advance, unlike in deceased donor LT (DDLT). Nutritional therapy, as well as rehabilitation at the time of referral of a potential recipient, should start a few months before LT to most effectively increase the SMM and BCM [7].

For adult recipients preparing for LDLT, Kaido et al. [10, 12] described a detailed preoperative nutritional therapy regimen. This regimen starts approximately 2 weeks before LDLT after the BIA assessment. The therapy consists of the following three components: a nutrient mixture enriched with BCAAs (Aminoleban® EN; Otsuka Pharmaceutical Co., Tokyo, Japan) or BCAAs nutrients (Livact®; Ajinomoto Pharma Co., Tokyo, Japan) as a late evening snack; synbiotics using a supplementation product enriched with glutamine, dietary fiber and oligosaccharide (GFO®; Otsuka Pharmaceutical Factory, Tokushima, Japan) three times daily, and a lacto-fermented beverage containing 5×10^8/mL of *Lactobacillus casei Shirota* strain (Yakult 400®; Yakult Honsha Co., Tokyo, Japan) once a day via feeding tube or orally until discharge. Additionally, patients with a low serum zinc level receive 1.0 g/day of polaprezinc (Promac D®; Zeria Pharmaceutical Co., Tokyo, Japan).

Dietitians should adjust the type and amount of food for each patient to maintain a total caloric intake at least 1.2 times the BEE (approximately, 35–40 kcal/kg and a protein intake of 1.2–1.5 g/kg), including BCAAs nutrients (scaled according to the degree of hepatic decompensation), adherent to the ESPEN guidelines [11, 41, 42]. Of the total non-protein energy requirements, 60–70 % should be administered as high-complex and simple carbohydrates, whereas lipids should make up the other 30–40 %. In malnourished patients, a daily energy intake of 50 kcal/kg is required for caloric repletion [25]. Excess calories should be avoided, as this promotes hepatic lipogenesis, liver dysfunction and increased carbon dioxide production, leading to increased work required for breathing [25, 43, 44].

Route of nutritional support

Enteral nutrition (EN) with a gastric or jejunal small-bore feeding tube is the preferable route of delivery of nutrition for all patients who are not able to maintain adequate oral intake so that they can still benefit from topical nutritional factors in the gut, and to maintain the integrity of the gastric mucosa and gut barrier. It is also less costly, being associated with fewer complications and a decreased hospital length of stay compared with parenteral nutrition (PN), which carries a risk of infection, fluid overload and electrolyte imbalance [45].

Enteral nutrition provides antigenic stimulation to the gut-associated lymphoid tissue and is a stimulus for biliary secretion of immunoglobulin A [11, 46]. These factors help to maintain the barrier against the translocation of luminal bacteria to the portal circulation, thus decreasing infectious complications, as indicated by the differential urinary excretion of carbohydrates of varying molecular weights [11, 46].

With EN, excessive feeding will lead to intolerance, causing diarrhea, bloating and vomiting. Because the gut provides a "gate-keeper" role, major complications related to excessive tube feed administration are generally kept to a minimum. However, with PN, there are no means of regulation, and the patient is forced to assimilate the entire substrate load [11, 45].

Feeding tubes do not increase the risk for esophageal variceal hemorrhage, but may be associated with an increased risk of epistaxis, sinusitis, impaired gastric emptying and tube feeding-associated diarrhea on long-term use, as well as with tube retraction, clogging and small intestinal obstruction. However, complications related to malpositioned feeding tubes are usually preventable if care is taken to ensure correct initial placement and by regularly monitoring the position [11, 47].

The indications for PN use in liver disease have recently been reviewed and published by the ESPEN for patients with fulminant hepatic failure and coma, and for patients who are moderately or severely malnourished and cannot achieve adequate caloric intake, either orally or through EN due to gastrointestinal dysfunction, such as esophageal bleeding, ileus or intestinal obstruction [41, 48]. Given the low glycogen stores in patients with liver disease, it is important to provide a glucose infusion in patients who require fasting and are not able to take oral nutrients or EN for more than 12 h [41, 42]. The use of "standardized" formulas should be restricted to stable patients with no fluid overload who need only maintenance fluid administration [48].

Considerations for carbohydrate supplementation

Glucose infusion should supply 2–3 g/kg body weight per day of glucose. The administration of glucose in excess will result in severe hyperglycemia, lipogenesis and increased carbon dioxide production [48, 49]. Patients with liver failure can have alterations in glucose homeostasis; therefore, careful monitoring of the serum glucose level is needed to avoid complications associated with hyperglycemia [49].

Considerations for lipid supplementation

Patients with advanced LC have decreased plasma levels of essential fatty acids and their polyunsaturated derivatives, such as arachidonate, that have been associated with lower survival. These are cell membrane components and

precursors of a wide array of biologically active compounds [24, 50].

Because fat is important for the nutrient repletion of malnourished patients, dietary fat should not be restricted unless true fat malabsorption has been diagnosed using a fecal fat test. Medium chain triglycerides, an alternative form of fat not requiring bile salts for absorption, can provide a concentrated source of calories to patients with fat malabsorption, and are available in both EN and PN formulations [24, 50].

Clinical essential fatty acid deficiency takes approximately 5–6 weeks to develop without linoleic acid or linolenic acid intake, so it is not likely to become an issue for most patients with liver failure except in those who are severely malnourished. Therefore, a short course of "fat-free" total parenteral nutrition (TPN) can be used in most patients [24, 51].

Many EN formulas provide a wide range of lipid dosages, from a variety of sources, for fatty acids. When prescribing TPN, many hospitals compound "three-in-one" TPN solutions containing amino acids, dextrose and lipids. The minimum lipid dose in such combinations should be 20 g/L or 2 % of the final concentration. More dilute lipid formulas are unstable in the presence of hypertonic dextrose and amino acids, resulting in separation of the lipid emulsion into oil and water [51].

A large dose of PN lipid can result in reticuloendothelial system blockade, which aggravates the infection risk and is exacerbated by rapid "piggyback" infusion techniques, and is ameliorated by slower continuous infusion. Lipid administration should not exceed 1 g/kg per day using the pre-hospital dry weight, and should be given over a period of 24 h if possible [50, 52].

Considerations for protein supplementation

Hyperammonemia results from the production of ammonia in the gut and kidneys and the decreased breakdown by the liver and skeletal muscle, which is caused by sarcopenia in malnourished patients with liver disease. It is well known that ammonia is directly toxic to brain astrocytes. This effect definitely contributes to HE. In addition, inflammation, infection and oxidative stress also play a role [53].

The protein intake should not be limited, as this may aggravate protein deficiency, and improvement in the nitrogen balance may be achieved without aggravating HE [54]. Supplementation with vegetable-sourced, rather than animal-sourced protein may be advantageous [55].

In practice, whole-protein formulas are generally recommended, and BCAA-enriched formulas should be used in patients who develop HE during re-feeding. The protein intake should be at least 1 g/kg/day initially, and then the 24-h urinary urea nitrogen level can be measured to assess the catabolic rate in patients with normal renal function. Further increases in protein intake can be adjusted accordingly. Progressive increases in protein supplementation should be implemented, up to 1.8-2.0 g/kg/day, as tolerated [52, 55].

Branched-chain amino acid supplementation

Branched-chain amino acid supplementation (leucine, isoleucine and valine) are not metabolized by the liver, and thus are preferentially used as amino acid sources in patients with liver failure. On the other hand, aromatic amino acids (AAAs) (phenylalanine, tryptophan and tyrosine) are not metabolized effectively in patients with liver failure, and thus accumulate [55–57]. The expected ratio, the so-called Fisher's ratio, or the BCAAs/tyrosine ratio (BTR) should be 3.5:1; however, this ratio often falls to 1:1 in patients with ESLD, allowing preferential transport of the AAAs to occur across the blood–brain barrier [56]. The AAAs are then metabolized to octopamine, phenylethylamine and phenylethanolamine, which are weak false neurotransmitters that inhibit the excitatory stimulation of the brain, competing with endogenous neurotransmitters, thus aggravating HE [56, 57]. In addition, tryptophan is metabolized to 5-hydroxytryptophan (serotonin), which can produce further lethargy [56, 57]. There has been a debate on the use of BCAA-enriched versus standard amino acid formulas [58–60] based on the hypothesis that a decreased BTR contributes to HE [61]. However, the ESPEN guidelines do not recommend using specialized formulas [41, 42].

Branched-chain amino acid supplementation induce the secretion of hepatocyte growth factor and glutamine production [62, 63]. Leucine activates the mammalian target of rapamycin signaling pathway, thus inhibiting protein degradation and activating glycogen synthase [7, 12]. Shirabe et al. [64] reported that preoperative oral BCAA supplementation reduced the incidence of post-transplant bacteremia and sepsis in LDLT patients. Nakamura et al. [65] reported that the phagocytic functions of neutrophils and killer lymphocytes obtained from LC patients were restored by oral BCAAs supplementation.

Recently, a pre-LT BCAA-enriched formula has been demonstrated to lower ammonia, and to improve the albumin and prealbumin levels, the total lymphocyte count, BTR, glucose intolerance, liver regeneration, immune system function, maturation of dendritic cells and the ability of peripheral blood mononuclear cells to proliferate in response to mitogens, thus preventing post-operative sepsis [7, 64, 66].

The initiation of oral BCAAs in patients in the early stage of liver disease may contribute to solving current LT problems, such as the donor shortage, and the availability

of only small liver grafts for patients awaiting LDLT. The use of oral BCAAs might also play a role in improving the post-LT mortality by preserving the hepatic reserve of scheduled liver transplant recipients [67, 68].

Micronutrient supplementation

Patients with ESLD are susceptible to severe deficiencies in folate and pyridoxal-5′-phosphate, the biologically active vitamin B6. Thiamine liver stores are depleted in alcoholic and hepatitis C-related LC [70, 71]. This depletion is associated with increased brain ammonia concentrations due to decreased activity of α-ketoglutarate dehydrogenase, a rate-limiting tricarboxylic acid cycle enzyme [69, 70]. Deficiencies in antioxidant micronutrients (selenium, vitamin E, vitamin C) are related to oxidative stress, which is common in such patients [71].

A typical feature of alcoholic liver disease is an increasingly severe reduction in hepatic vitamin A stores, which sometimes leads to infertility and night blindness [71–73]. In vitamin A-deficient cirrhotic patients, the supplementation of vitamin A, even at relatively moderate doses, may further aggravate liver injury, since high-dose vitamin A preparations may be hepatotoxic due to their polar retinoid metabolites, which cause hepatocellular apoptosis and may promote fibrogenesis [72, 73].

Magnesium and zinc deficiency are also common in patients with decompensated LC due to their decreased absorption and diuretic-induced increased urinary excretion [32, 33]. Clinically, zinc deficiency presents with alterations of smell and taste, alterations in protein metabolism and encephalopathy. Zinc supplementation improves the glucose intolerance and decreases the ammonia levels [32, 33, 74].

Bitetto et al. [75] observed that vitamin D may act as an immune modulator in LT, favoring the immune tolerance of the liver allograft. In addition, Bitetto et al. found that early vitamin D supplementation was independently associated with a lack of acute rejection, which is important, because low vitamin D levels are prevalent among LT candidates.

On the other hand, an excess of micronutrients can also be dangerous. Serum ferritin is associated with increased body iron, or can be a consequence of systemic necroinflammatory states. The level of serum ferritin can therefore serve as a predictor of mortality in LC patients [76].

Correction of liver osteodystrophy

Osteopenia and osteoporosis are highly prevalent in patients with ESLD, and represent a major cause of morbidity before and after LT [77]. These can be caused by hormonal changes in parathormone and calcitonin, increased circulating levels of bilirubin and cytokines, corticosteroids, and the use of immunosuppressive therapy in cholestatic diseases [78, 79]. Ingestion of alcohol can directly and indirectly promote bone loss; however, a poor diet, physical inactivity and the degree of liver insufficiency further contribute to the deterioration of bone [77, 78].

LT candidates should be encouraged to consume foods high in calcium and vitamin D. If consumption is low, calcium and vitamin D supplementation (1,200–1,500 mg/day) is highly recommended for patients with osteopenia, and should be given in combination with bisphosphonates for patients with established osteoporosis and/or a history of fractures. If steatorrhea is diagnosed, water-miscible forms of fat-soluble vitamins, including vitamin D, should be prescribed [79].

Protein metabolism generates a large amount of acid, which must be buffered by the skeleton and kidneys. The skeleton responds to high serum acidity by releasing a buffering agent, calcium, into the bloodstream, activating bone resorption. With more calcium entering the bloodstream, the kidneys respond by increasing urinary excretion, resulting in a net loss of calcium. There is also a link between high-fat diets and bone loss, as fat is suggested to inhibit osteoblast formation [77, 78].

Over-supplementation and the physical rehabilitation program

Patients with liver diseases commonly suffer from morbid obesity because of continued oral intake, along with the limitations in physical activity that are often recommended due to fear that exertion would hasten the progression of ESLD or worsen the complications. However, exercise has been documented to have no significant adverse effects on liver function tests or on symptoms. In fact, the adverse effects of inactivity and bed rest may not only worsen the complications of reduced physical functioning, muscle wasting and osteopenia, but may also be linked to decreased post-LT success [80, 81].

Obesity is also considered to be a predictor of hepatic steatosis in deceased [82] and living donors [13]. A fatty donor liver is strongly linked to decreased allograft function and decreased patient survival [83], and the presence of a fatty liver is the main reason for the discarding of potential donor livers [82]. Pre-LT obese patients may be more likely to have primary graft dysfunction or delayed graft function after LT [84, 85]. Weight loss is used to reduce the amount of liver fat among obese patients [84].

Dietitians need to resist the temptation to reach the impractical goal of producing anabolism. Attempts to replete the malnourished, metabolically stressed, pre-LT patient in excess of the patient's energy expenditure lead to

hyperglycemia and an increased incidence of infection. The goal of nutritional support for a patient with liver failure is to provide adequate protein and energy that is equivalent to, or slightly less than, the patient's energy expenditure. Therefore, energy restriction to 1,500 kcal/day is routinely used to encourage the mobilization of native fat stores [86].

Recently, a rehabilitation program has been introduced to encourage early post-operative mobilization and avert pulmonary dysfunction. Because LDLT is an elective procedure that differs from DDLT, a pre-LT rehabilitation program can be implemented until the day of LT [7].

Immunonutrition

The use of an immunomodulating diet (IMD) as a part of EN or PN is based on its downregulation of inflammatory cytokine production, its modulation of eicosanoid synthesis and its amelioration of post-LT immunosuppression, rather than its effects on nutrition per se [87, 88].

Glutamine dipeptide, arginine, nucleotides and ω-3 fatty acids (fish oil emulsion) intake have been suggested to minimize the ischemia or reperfusion damage of the donor organ [11, 64, 89]. Arginine stimulates the release of growth hormone and insulin, improves the nitrogen balance, promotes wound healing, strengthens immune function and enhances nitric oxide biosynthesis [87].

An IMD enriched with hydrolyzed whey peptide (HWP) (MEIN®; Meiji Dairies Co., Tokyo, Japan), which is a protein complex derived from milk, has been proven to decrease post-LT bacteremia, infections and mortality compared with a conventional elemental diet [90]. These benefits have been attributed to the antioxidant, antihypertensive, antiviral, antiinflammatory and antibacterial properties of HWP because it is rich in lactoferrin, β-lactoglobulin, α-lactalbumin, glycomacropeptide and immunoglobulins [11, 91]. Lactoferrin protects against the development of hepatitis caused by the sensitization of Kupffer cells by lipopolysaccharide, and inhibits the production of inflammatory cytokines, such as TNF-α, IL-1β and IL-6, by monocytes [4, 7, 74].

The considerable amount of steroids administered to patients after LT, as well as surgical diabetes and insulin resistance, can cause intra- and post-operative hyperglycemia, which has been associated with surgical site infections [92]. An IMD enriched with HWP contains isomaltulose disaccharide (glucose plus fructose with a glycosidic bond). Isomaltulose is often used instead of sugar in diets for patients with diabetes mellitus, since it prevents post-prandial hyperglycemia due to slow resolution. An IMD enriched with HWP has been found to significantly decrease the incidence of post-LT hyperglycemia [90, 92].

Patients undergoing emergency LDLT for acute liver failure (ALF) have little time to receive nutritional intervention. Therefore, early EN with an IMD enriched with HWP could be a good method to prevent post-LT complications due to infections [90].

Use of synbiotics

The bacterial translocation occurring in LC patients is usually related to bacterial overgrowth, increased intestinal permeability and immune alterations, and leads to intestinal edema, decreased peristalsis and infection. It also contributes to the pathogenesis of a hyperdynamic circulatory state and multiple organ dysfunction via pro-inflammatory cytokine responses [12, 93].

Probiotics are living bacteria found in fermented beverages, yogurt and sauerkraut that foster a hostile colonic environment against "bad" bacteria. Prebiotics are non-digestible dietary fiber that pass unchanged through the gastrointestinal tract and nourish probiotics. Synbiotics are a combination of both of these materials [94].

Sugawara et al. [95] reported that preoperative oral administration of synbiotics can enhance the immune response, attenuate the systemic post-operative inflammatory response and decrease the occurrence of post-LT infection and the duration of antibiotic therapy. These benefits of synbiotics are attributed to the ability of *Lactobacillus* to initiate immunoglobulin production, restore macrophage function, stimulate apoptosis and modulate lymphocyte function. In addition, *Lactobacillus* has been reported to attenuate cytokine release, increase mucin production, eliminate toxins and stimulate mucosal growth [96].

Probiotics such as *Enterococcus faecalis*, *Clostridium butyricum*, *Escherichia coli* strain Nissle 1917, *Lactobacillus casei* strain Shirota, *Bacillus mesentericus*, *Lactobacillus* and *Bifidobacterium* with fructooligosaccharides can all alter the gut microbiota, prevent bacterial translocation, decrease endotoxin levels and restore neutrophil phagocytic capacity [94], since the neutrophil function is impaired by endotoxemia upon bacterial translocation in patients with LC [97].

Lower ammonia levels, significant rates of minimal HE reversal and good adherence by patients, with greater improvement in all neuropsychological tests, have all been observed upon the use of probiotics compared with the use of conventional lactulose [98]. Furthermore, lactulose treatment was associated with occasional abdominal pain, cramping, diarrhea and flatulence. Synbiotic supplements were free of such adverse effects [98–100].

Nocturnal meals

Periods of fasting should be avoided in cirrhotic patients. Frequent meals should be implemented to combat a

catabolic state during the overnight fasting period. For this reason, nocturnal supplementation with a small bedtime snack and nocturnal glucose supplementation increase the carbohydrate, along with decreased lipid and protein oxidation rates the next morning, without significant BEE changes, thus improving the nitrogen balance and total body protein gain, helping to prevent catabolic states and undernutrition [101–103]. It has been reported that nocturnal BCAAs administration as a late evening snack improves the serum albumin level and glucose tolerance in LC patients [103].

Nutritional support after liver transplantation (during the immediate post-LT period and short-term after LT)

Nutritional changes after liver transplantation

The total body water decreases and body fat increases after LT, whereas the BCM remains unchanged [104]. Deficiencies in vitamin A and zinc immediately normalize after LT [105, 106]. Although an increased BEE may persist for a long period after LT [105, 107], overweight status and hypercholesterolemia have been observed after LT [107], accompanied by an increase in the saturated fatty acid content of fat tissue [106].

In children, malnutrition and growth retardation are usually present in all cases before LT. Anthropometry derangement recovers as soon as 6 months after LT. Height recovery occurs later [108]. A marked catch-up growth is observed in the children with the most severe growth retardation before LT; however, some children experience failure to thrive even after LT [109].

The nutritional status after LT depends on the allograft function; if the allograft fails or is rejected, many of the nutritional derangements present before LT will persist. Even in a well-functioning graft, some nutritional disturbances are not completely normalized in the long term after LT. Increased protein breakdown is often present during the first 2 weeks post-LT; thus, optimizing the nutrient intake over this period is needed to promote wound healing and hepatocyte recovery [106, 110].

The goal of nutrition therapy in the acute post-LT phase is to ensure adequate protein and calorie provision to avoid protein breakdown [111]. Hypermetabolism has been found to be predictive of the transplant-free survival, independently of the MELD and Child-Pugh scores, and tends to persist for at least a year post-OLT [112].

Patients with ALF are generally well nourished and do not have a pre-hospital history of weight loss. Patients without protein-calorie malnutrition will tolerate 5–6 days of NPO before needing nutritional support. Malnourished patients should start nutritional support sooner. Withholding nutritional support and inducing a cumulative caloric deficit of over 10,000 kcal has been associated with decreased survival [86].

Resuming EN within 12 h of LT has been shown to reduce post-operative viral infections and to produce better nitrogen retention. Patients should be advanced from nutritional support to an oral diet using smaller and more frequent feedings as soon as tolerated after LT. EN should not be discontinued until patients are able to maintain an adequate oral intake consistent with their nutritional requirements [10–12].

The intraoperative placement of the tip of the feeding tube in the proximal jejunum allows early EN after LT. For adult LDLT recipients, Kaido et al. [10–12, 113] described, in detail, an early post-operative EN regimen using a 9F Witzel enteral tube jejunostomy placed in the proximal jejunum at surgery, through which EN was started within 24 h after surgery. The starting total daily caloric intake until post-operative day (POD) 3 was 10–15 kcal/kg, which was gradually increased to 25–35 kcal/kg using an IMD enriched with HWP (MEIN®; Meiji Dairies Co., Tokyo, Japan). The initial infusion rate was 20 mL/h. If well tolerated, this was increased to 40 mL/h by POD 5. In cases of severe edema of the small intestine or severe diarrhea, the speed of IMD was decreased to 20 mL/h (=20 kcal/h) or an oral rehydration solution was used. After confirmation of the improvement of the edema or diarrhea, the regimen was resumed. Oral nutrition was started after the swallowing function was confirmed, usually around POD 5. Dietitians calculated the daily amounts of protein and carbohydrates required for each recipient and adjusted the speed of the EN according to the patient's oral intake. EN was stopped when the patient could tolerate adequate oral intake containing solid food. All patients resumed preoperative synbiotic supplementation (i.e., GFO®; Otsuka Pharmaceutical Factory, Tokushima, Japan) three times daily and a lactic-fermented beverage once a day via the feeding tube or orally until discharge. This technique allowed for long-term feeding without discomfort or the risk of pneumonia carried by trans-nasal feeding, and avoided the need for concomitant TPN, with its risk of infection.

The glucose utilization by the transplanted liver is reduced in the first hours of engraftment due to impaired mitochondrial respiration and inactivity of the tricarboxylic acid cycle [114]. During this time, energy is generated mostly from fatty acid oxidation. After approximately 6 h, a shift from fat to glucose utilization occurs in normally functioning liver grafts, while a failing liver continues to utilize mainly fat [114, 115]. Glucose administration immediately after OLT has been recommended in small quantities and without insulin to avoid suppressing the peripheral fat mobilization, judged clinically by the blood

glucose, lactate and triglyceride levels and by the arterial ketone bodies [114, 115].

The energy requirements are not elevated in the uncomplicated patient after LT. Therefore, calories should be provided at approximately 120–130 % of the calculated BEE [116, 117]. On the other hand, due to the elevated nitrogen loss upon increased protein catabolism during the acute post-LT phase due to steroids, LT patients should receive 1.5–2.0 g of protein per kilogram of dry (pre-hospital) weight to facilitate the repletion of the muscle mass [118]. Diabetic patients with liver failure receiving EN should be covered with a long-acting isophane insulin suspension on a sliding scale for episodes of hyperglycemia [119].

Metabolic alkalosis and depletion of the serum potassium, phosphorus and magnesium levels often occur in the acute post-LT period due to routine chronic diuretic use in cirrhotic patients, so the amount of fluid from abdominal drains, gastrointestinal losses or fluid overload should be monitored. Ninety percent of cases of metabolic alkalosis are chloride-sensitive and easily correctable. Chloride can be delivered using TPN as a vehicle [10–12, 113].

Long-term nutritional support after liver transplantation

Metabolic syndrome, hyperlipidemia and obesity are common in patients after the first 6 months post-LT, especially those with immobility, and are associated with an increased risk of major vascular events, diabetes mellitus, hypertension, cancer and the progression of fibrosis. These conditions contribute to the long-term morbidity and mortality [7, 48, 119, 120].

The weight gain generally occurs between 2 and 16 months after LT, and has been attributed to the appetite stimulation by corticosteroids. Immediately after LT, patients are often instructed to ingest a high-protein, high-calorie diet to counteract the weight loss associated with pre-LT cachexia and increased energy requirements for surgical recovery, but this can induce unwanted weight gain. Depressive moods have also been implicated in over- and under-eating and should be considered a factor in LT recipients. Therefore, patients should be instructed on a diet that promotes a healthy body composition which is low in fat, with adequate amounts of lean protein to promote muscle gain. Calories should be sufficient to spare protein from being used as energy, yet not in excess of energy requirements. Regular follow-up with a dietitian will help ensure patient compliance. Dietitians should frequently reassess the nutritional status to optimize the patient's diet during the transition from the acute to chronic post-LT phase [42, 50, 121–123].

Tacrolimus is thought to be associated with a less adverse cardiovascular risk profile than cyclosporine, with a significantly reduced prevalence of hypertension, hypercholesterolemia and obesity, together with significantly lower triglyceride levels. Corticosteroids also contribute to post-LT disturbances of these parameters. In patients with stable graft function, withdrawal of prednisolone over time reduces the prevalence of such disorders [112, 119]. Long-term administration of glucocorticoids results in lipid accumulation, weight gain, osteoporosis and muscle wasting by impairing the resting energy expenditure and substrate oxidation rates. Insulin resistance, the post-operative cytokine response and a post-menopausal status in females are other suggested mechanisms that inhibit a gain of muscle mass after LT [124].

Standard recommendations after LT include a "no added salt" diet (3 g sodium/day) to prevent water retention associated with steroid therapy. However, health professionals often encourage the addition of flavoring agents, including sodium, to foods to improve their taste to promote appetite. Therefore, the sodium intake may be higher than suspected [86].

Several risk factors for bone loss after LT include steroid use, malnutrition, muscle wasting, immobilization, pre-LT osteopenia or osteoporosis, previous fractures and immunosuppressive agents. Bone loss occurs mostly within the first three to 6 months after LT, and increases the risk of fractures within the first year. However, the osteopenia related to cholestasis tends to become stable at 1 year after LT following improved allograft function. Bisphosphonates may prevent bone loss after LT [79, 125–127].

Conclusion

Accurate assessment of the nutritional status and adequate intervention are prerequisites for perioperative nutritional treatment in patients who undergo LT. However, the metabolic abnormalities induced by liver failure make the traditional assessment of the nutritional status difficult. The presence of preoperative malnutrition and sarcopenia estimated by recently developed body BIA have a significant negative impact on the post-liver transplantation outcome. It is essential to provide adequate nutritional support during all phases of liver transplantation, including the preoperative administration of a BCAA-enriched nutrient mixture and the post-operative use of an IMD enriched with HWP. Perioperative nutritional therapy is indispensable to improve the outcomes after LT.

Conflict of interest None of the authors of this manuscript have any conflicts of interest to disclose.

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ORIGINAL ARTICLE

Perioperative Changes in Nutritional Parameters and Impact of Graft Size in Patients Undergoing Adult Living Donor Liver Transplantation

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Derangements of various serum biochemical nutritional/metabolic parameters are common in patients with end-stage liver disease who undergo liver transplantation (LT). The aim of this study was to explain the benefit of LT with respect to parameter changes and to examine the impact of the graft-to-recipient weight ratio (GRWR) on such changes. We investigated each parameter's course in 208 adult recipients for 1 year after living donor LT and analyzed changes in the parameters with a GRWR of 0.8% as the cutoff point. Bonferroni corrections were applied to account for multiple testing. Liver disease–induced high pretransplant ammonia and tyrosine levels and low branched-chain amino acids to tyrosine ratio (BTR) and zinc levels normalized within 2 weeks after transplantation, and the total lymphocyte count (TLC) normalized within 2 months, whereas low pretransplant prealbumin levels took 1 year to normalize. Branched-chain amino acids (BCAA), zinc, and TLC levels transiently dropped shortly after transplantation and then were corrected later. An accelerated recovery of ammonia and tyrosine levels and the BTR were found with larger grafts, especially early after transplantation, whereas zinc, prealbumin, BCAA, and TLC levels recovered regardless of the graft size. In conclusion, graft size had little effect on the recovery of nutritional/metabolic parameters except for ammonia and tyrosine levels. ***Liver Transpl 20:1486-1496, 2014.***

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In patients with end-stage liver disease undergoing liver transplantation (LT), protein-energy malnutrition is common and negatively affects clinical outcomes in terms of posttransplant survival and complications.[1] Therefore, the instigation of specialized nutritional status measurements and interventions is required. Derangements of various serum biochemical nutritional parameters such as zinc, prealbumin, branched-chain amino acids (BCAA), tyrosine, and total lymphocyte count (TLC) and related metabolic parameters such as the BCAA to tyrosine ratio (BTR) and ammonia are not uncommon in these patients as a result of the debilitating hepatic pathology and its medical management.[2-6] These parameters could be good indicators of nutritional/metabolic status trends after LT. However, their posttransplant changes with respect to the preoperative levels remain unclear.

Abbreviations: ALF, acute liver failure; BCAA, branched-chain amino acids; BMI, body mass index; BTR, branched-chain amino acids to tyrosine ratio; CT, computed tomography; CTP, Child-Turcotte-Pugh; GRWR, graft-to-recipient weight ratio; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; L/S, liver-to-spleen attenuation; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cirrhosis; POD, postoperative day; PSC, primary sclerosing cholangitis; TLC, total lymphocyte count; w1, week 1; w2, week 2; w3, week 3; w4, week 4.

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Studies reporting amino acid levels after LT have been performed only in the early postoperative period[7] or without a definite time course.[8] It is, therefore, not clear whether levels of circulating amino acids are normalized in the clinically stable long-term course after LT. We hypothesize that successful LT would be sufficient to correct the disturbed amino acid metabolism found in liver cirrhosis.

In deceased donor LT, the graft size is sufficient for the recipient. In contrast, in living donor liver transplantation (LDLT), the graft size is small and is an important factor for posttransplant survival. However, there is relatively little information on the short- and long-term changes in nutritional/metabolic parameters after LDLT that could reflect the adequacy of the graft mass to provide sufficient metabolic and synthetic function, which is the key factor in the success of LDLT. Although partial liver grafts undergo a rapid regenerative response, with the largest changes in the liver volume occurring during the first week after transplantation, regeneration is suppressed in small-for-size grafts after LDLT. Thus, grafts with an inadequate graft-to-recipient weight ratio (GRWR) cannot meet the functional demand of the recipients.[9] On the other hand, some have concluded that smaller grafts are capable of regeneration to a greater extent and that the regenerative liver response is proportional to the amount of liver transplanted.[10,11] Yoshida et al.[7] presumed improvements in some nutritional parameters shortly after LDLT to be derived from the GRWR discrepancy. Our hypothesis is that the posttransplant recovery of nutritional/metabolic parameters, especially in the early period after grafting, might be affected by GRWR. To obtain insight into these questions, the present retrospective longitudinal study was performed to clarify the short- and long-term courses of circulating levels of the aforementioned parameters after successful adult LDLT and to analyze the impact of GRWR on such posttransplant changes in LDLT recipients.

PATIENTS AND METHODS

Patients

The study subjects were 208 adult patients (age $\geq$ 18 years) who underwent primary LDLT at Kyoto University Hospital between February 2008 and August 2012. There were 98 males and 110 females, and the median patient age was 54 years (range = 18-69 years). The patients provided written informed consent before the start of the study, which was approved by the ethics committee of Kyoto University in accordance with the Declaration of Helsinki of 1996.

The median Model for End-Stage Liver Disease (MELD) score was 19 (range = 6–55). Sixty-eight patients were ABO-incompatible, and 140 were identical or compatible. The Child-Turcotte-Pugh (CTP) classifications were C, B, and A for 139, 55, and 14 patients, respectively. The indications for LT were hepatocellular carcinoma (HCC; n = 52), hepatocellular diseases such as hepatitis B or C virus–associated liver cirrhosis (n = 46), progressive intrahepatic cholestatic diseases including primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC; n = 34), acute liver failure (ALF; n = 15), biliary atresia after the Kasai procedure (n = 14), alcoholic liver cirrhosis (n = 11), metabolic liver diseases (n = 7), nonalcoholic steatohepatitis (NASH; n = 7), autoimmune hepatitis (n = 4), and other causes (n = 18).

Donor and Graft Selection

The selection criteria for donors and grafts have been described elsewhere.[12,13] Briefly, according to computed tomography (CT) scan volumetric analysis, the liver weight was calculated, and the graft type was selected. If necessary, portosystemic collateral ligation with splenectomy was performed for the prevention of the steal phenomenon after LT as well as the control of the portal venous pressure ($\leq$15 mm Hg). This allowed the lower limit of GRWR to be safely reduced to 0.6% and a left lobe graft to be used whenever feasible.[13,14] All grafts used had a liver-to-spleen attenuation (L/S) ratio on CT $\geq$ 1.1 to exclude grafts with hepatic steatosis > 30%.[15]

Surgical Procedures and Immunosuppressive Treatments

The selection criteria for the recipients as well as surgical and back-table techniques for the donors and recipients have been described in detail elsewhere.[16-18] Orthotopic adult LDLT was performed with a right lobe graft for 102 patients, with a left lobe graft for 100 patients, with a posterior segment graft for 5 patients, and with a whole liver graft as a domino graft from a patient with familial amyloid polyneuropathy for 1 patient. Each graft was perfused with cold histidine tryptophan ketoglutarate (0°C-4°C; Custodiol, Essential Pharmaceuticals, LLC, Newtown, PA). Immediately after the perfusion of the preservation solution, all resected liver grafts were measured. The actual graft weight was used for the calculation of GRWR. The median GRWR was 0.89% (range = 0.53%-1.50%). At the time of surgery in all recipients, a tube jejunostomy for enteral nutrition was placed in the proximal jejunum with a 9-Fr enteral tube.

The baseline immunosuppressive regimen consisted of tacrolimus or cyclosporine and low-dose steroids, as described elsewhere.[19] Patients who were ABO-incompatible also underwent preoperative plasma exchange to reduce A/B antibodies to 1:8 or more and received 300 mg of intravenous rituximab (anti-CD20 monoclonal antibody) approximately 2 weeks before LT. A hepatic artery infusion of prostaglandin E1 and methylprednisolone was started at the time of the surgery and was continued for 21 and 7 days, respectively, and this was followed by oral mycophenolate mofetil (500 mg twice daily).[20] All patients received intravenous antimicrobial prophylaxis with

ampicillin (0.5 g) and cefotaxime (0.5 g) twice daily for 3 days; this started 30 minutes before surgery.

Perioperative Nutritional Therapy

Preoperative nutritional therapy was administered for approximately 2 weeks before LDLT and consisted of the following components: a nutrient mixture enriched with BCAA (Aminoleban EN, Otsuka Pharmaceutical Co., Tokyo, Japan) or BCAA nutrients (Livact, Ajinomoto Pharmaceuticals Co., Ltd., Tokyo, Japan) as a late-evening snack, synbiotics with a supplementation product (GFO, Otsuka Pharmaceutical Factory, Inc., Tokushima, Japan) 3 times daily, a lactic fermented beverage once per day, and polaprezinc (Promac D, Zeria Pharmaceutical Co., Ltd., Tokyo, Japan) for patients with low zinc, as described previously.[21] Dietitians adjusted the type and amount of food for each patient to maintain a total daily caloric intake of 35 to 40 kcal/kg and a protein intake of 1.2 to 1.5 g/kg, including BCAA nutrients, according to the guidelines of the European Society of Parenteral and Enteral Nutrition.[22] We could not perform preoperative nutritional therapy for patients with ALF due to emergent LT, and also BCAA supplementation was unsuitable for those patients already having elevated plasma amino acids.[23]

Formulas containing BCAA and polaprezinc were discontinued after LDLT, and early postoperative enteral nutrition was started within the first 24 hours after surgery through the tube jejunostomy with an immune-modulating enteral diet enriched with hydrolyzed whey peptide (MEIN, Meiji Dairies Co., Tokyo, Japan); its composition[21] and its administration protocol[24,25] have been previously described. Oral nutrition was started after the ability to swallow was regained, usually on approximately postoperative day (POD) 5. Dietitians calculated the daily amounts of protein and carbohydrates required for each recipient and the speed of the enteral nutrition accordingly. Enteral feeding was stopped when adequate oral intake containing solid food was tolerated. For synbiotics, all patients received the aforementioned supplementation product 3 times daily and a lactic fermented beverage once per day via the feeding tube or orally until discharge.

Analyzed Parameters

Preoperative and postoperative laboratory parameters were retrospectively reviewed from the clinical charts of the recipients. The standard reference intervals for these parameters at our institute were as follows: zinc, 65 to 110 μg/dL; prealbumin, 20 to 40 mg/dL; TLC, 1200 to 3200/μL; ammonia, 20 to 60 μg/dL; BCAA, 344 to 713 μmol/L; tyrosine, 53 to 98 μmol/L; and BTR, 4.41 to 9.3. A longitudinal study was performed to examine peritransplant changes in the aforementioned parameters at the following serial time points: before the operation at admission (baseline); PODs 2, 3, and 5; week 1 (w1), week 2 (w2), week 3 (w3), and week 4 (w4); months 2, 3, and 6; and year 1 after transplantation. The baseline pretransplant level of each parameter was statistically compared with its counterparts at each time point in the posttransplant observation (follow-up) period, and the degree of significance of each comparison was plotted on graphs.

A statistical comparison was performed for the level of each parameter at each of the assigned peritransplant time points between recipients of grafts with a GRWR $< 0.8\%$ (n = 67) and recipients of grafts with a GRWR $\geq 0.8\%$ (n = 141). There were 31 patients who received grafts with a GRWR $< 0.7\%$ and 36 patients who received grafts with a GRWR between 0.7% and 0.8%. We also compared peritransplant parameters among recipients who were stratified as follows: those with a GRWR $< 0.7\%$ (n = 31), those with a GRWR between 0.7% and 0.8% (n = 36), and those with a GRWR $\geq 0.8\%$ (n = 141).

Perioperative changes in parameters were compared among patients with preoperative CTP classification A (n = 14), B (n = 55), or C (n = 139) at various time points and also among patients with diseases of other etiologies who received preoperative nutritional therapy (n = 193) and those with ALF (n = 15) who did not. We also compared nutritional recovery between ABO-incompatible recipients (n = 68) and ABO-compatible recipients (n = 140). Moreover, we examined these preoperative nutritional/metabolic parameters as risk factors for posttransplant mortality.

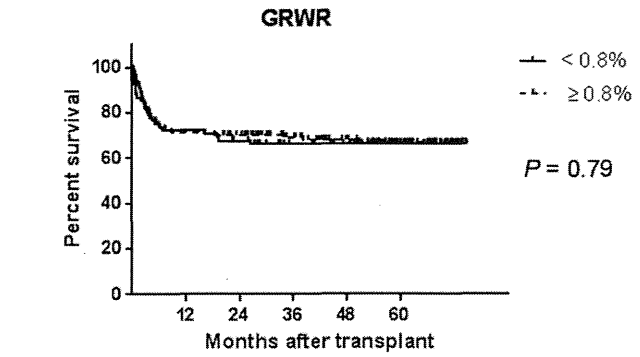
Statistical Analysis

Data were summarized as means and standard deviations for continuous variables. Continuous variables (or parameters) were nonparametrically analyzed with the Wilcoxon signed-rank test to assess postoperative changes from the preoperative state, whereas other comparisons, including those of groups with GRWR $<$ 0.8% and GRWR $\geq$ 0.8% at each time point, were compared with the Mann-Whitney U test or the one-way analysis of variance as appropriate. Two-tailed P values were corrected for multiple testing with the Bonferroni method[26] (with the statistical significance set at $P < 0.0045$, where $0.0045 = 0.05/11$) for 11 tests within each independent family of comparisons of each single parameter performed at the designated 11 peritransplant time points. Only the adjusted P values are presented here. Categorical variables were compared with the χ^2 test or Fisher's exact test as appropriate. The survival rate was calculated via Kaplan-Meier methods, with differences evaluated by log-rank testing. Any variable identified as significant ($P < 0.05$) in the univariate analysis was considered a candidate for the multivariate analysis using multiple logistic regression models. All statistical data were generated in JMP 5.0.1 (SAS Institute, Cary, NC) and Prism 6.02 (GraphPad Software, Inc., La Jolla, CA).

RESULTS

The 1-, 2-, 3-, 4-, and 5-year cumulative survival rates of the whole cohort were 72.6%, 69.2%, 68.1%,

67.3%, and 66.4%, respectively. Overall survival rates and graft survival, defined as the time from LT to death or retransplantation, did not significantly differ between recipients with GRWR $\geq$ 0.8% and those with GRWR < 0.8% [P = 0.79 (Fig. 1) and P = 0.87, respectively].



No. at risk						
< 0.8%	67	50	44	33	27	12
≥ 0.8%	141	100	92	70	51	31

Figure 1. Overall survival rates according to GRWR.

Baseline Assessments of the Whole Cohort

Marked decreases in zinc (45.4 ± 12.1 μg/dL), prealbumin (7.0 ± 2.4 mg/dL), and TLC (863.3 ± 207.3/μL) and marked increases in ammonia (98.1 ± 17.8 μg/dL) and tyrosine (138.8 ± 12.0 μmol/L) were seen before LDLT. The pretransplant BCAA level (395.2 ± 51.0 μmol/L) was low but still within the reference range. Consequently, the BTR (3.0 ± 0.5) was subnormal.

Peritransplant Changes in the Parameters

The low pretransplant zinc level steeply dropped for 2 to 3 days after LDLT and subsequently increased to reach the pretransplant level at about POD 5, continued to increase until it was normalized during w2, and gradually improved thereafter (Fig. 2A). The low pretransplant prealbumin level increased gradually after LDLT and took up to 1 year to normalize (Fig. 2B). The high pretransplant ammonia level notably declined immediately after LDLT to normalize within

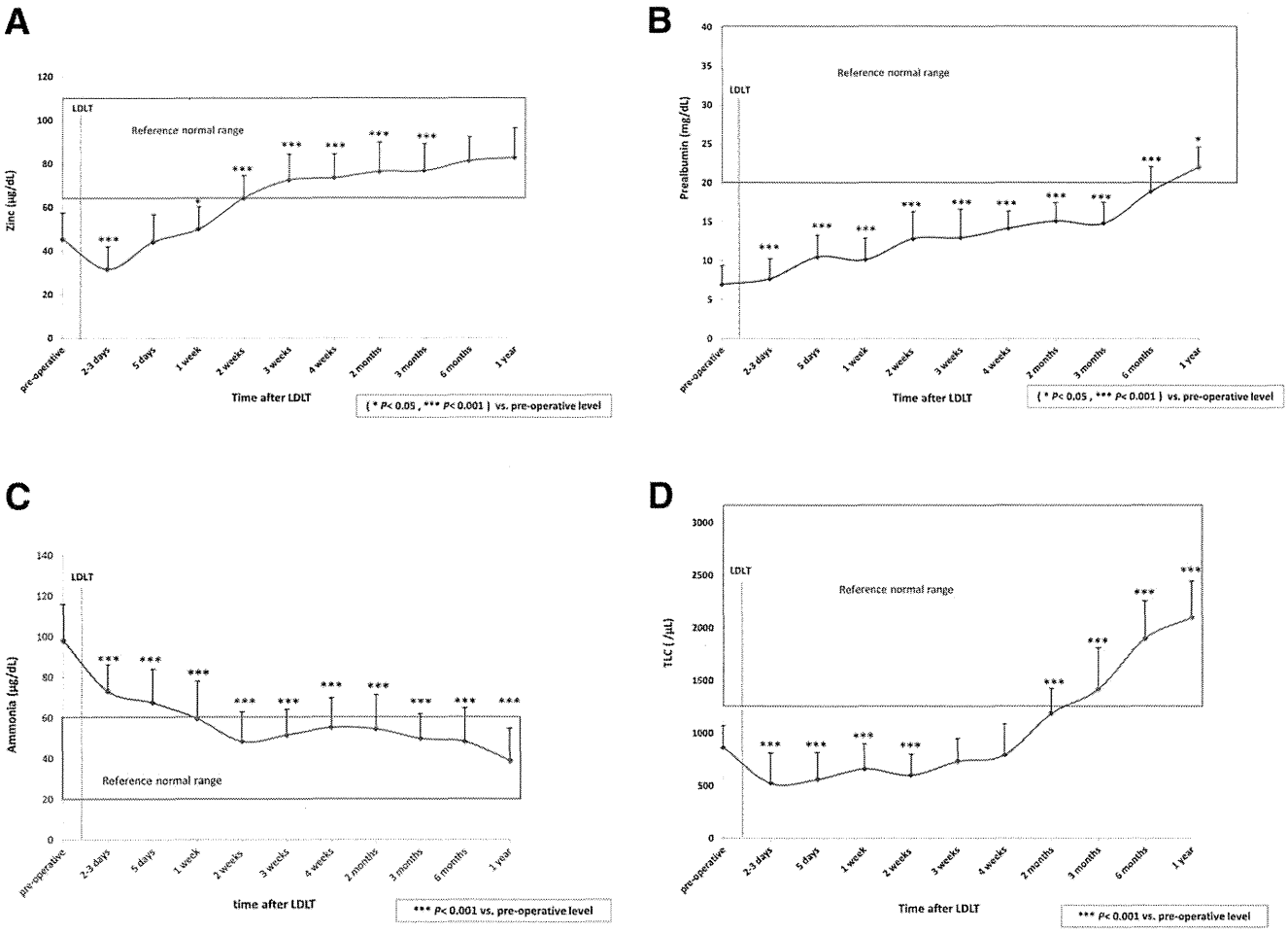


Figure 2. Time course of peritransplant changes of parameters: (A) zinc, (B) prealbumin, (C) TLC, (D) BCAA, (E) ammonia, (F) tyrosine, and (G) BTR.

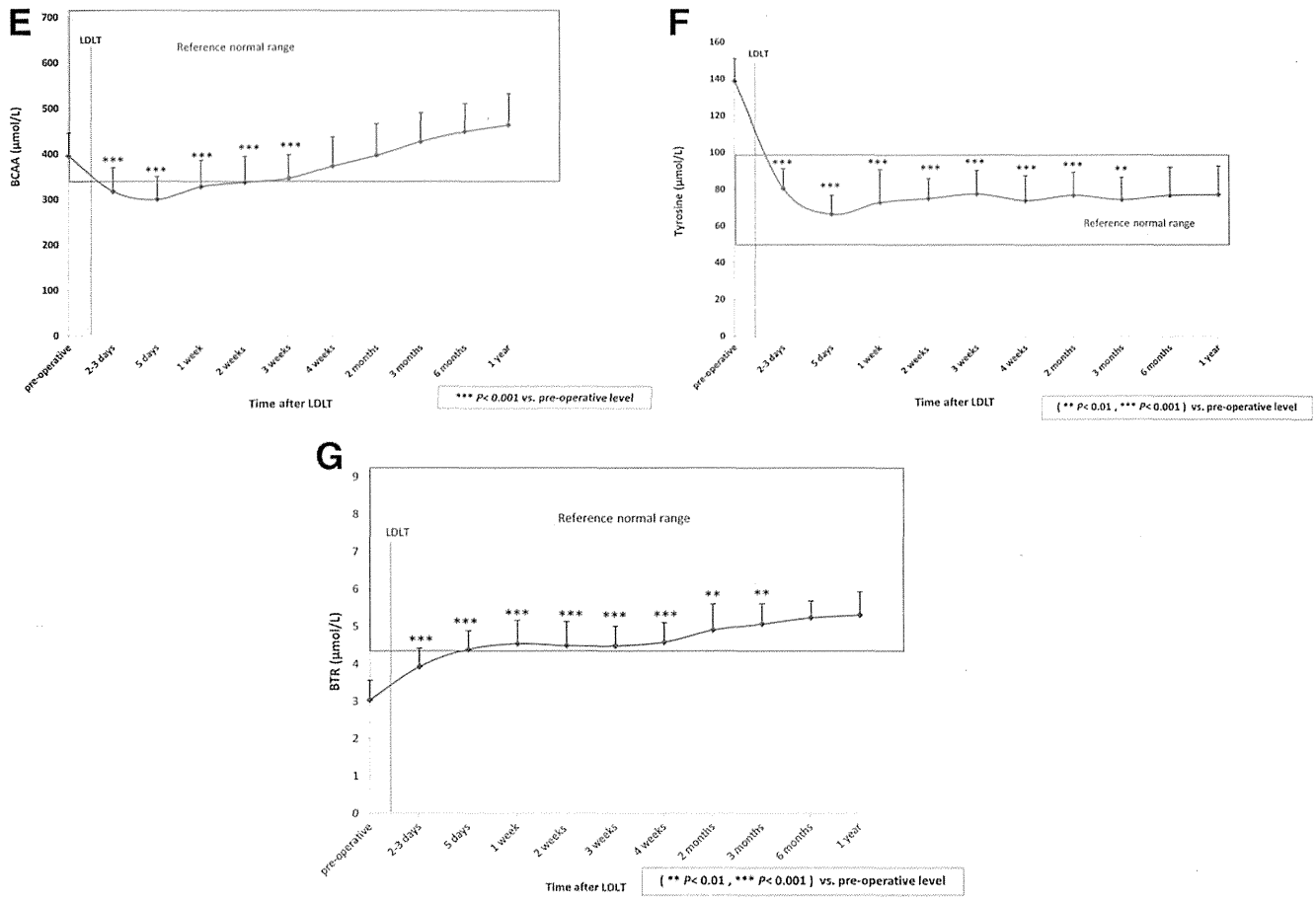


Figure 2. Continued.

w1 and continued to decrease slightly thereafter (Fig. 2C). The TLC level dropped shortly after LDLT, then gradually recovered to the normal level within 2 months after transplantation, and continued to increase thereafter (Fig. 2D). The BCAA level decreased over the first 5 days after LDLT to a subnormal level, then gradually increased until it normalized in w2, and further improved thereafter (Fig. 2E). The high pretransplant serum tyrosine level rapidly declined immediately after LDLT to return within the normal range by POD 2/3, then further decreased until POD 5, and remained relatively stable thereafter (Fig. 2F). Consequently, the BTR rose rapidly to normalize on POD 5, remained stationary for the next 3 weeks, and gradually improved thereafter (Fig. 2G).

Peritransplant Changes in the Parameters According to the GRWR: <0.8% Versus ≥0.8%

The backgrounds and peritransplant characteristics of the recipients with GRWR < 0.8% and those with GRWR ≥ 0.8% are given in Tables 1 and 2. There were no significant differences between the groups in age, sex, body mass index (BMI), CTP, MELD scores, etiology of disease, number of ABO-incompatible grafts, donor age, preoperative levels of the parameters examined, operative blood loss and transfusion units (erythrocyte concentrates), or cold and warm ischemia times.

There were no significant differences between the 2 groups with respect to zinc, prealbumin, TLC, or BCAA levels at any time point (Fig. 3A-D). Although the prealbumin and BCAA levels were close between the groups early after LDLT, at a longer time period after surgery, the GRWR ≥ 0.8% group showed somewhat persistent yet insignificant increases in prealbumin and BCAA levels in comparison with the levels in the GRWR < 0.8% group.

Ammonia and tyrosine levels declined faster and normalized earlier in the GRWR ≥ 0.8% group. The ammonia level significantly dropped from 98.6 ± 15.5 and 97.0 ± 17.7 μg/dL before LDLT to 46.0 ± 13.1 and 48.8 ± 17.1 μg/dL at w2 in the GRWR ≥ 0.8% group and the GRWR < 0.8% group ($P < 0.001$ and $P < 0.001$), respectively, with a significantly greater mean ratio of reduction in the GRWR ≥ 0.8% group versus the GRWR < 0.8% group ($P = 0.01$). The ammonia level was significantly lower in the GRWR ≥ 0.8% group versus the GRWR < 0.8% group on PODs 2 and 3 ($P = 0.001$) and remained decreased, although nonsignificantly, thereafter (Fig. 3E). The tyrosine level significantly dropped in the GRWR ≥ 0.8% group and

TABLE 1. Patient Characteristics

	GRWR ≥ 0.8% (n = 141)	GRWR < 0.8% (n = 67)	*P* Value
Donor age (years)	43.4 ± 11.9	41.0 ± 10.9	0.21
Recipient age at transplantation (years)	51.3 ± 12.5	48.9 ± 14.6	0.25
Sex: male/female (n/n)	65/76	33/34	0.77
BMI on admission (kg/m^2)	22.9 ± 4.3	23.8 ± 4.7	0.17
Underlying disease (n)			
HCC on top of viral hepatitis B or C	35	17	0.93
Viral hepatitis B/C-related cirrhosis	34	12	0.44
PBC/PSC	23	11	0.99
ALF	9	6	0.50
Biliary atresia after Kasai operation	8	6	0.38
Alcoholic cirrhosis	7	4	0.76
Metabolic diseases	4	3	0.54
NASH	5	2	0.83
Autoimmune hepatitis	3	1	0.76
Others	13	5	0.59
ABO compatibility (n)			0.35
Identical/compatible	98	42	
Incompatible	43	25	
Preoperative CTP classification: A or B/C	48/93	21/46	0.75
Preoperative MELD score	19.8 ± 8.5	21.7 ± 10.5	0.17
Baseline levels of parameters			
Zinc (μg/dL)	44.9 ± 10.5	46.4 ± 12.4	0.59
Prealbumin (mg/dL)	6.8 ± 2.3	7.3 ± 2.9	0.54
BCAA (μmol/L)	388.7 ± 49.9	402.7 ± 60.2	0.38
Tyrosine (μmol/L)	145.3 ± 13.3	151.5 ± 12.6	0.60
BTR	3.4 ± 0.5	3.5 ± 0.4	0.96
TLC (/μL)	852.3 ± 216.6	886.6 ± 213.0	0.78
Ammonia (μg/dL)	98.6 ± 15.5	97.0 ± 17.7	0.85

TABLE 2. Surgical Variables

Variable	GRWR ≥ 0.8% (n = 141)	GRWR < 0.8% (n = 67)	*P* Value
Graft type			<0.001
Left lobe	48	52	
Right lobe, including a posterior segment graft	93*	15	
Graft weight (g)	571.1 ± 163.6	427.5 ± 114.5	<0.001
Surgical duration (minutes)	919 ± 138	987 ± 181	0.35
Blood loss (mL)	9598 ± 3155	9769 ± 3190	0.92
Intraoperative erythrocyte transfusion (U)	20.9 ± 10.6	20.8 ± 12.6	0.74
Cold ischemia time (minutes)	57.3 ± 17.2	82.4 ± 13.1	0.64
Warm ischemia time (minutes)	39.9 ± 12.1	46.9 ± 17.3	0.39

*Including 1 domino graft.

the GRWR < 0.8% group from 135.3 ± 13.3 and 141.5 ± 12.6 μmol/L before LDLT to 59.7 ± 13.3 and 75.5 ± 13.7 μmol/L on POD 5 ($P < 0.001$ and $P < 0.001$), respectively, with a significantly higher mean ratio of reduction in the GRWR ≥ 0.8% group ($P = 0.02$). The tyrosine level was significantly lower in the GRWR ≥ 0.8% group versus the GRWR < 0.8% group on PODs 2 and 3 ($P = 0.001$) and remained decreased, although nonsignificantly, thereafter (Fig. 3F).

Consequently, the BTR increased faster and normalized earlier in the GRWR ≥ 0.8% group versus the GRWR < 0.8% group: it increased significantly from 3.0 ± 0.5 and 3.1 ± 0.4 before LDLT to 4.8 ± 0.5 and 3.9 ± 0.5 on POD 5 ($P < 0.001$ and $P = 0.02$), respectively, with a significantly greater mean ratio of increase ($P = 0.1$) in the GRWR ≥ 0.8% group. The BTR remained significantly higher in the GRWR ≥ 0.8% group versus the GRWR < 0.8% group during the first postoperative month [on PODs 2/3 and 5 and in w1, w2, and w3 ($P < 0.001$) and in w4 ($P = 0.002$)] and remained increased, although nonsignificantly, thereafter (Fig. 3G).

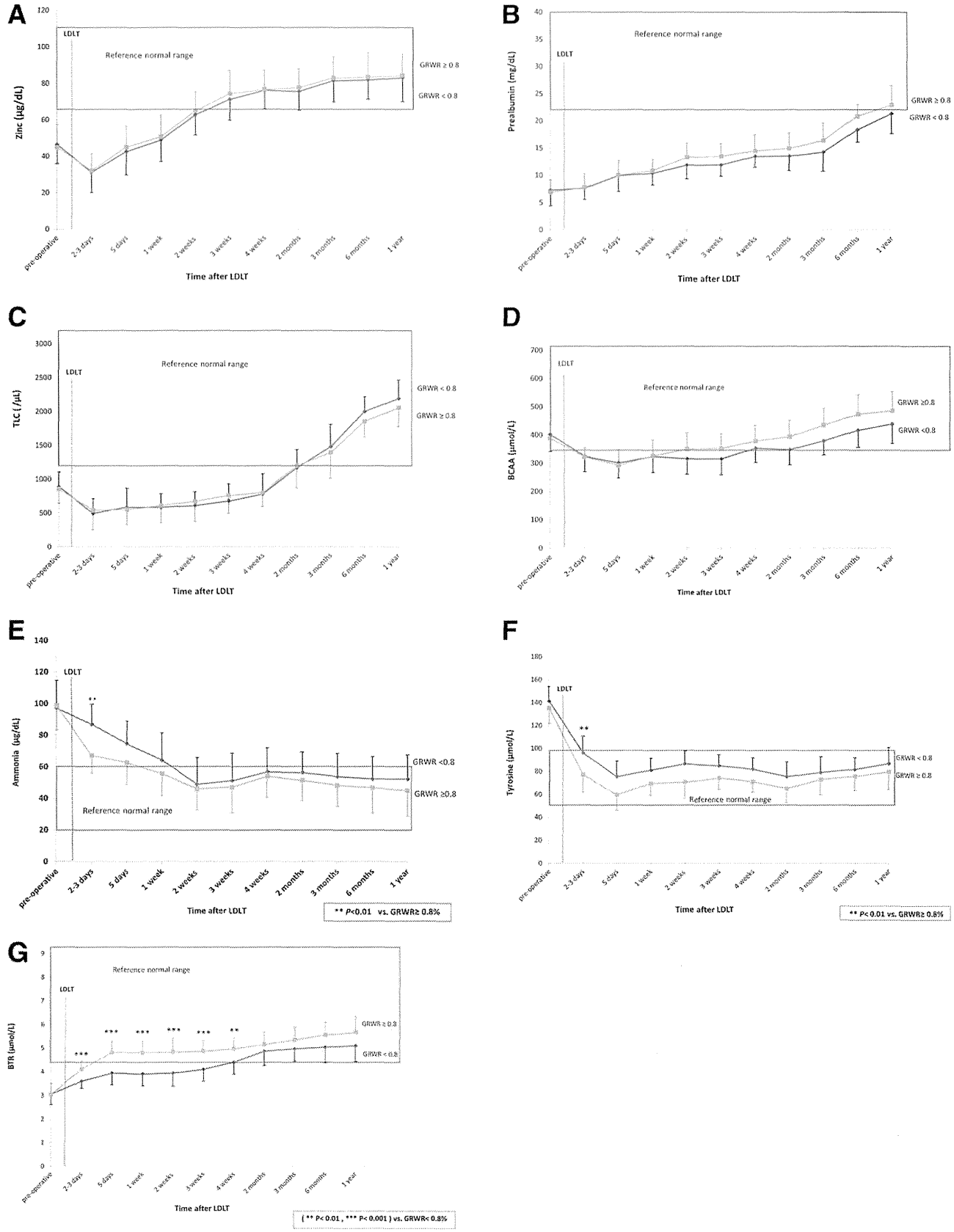


Figure 3. Time course of peritransplant changes of parameters according to GRWR (<0.8% versus ≥0.8%): (A) zinc, (B) prealbumin, (C) TLC, (D) BCAA, (E) ammonia, (F) tyrosine, and (G) BTR.

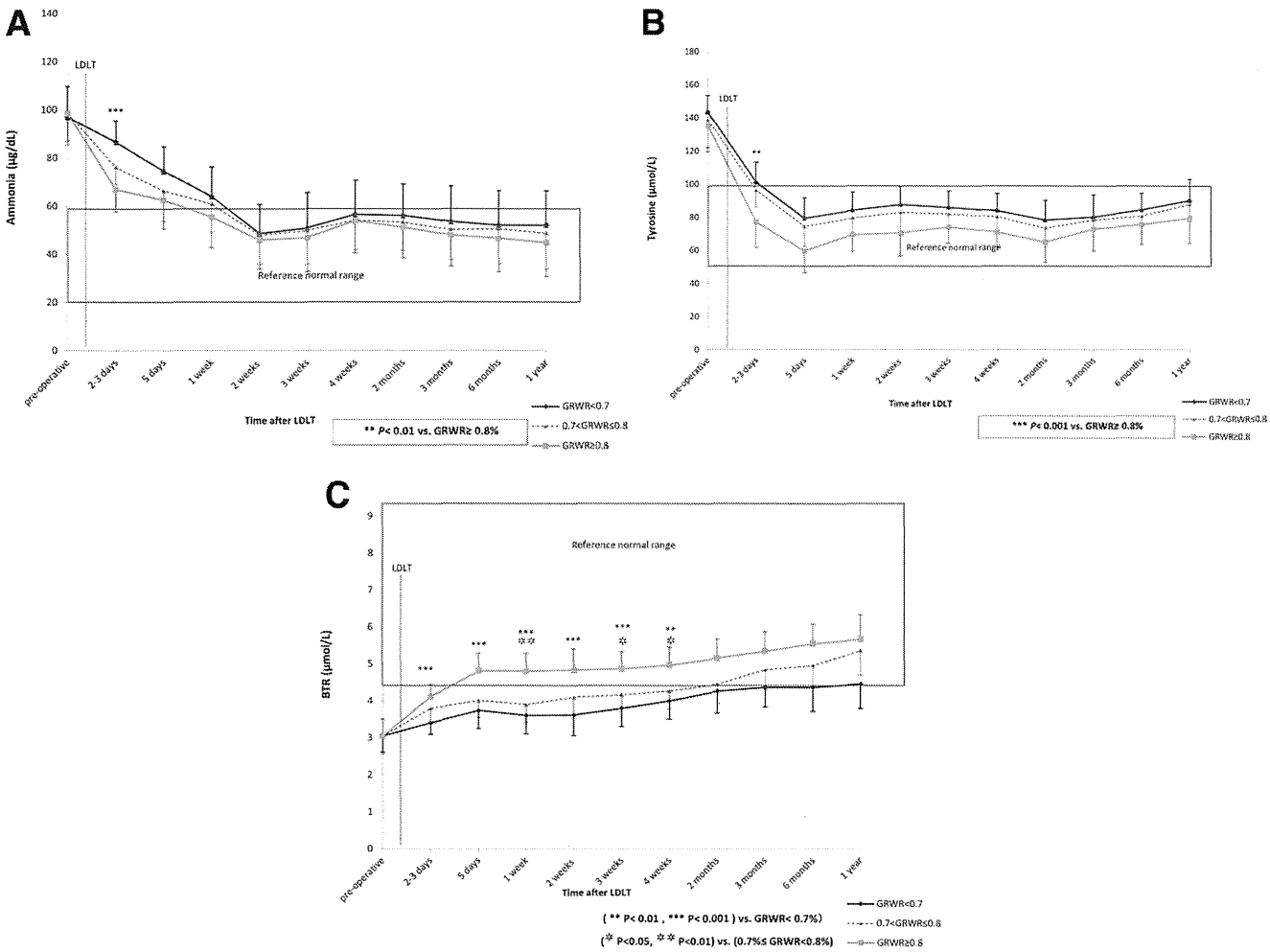


Figure 4. Comparison of time course of peritransplant levels of (A) ammonia, (B) tyrosine, and (C) BTR among patients with GRWR < 0.7%, between 0.7% and 0.8%, and ≥ 0.8%.

Peritransplant Changes in the Parameters According to the GRWR: <0.7% Versus 0.7% to 0.8% Versus ≥0.8%

Ammonia and tyrosine levels were significantly lower in the GRWR ≥ 0.8% group versus the GRWR < 0.7% group on POD 2/3 ($P < 0.001$ and $P = 0.001$, respectively) and remained decreased, although the difference did not reach significance (Fig. 4A,B). Levels of BTR were significantly higher in the group with GRWR ≥ 0.8% versus the group with GRWR < 0.7% during the first postoperative month [PODs 2/3 and 5 and w1, w2, and w3 ($P < 0.001$) and w4 ($P = 0.001$)] and was also significantly higher than that in the group with GRWR between 0.7% and 0.8% at w1, w3, and w4 ($P = 0.002$, $P = 0.01$, and $P = 0.04$, respectively; Fig. 4C). No other parameters differed significantly among the 3 groups at any of the time points analyzed.

Peritransplant Changes in the Parameters According to Preoperative CTP

Baseline preoperative zinc and prealbumin levels were significantly higher, whereas those of tyrosine and ammonia were significantly lower, in the group with CTP class A versus the group with class C ($P < 0.001$, $P < 0.001$, $P = 0.04$, and $P = 0.03$, respectively). Preoperative zinc and prealbumin levels were significantly higher in the group with class A versus the group with class B ($P = 0.04$ and $P < 0.001$, respectively). In contrast, none of the other parameters significantly differed among the 3 groups at any posttransplant time point examined.

Peritransplant Changes in the Parameters in ALF Recipients and Other Recipients

Preoperative baseline levels of ammonia, tyrosine, and prealbumin were significantly higher, whereas that of BTR was significantly lower, in the group with ALF versus the group without ALF ($P = 0.03$, $P = 0.01$, $P = 0.002$, and $P < 0.001$, respectively). Otherwise, preoperative levels of all other parameters did not significantly differ between the groups at any posttransplant time point analyzed.

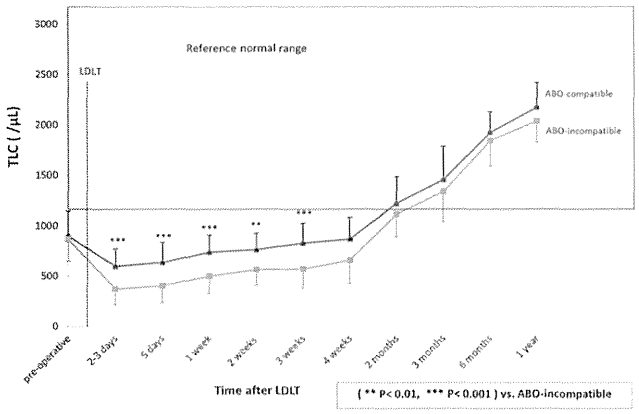


Figure 5. Time course of peritransplant changes of TLC in ABO-compatible and ABO-incompatible groups.

Peritransplant Changes in the Parameters in ABO-Incompatible and ABO-Compatible Recipients

Levels of zinc, prealbumin, BCAA, tyrosine, BTR, and ammonia did not significantly differ between the ABO-incompatible and ABO-compatible groups at any time point. However, TLC was significantly lower in the ABO-incompatible group versus the compatible group during the first 3 postoperative weeks [PODs 2/3 and 5, w1 and w3 ($P < 0.001$) and w2 ($P = 0.006$)] and remained low, although the difference was not significant (Fig. 5).

Risk Factor Analysis for Post-LT Survival

Univariate analysis revealed that none of the preoperative nutritional/metabolic parameters was a significant risk factor for posttransplant mortality (Table 3).

DISCUSSION

This is the first study to provide long-term collective profiling of nutritional/metabolic parameters in LT recipients. LDLT recipients tend to fall into a severe posttransplant catabolic phase because of the invasiveness of the operative procedure and the necessity for regeneration of the partial liver graft.[7] This might explain the temporarily decreased zinc and BCAA levels during the early postoperative period. Significance and increased utilization of zinc and BCAA for liver regeneration have been reported,[2,27] with the levels recovering later in the patient's course after surgery, regardless of the graft size, with the shift to an anabolic state. Presumably, the improved zinc level also followed the improvement in its absorption and decrease in its diuretic-induced urinary excretion after LT.

In the present study, the TLC level showed a prolonged decline during the initial posttransplant catabolic phase, presumably as a result of immunosuppressive therapy, and this may indicate the importance of an early, immunomodulating

TABLE 3. Univariate Analysis of Factors Affecting Posttransplant Patient Survival

Variable	Overall Survival (%)	*P* Value
Recipient age		
<60 years (n = 147)	86	0.38
≥60 years (n = 61)	92	
Donor age		
<50 years (n = 147)	91	0.48
≥50 years (n = 61)	84	
Sex		
Male (n = 98)	91	0.57
Female (n = 110)	84	
Original disease		
HCC (n = 52)	82	0.37
Non-HCC (n = 156)	90	
ABO blood type		
Compatible (n = 140)	91	0.24
Incompatible (n = 68)	82	
CTP score		
A or B (n = 69)	92	0.57
C (n = 139)	83	
MELD score		
<20 (n = 123)	91	0.77
≥20 (n = 85)	82	
GRWR		
<0.8% (n = 67)	88	0.79
≥0.8% (n = 141)	90	
Graft		
Right (n = 108)	89	0.55
Left (n = 100)	85	
Operative time		
<12 hours (n = 51)	89	0.08
≥12 hours (n = 157)	84	
Operative blood loss		
<10 L (n = 138)	92	0.09
≥10 L (n = 70)	82	
Pretransplant zinc level		
<40.5 μg/dL (n = 99)	84	0.73
≥40.5 μg/dL (n = 109)	89	
Pretransplant prealbumin level		
<5.6 mg/dL (n = 97)	83	0.34
≥5.6 mg/dL (n = 111)	91	
Pretransplant BCAA level		
<372.2 μmol/L (n = 99)	81	0.58
≥372.2 μmol/L (n = 109)	86	
Pretransplant BTR		
<2.8 (n = 100)	81	0.76
≥2.8 (n = 108)	86	
Pretransplant tyrosine		
<132 μmol/L (n = 100)	88	0.10
≥132 μmol/L (n = 108)	84	
Pretransplant TLC		
<700/μL (n = 100)	86	0.68
≥700/μL (n = 108)	86	
Pretransplant ammonia level		
<89 μg/dL (n = 104)	91	0.51
≥89 μg/dL (n = 104)	85	

enteral diet. Then, TLC gradually improved in parallel with an increase in lymphocyte proliferation upon recovery from protein-energy malnutrition and tapering of the immunosuppressive therapy.[4] The comparatively suppressed TLC in ABO-incompatible recipients during the first 3 weeks after transplantation might be attributable to the addition of immunosuppressants such as rituximab approximately 2 weeks before LT and complete B-cell elimination approximately 3 weeks after administration.[28]

Although CTP classification is one of the best tools for predicting mortality in patients with cirrhosis, one of its main limitations is the lack of an assessment of the nutritional and functional status.[29] Recovery of nutritional/metabolic parameters after successful LDLT occurred regardless of the pretransplant CTP class.

BCAA escape hepatic extraction with primary muscle uptake.[8] Thus, BCAA recovery regardless of graft size after the initial posttransplant decline might be attributed mainly to an improvement in cirrhosis-induced disturbances of muscular amino acid metabolism, namely, the hyperammonemia-activated glutamine synthesis, with a subsequent decrease in BCAA utilization and catabolism in skeletal muscle.[30] However, an influence of preoperative BCAA supplementation on baseline BCAA levels and levels in the early postoperative period should be also considered.

Tyrosine and ammonia levels decreased immediately after LDLT, presumably because of improvements in the visceral uptake capacity and hepatic metabolism. However, possible influences of preoperative malnutrition, preexisting extrahepatic shunts, or enteral nutrition cannot be excluded. Consistently, tyrosine clearance significantly improved 2 to 3 days after transplantation,[31] and ammonia levels improved within the first month after LDLT.[32] The tyrosine level was stabilized in the long term after LDLT, probably because of the improved graft hemodynamics and decreased basal proteolysis. The significant drop in ammonia and tyrosine levels seen with GRWR > 0.8% might be expected because of the greater liver mass for detoxifying or metabolizing these substrates.

Some limitations must be borne in mind. First, this was a retrospective, single-center study with an observational protocol. We gradually improved the perioperative nutritional regimen on the basis of our most recent findings to include preoperative BCAA and early post-LDLT enteral nutrition with an immunomodulating enteral diet enriched with hydrolyzed whey peptide. Therefore, a prospective analysis is needed to confirm the present findings. However, the study scale would be sufficient for follow-up of 208 recipients with diverse indications and under homogeneous immunosuppression regimens. Second, we were not able to collect all data at all time points. The exact duration and the amount of BCAA given in the preoperative nutritional therapy protocol varied among the individual patients, but because this was a retrospective study, these factors could not be adjusted. Third, graft function is dependent not only on size but also on graft quality. However, all grafts used had an L/S ratio $\geq$ 1.1, and both donor age and ischemia times were insignificantly different; therefore, large and small grafts were of nearly the same quality. Moreover, the baseline pretransplant parameter levels were insignificantly different. Fourth, we could not assess liver regeneration rates because neither CT nor magnetic resonance scanning was routinely performed at designated posttransplant follow-up visits. Fifth, many therapeutic interventions may have short-term effects on the functional development of hepatocytes or graft regeneration or directly alter the course of the parameters. However, we calculated the slopes within the first year after LT, when most patients received similar traditional therapies and the same perioperative nutritional therapy.

In conclusion, graft size had little impact on the recovery of nutritional parameters except for the ammonia and tyrosine levels. Further prospective studies are warranted to elucidate the role of nutritional parameters in the assessment of graft function and survival.

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