Chapter 60
Portal Hypertension and Liver Transplantation: Current Situation in Japan and Overseas

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Abstract Liver transplantation is the only curative treatment option for both portal hypertension and end-stage liver disease (ESLD). In Japan, 50–60 deceased-donor liver transplant (DDLTs) and 400–500 living-donor liver transplant (LDLTs) are performed per year. Spain is the most DDLT-active country, and South Korea is the most LDLT-active country, performing 52 times as many and 5 times as many liver transplants per capita than Japan, respectively. Managing portal hypertension, ascites, hepatorenal syndrome, and spontaneous bacterial peritonitis is the key for bridging the interim period in patients waiting for liver transplantation. The Baveno VI consensus workshop recommendation is an important strategy for portal hypertension patients. International ascites club guidelines are other crucial strategies for ESLD patients. For a successful liver transplantation, multidisciplinary approach is essential to manage patients during both pre- and posttransplant periods. Regarding post-liver transplant patients, although liver transplantation resolves portal hypertension, a small-for-size graft in LDLT, acute rejection, and recurrence of the original liver disease may lead to newly developing or recurring portal hypertension. Further studies are needed to develop a management strategy for portal hypertension in pre- and post-liver transplant patients.

Keywords Baveno VI consensus · International ascites club guideline · Deceased-donor · Living-donor · Liver transplantation

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60.1 Introduction

Portal hypertension, a hemodynamic abnormality resulting from cirrhosis, is linked to ascites, hepatic encephalopathy, and variceal bleeding. Liver transplantation is the only curative treatment option for both portal hypertension and end-stage liver disease (ESLD). For successful liver transplantation, multidisciplinary approach is essential to manage patients during both pre- and posttransplantation periods: hepatologists manage the underlying liver disease and evaluate liver function, endoscopists and radiologists control esophagogastric varices, transplant surgeons finally evaluate the indications for transplantation and perform the liver transplantation, anesthesiologists and intensivists manage patients during and immediately after transplantation, and infectious disease experts control infectious processes in immunosuppressed patients. In this chapter, we first describe the current status of liver transplantation in the world and in Japan. Next, we focus on cutting-edge trends in managing portal hypertension and characteristic complications in ESLD patients who are on the liver transplant waiting list.

60.2 Current Status of Liver Transplantation in the World and in Japan

The first human deceased-donor liver transplantation (DDLT) was performed in the early 1960s by Thomas Starzl in the United States (USA) [1], and these days DDLT is commonly performed worldwide, with the USA performing the most liver transplants of any country. As of July 18, 2016, there were 14,619 patients on the waiting list for a liver transplant in the USA, based on the Organ Procurement and Transplantation Network data [2]. In 2015, 6768 recipients received a deceased-donor liver, and 359 recipients received a living-donor liver. The second and third most active countries are China and Brazil, and the number of liver transplants in each of these countries exceeds that in any European country. The number of liver transplants in Brazil has doubled over the past 7 years and has increased from 949 in 2005 to 1756 in 2014 [3]. According to data collected by Eurotransplant, an international nonprofit organization responsible for encouraging and coordinating organ transplants in Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, the Netherlands, and Slovenia, 1707 patients were on the waiting list for a liver transplant at the end of June, 2016. In 2015, 1523 recipients in these countries received a deceased-donor liver, and 91 recipients received a living-donor liver [4]. In China, between 2000 and 2005, approximately 7477 transplants were performed, with 2970 transplants in 2005 alone [5]. During that period, sentenced convicts were the main organ source for transplantation. In 2010, China officially initiated a pilot program for voluntary organ donation to reduce the dependence on organs from executed convicts. Data from the China organ allocation and sharing system indicate that through September 17, 2011, 97 individuals donated organs, including 69 livers [6].

The first living-donor liver transplantation was attempted for a child by Raia and colleagues in Brazil in 1989, with the first successful case achieved by Strong and colleagues in 1990 [7, 8]. In 1992, Nagasue et al. reported the first pediatric LDLT in Japan [9]. Since 1994, when the Shinshu group reported the first successful adult-to-adult LDLT [10], the number of LDLT procedures for adult patients has increased around the world. Adult-to-adult LDLT is now an established treatment option for ESLD [10]. Approximately 400–500 liver transplants are performed per year in Japan. The number of patients on the waiting list for a DDLT in Japan on June 30, 2016, was 362. In 2015, 57 recipients received a deceased-donor liver [11]. In 2014, 418 recipients received a living-donor liver. Trotter and Cardenas considered that the low number of transplants performed in Japan is largely due to cultural prohibition against deceased-donor donation, as both Buddhism and Shintoism oppose deceased-organ donation. These views are slowly changing to a trend toward more acceptance [12].

LDLT is more common in Asian countries, and DDLT is the mainstay in Western countries. The liver transplantation activity per million population of each country is as follows [12]: DDLT activity in 2010 was 24.5 in Spain, 19 in Austria, 17 in the USA, 12.5 in Belgium, 11.5 in Italy, 10.5 in the UK, 9 in Germany, 8 in Brazil (2014), 7 in Australia, 6 in Korea, 5 in Hong Kong, 4 in Taiwan, and 0.47 in Japan (2015); and LDLT activity in 2010 was 0.7 in Spain, 3 in Belgium, 0.7 in Brazil (2014), 0.5 in Austria, 1.0 in the USA, 0.4 in Italy, 0.5 in the UK, 1.5 in Germany, 0.4 in Australia, 16 in Taiwan, 7 in Hong Kong, 17 in Korea, and 3.5 in Japan (2014) (Fig. 60.1). Spain is the most DDLT-active country and South Korea is the most LDLT-active country performing 52times as many and 5 times as many liver transplants per capita than Japan, respectively.

60.3 Allocation System

The Model for End-stage Liver Disease (MELD) score was initially developed to predict survival in patients with complications of portal hypertension undergoing elective placement of transjugular intrahepatic portosystemic shunts [13].

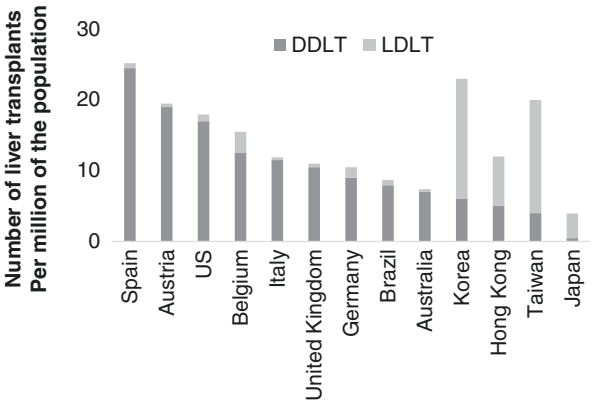

Fig. 60.1 The liver transplantation activity per million population of each country [12]. *US* United States, *DDLT* deceased-donor liver transplantation, *LDLT* living-donor liver transplantation

The MELD score is also an important stratification formula to predict the risk of death in patients on the waiting list for liver transplantation, and it has been used as a basic liver graft allocation system in the USA since 2002 [14]. The MELD score or a related system is now widely used for prioritizing ESLD patients on the liver transplant list. The MELD score is calculated based on the serum creatinine (mg/dL) and total bilirubin (mg/dL) concentrations, and the prothrombin time international normalized ratio. The pediatric end-stage liver disease (PELD) score, on the other hand, is calculated based on the albumin (g/dL) and total bilirubin (mg/dL) concentrations, the prothrombin time international normalized ratio, growth failure (based on sex, height, and weight), and age at listing. Allocation calculators are available on the following website "https://optn.transplant.hrsa.gov/resources/allocation-calculators/" [15].

Liver transplantation is less beneficial for patients with a MELD score of 15 or less [16]. Mortality risk of waiting list candidate and posttransplant recipient was studied among a cohort of 12,996 adult patients placed on the waiting list between 2001 and 2003. The recipients' mortality risk during the first posttransplant year is much higher for patients with lower MELD scores than for waiting list candidates (HR = 3.64 at MELD 6–11, HR = 2.35 at MELD 12–14; both $p < 0.001$) [16]. In Japan, the original scoring system based on the Child-Pugh score is used to stratify ESLD patients. The Japanese Liver Transplant Society is scheduled to begin using the MELD score to evaluate liver transplant candidates in 2018, which will make their allocation system more consistent with global standards.

60.4 Management of End-Stage Liver Disease Patients While on the Waiting List

60.4.1 Portal Hypertension

Managing portal hypertension is the key for bridging the interim period in patients waiting for a liver transplant. Generally, varices are present in 30–40% of compensated cirrhotic patients and 80% of decompensated cirrhotic patients. Varices have a similar prevalence rate in cirrhotic patients on the liver transplant waiting list to common cirrhotic patients [17]. A limitation of the predictive ability of MELD for transplantation patients is the clinical comorbidity of varices and variceal bleeding. Variceal bleeding remains an important cause of death in ESLD patients on the waiting list. Focusing on relation to Child-Pugh classification, gastroesophageal varices are present in approximately 40% of Child-Pugh A patients and 85% of Child-Pugh C patients [18]. Of patients with a low MELD score (<=20) on the waiting list for a liver transplant, 76% had varices and 39% died due to variceal bleeding [19]. There is still no worldwide consensus on the management of portal hypertension in patients waiting for a liver transplant. Cardenas and Gines made recommendations for prophylaxis against variceal bleeding in patients with cirrhosis awaiting

liver transplantation [20]. They classified the prophylaxis recommendations into primary and secondary practices (Table 60.1).

The Baveno VI consensus workshop developed recommendations for portal hypertension [21]. There were not many; however, liver transplantation was referred to in recommendation that related to Budd-Chiari syndrome or portal vein thrombosis. For example, Budd-Chiari syndrome/hepatic venous outflow tract obstruction should be managed according to a stepwise approach, including anticoagulation, angioplasty/thrombolysis, transjugular intrahepatic portosystemic shunt, and orthotopic liver transplantation at experienced centers (3b; B) (level of evidence from 1 = highest to 5 = lowest; grade of recommendation from A = strongest to D = weakest according to the Oxford System, [22]). Patients with a high prognostic index score (>=7) of Budd-Chiari syndrome with transjugular intrahepatic portosystemic shunt are likely to have a poor outcome, and thus orthotopic liver transplantation should be considered (3b; B), and liver transplantation should be considered in patients with manifestations refractory to the procedures (5; D). In terms of anticoagulation and portal vein thrombosis in cirrhosis, screening for portal vein thrombosis every 6 months is indicated for patients on the liver transplant waiting list (5;D). In this setting, the goal is to permit/facilitate liver transplant and reduce posttransplant mortality/morbidity, and anticoagulation should be maintained until transplantation to prevent rethrombosis (4; C). In untreated potential liver transplant candidates with portal vein thrombosis, follow-up with imaging every 3 months is recommended. Anticoagulation is recommended in case of progression (5; D). For patients who are not candidates for liver transplantation, there is currently no recommendation regarding anticoagulation treatment. Anticoagulation could be considered in selected cases (extension to superior mesenteric vein, known as a "strong" prothrombotic condition) (5; D). There were no other comments, however, regarding patients on the liver transplant waiting list.

Table 60.1 Recommendations for primary and secondary prophylaxis of variceal bleeding in patients with cirrhosis awaiting liver transplantation [20]

Primary prophylaxis
• Screen all patients on the waiting list with upper endoscopy
• No varices: No therapy indicated
But if the patients remain on the list, a repeat endoscopy should be performed in 1 year
• Small varices: Consider nonselective beta-blockers in patients with child B/C cirrhosis
• Medium/large varices: Beta-blockers or EVL may be used
Secondary prophylaxis
• Nonselective beta-blockers and EVL should be used for prevention of recurrent bleeding
• EVL should be done every 3–4 weeks until obliteration (approximately 3–4 sessions)
Surveillance endoscopy should be done 3 months after obliteration
• If previously on beta-blockers for primary prophylaxis, EVL should be added to drug treatment
Those previously treated with EVL and with no contraindication to beta-blockers should receive them
• TIPS is indicated in child A or B patients who rebleed despite combination therapy

EVL endoscopic variceal ligation, *TIPS* transjugular intrahepatic portosystemic shunt

The Japan Society for Portal Hypertension was established in 1994. With the increasing number of liver transplants being performed, the role of this society may become crucial. Collaboration between Japan and transplantation active countries may be the key to develop standardized protocols and procedures for managing portal hypertension in ESLD patients on waiting lists.

60.4.2 Ascites, Hepatorenal Syndrome, and Spontaneous Bacterial Peritonitis

In patients with severe cirrhosis, hepatorenal syndrome is the primary type of renal failure. Recent international ascites club guidelines recommend that patients with cirrhosis and ascites suspected of having an acute kidney injury should be managed as follows: (1) review drug chart—review of all medications, reduction or withdrawal of diuretic therapy, and withdrawal of all potentially nephrotoxic drugs, vasodilators, or nonsteroidal anti-inflammatory drugs; (2) plasma volume expansion in patients with clinically suspected hypovolemia; and (3) prompt recognition and early treatment of bacterial infections when diagnosed or strongly suspected. If no response after two consecutive days of diuretic withdrawal and plasma volume expansion with albumin, patients are diagnosed with hepatorenal syndrome, and treatment with a vasoconstrictor and added albumin are required [23]. Parenchymal renal disease is suspected when proteinuria exceeds 500 mg of protein/day and/or hematuria exceeds 50 red cells/high-power field [24]. Type 1 hepatorenal syndrome is defined as rapid progressive renal failure with doubling of the initial serum creatinine concentrations to a level greater than 2.5 mg/dL in less than 2 weeks. Type 1 hepatorenal syndrome has an extremely poor prognosis—less than 10% survival at 3 months [25]. Type 2 hepatorenal syndrome is defined as moderate renal failure (serum creatinine 1.5–2.5 mg/dL), with a stable or slowly progressive course. The prognosis of type 2 hepatorenal syndrome is also poor, with around 40% survival at 12 months [25]. Current guidelines recommend the administration of a vasopressin analogue in combination with albumin as the first-line therapeutic agent for hepatorenal syndrome [26]. The vasopressin analogue terlipressin is effective in approximately 40–50% of patients with hepatorenal syndrome. In Japan, the selective oral vasopressin V2 receptor antagonist tolvaptan is available to control ascites in patients with advanced cirrhosis.

Uncontrollable bacterial infection is considered a contraindication for liver transplantation and severe infection requires temporary removal from the waiting list. Spontaneous bacterial peritonitis accounts for 30% of the bacterial infections in cirrhotic patients. The 1-year survival probability after an episode of spontaneous bacterial peritonitis is only 40%. The diagnosis of spontaneous bacterial peritonitis is based on examination of the peritoneal fluid. When the polymorphonuclear count is greater than 250/mm, empiric antibiotic therapy is started. After successful treatment to stabilize spontaneous bacterial peritonitis, patients should be considered for liver transplantation as soon as possible.

60.4.3 Hyponatremia

Hyponatremia in ESLD is associated with a poor prognosis and a higher risk of hepatic encephalopathy. The MELD-Na score, which includes an evaluation of hyponatremia, is a new stratification formula to evaluate recipients for allocation [27]. Approximately 22% of patients with advanced cirrhosis and 50% of patients with refractory ascites or hepatorenal syndrome have serum sodium levels <130 meq/L. The selective oral vasopressin V2 receptor antagonist tolvaptan was reported to be useful for the treatment of hypervolemic hyponatremia [28]. Data regarding tolvaptan use in patients on the waiting list, however, are insufficient. Tolvaptan was temporarily approved in the USA for patients with cirrhosis and hyponatremia (serum sodium <125 meq/L), as well as for other conditions such as hypervolemic hyponatremia, but in January 2013, the US Food and Drug Administration warned of the potential risk of liver injury [29]. In Japan, the Ministry of Health, Labour, and Welfare approved tolvaptan for cirrhotic patients with ascites. Further studies are needed to clarify this issue.

60.5 Treatment of Portal Hypertension Post-liver Transplantation

In general, liver transplantation resolves portal hypertension. A small for size graft in LDLT, acute rejection, and recurrence of the original liver disease may lead to newly developing or recurring varices. Endoscopic surveillance may be important for patients who do not have an ideal postoperative course. Portal vein stenosis and thrombosis are uncommon complications after liver transplantation, with a frequency of around 3%. Occlusion of the portal vein immediately after transplantation has catastrophic consequences for the liver graft and leads to acute liver failure and eventually graft loss. Vascular stent placement into the portal vein is a favorable procedure for portal vein stenosis or thrombosis [30]. Although portal vein complications are asymptomatic in less than 50% of the cases, portal hypertension may cause various varices and require endoscopic treatment. There are several case reports regarding the management of posttransplantation shunt hepatic encephalopathy and the presence of a patent portosystemic shunt after liver transplantation due to portal occlusion or stenosis [31]. In one case report, a patient was successfully treated by placement of a self-expandable stent in the portal vein and the use of coils in the collateral veins. Although the portal vein was patent, the existence of portosystemic collaterals pretransplantation caused hepatic encephalopathy 10 months after transplantation despite a normal functioning liver graft. The patient was successfully treated by embolization of a large portosystemic shunt between the superior mesenteric vein and both gonadal veins [32]. In another case, a liver transplant recipient was successfully treated with percutaneous transhepatic coil embolization for the rupture of ectopic jejunum varices without portal

hypertension [33]. Further studies are needed to develop a management strategy for portal hypertension in post-liver transplant patients.

60.6 Conclusion

The world's longest-surviving liver transplant patient has lived for 42.7 years [34]. With the increasing number of both pre- and post-liver transplant patients worldwide, adequate management of portal hypertension and related diseases, refinement of the allocation system, and cooperation between specialists are essential for providing a favorable transplant outcome for patients with ESLD.

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