Sarcopenia Impacts on Short- and Long-term Results of Hepatectomy for Hepatocellular Carcinoma

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Objective: To evaluate the prevalence of sarcopenia among European patients with resectable hepatocellular carcinoma (HCC) and to assess its prognostic impact on overall and disease-free survival.

Background: Identification of preoperative prognostic factors in liver surgery for HCC is required to better select patients and improve survival. Recent studies have shown that preoperative discrimination of patients with low skeletal muscle mass (sarcopenic patients) using computed tomography was associated with morbidity and mortality after liver and colorectal surgery. Assessment of sarcopenia could be used to evaluate patients before hepatectomy for HCC.

Methods: All consecutive patients who underwent hepatectomy for HCC in our institution, between February 2006 and September 2012, were included. Univariate and multivariate analyses evaluating prognostic factors of postoperative mortality and cancer recurrence were performed, including preoperative, surgical, and histopathological factors.

Results: Among 198 patients who underwent hepatectomy for HCC, 109 patients had an available computed tomographic scan and represent the study cohort. After a median follow-up of 21.23 months, 27 patients (24.8%) died. There were 20 deaths among the 59 patients who had sarcopenia and only 7 deaths in the nonsarcopenic group. Sarcopenic patients had significantly shorter median overall survival than nonsarcopenic patients (52.3 months vs 70.3 months; $P = 0.015$). On multivariate analysis, sarcopenia was found to be an independent predictor of poor overall survival (hazard ratio = 3.19; $P = 0.013$) and disease-free survival (hazard ratio = 2.60; $P = 0.001$).

Conclusions: Sarcopenia was found to be a strong and independent prognostic factor for mortality after hepatectomy for HCC in European patients and could be used to evaluate eligibility of patients with HCC before surgery.

Keywords: Hepatocellular Carcinoma, sarcopenia, analytic morphomics, frailty, surgical outcomes

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Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer-related death worldwide,[1] accounting for 695,000 deaths per year.[2] In Western countries, the incidence of HCC has increased during the past decades, as in the United States where the incidence of HCC has tripled between 1975 and 2005.[3] In 70% to 90% of cases,[4,5] the development of HCC is linked to the occurrence of a chronic liver disease due to numerous etiologies, such as chronic viral infection, alcohol consumption, or metabolic syndrome, and therefore limits the possibility of curative treatments including liver resection and liver transplantation.[6,7] To assess the prognosis in patients with HCC and to guide therapeutic approach, many scoring systems have been proposed, which include different variables linked to tumor extension and liver function.[8–12]

Among these scoring system, only one (Barcelona Clinic Liver Cancer) takes into account physical status and none includes nutritional status that are both yet major prognostic factors. Thus, several studies have shown that malnutrition, which is found in 21% of oncological patients,[13] 17% to 46% of patients undergoing general surgery,[14,15] and up to 70% of the patients in the waiting list for liver transplantation,[16] significantly increases morbidity and mortality after surgery for cancer.[17–19] Moreover, malnutrition is also frequently observed in patients with cirrhosis[20,21] and has been recognized to predict poor survival in these patients.[22]

However, despite its high prognostic and predictive values in patients with cancer and/or cirrhosis, malnutrition remains unappreciated and neglected by clinicians, as illustrated by a recent study in which almost half of oncologists failed to identify factors that place patients at risk of malnutrition, such as weight loss and/or body mass index (BMI).[23] In addition, the prevalence of overweight and obesity had increased during the last decades, reaching 15% to 20% of the world population.[24,25] In these settings, commonly used methods to detect malnutrition, as anthropometric measurements (eg, involuntary weight loss and BMI), are not sensitive and a normal or high BMI might mask malnutrition. Furthermore, biochemical assessment of nutritional status using serum albumin or transthyretine is not suitable in cirrhosis, as these are synthesized by the liver and therefore their serum levels are influenced by liver disease and are not correlated with anthropometric measures in patients with liver disease.[26] These support a new strategy for the screening of malnutrition, in which body composition evaluation takes a greater role.

Emerging evidence suggests that severe muscle depletion (named sarcopenia) is independently associated with poor prognosis in many cancers,[27–30] with or without the loss of fat mass associated, and linked with functional status and chemotherapy toxicity.[31] For HCC, sarcopenia was recently identified as a significant prognostic factor of mortality before and after liver transplantation[32,33] and as a predictor of toxicity in cirrhotic patients with Child-Pugh A status treated with sorafenib.[31] Recently, loss of skeletal muscle mass was also described as a significant prognostic factor in Asian patients with HCC after hepatectomy[34] but without using the international definition of sarcopenia.[35] The purposes of this study were to evaluate the prevalence of sarcopenia among European patients with resectable HCC and to assess its prognostic impact on overall survival and disease-free survival.

PATIENTS AND METHODS

Patients

From February 2006 to September 2012, charts of all consecutive patients who underwent liver resection for HCC in our

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institution were reviewed (N = 198). Among these patients, only those with available cross-sectional abdominal images with computed tomographic (CT) scans within 2 months before surgery or 7 days after surgery were considered for analysis (N = 109). Characteristic data of these patients were collected in a prospectively maintained computer database and analyzed retrospectively. In addition, each medical record was reviewed to obtain missing data. The institution review board approved this observational study, and patient written consent was waived.

Preoperative Investigations

Preoperative assessment including complete medical history, physical examination, score of American Society of Anesthesiologist (ASA), anthropometric measurements, that is, stature, weight and BMI, etiology of liver disease, and liver function evaluated with the Child-Pugh classification, laboratory tests including complete blood cell count, coagulation profile, serum albumin rate, plasma levels of α-fetoprotein (AFP), and multiple-phase CT and/or magnetic resonance imaging, to provide diagnosis and evaluate HCC, was performed. All patients were discussed at a weekly multidisciplinary board gathering of surgeons, hepatologists, oncologists, pathologists, and radiologists, and eligibility for liver resection or liver transplantation was evaluated.

Surgical Procedure and Pathological Examination

Intraoperative ultrasonography was performed in all cases. When it was possible, hepatic resection was performed by laparoscopy, especially when HCC tumor was limited to the left lateral section of the liver or within segment 4B, 5, or 6. In other cases, a standardized laparotomy was performed. For each patient, the type of surgical procedure, operative time, and estimated blood loss were recorded.

Tumor specimen was evaluated histologically, and the degree of hepatic fibrosis was assessed by a single pathologist using the METAVIR scoring system[36]: F0, absent; F1, portal fibrosis without septa; F2, portal fibrosis with rare septa; F3, numerous septa; and F4, cirrhosis. Patients with F4 grade of fibrosis were considered as cirrhotic, whereas patients with F0 to F3 grade of fibrosis were considered as noncirrhotic. Tumor differentiation was according to the World Health Organization classification, and perinervous invasion, tumor capsule infiltration, biliary duct invasion, involvement of adjacent organ, macroscopic and microscopic vascular invasion, presence of satellite nodules, surgical margins, tumor size, tumor location, and the number of tumors were also analyzed.

Curative resection (R0) was defined by the absence of tumor tissue macroscopically or microscopically detectable after resection. An R1 resection indicates microscopic residual tumor (positive margins), and R2 indicates macroscopic residual tumor. Postoperative complications during 90 days after surgery were recorded for each patient according to the Dindo and Clavien classification.[37]

All patients had follow-up controls within the first month after surgery and every 6 months. Each follow-up visit included physical examination, plasma level of AFP, and triple-phase CT scan and/or liver ultrasonography. The last data of included patients were updated in March 2013.

Anthropometric Measurements

Weight and height were measured for all 109 patients before surgery. BMI was calculated as weight (kg)/height (m^2). Underweight (BMI <18.5), normal (18.5< BMI <24.9), overweight (25< BMI <29.9), and obesity (BMI >30) were categorized according to the World Health Organization classification.[38]

Imaging Analysis

Sarcopenia was defined according to the international consensus, that is, a skeletal muscle index (SMI) less than 52.4 cm^2/m^2 for men and an SMI of less than 38.9 cm^2/m^2 for women.[27,35] SMI is the total muscle area (TMA) measured on an axial section through the third lumbar vertebrae when both pedicles are visible with a preestablished density threshold in the (−29 to +150 Hounsfield units) normalized for stature [TMA (cm^2/height (m^2)].[39,40]

Two radiologists in consensus, blinded for all clinical, biological, other anthropometric characteristics, and follow-up, measured TMA (cm^2) using manual segmentation on a dedicated posttreatment station (Advantage Window v4.6; GE Healthcare, Buc, France) on enhanced CT scans—portal venous phase—performed for routine diagnostic and staging purposes.

CT parameters included unenhanced and enhanced multiphase acquisitions, 0.625-mm collimation, and 1.25 contiguous slice thickness.

Statistical Analysis

Categorical data were compared by the χ^2 test or the Fisher exact test. For continuous data, the independent-samples t test was used. Correlation between continuous variables was assessed using Pearson correlation coefficients and linear regression. Survival rates were calculated using the Kaplan-Meier method and included postoperative deaths. Overall survival was calculated from the date of surgery until death from any cause, and disease-free survival was calculated from the date of surgery until first recurrence or death from any cause. Patients were observed until their deaths or until March 20, 2013, at which time they were censored at the last date they were documented to have been alive (for overall survival) or recurrence-free (for disease-free survival). The log-rank test was used to compare survival curves, and the Breslow test (also named the Geham test), which measures outcomes that occur early more heavily than outcomes that occur later, was performed to underline survival advantage between groups. Univariate analyses for overall and disease-free survival were conducted using the Cox proportional hazard model to identify potential prognostic factors of survival. To take into account confounders into survival analysis, a multivariate analysis was performed using a Cox proportional backward stepwise procedure, including age, sex, and not redundant variables, that is associated with the outcome in univariate analysis at a P value of less than 0.15. The 0.1 level was defined for systematic entry into the model. The variation inflation factor and tolerance were calculated to assess multicollinearity before performing multivariate analysis, and multicollinear variables were excluded from the multivariate analysis. All statistical analyses were performed using SPSS, version 16.0 (SPSS Inc, Chicago, IL). A P value of 0.05 or less was considered as significant.

RESULTS

Among 198 consecutive patients who underwent hepatic resection for HCC between February 2006 and September 2012, a total of 109 patients had an available CT scan fulfilling the aforementioned criteria and represent the study cohort.

Preoperative characteristics for this study group are detailed in Table 1. The mean age of the patients was 61.6 (SD = 13.3) years, with a majority of men (male to female ratio = 5.4:1). In 45 cases (41%), HCC occurred in patients with liver cirrhosis.

Interestingly, in these oncological setting, we observed a large proportion of overweight (46 cases, 42.2%) and obese (14 cases, 12.8%) patients, whereas lumbar SMI was found to be low (mean = 48.29, SD = 9.58 cm^2/m^2). Men had a median lumbar SMI of 49.9 (range = 27.2–68.7) cm^2/m^2, significantly higher than 39.6 (range = 27.4–49.1) cm^2/m^2 for women ($P < 0.0001$) (Fig. 1A). Overall,

TABLE 1. Preoperative Patient and Disease Characteristics

Variable	Total (N = 109)	Nonsarcopenic (n = 50)	Sarcopenic (n = 59)	P
Sex				0.090
Men	92 (84.4)	39 (78)	53 (90)	
Women	17 (15.6)	11 (22)	6 (10)	
Age, mean (SD), yr	61.66 (13.30)	58.25 (13.08)	64.55 (12.92)	**0.013**
Age				0.129
<60	46 (42.2)	25 (50)	21 (36)	
≥60	63 (57.8)	25 (50)	38 (64)	
Weight, mean (SD), kg	74.87 (14.23)	75.93 (12.82)	73.97 (15.38)	0.475
Stature, mean (SD), cm	170.88 (7.66)	168 (7)	173 (7.5)	**<0.001**
BMI, mean (SD), kg/m²	25.64 (4.49)	26.85 (3.98)	24.62 (4.67)	**0.009**
BMI category, kg/m²				• **0.05**
<18.5	6 (5.3)	0	6 (10)	
18.5–24.9	43 (39.4)	17 (34)	26 (44)	
25–29.9	46 (42.2)	25 (50)	21 (36)	
≥30	14 (12.8)	8 (16)	6 (10)	
Obesity (BMI ≥30 kg/m²)				0.365
No	95 (87.2)	42 (84)	53 (90)	
Yes	14 (12.8)	8 (16)	6 (10)	
Serum albumin, mean (SD), g/L	39.82 (4.25)	40.78 (3.12)	39.13 (4.75)	**0.033**
Etiologies				0.689
Alcohol	12 (11)	5 (10)	7 (12)	
HBV	22 (20.2)	11 (22)	11 (19)	
HCV	27 (24.8)	12 (24)	15 (25.4)	
NASH	11 (10.1)	7 (14)	4 (7)	
Multifactorial	8 (7.3)	2 (4)	6 (10)	
Unknown	29 (26.6)	13 (26)	16 (27)	
ASA score				0.459
1–2	74 (67.9)	32 (64)	41 (71)	
3–4	35 (32.1)	18 (36)	17 (29)	
AFP >400				0.270
No	58 (71.6)	28 (78)	30 (67)	
Yes	23 (28.4)	8 (22)	15 (33)	
Portal or hepatic vein thrombosis				0.070
No	93 (85.3)	46 (92)	47 (80)	
Yes	16 (14.7)	4 (8)	12 (20)	
SMI, mean (SD), cm²/m²	48.29 (9.58)	55.06 (8.07)	42.55 (6.54)	**<0.0001**

The values given are number (%) unless indicated otherwise. Variables in bold are statistically significant ($P < 0.05$).
NASH indicates nonalcoholic steatohepatitis; HBV, hepatitis B virus; HCV, hepatitis C virus; ASA, American Society of Anaesthesiologists; AFP, alpha-foeto protein; SMI, skeletal muscle index; BMI, body mass index.

59 patients (54%) were classified as sarcopenic and 50 patients (46%) as nonsarcopenic.

The sarcopenic group and the nonsarcopenic group were comparable regarding patient comorbidity (ASA score), etiology of liver disease characteristics, blood level of AFP, and preoperative portal vein thrombosis. Sarcopenia was significantly more common in patients 60 years or older ($P = 0.013$) and was associated with a lower BMI ($P = 0.009$) (Table 1). Nevertheless, we observed a wide variation in BMI for the sarcopenic and nonsarcopenic groups, with a significant overlap between groups, limiting the utility of BMI as a predictor of sarcopenia (Fig. 1B). Thus, 3 patients having identical BMI (28 kg/m²) had various SMIs, ranging from 36.55 to 65 cm²/m². Conversely, an identical amount of skeletal muscle could be observed in normal, overweight, and obese patients (Fig. 2). In addition, sarcopenic patients had a lower preoperative serum albumin rate than nonsarcopenic patients ($P = 0.033$); even this difference was weak. Obviously, sarcopenic patients had a lower SMI than nonsarcopenic patients (mean = 42.55, SD = 6.54 cm²/m², vs mean = 55.06, SD = 8.07 cm²/m², respectively; $P < 0.0001$).

When comparing the sarcopenic and nonsarcopenic groups for intraoperative characteristics and pathological examination (Table 2), no significant differences were observed for the type of hepatectomy, length of surgery, tumor location, presence of cirrhosis in underlying hepatic parenchyma, rate of R0 tumor resection, and tumor extension (vascular invasion, biliary duct infiltration, and involvement of adjacent organ). On the contrary, sarcopenia was correlated with more undifferentiated HCC ($P = 0.015$) and the presence of satellite nodules ($P = 0.031$) than nonsarcopenic patients.

Postoperative Complications

The 60-day postoperative mortality and morbidity rates were 5.8% and 38.3%, respectively, without any significant difference between sarcopenic and nonsarcopenic patients (6.8% vs 2%, $P = 0.372$, and 39% vs 36%, $P = 0.749$, respectively). Severe postoperative complications rates (including grades III, IV and V of the Dindo and Clavien classification) were similar between sarcopenic and nonsarcopenic patients (20.3% vs 16%; $P = 0.560$) (Table 3).

Prognostic Factors for Overall Survival After Hepatectomy for HCC

During a median follow-up of 21.23 months [95% confidence interval (CI), 13.50–28.96], 27 patients (24.8%) died and the median overall survival was 55.4 months (95% CI, 50.24–60.56). There were 20 deaths among the 59 patients with sarcopenia and only 7 deaths

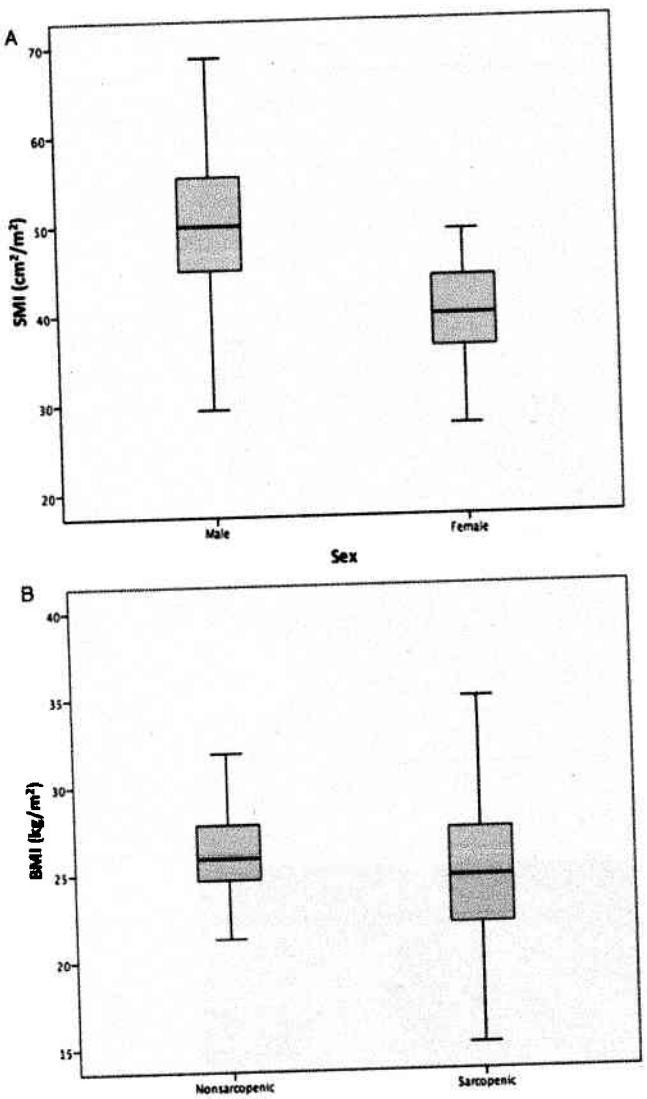

FIGURE 1. A, Box and whisker plot of the lumbar SMI in males and females. Boxes represent median values and interquartile ranges; whiskers represent the 5th and 95th percentiles. $P < 0.0001$ (independent-samples Student *t* test). B, Box and whisker plot of the BMI in sarcopenic and nonsarcopenic patients. Boxes represent median values and interquartile ranges; whiskers represent the 5th and 95th percentiles. $P = 0.009$ (independent-samples Student *t* test).

in the nonsarcopenic group. Sarcopenic patients had a significantly shorter median overall survival than nonsarcopenic patients (52.3 months vs 70.3 months, $P = 0.015$, and Breslow test: $P = 0.004$). Overall 1-year survival rate was also significantly lower in the sarcopenic group than in the nonsarcopenic group (69.8% vs 95.5%, respectively) (Fig. 3).

Table 4 includes univariate and multivariate Cox proportional hazards regression models for overall mortality after liver resection for HCC. On univariate analysis, the variables found to be statistically associated with poor overall survival were the ASA score of 3 or 4 ($P = 0.033$), involvement of adjacent organs ($P = 0.001$), pathological macroscopic vascular invasion ($P = 0.024$), presence of satellite nodule ($P = 0.021$), poor differentiated tumor ($P = 0.017$), and sarcopenia ($P = 0.020$).

On multivariate analysis, 3 variables were found to be independently associated with poor overall survival: involvement of adjacent organ by the tumor [hazard ratio (HR) = 6.16, $P = 0.002$], ASA score (HR = 3.09, $P = 0.005$), and sarcopenia (HR = 3.19, $P = 0.013$).

To evaluate whether the effect of SMI decrease was progressive, patients were stratified into tertiles by SMI, according to sex, and the direct effect of SMI on postoperative survival was looked at (Fig. 4). Patient in the largest SMI tertile had 1-year survival probability of 93.5% and 3-year survival of 73.4%. One- and 3-year overall survival rates were estimated at 67.3% and 62.1%, respectively, for the smallest SMI tertile ($P = 0.036$ between these groups). The survival advantage procured by a higher SMI seemed to be effective in the first postoperative year. Thus, mortality rates within the first postoperative year were 9.5%, 17.9%, and 37% for the largest, middle, and smallest tertiles, respectively ($P = 0.021$), whereas mortality rates between the first and second postoperative years were similar between tertiles (0%, 5.6%, and 5.2% for the largest, middle, and smallest tertiles, respectively (Fig. 5).

Prognostic Factors for Disease-Free Survival After Hepatectomy for HCC

The recurrence rate for patients followed up during this study was 56.9% (62 patients), and the estimated median of disease-free survival in our series was 17 months. During the follow-up period, 20 patients (40%) in the nonsarcopenic group and 42 patients (71.2%) in the sarcopenic group presented tumor recurrence ($P = 0.002$). Moreover, patients with sarcopenia had significantly shorter median disease-free survival than patients without sarcopenia (10.1 months vs 34.23 months, respectively; $P < 0.001$) (Fig. 6).

Table 5 provides univariate and multivariate Cox proportional hazards regression models for disease-free survival after hepatectomy for HCC. On univariate analysis, 8 variables were statistically associated with poor disease-free survival: involvement of adjacent organs by the tumor ($P < 0.001$), portal or hepatic vein thrombosis ($P = 0.011$), macroscopic vascular invasion ($P = 0.001$), microscopic vascular invasion ($P = 0.036$), presence of satellite nodule ($P < 0.001$), tumor size larger than 5 cm ($P = 0.047$), poor differentiated tumor ($P = 0.050$), and sarcopenia ($P = 0.001$).

On multivariate analysis, 4 variables were found to be independently associated with poor disease-free survival: age older than 60 years (HR = 0.53; $P = 0.026$), involvement of adjacent organ by the tumor (HR = 5.52; $P = 0.001$), presence of satellite nodule (HR = 2.32; $P = 0.005$), and sarcopenia (HR = 3.03; $P < 0.001$).

DISCUSSION

This retrospective study shows that sarcopenia was a strong and independent prognostic factor for mortality (HR = 3.19; 95% CI, 1.28–7.96; $P = 0.013$) and recurrence (HR = 3.03; 95% CI, 1.67–5.49; $P = 0.001$) after liver resection for HCC in European patients. This finding is in line with others studies that showed that sarcopenia is associated with mortality, morbidity, and recurrence after colorectal[41] and liver surgery[42,43] for cancer and also after liver transplantation.[32]

In clinical setting, preoperative prognosis assessment and selection of treatment are mainly based on one of the following tumor staging classifications: TNM, Cancer of the Liver Italian Program,[10] Barcelona Clinic Liver Cancer,[44] or Japan Integrated Staging.[10] These tumor staging classifications include tumor characteristics (tumor size, number of nodules, tumor markers) and underlying liver function but rarely patient characteristics, although general condition of HCC patients has been described recently as an independent

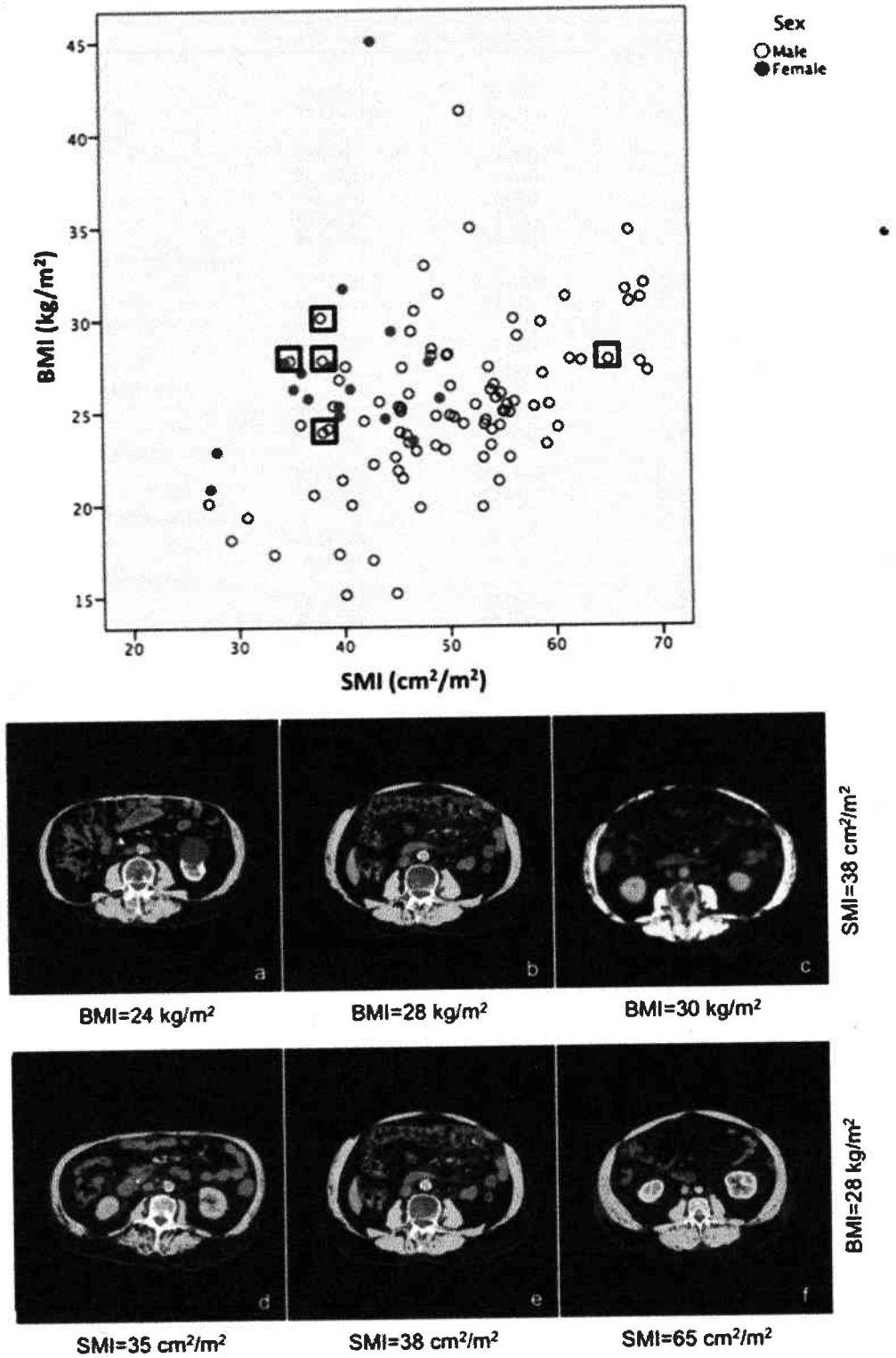

FIGURE 2. Scatter plot highlights the relationship and variation between SMI and BMI for male patients (circles) and female patients (points; Pearson $r = 0.48$; $P < 0.001$). Black boxes select patients with identical SMI or identical BMI for whom axial CT scans of the third lumbar vertebra region with skeletal muscle highlighted in red (29–150 Hounsfield units [HU]) are shown.

TABLE 2. Operative and Histopathological Characteristics

Variable	Total (N = 109)	Nonsarcopenic (n = 50)	Sarcopenic (n = 59)	P
Steatohepatitis				0.523
No	46 (45.5)	23 (49)	23 (43)	
Yes	55 (54.5)	24 (51)	31 (57)	
Stage of fibrosis*				0.743
F0	12 (11)	5 (10)	7 (11.9)	
F1	21 (19.3)	8 (16)	13 (22)	
F2	13 (11.9)	6 (12)	7 (11.9)	
F3	18 (16.5)	7 (14)	11 (18.6)	
F4	45 (41.3)	24 (48)	21 (35.6)	
Liver cirrhosis (F3 or F4 stage)				0.414
No	46 (42.2)	19 (38)	27 (45.8)	
Yes	63 (57.8)	31 (62)	32 (54.2)	
Perinervous invasion				0.659
No	104 (95.4)	47 (94)	57 (97)	
Yes	5 (4.6)	3 (6)	2 (3)	
Tumor capsule infiltration				0.060
No	61 (56)	33 (66)	28 (47.5)	
Yes	48 (44)	17 (34)	31 (52.5)	
Biliary duct infiltration				0.286
No	101 (92.7)	48 (96)	53 (89.8)	
Yes	8 (7.3)	2 (4)	6 (10.2)	
Involvement of adjacent organ				0.685
No	103 (94.5)	48 (96)	55 (93)	
Yes	6 (5.5)	2 (4)	4 (7)	
Macroscopic vascular invasion				0.155
No	64 (58.7)	33 (66)	31 (52.5)	
Yes	45 (41.3)	17 (34)	28 (47.5)	
Microscopic vascular invasion				0.140
No	42 (38.5)	23 (46)	19 (32.2)	
Yes	67 (61.5)	27 (54)	40 (67.8)	
Surgical radicality				0.335
R1/R2	12 (11.3)	7 (15)	5 (9)	
R0	94 (88.7)	41 (85)	53 (91)	
Tumor size >50 mm				0.111
No	52 (47.7)	28 (56)	24 (40.7)	
Yes	57 (52.3)	22 (44)	35 (59.3)	
Satellite nodules				**0.031**
No	51 (46.8)	29 (58)	22 (37.3)	
Yes	58 (53.2)	21 (42)	37 (62.7)	
Poor differentiation				**0.015**
No	95 (87.2)	48 (96)	47 (79.7)	
Yes	14 (12.8)	2 (4)	12 (20.3)	
Tumor location				0.496
Right lobe	55 (51.3)	28 (56)	27 (47)	
Left lobe	27 (24.8)	10 (20)	17 (29)	
Bilobar	26 (23.9)	12 (24)	14 (24)	
Extent of surgical resection				0.749
Minor hepatectomy	41 (37.6)	18 (36)	23 (38)	
Major hepatectomy	68 (62.4)	32 (64)	36 (62)	
Length of surgery >300 min				0.614
No	73 (81.1)	35 (83)	38 (79)	
Yes	17 (18.9)	7 (17)	10 (21)	
Blood loss >500 mL				0.982
No	74 (67.9)	34 (68)	40 (67.8)	
Yes	35 (32.1)	16 (32)	19 (32.2)	

The values given are number (%). Variables in bold are statistically significant ($P < 0.05$).

prognostic factor.[45] Preoperative assessment of global health status of patient is usually based on clinical judgment, often called "eyeball test,"[46] to detect patient's frailty.

Frailty is defined by Fried et al[47] as a biological syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiological systems and causing vulnerability to adverse outcomes. However, assessment of frailty is difficult, typically depending on multiple subjective components as self-reported exhaustion, weakness, low physical activity, and malnutrition, which are more difficult to identify in obese or overweight patients.

Now, the incidence of obesity and overweight has increased during the last decades reaching 15% to 20% of the world adult population and is frequently observed in patients with cancer, as

reported by our study in which 12.8% of patients were obese and 42% were overweight. This result is in concordance with observations in patients with gastrointestinal malignancies or cancers of the respiratory tract[27,48] and with patients undergoing liver transplantation for HCC.[49,50]

To deal with this demographic change and to better assess patient's frailty, quantification of skeletal muscle mass using preoperative CT have been proposed.[51] Despite many methods to quantify skeletal muscle mass and numerous definitions of sarcopenia, we choose to use the international definition and previously validated sex-specific cutoff[35] to be comparable with other populations and studies. With these criteria, we found that more than 50% of patients undergoing liver resection for HCC were sarcopenic, in accordance with the high prevalence of sarcopenia in patients with cancer[48] and cirrhotic patients.[30] Interestingly, sarcopenia was not only restricted to underweight patients but also observed in overweight and obese patients. Furthermore, there was a wide variation of BMI in sarcopenic and nonsarcopenic groups with significant overlap between groups, reflecting that sarcopenia was an occult condition in HCC patients, as it has been described for patients on the liver transplant wait list.[33]

TABLE 3. Distribution of Postoperative Complications According to the Dindo and Clavien Classification

Grade	Total (N = 109)	Nonsarcopenic (n = 50)	Sarcopenic (n = 59)
No complication	68 (62.4)	32 (64)	36 (61)
Grade I	9 (8.3)	6 (12)	3 (5.1)
Grade II	11 (10.1)	4 (8)	7 (11.9)
Grade III	4 (3.7)	1 (2)	3 (5.1)
Grade IV	12 (11)	6 (12)	6 (10.2)
Grade V	5 (4.6)	1 (2)	4 (6.8)

The values given are number (%).

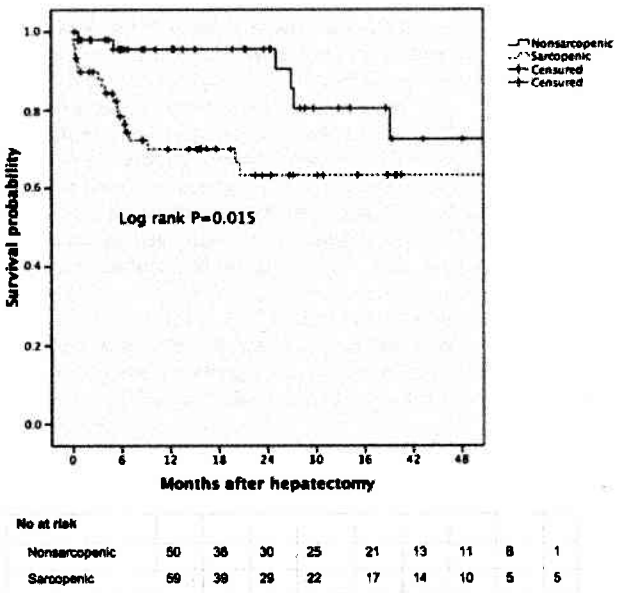

FIGURE 3. Kaplan-Meier curve showing overall survival according to sarcopenia.

TABLE 4. Prognostic Factors for Overall Survival on Univariate and Multivariate Analyses

Variables	No. Patients (N = 120)	Univariate Analysis HR (95% CI)	*P*	Multivariate Analysis HR (95% CI)	*P*
Sex male	101	1,71 (0.77–3.81)	0.189	2.17 (0.89–5.30)	0.088
Age >60 yr	68	0.75 (0.37–1.52)	0.430		
Obesity	16	0.22 (0.03–1.60)	0.134		
Serum albumin ≤35 g/L	20	1.49 (0.60–3.69)	0.389		
Cirrhosis	50	1.70 (0.84–3.46)	0.140		
ASA score 3–4	37	2.15 (1.06–4.35)	0.033	**3.09 (1.39–6.87)**	**0.005**
AFP >400	23	1.18 (0.49–2.84)	0.707		
Steatohepatitis	58	1.13 (0.56–2.29)	0.742		
Perinervous invasion	5	2.66 (0.80–8.80)	0.109		
Tumor capsule infiltration	53	0.99 (0.49–2.01)	0.994		
Biliary duct invasion	8	2.06 (0.79–5.36)	0.140		
Involvement of adjacent organ	8	5.32 (1.97–14.38)	0.001	**6.16 (1.95–19.48)**	**0.002**
Portal or hepatic vein thrombosis	20	2.21 (0.94–5.20)	0.068		
Macroscopic vascular invasion	50	2.26 (1.11–4.58)	0.024		
Microscopic vascular invasion	77	2.31 (0.99–5.37)	0.052		
Satellite nodule	64	2.47 (1.15–5.31)	0.021		
Resection free-margin	102	0.61 (0.23–1.61)	0.317		
Tumor size >5 cm	64	1.24 (0.58–2.62)	0.581		
Multicentric tumor	26	1.52 (0.70–3.31)	0.290		
Poor differentiation	19	2.88 (1.21–6.85)	0.017	2.46 (0.85–7.11)	0.096
Major hepatectomy	74	0.63 (0.31–1.29)	0.208		
Length of surgery >300 min	19	1.11 (0.41–2.96)	0.840		
Blood loss >500 mL	39	1.56 (0.77–3.16)	0.218		
Anatomical resection	98	1.19 (0.46–3.10)	0.723		
Postoperative complication	20	1.69 (0.77–3.67)	0.189		
Sarcopenia	59	2.78 (1.17–6.59)	0.020	**3.19 (1.28–7.96)**	**0.013**

ASA score indicates American Society of Anaesthesiologists score; AFP, alpha-foeto protein.
Variables in bold are statistically significant in multivariate analysis ($P < 0.05$).

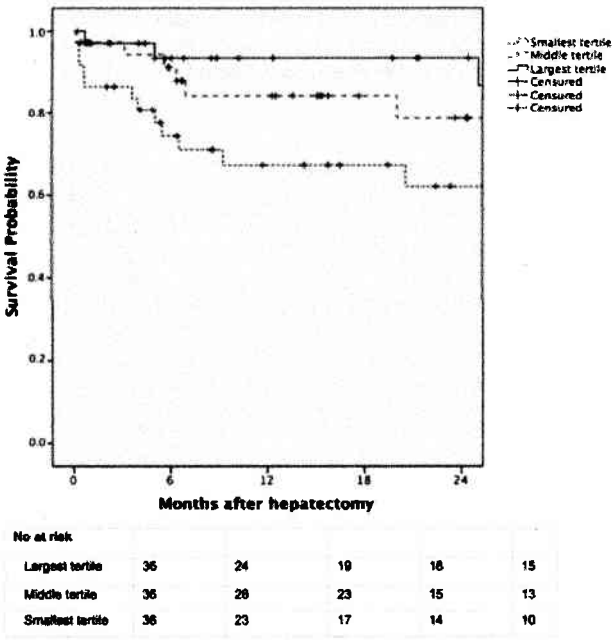

FIGURE 4. Kaplan-Meier curve showing overall survival according to the SMI tertile. Comparison between the largest and smallest tertiles is significant (log-rank: $P = 0.036$).

This observation underscores the necessity to use CT for specific detection of sarcopenia, which is an accurate and well-recognized approach for the quantification of skeletal muscle mass with a reported precision error of about 1.3% for lean muscle mass.[51] In addition, cross-sectional abdominal scanning by CT is routinely available for many HCC patients, generally used to assess tumor location, size, and to look for abdominal metastases. Thus, quantification of skeletal muscle mass is a precise, neither expensive nor time-consuming approach, and could be included in the preoperative assessment of all patients in an objective way by radiologists.

According to previous studies,[27,41,46,52,53] sarcopenia is more prevalent in older patients (60 years or older), but its presence is not correlated with severe comorbidities, confirming that sarcopenia is a part of patient's frailty but not patient's morbidity. Interestingly, sarcopenic patients have more undifferentiated HCCs ($P = 0.015$) and more satellite nodules ($P = 0.05$) than nonsarcopenic patients. As Englesbe et al[32] have described correlation between sarcopenia and MELD (Model For End-Stage Liver Disease) score among liver transplant recipients without HCC and Tandon et al[33] have shown the association between sarcopenia and underlying function disease, we have shown in this study that sarcopenia is also associated with tumor aggressiveness.

However, unlike Tandon et al,[33] we have not found a clear relation between sarcopenia and cirrhosis, and even a trend toward sarcopenic patients being less cirrhotic than patients without sarcopenia, in univariate analysis. Numerous potential confounders, such as tumor characteristics (perinervous invasion and tumor capsule infiltration, which were more observed in noncirrhotic group than cirrhotic

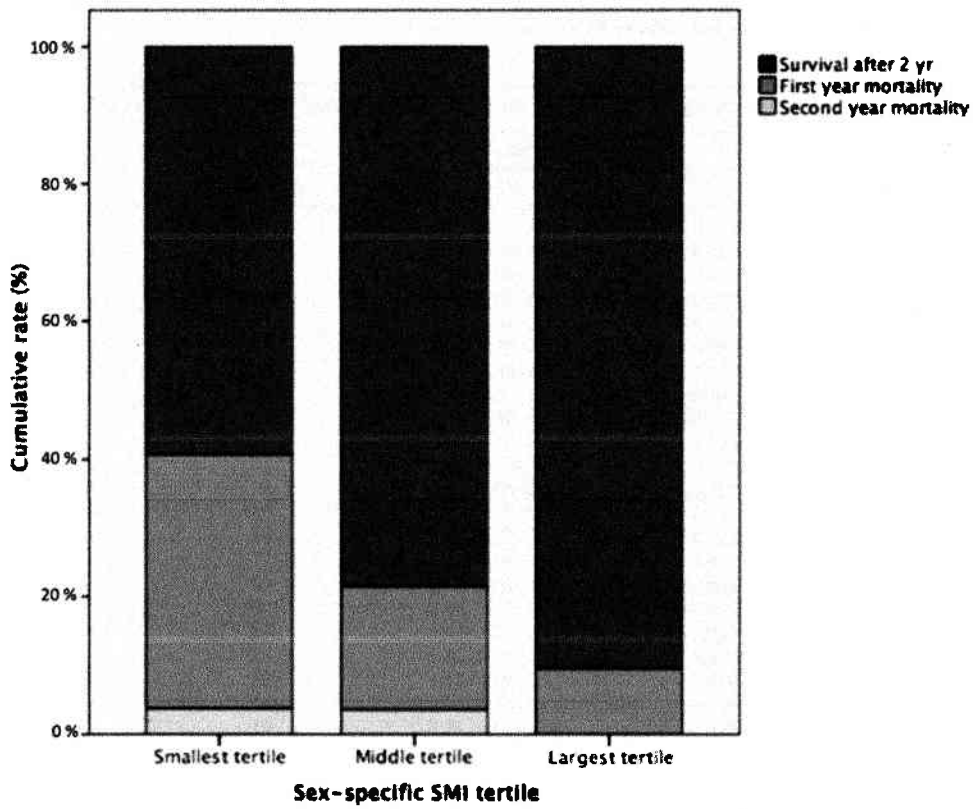

FIGURE 5. Cumulative rate of mortality within the first and the second years after surgery according to the sex-specific lumbar SMI tertile.

patients), could explain this result. Thus, sarcopenia is influenced by numerous factors depending not only on patient characteristics and quality of underlying hepatic parenchyma but also on tumor properties.

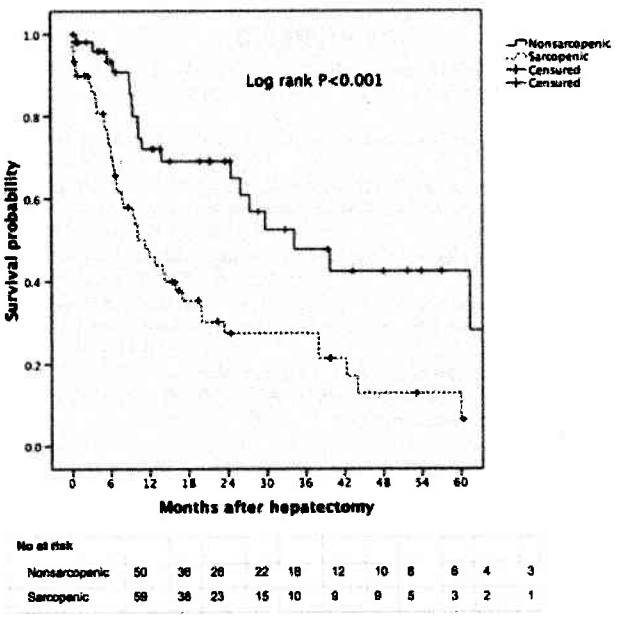

FIGURE 6. Kaplan-Meier curve showing disease-free survival according to sarcopenia.

As previously described in cancer of lung,[48] biliary tract,[54] pancreas,[55] and colon and rectum,[48] we have demonstrated that sarcopenia is a major and independent prognostic factor of overall and disease-free survival in patient undergoing hepatectomy for HCC. Moreover, as specific cutoff defining sarcopenic patients are not valid, yet in this specific disease,[34] we have also shown that progressive decrease in skeletal muscle mass is associated with an increased mortality, especially in the first postoperative year. Thus, evaluation of skeletal muscle mass by CT represents an interesting tool to identify patients with high risk of mortality or recurrence early after hepatectomy for HCC and should be integrated into scoring systems and therapeutic algorithm for HCC.

Furthermore, early detection and treatment of sarcopenia by different strategies could improve the postoperative outcome in such frail patients. Among these strategies, specific nutritional intervention with protein and branched-chain amino acid supplementation has shown promising results both by improving muscle mass in sarcopenic older adults[56,57] and by reducing complication after hepatectomy for HCC in cirrhotic patients.[58] In addition, to promote the increase of muscle mass rather than fat mass, this nutritional supplementation must be associated with exercise combining resistance and aerobic muscle training,[59,60] Some studies including patients with lung,[61,62] colorectal,[63] and esophageal[64] cancer have already demonstrated that such a multimodal approach before surgery, named "prehabilitation," is effective in reducing postoperative complication, but its effects on sarcopenia and its efficiency to improve outcome after hepatic surgery for cancer have yet to be established.

CONCLUSION

In summary, the results of this study indicate that sarcopenia, which is assessed on preoperative CT imaging, is a strong and

TABLE 5. Prognostic Factors for Disease-Free Survival on Univariate and Multivariate Analyses

Variables	No. Patients (N = 120)	Univariate Analysis		Multivariate Analysis	
		HR (95% CI)	P	HR	P
Sex male	101	1.068 (0.56–2.04)	0.842		
Age >60 yr	**68**	**0.67 (0.41–1.08)**	**0.100**	**0.53 (0.31–0.93)**	**0.026**
Obesity	16	0.77 (0.36–1.62)	0.489		
Serum albumin ≤35 g/L	20	1.78 (0.99–3.19)	0.054		
Cirrhosis	50	1.03 (0.63–1.68)	0.914		
ASA score 3–4	37	1.62 (0.98–2.66)	0.059		
AFP >400	23	1.51 (0.84–2.74)	0.170		
Steatohepatitis	58	1.035 (0.63–1.69)	0.892		
Perinervous invasion	5	1.66 (0.60–4.57)	0.328		
Tumor capsule infiltration	53	0.89 (0.55–1.44)	0.635		
Biliary duct invasion	8	1.22 (0.55–2.67)	0.622		
Involvement of adjacent organ	**8**	**6.62 (2.96–14.78)**	**<0.001**	**5.52 (2.10–14.85)**	**0.001**
Portal or hepatic vein thrombosis	20	2.17 (1.20–3.95)	0.011		
Macroscopic vascular invasion	50	2.23 (1.37–3.62)	0.001		
Microscopic vascular invasion	77	1.78 (1.04–3.06)	0.036		
Satellite nodule	**64**	**2.58 (1.51–4.39)**	**<0.001**	**2.32 (1.29–4.17)**	**0.005**
Resection free-margin	102	0.68 (0.33–1.38)	0.283		
Tumor size >5 cm	64	1.66 (1.01–2.73)	0.047		
Multicentric tumor	26	1.31 (0.75–2.27)	0.340		
Poor differentiation	19	1.93 (1.00–3.73)	0.050		
Major hepatectomy	74	0.88 (0.53–1.44)	0.600		
Length of surgery >300 min	19	1.29 (0.69–2.40)	0.428		
Blood loss >500 mL	39	1.37 (0.84–2.24)	0.206		
Anatomical resection	98	1.98 (0.95–4.16)	0.069		
Sarcopenia	**59**	**2.60 (1.49–4.54)**	**0.001**	**3.03 (1.67–5.49)**	**<0.001**

ASA score indicates American Society of Anaesthesiologists score; AFP, alpha-foeto protein.
Variables in bold are statistically significant in multivariate analysis ($P < 0.05$).

independent prognostic factor for mortality and recurrence after liver resection for HCC in European patients. This precise, objective, not expansive and not time consuming approach to detect patient's frailty should be integrated in scoring systems and therapeutic algorithm for HCC.

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