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Impact of sarcopenic obesity on outcomes in patients undergoing hepatectomy for hepatocellular carcinoma

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Structured Abstract

Objective: To evaluate preoperative body composition, including skeletal muscle and visceral adipose tissue, and to clarify the impact on outcomes after hepatectomy for hepatocellular carcinoma (HCC).

Background: Recent studies have indicated that sarcopenia is associated with morbidity and mortality in various pathologies, including cancer, and that obesity or visceral adiposity represents a significant risk factor for several cancers. However, the impact of sarcopenic obesity on outcomes after hepatectomy for HCC has not been fully investigated.

Methods: We retrospectively analyzed 465 patients who underwent primary hepatectomy for HCC between April 2005 and March 2015. Skeletal muscle mass and visceral adipose tissue were evaluated by preoperative computed tomography to define sarcopenia and obesity. Patients were classified into one of four body composition groups according to the presence or absence of sarcopenia and obesity.

Results: Body composition was classified as non-sarcopenic non-obesity in 184 patients (39%), non-sarcopenic obesity in 219 (47%), sarcopenic non-obesity in 31 (7%), and sarcopenic obesity in 31 (7%). Compared with patients with non-sarcopenic non-obesity, patients with sarcopenic obesity displayed worse median survival (84.7 vs. 39.1 months, P=0.002) and worse median recurrence-free survival (21.4 vs. 8.4 months, P=0.003). Multivariate analysis identified sarcopenic obesity as a significant risk factor for death (hazard ratio [HR]=2.504, P=0.005) and HCC recurrence (HR=2.031, P=0.006) after hepatectomy for HCC.

Conclusion: Preoperative sarcopenic obesity was an independent risk factor for death and HCC recurrence after hepatectomy for HCC.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers around the world[1]. Although advances in preoperative diagnosis and management of HCC have improved overall survival (OS) and recurrence-free survival (RFS) after hepatectomy for HCC, the postoperative recurrence rate remains high even among patients who undergo curative resection[2].

Sarcopenia was initially described by Rosenberg in 1989 as an age-related decrease in muscle mass[3]. In 2010, the European Working Group on Sarcopenia in Older People recommended that the definition of sarcopenia include both low muscle mass and low muscle strength or function[4]. Sarcopenia is currently defined as a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength, and many studies have described sarcopenia as associated with morbidity and mortality in various pathologies, including several cancers[5–8]. Our previous studies have identified preoperative low muscle quality as an independent risk factor for poor outcomes after hepatectomy for HCC[9,10]. Recent studies have also concluded that obesity represents a significant risk factor for various health disorders, including type 2 diabetes mellitus, hypertension, cardiovascular disease, nonalcoholic steatohepatitis, and several cancers, including HCC[11–14]. Moreover, sarcopenic obesity, as the state of being both obese and sarcopenia, has attracted much attention and recent studies have described sarcopenic obesity as a poor prognostic factor among patients with cirrhosis[15,16].

However, the impact of preoperative sarcopenic obesity on outcomes in patients undergoing hepatectomy for HCC has yet to be fully investigated. The present study therefore aimed to

evaluate preoperative body composition, including skeletal muscle and visceral adipose tissue, and to clarify the impact on outcomes after hepatectomy for HCC.

Methods

Patients

A total of 522 patients underwent primary hepatectomy for HCC at Kyoto University Hospital between April 2005 and March 2015. Fifty-seven patients who did not undergo preoperative plain computed tomography (CT) at the umbilical level were excluded from this study. As a result, 465 patients (367 males, 98 females) were enrolled in this study. All study protocols were approved by the Ethics Committee of Kyoto University and all procedures were conducted in accordance with the Declaration of Helsinki of 1996.

Image Analysis

In accordance with previous studies[17–19], we analyzed skeletal muscle and visceral adipose tissue from the latest preoperative unenhanced CT images (Aquillion 64; Toshiba Medical Systems, Tochigi, Japan). We measured cross-sectional skeletal muscle area at the level of the third lumbar vertebra (L3) and cross-sectional visceral adipose tissue area at the level of the umbilicus. Skeletal muscle area included the psoas, paraspinal (erector spinae, multifidus, and quadratus lumborum), and abdominal wall muscles (transversus abdominis, external and internal obliques and rectus abdominis). Skeletal muscle and visceral adipose tissue were

identified and quantified in Hounsfield units (HU) using an AquariusNET Server (TeraRecon, San Mateo, CA). A threshold range of -29 to 150 HU was used to define skeletal muscle, and a range of -150 to -50 HU was used to define visceral adipose tissue (Fig. 1A,B).

The quantity of skeletal muscle was evaluated by skeletal muscle index (SMI), calculated by normalizing the cross-sectional areas of skeletal muscle in centimeters squared by the height of the patient in meters squared. Low SMI was regarded as a proxy for low skeletal muscle mass, and thus sarcopenia. SMI differs significantly between males and females, and we have recently established sex-specific cutoff values using data from 657 healthy donors for living donor liver transplantation (LDLT) between 2005 and 2016 [20]. Cutoff values for SMI were defined as 40.31 cm^2/m^2 in males and 30.88 cm^2/m^2 in females.

Obesity was considered present if the visceral adipose tissue area was ≥ 100 cm^2 in both males and females. This value is widely used as a cutoff to define sarcopenic obesity in Asian populations and is diagnostic of visceral fat obesity and consequently metabolic syndrome in Japan[21–23].

Patients were classified into one of four body composition categories according to the presence or absence of sarcopenia and obesity: non-sarcopenic non-obesity (NN), non-sarcopenic obesity (NO), sarcopenic non-obesity (SN), and sarcopenic obesity (SO).

Postoperative morbidity

Data on postoperative morbidities were collected. The severity of morbidities was graded in accordance with the Dindo-Clavien classification[24]. Major morbidities were defined as any morbidities of Clavien

grade ≥ III.

Analyzed Parameters

OS and RFS rates after hepatectomy for HCC were investigated in each group. Prognostic factors were analyzed using the following variables: patient age, sex, body mass index (BMI), original disease, platelet count, indocyanine green retention test at 15 min (ICG-R15), Child-Pugh classification, period of hepatectomy (Apr 2005-Mar 2010 versus Apr 2010-Mar 2015), presence of diabetes, presence of hypertension, presence of dyslipidemia, history of cardiovascular disease, serum α-fetoprotein (AFP) level, serum des-γ-carboxyprothrombin (DCP) level, liver histology, tumor size, number of tumors, microvascular invasion (MVI), tumor differentiation, TNM classification, surgical procedure (minor resection [< segmentectomy] vs. major resection [≥ lobectomy]), operative time, operative blood loss, body composition, and presence of postoperative complications.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation, and were nonparametrically analyzed using the Mann-Whitney *U* test. Categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate. Cumulative OS rates were calculated using Kaplan-Meier methods, and differences between curves were evaluated using the log-rank test. Any variable identified as significant ($P < 0.050$) or showing a value of $P < 0.100$ in univariate analysis with the abovementioned tests was considered a candidate for multivariate Cox regression analysis,

and the results are shown as hazard ratios (HRs) with 95% confidence interval (CI). Values of $P < 0.050$ were considered significant. All statistical data were generated using JMP version 11.2 software (SAS Institute, Cary, NC) and Prism 6 software (GraphPad Software, La Jolla, CA).

Results

Patient Characteristics

The clinical characteristics of patients in each group are shown in Table 1. A total of 465 eligible patients were divided into the four body composition categories as follows: NN group, n=184 (39.5%); NO group, n=219 (47.1%); SN group, n=31 (6.7%); and SO group, n=31 (6.7%). Significant differences in patient age ($P<0.001$), sex ($P<0.001$), BMI ($P<0.001$), original disease ($P<0.001$), presence of hypertension ($P<0.001$), and dyslipidemia ($P=0.006$) were seen between the four body composition categories. Patients in the SO group were older, more frequently male, and less frequently with hepatitis B or C compared with patients in other groups. Tumor-related factors, including tumor size, number of tumors, MVI, tumor differentiation, and TNM stage, and surgical factors, including surgical procedure and blood loss, did not differ significantly between the 4 groups.

Postoperative morbidity

The overall morbidity rate was 35.1% (n=163); the morbidity rate of each group was: NN group 31.0% (n=57), NO group 35.6% (n=78), SN group 48.4% (n=15), and SO group 41.9% (n=13) (Table 1). There

were no significant differences in the morbidity rate between the four body composition categories (*P*=0.218). On the other hand, the major morbidity rate was 20.1% (n=97); the major morbidity rate of each group was: NN group 16.9% (n=31), NO group 20.1% (n=44), SN group 38.7% (n=12), and SO group 32.3% (n=10), with significant differences between the four categories (*P*=0.016). The overall morbidity rate and major morbidity rate tended to be lower in the latter half of the study period (April 2010–March 2015) than in the former half of the study period (April 2005–March 2010) (*P*=0.057 and *P*=0.093, respectively).

OS and RFS Rates after Hepatectomy for HCC

The 1-, 3-, 5-year OS rates after hepatectomy for HCC in patients with NN, NO, SN, and SO were 91.1%, 78.2% and 61.0% versus 91.2%, 72.6% and 58.2% versus 77.4%, 62.7% and 38.8% versus 83.9%, 45.6% and 45.6%, respectively (Fig. 2A). The 1- and 3-year RFS rates in patients with NN, NO, SN, and SO were 64.4% and 37.8% versus 64.9% and 38.1% versus 52.7% and 31.5% versus 33.8% and 19.3%, respectively (Fig. 2B). The OS and RFS rates after hepatectomy for HCC were significantly lower in the SO group than in the NN group (*P*=0.002, *P*=0.003, respectively; Fig. S1A, S1B). OS and RFS rates in the NO and SN groups did not differ significantly from those in the NN group (*P*=0.456, *P*=0.170, and *P*=0.685, *P*=0.660, respectively; Fig. 2A, B).

Risk Factors for Poor Outcomes in Patients Undergoing Hepatectomy for HCC

Table 2 shows the results of uni- and multivariate analyses of OS among patients who underwent hepatectomy for HCC. On multivariate analysis, poor differentiation (HR, 1.945; 95%CI, 1.167-3.199; *P*=0.011), advanced TNM stage (HR, 2.478; 95%CI, 1.313-3.940; *P*=0.003), major morbidity (HR, 1.906; 95%CI, 1.130-3.143; *P*=0.016) and sarcopenic obesity (HR, 2.504; 95%CI, 1.336-4.499; *P*=0.005) were independent risk factors for death after hepatectomy for HCC (Table 2).

The results of uni- and multivariate analyses of recurrence-free survival are shown in Table 3. Multivariate analysis identified advanced TNM stage (HR, 2.972; 95%CI, 1.957-4.526; *P*<0.001) and sarcopenic obesity (HR, 2.031; 95%CI, 1.233-3.222; *P*=0.006) as independent risk factors for HCC recurrence (Table 3).

Discussion

This retrospective study identified preoperative sarcopenic obesity as a significant risk factor associated with poor prognosis among patients who had undergone hepatectomy for HCC. Recent studies have described sarcopenia as associated with morbidity and mortality in various pathologies, including several cancers[5-7]. Preoperative low skeletal muscle mass was found to be an independent prognostic factor for mortality and recurrence after hepatectomy for HCC[8,25]. Furthermore, we recently reported that preoperative low skeletal muscle quality was an independent risk factor for poor outcomes after hepatectomy for HCC[9,10]. These findings demonstrated that preoperative low muscularity (muscle mass and muscle quality) was closely associated with morbidity and mortality after hepatectomy

for HCC. In addition, obesity represents a significant risk factor for various health disorders, including type 2 diabetes mellitus, hypertension, cardiovascular disease, nonalcoholic steatohepatitis and several cancers[11-14]. In the U.S. population, overweight and obesity have been associated with the risk of death from all cancers[12]. A recent study showed that visceral obesity, defined as a high visceral to subcutaneous adipose tissue area ratio (VSR), was associated with poor outcomes in patients with HCC[18]. Recent studies also described that sarcopenic obesity, the state of being both obese and sarcopenic, has attracted substantial attention as a prognostic factor for poor outcomes in patients with solid tumors[17,26] or cirrhosis[15,16]. However, there have been no studies fully investigating sarcopenic obesity, and its influence on outcomes after hepatectomy for HCC remains unclear. As far as we know, this present retrospective study is the first to investigate the impact of sarcopenic obesity on outcomes in patients undergoing hepatectomy for HCC.

This study included cases of patients for 10 years and meanwhile, progress had taken place in surgical procedures and curative treatments for HCC. Therefore, we investigated outcomes after hepatectomy for HCC by dividing the study period into two sub-periods, the former half and the latter half. The overall morbidity and major morbidity rates tended to be lower in the latter sub-period than in the former sub-period (P=0.057 and P=0.064, respectively), but the OS and RFS rates did not differ significantly between the two sub-periods (P=0.275 and P=0.398, respectively).

In the present study, patients were classified into one of four body composition categories: non-sarcopenic non-obesity, non-sarcopenic obesity, sarcopenic non-obesity, and sarcopenic obesity. Sarcopenic non-obesity was not a negative prognostic factor. However, when patients were classified into

one of two groups; sarcopenia and non-sarcopenia, the overall survival and recurrence-free survival rates were significantly lower in sarcopenic patients than in non-sarcopenic patients (P=0.005 and P=0.007, respectively). Moreover, multivariate analysis identified sarcopenia as a significant risk factor for death (HR,1.825; 95%CI, 1.218-2.653; P=0.004) and HCC recurrence (HR, 1.479; 95%CI, 1.047-2.036; P=0.027) after hepatectomy for HCC. On the other hand, obesity alone was not a negative prognostic factor. By dividing the subjects into four groups, we were able to more accurately investigate an independent risk factor for death and HCC recurrence after hepatectomy for HCC.

In terms of the mechanisms through which sarcopenic obesity represents an independent risk for mortality and morbidity, associations among immunity, inflammation, and myokines and adipocytokines (such as adiponectin and leptin) are considered as possibilities[27-29]. Recent studies have shown that skeletal muscle loss with increasing adiposity leads to increased levels of inflammatory adipokines such as leptin, tumor necrosis factor (TNF)-α, and interleukin (IL)-6, and to decreased concentrations of adiponectin or myokines such as IL-15[30]. In addition, leptin has been shown to promote HCC progression via tumor cells activating various growth and survival signaling pathways[31]. Similarly, accumulation of visceral adipose tissue increases concentrations of TNF-α, IL-6, and monocyte chemoattractant protein (MCP)-1, and decreases adiponectin[32]. Furthermore, excess visceral adipose tissue is strongly associated with increased insulin resistance[33]. All these changes are associated with progression of HCC. Sarcopenic obesity, in which severe obesity and low muscle mass are present concomitantly, represents the worst scenario, combining as it does the health risks of both obesity and depleted lean mass. On

the basis of these things, sarcopenic obesity may be linked to poor outcomes after hepatectomy for HCC through various mechanisms.

Preoperative interventions to improve body composition could plausibly lead to improved outcomes after hepatectomy for HCC. To improve body composition, several studies have recommended exercise (aerobic and resistance) in combination with adequate protein (leucine-enriched amino acids) and energy intakes as a key component[34]. Various studies have reported that eicosapentaenoic acid (EPA) supplementation exerted positive effects on the maintenance of weight and lean body mass, and EPA could reduce inflammation[35–37]. In a mouse model, regular exercise decreased liver tumor development and stimulated the phosphorylation of AMPK and its substrate, raptor, which decreased the kinase activity of mTOR[38]. We have previously described that in patients undergoing LDLT, preoperative nutritional therapy including branched-chain amino acids (BCAAs) significantly improved overall survival among patients showing preoperative sarcopenia[39]. On the basis of such findings, we are now conducting a prospective study to evaluate the effects of preoperative exercise and nutritional therapy on body composition and postoperative outcomes after hepatectomy for HCC. We hope that such investigations will improve outcomes after hepatectomy for HCC.

The present study had several limitations. First, the possibility of selection bias in patient inclusion in the study group must be considered, as 57 patients (10.9%) were excluded from this study. We excluded patients for the sole reason of having undergone no CT at the umbilical

level (in all cases, L3 level was higher than the umbilical level). However, perioperative factors did not show any significant differences between the excluded population and the study group. We therefore consider that little actual selection bias was present in terms of patient inclusion in the study. Second, we have to keep in mind whether our cutoff values are appropriate to define sarcopenia and obesity. Several studies have established definitions for sarcopenia according to different criteria, and the need for definitive criteria remains[40–42]. The present study used cutoff values for SMI based on data from healthy donors for LDLT[20], and those values were similar to findings from recent study in Japan[43]. Our cutoff values were therefore considered likely to be adequate to define sarcopenia, at least for Japanese populations. On the other hand, obesity is generally defined as BMI $\geq$ 25 kg/m^2 and visceral fat obesity or metabolic syndrome as visceral adipose tissue area $\geq$ 100 cm^2 in Japan[23]. In the present study, the prevalence of obesity differed according to the use of BMI or visceral adipose tissue area. According to BMI, 117 patients (25.2%) were classifiable as obese, compared with 250 patients (53.8%) according to visceral adipose area. As an indirect measurement of adipose tissue, BMI cannot accurately account for differences in fat distribution. Indeed, BMI did not identify more than half of the patients with excess visceral adipose tissue in the present study. In this study, obesity was defined as a visceral adipose tissue area $\geq$ 100 cm^2 in both sexes, but visceral adipose tissue area does differ significantly between males and females ($P<0.001$; Fig. S2). Further investigations are therefore necessary.

In conclusion, preoperative sarcopenic obesity represented an independent risk factor for death and HCC recurrence after hepatectomy for HCC. Body composition can potentially be used as a prognostic factor in patients undergoing hepatectomy for HCC.

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Figure Legends

Fig. 1 Cross-sectional computed tomography images at the third lumbar vertebra level (A), and at the umbilical level (B). The red shadows show the skeletal muscle areas, which were identified and quantified using -29 to 150 HU. The green shadows show the visceral adipose tissue areas, which were quantified using -150 to -50 HU.

Fig. 2 Overall survival rates after hepatectomy for HCC classified according to the four body composition categories (A).

Recurrence-free survival rates after hepatectomy for HCC classified according to the four body composition categories (B).

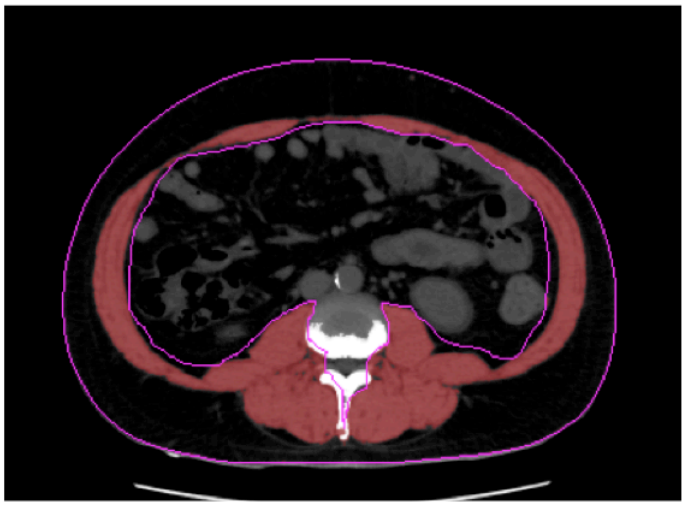
Fig. S1 Overall survival rates after hepatectomy for HCC focused on NN versus SO (A).

Recurrence-free survival rates after hepatectomy for HCC focused on NN versus SO (B).

Fig. S2 Comparison of visceral adipose tissue area between males and females.

Figure 1

A



B

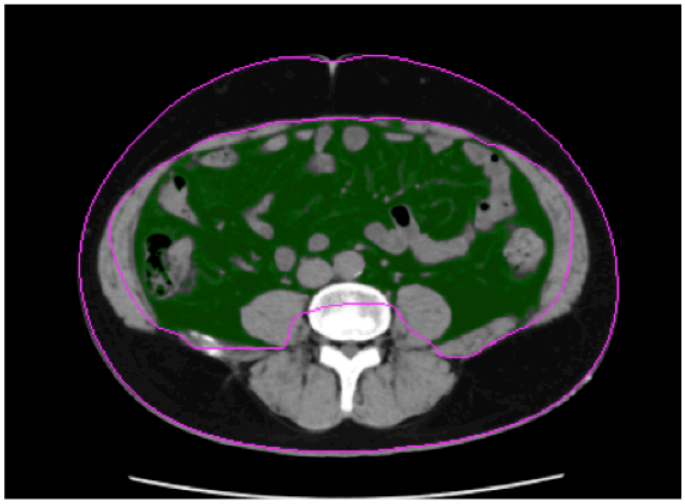
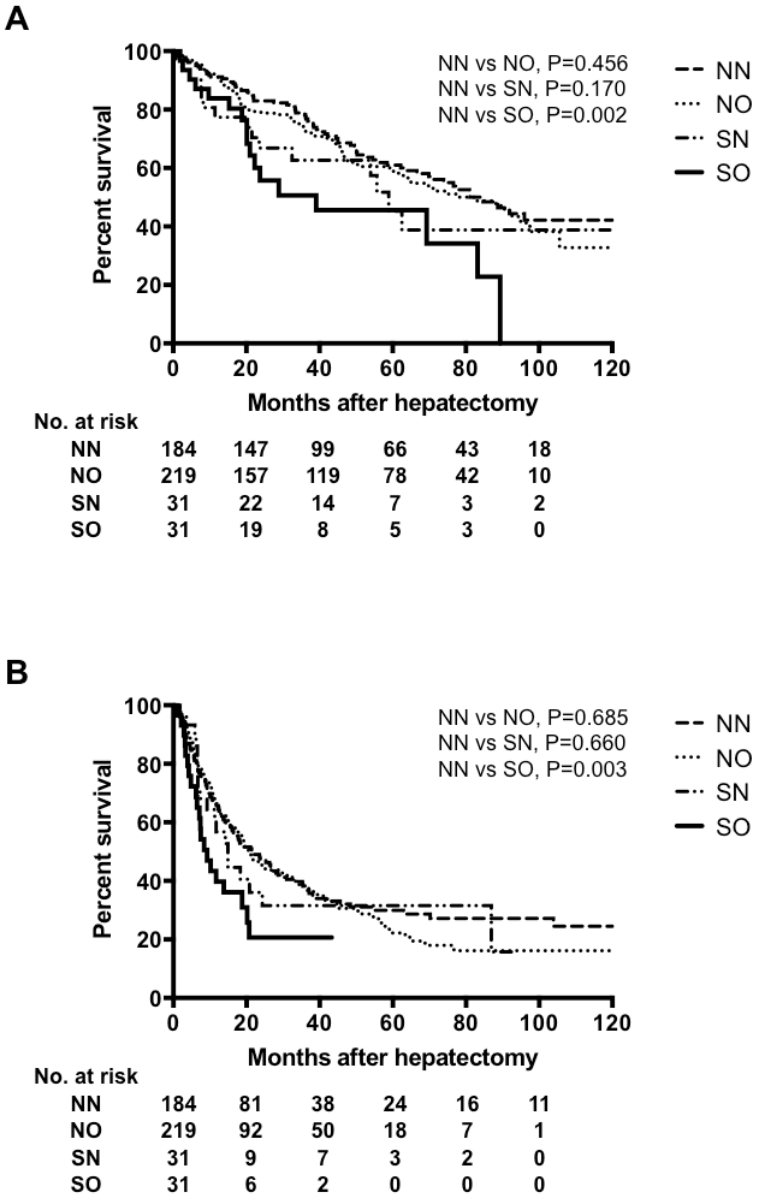
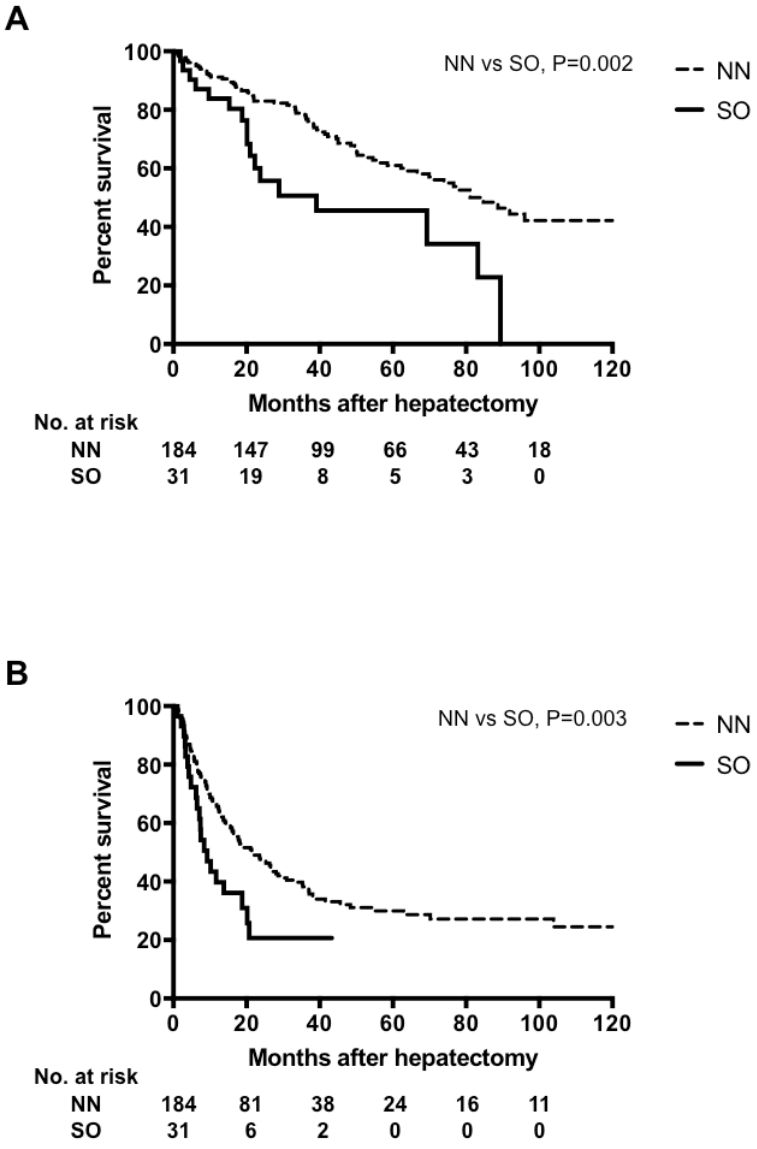


Figure 2


A
NN vs NO, P=0.456
NN vs SN, P=0.170
NN vs SO, P=0.002
NN
NO
SN
SO
Percent survival
100
80
60
40
20
0
0
20
40
60
80
100
120
Months after hepatectomy
No. at risk
NN 184 147 99 66 43 18
NO 219 157 119 78 42 10
SN 31 22 14 7 3 2
SO 31 19 8 5 3 0
B
NN vs NO, P=0.685
NN vs SN, P=0.660
NN vs SO, P=0.003
NN
NO
SN
SO
Percent survival
100
80
60
40
20
0
0
20
40
60
80
100
120
Months after hepatectomy
No. at risk
NN 184 81 38 24 16 11
NO 219 92 50 18 7 1
SN 31 9 7 3 2 0
SO 31 6 2 0 0 0

Supplemental Figure 1



Supplemental Figure 2

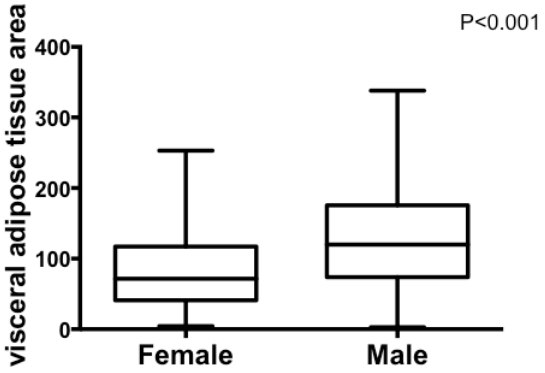


Table 1. Characteristics of patients included in the study

Characteristic	Total (n = 465)	NN (n = 184)	NO (n = 219)	SN (n = 31)	SO (n = 31)	*P*
Patient age (y)						
Mean (SD)	67.6 (9.60)	66.0 (10.1)	67.9 (9.2)	69.5 (9.0)	73.6 (7.8)	<0.001
Sex, n (%)						
Male	367 (78.9)	124 (67.4)	188 (85.8)	24 (77.4)	31 (100)	<0.001
Female	98 (21.1)	60 (32.6)	31 (14.2)	7 (22.6)	0	
BMI (kg/m^2)						
Mean (SD)	23.4 (3.6)	21.7 (2.4)	25.6 (3.3)	18.7 (2.1)	22.5 (2.9)	<0.001
Original disease, n (%)						
HBV or / and HCV	302 (64.9)	146 (79.3)	124 (56.6)	21 (67.7)	11 (35.5)	<0.001
Others	163 (35.1)	38 (20.7)	95 (43.4)	10 (32.3)	20 (64.5)	
Platelet count ($\times 10^4/mm^3$)						
Mean (SD)	155.2 (70.8)	148.7 (68.8)	156.9 (69.0)	173.6 (101.0)	163.5 (58.9)	0.244
ICG R15 (%)						
Mean (SD)	17.0 (9.9)	17.0 (10.2)	17.6 (9.6)	13.4 (8.1)	17.1 (10.6)	0.172
Child-Pugh, n (%)						
A	421 (90.5)	165 (89.7)	199 (90.9)	30 (96.8)	27 (87.1)	0.568
B	44 (9.5)	19 (10.3)	20 (9.1)	1 (3.2)	4 (12.9)	
Period of hepatectomy, n (%)						
Apr 2005-Mar 2010	272 (58.5)	113 (61.4)	129 (58.9)	17 (54.8)	13 (41.9)	0.228

Apr 2010-Mar 2015	193 (41.5)	71 (38.6)	90 (41.1)	14 (45.2)	18 (58.1)	
Comorbidity, n (%)						
Diabetes	143 (30.8)	46 (25.0)	80 (36.5)	7 (22.6)	10 (32.3)	0.063
Hypertension	215 (46.2)	63 (34.2)	120 (54.8)	14 (45.2)	18 (58.1)	<0.001
Dyslipidemia	43 (9.3)	8 (4.4)	29 (13.2)	1 (3.2)	5 (16.1)	0.006
Cardiovascular disease	24 (5.2)	6 (3.3)	17 (7.8)	1 (3.2)	0 (0)	0.098
AFP (ng/dl)						
Median (range)	21.9 (0.9-2873490)	54.7 (0.9-2873490)	13.5 (1.5-167928)	35.0 (1.2-1161)	10.6 (1.9-10690)	0.547
DCP (mU/l)						
Median (range)	183 (8-431000)	155 (8-431000)	165 (13-178000)	262 (13-101000)	492 (16-223000)	0.565
Liver histology, n (%)						
Normal liver + chronic hepatitis	226 (48.6)	85 (46.2)	104 (47.5)	16 (51.6)	21 (67.7)	0.158
Liver fibrosis + liver cirrhosis	239 (51.4)	99 (53.8)	115 (52.5)	15 (48.4)	10 (32.3)	
Tumor size (cm)						
Mean (SD)	5.1 (3.9)	5.0 (4.0)	5.0 (3.5)	5.4 (4.7)	6.2(5.1)	0.412
Number of tumors, n (%)						
Solitary	146 (31.4)	130 (70.7)	144 (65.8)	21 (67.7)	24 (77.4)	0.510
Multiple	319 (68.6)	54 (29.3)	75 (34.2)	10 (32.3)	7 (22.6)	
MVI, n (%)						
Positive	150 (32.3)	58 (31.5)	71 (32.4)	12 (38.7)	9 (29.0)	0.853
Negative	315 (67.7)	126 (68.5)	148 (67.6)	19 (61.3)	22 (71.0)	

Tumor differentiation, n (%)						
Well	52 (11.2)	21 (11.4)	24 (11.0)	6 (19.4)	1 (3.2)	0.809
Moderate	292 (62.8)	108 (58.7)	143 (65.2)	20 (64.5)	21 (67.8)	
Poor	108 (23.2)	48 (26.1)	47 (21.5)	4 (12.9)	9 (29.0)	
Unknown	13 (2.8)	7 (3.8)	5 (2.3)	1 (3.2)	0 (0)	
TNM stage, n (%)						
I	64 (13.8)	31 (16.8)	25 (11.4)	6 (19.4)	2 (6.5)	0.387
II	183 (39.3)	73 (39.7)	89 (40.6)	10 (32.3)	11 (35.5)	
III	147 (31.6)	54 (29.3)	74 (33.8)	10 (32.3)	9 (29.0)	
IV	71 (15.3)	26 (14.1)	31 (14.2)	5 (16.1)	9 (29.0)	
Surgical procedure						
≥ Lobectomy	175 (37.6)	69 (37.5)	78 (35.6)	12 (38.7)	16 (51.6)	0.395
< Segmentectomy	290 (62.4)	115 (62.5)	141 (64.4)	19 (61.3)	15 (48.4)	
Operative blood loss (ml)						
Mean (SD)	1247.8 (2179.3)	1215.5 (2138.6)	1295.4 (2404.4)	829.9 (683.9)	1508.5 (1651.1)	0.641
Dindo-Clavien classification, n (%)						
none	302 (64.9)	127 (69.0)	141 (64.4)	16 (51.6)	18 (58.1)	0.093
I or II	66 (14.2)	26 (14.1)	34 (15.5)	3 (9.7)	3 (9.6)	
III or IV	97 (20.9)	31 (16.9)	44 (20.1)	12 (38.7)	10 (32.3)	

AFP, serum α-fetoprotein; BMI, body mass index; DCP, serum des-γ-carboxyprothrombin; ICG R 15, indocyanine green retention test at 15 min; MVI, microvascular invasion; NN, non-sarcopenic non-obesity; NO, non-saropenic obesity; SN, sarcopenic non-obesity; SO, sarcopenic obesity

Table 2. Prognostic factors for overall survival on univariate and multivariate analysis (Cox proportional hazard model)

		Univariate			Multivariate		
Variables		**HR**	**95%CI**	***P***	**HR**	**95%CI**	***P***
Patient age (y)	< 65 (n = 165)	1.000		0.706			
	≥ 65 (n = 300)	1.057	0.794-1.420				
Sex	Male (n = 367)	1.000		0.719			
	Female (n = 98)	0.938	0.652-1.317				
BMI	< 25 (n = 348)	1.000		0.825			
	≥ 25 (n =117)	0.964	0.692-1.321				
Original disease	HBV or HCV (n = 302)	1.000		0.535			
	others (n = 163)	0.910	0.672-1.221				
Platelet count ($\times 10^4/mm^3$)	≥ 10 (n = 366)	1.000		0.036	1.000		0.872
	< 10 (n = 99)	1.415	1.0241-1.924		1.051	0.585-2.008	
ICG R15 (%)	< 15 (n = 231)	1.000		0.355			
	≥ 15 (n = 234)	1.141	0.863-1.512				
Child-Pugh	A (n = 421)	1.000		0.072	1.000		0.340
	B (n = 44)	1.538	0.960-2.342		1.468	0.646-3.014	
Period of hepatectomy	Apr 2005-Mar 2010	1.000		0.275			
	Apr 2010-Mar 2015	1.204	0.860-1.666				
Diabetes	No (n = 322)	1.000		0.612			
	Yes (n = 143)	1.082	0.795-1.455				

Hypertension	No (n = 250)	1.000		0.546			
	Yes (n = 215)	0.917	0.691-1.214				
Dyslipidemia	No (n = 422)	1.000		0.691			
	Yes (n = 43)	0.897	0.497-1.488				
Cardiovascular disease	No (n = 441)	1.000		0.142			
	Yes (n = 24)	0.595	0.253-1.170				
AFP (ng/dl)	< 20 (n = 224)	1.000		<0.001	1.000		0.121
	≥ 20 (n = 241)	2.038	1.525-2.747		1.549	0.892-2.759	
DCP (mU/l)	< 40 (n = 123)	1.000		0.049	1.000		0.749
	≥ 40 (n = 342)	1.386	1.000-1.960		0.910	0.520-1.647	
Liver histology	Normal liver or chronic hepatitis (n = 226)	1.000		0.721			
	Liver fibrosis or liver cirrhosis (n = 239)	1.052	0.796-1.392				
Tumor size (cm)	< 5.0 (n = 290)	1.000		<0.001			
	≥ 5.0 (n = 175)	1.793	1.354-2.371				
Number of tumors	Solitary (n = 319)	1.000		<0.001			
	Multiple (n = 146)	1.668	1.252-2.212				
MVI	Negative (n = 315)	1.000		<0.001			
	Positive (n = 150)	2.127	1.605-2.813				
Tumor differentiation	Well or moderate (n = 344)	1.000		<0.001	1.000		0.011

	Poor (n = 108)	2.173	1.600-2.923		1.945	1.167-3.199	
TNM stage	I or II (n = 247)	1.000		<0.001	1.000		0.003
	III or IV (n = 218)	2.478	1.861-3.322		2.267	1.313-3.940	
Surgical procedure	Minor resection (n = 290)	1.000		<0.001	1.000		0.866
	Major resection (n = 175)	1.628	1.227-2.155		0.952	0.541-1.669	
Operative blood loss (ml)	< 500 (n = 161)	1.000		<0.001	1.000		0.871
	≥ 500 (n = 304)	1.776	1.294-2.48		1.051	0.583-1.932	
Dindo-Clavien classification	none (n = 302)	1.000			1.000		0.016
	I or II (n = 66)	1.286	0.844-1.900	0.234			
	III or IV (n = 97)	2.024	1.465-2.766	<0.001	1.906	1.130-3.143	
Body composition	NN (n = 184)	1.000			1.000		0.005
	NO (n = 219)	1.122	0.827-1.529	0.461			
	SN (n = 31)	1.478	0.816-2.501	0.188			
	SO (n = 31)	2.202	1.254-3.653	0.007	2.504	1.336-4.499	

AFP, serum α-fetoprotein; BMI, body mass index; DCP, serum des-γ-carboxyprothrombin; ICG R 15, indocyanine green retention test at 15 min; MVI, microvascular invasion; NN, non-sarcopenic non-obesity; NO, non-saropenic obesity; SN, sarcopenic non-obesity; SO, sarcopenic obesity

Variables included in the multivariate analysis were platelet count, Child-Pugh classification, AFP, DCP, tumor differentiation, TNM stage, surgical procedure, operative blood loss, and SO. Tumor size, number of tumor, and MVI were not included to avoid colinearity, as they are included in TNM stage.

Table 3. Prognostic factors for recurrence-free survival on univariate and multivariate analysis (Cox proportional hazard model)

		Univariate			Multivariate		
Variables		**HR**	**95%CI**	***P***	**HR**	**95%CI**	***P***
Patient age (y)	< 65 (n = 165)	1.000		0.647			
	≥ 65 (n = 300)	1.056	0.834-1.332				
Sex	Male (n = 367)	1.000		0.862			
	Female (n = 98)	1.025	0.770-1.344				
BMI	< 25 (n = 348)	1.000		0.411			
	≥ 25 (n =117)	0.896	0.685-1.160				
Original disease	HBV or HCV (n = 302)	1.000		0.277			
	others (n = 163)	0.875	0.685-1.111				
Platelet count ($\times 10^4/mm^3$)	≥ 10 (n = 366)	1.000		0.127			
	< 10 (n = 99)	1.243	0.938-1.625				
ICG R15 (%)	< 15 (n = 231)	1.000		0.756			
	≥ 15 (n = 234)	1.037	0.826-1.301				
Child-Pugh	A (n = 421)	1.000		0.567			
	B (n = 44)	1.127	0.736-1.651				
Period of hepatectomy	Apr 2005-Mar 2010	1.000		0.398			
	Apr 2010-Mar 2015	0.901	0.703-1.146				
Diabetes	N0 (n = 322)	1.000		0.182			

	Yes (n = 143)	0.842	0.648-1.082				
Hypertension	N0 (n = 250)	1.000		0.884			
	Yes (n = 215)	0.983	0.782-1.234				
Dyslipidemia	N0 (n = 422)	1.000		0.331			
	Yes (n = 43)	0.818	0.525-1.214				
Cardiovascular disease	N0 (n = 441)	1.000		0.525			
	Yes (n = 24)	0.848	0.483-1.374				
AFP (ng/dl)	< 20 (n = 224)	1.000		<0.001	1.000		0.288
	≥ 20 (n = 241)	2.038	1.525-2.747		1.220	0.846-1.769	
DCP (mU/l)	< 40 (n = 123)	1.000		0.003	1.000		0.921
	≥ 40 (n = 342)	1.473	1.135-1.936		1.021	0.679-1.563	
Liver histology	Normal liver or chronic hepatitis (n = 226)	1.000		0.376			
	Liver fibrosis or liver cirrhosis (n = 239)	1.108	0.883-1.392				
Tumor size (cm)	< 5.0 (n = 290)	1.000		<0.001			
	≥ 5.0 (n = 175)	1.568	1.242-1.972				
Number of tumors	Solitary (n = 319)	1.000		<0.001			
	Multiple (n = 146)	1.706	1.345-2.153				
MVI	Negative (n = 315)	1.000		<0.001			
	Positive (n = 150)	1.891	1.490-2.388				

Tumor differentiation	Well or moderate (n = 344)	1.000		0.063	1.000		0.874
	Poor (n = 108)	1.300	0.986-1.689		0.968	0.643-1.432	
TNM stage	I or II (n = 247)	1.000		<0.001	1.000		<0.001
	III or IV (n = 218)	2.256	1.796-2.839		2.972	1.957-4.526	
Surgical procedure	Minor resection (n = 290)	1.000		0.002	1.000		0.837
	Major resection (n = 175)	1.453	1.150-1.829		0.958	0.639-1.441	
Operative blood loss (ml)	< 500 (n = 161)	1.000		0.083	1.000		0.424
	≥ 500 (n = 304)	1.234	0.973-1.575		0.847	0.566-1.277	
Dindo-Clavien classification	none (n = 302)	1.000					
	I or II (n = 66)	1.280	0.914-1.755	0.147			
	III or IV (n = 97)	1.128	0.837-1.496	0.422			
Body composition	NN (n = 184)	1.000			1.000		0.006
	NO (n = 219)	1.054	0.824-1.350	0.676			
	SN (n = 31)	1.108	0.660-1.756	0.684			
	SO (n = 31)	2.088	1.297-3.217	0.003	2.031	1.233-3.222	

AFP, serum α-fetoprotein; BMI, body mass index; DCP, serum des-γ-carboxyprothrombin; ICG R 15, indocyanine green retention test at 15 min; MVI, microvascular invasion; NN, non-sarcopenic non-obesity; NO, non-saropenic obesity; SN, sarcopenic non-obesity; SO, sarcopenic obesity

Variables included in the multivariate analysis were AFP, DCP, tumor differentiation, TNM stage, surgical procedure, operative blood loss, and SO. Tumor size, number of tumor, and MVI were not included to avoid colinearity, as they are included in TNM stage.