(PET negative status) significantly higher than in the surrounding non-cancerous hepatic parenchyma.

Histopathological study

A total of 67 HCC and three cHCC-CC were evaluated histologically. Formalin-fixed specimens were embedded in paraffin. Deparaffinized 4-μm sections were stained with hematoxylin–eosin for microscopic evaluation. The histopathological definition of HCC and the criteria for cHCC-CC were based on the classification proposed by the World Health Organization. The cHCC-CC contain unequivocal hepatocellular and cholangiocellular components that are intimately admixed. The HCC displayed a trabecular pattern with little stroma, a pseudoglandular pattern with or without bile production, abundant eosinophilic cytoplasm, and immunoreactivity for Hep par 1. The CC was defined by a definite glandular pattern with fibrous stroma, low columnar cells with round vesicular nuclei, mucin production confirmed by Alcian blue, and immunoreactivity for cytokeratin 19 but not Hep par 1.

Statistical analysis

All statistical analyses were performed using the StatView ver. 5.0 software package. Continuous variables were compared using the Mann–Whitney *U*-test or Student's *t*-test. The χ^2-test was used for categorical variables. The differences were considered to be significant if $P < 0.05$.

RESULTS

Patients with HCC

PATIENT CHARACTERISTICS ARE summarized in Table 1(a). The mean age (± SD) was 66 ± 12 years (range, 36–87), and the sex ratio (M : F) was 32:21. Thirty-two patients (60.4%) were seropositive for hepatitis C virus, 11 for hepatitis B surface antigen (20.8%) and 10 (18.8%) had non-B/non-C etiologies. Twelve of the 53 patients had a serum α-fetoprotein (AFP) level of more than 100 ng/mL (median, 11.8; range, 1.6–994 600) and 24 patients had a serum des-γ-carboxy prothrombin (DCP) level above 100 mAU/mL (median, 81; range, 10–109 730). Twenty-nine patients with solitary tumors were divided into two groups: PET positive ($n = 16$) and PET negative ($n = 13$). Although there was no significant difference in serum AFP levels between the PET positive and negative groups (110.2 ± 196.9 and 132.9 ± 372.7 ng/mL, respectively), the PET positive group had higher serum

Table 1 Characteristics of patients with HCC and clinicopathological data of HCC

a. Characteristics of patients with HCC

Characteristic	No. of patients (%)
Total number of patients	53
Age (years)	
Mean (range)	66 (36–87)
Sex	
Male : female	32 (60.4):21 (39.6)
Etiology of liver disease	
Hepatitis B	11 (20.8)
Hepatitis C	32 (60.4)
Other	10 (18.8)
Child–Pugh classification	
A	40 (75.5)
B	6 (11.3)
C	7 (13.2)
Tumor stage (UICC)	
I	21 (39.6)
II	25 (47.2)
III	5 (9.4)
IV	2 (3.8)
Type of hepatic surgery	
Resection	40 (75.5)
Liver transplantation	13 (24.5)
Tumor number	
Solitary	29 (54.7)
Multiple	24 (45.3)
Preoperative serum AFP (ng/mL)	
Median (range)	11.8 (1.6–99 4600)
Preoperative serum DCP (mAU/mL)	
Median (range)	81 (10–109 730)

b. Clinicopathological data of HCC

Characteristic	No. of HCC (%)
Total number of nodules	67
Tumor differentiation	
Well	7 (10.4)
Moderately	47 (70.1)
Poorly	9 (13.4)
Undifferentiated	1 (1.5)
Moderately with sarcomatous change	1 (1.5)
Poorly with sarcomatous change	2 (3.0)
Tumor size (cm)	
Mean ± SD	3.4 ± 3.4
Microvascular invasion	16 (23.9)

AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin; HCC, hepatocellular carcinoma; SD, standard deviation; UICC, Union for International Cancer Control.

Table 2 Association between PET status and clinicopathological data of HCC

Characteristic	PET negative ($n = 38$)	PET positive ($n = 29$)	*P*-value
Tumor differentiation (%)			<0.05
Well	7 (100)	0 (0)	
Moderately	31 (66)	16 (34)	
Poorly	0 (0)	9 (100)	
Undifferentiated	0 (0)	1 (100)	
Moderately with sarcomatous change	0 (0)	1 (100)	
Poorly with sarcomatous change	0 (0)	2 (100)	
Tumor size (cm)			
Mean ± SD	2.1 ± 1.5	5.1 ± 4.3	<0.05
Microvascular invasion (%)	4 (11)	12 (41)	<0.05

HCC, hepatocellular carcinoma; PET, positron emission tomography; SD, standard deviation; UICC, Union for International Cancer Control.

DCP levels than the PET negative group (529.6 ± 748.3 and 54.2 ± 50.7 mAU/mL, respectively; $P < 0.05$) (± SD). Using the modified Union for International Cancer Control staging system, we enrolled 21 (39.6%) stage I patients, 25 (47.2%) stage II patients, five (9.4%) stage III patients and two (3.8%) stage IV patients.

The characteristics of HCC are summarized in Table 1(b). The histological grades were well differentiated in seven HCC (10.4%), moderately differentiated in 47 (70.1%), poorly differentiated in nine (13.4%), undifferentiated in one (1.5%), moderately differentiated with sarcomatous change in one (1.5%) and poorly differentiated with sarcomatous change in two (3.0%). Mean tumor size (± SD) was 3.4 ± 3.4 cm, and microvascular invasion was observed in 16 HCC (23.9%). The detection rate of HCC by PET was 43.3%. The sensitivity of PET for the detection of HCC was significantly associated with tumor differentiation, tumor size and microvascular invasion (Table 2). None of the seven well-differentiated HCC were detected by PET. The mean maximum standardized uptake value (SUVmax) (± SD) was 4.7 ± 1.3 in moderately differentiated HCC with positive PET findings, 5.7 ± 2.3 in poorly differentiated HCC and 26.2 in undifferentiated HCC. One poorly differentiated HCC with a maximum diameter of 17.0 cm, direct invasion to the stomach, and lymph node and pulmonary metastases, had a high SUVmax of 11.3. Moderately differentiated HCC with sarcomatous change had a high SUVmax of 18.6, and poorly differentiated HCC with sarcomatous change also showed high FDG uptake (SUVmax 14.1 and 25.0) (Fig. 1). One poorly differentiated HCC with sarcomatous change had a high SUVmax of 14.1 despite the small size of the tumor (1.6 cm) and absence of microvascular invasion (Fig. 2). The patients with poorly differentiated HCC with sarcomatous change developed recurrences soon after surgery. One patient with an SUVmax of 14.1 had metastasis to the mediastinal lymph nodes 9 months after surgery, and another with an SUVmax of 25.0 developed intrahepatic metastasis 44 days after surgery.

Patients with cHCC-CC

Patient characteristics are summarized in Table 3. All three cHCC-CC were detected by PET and the SUVmax

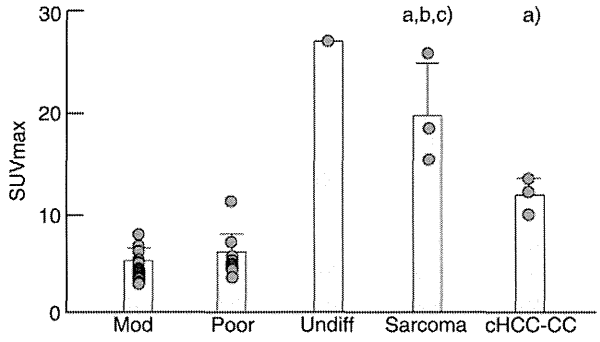

Figure 1 Maximum standardized uptake value (SUVmax) values of hepatocellular carcinoma (HCC) and combined hepatocellular and cholangiocarcinoma (cHCC-CC) with positive positron emission tomography (PET) findings. Undifferentiated HCC, moderately or poorly differentiated HCC with sarcomatous change, and cHCC-CC have high SUVmax values (>9.9), respectively. Data are expressed as mean ± standard deviation. (a) $P < 0.05$ vs mod; (b) $P < 0.05$ vs poor; (c) $P < 0.05$ vs cHCC-CC. Mod, moderately differentiated HCC; poor, poorly differentiated HCC; undiff, undifferentiated HCC; sarcoma, moderately or poorly differentiated HCC with sarcomatous change.

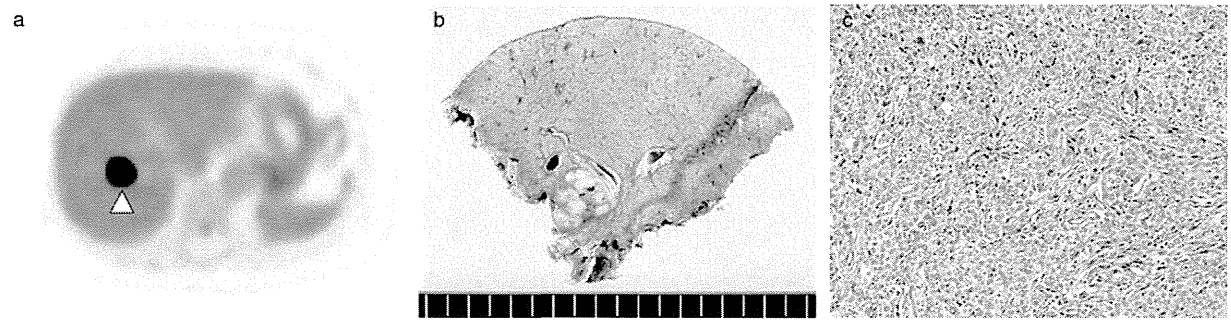

Figure 2 A 74-year-old female patient with poorly differentiated hepatocellular carcinoma (HCC) with sarcomatous change. (a) ^{18}F-Fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) image shows a liver mass with a maximum standardized uptake value (SUVmax) of 14.1 (arrow head). (b) Macroscopic image of the liver mass. (c) The liver tumor demonstrates histological features of poorly differentiated HCC with sarcomatous change (hematoxylin–eosin, original magnification ×100).

of cHCC-CC was 9.9, 12.0 and 13.0 (Fig. 1). One cHCC-CC had a high FDG uptake (SUVmax 12.0) despite the small size of the tumor (2.2 cm) and low levels of tumor markers (patient no. 1) (Fig. 3).

DISCUSSION

THE ROLE OF FDG PET/CT in the diagnosis and staging of HCC and other forms of liver cancer has been demonstrated in several reports.[6,7,19] However, preoperative evaluation of sarcomatous HCC and cHCC-CC with FDG PET/CT has not been reported so far. In the present study, we showed that sarcomatous HCC and cHCC-CC could be detected by PET/CT with high FDG uptake, and positive preoperative FDG uptake in HCC was significantly associated with tumor differentiation, tumor size and microvascular invasion.

Recently, several studies have shown that FDG-PET is useful for predicting tumor characterization, clinical outcome and prognosis in patients with HCC. Well-differentiated HCC regions were reported to show a tendency toward negativity by PET, whereas poorly differentiated types show increased FDG accumulation.[6,7] Our data also demonstrate that well-differentiated and some moderately differentiated HCC do not show FDG uptake exceeding that of the surrounding normal liver, whereas poorly differentiated and undifferentiated HCC have positive PET findings. There was no significant difference between the mean SUVmax of poorly differentiated HCC and that of moderately differentiated HCC with positive PET findings. On the other hand, the SUVmax of sarcomatous HCC were 18.6, 14.1 and 25.0, much higher than that of poorly differentiated HCC.

Table 3 Characteristics of patients with cHCC-CC

Characteristic	Patient no. 1	Patient no. 2	Patient no. 3
Age (years)/sex	78/M	54/M	47/M
Viral infection	HBsAg positive	Negative	HCVAb positive
Maximal tumor size (cm)	2.2	12.3	4.0
Microvascular invasion	Positive	Positive	Positive
Tumor stage (UICC)	II	IV	III
AFP (ng/mL)	4.3	16.4	18 286
DCP (mAU/mL)	20	45	231
CEA (ng/mL)	1.7	0.5	2.8
CA19-9 (U/mL)	7.4	76.6	31.9
Maximum SUV	12.0	9.9	13.0

CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; DCP, des-γ-carboxy prothrombin; HBsAg, hepatitis B surface antigen; HCVAb, anti-hepatitis C virus antibody; SUV, standardized uptake value; UICC, Union for International Cancer Control.

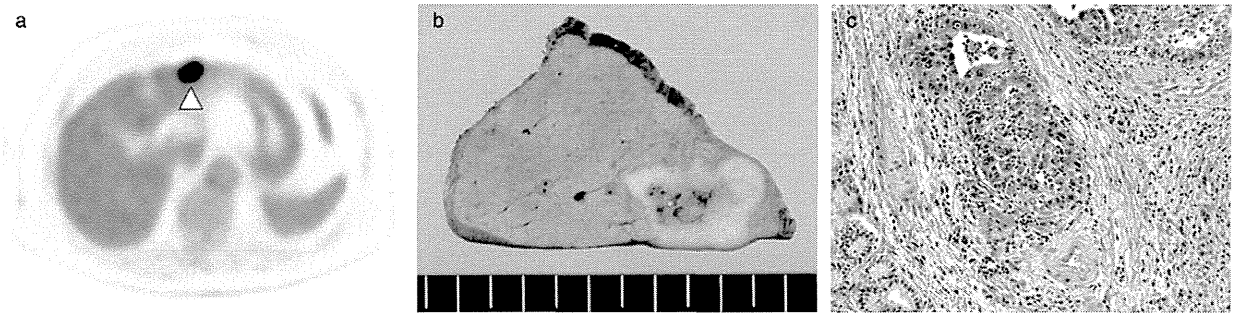

Figure 3 A 78-year-old male patient with combined hepatocellular and cholangiocarcinoma (cHCC-CC). (a) ^{8}F-Fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) image shows a liver mass with a maximum standardized uptake value (SUVmax) of 12.0 (arrow head). (b) Macroscopic image of the liver mass. (c) The liver tumor demonstrates histological features of cHCC-CC with microvascular invasion (hematoxylin–eosin, original magnification ×100).

Sarcomatous HCC is a rare histological variant of HCC.[13] Although the pathogenesis of sarcomatous HCC has not been clarified, the sarcomatous components are thought to be derived from a dedifferentiation or anaplasia, rather than from a combination of HCC and sarcoma.[13,20] Previous reports have suggested that anticancer therapy has an influence on the development of sarcomatous features in HCC, and the prognosis of patients with sarcomatous HCC is very poor due to frequent widespread metastases.[13,14,21] Although we performed curative resection for primary sarcomatous HCC, two of the three patients developed recurrences soon after surgery. Honda *et al.* reported that sarcomatous HCC appears as an irregularly demarcated intrahepatic mass with delayed or prolonged peripheral enhancement on CT.[22] However, it seemed to be difficult to make a correct preoperative diagnosis of sarcomatous changes by imaging or serological tumor markers. Our results show that FDG-PET may be a useful diagnostic tool for sarcomatous changes of HCC because the high FDG uptake of sarcomatous HCC seems to be related to its progression or aggressiveness.

In the present study, the SUVmax values of three cHCC-CC were higher than those of the poorly differentiated HCC. cHCC-CC is an uncommon subtype of primary liver cancer that contains elements of both HCC and CC.[15] Several studies have reported that the prognosis of patients with cHCC-CC was worse than that of patients with HCC because of frequent portal venous invasion and metastasis to lymph nodes and other organs.[16,17] Vascular invasion, tumor size and tumor stage were found to be prognostic factors for poor outcome in patients with cHCC-CC.[16,23] Moreover, recent studies have demonstrated that a large CC component in cHCC-CC and a high serum carbohydrate antigen 19-9 (CA19-9) level were also associated with poorer survival rates.[24,25] We demonstrated that one cHCC-CC showed high FDG uptake (SUVmax 12.0) despite the low CA19-9 level (7.4 U/mL) and small size of the tumor (2.2 cm) (patient no. 1). In addition, another cHCC-CC showed high FDG uptake (SUVmax 13.0) despite the small CC component in the tumor (1%) (patient no. 3) (data not shown). If the degree of FDG uptake in cHCC-CC also reflects the aggressiveness of the tumor like other malignant tumors, FDG-PET may become a useful diagnostic tool for the preoperative evaluation of cHCC-CC.

Our data show that the SUVmax of sarcomatous HCC and cHCC-CC are much higher than those of liver cancers reported to be associated with poor prognosis in previous studies. Seo *et al.* have demonstrated that high FDG uptake (SUVmax ≥5.0) was a predictive factor of postoperative early recurrence and poor survival in patients with HCC.[7] Riedl *et al.* have also reported that an SUVmax of 5.0 or greater was correlated with worse long-term prognosis after liver resection for colorectal metastases.[26]

In summary, our studies demonstrate that FDG-PET shows high FDG uptake in sarcomatous HCC and cHCC-CC that have been reported to be associated with poor prognosis after surgery. Therefore, FDG-PET may be an effective diagnostic tool for the non-invasive evaluation of the aggressiveness of primary liver cancer before surgical resection and liver transplantation. Further clinical studies are warranted.

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CASE REPORT

Renoportal anastomosis in right lobe living donor liver transplantation: report of a case

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Abstract End-stage liver disease is often accompanied by thrombosis of the portal vein and the formation of splanchnic collateral vessels. Successful liver transplantation in such situations is more likely if the surgeon uses a strategy to establish a graft inflow. A 59-year-old male with a decompensated liver secondary to idiopathic portal hypertension underwent living donor liver transplantation (LDLT) using a right lobe liver graft donated from his son. His portal venous trunk was atrophied and a splenorenal shunt drained the mesenteric venous flow into the systemic circulation. LDLT was performed with renoportal anastomosis (RPA) using his right internal jugular vein as an interposed venous graft, without dissecting the collateral vessels. Although he developed temporary functional hyperbilirubinemia, he was discharged from the hospital 23 days after LDLT. This case suggests that RPA is a useful technique to manage patients with an obstructed portal vein and a splenorenal shunt.

Keywords Living donor liver transplantation · Portal vein thrombosis · Splenorenal shunt

Abbreviations

LDLT	Living donor liver transplantation
LRV	Left renal vein
PV	Portal vein
RPA	Renoportal anastomosis
SRS	Splenorenal shunt

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Introduction

End-stage liver disease is often accompanied by thrombosis or atrophy of the portal vein (PV) or inferior vena cava, thus resulting in the formation of splanchnic collateral vessels [1, 2]. Although such complications are considered to be difficult to overcome, recent improvements in surgical techniques have allowed these conditions to be operable [2, 3]. Recent innovations in the surgical techniques for thrombosis or atrophy of the PV include portal venous thrombectomy, resection and reconstruction of the atrophied PV, or placement of a graft to bridge the mesenteric vein and the graft PV [4]. Renoportal anastomosis (RPA) is a strategy to establish a portal inflow in patients with an occluded portal inflow in patients undergoing liver transplantation and was first described by Kato et al. [3]. Despite the rationale for this technique, anastomosis has been reported in very few cases. This report presents a case in which RPA was performed using the patient's internal jugular vein during right lobe living donor liver transplantation (LDLT). The report also discusses the relevance of this technique to LDLT and examines the feature of each vein graft used in RPA.

A case report

A 59-year-old male was referred to our hospital for possible LDLT because of a decompensated liver. He was negative for viral hepatitis markers, including hepatitis B

and hepatitis C, or immune-mediated hepatic disorders, and was thought to have cryptogenic cirrhosis of an unknown origin. He had a history of ruptured esophageal varices that were treated by endoscopic sclerotherapy and subsequent partial splenic embolization. His hepatic profiles was: total bilirubin 2.9 mg/dl, albumin 2.0 g/dl, aspirate aminotransferase 44 IU/l, alanine aminotransferase 22 IU/l, creatinine 0.9 mg/dl, international normalized ratio 1.71, ammonia 100 μg/dl, white blood cell count 5,500 cells/μl, hemoglobin 13.4 g/dl, and platelet count 6.8×10^4 cells/μl. His Child-Pugh score was 11 (Grade C), and his model for end-stage liver disease score was 16. Abdominal computed tomography (CT) showed atrophy of the PV, an active splenorenal shunt (SRS) draining from the splenic vein into the left renal vein (LRV) via the left adrenal vein, and a deformed spleen because of the prior partial splenic embolization (Fig. 1). The donor was the 31-year-old son of the patient and had the identical blood type. He had no prior medical problems and his liver function tests were normal.

LDLT was started with the patient placed in a supine position with neck extension. A longitudinal incision was created on the right side of the neck and was deepened at the medial border of the sternocleidomastoid muscle. The right internal jugular vein was identified, taped, isolated from the surrounding tissue, and then removed. The length of the obtained internal jugular vein was 8 cm. The abdomen was opened via a bilateral subcostal incision with a midline extension. Total hepatectomy was performed as described elsewhere [5].

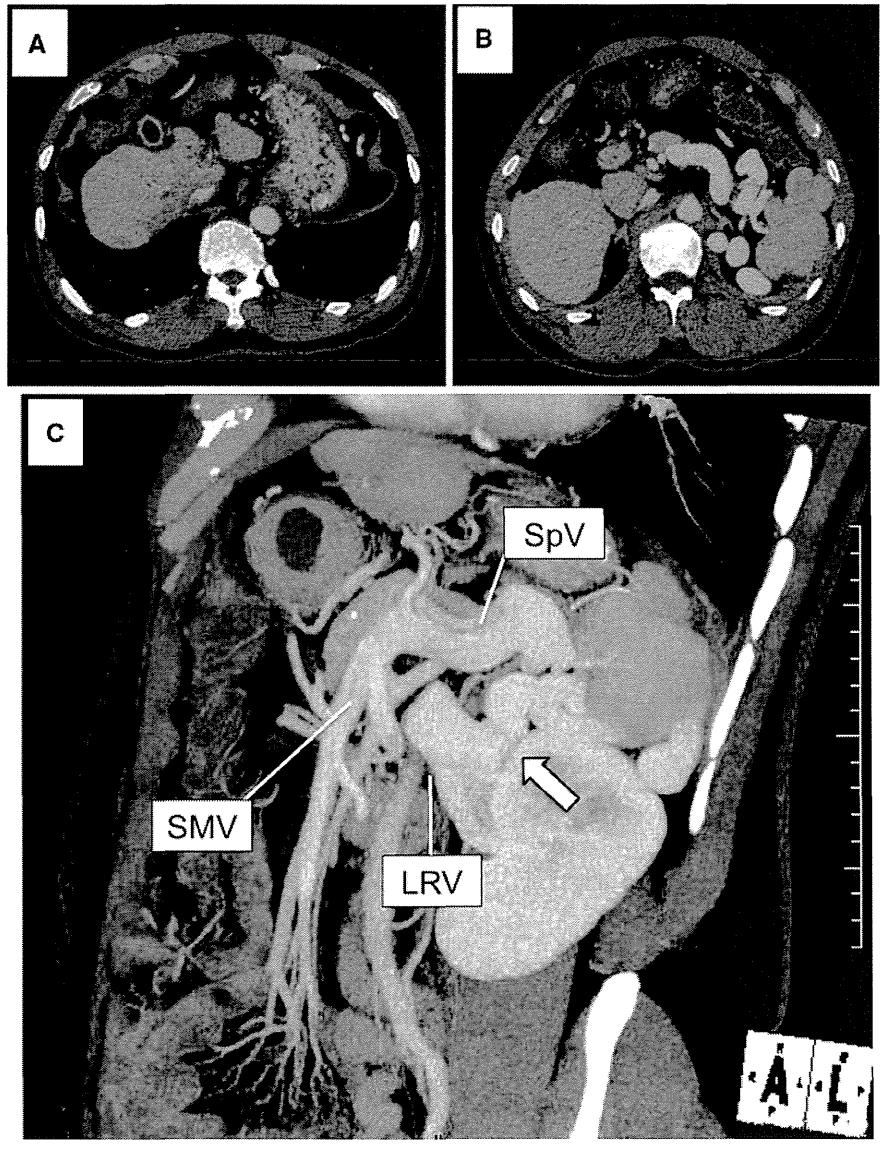

Fig. 1 Abdominal CT scans showing (**a**) atrophy of the liver with minimum portal flow and (**b**) a highly active splenorenal shunt with a deformed spleen. **c** Maximum intensity projection image. The *white arrow* indicates the junction of the splenorenal shunt into the LRV. *SMV* Superior mesenteric vein, *LRV* left renal vein, *SpV* splenic vein

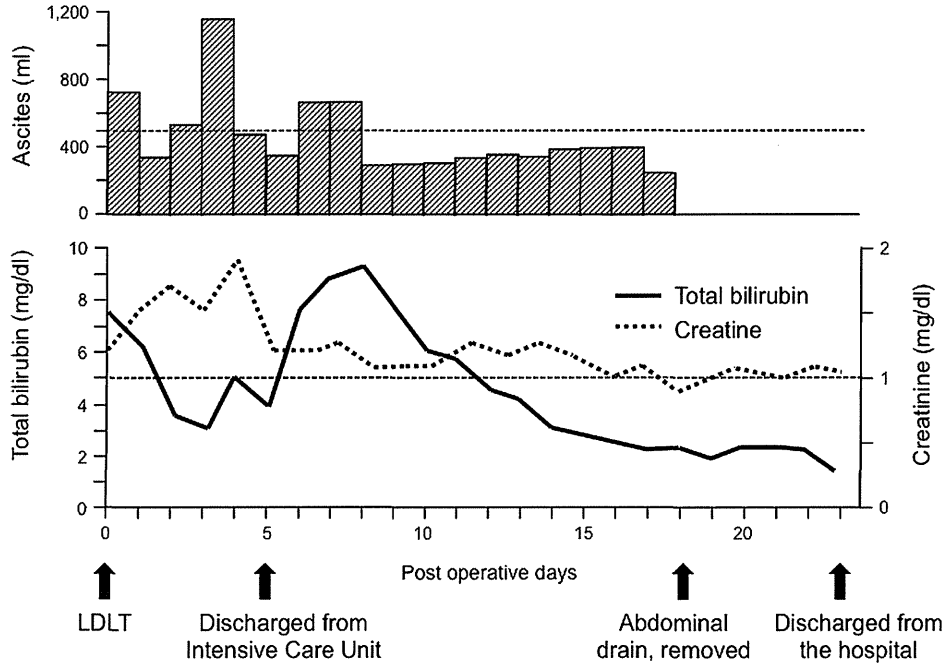

Fig. 2 Postoperative course. The patient showed a temporary increase in the output of ascites and hyperbilirubinemia

The right lobe LDLT graft donated from his son weighed 580 g, representing 44.1 % of the calculated standard liver volume. The graft had a right hepatic vein and a V5 vein for venous drainage. The opening of the V5 was anastomosed to the manually dilated explanted PV, which was connected to the right hepatic vein in a side-to-side fashion, to enable one-step venous anastomosis. A venovenous bypass was used for circulatory stabilization during the anhepatic phase.

The second portion of the duodenum was mobilized from the retroperitoneum and the LRV was identified and controlled with a tape, clamped, and divided. The supra- and infra-hepatic vena cava was clamped and total hepatectomy was performed. The right lobe graft was placed in the body and venous anastomosis between the conduit of the graft venous system and the vena cava was performed using continuous 5-0 PDS sutures. The right internal jugular vein was anastomosed to the LRV using continuous 6-0 PDS sutures coated with growth factor. The interposed jugular vein was then connected to the grafted PV. Reperfusion was initiated and the circulatory system remained stable. The cold, warm and anhepatic times were 150 min, 44 min and 284 min, respectively. Portal venous pressure at the end of surgery was 24 mmHg. The total surgical time and operative blood loss were 819 min and 6.3 L, respectively.

The patient's post-transplant course is shown in Fig. 2. Although the patient temporarily showed an increased output of ascites and hyperbilirubinemia, he was discharged from the hospital on postoperative day 23 with normal liver function tests. CT showed a patent smooth portal venous flow from the persistent large SRS scans at 4 months after surgery (Fig. 3).

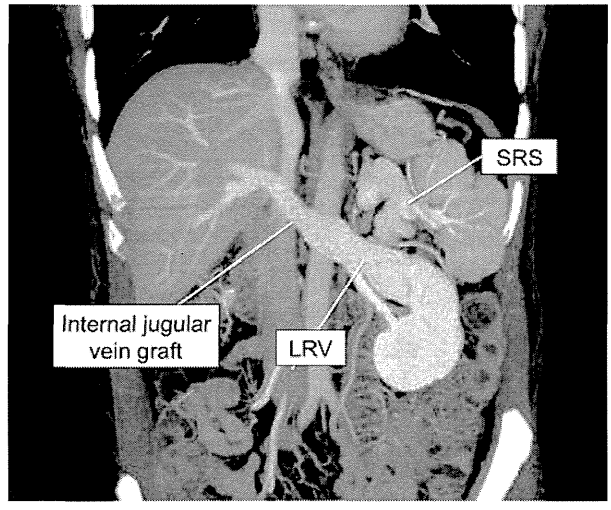

Fig. 3 Maximum intensity projection image taken 4 months after transplantation. *LRV* Left renal vein, *SRS* splenorenal shunt

Discussion

Thrombectomy or patch plasty of the PV followed by direct anastomosis between the graft and recipient PV may be possible for most patients with thrombosis or atrophy of the PV [4]. However, establishing an appropriate portal flow capacity is essential to prevent re-thrombosis of the

anastomosed PV or graft dysfunction because of the decreased portal inflow [5]. The obstruction of these vessels is necessary to prevent the occurrence of steal phenomenon in patients with major porto-systemic shunt vessels. However, the ligation of such large and fragile shunt vessels in a deep surgical field is technically difficult and may cause significant bleeding, morbidity or mortality [6].

RPA offers one solution to establish graft inflow in patients with a large SRS and either an occluded or markedly reduced portal inflow, using an anomalous shunt [7]. Marubashi et al. [8] first reported three patients who underwent this technique during LDLT. Moon et al. [9] used a prosthetic graft in an end-to-side fashion to establish a renoportal connection, and thus achieved an excellent graft function. However, a prosthetic graft has the disadvantage of its thickness and rigidity, and the patients must receive aspirin daily to prevent prosthetic graft thrombosis. Furthermore, they have the risk of developing prosthetic infection caused by immunosuppressant. Table 1 is the respective data of the variations in vein grafts. The internal jugular vein is used in this department. The removal of the internal jugular vein does not have any harmful effects on the central nervous system. An external iliac vein is usually 7–8 cm and shorter than the internal jugular vein. The main advantage of creating a RPA is that manipulation or dissection around the large and fragile shunt vessels is unnecessary. Moreover, an adequate blood flow into the graft is guaranteed, which drains from the mesenteric and left renal system. The PV flow/graft volume ratio in this case was 2.90 ml/min, which is considered to be an acceptable score.

However, this technique does have some disadvantages in comparison to direct portal anastomosis. First, an excessive inflow caused by the addition of a left venous return into a graft is possible after LDLT, in which a smaller graft is implanted. Graft dysfunction caused by an excessive portal inflow has been called small-for-size syndrome, and it is characterized by the production of persistent ascites and prolonged hyperbilirubinemia [10]. The present patient's maximum output of ascites was 1 L on postoperative day 4 and his maximum total bilirubin concentration was 9.4 mg/dl on postoperative day 8. Although these values do not necessarily indicate small-for-seize graft syndrome, the post-operative clinical characteristics of the present recipient, including a model for end-stage liver disease score of 16 and a sufficient graft volume/standard liver volume ratio of 44.1 %, are consistent with graft over-perfusion syndrome.

Possible congestion of the left kidney may be another disadvantage of RPA. The serum creatinine levels were elevated for 1 week, in the present patient with levels reaching 2.0 mg/dl. However, Lee et al. [11] reported that manipulation of the outflow of the LRV after the ligation of the proximal LRV in patients with a large SRS causes only a temporary renal impairment. These surgical procedures caused a temporary renal impairment in the present case, and the creatinine levels returned to the normal range within 1 month after LDLT.

Finally, the indications for RPA in patients with hepatitis C are considered to be another topic for debate. In our institute, splenectomy is suggested for patients undergoing LDLT for hepatitis C to treat hypersplenism and facilitate

Table 1 Primary disease, graft type, venous graft, and prognosis of patients that underwent RPA during LTx renoportal anastomosis in adult-to-adult living donor liver transplantation

Reference	Primary disease	Liver graft	GV/SLV (%)	GRWR	Vascular graft	Technique	Complications
Marubashi et al. [8]	PSC	Right	56	N/A	Jugular vein	End-to-end	Ascites
	Cryptogenic	Right	49	N/A	Jugular vein	End-to-end	–
	Wilson	Right	38	N/A	Jugular vein	End-to-end	Ascites, pneumonia
Moon et al. [15]	Hepatitis B	Right	46	N/A	Iliac vein	Side-to-end	Ascites
	Hepatitis B, HCC	Right	73	N/A	Iliac vein	End-to-end	–
	Hepatitis B, HCC	Dual graft (2 left lobe)	79	N/A	Iliac vein with IVC	Side-to-end	Cerebral hemorrhage, ascites, decrease of PV flow
	Hepatitis B, HCC	Right	45	N/A	Aorta	Side-to-end	–
	Alcoholic	Right	52	N/A	Aorta + GSV	Side-to-end	–
Moon et al. [9]	Hepatitis B	Right	N/A	1.14	ES-PTFE	Side-to-end	–
Present case	IPH	Right	44.1	0.81	Jugular vein	End-to-end	Ascites, hyperbilirubinemia

ES-PTFE Externally stented polytetrafluoroethylene, *GV* graft volume, *IPH* idiopathic portal hypertension, *N/A* not available, *PSC* primary sclerosing cholangitis, *SLV* standard liver volume, *GRWR* graft-recipient body weight ratio, *IVC* inferior vena cava, *GSV* great saphenous vein

post-transplant interferon treatment for the almost inevitable recurrence of hepatitis C [12]. Persistent hypersplenism in LDLT is a major cause of discounting interferon treatment discontinuation in patients with hepatitis C [12, 13]. Cirrhosis occurs in almost 10–30 % of patients with untreated hepatitis C within 5 years of liver transplantation [14]. Therefore, RPA, in which the spleen stays in place, should not be indicated for patients with hepatitis C. However, RPA may be considered in patients with hepatitis C with severe portal vein stenosis or thrombosis.

In summary, RPA is therefore thought to be a useful option for patients with portal occlusion and large SRS undergoing LDLT, particularly in cases selected based on appropriate indications by carefully considering the limitations of RPA.

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Abstract

Malnutrition is common in liver cirrhotic patients who will undergo liver resection or liver transplantation. A precise evaluation of their nutrition status is thus difficult because of the presence of ascites and the edema caused by their impaired protein synthesis. Both perioperative enteral and parenteral nutrition have benefits in reducing the morbidity and mortality of liver surgery, and in general, oral nutrition supplements are recommended. Branched-chain amino acids (BCAAs) promote protein and glycogen synthesis and regulate immune system function. Synbiotics, a combination of pro- and prebiotics, is reported to enhance immune responses. Oral nutrition support with BCAAs, synbiotics, and an immune-enhancing diet have a beneficial effect on preventing the perioperative infections associated with hepatic resection or liver transplantation. (*JPEN J Parenter Enteral Nutr.* 2013;37:318-326)

Keywords

nutrition; infection; bacteremia; liver cirrhosis; liver surgery; hepatic resection; liver transplantation; branched-chain amino acids; synbiotics

Clinical Relevancy Statement

In liver surgery and transplantation, postoperative infection is one of the most important problems that cause postoperative morbidity and mortality. The nutrition therapy may improve the clinical outcome in cirrhotic patients undergoing hepatic surgery and liver transplantation. This review focused on the role of nutrition supports especially on perioperative infection or sepsis.

Introduction

Malnutrition is a common complication of chronic liver diseases, and it is an independent risk factor for survival in patients with liver cirrhosis.[1-3] Inadequate dietary protein intake may have a deleterious effect on hepatic encephalopathy, nutrition status, and clinical outcome in patients with end-stage liver failure.[4,5] In patients with an indication for liver surgery and/or transplantation, a decreased liver function with nutrition deficiency is common. This poor nutrition status before hepatic resection or transplantation has been suggested to increase the risk of postoperative complications and/or mortality.[6-12] However, other reports suggest that the nutrition parameters and markers of disease severity do not correlate with the outcomes after liver transplantation.[13]

The branched-chain amino acids (BCAAs)—leucine, isoleucine, and valine—are essential amino acids, especially in patients with liver cirrhosis, and may have an effect on hepatic encephalopathy, immunity, and infections.[14-17]

Postoperative infections are one of the most important problems leading to postoperative morbidity and mortality in patients who undergo liver surgery or transplantation.[18] The recipients' preoperative malnutrition is a risk factor that increases infectious complications after liver transplantation.[12,19-21] In fact, several reports have shown that a decreased liver function before liver transplantation may be related to postoperative bacteremia.[22-25] The use of nutrition therapy may improve the clinical outcome in cirrhotic patients undergoing general surgery and liver transplantation.[8]

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This review focuses on the role of nutrition support, especially on the development of perioperative infection or sepsis after hepatic resection and liver transplantation. The reports mainly published after 1995 were assembled and discussed.

Prevalence of Malnutrition in Cirrhotic Patients

Malnutrition develops in patients with cirrhosis independent of the etiology.[6,26] The prevalence of malnutrition is reported to be 50%–90% in cirrhotic patients.[27] A multicenter Italian study including more than 1400 patients with cirrhosis showed malnutrition to be recognized in 20% of patients with Child-Pugh class A and in 50%–60% of patients with Child-Pugh class C.[8,28] Actually, the prevalence of malnutrition in cirrhotic patients may depend on how the nutrition assessment was performed.[8]

Mechanisms Responsible for the High Frequency of Infections in Cirrhosis

Cirrhotic liver patients show a high frequency of infections such as spontaneous bacterial peritonitis (SBP), bacteremia/sepsis, respiratory tract infections, urinary tract infections, meningitis, endocarditis, phlegmonous colitis, and hepatic abscess.[29] Bacterial translocation is reported to be a key mechanism of SBP.[30] The pathogenetic mechanisms of such a high susceptibility of infections may be associated with polymorphonuclear leucocyte dysfunction, complement deficiency, reticuloendothelial system dysfunction, macrophage dysfunction, increased production of interleukins, and decreased tumor necrosis factor (TNF)–α activity.[29]

Assessment of Nutrition Status

Assessing the nutrition status of patients with liver dysfunction is often difficult because of the fluid collections caused by the impaired protein synthesis in these patients. Weight is not a reliable indicator of malnutrition because of the presence of ascites and edema, which may lead to an increase in body weight despite a reduction in lean body mass.[6] Body mass index (BMI) may afford a more reliable indicator of malnutrition if different cutoff values are used depending on the presence and severity of ascites.[31]

Anthropometry measurements include the triceps skin-fold thickness, mid-arm circumference (MAC), and mid-arm muscle circumference (MAMC), assessing the skeletal muscle mass.[32-34] Subjective global assessment (SGA) is a technique that combines multiple elements of nutrition assessment to classify the severity of malnutrition (Supplement 1).[32,35-37] These components include weight loss during the previous 6 months, changes in dietary intake, gastrointestinal symptoms, functional capacity, metabolic demands, signs of muscle wasting, and the presence of edema in the lower extremities.[35] The SGA is not affected by fluid retention or the formation of ascites.[38] A modified SGA, named the Royal Free Hospital–SGA, combines a subjective assessment of the nutrition status with BMI, MAMC, and dietary intake.[38,39] Assessment of muscle function, determined by measuring hand-grip strength and respiratory muscle strength, has also been used in nutrition evaluation.[12,31,40] Recently, sarcopenia in the lumbar skeletal muscle, as calculated by computed tomography, has been used to evaluate the nutrition state or degree of liver dysfunction.[41] In patients undergoing liver transplantation, it is reported that sarcopenia correlates with post–liver transplant mortality.[42] Concerning muscular status, the level of 3-methylhistidine is a marker of muscular proteolysis and can be used as a nutrition marker.[43]

Depletion of the body cell mass (BCM) is a useful estimation of nutrition status.[11,44] Bioelectrical impedance is a more readily available tool for estimating the BCM.[45] An evaluation of the status of energy metabolism might be a reasonable component of a nutrition assessment because there seems to be a correlation between hypermetabolism and malnutrition.[6]

The concentrations of rapid turnover proteins, such as serum albumin, prealbumin, retinal-binding protein (RBP),[46] and transferrin,[47] may be low because of low levels of synthesis, rather than because of poor nutrition status.[6] Some reports have suggested that alterations in serum albumin level improve both surgical and postsurgical complications of liver transplantation.[48-50] These proteins, especially serum albumin, correlate with liver function and may not be reliable as a nutrition marker in cirrhotic patients.[51] In patients with relatively stable liver disease, rapid turnover proteins may be simple and useful nutrition markers.

Various other measures can indicate the nutrition status. For example, an imbalance in the plasma levels of aromatic amino acids (AAAs) and BCAA, the so-called Fisher's ratio, or the BCAA/tyrosine ratio (BTR) has been demonstrated to have a causal role in hepatic encephalopathy.[52]

The nonprotein respiratory quotient (npRQ), a unitless number estimated from carbon dioxide production, is used to evaluate the nutrition status of patients with liver cirrhosis.[53]

The homeostasis model assessment (HOMA), a method used to quantify insulin resistance and β-cell function,[54,55] has been reported to accurately reflect nutrition status in patients with nonalcoholic fatty liver disease.[55]

Combinations of some anthropometric measurements, physical examinations, and laboratory data can be more reliable to assess nutrition status in patients with relatively stable liver disease who are scheduled to undergo a liver resection. A marker that is not related to the fluid collection, such as sarcopenia, might reliably determine nutrition status in patients with severe liver dysfunction expecting liver transplantation.

Parenteral Nutrition

In vitro, liver regeneration can be accelerated by administering a parenteral nutrition (PN) solution tailored to normalize the plasma amino acids associated with compromised liver function.[56] Fan et al[57] reported that perioperative intravenous (IV)

Table 1. ESPEN and A.S.P.E.N. Guidelines for Cirrhotic Patients.

ESPEN guidelines[32]	35–40 kcal/kg/d Enteral nutrition is recommended. Supplemental nutrition, especially BCAA-enriched formula, is preferred.
A.S.P.E.N. guidelines[119]	
Without encephalopathy	25–35 kcal/kg/d
With acute encephalopathy	35 kcal/kg/d
Stable and malnourished	30–40 kcal/kg/d

A.S.P.E.N., American Society for Parenteral and Enteral Nutrition; BCAA, branched-chain amino acid; ESPEN, European Society for Clinical Nutrition and Metabolism.

nutrition support, in addition to oral diet, can reduce the complications after major hepatectomy in cirrhotic patients. PN is indicated for malnourished cirrhotic patients who cannot be nourished sufficiently by either the oral or enteral routes.[58] It has been reported that enteral nutrition (EN) and PN were equally effective for maintaining nutrition status after liver transplantation and decreasing complications and cost.[59] Plauth et al[60] suggested that parenteral feeding might be superior to enteral feeding in patients with portosystemic shunting because enteral feeding might worsen hyperammonemia.

Enteral Nutrition

The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines (see Table 1) advocate that patients with liver cirrhosis should receive 35–40 kcal/kg/d with 1.2–1.5 g/kg protein/d.[32] In general, oral nutrition supplements are recommended for patients without any contraindications such as ileus.[32] If patients cannot maintain adequate oral intake, tube feeding is recommended even when esophageal varices are present.[32] It was recently reported that protein restriction in patients with liver failure has no impact on the encephalopathy and even worsens nutrition status.[61] Cordoba et al[4] reported that diets with a normal protein content can be safely administered to cirrhotic patients with episodic hepatic encephalopathy. Many reports have described the effects of oral nutrition supplementation in patients with alcoholic cirrhosis.[62-66] For example, Le Cornu et al[67] reported that regular dietary counseling is as effective for increasing energy intake as providing a nutrition supplement. Other reports also have exhibited the superiority of the safety and efficacy in terms of postoperative complication rates for postoperative early EN compared with PN.[68-70] The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) guidelines (see Table 1) also support the concept that EN is favored to preserve gut integrity and immune markers and to simplify glycemic management.[71] In adult living donor liver transplantation, Kaido et al[72] reported that EN is a promising strategy to improve postoperative mortality and morbidity rates.

Branched-Chain Amino Acids

Oral supplementation with essential amino acids can improve hepatic encephalopathy and the quality of life in not only cirrhotic patients but also institutionalized elderly patients.[73-75] Supplemental BCAA is commonly applied in patients with liver cirrhosis,[76,77] especially compensated cirrhosis[78,79] or hepatocellular carcinoma.[80-85] The ESPEN guidelines recommend the use of BCAA-enriched supplements in patients with hepatic encephalopathy.[32] It was proposed that depletion of BCAAs, as seen in many patients with advanced liver disease, promotes the development of hepatic encephalopathy by enhancing the passage of AAAs across the blood-brain barrier, resulting in the synthesis of false neurotransmitters.[6] In addition, the administration of solutions enriched with BCAAs has been shown to improve cerebral perfusion in cirrhotic patients.[86]

In prospective studies, it was reported that long-term oral supplementation with a BCAA mixture improved the serum albumin level, as well as the cellular energy metabolism and quality of life in cirrhotic patients.[77,87] The timing of the supplementation with BCAA is also important. It was reported that nocturnal BCAA administration as a late evening snack (LES) improved the serum albumin level in cirrhotic patients who showed no improvement in their serum albumin levels with daytime BCAA administration.[53,88,89] Recently, many reports have shown that BCAA supplementation can improve not only energy metabolism and BTR but also glucose tolerance.[90-95]

There have been reports that perioperative administration of BCAA to patients undergoing hepatic resection quickly improves liver function during the early postoperative period.[81,96,97] Ishikawa et al[98] reported that short-term oral nutrition support with BCAA was associated with higher serum erythropoietin levels in patients with nonhepatitis liver disease who underwent curative hepatic resection. They suggested that it had benefits in protecting liver cells from ischemic injury and preventing intraoperative hemorrhage.[98]

In liver transplantation patients, perioperative supplementation with BCAA-enriched nutrients can improve the nutrition and metabolic disorders associated with end-stage liver disease.[99] Early interventional oral BCAAs might prolong the liver transplant waiting period by preserving the hepatic reserve in patients with cirrhosis.[100] Recently, the effectiveness of amino acid (ie, glycine, taurine, N-acetylcysteine, arginine, and methionine) supplementation in protecting against ischemia/reperfusion injury (IRI) has attracted attention.[101]

Figure 1 shows a schematic representation of the activities of BCAA. BCAA, especially leucine, activates the mTOR signaling pathways and inhibits protein degradation in vitro, thus resulting in the promotion of protein synthesis.[102,103] Furthermore, in a cirrhotic rat model, leucine activated glycogen synthase via mTOR signaling and improved glucose metabolism.[104] Several reports have suggested that BCAA

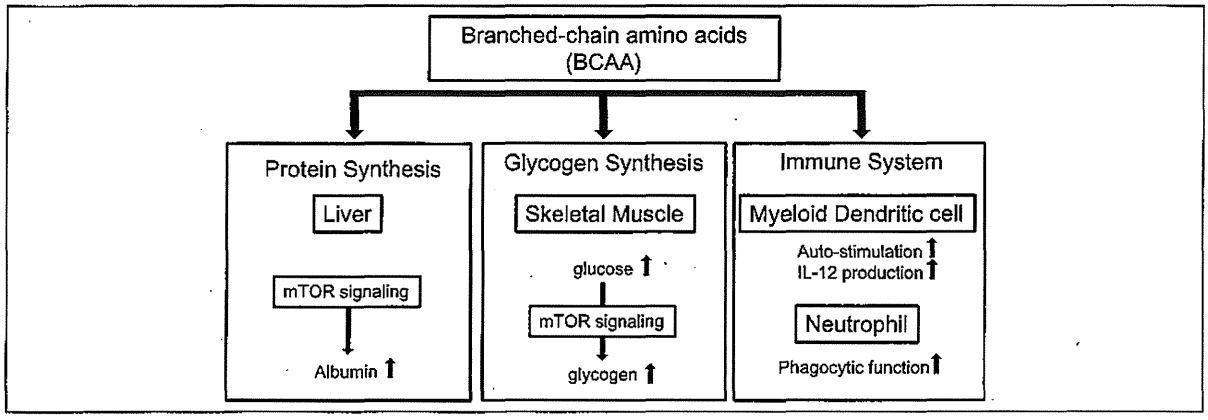

Figure 1. A schematic representation of the activities of branched-chain amino acids (BCAAs). BCAAs promote protein synthesis by activating mTOR signaling in the liver. In the skeletal muscle, BCAAs promote glycogen synthesis via the activation of mTOR signaling. In addition, BCAAs regulate immune system function by activating the myeloid dendritic cell function and improving the phagocytic function of neutrophils.

supplementation can restore or regulate the immune function in patients with advanced cirrhosis.[105-109] Calder[14] reported that the essentiality of BCAA for the function of immune cells relates to protein synthesis. Kakazu et al[107,108] reported that an elevation of the BCAA level improved the function of myeloid dendritic cells and that this was beneficial to immune function. Nakamura et al[105,106] reported that the phagocytic functions of neutrophils and the natural killer activity of lymphocytes obtained from patients with liver cirrhosis were restored by oral supplementation with BCAAs.

Synbiotics

Selective bowel decontamination increases the incidence of cholangitis and bacterial infections.[110] Synbiotics, a combination of pro- and prebiotics, increase the intestinal content of lactic acid–type bacteria in hepatic encephalopathy patients with end-stage liver failure.[48] Sugawara et al[111] reported that preoperative oral administration of synbiotics can enhance immune responses, attenuate systemic postoperative inflammatory responses, and improve the intestinal microbial environment.

Beneficial Effects of Nutrition Support Against Infections Associated With Liver Surgery (Table 2)

Fan et al[57] evaluated the effects of perioperative PN in addition to a typical oral diet, from 7 days before hepatic resection and continued for 7 days after the operation. Perioperative PN in addition to a normal oral diet was associated with a significant reduction in infectious complications (a normal oral diet plus PN: 17% vs control: 37%).[57] This relatively large prospective study has sufficient power to show the benefits of nutrition support for preventing the occurrence of infection after liver surgery. Shirabe et al[69] prospectively compared postoperative early EN and PN. Early enteral feeding had a tendency to reduce the infection rate after major hepatic resection (early EN: 8% vs PN: 31%), without statistical significance due to the small number of patients. Mochizuki et al[70] retrospectively and prospectively compared postoperative EN and PN. Although it was a retrospective study with nonrandomized prospective data, the infection rate of patients in the early EN group, especially high-risk patients, was markedly decreased.[70] Okabayashi et al[112] evaluated the benefits of perioperative supplementation of BCAA-enriched nutrients in patients undergoing hepatic resection. Postoperative surgical site infection tended to be lower in the BCAA supplementation group (5%) than in the control group (15.3%). However, this retrospective study only briefly discussed "infectious" complications, and therefore the impact of BCAA supplementation on preventing postoperative infections still remains insufficiently described, and thus further studies are expected.

In hepatic resection for patients with liver disease, perioperative nutrition support, either enteral or parenteral, can reduce septic complications. Furthermore, postoperative early EN, especially BCAA-enriched nutrition, may prevent postoperative infections.

Beneficial Effects of Nutrition Support Against Infections Associated With Transplantation (Table 3)

Hasse et al[113] evaluated the benefits of receiving EN via nasointestinal feeding tubes before initiating an oral diet. Nutrition support therapy decreased the incidence of viral

Table 2. Beneficial Effects of Perioperative Nutrition Support in Reducing Infections in Patients Undergoing Hepatic Resection.

Authors	Study Design	Patient No.	Nutrition Therapy (Infection Rates)
Fan et al,[57] 1994	Prospective study	124 (64 with PN and 60 with oral diet alone)	Pre- and postoperative PN in addition to oral diet (17%) and oral diet alone (37%)
Shirabe et al,[69] 1997	Prospective study	26 (13 with early EN and 13 with PN)	Postoperative early EN (8%) and PN (31%)
Mochizuki et al,[70] 2000	Retrospective and prospective study	67 (19 with early EN and 48 with PN)	Postoperative early EN (30%) and PN (73.1%)
Okabayashi et al,[112] 2008	Retrospective study	112 (40 with BCAA supplementation and 72 with control)	Pre- and postoperative BCAA-enriched nutrition (5%) and control (15.3%)

BCAA, branched-chain amino acid; EN, enteral nutrition; PN, parenteral nutrition.

Table 3. Beneficial Effects of Perioperative Nutrition Support in Reducing Infections in Patients Undergoing Liver Transplantation.

Authors	Study Design	Patient No.	Nutrition Therapy (Infection Rates)
Hasse et al,[113] 1995	Prospective study	31 (14 with tube feeding and 17 with control)	Postoperative tube feeding (21.4%) and control (47.1%)
Rayes et al,[114] 2002	Prospective study	95 (32 with selective bowel decontamination, 31 with *Lactobacillus*, and 32 with placebo)	Postoperative early EN with *Lactobacillus* (13%) and control (48%)
Rayes et al,[115] 2005	Prospective study	66 (33 with lactic acid bacteria and fiber and 33 with fiber only)	Postoperative early EN with lactic acid bacteria and fiber (3%) and only fiber (48%)
Plank et al,[117] 2005	Retrospective study	32 (15 with perioperative immunonutrition and 17 with control)	Pre- and postoperative immune-enhancing diet (33%) and control (71%)
Kaido et al,[118] 2010	Prospective study	30 (10 with postoperative early immunomodulating nutrition and 20 with conventional enteral diet)	Postoperative early EN with immunomodulating diet (10%) and control (50%)
Shirabe et al,[22] 2011	Retrospective study	236 (129 with BCAA supplementation and 107 with control)	Preoperative BCAA supplementation (6.7%) and control (22.0%)

BCAA, branched-chain amino acid; EN, enteral nutrition.

infection (enteral tube feeding: 0% vs control: 17.7%) and showed a trend to decrease bacterial (enteral tube feeding: 14.3% vs control: 29.4%) and overall (enteral tube feeding: 21.4% vs control: 47.1%) infections.[113] Although this was a small-group study, this proves the benefits of early EN in preventing both viral and bacterial infections. Shirabe et al[22] evaluated the effectiveness of preoperative oral supplementation with BCAA. Preoperative BCAA supplementation reduced the incidence of bacteremia (BCAA supplementation: 6.7% vs control: 22.0%) after living donor liver transplantation. Although it is a retrospective study, it was valuable because it included a large number of patients and the infectious complication rates were quite low in the preoperative BCAA supplementation group. Some *Lactobacillus* species have been shown to initiate immunoglobulin production, restore macrophage function, stimulate apoptosis, and modulate lymphocyte function.[114] In addition, *Lactobacillus* is reported to influence cytokine release, increase mucin production, eliminate toxins, and stimulate mucosal growth.[114] Rayes et al[114,115] reported the benefits of a perioperative supply of synbiotics. The patients who received living *Lactobacillus plantarum 299* plus fiber developed fewer bacterial infections (13%) than did control patients (48%).[114] In addition, the incidence of postoperative bacterial infections was lower (3%) with lactic acid bacteria and fiber than in the 48% of patients who consumed only fiber.[115] Supplementation with ω-3 fatty acids downregulated proinflammatory cytokine production and modulated eicosanoid synthesis.[116] In addition, arginine stimulated the release of growth hormone and insulin, improved nitrogen balance and wound healing, upregulated

immune function, and enhanced nitric oxide (NO) biosynthesis.[116] Plank et al[117] evaluated the effects of a pre- and postoperative enteral immune-enhancing diet. Infectious complications were less common in patients who received immunonutrition (33% in the immunonutrition group and 71% in the control group), although there were no significant differences.[117] Similarly, Kaido et al[118] reported the benefit of postoperative early EN with an immunomodulatory diet. The incidence of posttransplant bacteremia was lower in the immunomodulatory diet group (10%) than in the conventional enteral diet group (50%).[118] This prospective study showed a much lower rate of infectious complications in the immune-enhancing diet group. A randomized controlled study evaluating the effect of preoperative long-term immunonutrition in patients listed for liver transplantation is planned in Europe.[116]

In summary, in patients undergoing liver transplantation, early posttransplant tube feeding is recommended. As early postoperative nutrition, solutions containing pre- and probiotics have some effects to prevent postoperative infections. Preoperative supplementation with BCAA may improve patient malnutrition and reduce the risk of postoperative infections. A pre- and postoperative immune system–enhancing diet increasingly has been demonstrated to have benefits in preventing posttransplant infectious complications.

Conclusions

Malnutrition is common in patients with liver cirrhosis undergoing liver resection or liver transplantation. Oral nutrition support with BCAA, synbiotics, and an immune-enhancing diet can have a beneficial effect on preventing the postoperative infections associated with hepatic resection or liver transplantation.

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