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ORIGINAL ARTICLE

Impact and risk factors for skeletal muscle mass loss after hepatic resection in patients with hepatocellular carcinoma

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hepatocellular carcinoma, postoperative complications, prognosis, skeletal muscle mass.

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Author contribution: Shinji Itoh participated in study conception, design, acquisition of data, analysis, interpretation of data, and drafting of the article. Tomoharu Yoshizumi, Takahiro Tomiyama, Norifumi Iseda, Takeo Toshima, Akinari Morinaga, Tomonari Shimagaki, Huanlin Wang, Takeshi Kurihara, Yoshihiro Nagao, and Noboru Harada participated in acquisition of data. Akihiro Nishie and Kousei Ishigami participated in analysis, and interpretation of data. Masaki Mori participated in critical revision of the manuscript.

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Abstract

Background and Aim: The aims of this study were to determine whether a postoperative decrease in skeletal muscle mass (SMM) after hepatic resection can predict long-term outcomes in patients with hepatocellular carcinoma (HCC) and identify risk factors for SMM loss in patients who undergo hepatic resection.
Methods: This was a large retrospective study of 400 patients who underwent hepatic resection for HCC and pre- and postoperative computed tomography (CT) scans. SMM was measured at the third lumbar vertebrae, and the postoperative change in SMM compared with preoperative values was calculated as Δ SMM. The cutoff value for the post-/preoperative ratio was set at 0.9.
Results: Sixty patients (15.0%) developed SMM loss. These patients had a significantly prolonged prothrombin time ($P = 0.0092$), longer duration of surgery ($P = 0.0021$), more blood loss ($P = 0.0040$), and higher rate of postoperative complications ($P = 0.0037$) than those without SMM loss. Multivariate analysis revealed that prolonged prothrombin time and postoperative complications were independent risk factors for SMM loss after hepatic resection. Patients with SMM loss had significantly shorter overall survival ($P = 0.0018$) than the other patients had. SMM loss was an independent prognostic factor for overall survival (hazard ratio 1.551, 95% confidential interval 1.028–2.340, $P = 0.0363$).
Conclusions: We demonstrated an association of SMM loss with postoperative complications and long-term prognosis in patients with HCC. Patients with prolonged prothrombin time, or postoperative complications, may need to maintain their SMM. Further prospective studies are needed to investigate whether nutritional support can improve SMM loss.

Introduction

Hepatocellular carcinoma (HCC) is the major primary liver malignancy, and the fourth most common cause of cancer-related deaths worldwide.[1] Hepatic resection has been established as one of the most effective treatments for liver malignancies, including HCC.[2,3] Although surgical techniques and perioperative management have recently been developed, the high morbidity rate associated with hepatic resection remains problematic.[4,5]

Sarcopenia, defined as progressive and generalized loss of skeletal muscle mass (SMM) and strength, is associated with a risk of adverse outcomes such as physical disability, poor quality of life, and death.[6] A correlation between sarcopenia diagnosed by SMM and unfavorable prognosis has been reported for patients with various types of malignancies.[7–9] For patients with HCC, we previously reported that preoperative loss of SMM was an independent factor for poor survival after hepatic resection.[10,11] However, to date, decreased SMM after hepatic resection in patients with HCC and its impact on postoperative long-term prognosis have not been fully examined.

The aims of this study were to assess loss of SMM after hepatic resection in a large group of patients with HCC, to investigate the association of SMM loss after hepatic resection with

long-term outcome, and to identify risk factors for SMM loss in patients who have undergone hepatic resection.

Methods

Patients. This study included 400 patients with HCC who were treated at the Department of Surgery and Science, Kyushu University Hospital between November 2000 and May 2016. The study protocol was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the institutional review board (approval codes: 2019-234).

Surgical procedures and postoperative outcomes. Patients were carefully selected for major hepatic resection based on computed tomography (CT)-volumetric analysis of the remnant liver to prevent postoperative liver failure.[3,5] The type of hepatic resection was determined according to the preoperative indocyanine green retention rate at 15 min (ICGR15).[12] Patients with ICGR15 ≥30% were selected for limited resection. Two-thirds of nontumorous liver parenchyma could be removed if the ICGR15 was ≤10%, and less than one-third of it could be resected if ICGR15 was 10–19%. Patients with an ICGR15 of 20–29% received single segmentectomy or less. Intraoperative ultrasonography was performed to mark the plane of transection. Parenchymal transection was performed using the Cavitron Ultrasonic Surgical Aspirator system, (Valleylab Inc., Boulder, CO, USA) and a monopolar dissecting sealer (TissueLink; Salient Surgical Technologies, Portsmouth, NH, USA) powered by a VIO system (VIO 300D; ERBE Elektromedizin, Tubingen, Germany).[13] Inflow vascular control was performed with the Pringle manoeuver with 15 min of occlusion alternating with 5 min of reperfusion. One or two closed-suction drainage tubes were usually placed at the raw surface of the liver.

Postoperative management was performed as previously described.[4] Postoperative complications were categorized using the Clavien-Dindo classification.[14] Postoperative complications at 30 days after hepatic resection were classified as grade ≥3a.

Imaging and assessment of SMM. The degree of SMM was measured from preoperative CT scans as previously described.[10,11] A transverse CT image at the third lumbar vertebra in the inferior direction was assessed on each scan. Skeletal muscle was identified and quantified by thresholds of −29 to +150 HU (water is defined as 0 HU and air as 1000 HU). Multiple muscles were quantified, including the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal oblique abdominal muscles, and rectus abdominis. CT measurements were calibrated with water and air at fixed intervals. The SMM was measured by manual outlining on CT images. Postoperative SMM was calculated by CT images filmed around 3–4 months postoperatively. The SMM was standardized using the formula: (cross-sectional area of the total skeletal muscle at the third lumbar vertebra level in cm^2)/(height [m] × height [m]). Preoperative low SMM was defined using the following previously published formula: <42 cm^2/m^2 for men and <38 cm^2/m^2 for women.[15]

The post-/preoperative ratio was defined as the postoperative SMM divided by the preoperative SMM. The cutoff value for post-/preoperative ratio was defined as 0.9 to match the results of a previous study, suggesting that 10% loss of SMM is an independent unfavorable predictor for survival in patients with lung cancer.[16]

Prognostic biomarkers. The neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio,[17] prognostic nutrition index,[18] and the controlling nutritional status score[19] were calculated. Baseline blood data were obtained the day before surgery. The neutrophil-to-lymphocyte ratio was calculated from the differential count by dividing the neutrophil count by the lymphocyte count. The lymphocyte-to-monocyte ratio was calculated from the differential count by dividing the lymphocyte count by the monocyte count. The prognostic nutrition index was calculated using the following formula: 10 × serum albumin (g/dL) + 0.005 × total lymphocyte count ($/mm^3$). The controlling nutritional status score was determined on the basis of the serum albumin, peripheral lymphocyte count, and total cholesterol level, as previously described.[19] All these indices were reported as continuous variables for analysis.

Statistical analysis. Continuous variables were presented as the median and were compared using the Mann–Whitney *U*-test. Categorical variables were reported as percentages and compared using the χ^2 test or Fisher's exact test. Cumulative overall survival (OS) and recurrence-free survival rates were calculated using the Kaplan–Meier method, and differences between the curves were evaluated using the log-rank test. Survival data were used to establish a univariate Cox proportional hazards model. Covariates that were significant at $P < 0.05$ were included in the multivariate Cox proportional hazards model. A logistic regression analysis was performed to identify clinical variables for SMM loss after hepatic resection. Estimation of the cutoff values for predicting complications was performed by calculating the areas under the receiver operating characteristic (ROC) curves.

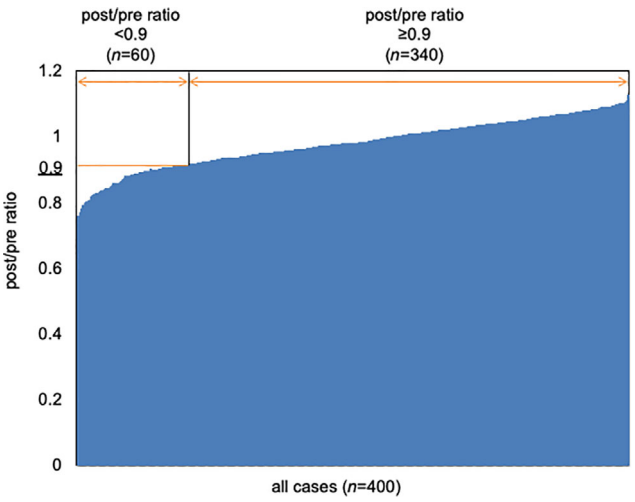


Figure 1 Histogram of the post-/pre-ratios. The median post-/pre-ratio was 0.97 (interquartile range, 0.92–1.03). Of the 400 patients with hepatocellular carcinoma, 60 (15.0%) were classified into the skeletal muscle mass loss group with a cutoff value of 0.9 for the post-/pre-ratio. Post-/pre-ratio, postoperative skeletal muscle mass (SMM) (cm^2/m^2) divided by preoperative SMM (cm^2/m^2).

The ROC curve is a plot of sensitivity *versus* 1—specificity for all possible cutoff values. The most commonly used index of accuracy is the area under the ROC curve (AUC), where values close to 1.0 indicate high diagnostic accuracy, and 0.5 indicates a test of no diagnostic value. The optimal cutoff values used were selected based on the sensitivity and specificity. The predictive accuracy of selected variables for complications was evaluated by an AUC derived from a ROC curve. All statistical analyses were performed using JMP software (SAS Institute Inc., Cary, NC, USA).

Results

SMM in patients with HCC. The pre- and postoperative SMM values in the 400 patients were as follows: median, 47.31 cm^2/m^2 (interquartile range [IQR], 41.50–53.21 cm^2/m^2) and 45.80 cm^2/m^2 (IQR, 40.23–51.78 cm^2/m^2), respectively. A histogram of post-/preoperative ratio for all cases is shown in Figure 1. The median post-/preoperative ratio was 0.97 (IQR, 0.92–1.03).

Clinicopathological features. All the patients were categorized according to the degree of SMM loss based on a post-/preoperative ratio cutoff value of 0.9. Sixty of the 400 patients (15%) were classified as the SMM-loss group (Fig. 1). The clinicopathological characteristics for all the patients are shown in Table 1. A prolonged prothrombin time was significantly correlated with postoperative decrease in SMM ($P = 0.0092$). The post-/preoperative ratio <0.9 group was significantly associated with a long duration of surgery ($P = 0.0021$), high blood loss ($P = 0.0040$), high rate of postoperative complications ($P = 0.0037$), and long postoperative hospital stay ($P < 0.0001$).

Prognostic biomarkers and SMM loss. The immunonutritional prognostic scores of each patient were calculated. No significant correlations were found between any of these biomarkers and SMM loss (Table 2). Preoperative SMM was compared between the two groups, no significant difference was found in terms of the proportion of patients with preoperative low SMM.

Survival analysis and risk factors for survival. The post-/preoperative ratio <0.9 patients had a significantly shorter

Table 1 Comparison of clinicopathologic factors between two groups of patients with hepatocellular carcinoma, classified by degree of skeletal muscle mass loss (post-/pre-ratio <0.9)

Variable	Post-/pre-ratio ≥0.9 ($n = 340$)	Post-/pre-ratio <0.9 ($n = 60$)	*P* value
Age (years)	68 (61–74)	68 (58–73)	0.4000
Sex, male/female	257/53	49/11	0.3059
BMI (kg/m^2)	22.59 (20.57–24.91)	23.12 (20.60–25.19)	0.6423
Preoperative skeletal muscle mass (cm^2/m^2)	47.22 (41.06–53.29)	47.53 (43.69–53.19)	0.4491
Diabetes mellitus	94 (27.7%)	15 (26.0%)	0.6620
HBs-Ag positive	61 (17.9%)	11 (18.3%)	0.9419
HCV-Ab positive	177 (52.0%)	34 (56.6%)	0.5098
Total bilirubin (mg/dL)	0.7 (0.6–1.0)	0.8 (0.7–1.0)	0.1011
Albumin (g/dL)	4.0 (3.7–4.2)	3.9 (3.6–4.2)	0.1161
Prothrombin time (%)	89 (82–97)	85 (77–93)	0.0092
ICGR15 (%)	12.2 (8.2–18.3)	14.0 (9.5–21.3)	0.0884
Platelet count (10^4 μL)	15.0 (11.4–18.7)	15.5 (9.4–19.0)	0.8653
Child–Pugh, A/B	329/11	58/2	0.9685
AFP (ng/mL)	10.5 (4.2–96.2)	17.0 (5.6–300)	0.1036
DCP (mAU/mL)	73 (24–506)	137 (26–1089)	0.1526
Tumor size (cm)	3.3 (2.3–5.0)	3.6 (2.1–6.4)	0.4682
Solitary/multiple	265/75	47/13	0.9461
Poorly differentiation	104 (30.6%)	21 (35.0%)	0.5059
Microscopic vascular invasion	114 (33.5%)	21 (35.0%)	0.8242
Microscopic intrahepatic metastasis	64 (18.8%)	16 (26.6%)	0.1614
F3 or F4	142 (41.8%)	29 (48.3%)	0.3524
Anatomical hepatic resection	212 (62.3%)	36 (60.0%)	0.7292
Major hepatic resection	70 (20.5%)	11 (18.3%)	0.6886
Duration of surgery (min)	316 (245–390)	368 (286–440)	0.0021
Blood loss (g)	413 (211–803)	597 (355–1097)	0.0040
Blood transfusion	40 (11.7%)	12 (20.0%)	0.0803
Postoperative complications	46 (13.5%)	17 (28.3%)	0.0037
Postoperative hospital stay (days)	13 (10–17)	18 (13–23)	<0.0001

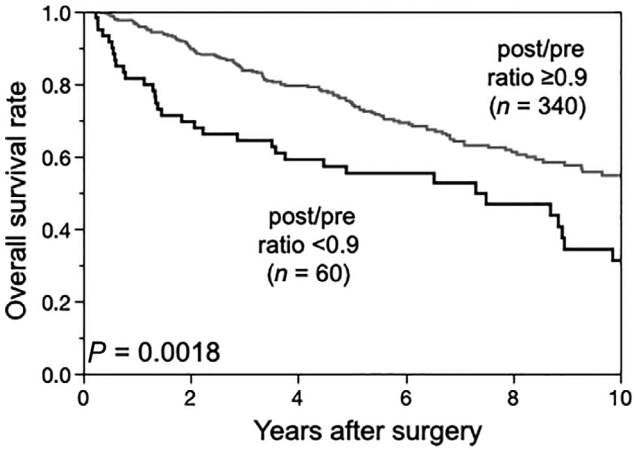
The data are presented as n (%) or median (interquantile range). Post-/pre-ratio, postoperative skeletal muscle mass (cm^2/m^2) divided by preoperative skeletal muscle mass (cm^2/m^2).

AFP, alpha-fetoprotein; BMI, body mass index; DCP, *des*-gamma-carboxyprothrombin; HBs-Ag, hepatitis B surface antigen; HCV-Ab, hepatitis C virus antibody; ICGR15, indocyanine green retention rate at 15 min.

Table 2 Preoperative prognostic biomarkers between two groups of patients with hepatocellular carcinoma, classified by degree of early skeletal muscle mass loss (post-/pre-ratio <0.9)

Variable	Post-/pre-ratio ≥0.9 ($n = 340$)	Post-/pre-ratio <0.9 ($n = 60$)	*P* value
Preoperative low skeletal muscle mass	81 (23.8%)	9 (15.0%)	0.0909
NLR	1.72 (1.29–2.43)	1.62 (1.15–2.68)	0.7114
LMR	4.88 (3.61–5.94)	4.62 (3.49–6.57)	0.7446
PNI	48.0 (44.6–51.4)	47.0 (41.8–50.6)	0.0897
CONUT	2 (1–3)	2 (1–3)	0.0801

The data are presented as *n* (%) or median (interquartile range). Post-/pre-ratio, postoperative skeletal muscle mass (cm^2/m^2) divided by preoperative skeletal muscle mass (cm^2/m^2).
CONUT, controlling nutritional status; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutrition index.



Number at risk

Years	0	2	4	6	8	10
post/pre ratio ≥0.9	340	290	228	148	95	56
post/pre ratio <0.9	60	42	33	24	17	11

Figure 2 Kaplan–Meier curves for overall survival in patients with hepatocellular carcinoma according to the post-/pre-ratio cutoff value 0.9. Post-/pre-ratio, postoperative skeletal muscle mass (SMM) (cm^2/m^2) divided by preoperative SMM (cm^2/m^2).

OS than the other patients had ($P = 0.0018$). The Kaplan–Meier curves are shown in Figure 2. OS was associated with SMM loss in the patients without preoperative low SMM (Fig. 3a) and those with preoperative low SMM (Fig. 3b). A significant difference in OS was found between the SMM-loss and other patients without preoperative low SMM ($P = 0.0378$; Fig. 3a). In the patients with preoperative low SMM, the SMM-loss group had a worse prognosis ($P < 0.0001$; Fig. 3b).

In the univariate analysis for the relationships between OS and clinicopathological factors, the significant prognostic factors were age ($P = 0.0137$), body mass index ($P = 0.0082$), hepatitis C virus antibody ($P = 0.0438$), serum total bilirubin ($P = 0.0222$), serum albumin ($P < 0.0001$), prothrombin time ($P = 0.0046$), preoperative low SMM ($P = 0.0339$), alpha-fetoprotein ($P < 0.0001$) and des-gamma-carboxyprothrombin ($P < 0.0001$), tumor size ($P < 0.0001$), tumor number ($P < 0.0001$), poor tumor differentiation ($P < 0.0001$), microscopic vascular invasion ($P < 0.0001$), microscopic intrahepatic metastasis ($P < 0.0001$), duration of surgery ($P = 0.0019$), blood transfusion ($P < 0.0001$), postoperative complication ($P = 0.0014$), and post-/preoperative ratio <0.9 ($P = 0.0021$) (Table 3).

Table 3 shows the results of the multivariate analysis of the relationships between OS and clinicopathological factors. The independent prognostic factors for OS were age ($P = 0.0018$), hepatitis C virus antibody ($P = 0.0371$), serum albumin ($P = 0.0470$), prothrombin time ($P = 0.0014$), tumor size ($P = 0.0155$), poor tumor differentiation ($P = 0.0050$), microscopic vascular invasion ($P = 0.0336$), microscopic intrahepatic metastasis ($P = 0.0016$), blood transfusion ($P < 0.0001$), postoperative complications ($P = 0.0054$), and post-/preoperative ratio <0.9 ($P = 0.0363$).

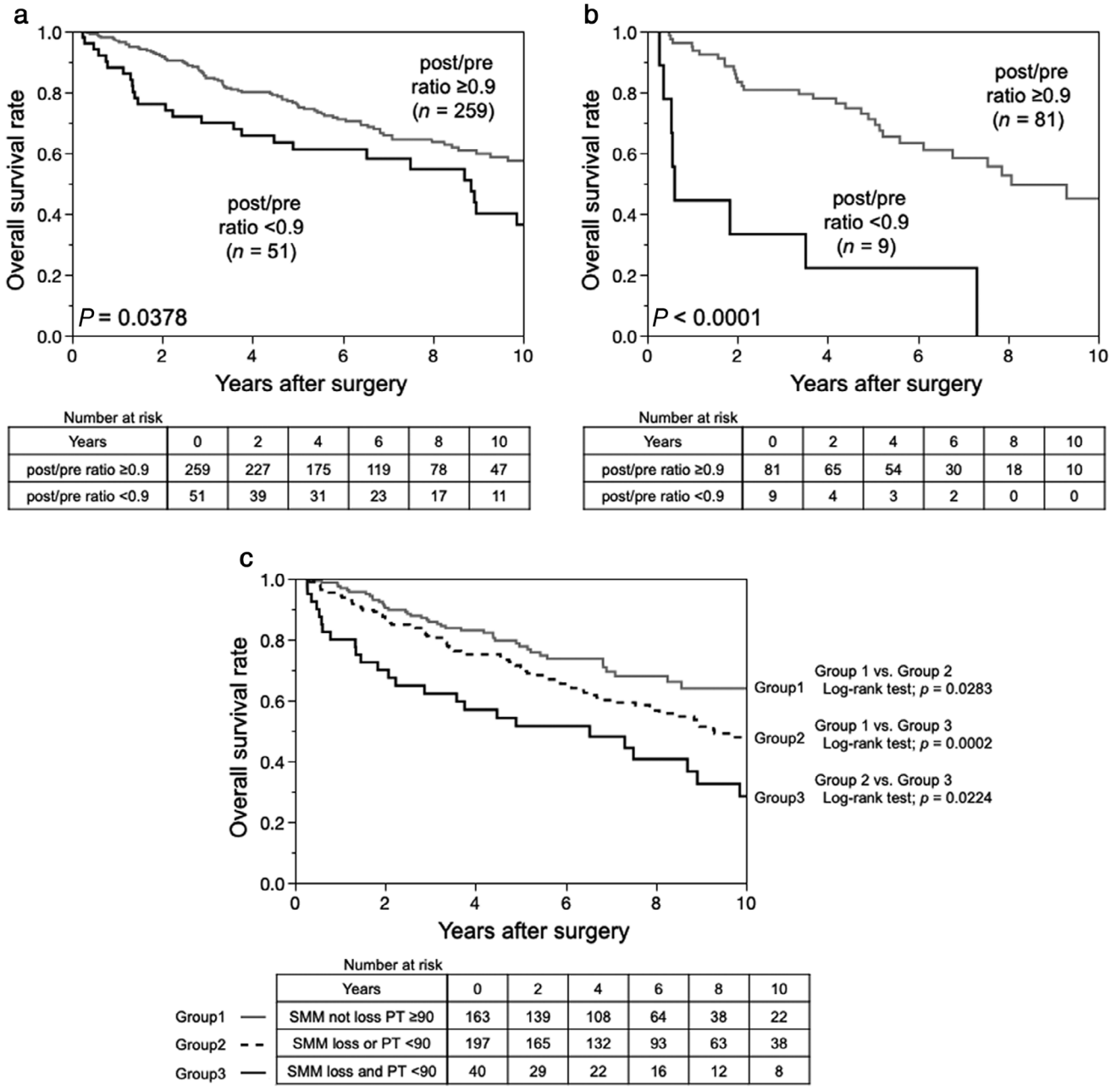
Next, we evaluated the significance of SMM loss stratified by prothrombin time in patients with HCC. The best cutoff value for the prothrombin time for OS was determined using an ROC curve. Prothrombin time <90% (AUC = 0.614) was the best cutoff value for OS following hepatic resection. Patients were divided into the following three groups: SMM not loss/prothrombin time (PT) ≥90%, $n = 163$; SMM loss or PT <90%, $n = 197$; SMM loss/PT <90%, $n = 40$. We found that OS was significantly different among the three groups (Fig. 3c).

No significant difference for recurrence-free survival was observed between the SMM-loss and other patients (Figure S1).

Risk factors for SMM loss after hepatic resection. The best cutoff values for the prothrombin time, duration of surgery, and blood loss for SMM loss were determined using an ROC curve. Prothrombin time <80% (AUC = 0.605), duration of surgery ≥360 min (AUC = 0.624), and a blood loss ≥420 g (AUC = 0.616) were the best cutoff values for SMM loss after hepatic resection (Figure S2). Table 4 shows the results of the multivariate analysis used to identify the clinical factors that were significantly associated with SMM loss after hepatic resection. Prothrombin time <80% ($P = 0.0011$) and postoperative complications ($P = 0.0474$) remained significant independent predictors of SMM loss after hepatic resection.

Discussion

This retrospective study demonstrated that postoperative decrease of SMM during the 3 months after hepatic resection was significantly associated with poor survival in patients with HCC. In relation to positive and negative preoperative low SMM status, patients with postoperative SMM loss experienced worse survival than those without SMM loss. The significant risk factors for



Number at risk

Years	0	2	4	6	8	10
post/pre ratio ≥0.9	259	227	175	119	78	47
post/pre ratio <0.9	51	39	31	23	17	11

Number at risk

Years	0	2	4	6	8	10
post/pre ratio ≥0.9	81	65	54	30	18	10
post/pre ratio <0.9	9	4	3	2	0	0

Number at risk

	Years	0	2	4	6	8	10
Group1	SMM not loss PT ≥90	163	139	108	64	38	22
Group2	SMM loss or PT <90	197	165	132	93	63	38
Group3	SMM loss and PT <90	40	29	22	16	12	8

Figure 3 Kaplan–Meier curves for overall survival in patients with hepatocellular carcinoma according to the post-/pre-ratio cutoff value of 0.9 in the preoperative (a) non-preoperative low skeletal muscle mass (SMM) and (b) preoperative low SMM cohorts, and (c) according to SMM loss and prothrombin status. Post-/pre-ratio, postoperative SMM (cm^2/m^2) divided by preoperative SMM (cm^2/m^2); PT, prothrombin time.

postoperative SMM loss were postoperative complications and preoperative prolonged prothrombin time.

Several studies have reported that SMM loss after surgery had an impact on postoperative prognosis for patients with cancer. Miyake et al. reported that a 10% loss of psoas major muscle area 3 months after surgery was an independent prognostic factor for patients with urothelial carcinoma of the bladder.[20] Nakashima et al. showed that a decrease in SMM at 6 months after surgery was associated with a prognostic effect on OS in patients who underwent surgical resection for esophageal carcinoma.[21] Our findings are consistent with these results. To the best of our knowledge, this is the first report to shows SMM loss after hepatic resection and its association with postoperative complications and long-term survival in a large number of patients with HCC.

The cause-or-effect association of postoperative SMM loss and complications is complicated for cancer patients. Most of the complications occur within 30 days after hepatic resection, even

Table 3 Univariate and multivariate analyses of factors related to overall survival in patients with hepatocellular carcinoma who underwent hepatic resection (Cox proportional hazards analysis)

Factors	Univariate analysis Hazard ratio (95% CI) *P*	Multivariate analysis Hazard ratio (95% CI) *P*
Age	1.020 (1.004–1.038)	1.027 (1.010–1.045)
	0.0137	0.0018
Sex		
Male	1.341 (0.900–1.998)	
Female	0.1487	
BMI	0.929 (0.880–0.980)	0.989 (0.921–1.062)
	0.0082	0.7717
Diabetes mellitus		
Positivity	1.072 (0.749–1.534)	
Negativity	0.7003	
HBs-Ag		
Positivity	0.746 (0.489–1.136)	
Negativity	0.1724	
HCV-Ab		
Positivity	1.393 (1.009–1.925)	1.490 (1.024–2.170)
Negativity	0.0438	0.0371
Total bilirubin	1.816 (1.106–3.076)	1.455 (0.850–2.492)
	0.0222	0.1713
Albumin	0.424 (0.307–0.595)	0.669 (0.450–0.994)
	<0.0001	0.0470
Prothrombin time	0.979 (0.964–0.993)	0.970 (0.952–0.988)
	0.0046	0.0014
ICGR15	1.010 (0.991–1.027)	
	0.2674	
Platelet count	1.003 (0.979–1.027)	
	0.7494	
Child–Pugh		
B	1.455 (0.675–3.136)	
A	0.3375	
Preoperative skeletal muscle mass loss	1.479 (1.030–2.124)	1.200 (0.739–1.948)
	0.0339	0.4590
AFP	1.000 (1.000–1.000)	1.000 (0.999–1.000)
	<0.0001	0.3763
DCP	1.000 (1.000–1.000)	1.000 (0.999–1.000)
	<0.0001	0.3483
Tumor size	1.115 (1.072–1.157)	1.074 (1.013–1.138)
	<0.0001	0.0155
Tumor number		
Multiple	2.064 (1.466–2.906)	1.151 (0.738–1.794)
Single	<0.0001	0.5330
Poor differentiation		
Present	2.052 (1.493–2.820)	1.701 (1.173–2.465)
Absent	<0.0001	0.0050
Microscopic vascular invasion		
Present	2.012 (1.468–2.757)	1.525 (1.033–2.252)
Absent	<0.0001	0.0336
Microscopic intrahepatic metastasis		
Present	3.260 (2.313–4.596)	2.125 (1.330–3.394)
Absent	<0.0001	0.0016
Liver fibrosis		
F3 or F4	1.148 (0.838–1.572)	
F1 or F2	0.3895	
Operation procedure		
Nonanatomical	0.731 (0.524–1.021)	
Anatomical	0.0662	
Duration of surgery	1.001 (1.000–1.002)	0.999 (0.998–1.001)
	0.0019	0.7656
Blood loss	1.000 (0.999–1.000)	
	0.1716	
Blood transfusion		
Present	3.444 (2.344–5.059)	2.782 (1.767–4.378)
Absent	<0.0001	<0.0001
Postoperative complications		
Present	1.859 (1.270–2.723)	1.776 (1.185–2.660)
Absent	0.0014	0.0054
Post-/pre-ratio		
<0.9	1.820 (1.243–2.664)	1.551 (1.028–2.340)
≥0.9	0.0021	0.0363

AFP, alpha-fetoprotein; BMI, body mass index; CI, confidence interval; DCP, *des*-gamma-carboxyprothrombin; post-/pre-ratio, postoperative skeletal muscle mass (cm^2/m^2) divided by preoperative skeletal muscle mass (cm^2/m^2); HBs-Ag, hepatitis B surface antigen; HCV-Ab, hepatitis C virus antibody; ICGR15, indocyanine green retention rate at 15 min.

though the recognition of these complications is sometimes in the late phase after surgery. Therefore, it is suggested that SMM loss 3 months after hepatic resection may have an effect on the patient's critical condition, caused by postoperative complications. Our previous study showed that postoperative complications were predictive of worse OS in patients with HCC.[22] These data reveal that postoperative complications are a predictive factor for SMM loss after hepatic resection, and an independent prognostic factor for OS.

In the current study, postoperative SMM loss indicated poor OS in HCC patients with or without preoperative low SMM. Nakashima et al. showed a correlation between reduced postoperative SMM and prognosis in patients with preoperative low SMM, but not for those without preoperative low SMM in esophageal cancer.[21] With regard to hepatic resection for HCC, even in patients without preoperative low SMM, careful attention should be paid to postoperative SMM loss. On the other hand, the RFS did not differ significantly between the SMM-loss patients and other patients. The SMM loss was not significantly associated with preoperative tumor factors and inflammatory biomarkers such as NLR and LMR, which were known to be correlated with aggressive tumor behavior.[17] It might be possible that this diminished the potential effect of SMM loss.

A preoperative prolonged prothrombin time was not only an independent predictor of postoperative SMM loss but also a strong prognostic factor of OS. Prolonged prothrombin time is one of the usual markers of impaired liver function caused by chronic liver diseases. Chronic liver diseases are reported to cause SMM low.[23] Among several clinical and biological variables such as ascites, encephalopathy, jaundice, prolonged

Table 4 Multivariate analyses of preoperative factors associated with early skeletal muscle mass loss (post-/pre-ratio <0.9) in patients who underwent hepatic resection (logistic regression analysis)

Variable	Hazard ratio	95% Confidence interval	*P* value
Prothrombin time <80%	2.756	1.502–5.059	0.0011
Duration of surgery ≥360 min	1.695	0.898–3.199	0.1033
Blood loss ≥420 g	1.789	0.906–3.530	0.0935
Postoperative complications	1.989	1.007–3.928	0.0474

Post-/pre-ratio, postoperative skeletal muscle mass (cm^2/m^2) divided by preoperative skeletal muscle mass (cm^2/m^2).

prothrombin time, hyperbilirubinemia, and hypoalbuminemia reflexed liver dysfunction, prolonged prothrombin time might be most related to SMM loss. Our current study revealed that the three groups divided by prothrombin time and postoperative SMM loss displayed different prognostic features, and patients with prolonged prothrombin time and SMM loss had worst OS of the three. Therefore, patients with prolonged prothrombin time need careful pre- and postoperative support to maintain their SMM.

It is important to encourage physical activity and consider nutritional intervention in the care of new patients. With regard to nutritional intervention, L-carnitine has been reported to suppress SMM loss in patients with liver cirrhosis.[24] Future, well-planned clinical trials of a large number of patients with adjustment for some variables such as age, sex, tumor staging, liver function, and postoperative complications should focus on the impact of physical activity and nutritional intervention.

This is the largest retrospective cohort study to focus on postoperative changes in SMM after hepatic resection in patients with HCC. We believe that the current results are meaningful and reliable for surgeons who treat HCC. However, the present study had a limitation. This was a single-institutional and retrospective study. Nevertheless, determining the importance of a decrease in SMM after hepatic resection by performing prospective controlled trials is considered difficult. Moreover, few studies have reported the clinical significance of postoperative changes in SMM in patients with hepatobiliary and pancreatic malignancies. Therefore, accumulation of clinical data of retrospective studies from multiple institutions could be useful.

In conclusion, this large retrospective study demonstrated the association of SMM loss with postoperative complications and long-term prognosis in patients with HCC. Patients with prolonged prothrombin time or postoperative complications may need to maintain their SMM. Further prospective studies are needed to investigate whether nutritional support can improve SMM loss.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Figure S1. Kaplan-Meier curves showing recurrent free survival of patients with hepatocellular carcinoma according to skeletal muscle mass loss.

Figure S2. Receiver operating characteristic (ROC) curve using the prothrombin time, duration of surgery, and blood loss as predictor of skeletal muscle mass after hepatic resection with an optimal cutoff value of 80, 360, and 420, respectively. The area under the ROC curves (AUC) of the prothrombin time, duration of surgery, and blood loss was 0.605, 0.624, and 0.616, respectively.