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Impact of psoas muscle index on short-term outcome after living donor liver transplantation

LIVER

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Original Article

ABSTRACT

Background/Aims: Living donor liver transplantation is an operation with high morbidity and mortality rates. The purpose of this study was to examine factors affecting the short-term outcome after living donor liver transplantation.

Materials and Methods: Forty-seven adult patients who underwent living donor liver transplantation from September 2001 to December 2014 were included. Short-term post-transplant outcomes were evaluated in terms of the onset of postoperative complications of grade 3a and above (Clavien–Dindo classification) and postoperative 120-day mortality. Univariate and multivariate analyses were used to determine possible predictive factors among perioperative variables such as preoperative psoas muscle index (PMI), blood laboratory test results, perioperative nutritional therapy, and operative factors.

Results: Lower PMI (lower than the first quartile of PMI of donors), higher blood urea nitrogen level (≥14 mg/dL), and blood type incompatibility were independent risk factors for the development of postoperative complications. The 120-day survival rates were significantly lower for the lower PMI group (n=30, 66.7%) than for the higher PMI group (n=17, 94.1%, p=0.034).

Conclusion: A significant correlation was observed between preoperative PMI and short-term postoperative outcomes. Sarcopenia estimated by PMI may serve as a measure of patient frailty and a target for risk stratification.

Keywords: Living donor liver transplantation, psoas muscle index, skeletal muscle mass

INTRODUCTION

In Japan, where deceased donor liver grafts are rarely available, living donor liver transplantation (LDLT) is generally performed on patients with end-stage liver disease who are in poor general condition or have low physiologic reserves related to their disease severity (1). Substantial mortality still occurs shortly after the procedure as a result of postoperative complications (2,3). Several factors have been reported to worsen the prognosis after liver transplantation, including preoperative infectious comorbidity, surgical stress such as massive blood loss and long operation time, postoperative infection related to immunosuppressive therapy, and acute rejection (2).

Recent reports have identified sarcopenia (loss of skeletal muscle mass) as one of the important factors that affects postoperative mortality (4-6). The skeletal muscle mass is under investigation as a prognostic factor for liver transplantation and a range of other operations and procedures (4,7,8).

Thus, the reason that the skeletal muscle mass is important as a postoperative prognostic factor is because it is commonly used an objective index. The skeletal muscle mass is used in addition to the conventionally used eyeball test, which is a subjective evaluation of a patient's physique at a glance as an indicator of the patient's global health status and how well the patient would be able to withstand surgery (9).

The present study investigated the effects of the skeletal muscle mass and other perioperative factors on the

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onset of complications and the postoperative 120-day survival rate in patients who underwent LDLT at our institution.

MATERIALS AND METHODS

Patients

Sixty patients underwent LDLT at Ehime University Hospital between September 2001 and December 2014. Among them, 47 adult patients whose abdominal computed tomography (CT) images performed within 60 days before transplantation were available were enrolled. Clinical, imaging, and surgical data for patients were retrospectively collected from medical records and the hospital database. Written informed consent was obtained from all patients. This study was approved by the Institutional Review Board of Ehime University Hospital.

Endpoints

The primary endpoint was the development of major complications during postoperative hospitalization, and the secondary endpoint was 120-day mortality after LDLT. Major complications were defined as those corresponding to grade 3 (patient condition requiring surgical, endoscopic, or radiological intervention) and above according to the Clavien–Dindo (CD) classification (10).

Possible prognosis factors

The following parameters were investigated. Patient factors included recipient sex, recipient and donor age, blood type compatibility, underlying disease [hepatitis C virus (HCV) or non-HCV], preoperative history of spontaneous bacterial peritonitis, Child–Pugh classification, Model for End-stage Liver Disease (MELD) score, and the psoas muscle index (PMI) as an index of the total skeletal muscle mass. To calculate PMI, the outer margin of the cross-section of the major psoas muscle at the level of the caudal end of the third lumbar vertebral body was manually traced on preoperative abdominal contrast CT images, and the sum of the left and right cross-sectional areas was divided by the square of the height (8,11). Preoperative blood laboratory test results were investigated for total lymphocyte count and hemoglobin, total protein, albumin, total cholesterol, blood urea nitrogen (BUN), and creatinine levels. Perioperative nutritional therapy was investigated in terms of the use of preoperative nutritional therapy [administration of a branched chain amino acid (BCAA) formulation from 2 weeks before surgery] and postoperative enteral nutrition (administration of an elemental diet via a jejunostomy tube from immediately after surgery) (6). Surgical factors consisted of operating time, intraoperative blood loss volume, graft-to-recipient weight ratio, and graft type (right lobe/left lobe).

Statistical analysis

In the analysis of risk factors for the development of severe complications, continuous variables were evaluated by the Mann–Whitney U test and categorical variables by the c^2 test in univariate analysis. Variables for which p was <0.05 were considered as candidates for multivariate analysis. As the number of patients in this study was less, it was possible that even if a significant difference was observed, the result would have a low reliability. Hence, regardless of the number of patients, we calculated as the absolute difference between the two groups the effect size [a chi-square test ("Cramer's V"); the Mann–Whitney U test ("r")] for each variable with which a significant difference was obtained (12). Logistic regression analysis was performed as multivariate analysis. In the present study, the first quartiles of PMI of donors more than 35 years of age as the representative values of healthy controls were used as cutoff values for PMI. PMI cutoff values were based on the following. First, many definitions of sarcopenia have been set based on the muscle mass of healthy controls (13). Second, it has been reported that the proportion of sarcopenia among Japanese people is 25.0% in men and 24.2% in women (14). Third, there was no significant difference in the present study between the age distribution of recipients and donors more than 35 years of age (data not shown). For the continuous variables, the optimum cutoff values were calculated using a receiver operating characteristic (ROC) curve (15). The 120-day survival rates were calculated using the Kaplan–Meier method, and differences between curves were evaluated by the log-rank test. P<0.05 was considered significant. The software package JMP®11 (SAS Institute, Inc.; Cary, NC, USA) was used for statistical analysis.

RESULTS

Patients' characteristics are shown in Table 1. In comparing recipients' PMIs with that of the donors, no significant difference was recognized in men (p=0.155); however, in women, recipients' PMIs were significantly lower than donors' PMIs (p=0.005). For recipients, a significant difference was observed in PMI between patients with and without complications, both for men (p=0.004) and women (p=0.015) (Figure 1). The first quartiles of donors' PMIs were 612.5 in men and 442.9 in women; these were used as the cutoff values of PMI for recipients (Figure 1).

Table 2 shows the major complications that developed during the patients' postoperative hospitalizations based on the CD classification. Grade 5 (death) was seen 11 patients between 11 and 118 days (median, 30 days) after LDLT, with the most common causes of death being acute rejection in 3 patients, sepsis in 3, and pneumonia in 2. Grade 4a complications occurred in 5 patients, all of whom developed acute respiratory distress syndrome/acute lung injury. Grade 3b complications were seen in 9 patients and consisted of intraperitoneal hemorrhage in 8 patients. Grade 3a complications developed in 7 patients, including stenosis at the biliary duct anastomosis, gastrointestinal hemorrhage, intraperitoneal abscess, and pneumonia.

Risk factors for the development of severe complications during postoperative hospitalization (Table 3, 4).

Univariate analysis revealed that patients with complications (n=32) had a significantly higher incidence of low PMI

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Table 1. Patients' characteristics

Gender: Men/Women	24/23
Recipient age	54 (26-66)
Donor age	39 (20-67)
Blood type: Identical or Compatible/Incompatible	41/6
Child-Pugh classification: B/C	8/38
MELD score	19 (5-48)
PMI (Donor / Men) (mm^2/m^2)	743.5 (374.6-1405.1)
PMI (Donor / Women) (mm^2/m^2)	495.2 (292.5-649.4)
PMI (Recipient / Men) (mm^2/m^2)	593.0 (413.0-1205.3)
PMI (Recipient / Women) (mm^2/m^2)	360.7 (225.4-928.3)
Original disease	
PBC	12
FHF	4
HCC	11
LC (HCV)	17
LC (HBV)	6
LC (NASH)	2
LC (alcohol)	3
LC (unknown origin)	1
AIH	1
Others	2
Preoperative SBP: Present/Absent	5/42
Preoperative blood test	
Hemoglobin (g/dL)	9.3 (6.2-15.1)
Lymphocyte (/mL)	764 (165-2390)
Total protein (g/dL)	6.1 (3.0-8.3)
Albumin (g/dL)	2.7 (1.6-3.8)
Total cholesterol (mg/dL)	121 (25-803)
Blood urea nitrogen (mg/dL)	15 (1-85)
Creatinine (mg/dL)	0.8 (0.4-5.5)
Preoperative nutrition treatment: Present/Absent	35/12
Postoperative enteral nutrition treatment: Present/Absent	29/18
Operative time (minuites)	845 (600-1734)
Intraoperative blood loss (mL)	6430 (580-34000)
GRWR	0.8 (0.45-1.5)
Graft: Left/Right	26/21

Values are given as median (range) or number.
MELD: Model for End-stage Liver Disease; PMI: psoas muscle index; PBC: primary biliary cirrhosis; FHF: fulminant hepatic failure; HCC: hepatic cell carcinoma; LC: liver cirrhosis; HCV: hepatitis C virus; HBV: hepatitis B virus; NASH: nonalcoholic steatohepatitis; AIH: autoimmune hepatitis; SBP: spontaneous bacterial peritonitis; GRWR: graft-to-recipient weight ratio

(p=0.003) and higher levels of BUN (p= 0.021) than those without complications (n=15). Complications occurred more frequently in patients with incompatible blood type matching

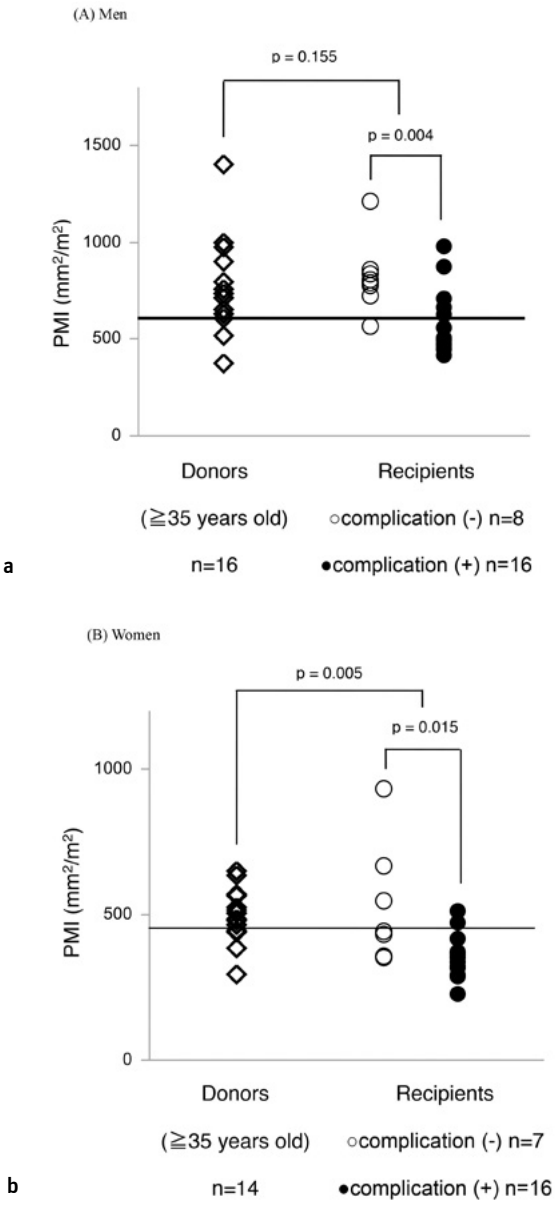

Figure 1. PMI distribution in men (a) and women (b). Transverse lines [(a) 612.5 mm^2/m^2 and (b) 442.9 mm^2/m^2] show the first quartile of PMI of donors more than 35 years of age as the cutoff value of PMI used in the analysis (PMI: psoas muscle index)

than in those with identical or compatible matching (p=0.025). Left lobe grafts had been more frequently received in patients with complications (p=0.037). The effect size was moderate for each variable in which a significant difference was obtained.

The optimal cutoff value for BUN levels with respect to the development of severe complications was determined to be 14 mg/dL according to ROC analysis. Multivariate analysis revealed that low PMI [odds ratio (OR)=6.555; confidence interval (CI): 1.428–37.156; p=0.015] and high BUN levels (OR=6.520; CI: 1.475–37.244; p=0.013) were independent risk factors.

In this study, blood type compatibility was not included in the multivariate analysis because complications occurred in all pa-

Table 2. Complications (CD classification Grade III and above)

CD classification	Complication	Number
V	Death	11
	Acute rejection reaction	3
	Pneumonia	2
	Sepsis	1
	Pneumonia + Sepsis	1
	Retropharyngeal abscess + Sepsis	1
	Rupture of hepatic aneurysm	1
	Perforative peritonitis	1
	Intracerebral bleeding [caused by DIC]	1
IVa	ARDS/ALI	5
IIIb	Intraabdominal hemorrhage	8
	Gastrointestinal perforation	1
IIIa	Anastomotic biliary stricture	2
	Gastrointestinal hemorrhage	1
	Intraabdominal abscess	1
	Intrathoracic hemorrhage	1
	Pneumonia	1
	Rhinorrhagia	1

CD classification: Clavien-Dindo classification; DIC: disseminated intravascular coagulation syndrome; ARDS/ALI: acute respiratory distress syndrome/acute lung injury

tients with incompatible matching (16). However, blood type mismatch is thought to be a strong risk factor for severe complications, with 100% specificity (17).

Risk factors for 30- and 120-day mortalities after LDLT (Figure 2)

The 30-day non-survivors (1 man and 3 women) had lower PMI preoperatively. The analysis of the cutoff PMI value used in the evaluation of postoperative complications revealed that the postoperative 120-day survival rate was 86.7% for the low PMI group (n=30) and 100% for the high PMI group (n=17) (p=0.122). Similarly, the 30-day survival rate did not significantly differ between the high BUN level group (14 mg/dL) and the low BUN level group (p=0.219) or between the incompatible and identical/compatible blood type groups (p=0.436).

However, among the 120-day non-survivors (3 men and 8 women), 10 patients (2 men and 8 women) had lower PMI preoperatively. The analysis of the cutoff PMI value used in the evaluation of postoperative complications revealed that the postoperative 120-day survival rate was 66.7% for the low PMI group (n=30) and 94.1% for the high PMI group (n=17) (p=0.034, Figure 2). On the other hand, the 120-day survival rate did not significantly differ between the high BUN level group (14 mg/dL) and the low BUN level group (p=0.605) or between the incompatible and identical/compatible blood type groups (p=0.688).

DISCUSSION

Many studies in recent years have shown an association between sarcopenia (a decrease in total skeletal muscle mass) and poor prognosis for a range of surgical procedures and other conditions (4,7,8). Numerous indices are used as indicators of the total skeletal muscle mass, and these can be broadly divided into 2 categories: 1) the measurement of the skeletal muscle cross-sectional area on CT or magnetic resonance imaging (MRI) and 2) the measurement of the total skeletal muscle mass by means of bioelectrical impedance analysis (BIA). Shen et al. (18) showed that the total cross-sectional area of the skeletal muscle (major psoas, erector spinae, lumbar quadrate, transverse abdominal, internal and external abdominal oblique, and abdominal rectus muscles) at the level of the caudal end of the third lumbar vertebra on abdominal CT or MRI was useful for estimating the total skeletal muscle mass. Thereafter, cross-sectional areas of various skeletal muscles have been used in different studies (4,5,8,19-22). On the other hand, Kaido et al. (6) used BIA to estimate the total skeletal muscle mass and investigated its association with mortality rates after LDLT.

Although the exact mechanism underlying the effect of the preoperative total skeletal muscle mass on the postoperative course remains unclear, some explanations have been proposed. First, because the skeletal muscle is responsible for generating body heat to maintain the core body temperature, a loss of skeletal muscle mass may lead to a drop in the body temperature, reducing immune function (23,24). Second, as the skeletal muscle is generally destroyed during surgical stress and glutamine released from skeletal muscles activates lymphocytes and monocytes to maintain their immune function, a loss of the skeletal muscle mass may reduce the amount of glutamine released and immunity activated by lymphocytes and monocytes (25,26). Third, hypercatabolism and decreased anabolism due to aging or disease progression, which causes a loss of the skeletal muscle mass, may hinder wound healing and worsen surgical prognosis (27,28).

The present study utilized PMI as an index of the total skeletal muscle mass (8). Although various indices as optimum cutoff values for PMI have been used based on PMIs of healthy people in previous studies, most optimum cutoff values were intended for Westerners (12). Therefore, in the present study, the first quartiles of PMIs of donors more than 35 years of age and who had no significant difference in age compared to recipients were used as the cutoff values for PMI. As a result, it was found that a preoperative lower PMI was independently predictive of the development of complications during postoperative hospitalization. In addition, a lower PMI was significantly associated with a poor postoperative 120-day survival rate. On the other hand, there is an argument that PMI may not necessarily reflect the total skeletal muscle mass (6,29). In ad-

Table 3. Univariate analysis of complications (CD classification Grade III and above)

	Complication (-) (n=15)	Complication (+) (n=32)	p	Effect size
Gender: Men/Women	8/7	16/16	0.831	
Recipient age	54 (33-63)	55 (26-66)	0.656	
Donor age	38 (22-59)	40 (20-67)	0.656	
Blood type: Identical or Compatible/Incompatible	15/0	26/6	0.025	0.33
Child-Pugh classification: B/C	1/14	7/24	0.153	
MELD score	20 (12-38)	17 (5-48)	0.153	
PMI: <cutoff value/cutoff value≤	5/10	25/7	0.003	0.43
Original disease: HCV/nonHCV	5/10	12/20	0.781	
Preoperative SBP: Present/Absent	1/14	4/28	0.530	
Preoperative blood laboratory test				
Hemoglobin (g/dL)	10.2 (7.3-13.3)	9.2 (6.2-15.1)	0.222	
Lymphocyte (/mL)	630 (165-1443)	826 (182-2390)	0.198	
Total protein (g/dL)	6.1 (4.6-7.9)	6.2 (3.0-8.3)	0.891	
Albumin (g/dL)	2.7 (2.2-3.6)	2.7 (1.6-3.8)	0.723	
Total cholesterol (mg/dL)	109 (55-248)	128 (25-803)	0.256	
Blood urea nitrogen (mg/dL)	11 (1-35)	18 (6-85)	0.021	0.34
Creatinine (mg/dL)	0.80 (0.44-1.90)	0.80 (0.40-5.52)	0.515	
Preoperative nutritional therapy: Present/Absent	10/5	25/7	0.408	
Postoperative enteral nutritional therapy: Present/Absent	7/8	22/10	0.149	
Operative time (minutes)	868 (600-1100)	832 (665-1734)	0.576	
Intraoperative blood loss (mL)	4450 (1865-29220)	6470 (580-34000)	0.110	
GRWR	0.86 (0.54-1.50)	0.78 (0.45-1.36)	0.332	
Graft: Left/Right	5/10	21/11	0.037	0.30

Values are given as median (range) or number.
MELD: Model for End-stage Liver Disease; PMI: psoas muscle index; HCV: hepatitis C virus; SBP: spontaneous bacterial peritonitis; GRWR: graft-to-recipient weight ratio

Table 4. Multivariate analysis of complications (CD classification Grade III and above)

	Odds ratio	95% CI	p
PMI	6.555*	1.428-37.156	0.015
Blood urea nitrogen (mg/dL)	6.520**	1.475-37.244	0.013
Graft	2.307***	0.488-11.270	0.287

*<cutoff value/cutoff value
**≤cutoff value≤/<cutoff value
***Left/Right
CI: confidence interval; PMI: psoas muscle index

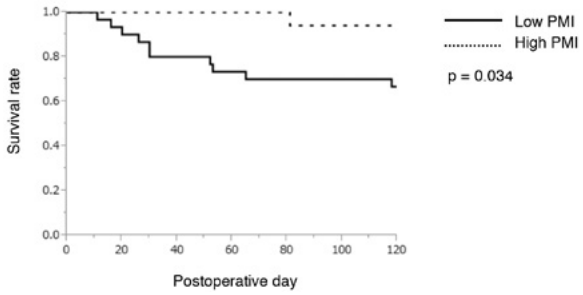

Figure 2. Postoperative 120-day survival rates in the group of recipients with low PMI and the group of recipients with high PMI

dition, it has recently become a matter of debate that not only the muscle mass but also muscle quality and muscle strength are associated with prognosis after surgery (22,30,31). The European Working Group on Sarcopenia in Older People has primarily defined sarcopenia as the presence of both low muscle mass and low muscle function (strength or performance) (12). Although these previous reports have suggested the necessity of defining the optimal diagnostic criteria for sarcopenia, the present study indicated that PMI, as a simple and easily measurable index to assess sarcopenia, strongly correlates with the short-term outcome after LDLT.

We also found that high BUN levels were an independent risk factor for severe complications after LDLT. Generally, BUN levels are one of the indices for renal function. Renal dysfunction, as reflected by an increase in serum creatinine levels, is a well-known

risk factor for severe complications after liver transplantation. Creatinine levels are therefore included in the formula for calculating the MELD score. However, in the present study, BUN, and not creatinine, levels were recognized as a risk factor for poor short-term outcome after LDLT. In patients with end-stage liver disease, an overproduction of BUN may occur in tandem with skeletal muscle loss due to decreased protein anabolism and hypercatabolism, even if renal function is maintained. However, because a correlation between BUN levels and PMI was not seen (r^2=0.005, data not shown) in the present study, the high BUN levels may result not only from protein hypercatabolism but also might be related to other causes such as dehydration.

In this study, BUN levels were a risk factor for the onset of severe complications but not for postoperative mortality. The optimal cutoff value of BUN levels with respect to the development of severe complications was determined to be 14 mg/dL, according to ROC analysis. In multivariate analysis with this cutoff value, BUN levels were shown to be the independent factor for the development of severe complications. However, this cutoff value is too low, and we were surprised at this value. The present study defined severe complications as grade 3 and above according to the CD classification. Complications belonging to grade 3 are those requiring surgical, endoscopic, or radiological intervention. Compared to death (grade 5), the state represented by grade 3 is very mild. Indeed, high BUN levels may certainly affect post-transplant mortality; however, many other factors would also have an effect on post-transplant mortality.

All recipients who underwent ABO-incompatible liver transplantation developed severe complications. It has been reported that ABO-mismatch recipients have a higher risk of acute rejection (32). In the present study, 2 out of 6 recipients with ABO-incompatible liver grafts developed acute rejection. Although incompatible blood type matching was one of the risk factors found for postoperative complications, the short-term survival rate was comparable to identical/compatible cases.

In this study, we investigated the presence or absence of HCV-related disease with respect to etiology. However, it has been said that the outcome of LDLT performed for patients with acute liver failure, including fulminant hepatitis, is good (32). Among the 47 patients enrolled in the present study, there were only 4 with acute liver failure. One of these patients (experiencing fulminant hepatitis from autoimmune hepatitis) had a low PMI and good outcome (no complications). However, in spite of a high PMI, another patient (having fulminant hepatitis from HBV infection) died early after LDLT. Therefore, we could not conclude that the outcome of LDLT performed for patients with acute liver failure is good.

The present study has a number of limitations. The first is that this was a retrospective study at a single institution, and the absolute number of subjects was less. Failure to detect significant effects on post-transplant outcomes by other possible variables, such as the administration of a BCAA formulation, and the finding that PMI was a risk factor for 120-day mortality but not for 30-day mortality after LDLT may have been related to the inadequate patient number (33). The second limitation is that the 120-day survival rate in the present cases was relatively low (36/47, 77%) compared to that in previously reported studies (2,34). This is due to the high mortality rate of female patients (8/23, 35%). It has been definitely observed that women before menopause generally have better long-term outcomes after liver transplantation than men and postmenopausal women through the influence of the hormonal milieu (35). However, most female recipients in our series were postmenopausal, and as shown in Figure 1, they had a low PMI (lower than the first quartile of donors). Because surgical outcomes in the present study, such as operative time and blood loss, were comparable to those reported from other centers, the compromised short-term survival rate may be partly related to patients' poor pre-transplant general conditions (33). The third limitation is that we could not look for significant nutritional parameters other than PMI. As described above, the study cohort size was very small. Hence, we did not want the investigated parameters to increase. In addition, we aimed to find common and easily measurable parameters that predicted outcome after LDLT. The measurement of PMI is easy as was stated earlier in this paper. Other parameters that were examined in this study, such as total protein, albumin, and hemoglobin levels and lymphocyte count, are also common in everyday clinical practice. Although the body mass index (BMI) is also an easily measurable nutrition parameter, we did not include it. The reason was that because many LDLT recipients have serious ascites and edema, their BMI was thought to be inaccurate compared with people without ascites and edema. Further, we did not consider intramuscular adipose tissue content (IMAC) because patients that were included in this study were recipients who underwent LDLT between September 2001 and December 2014 (21). Many patients in the present study had CT images by which IMAC could not be calculated. The fourth limitation was the lack of focus on postoperative changes in sarcopenia. There were variations in the time point at which post-transplant CT was performed, and it was not performed for patients who died early after LDLT. Therefore, we could not evaluate postoperative changes in sarcopenia. Hereafter, we believe that post-transplant CT should be routinely performed to evaluate changes in the skeletal muscle mass.

In conclusion, the present study suggests a significant correlation between PMI before liver transplantation and surgical prognosis. Therefore, PMI, which is easy to measure on preoperative abdominal CT or MRI, may improve the accuracy of the predictions of prognosis after liver transplantation. Sarcopenia estimated by PMI may serve as a measure of patient frailty and as a target for risk stratification in patient selection criteria.

This was a retrospective study based on clinical and laboratory parameters set forth in the aims and methods of the study.

Ethics Committee Approval: Ethics committee approval was received for this study from the Institutional Review Board of Ehime University Hospital.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - T.I., J.W.; Design - T.I.; Supervision - T.T., Y.T.; Materials - T.I., J.W., T.T.; Data Collection and/or Processing - T.I.; Analysis and/or Interpretation - T.I.; Literature Review - T.I.; Writer - T.I.; Critical Review - J.W., T.T., Y.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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