Skeletal Muscle Volume and Intramuscular Adipose Tissue Are Prognostic Predictors of Postoperative Complications After Hepatic Resection

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Abstract. *Background/Aim:* Recently, skeletal muscle quality was important in patients with malignant tumors to predict the surgical outcome. The relationship between postoperative complications of Clavien–Dindo grade III or more and prognosis in patients who have undergone hepatic resection for hepatic malignancies were investigated. *Patients and Methods:* Patient data were retrospectively collected for 146 consecutive patients who underwent curative hepatic resection in the Department of Hepatobiliary and Pancreatic Surgery, Gunma University, Japan, for hepatic malignancy. The patients were assigned to two groups according to the presence of postoperative complications. The clinicopathological and surgical outcomes were analyzed. Skeletal muscle area (SMA) and intramuscular adipose tissue content (IMAC) were also evaluated. *Results:* No hospital deaths occurred. Postoperative complications were identified in 12 patients (8.2%). Univariate and multivariate analyses revealed that the independent risk factors for postoperative complications were hemodialysis, psychiatric disorder, high CONUT (controlling nutritional status) score and patients both with low SMA and high IMAC. *Conclusion:* Intensive surgical care is necessary for high-risk patients with hemodialysis, psychiatric disorder, high CONUT count and/or low skeletal muscle quality to reduce postoperative complication.

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Postoperative complications may lead to systemic inflammation and there is increasing evidence that increased systemic inflammation correlates with adverse effects on the short- and long-term outcomes of various cancers (1-7). Additionally, postoperative complications are distressing for patients and medical staff and lead to higher medical costs. Hepatic resection was previously thought to be dangerous because of a bleeding tendency or liver dysfunction. We previously reported that postoperative complications were identified in 17.1% of patients who have undergone hepatic resection for hepatocellular carcinoma (2). Although recently, improvements in operative methods and perioperative care have decreased morbidity and mortality rates (3, 4), relatively high morbidity rates associated with hepatic resection remain problematic. Therefore, identification of predictors of post-hepatic resection complications is needed.

Recently, sarcopenia is reported not only to be a predictor of morbidity but has been found to be a predictor of poor prognosis in patients with many cancers (8-13). Sarcopenia is a syndrome characterized by the progressive and generalized loss of skeletal muscle mass and strength, accompanied by an increased risk of adverse outcomes such as physical disability, poor quality of life, and death (14, 15). In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) published a clinical definition of and consensus diagnostic criteria for sarcopenia, and proposed an algorithm evaluating muscle strength and physical performance, in addition to skeletal muscle mass volume, which means that both skeletal muscle volume and quality are important (16).

The method of evaluating the quality of muscle includes many different ways such as hand grip strength, gait speed or intramuscular adipose tissue content (IMAC) (17-20). Especially, intramuscular adipose tissue content is reported to be a significant predictor of both muscle function and mobility function in older adults (17). IMAC was also used

widely to evaluate the low-quality of skeletal muscle in many cancers, which leads to predictive marker of survival or morbidity. IMAC can be measured easily and retrospectively.

A retrospective study was performed to investigate the short-term outcomes of patients with postoperative complications who had undergone hepatic resection for hepatic malignancy including hepatocellular carcinoma (HCC), cholangiocellular carcinoma (CCC), metastatic liver cancer and biliary cancer. Skeletal muscle area (SMA) and IMAC were also evaluated.

Patients and Methods

Patient characteristics. Patient data were retrospectively collected for 146 consecutive patients who underwent curative hepatic resection in the Department of Hepatobiliary and Pancreatic Surgery, Gunma University, Japan for hepatic malignancy with between January 2016 and December 2017. In this period, perioperative management was standardized by one team. The hepatic resection combined with biliary reconstruction or anastomosis of digestive tract were excluded. The patients were assigned to two groups according to the presence of postoperative complications. The clinicopathological and surgical outcome were analyzed. Postoperative complications were defined by Clavien-Dindo grade III or more (those which require surgical intervention) within 1 month of hepatectomy (21).

A transverse CT scan of the third lumbar vertebrae (L3) in the inferior direction was used to identify and quantify skeletal muscle by Hounsfield unit (HU) thresholds of -29 to +150, with water and air having HUs of 0 and 1000, respectively. Muscles identified included the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis muscles. The cross-sectional areas (cm²) of skeletal muscles in the L3 region were measured by manual outlining on the CT images according to the previous report (8, 9). SMA was calculated by dividing the cross-sectional areas (cm²) of skeletal muscle with the height (m²) and was defined as low in patients with less than 42 cm²/m² in men and less than 38 cm²/m² kg in women according to the guideline of sarcopenia (22). IMAC was calculated by dividing the CT value of the multifidus muscles with the CT value of subcutaneous fat according to the previous report (10-13). The optimal cut-off values of IMAC were determined for men and women separately using receiver operating characteristic curves. IMAC was defined as high in patients with higher than -0.730 in men and higher than -0.502 in women.

Preoperative controlling nutritional status (CONUT) scores were calculated based on serum albumin concentrations, peripheral lymphocyte counts, and total cholesterol concentrations (23, 24). [1] Albumin concentrations ≥ 3.5 g/dl, 3.0-3.49 g/dl, 2.5-2.99 g/dl, and < 2.5 g/dl were scored as 0, 2, 4, and 6 points, respectively. [2] Total lymphocyte counts $\geq 1,600/\text{mm}^3$, 1,200-1599/ mm^3 , 800-1199/ mm^3 , and $< 800/\text{mm}^3$ were scored as 0, 1, 2, and 3 points, respectively. [3] Total cholesterol concentrations ≥ 180 mg/dl, 140-179 mg/dl, 100-139 mg/dl, and < 100 mg/dl were scored as 0, 1, 2 and 3 points, respectively. The CONUT score was defined as the sum of [1], [2], and [3].

Patients with diabetes were defined as those using oral hypoglycemic agents or insulin.

Surgical procedures. The details of the surgical techniques and patient selection criteria have been reported previously (25). Our criteria for hepatic resection were that ascites was not detected or was controllable by diuretics; serum total bilirubin level was < 2.0 mg/ml; and the ICGR₁₅ value was less than 40%. The surgical procedure comprised making a J-shaped incision for routine abdominal access, slow and gentle hepatic dissection using an ultrasonic dissector with a coagulator (CUSA Excel; Integra, USA), systematic ligation of all sizable vessels, and close ultrasonographic guidance along the transection line. Intraoperative vascular control was achieved by the Pringle maneuver (26).

Histological study. All of the resected specimens were cut into serial 5- to 10-mm-thick slices and fixed in 10% formalin. After macroscopic examination, the biggest slice was trimmed for embedding in paraffin and cut into 4- μm sections for microscopy. The sections were stained with hematoxylin and eosin. The histological diagnosis was assessed by the pathologist.

Statistical analysis. The associations of continuous and categorical variables with the relevant outcome variables were assessed using the Student's *t*-test and the χ^2 test, respectively. A logistic stepwise regression analysis to predict the presence of postoperative complication was performed with variables displaying a *p*-value less than 0.05 in univariate analyses. The serum albumin level and creatinine were excluded for a logistic stepwise regression analysis because these were confounding factors for CONUT score and hemodialysis, respectively.

All analyses were performed with Statview 5.0 software (Abacus Concepts, Berkeley, CA, USA). A *p*-value less than 0.05 was considered statistically significant.

Results

Clinical characteristics of patients with hepatic resection are shown in Table I. No hospital deaths occurred. Median blood loss was 167 ml during surgery. Postoperative complications were identified in 12 patients (8.2%). Mean patients age was 68 years old, and patients aged 80 years and older were 12.3% (n=18). High age (≥ 80) was not a significant risk factor of postoperative complication. Univariate and multivariate analyses revealed that the independent risk factors for postoperative complications were hemodialysis, psychiatric disorder, high CONUT (controlling nutrition status) count and patients both with low SMA and high IMAC. Postoperative complications were identified in 7 cases among 39 patients with both low SMA and high IMAC (17.9%).

Postoperative complications were identified in 12 patients (8.2%). The types of postoperative complications are shown in Table II. Relevant clinicopathological characteristics of patients with and without postoperative complications are shown in Table III. Regarding host-related factors, the postoperative complication group had the presence of hemodialysis, psychiatric disorder, both with low SMA and high IMAC, low serum albumin level, high serum creatinine level and high CONUT score. Regarding surgical factors, the postoperative complication group had longer operation times

Table I. *Clinical characteristics of patients with hepatic resection.*

Factors	Value or number of patients (n=146)	
Age (years)	Median 68	Range 28-89
Gender (Male/Female)	106/40	
BMI (kg/m ²)	Median 22.7	Range 14.8-31.4
NBNC/HBV/HCV	108/22/16	
Diabetes mellitus	32 (21.9%)	
Hemodialysis	3 (2.1%)	
Brain infarction or bleeding	9 (6.1%)	
Ischemic heart disease	9 (6.1%)	
Respiratory disorder	10 (6.8%)	
Psychiatric disorder	9 (6.1%)	
Anti-coagulant or -platelet therapy	17 (11.6%)	
Steroid use	3 (2.1%)	
SMA (cm ² /m ²)	Median 36.8	Range 20.9-58.4
IMAC	Median -0.60	Range -1.25 - -0.27
Albumin (g/dl)	Median 4.1	Range 2.6-5.1
Total bilirubin (mg/dl)	Median 0.7	Range 0.3-27.8
Platelet count (10 ⁴ /μl)	Median 17.7	Range 3.5-28.4
Creatinine (mg/dl)	Median 0.76	Range 0.38-9.01
ICGR15 (%)	Median 13.1	Range 1.5-60.4
CONUT score	Median 2	Range 0-8
Child A/B	141/5	
Liver cirrhosis (F3+F4)	12 (8.2%)	
Disease	HCC 55 (37.6%)	
	ICC 13 (8.9%)	
	Metastatic 66 (45.2%)	
	biliary tract cancer 12 (8.2%)	
Tumor size (cm)	Median 2.6	Range 0.7-16
Solitary/multiple	110/36	
Surgical procedure	Lobectomy 45 (30.8%)	
	Segmentectomy 17 (11.6%)	
	Subsegmentectomy 20 (13.7%)	
	Partial 64 (43.8%)	
Operation time (min)	Median 368	Range 128-682
Blood loss (g)	Median 167	Range 0-2994
Blood transfusion	7 (4.8%)	

HBV: Hepatitis B antigen-positive; HCV: Hepatitis C antibody-positive; SMA: smooth muscle area; IMAC: intramuscular adipose tissue; CONUT: controlling nutrition status; HCC: hepatocellular carcinoma; ICC: intrahepatic cholangiocarcinoma.

and greater blood loss than patients without complications. The mean length of hospital stay was significantly longer in patients with postoperative complications.

Relevant clinicopathological characteristics of patients with and without low SMA and high IMAC are shown in Table IV. The mean length of hospital stay was significantly longer in patients with both high IMAC and low SMA. Postoperative complications were identified in 7 cases among 39 patients with sarcopenia (17.9%). There were no significant differences except for sex between patients with and without low SMA and high IMAC.

The results of the logistic regression analysis are shown in Table V: the presence of psychiatric disorder, hemodialysis,

Table II. *Type of postoperative complication over Dindo-Clavien complication grade III.*

	No. of patients (%)
Bile leakage	4 (2.7)
Ascites or pleural effusion	2 (1.4)
Pneumonia	2 (1.4)
Intra-abdominal abscess	1 (0.7)
Brain infarction	1 (0.7)
Obstruction of blood dialysis shunt	1 (0.7)
Re-intubation due to delayed awakening from anesthesia	1 (0.7)
Total	12 (8.2%)

Table III. Comparison of the clinicopathological factors between the two groups classified by postoperative complication.

Variables	Without complication (n=134)	With complication (n=12)	p-Value
Host related factor			
Age	66.9±11.8	70.3±8.8	0.34
High aged (≥80)	10 (7.8%)	2 (11.1%)	0.64
Male/Female	96/38	10/2	0.51
HBV	19 (14.2%)	2 (13.3%)	0.81
HCV	22 (16.4%)	4 (33.3%)	0.14
Body mass index (kg/m ²)	22.6±3.1	22.0±2.4	0.57
Comorbidity	52 (38.8%)	8 (66.7%)	0.06
Diabetes mellitus	28 (20.9%)	4 (33.3%)	0.29
Hemodialysis	1 (0.8%)	2 (16.7%)	0.02
Brain infarction or bleeding	9 (6.7%)	0 (0%)	0.45
Ischemic heart disease	9 (6.7%)	0 (0%)	0.45
Respiratory disorder	9 (6.7%)	1 (8.3%)	0.59
Psychiatric disorder	6 (4.5%)	3 (25.0%)	0.03
Anti-coagulant or -platelet therapy	17 (12.7%)	0 (0%)	0.36
Steroid use	3 (2.2%)	0 (0%)	0.77
SMA (cm ² /m ²)	37.5±7.6	36.9±7.1	0.80
IMAC	-0.64±0.16	-0.66±0.17	0.67
with high IMAC and low SMA	32 (23.9%)	7 (58.3%)	0.02
Albumin (g/dl)	4.0±0.4	3.8±0.5	0.03
Total bilirubin (mg/dl)	1.0±2.3	0.9±0.3	0.90
Platelet count (10 ⁴ /μl)	20.8±2.0	17.6±6.7	0.64
Creatinine (mg/dl)	0.8±0.2	2.0±2.9	<0.01
ICGR15(%)	14.1±8.6	11.7±7.3	0.82
CONUT score	1.9±1.4	2.8±1.7	0.03
Child-Pugh A/B	131/3	10/2	0.05
Fibrosis (F0,1,2/3,4)	10 (8.6%)	2 (6.7%)	0.72
Tumor related factor			
HCC/CCC/metastasis/biliary	46/12/64/12	9/1/2/0	0.24
Tumor size (cm)	3.6±2.9	4.2±3.0	0.53
Solitary/multiple	101/33	9/3	0.97
Surgical factor			
Operation time (min)	372±116	438±97	0.03
Blood loss (g)	277±437	538±625	0.03
Transfusion (+)	7 (5.2%)	0 (0%)	0.54
Anatomical/non-anatomical	76/58	6/6	0.76
Hospital stay (day)	12±5	57±51	<0.01
Hospital death	0	0	–

Data are expressed as means±standard deviations or number of patients (percentage) as appropriate. HBV: Hepatitis B antigen-positive; HCV: Hepatitis C antibody-positive; SMA: skeletal muscle area; IMAC: intramuscular adipose tissue content; ICGR15: indocyanine green dye retention test at 15 min; CONUT: controlling nutritional status, HCC: hepatocellular carcinoma; CCC: cholangiocellular carcinoma; Metastatic: metastatic liver cancer; biliary: biliary cancer.

low SMA and high IMAC and high CONUT score were independent predictors of occurrence of postoperative complications.

Discussion

According to multivariate analysis, in this retrospective study, the presence of psychiatric disorder, hemodialysis, low SMA

and high IMAC and high CONUT score were independent predictors of occurrence of postoperative complications in patients with hepatic resection for hepatic malignancies.

Mavros *et al.* reported that postoperative complications classified as Clavien–Dindo grade III or more were identified in 5.6% of patients and were independently associated with decreased long-term survival after surgery for colorectal liver metastases (7). Postoperative complications were significantly

Table IV. Comparison of the clinicopathological factors between the two groups classified by the status of IMAC and SMA.

Variables	Without high IMAC and low SMA (n=107)	With high IMAC and low SMA (n=39)	p-Value
Host related factor			
Age	67.2±11.6	67.1±11.4	0.96
High aged (≥80)	14 (13.1%)	4 (10.3%)	0.78
Male/Female	72/35	34/5	0.02
HBV	18 (16.8%)	2 (5.1%)	0.10
HCV	18 (16.8%)	10 (25.6%)	0.24
Body mass index (kg/m ²)	22.6±3.4	22.3±2.1	0.57
Comorbidity	43 (40.2%)	17 (43.6%)	0.71
Diabetes mellitus	23 (21.5%)	9 (23.1%)	0.82
Hemodialysis	2 (1.9%)	1 (2.6%)	0.87
Brain infarction or bleeding	7 (6.5%)	2 (5.1%)	0.88
Ischemic heart disease	9 (8.4%)	0 (0%)	0.11
Respiratory disorder	8 (6.7%)	2 (5.1%)	0.80
Psychiatric disorder	6 (5.6%)	3 (7.7%)	0.71
Anti-coagulant or -platelet therapy	15 (14.0%)	2 (5.1%)	0.24
Steroid use	3 (2.8%)	0 (0%)	0.56
SMA (cm ² /m ²)	38.3±8.1	35.2±5.1	0.02
IMAC	-0.68±0.16	-0.53±0.1	0.01
Albumin (g/dl)	4.1±0.4	3.9±0.5	0.11
Total bilirubin (mg/dl)	1.0±0.2	0.8±0.5	0.66
Platelet count (10 ⁴ /μl)	21.1±26.6	19.2±8.5	0.65
Creatinine (mg/dl)	0.9±0.8	0.9±1.1	0.58
ICGR15(%)	13.6±8.5	14.7±8.5	0.53
CONUT score	1.9±1.4	1.9±1.4	0.88
Child-Pugh A/B	105/2	36/3	0.11
Fibrosis(F0,1,2/3,4)	23 (21.5%)	7 (23.3%)	0.82
Tumor related factor			
HCC/CCC/metastatic/biliary	40/10/48/9	15/3/16/3	0.60
Tumor size (cm)	3.6±2.9	4.2±3.0	0.53
Solitary/multiple	101/33	9/3	0.97
Surgical factor			
Operation time (min)	366±11	409±18	0.05
Blood loss (g)	297±496	302±341	0.95
Transfusion (+)	7 (6.5%)	0 (0%)	0.19
Anatomical/non-anatomical	59/48	23/16	0.71
Postoperative complications	5 (4.7%)	7 (17.9%)	0.02
Hospital stay (day)	14±11	20±32	0.02
Hospital death	0 (0%)	0 (0%)	-

Data are expressed as means±standard deviations or number of patients (percentage) as appropriate. HBV: Hepatitis B antigen-positive; HCV: Hepatitis C antibody-positive; SMA: skeletal muscle area; IMAC: intramuscular adipose tissue content; ICGR15: indocyanine green dye retention test at 15 min; CONUT: controlling nutritional status; HCC: hepatocellular carcinoma; CCC: cholangiocellular carcinoma; Metastatic: metastatic liver cancer; biliary: biliary cancer.

predictive of a worse overall survival, even when adjustments are made for other known predictors in patients who had undergone hepatic resection for hepatocellular carcinoma at some high-volume institutions (2). Postoperative complication will be important oncologically.

The quality of skeletal muscle was not clearly defined to this day. We previously reported that patients with both low

skeletal muscle mass and function had significantly worse liver function, greater estimated blood loss, greater incidence of severe postoperative complications and longer postoperative hospital stay (17), however measuring skeletal muscle quality is difficult because hand grip or gait speed have to be measured prospectively. On the other hand, measuring IMAC is easily performed retrospectively. Van

Table V. Logistic regression of predictive factor for the occurrence of postoperative complication.

Variables	Odd's ratio	5% confidence interval	p-Value
Psychiatric disorder	1.83	2.36-16.69	0.01
Hemodialysis	3.94	2.29-13.56	0.01
High IMAC and low SMA	6.12	1.44-32.60	0.01
High CONUT score	1.69	1.02-2.85	0.04

SMA: Skeletal muscle area; IMAC: intramuscular adipose tissue content; CONUT: controlling nutritional status.

Rijssen LB reported that in patients undergoing pancreaticoduodenectomy for periampullary and non-pancreatic cancer, low muscle quality was independently associated with decreased survival and an increased incidence of major postoperative complications (19). They measured the skeletal muscle attenuation index which was calculated by measuring the average HUs of the total muscle area at the L3 level. Also, Hamaguchi Y and Kaibori M *et al.* reported high IMAC, which means greater fat accumulation in skeletal muscle, was predictive of worse overall survival after hepatic resection in patients with HCC (11, 18). Additionally, on multivariate analysis, preoperative high IMAC was an independent risk factor for increased major postoperative complications and infectious complications (10). Muscle steatosis is associated to insulin resistance (27), but the detailed mechanism is not clear. Lipid accumulation to muscle is reported to be associated with hepatic insulin resistance and lead to lipid accumulation in the liver, which means liver dysfunction (28). Skeletal muscle is the organ which secrete many growth factors and cytokines (29). The mechanisms of secreted factor for liver function need to be clarified in the future.

Evaluating preoperative comorbidity is important for predicting postoperative complications. Patients undergoing hemodialysis are reported to have a substantially increased risk of mortality and morbidity after hepatic resection according to the national database in Japan (30). Toshima *et al.* reported that massive effusion was significantly higher in patients with renal dysfunction after hepatic resection for HCC (31). The surgical mortality in psychiatric populations was reported to be higher than in a comparable non-psychiatric population (32), although on the other hand patients with psychiatric disorders are not accompanied with excess surgical risk during major surgery for digestive malignancies compared to patients without psychiatric disorders (33). Further studies in larger patient populations are required.

CONUT score, which is an objective tool that is widely used to assess the nutritional status in patients, is reported to be useful for predicting the prognosis of HCC after hepatic

resection (24). CONUT score is also reported to be associated with postoperative complications in many cancers (34, 35).

This retrospective analysis showed that the presence of psychiatric disorder, hemodialysis, low SMA and high IMAC and high CONUT score were independent predictors of occurrence of postoperative complications in patients undergoing hepatic resection for hepatic malignancies. Intensive surgical care is necessary for these high-risk patients. Low skeletal muscle mass plus high muscle steatosis is a candidate for preoperative nutrition and rehabilitation.

Conflicts of Interest

All Authors declare no conflicts of interest.

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