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Impact of body composition on survival and morbidity after liver resection in hepatocellular carcinoma patients

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ABSTRACT

Background: Hepatocellular carcinoma is the most common innate liver tumor. Due to improved surgical techniques, even extended resections are feasible, and more patients can be treated with curative intent. As the liver is the central metabolic organ, preoperative metabolic assessment is crucial for risk stratification. Sarcopenia, obesity and sarcopenic obesity characterize body composition and metabolic status. Here we present the impact of body composition on survival after liver resection in patients with hepatocellular carcinoma.

Methods: A retrospective database analysis of 70 patients who were assigned for liver resection due to hepatocellular carcinoma was conducted. For assessment of sarcopenia and obesity, skeletal muscle surface area was measured at lumbar vertebra 3 level (L3) in preoperative four-phase contrast enhanced abdominal CT scans, and L3 muscle index and body fat percentage were calculated.

Results: Univariate analysis comparing the survival curves using the score test demonstrated superior postoperative overall survival for sarcopenic ($P = 0.035$) and sarcopenic obese ($P = 0.048$) patients as well as a trend favoring obese ($P = 0.130$) subjects. Whereas multivariate analysis could not identify significant difference in postoperative survival regarding sarcopenia, obesity or sarcopenic obesity. Only large tumor size, multifocal disease and male gender were risk factors for long-term survival.

Conclusions: Sarcopenia, obesity and sarcopenic obesity are indeed no risk factors for poor postoperative survival in this study. Our data do not support the evaluation of sarcopenia, obesity and sarcopenic obesity before liver resection in hepatocellular carcinoma patients.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy worldwide and the HCC-related deaths are more than 700,000 in 2012 [1]. Although there are still 5%–30% of cryptogenic HCCs [2], the majority of HCCs is related to cirrhosis and a certain liver disease like hepatitis B (HBV), HCV or non-alcoholic steatohepatitis (NASH). The liver is the central metabolic organ regulating glucose, fat and protein metabolisms, and is metabolically connected to various tissues, including adipose tissue and muscles [3]. For this reason, a dysfunction of the liver following HCC associated parenchymatous liver disease, especially cirrhosis, influences the entire metabolism and impairs the patient's condition.

Regarding the impaired metabolic condition within liver disease, the preoperative risk assessment and evaluation of liver function is crucial for patient's counseling. Child-Pugh or Model of End Stage Liver Disease (MELD) score are common tools to predict mortality in patients with cirrhosis. Unfortunately, the nutritional status and body composition are not directly represented in these scores. Sarcopenia, which constitutes a good reproducible resource for objective nutritional/metabolic assessment, can be measured non-invasively using preoperative cross-sectional CT scans [4]. Cachexia and a weak metabolic status are represented by sarcopenia. Recent publications have shown a strong association of sarcopenia with a poor long-term prognosis for patients with distal

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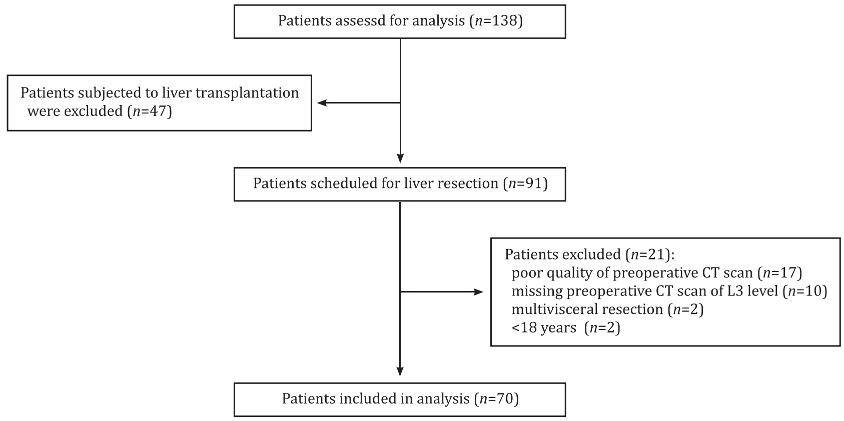

Fig. 1. A flow chart of patients selection.

esophageal or upper gastric cancer who underwent surgery [5,6] as well as for patients with pancreatic ductal adenocarcinoma [7].

In times of obesity as a worldwide pandemic and increasing numbers of NASH, obesity also should be evaluated as independent risk factor for morbidity after liver resection. Several studies have shown that sarcopenia, obesity and their combination sarcopenic-obesity impair long-term patient outcome [8] and outcome after liver resection [9,10], but others did not [11]. Herein, we aimed to assess the impact of sarcopenia, obesity and sarcopenic obesity on survival and morbidity after liver resection for HCC patients.

Methods

Study population

All patients who were assigned to surgery for HCC at the Department of General, Visceral and Transplantation Surgery at the University Hospital of the RWTH Aachen between January 2010 and December 2014 were evaluated. A total of 138 patients were assessed for analysis. Out of these, 47 patients were subjected to liver transplantation and were therefore excluded from the analysis. Ninety-one patients were scheduled for partial liver resection. Only patients with a preoperative four-phase contrast enhanced abdominal CT scan up to three months before resection were included. Patients were further excluded due to: 1) the insufficient quality of the preoperative contrast enhanced CT scan ($n = 17$); 2) multivisceral resections ($n = 2$); 3) younger than 18 years old ($n = 2$). Therefore, a retrospective database-analysis of consecutive 70 patients was conducted. The study flow chart is shown in Fig. 1. All data were prospectively collected in a hepatobiliary database and retrospectively analyzed. Parameters such as gender, body weight, height, age, medical condition, basic laboratory assessment [international normalized ratio (INR), thrombocytes, serum albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT)], alcohol abuse, MELD score, Child-Pugh and tumor size were all included in the hepatobiliary database. MELD and Child-Pugh scores were calculated within two days before resection.

Treatment strategy

All patients who were referred for surgical treatment to our institution were classified according to the Barcelona Clinic Liver Cancer (BCLC) system [12,13]. Patients with distant metastases did not undergo surgery and were subjected to a palliative concept. Indications for partial liver resection were made by experienced hepatobiliary surgeons and were approved by the institutional interdisciplinary tumor board in all cases. Early stage tumors (Stage 0 and Stage A) were scheduled for liver resection after preoperative preparation was completed. In patients staged BCLC B to BCLC C, risk stratification was conducted according to the LiMAx algorithm [14,15]. Liver function was evaluated by the LiMAx (maximum liver function capacity, Humedics GmbH, Berlin, Germany) test and future liver remnant (FLR) as well as future remnant liver function (FRLF) were calculated. Patients without extrahepatic spread and compensated liver function were scheduled for surgery whereas patients with a FRLF < 100 µg/kg/h or BCLC stage D were either planned for TACE, sorafenib or best supportive care. Bilateral HCCs were treated in a multimodal concept when an R0 situation was possible.

Liver resection, histological assessment and follow-up

All liver resections were classified according to the IHPBA Brisbane nomenclature [16]. For statistical analysis, patients who had undergone single segmental resection, left lobectomy or resection of two other segments in different combinations were submitted to the "segmental resection" group. Extended right or left hepatectomy as well as resections with concomitant biliary or vascular reconstructions were submitted to the extended resection group. To assess the influence of liver resection on postoperative survival in the univariate and multivariate analysis, resections were categorized as major for resections of three or more segments and minor in all other cases. HCC diagnosis was obtained by histopathological analysis and histological grading, vessel invasion, tumor size and resection margins were defined by an experienced staff pathologist. Standard follow-up comprised outpatient visits every three months in the first year and liver imaging annually up to five years after surgery.

Body composition

Image analysis

Images were analyzed on a 2.8-GHz Intel Core 2 Duo 24" iMac (Apple Inc., Cupertino, CA, USA) using OsiriX® (Pixmeo SARL, Bernex, Switzerland). Skeletal muscle surface area was measured at the third lumbar vertebra (L3) level as it is common for studies calculating sarcopenia [17–19]. The L3 region encompasses psoas, paraspinal muscles (erector spinae, quadratus lumborum), and abdominal wall muscles (transversus abdominus, external and internal obliques, rectus abdominus). A Hounsfield unit (HU) ranging from −30 to 110 was chosen to semi-automatically outline the L3 muscle area.

Sarcopenia

Skeletal muscle surface area at L3 level was measured at two adjacent CT slides using OsiriX® and L3 muscle index [average skeletal muscle area (cm^2)/height^2 (m^2)] was calculated. Based on internationally accepted cut-off values patients were classified sarcopenic if the L3 muscle index was < 43 in men with a BMI < 25 kg/m^2, or < 53 in men with a BMI > 25 kg/m^2. Women were considered sarcopenic if the L3 muscle index was < 41 irrespective of the BMI. In previous studies these cut-off points were associated with higher mortality [20].

Obesity

Total fat-free body mass (kg) was estimated as 0.30 × (skeletal muscle at L3 by use of CT [cm^2] + 6.06) [18] and body fat percentage was calculated {[total body weight (kg) – fat-free body mass(kg)] / total body weight(kg)} × 100%. Obesity was defined based on the top two body fat percentage quintiles for men and women, respectively [21–23].

Sarcopenic obesity

An imbalance between obesity and muscle mass is associated with impaired health outcomes especially in older individuals [24]. Therefore, patients who were classified both sarcopenic and obese according to the cut-off values above were submitted to the sarcopenic obesity group.

Outcome parameters

The impact of sarcopenia, obesity and sarcopenic obesity on morbidity and mortality was analyzed. Primary outcome parameter was postoperative overall survival which is defined as long-term survival after surgery. Additional parameters were postoperative morbidity and liver surgery specific composite endpoints (LSSCEP) composed of ascites, post-resectional liver failure, bile leakage, intra-abdominal hemorrhage, 30-day mortality and intra-abdominal abscess, according to van den Broek et al. [25]. Complications were scored by Clavien–Dindo classification considering a score ≥ 3b as major complication [26].

Statistical analysis

Data were analyzed using R version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria) [27]. Continuous variables are expressed as mean values ± standard deviation (SD) and compared with *t* test (equal variances) or Welch test (unequal variance) respectively. Categorical data are presented by frequencies and percentage. They were compared between groups using Fishers exact test. Survival times are presented in months. Survival curves for postoperative overall survival and disease-free survival were estimated using the Kaplan–Meier method. To avoid overfitting in the multivariate Cox regression analysis, prognostic factors were selected using the bi-directional stepwise model selection algorithm based on Akaikes Information Criterion (AIC) [28] instead of selecting prognostic factors based on a cut-off value for the univariate *P* value. The model selection was conducted with the function step AIC of the MASS package. A subgroup analysis was conducted to assess the impact of body composition in the subgroup of patients without multimodal treatment strategy. Statistical tests were performed two-tailed and *P* values < 0.05 were considered as significant test results.

Results

Population cohort

Between January 2010 and December 2014, a total of 91 patients were scheduled for liver resection due to HCC. Among these patients 70 patients were acceptable for analysis according to the predefined cut-off values. Thirty-three patients were sarcopenic, 28 obese and 21 sarcopenic-obese. Sixty-five patients were assigned to Child-Pugh class A and 5 patients to Child-Pugh class B. Baseline characteristics were not related to obesity or sarcopenia, and the majority of basic laboratory values did not differ significantly between groups (Table 1).

Body composition

Sarcopenia

Mean tumor size, length of hospital stay and MELD score as well as proportion of patients with American Society of Anesthesiologists (ASA) > 2, with recurrent HCC or beyond Milan criteria were comparable between sarcopenic and non-sarcopenic patients (Table 1). The proportion of males, alcohol abuse, cirrhosis and patients treated in a multimodal treatment strategy were slightly higher in patients without sarcopenia but did not reach statistical significance. Patients with sarcopenia had more often multifocal HCC and more frequently at least one tumor larger than 5 cm than non-sarcopenic patients. While these imbalances were not statistically significant, the mean AST laboratory value was significantly lower in sarcopenic patients compared to non-sarcopenic patients ($P = 0.0493$).

Obesity

There were no significant differences regarding disease specific or basic characteristics between obese and non-obese patients (Table 1). Small non-significant imbalances were observed in the proportion of patients with cirrhosis, multifocal HCCs, multimodal treatment and recurrence, which tended to be higher in non-obese patients. The proportion of patients with tumor larger than 5 cm was slightly but not significant higher in obese patients.

Sarcopenic obesity

The proportion of males, patients beyond Milan criteria, and with ASA > 2, as well as mean age, alcohol abuse, MELD score, length of hospital stay and tumor size was comparable between sarcopenic-obese and non-sarcopenic-obese patients (Table 1). The proportion of patients with recurrent HCC, multimodal treatment, multifocal HCCs and cirrhosis was slightly higher in non-sarcopenic obese patients. These imbalances were not statistically significant. However, the mean AST value was significantly lower in sarcopenic obese patients ($P = 0.0063$).

Complications

Overall surgical complication rate was 26% and major complications were present in 11% of all patients (Table 2). There were no statistically significant differences regarding sarcopenia, obesity or sarcopenic obesity. Furthermore, the presence of liver surgery specific composite endpoints (LSSCEPs) did not differ significantly between groups. Wound infections were recorded in 10% of all patients and were lower in sarcopenic and sarcopenic obese patients compared to non-sarcopenic or non-obese patients with a difference between the groups of 13% regarding sarcopenia and 10% regarding obesity, but did not reach statistical significance.

Postoperative overall survival (POS)

Kaplan–Meier curves depending on sarcopenia, obesity and sarcopenic obesity are depicted in Fig. 2. Survival rates, median survival and the corresponding confidence intervals for sarcopenia, obesity and sarcopenic obesity are shown in Table 3. For example, median postoperative overall survival was 2.54 years in sarcopenic patients and 1.44 years in non-sarcopenic patients. One- and three-year postoperative overall survival rates are 72.7% and 45.0%

Table 1
Patients characteristics.

Characteristics	All	Sarcopenia		*P* value	Obesity		*P* value	Sarcopenic obesity		*P* value
		Yes	No		Yes	No		Yes	No	
Basic characteristics										
Number	70	33	37		28	42		21	49	
Male gender	49 (70%)	21 (64%)	28 (76%)	0.3061	20 (71%)	29 (69%)	1.0000	15 (71%)	34 (69%)	1.0000
Age (yr)	67.74 ± 12.95	66.97 ± 16.84	68.43 ± 8.23	0.6530	69.18 ± 12.14	66.79 ± 13.53	0.4432	69.67 ± 13.28	66.92 ± 12.86	0.4283
ASA > 2	47 (67%)	22 (67%)	25 (68%)	1.0000	20 (71%)	27 (64%)	0.6093	15 (71%)	32 (65%)	0.7827
Alcohol abuse	19 (27%)	6 (18%)	13 (35%)	0.1777	9 (32%)	10 (24%)	0.5842	5 (24%)	14 (29%)	0.7755
Beyond Milan criteria	58 (83%)	27 (82%)	31 (84%)	1.0000	24 (86%)	34 (81%)	0.7508	17 (81%)	41 (84%)	0.7432
MELD score	8.19 ± 2.50	8.14 ± 2.30	8.24 ± 2.70	0.8616	8.23 ± 2.41	8.17 ± 2.58	0.9211	8.21 ± 2.49	8.18 ± 2.53	0.9723
Body composition										
Weight (kg)	78.96 ± 15.50	75.94 ± 15.65	81.65 ± 15.07	0.1249	85.50 ± 16.06	74.60 ± 13.64	**0.0032**	80.95 ± 15.12	78.10 ± 15.74	0.4849
Height (m)	1.73 ± 0.08	1.72 ± 0.08	1.71 ± 0.07	0.3007	1.72 ± 0.08	1.71 ± 0.07	0.4500	1.73 ± 0.07	1.71 ± 0.07	0.2012
BMI (kg/m^2)	26.64 ± 4.62	25.29 ± 4.32	27.85 ± 4.61	**0.0191**	28.61 ± 4.82	25.33 ± 4.04	**0.0045**	26.73 ± 3.92	26.61 ± 4.93	0.9100
L3 muscle index (cm^2/m^2)	47.98 ± 10.38	40.83 ± 7.54	54.36 ± 8.20	**<0.001**	44.19 ± 9.68	50.50 ± 10.16	**0.0111**	40.30 ± 6.52	51.27 ± 10.01	**<0.001**
Disease specific characteristics										
Recurrent HCC	9 (13%)	4 (12%)	5 (14%)	1.0000	2 (7%)	7 (17%)	0.2988	1 (5%)	8 (16%)	0.2611
Multimodal treatment strategy	11 (16%)	3 (9%)	8 (22%)	0.1968	3 (11%)	8 (19%)	0.5065	2 (10%)	9 (18%)	0.4852
Largest tumor diameter (cm)	7.08 ± 0.30	7.35 ± 1.80	6.85 ± 0.30	0.6395	7.42 ± 3.20	6.86 ± 0.30	0.5809	7.35 ± 3.20	6.97 ± 0.30	0.7254
Tumor > 5 cm	44 (63%)	22 (67%)	22 (59%)	0.6233	20 (71%)	24 (57%)	0.3135	14 (67%)	30 (61%)	0.7896
Multifocal disease	35 (50%)	13 (39%)	22 (59%)	0.1503	12 (43%)	23 (55%)	0.4646	7 (33%)	28 (57%)	0.1165
Cirrhosis	43 (61%)	18 (55%)	25 (68%)	0.3282	15 (54%)	28 (67%)	0.3211	10 (48%)	33 (67%)	0.1800
AFP (μg/L)[a]	4943 ± 13,513	5547 ± 14,863	4393 ± 12,487	0.7861	1261 ± 4326	6415 ± 15,594	0.2693	12 ± 15	6287 ± 15,008	0.2210
Tumor (%)[b]				0.9498			0.5038			0.4465
1	20 (32%)	10 (31%)	10 (32%)		10 (38%)	10 (27%)		9 (43%)	11 (26%)	
2	22 (35%)	12 (38%)	10 (32%)		7 (27%)	15 (41%)		6 (29%)	16 (38%)	
3	21 (33%)	10 (31%)	11 (35%)		9 (35%)	12 (32%)		6 (29%)	15 (36%)	
Grade (%)[c]				1.0000			1.0000			1.0000
1	3 (5%)	1 (3%)	2 (6%)		1 (4%)	2 (5%)		1 (5%)	2 (5%)	
2	50 (81%)	24 (83%)	26 (79%)		20 (83%)	30 (79%)		15 (79%)	35 (81%)	
3	9 (15%)	4 (14%)	5 (15%)		3 (13%)	6 (16%)		3 (16%)	6 (14%)	
Vein invasion 1 (%)[d]	30 (57%)	16 (57%)	14 (56%)	1.0000	10 (53%)	20 (59%)	0.7750	8 (47%)	22 (61%)	0.3842
Resection				0.8086			0.7603			0.9745
Segmental resection	39 (56%)	17 (52%)	22 (59%)		15 (54%)	24 (57%)		10 (48%)	29 (59%)	
Left hemihepatectomy	6 (9%)	3 (9%)	3 (8%)		3 (11%)	3 (7%)		2 (10%)	4 (8%)	
Right hemihepatectomy	5 (7%)	2 (6%)	3 (8%)		2 (7%)	3 (7%)		2 (10%)	3 (6%)	
Complex hepatectomy	20 (29%)	11 (33%)	9 (24%)		8 (29%)	12 (29%)		7 (33%)	13 (27%)	
Length of hospital stay (d)	14.26 ± 14.07	14.39 ± 16.65	14.14 ± 11.52	0.9407	12.93 ± 11.66	15.14 ± 15.54	0.4989	13.95 ± 12.91	14.39 ± 14.66	0.9019
Basic laboratory values										
AST (U/L)	53.67 ± 38.42	44.39 ± 23.15	62.17 ± 47.14	**0.0493**	46.07 ± 30.81	58.55 ± 42.23	0.1616	38.81 ± 20.24	60.17 ± 42.65	**0.0063**
Thrombocytes (10^9/L)	232.59 ± 106.38	236.48 ± 118.58	229.03 ± 95.40	0.2893	242.48 ± 126.83	226.24 ± 91.99	0.5134	240.19 ± 138.56	229.27 ± 90.36	0.3442
INR	1.05 ± 0.10	1.03 ± 0.10	1.06 ± 0.10	0.7757	1.04 ± 0.09	1.05 ± 0.10	0.5681	1.03 ± 0.10	1.05 ± 0.09	0.7427
Bilirubin (mg/dL)	0.66 ± 0.37	0.67 ± 0.38	0.65 ± 0.36	0.8478	0.57 ± 0.27	0.72 ± 0.41	0.0709	0.60 ± 0.29	0.69 ± 0.40	0.3058
γGT (U/L)	212.88 ± 228.73	190.53 ± 179.50	234.55 ± 269.14	0.4399	234.65 ± 271.20	198.36 ± 197.95	0.5609	209.90 ± 190.53	214.20 ± 245.80	0.9393

ASA: American Society of Anesthesiologists; MELD: model for end-stage liver disease; BMI: body mass index; INR: international normalized ratio; AST: aspartate aminotransferase; AFP: alpha fetoprotein. [a]: $n = 42$, [b]: $n = 63$, [c]: $n = 62$, [d]: $n = 53$.

Table 2
Complications.

Complications	All	Sarcopenia		*P* value	Obesity		*P* value	Sarcopenic obesity		*P* value
		Yes	No		Yes	No		Yes	No	
Number	70	33	37		28	42		21	49	
Overall surgical complication	18 (26%)	8 (24%)	10 (27%)	1.0000	7 (25%)	11 (26%)	1.0000	6 (29%)	12 (25%)	0.7693
Major complication	8 (11%)	4 (12%)	4 (11%)	1.0000	3 (11%)	5 (12%)	1.0000	3 (14%)	5 (10%)	0.6889
Clavien-Dindo				0.6951			0.8345			0.5712
1	1 (1%)	0	1 (3%)		0	1 (2%)		0	1 (2%)	
2	1 (1%)	1 (3%)	0		1 (4%)	0		1 (5%)	0	
3a	8 (11%)	3 (9%)	5 (14%)		3 (11%)	5 (12%)		2 (10%)	6 (12%)	
3b	3 (4%)	2 (6%)	1 (3%)		2 (7%)	1 (2%)		2 (10%)	1 (2%)	
4a	1 (1%)	1 (3%)	0		0	1 (2%)		0	1 (2%)	
4b	0	0	0		0	0		0	0	
5	4 (6%)	1 (3%)	3 (8%)		1 (4%)	3 (7%)		1 (5%)	3 (6%)	
LSSCEP										
Number of patients	21 (30%)	7 (21%)	14 (38%)	0.1916	7 (25%)	14 (33%)	0.5961	5 (24%)	16 (33%)	0.5745
Ascites	6 (9%)	2 (6%)	4 (11%)	0.6767	1 (4%)	5 (12%)	0.3905	1 (5%)	5 (10%)	0.6607
Post-resectional liver failure	4 (6%)	3 (9%)	1 (3%)	0.3368	2 (7%)	2 (5%)	1.0000	2 (10%)	2 (4%)	0.5780
Bile leakage	6 (9%)	2 (6%)	4 (11%)	0.6767	2 (7%)	4 (10%)	1.0000	1 (5%)	5 (10%)	0.6607
Intra-abdominal hemorrhage	0	0	0	1.0000	0	0	1.0000	0	0	1.0000
Intra-abdominal abscess	9 (13%)	5 (15%)	4 (11%)	0.7257	3 (11%)	6 (14%)	0.7322	3 (14%)	6 (12%)	1.0000
Mortality	4 (6%)	1 (3%)	3 (8%)	0.6165	1 (4%)	3 (7%)	0.6450	1 (5%)	3 (6%)	1.0000
Nonsurgical complication										
Pulmonal	6 (9%)	2 (6%)	4 (11%)	0.6770	2 (7%)	4 (10%)	1.0000	1 (5%)	5 (10%)	0.6610
Cardiovascular	2 (3%)	1 (3%)	1 (3%)	1.0000	1 (4%)	1 (2%)	1.0000	1 (5%)	1 (2%)	0.5130
Gastrointestinal	2 (3%)	2 (6%)	0	0.2190	2 (7%)	0	0.5700	2 (10%)	0	0.0870
Urologic	2 (3%)	1 (3%)	1 (3%)	1.0000	1 (4%)	1 (2%)	1.0000	1 (5%)	1 (2%)	0.5130
Sepsis	0	0	0	1.0000	0	0	1.0000	0	0	1.0000
Wound infection	7 (10%)	1 (3%)	6 (16%)	0.1103	1 (4%)	6 (14%)	0.2298	1 (5%)	6 (12%)	0.6660

LSSCEP: liver surgery specific composite endpoints.

Table 3
Median survival, 1- and 3-year survival rates.

Groups	Median survival (yr, 95% CI)	1-year survival rate (95% CI)	3-year survival rate (95% CI)
Sarcopenia	2.54 (-)	72.7% (59.0%–89.6%)	45.0% (29.5%–68.6%)
Non-sarcopenia	1.44 (1.05–2.07)	67.6% (54.0%–84.5%)	13.6% (5.6%–32.9%)
Obesity	2.07 (-)	82.1% (69.1%–97.6%)	38.5% (22.6%–65.5%)
Non-obesity	1.51 (0.93–2.51)	61.9% (48.8%–78.5%)	20.4% (10.6%–39.2%)
Sarcopenic obesity	2.63 (-)	81.0% (65.8%–99.6%)	48.6% (29.0%–81.4%)
Non-sarcopenic obesity	1.51 (1.05–2.07)	65.3% (53.3%–80.1%)	19.5% (10.5%–36.0%)

95% CI: confidence interval. -: not estimable.

in sarcopenic patients, and 67.6% and 13.6% in non-sarcopenic patients, respectively. The univariate analysis comparing the survival curves using the score test showed a significantly improved POS in patients with sarcopenia compared to non-sarcopenic patients (HR = 1.944, $P = 0.035$). Obesity and sarcopenic obesity were also associated with superior POS (obesity HR = 1.580, $P = 0.130$ and sarcopenic obesity HR = 1.860, $P = 0.048$). Univariate analyses showed that gender, multifocality, cirrhosis, length of hospital stay, major complication and sarcopenia were significant predictors for POS (Table 4).

All predictors shown in Table 4 and the AST value were included in the bi-directional model selection for the multivariate analysis, excluding only tumor size and sarcopenic obesity due to multicollinearity. The model selection algorithm identified gender, obesity, tumor > 5 cm and multifocality as predictive covariates for postoperative overall survival, as summarized in Table 4. Obesity was identified by the model selection algorithm as independent predictor for the multivariate analysis. However, it did not have a statistically significant influence on POS (HR = 1.709, $P = 0.0903$). Only gender (HR = 0.386, $P = 0.0117$), tumor size > 5 cm (HR = 2.436, $P = 0.0069$) and multifocality (HR = 2.786, $P = 0.0015$) were significant prognostic factors for postoperative overall survival and were associated with lower respective higher hazard rate. Male patients had a 2.6 times higher risk of death in comparison to female patients. Patients with a tumor size > 5 cm had a 2.4 higher risk of death in comparison to patients with a tumor size < 5 cm, and patients with multifocal HCCs had a 2.8 times higher risk of death in comparison to patients with monofocal disease. To clarify the impact of body composition on long-term survival after surgery alone, a subgroup analysis was conducted for patients without multimodal treatment ($n = 59$). Except for the influence of sarcopenia, which was no longer significant in univariate analysis, the results of all analyses remained unaffected (Table 5).

Despite showing significant influence on postoperative overall survival in the univariate analysis, sarcopenia was not identified as an independent predictor in the multivariate analysis due to multicollinearity with obesity. Substituting obesity for sarcopenia in the multivariate analysis adjusted for gender, tumor size > 5 cm and multifocality, sarcopenia does not show any significant effect on postoperative survival (HR = 1.371, $P = 0.310$).

Prediction models

In order to depict the influence of advanced HCCs on survival, we designed prediction models for high-risk and low-risk patients on the basis of the prognostic factors of the multivariate

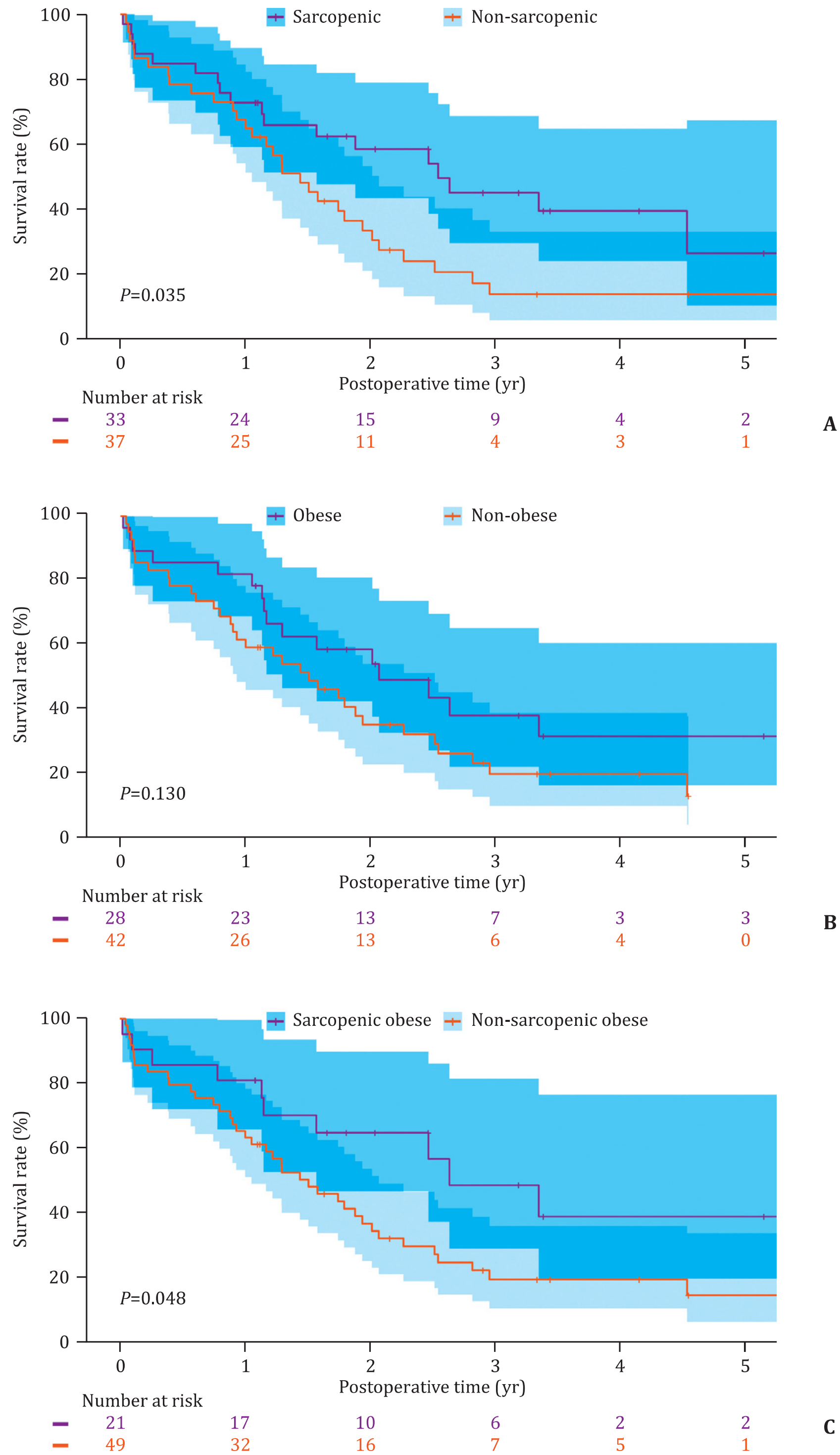

Fig. 2. Kaplan–Meier curves of postoperative overall survival for patients with and without sarcopenia **(A)**, obesity **(B)** and sarcopenic obesity **(C)**.

analysis. High-risk patients were defined as male, with presence of tumors > 5 cm and multifocal disease. Low-risk patients were defined as female, with tumors ≤ 5 cm and without multifocal disease. The influence of obesity on high- and low-risk patients is shown in Fig. 3. Notably, the predicted survival curve for a high-risk patient is considerably worse than for a low-risk patient disregarding of presence of obesity. Yet, obesity can be associated with slightly superior survival for future high-risk patients.

Discussion

HCC is the most common innate liver tumor and its incidence has been growing during the last 30 years [29]. Although it is still associated with a poor prognosis, advances in surgical (liver transplantation or partial hepatectomy) and non-surgical techniques provide further treatment options even for patients with cirrhosis or advanced stage disease. Besides established locoregional

Table 4
Predictors for survival.

Predictors	Univariate		Multivariate	
	P value	HR (95% CI)	*P* value	HR (95% CI)
Age	0.2607	1.013 (0.990, 1.036)		
Gender (Female versus Male)	**0.0131**	0.397 (0.192,0.824)	**0.0117**	**0.386 (0.184, 0.809)**
ASA > 2 (versus ASA ≤ 2)	0.2963	1.387 (0.751, 2.561)		
Beyond Milan (versus within Milan)	0.1105	1.936 (0.860, 4.359)		
MELD score	0.6658	0.974 (0.866, 1.096)		
Alcohol abuse	0.8358	0.937 (0.507, 1.731)		
Sarcopenia	**0.0382**	1.866 (1.034, 3.365)		
Obesity	0.1350	1.582 (0.867, 2.886)	0.0903	1.709 (0.919, 3.177)
Sarcopenic obesity	0.0528	1.944 (0.992, 4.010)		
Recurrent HCC	0.7847	1.119 (0.499, 2.505)		
Multimodal treatment strategy	0.3984	1.416 (0.632, 3.174)		
Tumor size	0.1909	1.045 (0.978, 1.116)		
Patient with tumor > 5 cm	0.2011	1.477 (0.812, 2.678)	**0.0069**	2.436 (1.278, 4.645)
Multifocal	**0.0028**	2.466 (1.364, 4.459)	**0.0015**	2.786 (1.483, 5.236)
Cirrhosis	**0.0481**	0.538 (0.291, 0.995)		
Major resection	0.3860	1.291 (0.725, 2.298)		
Length of stay	**0.0016**	1.027 (1.010, 1.045)		
Complications				
None	Reference			
Minor	0.3304	1.567 (0.634, 3.872)		
Major	**0.0001**	5.460 (2.311, 12.899)		

ASA: American Society of Anesthesiologists; MELD: Model for End-stage Liver Disease; HR: hazard ratio; HCC: hepatocellular carcinoma.

Table 5
Predictors for survival of subgroup analysis (without multimodal treatment, $n = 59$).

Predictors	Univariate		Multivariate	
	P value	HR (95% CI)	*P* value	HR (95% CI)
Age	0.1948	1.0164 (0.9917, 1.0416)		
Gender (Female versus Male)	**0.0283**	**0.4196 (0.1931, 0.9116)**	**0.0266**	**0.4060 (0.1830, 0.9000)**
ASA > 2 (versus ASA ≤ 2)	0.2211	1.5259 (0.7755, 3.0023)		
Beyond Milan (versus within Milan)	0.2605	1.6025 (0.7048, 3.6435)		
MELD score	0.6565	0.9725 (0.8598, 1.0998)		
Alcohol abuse	0.9173	1.3451 (0.6885,2.6277)		
Sarcopenia	0.0766	1.7636 (0.9411, 3.3050)		
Obesity	0.2527	1.4503 (0.7670, 2.7425)	0.3569	1.3750 (0.6980, 2.7110)
Sarcopenic obesity	0.1689	1.6507 (0.8082, 3.3714)		
Recurrent HCC	0.8483	1.0834 (0.4769, 2.4611)		
Tumor size	0.1764	1.0514 (0.9777, 1.1307)		
Patient with tumor > 5 cm	0.2346	**0.6684 (0.3440, 1.2988)**	**0.0193**	**2.3650 (1.1496, 4.8643)**
Multifocal	**0.0010**	**2.9880 (1.5598, 5.7240)**	**0.0009**	**3.2680 (1.6266, 6.5672)**
Cirrhosis	**0.0372**	0.4981 (0.2586, 0.9594)		
Major resection	0.3856	1.3451 (0.6885, 2.6277)		
Length of stay	**0.0003**	1.0321 (1.0144,1.0500)		
Complications				
None	Reference			
Minor	0.0797	2.3022 (0.9061, 5.8490)		
Major	**0.0002**	6.1005 (2.3185, 15.6270)		

ASA: American Society of Anesthesiologists; MELD: Model for End-stage Liver Disease; HR: hazard ratio; HCC: hepatocellular carcinoma.

therapies like microwave ablation or chemoembolization, new treatment options such as drug-eluting bead transarterial chemoembolization (TACE) or selective internal radiation therapy, are emerging. Therefore, multimodal strategies are feasible, and patients should receive tailored treatment approaches, considering their tumor burden, liver function and performance status. As the liver is the central metabolic organ, the metabolic condition within liver disease is crucial for patients counseling and individual treatment concepts. Sarcopenia, which describes skeletal muscle depletion, is known to be a complication and independent risk factor for mortality in patients with liver disease [30].

In this retrospective analysis of 70 patients we analyzed the impact of body composition (sarcopenia, obesity and sarcopenic obesity) on survival after hepatic resection for HCC. Surprisingly and in contrast to several malignant diseases, sarcopenia was associated with superior postoperative survival after hepatic resection in univariate analysis [5-7]. In multivariate analysis adjusted for tumor size, focality and gender, sarcopenia also tended to be superior for postoperative survival but without being statistically significant. On contrary Harimoto et al. identified sarcopenia as an independent risk factor predictive for poor overall survival after partial hepatectomy in an Asian cohort of patients with HCC [10]. The conflicting results in outcome of the studies might be explained by differences between the Japanese and European study population. For example, the BMI of sarcopenic patients was lower in the Japanese cohort (BMI 20.5 kg/m^2 Japanese vs 25.3 kg/m^2 European). On the other hand, sarcopenia has been reported to predict reduced survival in HCC in two further studies, one Asian and one European [30,31]. These studies focused on overall survival in HCC independent of hepatic resection; however, sarcopenia was again identified as independent risk factor for poor survival in the Asian as well as in the European cohort. Regarding

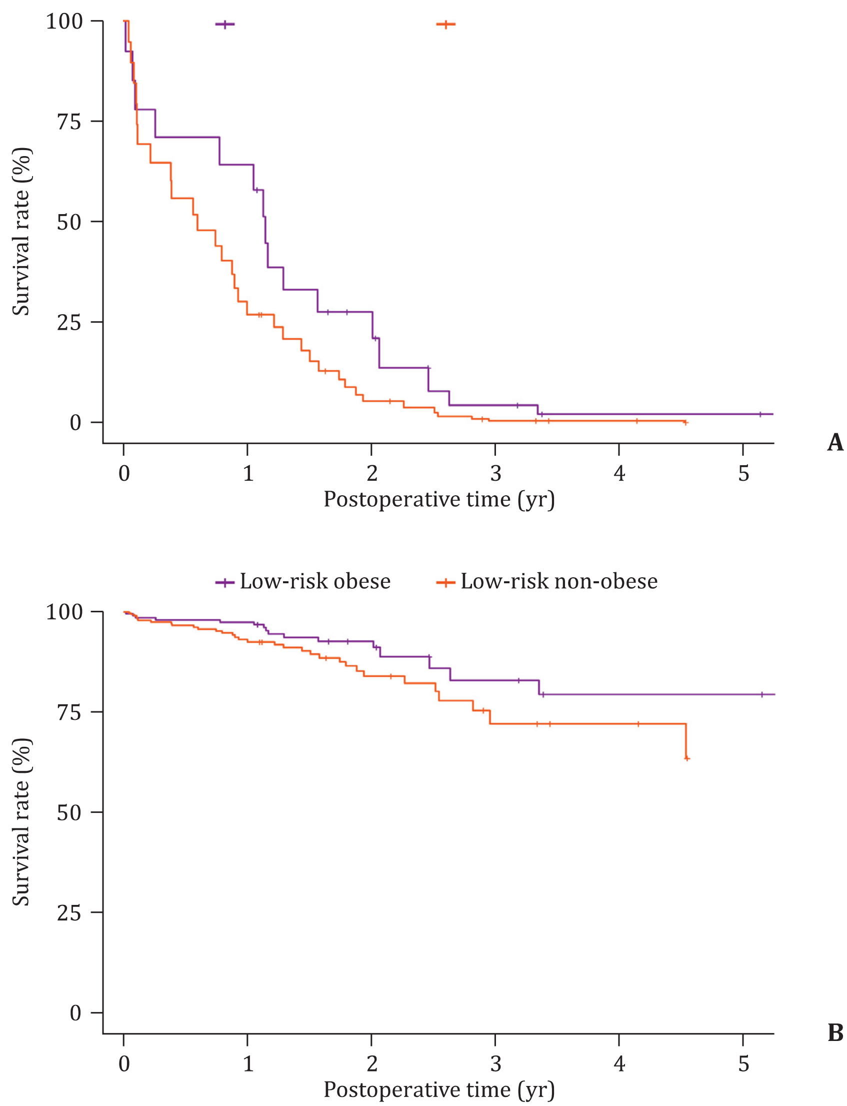

Fig. 3. Prediction models for **(A)** high-risk and **(B)** low-risk patients on the basis of the prognostic factors of the multivariate analysis. High-risk patients were defined as male, with presence of tumors > 5 cm and multifocal disease. Low-risk patients were defined as female, with tumors ≤ 5 cm and without multifocal disease.

these two studies the different ethnical background between Harimoto's and our cohort appears not to be the only reason for the conflicting results. Furthermore, the inclusion criteria differed in both studies. In contrast to the Japanese study we included patients with recurrent HCC as well as patients treated within a multimodal treatment strategy. Tumor size and the proportion of patients with multiple HCCs were also higher in our study resulting in patients with a more advanced stage of disease, which were not available for liver transplantation as the best treatment option. In the present study 83% of all patients were beyond Milan criteria, 13% had recurrent HCC and 16% were treated within a multimodal treatment strategy including a resection and a locoregional therapy such as radiofrequency ablation. Multivariate analysis could identify tumor size > 5 cm, multifocality and gender as significant prognostic factors for postoperative overall survival. Conflicting results regarding sarcopenia were also apparent regarding resection of colorectal liver metastases. Van Vledder et al. reported about lower survival rates for sarcopenic patients undergoing resection of colorectal liver metastases [32] whereas Peng et al. and Lodewick et al. concluded that sarcopenia did not result in worse overall survival [9,11]. However, no other study in the literature could find superior survival in sarcopenic patients after liver resection.

In contrast to sarcopenia the influence of moderate obesity on superior survival in cancer as well as in surgical patients is well known [33–35]. This phenomenon is known as the "obesity paradox". In the present study obesity was defined following body-fat percentage but mean BMI in obese patients was only 28.61 kg/m^2 which represents overweight but no severe obesity following WHO classification. In line with our results several studies show that especially older people benefit from moderate obesity in disease or surgery [33–36]. Hypotheses to explain the "obesity paradox" include increased lean body mass and protective peripheral body fat, which serves as a nutrient reserve and confers a survival advantage in times of stress.

Contrary to obesity, alcohol-related HCC is associated with a poor prognosis in surgical treatment for HCC due to the poor liver function of individuals who abuse alcohol at the time of diagnosis [37,38]. Here, we could not identify alcoholic abuse as a risk factor for poor prognosis. This is probably due to our preoperative risk stratification algorithm, which is based on a subtle analysis of the quantitative and functional parenchymal liver function assessed by laboratory parameters, the LiMAx test and CT or MRI-based 3D-calculation of the FLR and FRLF, excluding patients with inadequate liver function from surgical treatment [14,15].

Multivariate analysis presented gender, tumor size > 5 cm and multifocality as prognostic factors for postoperative overall survival. In our study, male patients have a 2.6 times higher risk of death in comparison to female patients. Several studies report about gender differences in clinical outcome of HCC patients [39,40]. These studies propose a survival benefit for female patients. As a reason for superior female overall survival clinical and experimental data suggest a protective effect of estrogens in female patients [41,42]. In a HCC mouse model, Prieto et al. observed an estrogen-mediated inhibition of IL-6 secretion from Kupffer cells as a mechanism for reduced cancer risk [43]. On the other hand a recent publication could not find any gender specific differences in clinical outcome of HCC patients [44].

Large tumor size and multifocality present an advanced stage disease and are associated with poorer prognosis in this analysis as well as in literature [45–47]. Tumor size and number are included in staging and treatment algorithms like BCLC staging system. Nevertheless, several studies have indicated that even for patients with BCLC stage B HCC a surgical treatment strategy is superior to a locoregional therapy option like TACE [48,49]. However, the influence of gender, tumor number and tumor size was included in prediction models for high- and low-risk patients (Fig. 3) demonstrating the impact of advanced disease on postoperative overall survival.

Several limitations should be considered regarding this study. Firstly, the retrospective nature of this analysis must be named. Furthermore, the inclusion criteria encompassed patients with advanced stage disease for example recurrent HCC or treatment within a multimodal treatment strategy. Another limitation is that body composition was only based on muscle area or body fat percentage instead of involving functional parameters like walking distance. After all the patient number in this study could be a reason for absent significance in multivariate analysis.

In conclusion, neither obesity, sarcopenia nor sarcopenic obesity has detrimental effect on postoperative survival in HCC patients undergoing surgery. The present analysis showed that sarcopenia and obesity can even be associated with a positive effect on survival. However, in the presence of various factors negative for survival, the present cohort was too small to verify the positive effects of sarcopenia and obesity. Therefore, we cannot suggest including the calculation of L3 muscle index and body fat percentage calculation into clinical routine prior to liver surgery for HCC. We recommend repeating the study in a larger cohort.

Contributors

KA analyzed and interpreted the data and wrote the main body of the manuscript under the supervision of BM. UD performed statistical analysis. LT measured skeletal muscle surface area in contrast enhanced abdominal CT scans. ERM and SW contributed substantially to the acquisition of data. UFT provided advice on medical aspects and contributed to the interpretation of data for the work. NUP and BM conceptualized and designed the study. KA is the guarantor.

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Ethical approval

This study was approved by the local ethics committee (EK 343/15) and was conducted in accordance to the principles of *the Declaration of Helsinki* and “good clinical practice” guidelines.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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