [896].

It is common to wait for at least 3–12 months after LT before administering vaccines once maintenance of immunosuppression has been achieved [238]. Only influenza vaccination is an exception during influenza outbreaks. It is recommended to give the inactivated influenza vaccine as early as 1–3 months after LT [897]. It is recommended to wait at least 1 month after LT to be vaccinated for COVID-19, preferably with the mRNA vaccine [240]. Recent studies have reported that the recombinant zoster vaccine is safe and effective for varicella-seronegative transplant recipients [898–900].

Live vaccines are generally contraindicated after LT. Administrating live vaccines such as measles, mumps, rubella, and varicella vaccine prior to transplantation is recommended in general. However, recent studies on pediatric LT suggest that live virus vaccinations, such as the varicella vaccine, measles, mumps, and rubella, might be safe after LT [901–903]. Larger-scale studies should be performed to evaluate the effectiveness of live virus vaccination in relation to immunosuppression, because there is concern that immunization with live virus vaccines may result in adverse events due to the proliferation of attenuated vaccine strains.

In TB-endemic Asian countries, Bacille Calmette-Guérin (BCG) is routinely administered at birth as part of the global Essential Program on Immunization for the prevention of TB. When given to infants with no previous exposure to mycobacteria, BCG demonstrates a 70–80% effectiveness against all forms of TB when administered at birth [904]. However, its efficacy is significantly lower when used as a primary vaccination for older children and adults. Therefore, live *Mycobacterium bovis* BCG vaccination is not recommended for the recipients after LT. Once immunosuppression has been initiated, it is essential to be vigilant for symptoms of possible TB disease and regularly screen the individual's history for any potential new exposures to TB.

It is also recommended to periodically monitor hepatitis B surface antibody (anti-HBs) titers after 4 weeks from the last dose of vaccine. Revaccination can be done in nonresponders or those with anti-HBs < 10 IU/mL. Monitoring total anti-HAV is indicated only if ongoing risk for exposure (*e.g.*, planned travel to high-risk area). If recipient had no tetanus booster in the past 10 years, Tdap vaccination is recommended after LT. Vaccinations which are routinely recommended for general population should be administered if possible [238].

[Recommendations]

• Influenza vaccine (annually) and pneumococcal vaccine (every 5 years) after LT are recommended for re-immunization (B1).

Drug-induced liver injury

Due to the frequent use of multiple medications to prevent rejection and treat comorbid conditions, such as infections, LT recipients are at an increased risk for developing druginduced liver injury (DILI). However, the precise diagnosis of DILI in LT recipient is challenging because it requires ruling out all possible causes of graft dysfunction and there is currently no specific tool to assess the causal relationship between drug use and liver injury.

In one retrospective study, 29 (1.7%) cases of DILI were identified in 1689 LT recipients [905]. DILI was diagnosed based on the presence of all required clinical criteria and liver histology findings consistent with DILI. The median duration of drug use prior to the diagnosis of DILI was 57 days and the majority of cases occurred within the first 150 days after LT. Among patients diagnosed with DILI, 52% were female and the severity of DILI was mild or moderate in 92% of cases. Antibiotics (48%) were the most common cause, followed by immunosuppressants (14%), lipid-lowering agents (7%), and antivirals (7%). However, according to another retrospective study in China, which included 131 cases of biopsy-proven DILI, antifungal drugs were the most common cause of DILI (29%) [906]. This discrepancy may result from the differences in the diagnostic criteria for DILI and the method used to identify the causative agent. In addition, considering that mild to moderate DILI is likely to be underreported, the incidence of DILI in actual clinical practice may be higher.

When DILI is suspected in LT recipients, an initial screening for hepatotoxic drugs is required. In addition to the dose and duration of the treatment, the time interval between treatment initiation and the development of laboratory abnormalities and/or clinical symptoms should be considered. Subsequently, it is necessary to rule out potential causes of graft dysfunction, including rejection, recurrence of underlying disease, ischemic injury, opportunistic infections, and vascular/biliary complications [907]. This procedure should be accompanied by Doppler ultrasound of the graft and measurement of immunosuppressive agent levels. Lastly, drug-drug interactions (DDIs) should be taken into account. DDI between immunosuppressants and other commonly prescribed agents in LT recipients may induce liver injury, either by increasing the toxic impact of a drug or by decreasing the immunosuppressive effect, resulting in rejection [907]. Especially, statins and anti-HCV, anti-HIV, and anti-tuberculosis agents must be administered with special

caution for DDIs [851, 908–911]. If DILI is strongly suspected after the above steps, a definitive diagnosis can be made by withdrawing the suspect drug and observing the recovery of liver function. In uncertain situations, a liver biopsy should be considered to confirm the diagnosis.

[Recommendations]

When DILI is suspected in an LT recipient, screening for hepatotoxic agents, exclusion of other causes of graft dysfunction, and consideration of DDI with immunosuppressive agents are required. (B2).

Reproductive health and pregnancy

LT improves gonadal function in female with end-stage liver diseases and provides a greater probability of achieving pregnancy [912]. After LT, menstruation can occur as early as after 1–2 months, with 70–95% of patients experiencing normalization within a year [913–915]. However, anovulation and gynecological pathologies can occur after LT when an imbalance between progesterone and estrogen persists [916].

LT improves several factors that affect sexual function; however, it has limited efficacy in restoring pre-transplant sexual dysfunction [917, 918]. In male patients, free testosterone levels increase after LT, but the recovery of gonadal function is incomplete in some patients [918].

Pregnancy after LT

A report from a US registry that assessed pregnancy outcomes in solid organ transplant recipients reported that > 2 years of the transplant-to-conception interval was associated with reduced rates of low birth weight (LBW), rejection, and graft loss [919]. Another study demonstrated increased risks of prematurity, LBW, and acute cellular rejection (ACR) in recipients who conceived within 1 year after LT [920]. Therefore, delaying conception for at least 1 year after LT is recommended.

A higher rate of maternal risks, including hypertension and pre-eclampsia, but comparable maternal death rates following pregnancy in female LT recipients compared to those of the general population, have been reported [921]. In addition, high-risk recipients who have complications after LT could often have a poorer prognosis; therefore, a delay in conception and close observation are required in those patients. Generally, a two-threefold increase in pregnancyinduced complications and death has been observed in LT recipients [922].

Maternal outcomes Maternal death rates have been reported to be comparable in LT recipients when com-

pared with those of the general population, with death rates of 0-1% [922, 923]. In previous studies, higher rates of PIH in the LT recipient group versus the control group (16–30% vs. 9%) were reported [922, 924]. The reported rates of pre-eclampsia were 7–12%, which have gradually decreased over time as a result of better management of immunosuppression and risk factors associated with pre-eclampsia [925–927].

The reported rates of graft rejection in pregnant LT recipients are highly variable, ranging from 0 to 20% [920, 922, 928, 929]. Rates of postpartum graft rejection range from 3 to 12% [920, 928, 930, 931]. Graft loss during pregnancy due to the ACR is rare, but graft loss after delivery due to recurrent AIH and chronic rejection has been reported [930].

The rate of gestational diabetes (GD) in pregnant LT recipients varies between 0 and 11% [920, 923, 924]. A North American population-based study demonstrated that the GD rate was significantly higher in the LT recipients than in the general population (8.6% vs. 5.4%, respectively) [923]. The rates of antepartum hemorrhage were comparable between those of LT recipients and the general population; however, postpartum hemorrhage was significantly more prevalent in LT recipients when compared with controls (8% vs. 3%) [922].

The frequency of infections during pregnancy was comparable between LT recipients and the general population [922, 932]; however, urinary infections were more frequent during pregnancy in LT recipients compared with non-LT recipients (5.3% vs. 1.4%) [923]. Consequently, pregnant LT recipients are high-risk patients and should be managed by a multidisciplinary team that includes experienced obstetricians and transplant physicians.

Fetal outcomes The live birth rate in pregnancies of LT recipients is 65% and has increased over time probably due to the intensive care for high-risk patients and decreased rate of unplanned pregnancies [920, 931, 933]. The rate of spontaneous abortions in LT recipients ranges from 11 to 19% [920, 928, 931]. In pregnant LT recipients, a stillbirth rate of 0–1.2% has been demonstrated in most studies [927, 928, 934].

Preterm birth is common in LT recipients, with reported rates ranging from 14 to 53% [920, 931, 933]. A previous study reported a rate of 39% in LT recipients, which is much higher than the rate in the general US population (14%) [924].

A meta-analysis showed a significantly lower mean birth weight in LT recipients (2866 g) than in the general US population (3298 g) [924]. Rates of intrauterine growth restriction (IUGR) in LT recipients vary between 5 and 20%, and some studies have demonstrated that IUGR rates in LT recipients are statistically more frequent when compared with those of the general population [934–936].

Recurrent CMV infection in female patients who receive immunosuppressive therapy has been reported to cause congenital CMV infections [937]. This can result in serious fetal complications, including hydrops fetalis, stillbirth, mental retardation, visual or hearing loss, prematurity, or death, if untreated [938].

Low rates of congenital abnormalities in children of LT recipients, with rates ranging from 0 to 4%, have been reported [919, 922, 930, 939]. Furthermore, there is no clear evidence that the malformation rate is different between LT recipients and the general population.

[Recommendations]

• Pregnancy should be delayed for at least 1 year after LT and should be attempted when patients have stable allograft function, are on maintenance doses of immunosuppression, and have no serious complications (A2).

Immunosuppression during pregnancy

For female LT recipients who wish to become pregnant, the choice of immunosuppression should be made after discussing the effects of immunosuppression on the mother and fetus. Considering the benefits of immunosuppression in maintaining graft function during pregnancy, the maintenance of immunosuppressive therapy is generally recommended. Recently published systematic literature reviews by the European League Against Rheumatism showed the compatibility of AZA, CsA, Tac, and glucocorticosteroids in pregnancy and lactation [940]. However, AZA should be avoided, if possible, because of the increased risk of auditory nerve agenesis in children [941]. MMF is a confirmed teratogen that is associated with an increased rate of spontaneous abortion and congenital malformations; therefore, it must not be used during pregnancy [942]. Tac appears to be effective in the maintenance of adequate immunosuppression during pregnancy [943]

Corticosteroids are safe during pregnancy [944, 945]. However, high-dose or prolonged administration of systemic corticosteroids during pregnancy could lead to the development of IUGR [946, 947]. CsA does not increase the risk of congenital malformations when compared with non-exposed patients; however, a moderate risk of IUGR exists [930, 948, 949]. Levels of CsA and Tac should be closely monitored with dose adjustments for the increased blood volume during the second half of pregnancy [920].

Several weeks of fluid retention and normalization after delivery can lead to changes in the levels of immunosuppressants in LT recipients. Therefore, repeated tests for immunosuppressant levels are required within a month of delivery [912]. International consensus has suggested that breastfeeding does not need to be an absolute contraindication for LT recipients [950]. Breastfeeding in patients with CsA is not contraindicated in clinical practice; however, the American Academy of Pediatrics has recommended against breastfeeding with CsA due to concerns regarding possible immuno-suppression in infants [951].

[Recommendations]

- Tac is safe and effective in the maintenance of immunosuppression, and CsA and prednisone can be used during pregnancy (B1)
- CNIs should be maintained at therapeutic levels throughout pregnancy (B1).
- MMF or mTOR inhibitors to be avoided in pregnancy (B1)
- Continuation of steroid is safe (A1)

Psychological distress

Major psychiatric illness, active drug use, and alcohol consumption are associated with low compliance and graft injury and are consolidated contraindications for LT [197]. The rate of recidivism in patients with polysubstance abuse disorders whose LT is nearly 27%, but it was not related to post-LT survival [952]. Alcohol use disorders are related to approximately a third of mood disorders [953, 954].

Depression is a common clinical problem in LT, with 15% of LT candidates having one or more depressive symptoms [955]. Anxiety and neuroticism were significant in 31.1% of LT candidates, and those were associated with worse psychosocial outcomes 1 year after LT [956]. In a prospective cohort study, depressive symptoms pre-LT were associated with a three- to fourfold decrease in the risk of graft failure and mortality [957]. On the other hand, another retrospective study reported that pre-LT depression was not associated with clinical outcomes in terms of graft rejection and mortality; however, patients on effective antidepressant therapy had a lower rate of ACR in comparison with those who are not on antidepressants [958].

A multidisciplinary team should help patients develop a positive attitude toward transplant and help recipients attain post-traumatic growth. A study showed that active coping, instrumental support, emotional support, and acceptance were significant predictors of post-traumatic growth [959]. A transplant is a stressful event, but at the same time, it can help patients become more confident and develop new adaptive strategies for managing difficulties in their lifetime.

In a study regarding long-term transplant outcome (10 years after LT), LT recipients with unsuccessfully treated depression had a substantially higher mortality rate of 68% compared to the rate in those who received effective antidepressants (48%) and in non-depressed patients (44%) [960]. Interestingly, efficient psychosocial treatments are

more closely related to patient survival than viral replication, MELD score, and donor age.

The coping strategy, which refers to all abilities used to face stressful situations, is the mainstay of psychosocial treatment for LT recipients. Patients should be encouraged to use action-oriented methods and avoid passive reactions that can negatively impact their prognosis [959, 961]. The aforementioned study revealed that active coping is a relevant predictor of a short duration of hospitalization after LT [962].

[Recommendations]

• Active psychosocial treatment is required in LT candidates who have psychological distress to improve the post-LT outcome (B1).

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12072-023-10629-3.

Acknowledgements These guidelines were funded by the organizing committee of the 31st Conference of the Asian Pacific Association for the Study of the Liver (APASL 2022). The authors want to express sincere appreciation to the transplant infection control committee of Korean Society of Transplantation for editorial supervision of contents related to infectious issues.

Author contributions D-SK contributed to design of work, drafting of the manuscript, and critical revision. Y-IY, BKK, JYP, JK, DHS, DJJ, YRC, J-HL, HJC, KTY, SYY, C-SP, D-GK, HWL, W-MC, YEC, W-HK, JR, JGL, YC, PSS, HAL, and JHK were involved in drafting of the manuscript and critical revision. AC, AK, SHB, MAM, SST, ZA, AS, SA, AA, AK, PR, RB, CP, KCL, JL, M-LY, JG, TT, S-YH, CCY, MR, HCL, MO, and SKS performed critical revision. JMY was involved in critical revision and funding. K-SS contributed to design of work and critical revision.

Funding These guidelines were funded by the organizing committee of the 31st Conference of the Asian Pacific Association for the Study of the Liver (APASL 2022).

Data availability This article does not have separate data to provide.

Declarations

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval Not applicable.

Informed consent Not applicable.

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