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Original Article

Sarcopenia is a poor prognostic factor following hepatic resection in patients aged 70 years and older with hepatocellular carcinoma

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Aim: The present study investigated the effect of sarcopenia on short- and long-term surgical outcomes and identified potential prognostic factors for hepatocellular carcinoma (HCC) following hepatectomy among patients 70 years of age and older.

Methods: Patient data were retrospectively collected for 296 consecutive patients who underwent hepatectomy for HCC with curative intent. Patients were assigned to two groups according to age (younger than 70 years, and 70 years and older), and the presence of sarcopenia. The clinicopathological, surgical outcome, and long-term survival data were analyzed.

Results: Sarcopenia was present in 112 of 296 (37.8%) patients with HCC, and 35% of patients aged 70 years and older. Elderly patients had significantly lower serum albumin levels, prognostic nutrition index, percentage of liver cirrhosis, and histological intrahepatic metastasis compared with patients younger than 70 years. Overall survival and disease-free survival rates in patients with sarcopenia correlated with significantly poor prognosis in the group aged 70 years and older. Multivariate analysis revealed that sarcopenia was predictive of an unfavorable prognosis.

Conclusion: This retrospective analysis revealed that sarcopenia was predictive of worse overall survival and recurrence-free survival after hepatectomy in patients 70 years of age and older with HCC.

Key words: elderly, hepatectomy, hepatocellular carcinoma, prognosis, sarcopenia

INTRODUCTION

THE WORLD'S POPULATION is rapidly ageing. Between 2000 and 2050, the proportion of the world's population aged over 60 years will double from approximately 11% to 22%[1] and the age of patients with some malignancies has also been increasing. In such a society, abuse of elderly people is an important public health problem. In 1989, Irwin Rosenberg[2] proposed the term "sarcopenia" to describe the age-related decline of muscle mass. Sarcopenia is a syndrome characterized by the progressive and generalized loss of skeletal muscle mass and strength, with a risk of adverse outcomes such as physical disability, poor quality of life, and death.[3–5] It is the result of multiple physiologic derangements, ultimately resulting in an insidious functional decline. Skeletal muscle mass is highly important in immune function, glucose disposal, protein synthesis, and mobility; therefore, decreases in skeletal muscle can result in a plethora of physiologic impairments.[6] Traditional measures of nutritional assessment, such as body mass index and serum albumin, do not accurately predict outcome in the injured elderly. In the future aging society, patients with sarcopenia will be a social issue.

Sarcopenia represents not only a potential new predictor for mortality and discharge disposition, but was also identified as a poor prognostic factor for pancreatic cancer, colorectal liver metastases, melanoma, liver cirrhosis, and liver transplantation.[7–12] We previously published that sarcopenia was predictive of a worse OS even when adjusted for other known predictors in 186 patients with HCC after hepatectomy.[13] Because of advances in the diagnosis and management of HCC, significant improvements in OS and DFS rates for HCC after hepatectomy have been

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achieved. In particular, sufficient evidence exists that hepatectomy can be safely undertaken in selected elderly patients.[14–16] However, even when curative resection is carried out, a considerable number of patients develop intrahepatic or extrahepatic recurrence postoperatively. The prognostic assessment of patients with HCC after hepatectomy and recurrence in this population are important clinical issues.[17–19] Both tumor- and host-related factors are related to the clinical outcome, but it is difficult to evaluate the general condition of patients excluding liver function before hepatectomy, especially in elderly patients. Conventional methods, such as the Child–Pugh classification, were the first systematic approaches used to determine the severity of cirrhosis and select the patients who could tolerate hepatic resection; however, these methods do not reflect the patient's general condition. Given this background, predicting the clinical and prognostic outcome of HCC patients in elderly is of considerable importance.

In this study, a retrospective study was carried out at our institution to investigate the outcome of elderly patients with sarcopenia who underwent hepatic resection. The outcome of these patients was compared to that of patients without sarcopenia undergoing hepatic resection during the same period.

METHODS

Patient characteristics

ALL PATIENTS WHO underwent curative hepatic resection as initial treatment at the Department of Surgery II, Kyushu University Hospital (Fukuoka, Japan) from January 2004 to December 2013 were enrolled in this study. Curative resection was defined as complete macroscopic removal of the tumor. All patients underwent preoperative CT in Kyushu University Hospital. A transverse CT image of the third lumbar vertebrae (L3) in the inferior direction was assessed from each scan. Skeletal muscle was identified and quantified by Hounsfield unit thresholds of −29 to +150 according to a previous report.[8,13] According to the Hounsfield unit scale, the radiodensity of water is 0 U and that of air is −1000 U. Multiple muscles were identified, including the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis as a previous report. The CT measurement was calibrated with water and air at fixed intervals. The cross-sectional areas (cm^2) of skeletal muscles in the L3 region were measured by manual outlining on the CT images and checked by the radiologist. The formulae to calculate skeletal muscle area were 126.9 × BSA − 66.2 in men and 125.6 × BSA − 81.1 in women according to a previous report by Yoshizumi *et al.*[20] Using these formulae, sarcopenia in Japanese patients was defined so that the actual skeletal muscle area was 85% smaller than the calculated skeletal muscle area. The clinicopathological backgrounds and rates of OS and RFS were compared between the two groups, which were divided according to the presence of sarcopenia.

The prognostic factors were examined with respect to OS and RFS on the basis of the following variables: sarcopenia (absence vs presence); skeletal muscle mass; age; gender (male vs female); body mass index; HBs Ag (HBs Ag[+] vs HBs Ag[−]); HCV antibody (HCV[+] vs HCV[−]; serum albumin level; serum total bilirubin level; serum aspartate aminotransferase level; platelet number; ICGR15; C reactive protein; PNI; Child–Pugh classification (A vs B); histological liver cirrhosis (normal liver + chronic hepatitis vs liver fibrosis and liver cirrhosis); tumor size; tumor number (solitary vs multiple); TNM stage according to the Liver Cancer Study Group in Japan[21] (I + II vs III + IV); tumor differentiation (well differentiated + moderately differentiated vs poorly differentiated); microvascular invasion (absence vs presence); im (absence vs presence); serum α-fetoprotein level; des-γ-carboxy prothrombin level; operative procedure (anatomical vs non-anatomical); operative time; estimated blood loss; and postoperative complication (absence vs presence). The patients with diabetes were defined as the use of oral hypoglycemic agent or insulin. Postoperative complications within 1 month after hepatectomy, included liver failure, encephalopathy, gastrointestinal bleeding, i.p. abscess, abdominal hemorrhage, bile leakage, pleural effusion, intractable ascites, and wound infection. The more severe Clavien–Dindo grade III complications,[22] which required surgical interventions, were defined as the presence of postoperative complication.

Surgical procedures

The details of surgical techniques and patient selection criteria have been reported previously.[19] Our criteria for hepatic resection were that ascites was not detected or were controllable by diuretics, serum total bilirubin level was <2.0 mg/mL, and the ICGR15 value was less than 40%. These included a J-shaped incision for routine abdominal access, a slow and gentle hepatic dissection using an ultrasonic dissector with a coagulator (CUSA Excel; Integra, Plainsboro, NJ, USA), with systematic ligation of all sizable vessels, and close ultrasonographic guidance along the transection line. Cholecystectomy was carried out in all patients if the gallbladder was present. An intraoperative bile leakage test was routinely undertaken to identify bile leakage. With this procedure, we recognized small bile leakage sites on the cut liver surface and could repair them by Z-suturing using 6-0PDSII (Johnson & Johnson, Tokyo,

Japan). Intraoperative vascular control was achieved by the Pringle maneuver.[24]

Follow-up strategy and recurrence pattern

After discharge, all patients were examined for recurrence by ultrasonography and tumor markers, such as α-fetoprotein and des-γ-carboxy prothrombin, every month and by CT every 6 months. When recurrence was suspected, additional examination such as hepatic angiography were carried out. We treated recurrent HCC by repeat hepatectomy, ablation therapy, and lipiodolization, according to a strategy described previously.[25]

Histological study

All of the resected specimens were cut into serial 5–10-mm-thick slices and fixed in 10% formalin. After

Table 1 Comparison of clinicopathological factors between two groups of patients with hepatocellular carcinoma (HCC), classified by age

Variables	<70 years (n = 157)	≥70 years (n = 139)	P-value
Male / female	123/34	98/41	0.122
HBV	20 (18.0%)	8 (10.1%)	0.243
HCV	65 (58.6%)	51 (68.0%)	0.250
Skeletal muscle mass, cm^2/m^2	74.4 ± 11.9	70.9 ± 12.8	0.018
Sarcopenia (+)	55 (35.0%)	57 (41.0%)	0.337
Body mass index, kg/m^2	22.8 ± 3.1	23.1 ± 3.3	0.356
Diabetes mellitus	49 (31.2%)	38 (27.3%)	0.495
Albumin, g/dL	4.0 ± 0.5	3.9 ± 0.5	0.009
Total bilirubin, mg/dL	0.8 ± 0.4	0.7 ± 0.4	0.307
AST, IU/L	51 ± 36	56 ± 46	0.475
Platelet count, $10^4/\mu L$	15.4 ± 6.4	16.3 ± 6.8	0.230
ICGR15, %	13.8 ± 7.6	14.7 ± 7.4	0.337
CRP	0.41 ± 1.2	0.41 ± 1.8	0.997
PNI	**48.4 ± 6.3**	**46.1 ± 6.4**	0.002
Child–Pugh A / B	151/6	131/8	0.190
Hepatitis grade, none / mild / severe	13/80/18	11/55/9	0.652
Liver cirrhosis, nl + ch/lf + lc	71/86	83/56	0.006
Tumor size, cm	4.0 ± 3.2	4.0 ± 2.9	0.989
Solitary / multiple	121/36	113/23	0.171
Stage, I / II / III / IV	24/83/39/11	24/73/35/7	0.884
Differentiation, well / mod / poor	10/77/24	9/50/16	0.690
mvi (+)	53 (33.7%)	48 (34.5%)	0.889
im (+)	30 (19.1%)	12 (8.6%)	0.010
AFP, ng/mL	5569 ± 47 209	74 838 ± 15 567	0.529
DCP, mAU/L	3831 ± 14 797	3685 ± 22 463	0.947
Anatomical / non-anatomical	76/35	47/28	0.508
Operative time, min	368 ± 114	355 ± 154	0.512
Estimated blood loss, g	648 ± 528	885 ± 2887	0.398
Blood transfusion (+)	12(10.8%)	10(13.3%)	0.649
Postoperative complications	29 (18.4%)	22 (15.8%)	0.613
Postoperative hospital stay, days	18 ± 18	17 ± 15	0.501

Data are expressed as means ± standard deviations or number of patients (percentage) as appropriate. AFP, α-fetoprotein; AST, aspartate aminotransferase; ch, chronic hepatitis; CRP, C reactive protein; DCP, des-γ-carboxy prothrombin; HBV, hepatitis B antigen-positive; HCV, hepatitis C antibody-positive; ICGR15, indocyanine green dye retention test at 15 min; im, intrahepatic metastasis; lc, liver cirrhosis; lf, liver fibrosis; mod, moderately differentiated HCC; mvi, microvascular invasion; nl, normal liver; poor, poorly differentiated HCC; PNI, prognostic nutrition index; Stage, TNM stage defined by the Liver Cancer Study Group of Japan; well, well differentiated HCC.

macroscopic examination, the slice with the greatest dimensions was trimmed for embedding in paraffin and cut into 4-μm microscopic sections. The sections were stained with hematoxylin–eosin. Tumor differentiation, microvascular invasion, im, and histological liver cirrhosis were examined by the pathologist according to the guidelines of the Liver Cancer Study Group in Japan.

Statistical analysis

The associations of continuous and categorical variables with the relevant outcome variables were assessed using Student's *t*-test and the χ^2-test, respectively. The survival curves and RFS after hepatectomy of the two groups were analyzed by the Kaplan–Meier method and compared with the log–rank test. To identify the prognostic factors after hepatectomy, all variables over $P < 0.1$ in univariate analysis were included in the multivariate Cox proportional model in the analyses of both OS and RFS.

All analyses were carried out with Statview 5.0 software (Abacus Concepts Inc., Berkeley, CA, USA). *P*-values less than 0.05 were considered statistically significant.

RESULTS

IN TOTAL, SARCOPENIA was identified in 112 patients (37.8%): 83 men and 29 women among the 296 patients with HCC. Sarcopenia was identified in 35% of patients aged 70 years or older. The clinicopathological characteristics of all patients are shown in Table 1. Skeletal muscle in patients aged 70 years and older was significantly smaller than in patients younger than 70 years,

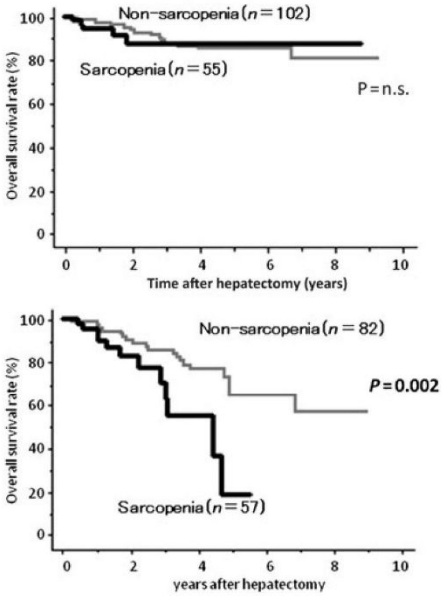

Figure 1 Overall survival curves in patients with sarcopenia or without sarcopenia in patients younger than 70 years (a) and 70 years and older (b). Overall survival rates in patients with sarcopenia indicated significantly poor prognosis in the group aged 70 years and older. n.s., Not significant.

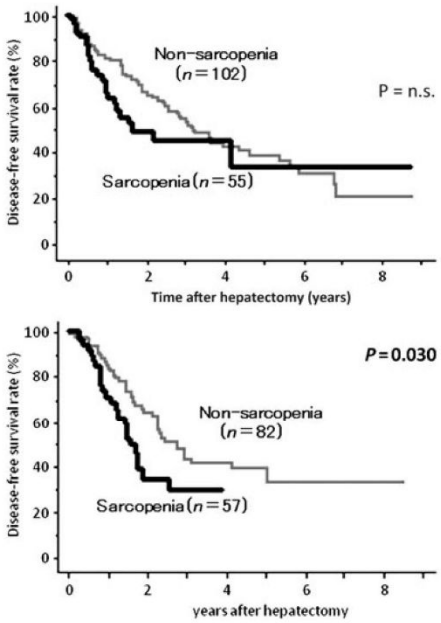

Figure 2 Disease-free survival rates in patients younger than 70 years (a) and aged 70 years and older (b) with or without sarcopenia. Disease-free survival rates in patients with sarcopenia correlated with significantly poor prognosis in the older age group. n.s., Not significant.

but the number with sarcopenia was not different between the two groups. Elderly patients had significantly lower serum albumin levels, lower level of PNI, percentage of liver cirrhosis, and histological im compared with the younger patient group. There were no significant differences regarding other host-related factors, tumor-related factors, or surgical outcome between the two groups.

Figure 1 shows OS curves in patients with or without sarcopenia. Overall survival curves are shown in patients younger than 70 years (Fig. 1a) and those 70 years of age and older (Fig.1b). Overall survival rates in patients with sarcopenia were significantly correlated with poor prognosis in patients aged ≥70 years ($P = 0.002$). Figure 2 shows DFS rates in patients with or without sarcopenia in patients younger than 70 years (Fig. 2a) and those aged ≥70 years (Fig. 2b). Disease-free survival rates in patients with sarcopenia also significantly associated with poor prognosis in the older patient group ($P = 0.030$).

Table 2 Cox proportional hazard model of the all clinical characteristics on overall survival using univariable and multivariable analyses in patients 70 years of age and older

	Univariable analysis		Multivariable analysis	
Variables	Hazard ratio	*P*-value	Hazard ratio	*P*-value
Gender (male)	0.869 (0.387, 1.955)	0.7349		
HBs Ag(+)	1.692 (0.401, 7.142)	0.4738		
HCV ab(+)	1.757 (0.815, 3.787)	0.1503		
Diabetes mellitus	0.951 (0.426, 2.118)	0.9028		
Sarcopenia (+)	3.125 (1.470, 6.622)	0.0030	2.544 (1.206, 5.5865)	0.0199
Body mass index, kg/m^2	0.873 (0.780, 0.978)	0.0192		
Albumin, g/dL	0.651 (0.303, 1.403)	0.2736		
Total bilirubin, mg/dL	0.794 (0.297, 2.126)	0.6465		
AST, IU/L	0.985 (0.970, 1.001)	0.0593		
Platelet count, $10^4/\mu L$	0.982 (0.931, 1.035)	0.4965		
ICGR15, %	1.013 (0.970, 1.059)	0.5521		
CRP, mg/dL	1.155 (0.863, 1.547)	0.3318		
PNI	0.950 (0.896, 1.008)	0.0875		
Child–Pugh B	7.751 (2.597, 23.25)	0.0002	7.751(1.439, 29.41)	0.0149
Liver cirrhosis, lf + lc	1.295 (0.653, 2.564)	0.4591		
Tumor size, cm	1.001 (0.888, 1.127)	0.9911		
Multiple tumor number	2.439 (1.157, 5.154)	0.0191	2.695 (1.205, 6.024)	0.0158
Stage (III + IV)	1.342 (0.646, 2.785)	0.4302		
Poor differentiation (+)	2.375 (1.191, 4.739)	0.0140	3.521 (1.667, 7.463)	0.0010
mvi (+)	1.639 (0.604, 2.450)	0.5826		
im (+)	1.644 (0.576, 4.695)	0.3528		
AFP, ng/mL	1.000 (1.000, 1.000)	0.3092		
DCP, mAU/L	1.000 (1.000, 1.000)	0.0638		
Operative procedures (Anatomical)	1.479 (0.739, 2.958)	0.2686		
Operative time, min	1.001 (0.998, 1.003)	0.7028		
Estimated blood loss, g	1.000 (1.000, 1.001)	0.5613		
Blood transfusion (+)	1.960 (0.843, 4.566)	0.1177		
Postoperative complications (+)	1.472 (0.638, 3.401)	0.3637		
Postoperative hospital stay, days	1.012 (0.996, 1.029)	0.1353		

Values in parentheses are 95% confidence intervals.
AFP, α-fetoprotein; AST, aspartate aminotransferase; CRP, C reactive protein; DCP, des-γ-carboxy prothrombin; HBs Ag, hepatitis B surface antigen-positive; HCV ab, hepatitis C antibody-positive; ICGR15, indocyanine green dye retention test at 15 min; im, intrahepatic metastasis; lc, liver cirrhosis; lf, liver fibrosis; mvi, microvascular invasion; PNI, prognostic nutrition index; poor differentiation, poorly differentiated hepatocellular carcinoma; Stage, TNM stage defined by the Liver Cancer Study Group of Japan.

The prognostic factors for OS and DFS in patients 70 years of age and older, according to univariate and multivariate analyses, are shown in Tables 2, 3, respectively. The significant prognostic factors for OS in the univariate analysis were presence of sarcopenia, Child–Pugh B, multiple tumor number, and poor differentiation. The significant prognostic factors for RFS in the univariate analysis were presence of sarcopenia, serum C reactive protein levels, tumor size, multiple tumor number, stage III + IV disease, presence of im, blood loss, and blood transfusion. Multivariate analysis identified four poor prognostic factors (sarcopenia, multiple tumor number, Child–Pugh B, and poor differentiation) that influenced OS, and three poor prognostic factors (sarcopenia, stage III + IV disease, and blood transfusion) that influenced DFS.

Table 4 shows the comparison of clinicopathological factors between the two groups classified by sarcopenia in patients 70 years of age and older. Patients with sarcopenia had less skeletal muscle, were more likely to be hepatitis B positive, and less likely to be hepatitis C negative. There were no significant differences regarding other parameters between the two groups in patients 70 years of age and older.

Table 3 Cox proportional hazard model of all clinical characteristics on disease-free survival using univariable and multivariable analysis in patients with hepatocellular carcinoma aged 70 years and older

	Univariable analysis		Multivariable analysis	
Variables	Hazard ratio	*P*-value	Hazard ratio	*P*-value
Gender (male)	1.733 (0.903, 3.324)	0.0981		
HBs Ag(+)	1.244 (0.879, 3.984)	0.7133		
HCV ab(+)	0.829 (0.507, 1.355)	0.4559		
Diabetes mellitus	0.675 (0.372, 1.222)	0.1948		
Sarcopenia (+)	1.766 (1.048, 2.976)	0.0324	1.821 (1.037, 3.194)	0.0366
Body mass index, kg/m^2	0.958 (0.889, 1.032)	0.2555		
Albumin, g/dL	0.940 (0.562, 1.572)	0.8129		
Total bilirubin, mg/dL	1.043 (0.529, 2.055)	0.9039		
AST, IU/L	0.998 (0.991, 1.004)	0.4929		
Platelet count, $10^4/\mu L$	0.985 (0.950, 1.020)	0.3968		
ICGR15, %	1.021 (0.990, 1.053)	0.1810		
CRP, mg/dL	1.347 (1.144, 1.587)	0.0004		
PNI	0.976 (0.941, 1.012)	0.1876		
Child–Pugh B	3.058 (1.066, 8.772)	0.0376		
Liver cirrhosis, lf + lc	1.075 (0.650, 1.776)	0.7786		
Tumor size, cm	1.087 (1.009, 1.171)	0.0291		
Multiple tumor number	2.890 (1.661, 5.025)	0.002		
Stage (III + IV)	2.439 (1.641, 3.606)	0.0001	2.044(1.004, 4.167)	0.0487
Poor differentiation (+)	1.436 (0.840, 2.457)	0.1856		
mvi (+)	1.486 (0.906, 2.433)	0.1172		
im (+)	3.184 (1.602, 6.329)	0.0009		
AFP, ng/mL	1.000 (1.000, 1.000)	0.2427		
DCP, mAU/L	1.000 (1.000, 1.000)	0.1115		
Operative procedures (Anatomical)	1.590 (0.972, 2.597)	0.0647		
Operative time, min	1.000 (0.998, 1.002)	0.7304		
Estimated blood loss, g	1.000 (1.000, 1.001)	0.0495		
Blood transfusion (+)	2.398 (1.266, 4.545)	0.0073	2.941 (1.086, 8.000)	0.0339
Postoperative complications (+)	0.988 (0.515, 1.893)	0.9711		
Postoperative hospital stay, days	1.001 (0.987, 1.016)	0.8472		

Values in parentheses are 95% confidence intervals.
AFP, α-fetoprotein; AST, aspartate aminotransferase; CRP, C reactive protein; DCP, des-γ-carboxy prothrombin; HBs Ag, hepatitis B surface antigen-positive; HCV ab, hepatitis C antibody-positive; ICGR15, indocyanine green dye retention test at 15 min; im, intrahepatic metastasis; lc, liver cirrhosis; lf, liver fibrosis; mvi, microvascular invasion; PNI, prognostic nutrition index; poor differentiation, poorly differentiated hepatocellular carcinoma; Stage, TNM stage defined by the Liver Cancer Study Group of Japan.

Table 4 Comparison of clinicopathological factors between the two groups of patients with hepatocellular carcinoma (HCC) classified by sarcopenia, aged 70 years and older

Variables	With sarcopenia ($n = 57$)	Without sarcopenia ($n = 82$)	*P*-value
Age, years	76.5 ± 3.9	75.9 ± 4.0	0.345
Male / female	40/17	58/24	0.943
HBV	6 (10.5%)	1 (1.2%)	0.019
HCV	27 (47.3%)	56 (68.3%)	0.021
Skeletal muscle mass, cm^2/m^2	61.7 ± 10.7	77.4 ± 9.8	<0.001
Body mass index, kg/m^2	23.3 ± 3.2	23.0 ± 3.5	0.6445
Diabetes mellitus	15 (26.3%)	25 (30.5%)	0.4373
Albumin, g/dL	3.8 ± 0.4	3.9 ± 0.5	0.9717
Total bilirubin, mg/dL	0.8 ± 0.4	0.8 ± 0.43	0.9345
AST, IU/L	44 ± 33	49 ± 35	0.4086
Platelet count, $10^4/\mu L$	16.1 ± 6.7	16.4 ± 6.9	0.8190
ICGR15, %	14.5 ± 7.5	14.9 ± 7.5	0.7520
CRP	0.60 ± 1.74	0.28 ± 0.64	0.1427
PNI	45.7 ± 5.9	46.3 ± 6.8	0.6090
Child–Pugh A/B	53/4	78/4	0.7164
Hepatitis grade,			
none / mild / severe	10/43/4	11/63/8	0.3695
Liver cirrhosis, nl + ch/lf + lc	38/19	45/37	0.2176
Tumor size, cm	4.0 ± 2.8	4.0 ± 3.0	0.9012
Solitary / multiple	44/13	72/10	0.1095
Stage, I / II / III / IV	9/31/14/3	15/42/21/4	0.9758
Differentiation,			
well / mod / poor	3/41/13	10/52/20	0.829
mvi (+)	18 (31.5%)	30 (36.5%)	0.889
im (+)	5 (8.8%)	7(8.5%)	0.961
AFP, ng/mL	3890 ± 22 484	2231 ± 7743	0.539
DCP, mAU/L	1923 ± 8969	4910 ± 28 291	0.4427
(Anatomical / non-anatomical)	23/34	34/48	0.8956
Operative time, min	329 ± 107	344 ± 117	0.4649
Estimated blood loss, g	625 ± 640	612 ± 540	0.9026
Blood transfusion (+)	9(17.3%)	14(17.0%)	0.876
Postoperative complications	7 (12.2%)	15 (18.3%)	0.4791
Postoperative hospital stay, days	15 ± 11	18 ± 17	0.2330

Data are expressed as means ± standard deviations or number of patients (percentage) as appropriate. AFP, α-fetoprotein; AST, aspartate aminotransferase; ch, chronic hepatitis; CRP, C reactive protein; DCP, des-γ-carboxy prothrombin; HBV, hepatitis B antigen-positive; HCV, hepatitis C antibody-positive; ICGR15, indocyanine green dye retention test at 15 min; im, intrahepatic metastasis; lc, liver cirrhosis; lf, liver fibrosis; mod, moderately differentiated HCC; mvi, microvascular invasion; PNI, prognostic nutrition index; nl, normal liver; poor, poorly differentiated HCC; Stage, TNM stage defined by the Liver Cancer Study Group of Japan; well, well differentiated HCC.

Prognostic nutrition index was correlated with skeletal muscle mass (PNI = 40.019 + 0.086 × skeletal muscle mass, $r^2 = 0.030$, $P = 0.045$) (Fig. 3) in elderly patients.

DISCUSSION

USING MULTIVARIATE ANALYSIS, this retrospective study indicated that sarcopenia is an independent prognostic factor for OS and DFS among patients 70 years of age and older with HCC. This is the first report to discuss the relationship between sarcopenia and prognosis in elderly patients with HCC after hepatectomy.

Our previous study[13] revealed the relationship between sarcopenia and prognosis, but subgroup analysis regarding aging was not investigated. With the proportion of elderly increasing rapidly worldwide, it is feared that the number of patients with sarcopenia may gradually increase in the forthcoming years, especially in cancer patients.

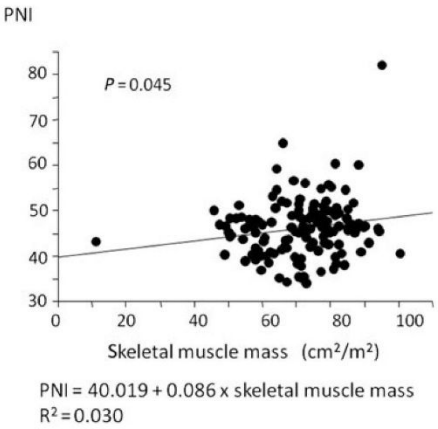

Figure 3 Prognostic nutrition index (PNI) was weakly correlated with skeletal muscle mass (PNI = 40.019 + 0.086 × skeletal muscle mass, $r^2 = 0.030$, $P = 0.045$) in elderly patients.

There are some reports that muscle mass as measured by CT is associated with the prognosis of sarcopenia.[7–13] Computed tomography is a gold standard for quantifying skeletal muscle mass, and it constitutes a good resource for objective and detailed nutritional and metabolic assessment of patients. Moreover, a CT scan is always carried out before hepatectomy, and it is a feasible method of precisely assessing sarcopenia. However, the definition of sarcopenia using CT measurement has been set using an unfounded cut-off level, and has not been accurately determined as yet, especially in Japanese people. We reported[13] survival rates in patients with sarcopenia in which cut-off values for skeletal muscle were 43.75 cm^2/m^2 in men and 41.10 cm^2/m^2 in women, according to a previous report in Germany.[8] Yoshizumi *et al.*[20] retrospectively studied healthy Japanese adults to establish formulae to calculate standard muscle area to enable an easy and accurate definition of sarcopenia. They analyzed skeletal muscle area using CT data from healthy adults and found that BSA significantly correlated with skeletal muscle area. Sarcopenia can be defined as a difference between measured and calculated data using this newly established formula. Using this criteria, sarcopenia was present in 37.8% patients with HCC compared with 40.3% in a previous report,[13] which was a similar proportion.

In this study, elderly patients had a significantly lower serum albumin levels, lower PNI levels, percentage of liver cirrhosis, and histological im compared with those aged younger than 70 years. In aging people, liver function such as serum albumin level will be gradually decreasing.[26] Inflammation-based prognostic scores such as PNI reflect the nutrition and immune status, which are useful prognostic parameters.[27,28] The PNI was correlated with skeletal muscle mass in elderly patients. Skeletal muscle in patients 70 years of age and older was significantly smaller than that of patients younger than 70 years, but the number with sarcopenia was not different between the two groups. To date, sufficient evidence exists that hepatectomy can be safely undertaken in selected elderly patients who have sufficient skeletal muscle.[14–16] The problem with this study was that it was retrospective and the population of elderly was selected.

The Child–Pugh classification was the first systematic and conventional approach used to determine the severity of cirrhosis and select patients who could tolerate hepatic resection; however, it is not always a reliable indicator of hepatic reserve, and it has a limited role in predicting postoperative outcome. To evaluate the general condition of patients before hepatectomy, no useful, objective, easy, and precise marker has been identified. The European Working Group on Sarcopenia in Older People recommends using the presence of both low muscle mass and low muscle function for the diagnosis of sarcopenia.[3] However, muscle function is difficult to evaluate, and thus, low muscle mass was investigated in this study. Among patients 70 years of age and older with HCC, there was no correlation between sarcopenia and age, sex, liver function, tumor-associated factor, or operative factor except for skeletal muscle. There is no report concerning the relationship between viral status and sarcopenia.

Among the significant prognostic factors of OS and DFS, skeletal muscle mass, tumor number, and stage can be evaluated before hepatectomy. The identification of sarcopenia patients before hepatectomy might permit early preventive strategies to maintain muscle mass in order to improve their prognosis or improve the patient selection criteria for hepatectomy.

The mechanism by which sarcopenia shortens the survival of malignant patients remains poorly understood. Skeletal muscle was recently identified as an endocrine organ.[6] It has therefore been suggested that cytokines and other peptides are produced, expressed, and released by muscle fibers, such as tumor necrosis factor-α, interleukin-6, and insulin-like growth factor 1. Low levels of skeletal muscle also indicate a systemic inflammatory response. Further study is needed to clarify the molecular mechanism concerning muscle–liver cross-talk.

This retrospective analysis revealed that sarcopenia was predictive of a worse OS and RFS after hepatectomy in

patients aged 70 years and older with HCC. As the aging population increases, this information will be useful for elderly people who need surgery.

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Three-dimensional Printing and Biotexture Modeling for Preoperative Simulation in Living Donor Liver Transplantation for Small Infants

TO THE EDITOR:

Living donor liver transplantation (LDLT) has become an established modality to treat end-stage liver disease in pediatric patients. However, problems with graft size, such as large-for-size grafts, have limited the applicability of this modality in small infants or neonates. Various technical modalities, including reduced,[1] hyperreduced,[2] monosegmental,[3] and even reduced monosegmental grafts,[4] have been developed to overcome size discrepancies between the graft and the recipient. Trimming or reduction of a liver graft is sometimes difficult because the surgeon should consider appropriate reduction of the volume of the graft while preserving the integrity of vascular structures, such as the portal vein (PV) and hepatic vein (HV). Nonetheless, complicated liver vascular structures and relevant liver volume are currently visually comprehensible and measurable using widely available 3-dimensional (3D) image-processing software. However, the actual perception of size matching between a reduced graft and a small abdominal cavity of a small infant after total hepatectomy can be difficult. Therefore, decision making on how to reduce the size of the graft has often been subjective because it is "largely based on an experienced surgeon's clinical assessment of the size, shape, and thickness of the graft relative to the size of the children's abdomen."[2] Diverse applications of the 3D printing technique have emerged throughout the last decade, which could change the paradigm of the industrial as well as medical arena. Although medical application of this modality is still in the early stages, there have been sporadic reports using this modality in the surgical field within the past few years. In the setting of liver transplantation, Zein et al.[5] reported the use of 3D-printed synthetic livers for preoperative planning in adult LDLT.

This modality could be particularly helpful for complex pediatric LDLT because objective simulation of reduction of a graft according to the vascular structures and fitting of the trimmed graft to the recipient's body is possible preoperatively.

We herein describe our experience of pediatric LDLT for a small infant using biotexture models of a liver graft and the recipient's body that were created by a 3D printer.

The recipient was an 11-month-old girl with biliary atresia after Kasai procedure. Her body weight was 6.1 kg. The donor was her healthy 38-year-old father whose blood type was incompatible to the recipient. The estimated graft volume of the left lateral segment (LLS) graft of the donor by a 3D computed tomography (CT) scan was 295 mL, corresponding to a graft-to-recipient weight ratio (GRWR) of 4.9% (Fig. 1A). This was a large-for-size graft and not acceptable for transplant in its present form according to our criteria. The 3D images of vessels showed a single PV, a single left hepatic artery (HA), and a single HV (Fig. 1B) that needed to be reconstructed. The anatomy of the PV and HV was normal. Bile duct configuration was

Abbreviations: 3D, 3-dimensional; CT, computed tomography; DICOM, Digital Imaging and Communication in Medicine; GRWR, graft-to-recipient weight ratio; HA, hepatic artery; HV, hepatic vein; LDLT, living donor liver transplantation; LHV, left hepatic vein; LLS, left lateral segment; PDS, polydioxanone suture; PV, portal vein, s, segment; STL, stereolithographic.

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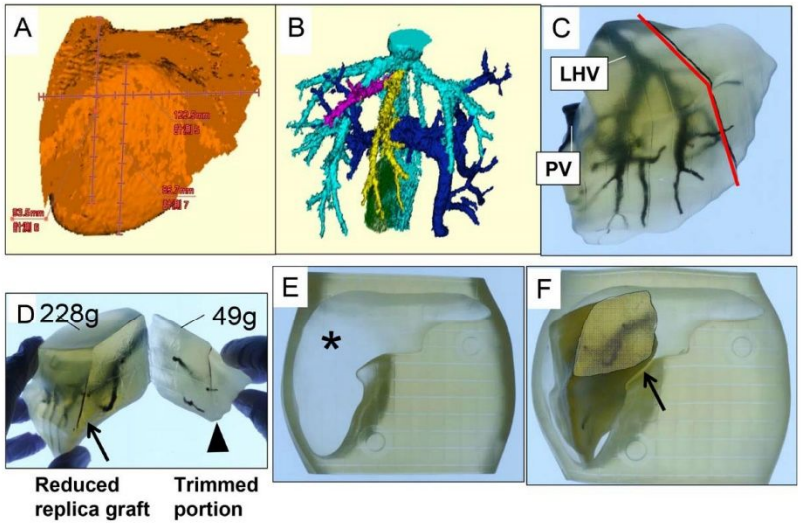

FIG. 1. Preoperative 3D image reconstruction of the LLS graft. (A) Volumetric analysis: Graft volume, 295 mL; GRWR, 4.9%. (B) Anatomy of the HV and the PV. (C) Prototype LLS created by 3D printing: Replica weight, 277 g; Replica (LLS)-to-recipient weight ratio, 4.5%. A red line indicates the expected cutting line. (D) Simulation of graft reduction. Reduced replica graft weight, 228 g; Replica GRWR, 3.7%. A black arrow indicates reduced replica graft. A black arrowhead indicated the trimmed portion. (E) Model of the recipient's abdomen while retracting the original liver bed. The asterisk indicates the space of the liver. (F) Simulated assembly of the graft and recipient abdominal body models. Reduced graft model (black arrow) fitting into the space of the liver of the recipient model.

also normal, for which a single left hepatic duct needed to be reconstructed.

Creation of the real-sized 3D printing models of the LLS graft of the donor, as well as the recipient abdominal cavity, by extracting the diseased liver were undertaken to simulate the transplant. All of the manufacturing processes were performed at a private company (Fasotec, Chiba, Japan). The detailed manufacturing processes are as follows. Image acquisition was performed with a contrast CT scan of 1-mm slice thickness, and the data were saved in the common Digital Imaging and Communication in Medicine (DICOM) format. The DICOM data of the liver parenchyma, the PV, the HV, and the recipient's body were processed to 3D image data (stereolithographic [STL] data) using software (ZedView, Data Design, Nagoya, Japan). The STL data were then transferred to a dedicated image postprocessing workstation, and a computer-aided design model of the segmented structures was generated using a specific modeling software (Free Form, K's Design Lab, Tokyo, Japan). The data were transferred to an ink jet 3D printer (Objet Connex500, Stratasys Japan, Tokyo, Japan) and the 3D solid object of the graft, and the recipient's abdomen for which original liver space was removed were independently created by additive manufacturing using acrylic-based photopolymer resin (TangoPlus and TangoBlackPlus, Objet Japan, Nagoya, Japan; Fig. 1C-F). The actual weight of the replica of the LLS graft was 277 g, which was almost compatible with the estimated graft volume as measured by conventional 3D volumetry.

Fitting of the prototype graft to the recipient's abdominal model was performed. As expected, the graft was too large to be transplanted in its present form. A part of the segment (S) portion of the replica, S2, was trimmed off along with, while still maintaining, the main trunk of the left HV with the graft (Fig. 1C,D). The actual weight of the trimmed portion was 49 g and the remnant portion of the replica was 228 g,

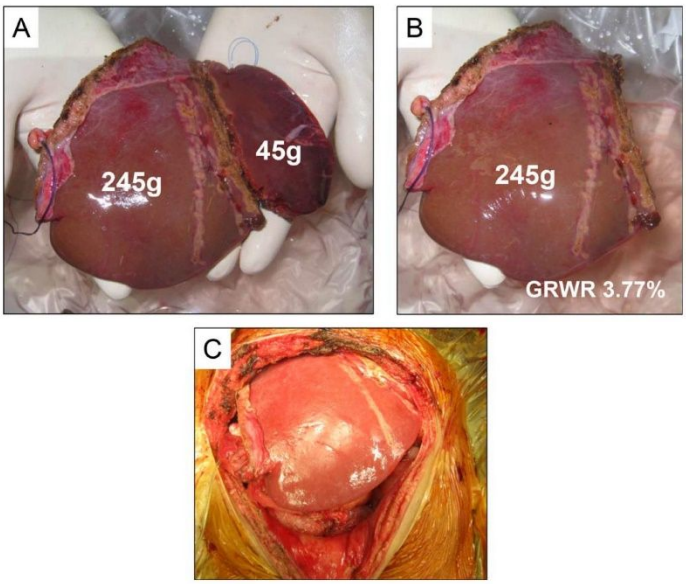

FIG. 2. LDLT. (A) The procured graft at the back table. (B) Reduced graft: Graft volume, 245 g; GRWR, 3.77%. (C) The graft after reperfusion.

which corresponded to a GRWR of 3.7%. The remnant portion of the replica was then fitted to the recipient replica again and it fit the space well (Fig. 1F). LDLT was performed at the Kyushu University Hospital, Fukuoka, Japan, after obtaining approval from the Ethics and Indications Committee of Kyushu University.

The donor procedure was performed in the usual fashion. The left hepatic vein (LHV) was marked with electrocautery on the surface of the liver using intraoperative ultrasound. As simulated preoperatively, a reduction of the LLS graft was performed in situ by resecting off a part of the S2 portion along with the marked LHV while preserving S2 and S3 Glissonian pedicles with the graft (modified S3 monosegment graft). The actual weight of the resected portion was 45 g and the remnant portion was 245 g, which corresponded to an actuarial GRWR of 3.8%.

In the recipient, total hepatectomy was performed in the usual manner. The reduced LLS graft was positioned orthotopically, and then the LHV was anastomosed to the recipient's inferior vena cava triangular cuff with continuous 5-0 polydioxanone suture (PDS). The graft's left PV was connected to the recipient's main PV trunk using 6-0 PDS continuous sutures with a growth factor. Reperfusion of the graft was prompt and smooth. The HA was reconstructed between the donor's left HA and the recipient's left HA with 8-0 Prolene (Ethicon, Somerville, NJ) interrupted sutures under a microscope. Bile duct reconstruction was performed by Roux-en-Y hepaticojejunostomy. The total operative time was 10 hours and 45 minutes. The cold, warm, and anhepatic times were 43, 35, and 58 minutes, respectively. Blood loss was only 150 mL without any autologous blood transfusion. Primary closure of the abdominal wall of the recipient was possible without tension (Fig. 2C). The immunosuppressive regimen consisted of tacrolimus and steroids. The postoperative course was complicated by repeated infection episodes after the treatment of acute cellular rejection with a steroid bolus; however, no large-for-size syndrome associated with the large-for-size graft developed. Unfortunately, the patient died of intracranial hemorrhage at 135 days after transplant with a functioning graft.

LDLT is currently the treatment of choice for pediatric patients with end-stage liver disease, with excellent 5-year survival rates approaching 90%. However, results of LDLT for small infants are poor. One of the reasons for these inferior results has been attributable to the problem of graft size (eg, large-for-size syndrome in which the transplanted graft cannot be placed in a small abdominal cavity). Furthermore, a large-for-size graft is associated with various vascular complications, including PV thrombosis, as well as HA thrombosis. These complications could be due to hemodynamic imbalance, which leads to hypoperfusion and oxygenation of the graft. Compression of the transplanted graft by primary closure of the abdominal wall is another cause for hemodynamic disturbance.

To overcome this problem, various technical innovations, including the use of reduced grafts, monosegmental grafts, and even reduced monosegmental grafts, have been reported.[1-4] However, application of these techniques is subjective, requiring an experienced surgeon's judgment on how to trim the liver.

Preoperative simulation by using a 3D prototype that looks exactly like a real liver graft and the abdomen of the recipient might be especially helpful for LDLT for small infants or neonates. In small infants or neonates with a narrow abdominal cavity, a complex and considerable reduction in graft volume is often necessary, while maintaining essential vascular structures. Advantages of this 3D printing technique over currently available 3D images are that surgeons can simulate donor surgery with a real-sized liver prototype and have a real sense of the size, vascular anatomy, and thickness of the reduced graft, which is virtually impossible with the conventional 3D images. In the present case, a reduction in the LLS graft was actually straightforward without sacrificing the major PV and HV branches. Nonetheless, we believe that this modality can be useful for more complex cases, such as those weighing less than 5 kg with a large-for-size graft.

A favorable characteristic of the present model is the texture of the model. The texture of the parenchyma is relatively soft and transparent, in which vascular structures, such as the PV and the HV, are clearly visible (Figs. 1C-E). Furthermore, the model can be easily cut with a knife, which is a good characteristic for a model of reduced graft LDLT.

Limitations of routine use of this modality are the cost and time to create prototypes. The exact cost of this 3D printing has not been fixed yet, whereas the actuarial cost of our case was approximately US $2000. At least 1 day is necessary from data acquisition to create a 3D prototype. Therefore, this technique cannot be used in an emergent situation. The biotexture material (acrylic-based photopolymer resin) used in our case has not been approved by the Food and Drug Administration in the United States. Therefore, the prototype graft cannot be used in the operative field. Furthermore, the colors available for material at present for transparent vasculature are only black and white, which preclude the use of realistic colors, such as red and blue. However, we believe that improvement in the performance of the printer itself and the development of new materials might overcome these problems in the near future. It would be ideal if we could temporally bring the 3D printing graft into the real recipient abdominal cavity after total hepatectomy and see how the size and thickness of the expected graft fit the abdomen.

In conclusion, preoperative simulation using 3D printing models of a liver graft and the recipient's body is a technical innovation in pediatric LDLT, especially for small infants. Further application of this technique might improve technical accuracy and expand the indication for pediatric LDLT.

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