Original Paper

Preoperative Low Muscle Mass and Low Muscle Quality Negatively Impact on Pulmonary Function in Patients Undergoing Hepatectomy for Hepatocellular Carcinoma

Hisaya Shirai   Toshimi Kaido   Yuhei Hamaguchi   Atsushi Kobayashi
Shinya Okumura   Siyuan Yao   Shintaro Yagi   Naoko Kamo   Kojiro Taura
Hideaki Okajima   Shinji Uemoto

Division of Hepato-Biliary-Pancreatic and Transplant Surgery, Department of Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Abstract

Background: Sarcopenia is a prognostic factor for mortality in digestive surgery. However, the correlation between preoperative cardiopulmonary function and sarcopenia in patients undergoing hepatectomy for hepatocellular carcinoma (HCC) remains unclear. **Methods:** The present study investigated the impact of preoperative sarcopenia on cardiopulmonary function in 402 patients who underwent first hepatectomy for HCC between April 2005 and April 2015. The quantity and quality of skeletal muscle were evaluated using psoas muscle index (PMI) and intramuscular adipose tissue content (IMAC), respectively, as determined from preoperative computed tomography imaging. Correlations between preoperative cardiopulmonary function and sarcopenic factors (PMI and IMAC) were evaluated. **Results:** No significant correlations were found between left ventricular ejection fraction and the two sarcopenic factors. On the other hand, preoperative vital capacity (VC) and forced expiratory volume in 1 s (FEV$_1$) correlated significantly with PMI ($p < 0.001$ each) in males and with IMAC ($p < 0.001$ each) in females. Moreover, VC and FEV$_1$ in the preoperative low PMI ($p < 0.001$ each) and high IMAC ($p = 0.002$ and $p < 0.001$, respectively) groups were significantly lower than in the normal group in males. In females, VC and FEV$_1$ were significantly lower in the preoperative high IMAC group than in the normal group ($p < 0.001$ each). **Conclusion:** Preoperative low muscle mass in males and low muscle quality in males and females were significantly associated with pulmonary dysfunction.

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Toshimi Kaido, MD, PhD
Division of Hepato-Biliary-Pancreatic and Transplant Surgery
Department of Surgery, Graduate School of Medicine, Kyoto University
54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606-8507 (Japan)
E-Mail kaido@kuhp.kyoto-u.ac.jp

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Introduction

Sarcopenia was initially described as an age-related decrease in muscle mass [1] and is currently considered as a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength due to various causes. The definition of sarcopenia is now proposed to comprise low muscle mass and impaired muscular function [2, 3]. Sarcopenia is thus not only a condition affecting the elderly and can be observed at any age as a result of inflammatory conditions (including malignancies), malnutrition, and disuse. We have so far reported the negative impacts of preoperative sarcopenia on outcomes after living donor liver transplantation [4, 5], hepatocellular carcinoma (HCC) [6, 7], extrahepatic biliary malignancies [8], and pancreatic cancer [9]. Various lines of evidence have also shown that sarcopenia is predictive of mortality in various diseases and after various surgeries [10–13]. Among them, HCC is the sixth most common human cancer and the third most common cause of cancer-related death [14]. Hepatectomy plays an important role in the treatment of HCC [15]. However, HCC patients with insufficient cardiopulmonary function cannot undergo hepatectomy.

A previous study demonstrated that among patients with chronic heart failure (CHF), patients with muscle wasting showed significantly lower left ventricular ejection fraction (EF) than patients without muscle wasting [16]. Moreover, Moon et al. [17] revealed an association between low muscle mass and pulmonary function in healthy Korean men and women ≥65 years old.

We previously reported the impact of sarcopenia and pulmonary dysfunction in living donor liver transplantation and the impact of pulmonary dysfunction in patients undergoing living donor liver transplantation [18]. Ezaki et al. [19] classified 139 Japanese patients with HCC undergoing hepatectomy into three groups according to age, and revealed that there was a statistically marked decline in the preoperative cardiac and pulmonary function in the group aged >66 years. Although they reported that there was no significant difference among the three groups in postoperative complications, mortality, and survival, they did not directly discuss the impact of pulmonary dysfunction in HCC patients. There has been no report directly discussing the impact of pulmonary dysfunction in HCC patients. Moreover, the impact of sarcopenia on cardiopulmonary function in patients undergoing digestive surgery, particularly patients with HCC undergoing hepatectomy, remains unclear. The present study investigated the correlations between preoperative cardiopulmonary function and sarcopenic parameters such as muscle mass and muscle quality in patients undergoing hepatectomy for HCC.

Patients and Methods

Patients and Data Collection
Between April 2005 and April 2015, a total of 572 patients underwent hepatectomy for HCC at Kyoto University Hospital. Seventy-two patients who did not undergo preoperative plain computed tomography (CT) at the level of the third lumbar vertebra were excluded from this study. Another 12 patients who underwent neither preoperative echocardiography nor preoperative spirometry in our hospital and 86 patients who underwent hepatectomy more than twice were excluded as well. As a result, 402 patients (325 men, 77 women) with results of echocardiography or preoperative spirometry data were registered in this study.

Data of preoperative blood examinations, including complete blood count, serum biochemistry, tumor marker, and indocyanine green retention test at 15 min, were collected. A pathological examination was performed for evaluating tumor size, tumor number, vascular invasion, tumor differentiation, and background liver in accordance with the rules of the Liver Cancer Study Group of Japan.

Echocardiography was performed in 82 patients (63 men, 19 women) and spirometry in 399 patients (323 men, 76 women). Seventy-nine patients (61 men, 18 women) underwent both echocardiography and spirometry. Echocardiography alone was performed in 3 patients (2 men, 1 woman) and spirometry alone

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in 320 patients (262 men, 58 women). Cardiac functions such as left ventricular EF were measured from preoperative echocardiography. Pulmonary functions such as vital capacity (VC), percentage of predicted VC (%VC), forced expiratory volume in 1 s (FEV_1), and percentage of predicted FEV_1 (%FEV_1) were determined from spirometry. We defined restrictive ventilatory impairment as %VC <80% and obstructive ventilatory impairment as %FEV_1 <70% of forced VC (FVC), with combined ventilatory impairment then defined as the presence of both restrictive and obstructive ventilatory impairment. All preoperative CT imaging was performed using a multidetector CT scanner (Aquilion 64; Toshiba Medical Systems, Otawara, Japan).

Image Analysis

The quantity of skeletal muscle was indicated by the psoas muscle index (PMI). The quality of skeletal muscle was indicated by the intramuscular adipose tissue content (IMAC). PMI and IMAC were measured from preoperative CT images at the level of the third lumbar vertebra for all patients (Fig. 1). Cross-sectional areas of bilateral psoas muscles were measured by manual tracing (Fig. 1a), and PMI was calculated by normalizing this cross-sectional area of bilateral psoas muscles to the square of the patient's height in meters. IMAC was calculated as previously described by Kitajima et al. [20]: IMAC = mean CT attenuation value (in Hounsfield units) for region of interest in multifidus muscle / mean CT attenuation value for region of interest in subcutaneous fat.

Subfascial muscular tissue in the multifidus muscle on preoperative cross-sectional plain CT at the level of the third lumbar vertebra was precisely traced, and CT attenuation values were measured using the AquariusNET server (TeraRecon, San Mateo, CA, USA) (Fig. 1b). CT attenuation values of subcutaneous fat were measured for four circular regions of interest in subcutaneous fat away from major vessels (Fig. 1c).

Analyzed Parameters

We analyzed correlations among PMI or IMAC and preoperative cardiopulmonary parameters including EF, VC, %VC, FEV_1, and %FEV_1. Correlations of PMI and IMAC with preoperative pulmonary functions were examined. We then examined the relationship between preoperative pulmonary function and degrees of depletion of both skeletal muscle mass and quality. We previously reported sex-specific cutoffs for low PMI of 6.36 cm^2/m^2 for men and 3.92 cm^2/m^2 for women (mean –2 standard deviations [SDs]) [21, 22]. Based on these donor cutoffs (i.e., cutoffs for healthy young adults), we divided the 399 patients who had undergone spirometry into two groups: a preoperative low PMI group showing low muscle mass (mean below –2 SDs), $n = 133$ (122 men, 11 women), and a normal PMI group (mean equal to or above –2 SDs), $n = 266$ (201 men, 65 women).

As sex-specific cutoffs for low IMAC, we again applied donor cutoffs, using high IMAC cutoffs of –0.358 for men and –0.229 for women (mean + 2 SDs) [22]. Based on these values, we divided the 399 patients who had undergone spirometry into another two groups: a preoperative high IMAC group showing low muscle quality (mean below +2 SDs), $n = 221$ (174 men, 47 women), and a normal IMAC group (mean equal to or above +2 SDs), $n = 178$ (149 men, 29 women). Multiple comparisons of survival curves according preoperative pulmonary function and risk factors for poor survival were then performed.

Statistical Analysis

Data are presented as mean ± SD for continuous variables unless otherwise indicated. Continuous variables were analyzed nonparametrically using the Mann-Whitney U test. Categorical variables were compared using the χ^2 test or the Fisher exact test, as appropriate. Cumulative overall survival rates were calculated using the Kaplan-Meier method and differences between curves were evaluated using the Wilcoxon test. In survival time analysis according to group, pairwise comparison of each level of group variable was performed using the Holm method and the p value from the Wilcoxon test, and adjusted p values were determined. p values <0.05 were considered to indicate statistical significance. All statistical data were generated using the JMP Pro version 12 software (SAS Institute, Cary, NC, USA).

Results

Patient Characteristics

The clinicopathological characteristics of the 402 patients are shown in Table 1. Median patient age was 67 years (range, 33–89 years). Child-Pugh classification was A for 364 patients
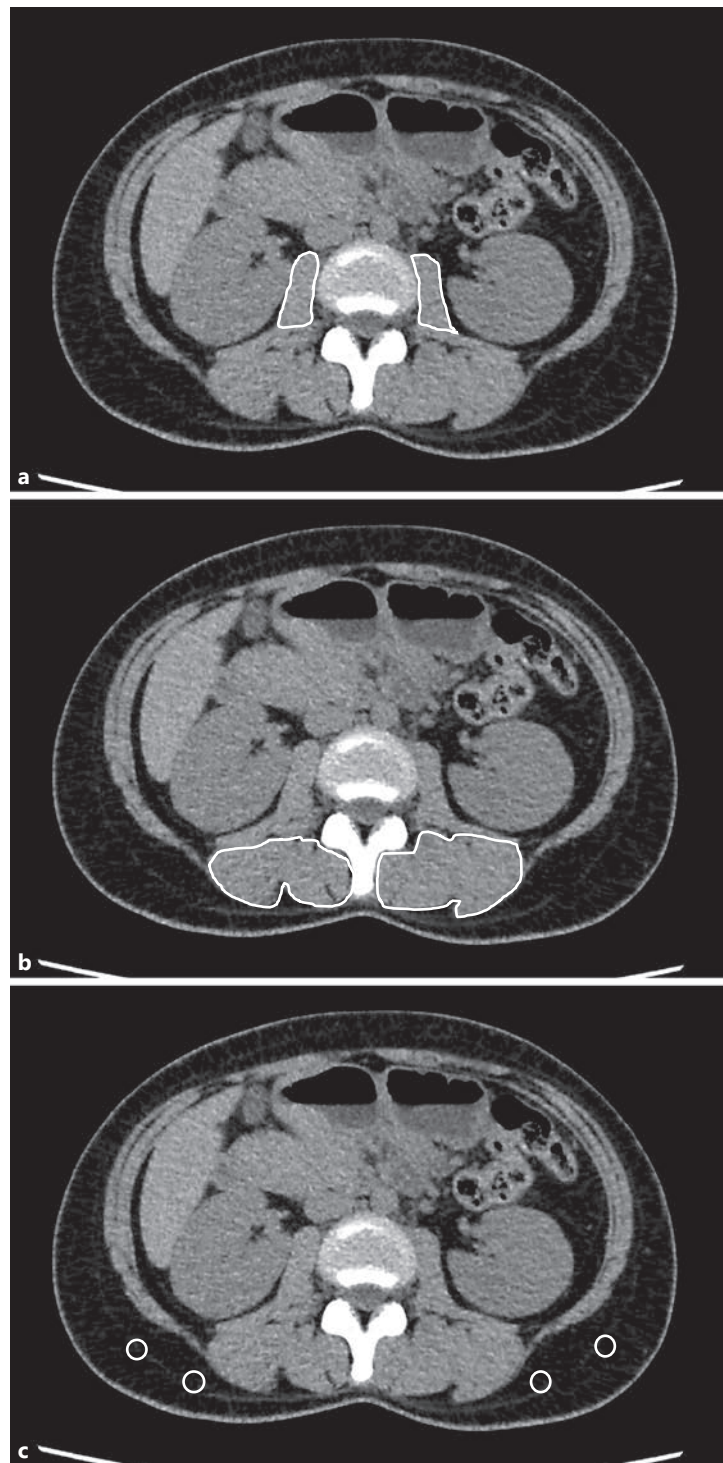
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Fig. 1. Cross-sectional computed tomography images at the level of the third lumbar vertebra. **a** Areas of bilateral psoas muscle were measured by manual tracing. **b** Subfascial muscular tissue in multifidus muscle was precisely traced. **c** Four small circles were placed on subcutaneous fat away from major vessels. Regions of interest of the multifidus muscle and subcutaneous fat (Hounsfield units) were measured by the AquariusNET server.

(91%) and B for 38 patients (9%). Preoperative median EF was 69.6% (range, 44.5–84.0%). Preoperative median VC was 3.32 L (range, 1.68–5.31 L), and preoperative median %VC was 104.1% (range, 65–150.9%). Preoperative median FEV_1 was 2.40 L/s (range, 0.86–4.47 L/s), and preoperative median %FEV_1 was 76.3% (range, 33.3–100.0%).

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Table 1. Clinicopathological patient characteristics

Age, years	67.4±9.5
Sex (male/female)	325/77
Body mass index	23.2±3.5
Child-Pugh classification (A/B/C)	364/38/0
Etiology of HCC (HBV and/or HCC/others)	264/138
Previous treatment for HCC (yes/no)	109/293
Smoking (current/former/never)	118/142/142
Respiratory past history (yes/no)	63/339
Pulmonary function (normal/restrictive/obstructive/combined)	290/21/81/7
Ejection fraction, %	69.6±7.9
Indocyanine green retention test at 15 min, %	17.1±10.1
Platelet count, ×10^4/mm^3	155±72.7
Total bilirubin, mg/dL	0.9±0.6
Albumin, g/dL	3.9±0.5
Alpha-fetoprotein, ng/mL	21.9 (0.9–2,873,490)
Des-gamma-carboxy prothrombin, mU/L	181 (8–431,000)
Surgical procedure (≥lobectomy/<segmentectomy)	138/264
Operative time, min	385±139.2
Operative blood loss, g	1,295±2,312
TNM stage (I/II/III/IV)	55/179/116/47
Number of tumors (solitary/multiple)	270/132
Differentiation of HCC (good/moderate/poor/unknown)	43/255/90/14
Microvascular invasion (positive/negative)	62/340
Preoperative psoas muscle index	
Males	6.908±1.621
Females	5.172±1.250
Preoperative intramuscular adipose tissue content	
Males	−0.337±0.134
Females	−0.170±0.173

Values are presented as mean ± standard deviation, median (range), number of patients, or percentage. HBV, hepatitis B virus; HCC, hepatocellular carcinoma; TNM, Tumor Node Metastasis stage (as defined by the Liver Cancer Study Group of Japan).

Correlations between Preoperative EF and Sarcopenic Factors

For males, EF did not correlate significantly with PMI ($r = -0.190$, $p = 0.135$; online suppl. Fig. 1A; for all online suppl. material, see www.karger.com/doi/10.1159/000484487) or IMAC ($r = -0.199$, $p = 0.118$; online suppl. Fig. 1B). Likewise, for females, EF did not correlate significantly with PMI ($r = -0.198$, $p = 0.415$; online suppl. Fig. 1C) or IMAC ($r = -0.330$, $p = 0.168$; online suppl. Fig. 1D).

Correlations between PMI and Preoperative Pulmonary Parameters

For males, significant but weak positive correlations were observed between PMI and VC ($r = 0.255$, $p < 0.001$; Fig. 2a) or FEV$_1$ ($r = 0.257$, $p < 0.001$; Fig. 2c), but no correlations were evident between PMI and %VC ($r = 0.149$, $p = 0.007$; Fig. 2b) or %FEV$_1$ ($r = 0.078$, $p = 0.160$; Fig. 2d). In contrast, for females, PMI was not correlated with any preoperative pulmonary parameters: VC ($r = 0.038$, $p = 0.743$; Fig. 2e), %VC ($r = 0.006$, $p = 0.962$; Fig. 2f), FEV$_1$ ($r = 0.060$, $p = 0.605$; Fig. 2g), and %FEV$_1$ ($r = 0.052$, $p = 0.656$; Fig. 2h).

Correlations between IMAC and Preoperative Pulmonary Parameters

For males, a significant but weak negative correlation was observed between IMAC and FEV$_1$ ($r = 0.203$, $p < 0.001$; Fig. 3c), although no other preoperative pulmonary parameters
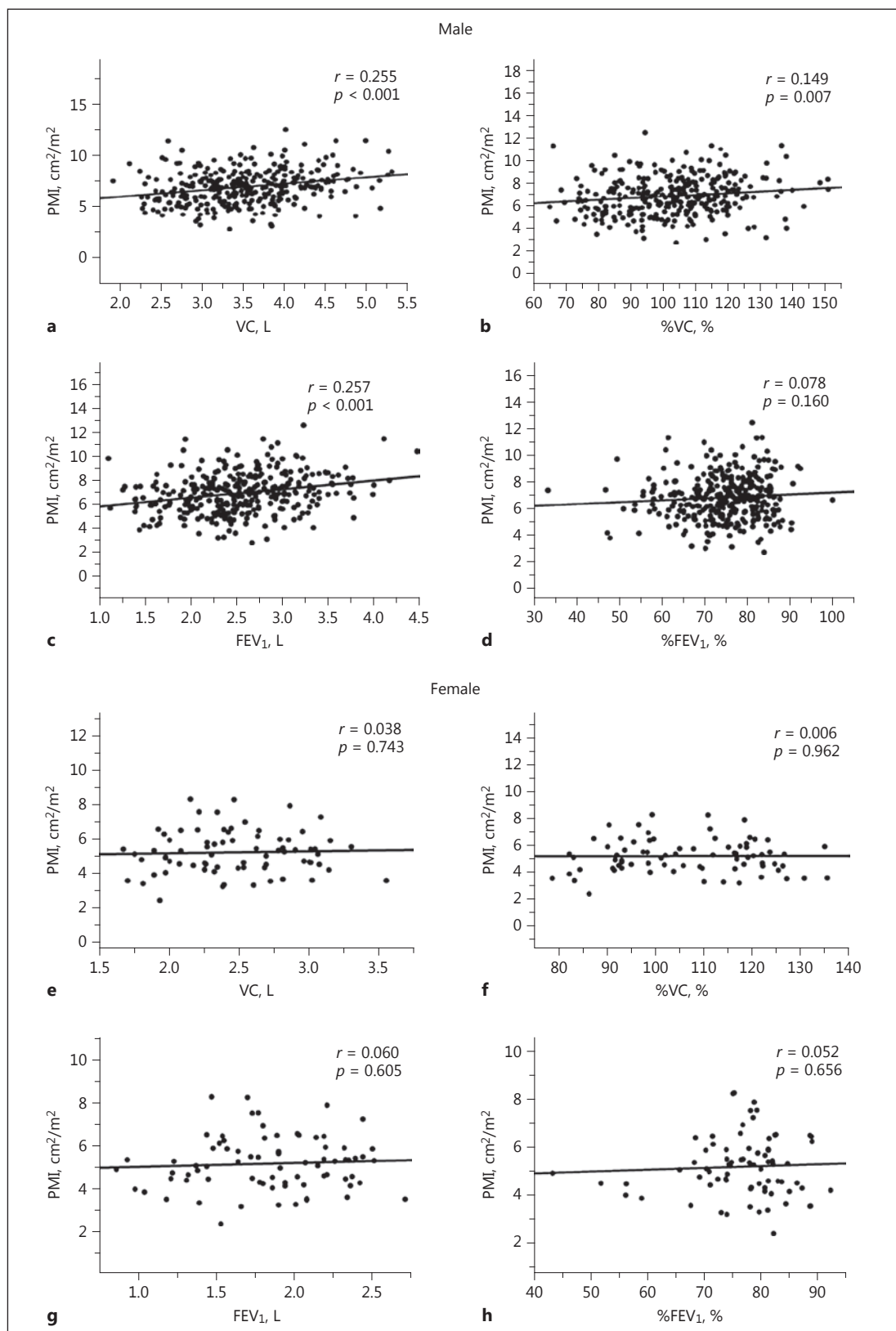
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Fig. 2. Correlations between PMI and preoperative pulmonary parameters in males (**a**: VC; **b**: %VC; **c**: FEV_1; **d**: $\%FEV_1$) and females (**e**: VC; **f**: %VC; **g**: FEV_1; **h**: $\%FEV_1$). FEV_1, forced expiratory volume in 1 s; $\%FEV_1$, percentage of predicted FEV_1; PMI, psoas muscle index; VC, vital capacity; %VC, percentage of predicted VC.

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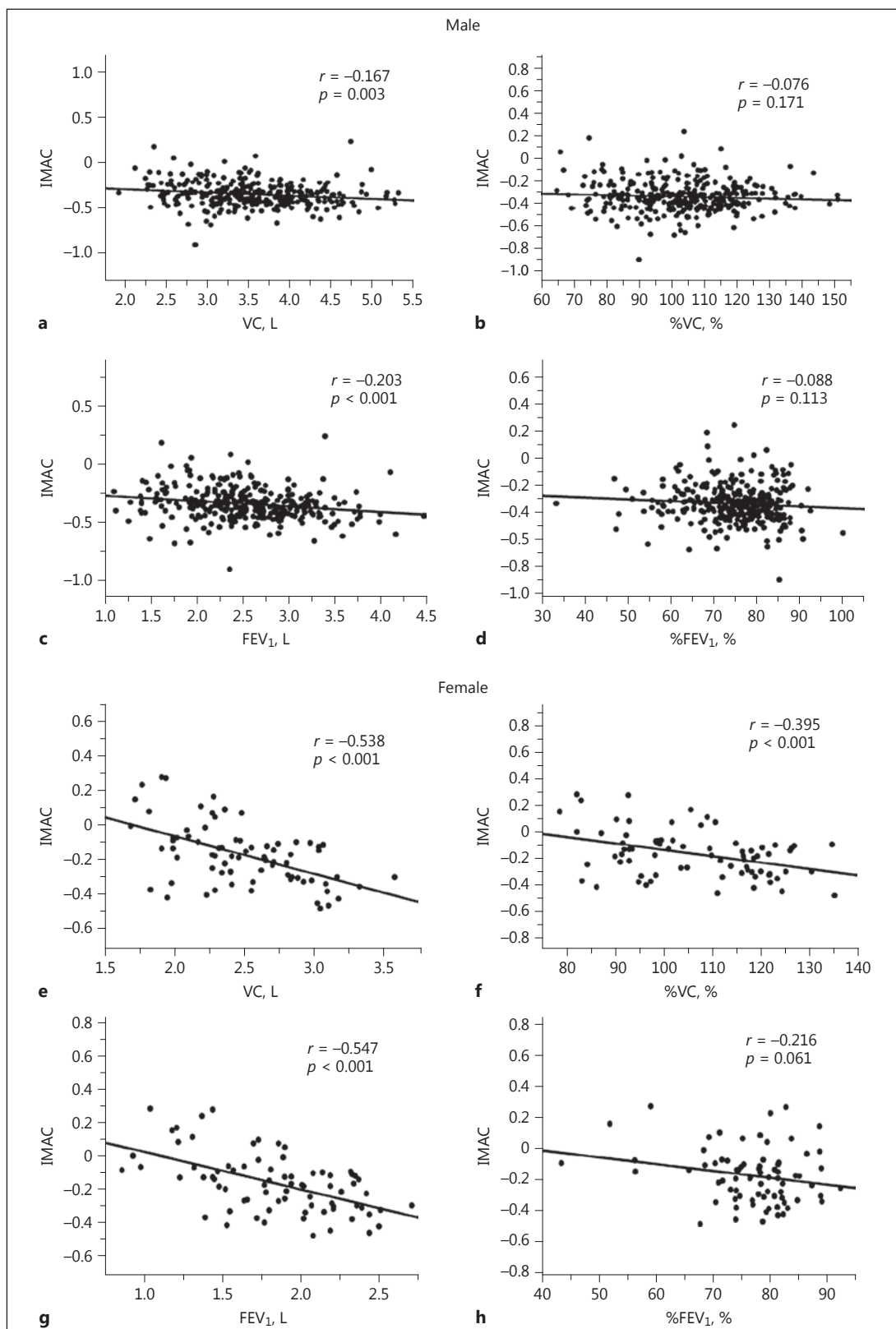

Fig. 3. Correlations between IMAC and preoperative pulmonary parameters in males (**a**: VC; **b**: %VC; **c**: FEV_1; **d**: %FEV_1) and females (**e**: VC; **f**: %VC; **g**: FEV_1; **h**: %FEV_1). FEV_1, forced expiratory volume in 1 s; %FEV_1, percentage of predicted FEV_1; IMAC, intramuscular adipose tissue content; VC, vital capacity; %VC, percentage of predicted VC.

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Table 2. Baseline characteristics according to low muscle mass and quality in both sexes

Pulmonary parameter	Male (n = 323)			Female (n = 76)		
	normal muscle mass (n = 201)	Low muscle mass (n = 122)	p value	normal muscle mass (n = 11)	low muscle mass (n = 65)	p value
VC, L	3.67±0.68	3.31±0.58	<0.001	2.48±0.40	2.45±0.58	0.707
%VC, %	105.1±16.0	99.9±15.7	0.004	106.4±13.1	107.9±21.3	0.768
FEV_1, L	2.65±0.60	2.36±0.51	<0.001	1.85±0.42	1.81±0.51	0.751
$%FEV_1$, %	75.3±8.9	74.0±9.1	0.162	76.7±8.5	78.0±9.0	0.611
Pulmonary parameter	Male (n = 323)			Female (n = 76)		
	normal muscle quality (n = 149)	low muscle quality (n = 174)	p value	normal muscle quality (n = 29)	low muscle quality (n = 47)	p value
VC, L	3.65±0.62	3.42±0.69	0.002	2.69±0.44	2.34±0.37	<0.001
%VC, %	104.7±14.6	101.8±17.1	0.087	110.6±14.5	104.1±13.9	0.055
FEV_1, L	2.69±0.60	2.42±0.55	<0.001	2.07±0.34	1.70±0.41	<0.001
$%FEV_1$, %	75.7±8.6	74.0±9.2	0.102	79.6±5.69	75.3±9.58	0.073

Values are presented as mean ± standard deviation. FEV_1, forced expiratory volume in 1 s; $%FEV_1$, percentage of predicted FEV_1; VC, vital capacity; %VC, percentage of predicted VC.

correlated significantly with IMAC. For females, IMAC correlated significantly with VC ($r = -0.538$, $p < 0.001$; Fig. 3e), %VC ($r = -0.395$, $p < 0.001$; Fig. 3f), and FEV_1 ($r = -0.547$, $p < 0.001$; Fig. 3g).

Analysis according to Preoperative PMI Status
In males, VC, %VC, and FEV_1 were significantly lower in the preoperative low PMI group than in the normal PMI group ($p < 0.001$, $p = 0.004$, and $p < 0.001$, respectively) (Table 2). In females, preoperative pulmonary functions did not significantly differ between the low PMI and the normal PMI group (Table 2).

Analysis according to Preoperative IMAC Status
In males, VC and FEV_1 were significantly lower in the preoperative high IMAC group than in the normal IMAC group ($p = 0.002$ and $p < 0.001$, respectively) (Table 2). In females, VC and FEV_1 were also significantly lower in the high IMAC group than in the normal IMAC group ($p < 0.001$ and $p < 0.001$, respectively) (Table 2).

Overall Survival Rate after Hepatectomy according to Preoperative Pulmonary Function
The overall survival rate after hepatectomy was significantly lower in patients with preoperative restrictive ventilatory impairment ($n = 21$; 20 men, 1 woman) compared with patients with preoperative normal pulmonary function ($n = 290$; 225 men, 65 women; $p = 0.021$) (Fig. 4).

Risk Factors for Poor Survival in Patients Undergoing Hepatectomy
The results of uni- and multivariate analyses of overall survival in patients undergoing hepatectomy for HCC are shown in Table 3. In univariate analysis, previous treatment for HCC, low platelet count ($<10 \times 10^4/mm^3$), high α-fetoprotein (≥ 20 ng/dL), tumor size (≥ 5.0 cm), number of tumors (solitary), tumor differentiation (poor), TNM stage (stage III or IV), surgical procedure ($\geq$lobectomy), operative blood loss (≥ 500 g), preoperative high IMAC,

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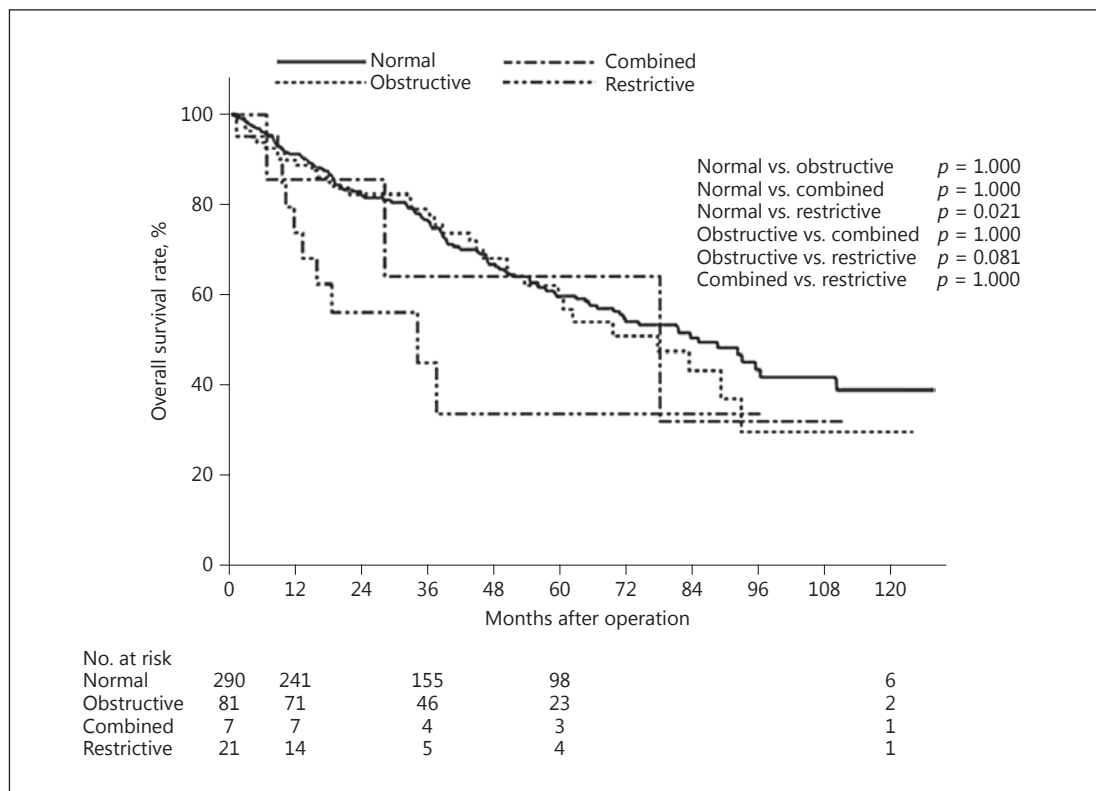
Fig. 4. Overall survival after hepatectomy for patients classified according to pulmonary function.

and restrictive ventilatory impairment were identified as significant poor risk factors among patients undergoing hepatectomy.

Multivariate analysis revealed liver histology (liver fibrosis or cirrhosis), tumor size (≥5.0 cm), TNM stage (III or IV), and preoperative high IMAC as independent risk factors, but preoperative restrictive ventilatory impairment was not a significant risk factor even though the overall survival of patients with preoperative restrictive ventilatory impairment was significantly lower than that of patients with normal pulmonary function.

Discussion

To the best of our knowledge, this retrospective study of 402 patients is the first to investigate the relationship between preoperative cardiopulmonary function and sarcopenic factors in patients undergoing first hepatectomy for HCC. In the present study, low pulmonary function was closely associated with sarcopenic factors such as PMI and IMAC. Pulmonary function progressively decreases after 20–25 years of age [23]. With age, parenchymal lung tissue is lost, chest wall compliance decreases, and intercostal muscle mass and force are reduced as the elastic elements in the lungs degenerate [24]. Moon et al. [17] revealed an association between low muscle mass and pulmonary function in healthy Korean men and women aged ≥65 years. Moreover, Jeon et al. [25] showed that low pulmonary function, as represented by decreased FEV_1 or VC, was associated with low muscle mass in older adults. Findings from the present study of patients undergoing hepatectomy for HCC are in line with those reports.

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Table 3. Univariate and multivariate analyses of prognostic factors for survival after hepatectomy

Variable	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age						
<65 years (*n* = 145)	1.000	(reference)				
≥65 years (*n* = 257)	1.068	0.772–1.489	0.695			
Sex						
Male (*n* = 325)	1.000	(reference)				
Female (*n* = 77)	1.084	0.714–1.592	0.695			
Body mass index						
<25 (*n* = 313)	1.000	(reference)				
≥25 (*n* = 89)	0.846	0.557–1.242	0.402			
Etiology of HCC						
HBV and/or HCC (*n* = 264)	1.000	(reference)	0.718			
Others (*n* = 138)	0.842	0.592–1.179	0.322			
Previous treatment for HCC						
Yes (*n* = 109)	1.000	(reference)		1.000	(reference)	
No (*n* = 293)	0.689	0.497–0.964	0.030	0.715	0.494–1.045	0.083
Platelet count						
<10 × 10^4/mm^3 (*n* = 89)	1.000	(reference)		1.000	(reference)	
≥10 × 10^4/mm^3 (*n* = 313)	0.543	0.389–0.768	<0.001	0.721	0.487–1.080	0.111
ICG R15						
<15% (*n* = 199)	1.000	(reference)				
≥15% (*n* = 203)	1.202	0.875–1.658	0.256			
Child-Pugh classification						
A (*n* = 364)	1.000	(reference)		1.000	(reference)	
B (*n* = 38)	1.635	0.978–2.577	0.060	1.484	0.855–2.450	0.155
Alpha-fetoprotein						
<20 ng/dL (*n* = 194)	1.000	(reference)		1.000	(reference)	
≥20 ng/dL (*n* = 208)	1.865	1.345–2.614	<0.001	1.432	0.996–2.078	0.052
Des-gamma-carboxy prothrombin						
<40 mU/L (*n* = 104)	1.000	(reference)				
≥40 mU/L (*n* = 298)	1.344	0.926–2.007	0.123			
Liver histology						
Normal liver or chronic hepatitis (*n* = 196)	1.000	(reference)		1.000	(reference)	
Liver fibrosis or cirrhosis (*n* = 206)	1.366	0.993–1.889	0.055	1.518	1.059–2.185	0.023
Tumor size						
<5.0 cm (*n* = 250)	1.000	(reference)		1.000	(reference)	
≥5.0 cm (*n* =152)	1.923	1.400–2.640	<0.001	1.848	1.234–2.775	0.003
Number of tumors						
Solitary (*n* = 270)	1.000	(reference)		1.000	(reference)	
Multiple (*n* = 132)	1.773	1.283–2.437	<0.001	1.243	0.851–1.812	0.260
Tumor differentiation (n = *388*)						
Good or moderate (*n* = 298)	1.000	(reference)		1.000	(reference)	
Poor (*n* = 90)	1.949	1.370–2.733	<0.001	1.438	0.978–2.086	0.064
TNM stage						
I or II (*n* = 207)	1.000	(reference)		1.000	(reference)	
III or IV (*n* = 195)	2.854	2.045–4.034	<0.001	2.057	1.345–3.155	<0.001

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Table 3 (continued)

Variable	Univariate			Multivariate		
	HR	95% CI	p value	HR	95% CI	p value
Surgical procedure						
<Segmentectomy (n = 264)	1.000	(reference)		1.000	(reference)	
≥Lobectomy (n = 138)	1.688	0.431–0.818	0.002	1.152	0.766–1.735	0.498
Operative time						
<360 min (n = 181)	1.000	(reference)		1.000	(reference)	
≥360 min (n = 221)	1.344	0.978–1.854	0.069	0.904	0.625–1.313	0.593
Operative blood loss						
<500 g (n = 136)	1.000	(reference)		1.000	(reference)	
≥500 g (n = 266)	2.041	1.041–3.062	<0.001	1.155	0.729–1.869	0.546
Preoperative PMI						
Normal (n = 268)	1.000	(reference)				
Low (n = 134)	1.176	0.843–1.625	0.337			
Preoperative IMAC						
Normal (n = 179)	1.000	(reference)		1.000	(reference)	
High (n = 223)	1.817	1.310–2.545	<0.001	2.030	1.421–2.930	<0.001
Preoperative pulmonary function (n = 399)						
Normal (n = 290)	1.000	(reference)		1.000	(reference)	
Restrictive (n = 21)	2.093	1.023–3.814	0.044	1.569	0.733–3.047	0.231
Obstructive (n = 81)	1.110	0.740–1.621	0.604	1.146	0740–1.735	0.532
Combined (n = 7)	1.258	0.309–3.339	0.705	3.509	0.559–12.018	0.152

CI, confidence interval; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR, hazard ratio; ICG R15, indocyanine green retention test at 15 min; IMAC, intramuscular adipose tissue content; PMI, psoas muscle index; TNM, Tumor Node Metastasis stage (as defined by the Liver Cancer Study Group of Japan).

In males, VC correlated significantly with PMI (Fig. 2a). Moreover, FEV_1 significantly correlated with both PMI (Fig. 2c) and IMAC (Fig. 3c). In contrast, in females, PMI did not correlate with either %VC or VC, while IMAC correlated significantly with both VC (Fig. 3e) and %VC (Fig. 3f). FEV_1 only showed a significant correlation with IMAC in females (Fig. 3g). When patients were divided into two groups by PMI using each sex-specific cutoff, most analyses showed significant differences between low PMI and pulmonary functions in males. In contrast, no significant correlations were found in females. As for IMAC, similar significant differences were found in both males and females. We speculate that this difference was related to the lower skeletal muscle mass in females than in males. Moreover, the range of distribution of PMI was narrower in females than in males. This reduction in differences in PMI might have resulted in the lack of significant correlation between PMI and pulmonary function among females. On the other hand, IMAC as a parameter of muscle quality showed no differences in quantity or distribution between males and females. Significant close relationships were thus found between IMAC levels and pulmonary functions in both males and females.

This study showed the discrepancy in the result between FEV_1 and %FEV_1 in males (Fig. 2), except for %VC in men and the result between VC and %VC as well as FEV_1 and %FEV_1 (Fig. 3), except for %VC in females. %VC is a derived value of VC, which is usually defined as VC of the patient divided by average VC in the population for any person of similar age, sex,

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and height. $\%FEV_1$ is defined as FEV_1/FVC ratio. Therefore, these predicted values or calculated ratios, $\%VC$ or $\%FEV_1$, might not reflect more directly than absolute values as VC or FEV_1.

In contrast, cardiac function did not correlate with any sarcopenic factors. Lin et al. [26] revealed that age-related cardiac sarcopenia occurs in mice and that left ventricular remodeling due to increased end-diastolic pressure could be one mechanism underlying age-related left ventricular dysfunction. Fülster et al. [16] reported that in patients with CHF, patients with muscle wasting showed significantly lower left ventricular EF than patients without muscle wasting. However, the present study found no significant relationship between EF and sarcopenic factors. This may have been because this study included 175 patients >70 years old who could undergo hepatectomy. Patients with heart diseases such as CHF are usually excluded as candidates for hepatectomy because such patients often cannot tolerate an operation under general anesthesia. Such selection biases in the present study might have contributed to the lack of a significant relationship between EF and sarcopenic factors. Moreover, to date no evidence has indicated an association between sarcopenia and cardiac function in healthy elderly individuals. Under extreme conditions such as CHF, sarcopenia might influence cardiac function.

The overall survival rate was significantly lower in patients with preoperative pulmonary restrictive impairment than in those with normal preoperative pulmonary function. Although restrictive impairment was a poor risk factor in univariate but not multivariate analysis, preoperative pulmonary dysfunction could increase the incidence of postoperative morbidities such as atelectasis or pneumonia, leading to worse survival.

Several reports have shown the effectiveness of preoperative rehabilitation in decreasing postoperative complication in patients with esophageal [27], colorectal [28], and lung cancers [29]. Koya et al. [30] demonstrated that therapeutic exercise improved cardiopulmonary function evaluated by a 6-min walking test in HCC patients.

We previously reported the impact of nutritional therapy on prognosis in patients undergoing living donor liver transplantation [4]. Taken together, perioperative nutrition therapy and rehabilitation would be important for patients with preoperative sarcopenia or pulmonary dysfunction undergoing hepatectomy for HCC. We are planning to perform perioperative intervention therapy with respiratory rehabilitation and nutritional therapy using branched-chain amino acids.

Several limitations must be considered for the present study. First, this was a retrospective study conducted in a single institution. Whether pulmonary dysfunction was the cause or result of sarcopenia remains unclear. We speculate that both causal relationships are possible. Preexisting sarcopenia might induce pulmonary dysfunction in some patients, and sarcopenia might develop as a result of pulmonary dysfunction in some patients. We are therefore conducting a prospective analysis to clarify the direction of causality between sarcopenia and lung function by measuring these parameters at various time points before and after hepatectomy. Second, the Asian and European Working Group on Sarcopenia in Older People proposed the inclusion of not only low muscle mass, but also low muscle function in the definition of sarcopenia. However, the present study did not estimate low muscle function (i.e., strength or performance). We are therefore now prospectively investigating the relationship between muscle function and cardiopulmonary functions. Third, selection bias was seen for patient inclusion in the study group. As mentioned above, hepatectomy is not usually performed in patients with CHF or severe pulmonary dysfunction, since such patients are at an unacceptable risk of not tolerating the surgery. Patients with severe cardiopulmonary dysfunction might thus have tended to be excluded from the present study.

In conclusion, the present results show that preoperative low muscle mass and low muscle quality are closely related to pulmonary dysfunction in patients undergoing hepa-

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tectomy. Although analysis of the causal relationships is needed, perioperative pulmonary rehabilitation may be useful to prevent pulmonary complications and improve overall survival after hepatectomy for HCC, especially among patients with sarcopenia.

Statement of Ethics

All study protocols were approved by the ethics committee of Kyoto University and conducted in accordance with the 1996 revision of the Declaration of Helsinki.

Disclosure Statement

None of the authors of this paper have any conflicts of interest to declare. No financial support from any source was received for this study.

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