Importance of computed tomography muscle quality and continuous versus cut-off-based sarcopenia detection in major hepatic surgery

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Background: The role of the computed tomography (CT)-derived skeletal muscle index (SMI) as a parameter of muscle quantity on the outcome after major liver resection remains contradictory and that of the muscle radiodensity attenuation (MRA) as a parameter of muscle quality has not been sufficiently evaluated. This observational study aimed to investigate the influence of metric SMI and MRA values and cut-off-based CT sarcopenia detection on liver-surgery specific complications measured by the new FABIB (liver failure, ascites, biliary leakage, infection, bleeding) score and survival after hemihepatectomy.

Methods: A total of 183 patients with major hepatectomy were retrospectively included. The SMI and MRA were determined from the abdominal muscle area of preoperative CT scans. Patients were classified as sarcopenic by the SMI and MRA cut-off values of Prado *et al.*, Martin *et al.*, and van der Werf *et al.* Postoperative complications were documented according to the Clavien-Dindo classification and FABIB score. The relation of the continuous, non-categoric SMI and MRA values and of the cut-off-based sarcopenia detection to the postoperative complications and survival was analyzed by multivariable linear, logistic, and Cox proportional hazards regression.

Results: A higher MRA was associated with less severe postoperative complications in the Clavien-Dindo [−0.59 (95% CI: −0.95 to −0.23), P=0.002] and the FABIB score [−0.65 (95% CI: −1.19 to −0.12), P=0.017]. An increase of the SMI did not result in less severe complications in the Clavien-Dindo [0.14 (95% CI: −0.27 to 0.55), P=0.503] or FABIB score [0.17 (95% CI: −0.42 to 0.76), P=0.572]. For patients classified as sarcopenic by the cut-off-based systems no relevant relation to postoperative complications was found. Overall survival was better for a higher MRA [hazard ratio (HR): 0.75 (95% CI: 0.58–0.97), P=0.029], as long-term survival was for a higher SMI [HR: 0.68 (95% CI: 0.47–0.96), P=0.031]. Only below van der Werf's MRA cut-off the probability of overall and long-term survival was reduced [HR: 2.32 (95% CI: 1.18–4.54), P=0.015; 2.68 (95% CI: 1.25–5.74), P=0.011].

Conclusions: The MRA has a stronger influence on complications in the Clavien-Dindo classification and the liver-surgery specific FABIB score than the SMI. Continuous, non-categoric MRA and SMI values are

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superior to cut-off-based systems in predicting the outcome after major hepatic surgery.

Keywords: Sarcopenia; surgery; muscles; hepatectomy; computed tomography (CT)

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Introduction

Sarcopenia defined as age-related loss of muscle mass and function (1) is a common comorbidity with a prevalence which ranges about 10% (2). It is known to cause longer hospital stays (3), to be associated with higher mortality in the elderly population (4), and with a worse prognosis in cancer (5) or after surgery (6). To determine sarcopenia, the muscle status can be assessed by clinical tests (e.g., handgrip), by dual-energy absorptiometry, bioelectrical impedance analysis, magnetic resonance imaging (MRI), or computed tomography (CT). Besides clinical tests, CT, due to its three-dimensional nature, independence of the patients' hydrational status, and high availability in chronically or severely ill patients, is considered the gold standard to assess muscle quantity or quality (1).

Since 2011 the impact of sarcopenia, as assessed by CT, on short-term, long-term, or disease-free survival (DFS) after major liver resection has been investigated by several studies. The majority described a negative influence of sarcopenia or sarcopenia obesity on survival (7,8). However, some contradictory results have been published, as well. One study found a negative impact of sarcopenia only for patients aged 70 years or older (9). Two other studies could not prove any influence of preoperative sarcopenia on overall survival (10,11). Also, most studies have been carried out in Asian populations, while investigations for Caucasian populations remain rare (10,12).

Almost all studies focused on assessing the skeletal muscle index (SMI) as a CT parameter of the skeletal muscle mass (7). However, another easily achievable CT information is the skeletal muscle attenuation (MRA). The MRA provides information about fat accumulation within the muscle fibers (13), which indicates lower muscle quality (14). As an additional parameter besides muscle mass or muscle function muscle quality is expected to gain importance (1). However, so far, only one study on CT body composition and major hepatectomy has included an analysis on muscle radiodensity (15) but did not follow the recommended measurement approach (16,17).

Concerning clinical outcome parameters, apart from overall survival or DFS, most studies on sarcopenia and major hepatectomy focused on postoperative complications as assessed by the Clavien-Dindo classification [e.g., (8,12,18)] while some did not employ any classification system (15). However, the Clavien-Dindo classification provides a general scoring system for post-surgical complications (19) and does not optimally mirror liver surgery-specific complications. A classification system that includes specific complications in liver surgery is the novel FABIB (liver failure, ascites, biliary leakage, infection, bleeding) score (20,21), an acronym of liver failure, ascites, biliary leakage, infection, and bleeding, in which each complication is graded by A, B, and C according to the severity.

This study aimed to address the described gaps in knowledge by investigating the role of the CT-derived SMI as parameter of muscle quantity and the MRA as parameter of muscle quality on survival and postoperative complications after major hepatectomy according to the Clavien-Dindo classification and FABIB score. This article is presented in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-21-5948/rc).

Methods

Study collective

Inclusion criteria of this retrospective observational study were (I) major liver resection, defined as the anatomic resection of ≥3 segments due to benign or malignant hepatobiliary disease between July 2012 to December 2019 at the Department of General, Visceral, and Thoracic Surgery at the University Medical Center Hamburg Eppendorf, a tertiary center for hepatobiliary disease, and (II) available CT scans within a maximum of three months before surgery.

Exclusion criteria were (I) CT scans with an open abdomen which would hinder the assessment of the skeletal

Table 1 Definition and severity grading of the liver surgery-specific complications measured by the FABIB score

Definition of complication	Severity grade A (+1)	Severity grade B (+2)	Severity grade C (+3)
Liver failure: an increased INR and concomitant hyperbilirubinemia on or after POD 5	Requiring no change of the patient's clinical management (C-D grade 0)	Requiring management deviating from the regular course but no invasive therapy (C-D grade 1 or 2)	Need for invasive treatment (≥ C-D grade 3a)
Ascites: with drain: drainage of clear ascitic fluid exceeding 500 mL/day after POD 3; without drain: distension of the abdomen with ascites detectable by ultrasound examination	Requiring no change of the patient's clinical management; or diuretics with same dosage as preoperatively (C-D grade 0)	Requiring pharmacological treatment or diuretics with higher dosage than preoperatively (C-D grade 2)	More than 1,000 mL/day after POD 7 with drain kept despite of pharmacological treatment or need for invasive treatment (≥ C-D grade 2)
Bile leak: bilirubin concentration in the drain fluid at least 3 times the serum bilirubin concentration on or after POD 3 or the need for radiologic or operative intervention resulting from biliary collections or bile peritonitis	Requiring no change in patients' clinical management (C-D grade 0)	Requiring invasive treatment without re-operation or drainage over 7 days (C-D grade 0 or ≥ C-D grade 3a)	Requiring re-operation (≥ C-D grade 3b)
Infection: infections including catheter-related, pulmonary, intra-abdominal, urinary tract, and surgical site infections	Requiring antibiotic treatment or wound infections opened at the bedside (≥ C-D grade 1)	Requiring surgical, endoscopic, or radiological intervention without general anesthesia (≥ C-D grade 3a)	Requiring intervention under general anesthesia or sepsis requiring treatment in the intensive care unit (≥ C-D grade 3b)
Bleeding: drop in Hb level >3 g/dL compared with the postoperative baseline level and/or any postoperative transfusion of PRBC for a falling Hb and/or the need for intervention to stop bleeding	A drop in Hb level >3 g/dL or transfusion of up to two units of PRBC (C-D grade 0 or grade 2)	Requiring transfusion of more than two units of PRBC (C-D grade 2)	Need for invasive re-intervention such as embolization and/or re-laparotomy defines (≥ C-D grade 3a)

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muscle area (SMA) and thus SMI; and (II) CT scans with major artifacts, e.g., due to osteosyntheses material which influence MRA values. Also, non-contrast-enhanced CT scans were excluded, as most patients before hepatectomy receive contrast-enhanced scans and MRA values differ between non-contrast-enhanced and contrast-enhanced scans. After application of the defined in- and exclusion criteria to a total of 295 Caucasian patients with major liver resection, 183 suitable patients were identified.

For this retrospective study, which was conducted in accordance with the Declaration of Helsinki (as revised in 2013), a waiver was obtained from the local ethics committee (Ärztekammer Hamburg, Germany). General informed, written consent was retrospectively available from all participants.

Morbidity and mortality

The liver surgery-specific postoperative complications and severity as defined in the FABIB system (*Table 1*) and, for comparison purposes, complication grading according to the Clavien-Dindo classification (19) were documented as a routine practice using a hospital information system. To calculate the FABIB score for each complication, the

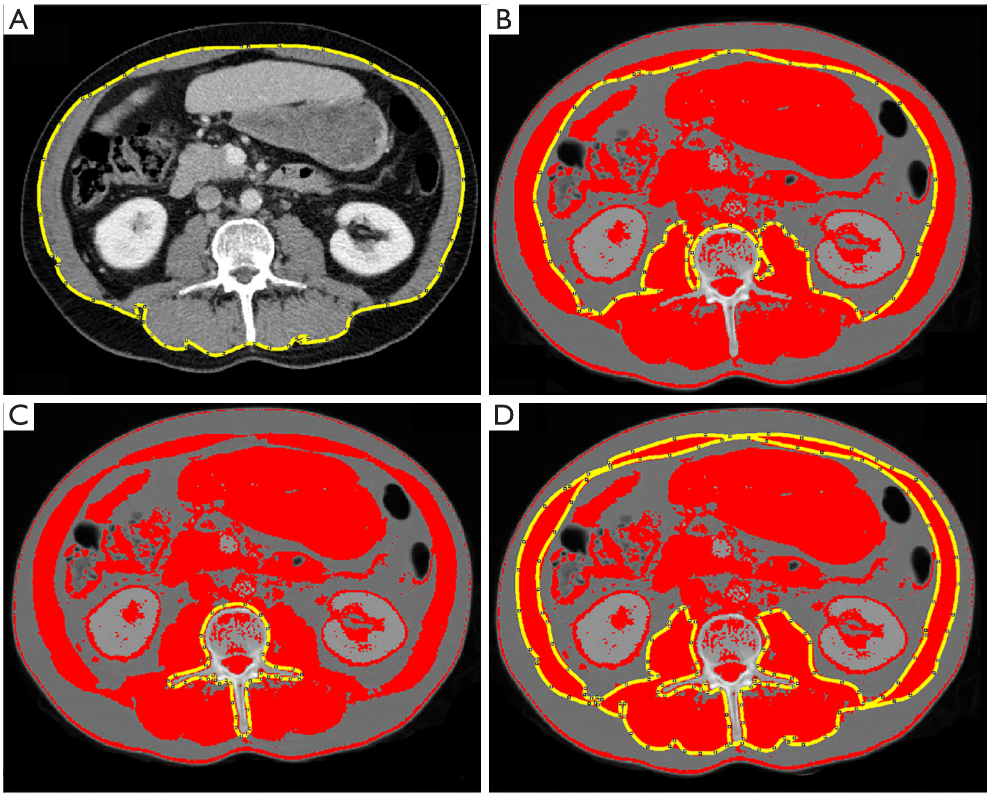

Figure 1 CT body composition. To determine the SMA and the skeletal MRA ROIs were drawn on axial CT slices at the mid-height of the third lumbar vertebra (L3). ROIs were defined along the outer abdominal muscle circumference (A), the inner abdominal muscle circumference (B), around the circumference of L3 (C), and along the whole abdominal muscle circumference (D). After application of a muscle specific threshold (–29 to +150 Hounsfield units) the SMA was given by SMA = A – B – C according to Gomez-Perez *et al.* The SMI was calculated by SMA/body height (cm^2/m^2). The MRA was derived from the ROI around the whole abdominal muscle circumference (D). CT, computed tomography; SMA, skeletal muscle area; MRA, muscle radiodensity attenuation; ROIs, regions of interest; SMI, skeletal muscle index.

numerical values of 1–3 were assigned to the severity grades A–C (*Table 1*). The total sum yields the FABIB score, which ranges from 0 to 15.

Additionally, the 90-day mortality and length of survival were recorded. For long-term and overall survival analysis, the time from the date of surgery to either the date of death or to the last follow-up was used, whichever occurred first. If no event was recorded, the patients were censored at the last contact [maximum follow-up 2,803 days, median follow-up 1,453 days (95% CI: 1,107 to 1,675 days)] for statistical evaluation. To eliminate the bias of the 90-day mortality on long-term survival analysis, patients who died within 90 days following surgery were excluded from the long-term survival analysis.

CT body composition and cut-off-based sarcopenia classification

Axial CT slices (slice thickness 5 mm) at the height of the third lumbar vertebra (L3) on portal venous CT scans were exported and further processed with the open-source software ImageJ (National Institutes of Health, Laboratory for Optical and Computation Instrumentation). Regions of interest were defined along the outer abdominal muscle parameter (*Figure 1A*), inner muscle parameter (*Figure 1B*), and the circumference of L3 (*Figure 1C*). The most commonly used muscle-specific threshold of –29 to +150 Hounsfield units (HU) (16) was applied and the SMA

Table 2 Patient characteristics

Characteristics	N (%) or mean (SD)
Age (mean in years)	62.6 (12.3)
Gender	
Male	103 (56.3)
Female	80 (43.7)
BMI (mean in kg/m²)	25.0 (4.6)
Diagnosis	
Colorectal liver metastases	51 (27.9)
Hepatocellular carcinoma	21 (11.5)
Intrahepatic cholangiocarcinoma	29 (15.8)
Extrahepatic cholangiocarcinoma	49 (26.8)
Gallbladder carcinoma	4 (2.2)
Other malignancy	14 (7.7)
Other non-malignant disease	15 (8.2)
Procedure	
Hemihepatectomy	72 (39.3)
Extended hemihepatectomy	111 (60.7)
Surgery time (in hours)	
<5	68 (37.2)
5–8	59 (32.2)
>8	56 (30.6)
Liver tissue quality	
Normal	129 (70.5)
Post-chemotherapy	18 (9.8)
Fibrosis	20 (10.9)
Cirrhosis	4 (2.2)
Steatosis >20%	12 (6.6)

BMI, body mass index; SD, standard deviation.

calculated according to Gomez-Perez *et al.* (22). The SMI was then given by SMA/body height^2 (cm^2/m^2). After application of the muscle-specific threshold, the MRA of the whole abdominal muscle in HU (*Figure 1D*) was noted.

Patients were classified as sarcopenic according to their SMI and the sex-specific cut-off of Prado *et al.* (men ≤52.4 cm^2/m^2; women ≤38.5 cm^2/m^2) (23), the cut-off of Martin *et al.* which for men also considers the body mass index (BMI) (BMI <25 kg/m^2: SMI <43 cm^2/m^2; BMI ≥25 kg/m^2: SMI <53 cm^2/m^2; women BMI independent: <41 cm^2/m^2) (24), and below the 5th percentile of the sex, age, and BMI specific cut-off values for the SMI and MRA of van der Werf *et al.* (25).

Statistical analysis

Continuous variables are summarized as mean and standard deviation. Categorical variables are summarized as absolute numbers and percentages.

To investigate the impact of continuous MRA and SMI values and of cut-off-based sarcopenia detection (in total six predictors of interest) on complications (Clavien-Dindo classification and FABIB score) and survival, regression analyses were conducted. For continuous endpoints (Clavien-Dindo and FABIB) multivariable linear regression was used. For binary endpoints (90-day survival) logistic regression was calculated. For time-to-event endpoints (overall survival and long-term survival) Cox proportional hazards regression and Kaplan-Meier plots were used. In each regression model one of the endpoints was the dependent variable of the regression and one of the predictors of interest together with a specified list of adjusting variables were the independent variables. Adjusting variables for all regression models were sex, age, BMI, malignancy, liver tissue quality (normal, post-chemotherapy, fibrosis), surgery type, and surgery time. Subgroup analyses for the patients who were resected for benign or malignant reasons were not performed as the number of benign resections (*Table 2*) would not have been sufficient. As the cut-off-based sarcopenia classifications of Prado *et al.*, Martin *et al.*, and van der Werf *et al.* already include sex, and the percentiles of van der Werf *et al.* are sex, age, and BMI specific the corresponding variables were not included in the analyses for these predictors of interest. As all patients without malignancy survived the first 90 days after surgery, the 90-day mortality analysis could not be adjusted for "malignancy".

Each regression analysis was conducted using all complete cases since only one variable had a few missing data points (6% of the SMI and MRA cut-off values of van der Werf *et al.*). Those missing data points were caused by the cut-off values of van der Werf *et al.* which have been defined for patients ≤79 years and BMI values ≤35 kg/m². In our study collective 6% of all patients were either older than 79 years or had a BMI greater than 35 kg/m² and could therefore not be assigned to the categories published by van der Werf *et al.* (25)

P values were not adjusted for multiple testing and since

Table 3 Liver surgery-specific postoperative complications in this study cohort according to the Clavien-Dindo classification and FABIB score

Variables	N (%)
Complications	
Liver failure	40 (21.9)
Biliary leakage	64 (35.0)
Infection	88 (48.1)
Ascites	69 (37.7)
Bleeding	30 (16.4)
Clavien-Dindo classification	
No complications	41 (22.4)
I	7 (3.8)
II	60 (32.8)
IIIa/IIIb	27 (14.8)/23 (12.6)
IVa/IVb	1 (0.5)/2 (1.1)
V	22 (12.0)
FABIB score	
0	50 (27.3)
1–5	95 (51.9)
6–10	35 (19.1)
11–15	3 (1.6)

FABIB score, liver-surgery specific complication score (acronym of liver, failure, ascites, biliary leakage, infection, and bleeding).

this was a retrospective exploratory study they should be interpreted as descriptive summary statistics, not as results of confirmatory hypothesis testing with a certain, e.g., 5%, cut-off. Thus, effect sizes and corresponding 95% confidence intervals (CIs) are described for associations of clinical relevance. All analyses were performed with R version 3.5.3.

Results

Study collective

The final study collective consisted of 183 Caucasian patients, of which 80 (43.7%) were female and 103 (56.3%) were male. Mean age was 63±12 years with a minimum of 28 and a maximum of 84 years. Mean BMI was 25±4.6 kg/m^2 with a range between 17.5 and 40.0 kg/m^2. Most patients, 168 (91.8%), received hepatectomy because of malignant hepatic lesions, of which in 111 (60.7%) extended hepatectomy was indicated. Mean surgery time was 5.9±2.1 hours. All patient characteristics are provided in *Table 2*.

Postoperative morbidity and mortality

Sixty-seven (36.6%) patients suffered from complications according to grade I and II of the Clavien-Dindo classification, 75 (41.0%) suffered from severe complications including the grades III to V (*Table 3*). According to the FABIB score mean point value was 3.1±3.0. For detailed information about grading results and frequency of liver failure, biliary leakage, infection, ascites, and bleeding please see *Table 3*.

CT body composition and cut-off-based sarcopenia results

The MRA and SMI were normally distributed within the study collective (*Figure 2*). Mean MRA was 37±10 HU, mean SMI 42.0±9.6 cm^2/m^2.

A total of 81 male patients (78.6% among all men) and 51 female patients (63.8% among all women) were classified as sarcopenic according to Prado *et al.* According to Martin *et al.* 66 male patients (64.1% among all men) and 60 female patients (75.0% among all women) were sarcopenic. The total observations for the categorization of patients below or above the sex, age, and BMI specific 5th percentiles of van der Werf *et al.* was n=172 (97 male, 75 female). Of these, 20 male patients (20.6% among the men) and 14 female patients (18.7% among the women) had an SMI below the 5th percentile. For 9 male (9.3% among the men) and 4 female (5.3% among the women) patients, the MRA values were below the 5th percentile.

Prediction of postoperative complications based on CT body composition and cut-off-based sarcopenia

Patients with an increase of the MRA showed less severe postoperative complications according to the Clavien-Dindo classification [−0.59 per MRA increase of 10 HU (95% CI: −0.95 to −0.23), P=0.002] (*Figure 3A*).

However, an increase of the SMI did not result in less severe complications [0.14 per SMI increase of 10 units (95% CI: −0.27 to 0.55), P=0.503].

Also, the effect on the Clavien-Dindo grading was found to be contradictory for patients who were classified as sarcopenic according to the SMI based cut-off of Prado *et al.* [−0.61 (95% CI: −1.36 to 0.13), P=0.106] and Martin *et al.*

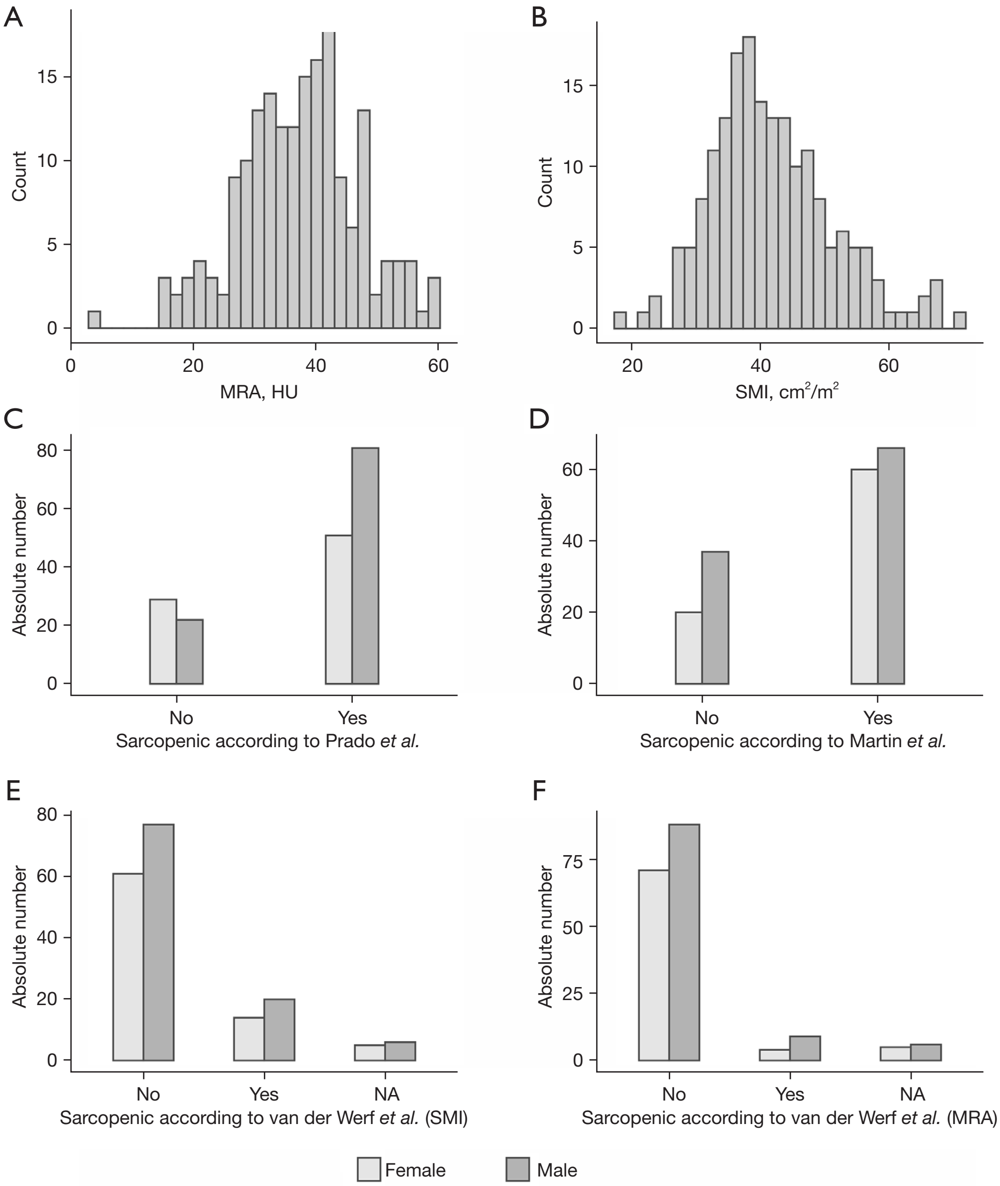

Figure 2 Distribution of CT body composition parameters and cut-off-based sarcopenia results. The skeletal MRA in HU (A) and the SMI (B) were normally distributed among the study collective. Both, male and female patients were more often classified as sarcopenic than as non-sarcopenic according to the cut-off system of Prado *et al.* (C) and Martin *et al.* (D). According to the age, sex, and body mass index specific percentiles of van der Werf *et al.* (E,F) less patients were sarcopenic than by Prado *et al.* or Martin *et al.* MRA, muscle radiodensity attenuation; HU, Hounsfield units; SMI, skeletal muscle index; CT, computed tomography.

[−0.27 (95% CI: −0.95 to 0.42), P=0.440], with sarcopenic patients showing less postoperative complications (*Figure 3A*). No relevant difference in complications was found for patients below the sex, age, and BMI specific 5th percentiles of the SMI according to van der Werf *et al.* [0.07 (95% CI: −0.71 to 0.86), P=0.856]. Also, while the Clavien-Dindo score was 0.88 points higher for patients below the sex, age, and BMI specific 5th percentiles for the MRA this was relativized by a large 95% CI of −0.31 to 2.06 (P=0.146) (*Figure 3A*).

Concerning the FABIB score, similarly, an increase of the MRA of 10 HU resulted in a decrease of the FABIB

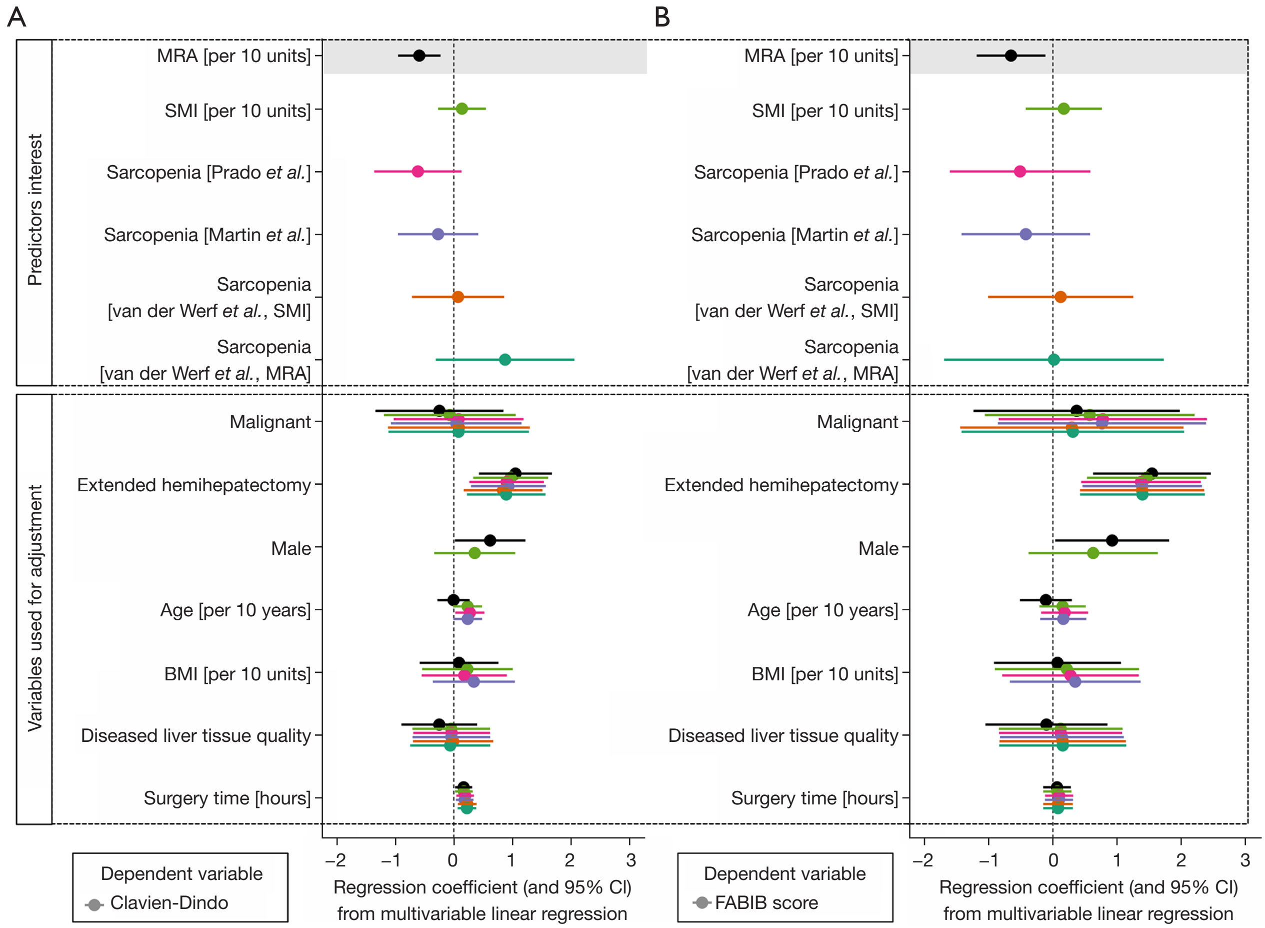

Figure 3 Forest-plot of multivariable linear regression using either the MRA, the SMI, or cut-off-based sarcopenia results as predictors of interest and postoperative complications according to the Clavien-Dindo classification (A) or FABIB score (B) as response variable while adjusting for malignancy, type of surgery, sex, age, BMI, liver tissue quality, and surgery time. Distance from the dotted line indicates the effect size of each predictor with the 95% CI given by the length of the whisker. For each predictor the effects of the adjusting variables are provided in the color in which the predictor is displayed, e.g., for the MRA in black. As some variables, e.g., sex are already included in the cut-off-based sarcopenia classifications they were not adjusted for in the corresponding analyses. Significance is indicated by a grey background. A decrease of the MRA showed a negative effect on postoperative complications. Sarcopenic patients according to Prado *et al.* and Martin *et al.* had more postoperative complications in both scores with however large 95% CI. Patients who were classified as non-sarcopenic according to the MRA cut-off values of van der Werf *et al.* showed less severe postoperative complications in the Clavien-Dindo classification but not in the FABIB score. Surgery time is provided in hours. MRA, muscle radiodensity attenuation; SMI, skeletal muscle index; BMI, body mass index; CI, confidence interval; FABIB score, liver-surgery specific complication score (acronym of liver, failure, ascites, biliary leakage, infection, and bleeding).

score of 0.65 points (95% CI: 1.19–0.12 points, P=0.017) (*Figure 3B*). Comparable to the model for the Clavien-Dindo score, for patients classified as sarcopenic according to Prado *et al.* and Martin *et al.* regression coefficients for the FABIB score were negative, those patients thus did not display more postoperative complications (*Figure 3B*, *Table 4*). For patients whose SMI or MRA was below the 5th percentile of van der Werf *et al.* regression coefficients were about zero [0.12 (95% CI: −1.01 to 1.25), P=0.832; 0.02 (95% CI: −1.69 to 1.73), P=0.984], they thus did not show a relevantly higher FABIB score than patients above the 5th percentile.

Table 4 Multivariable linear regression modeling for the FABIB score using continuous CT body composition results or cut-off-based sarcopenia results together with adjusting variables as independent variables

Adjusting variables	FABIB score value																	
	Predictors																	
	Increase of MRA (per 10 units)			Increase of SMI (per 10 units)			Sarcopenic (Prado *et al.*)			Sarcopenic (Martin *et al.*)			SMI <5th percentile (van der Werf *et al.*)			MRA <5th percentile (van der Werf *et al.*)		
	Est.	95% CI	P	Est.	95% CI	P	Est.	95% CI	P	Est.	95% CI	P	Est.	95% CI	P	Est.	95% CI	P
	−0.65	−1.19 to −0.12	0.017	0.17	−0.42 to 0.76	0.572	−0.51	−1.60 to 0.58	0.358	−0.42	−1.42 to 0.58	0.407	0.12	−1.01 to 1.25	0.832	0.02	−1.69 to 1.73	0.984
Malignancy	0.37	−1.24 to 1.98	0.650	0.57	−1.06 to 2.21	0.489	0.78	−0.84 to 2.40	0.345	0.76	−0.86 to 2.38	0.353	0.30	−1.44 to 2.03	0.738	0.31	−1.42 to 2.04	0.724
Extended hemihepatectomy	1.54	0.63 to 2.46	0.001	1.46	0.53 to 2.39	0.002	1.37	0.44 to 2.30	0.004	1.39	0.46 to 2.32	0.004	1.39	0.42 to 2.36	0.005	1.39	0.42 to 2.37	0.005
Surgery time (hours)	0.06	−0.15 to 0.28	0.555	0.07	−0.15 to 0.29	0.533	0.10	−0.12 to 0.32	0.381	0.09	−0.12 to 0.31	0.392	0.08	−0.15 to 0.31	0.495	0.08	−0.15 to 0.31	0.493
Liver tissue quality	−0.10	−1.05 to 0.85	0.835	0.12	−0.84 to 1.09	0.803	0.12	−0.84 to 1.08	0.805	0.14	−0.82 to 1.10	0.775	0.15	−0.83 to 1.14	0.761	0.15	−0.84 to 1.14	0.759
Age (per 10 years)	−0.11	−0.51 to 0.29	0.595	0.15	−0.21 to 0.51	0.410	0.18	−0.18 to 0.55	0.325	0.16	−0.20 to 0.52	0.376	–	–	–	–	–	–
BMI (per 10 units)	0.07	−0.92 to 1.06	0.886	0.22	−0.90 to 1.34	0.701	0.27	−0.79 to 1.34	0.611	0.35	−0.67 to 1.37	0.501	–	–	–	–	–	–
Gender male	0.92	0.04 to 1.81	0.042	0.63	−0.38 to 1.63	0.220	–	–	–	–	–	–	–	–	–	–	–	–

FABIB score, score of specific postoperative complication for hepatic surgery; CT, computed tomography; Est., regression estimates; CI, confidence interval; MRA, muscle radiodensity attenuation; SMI, skeletal muscle index; BMI, body mass index.

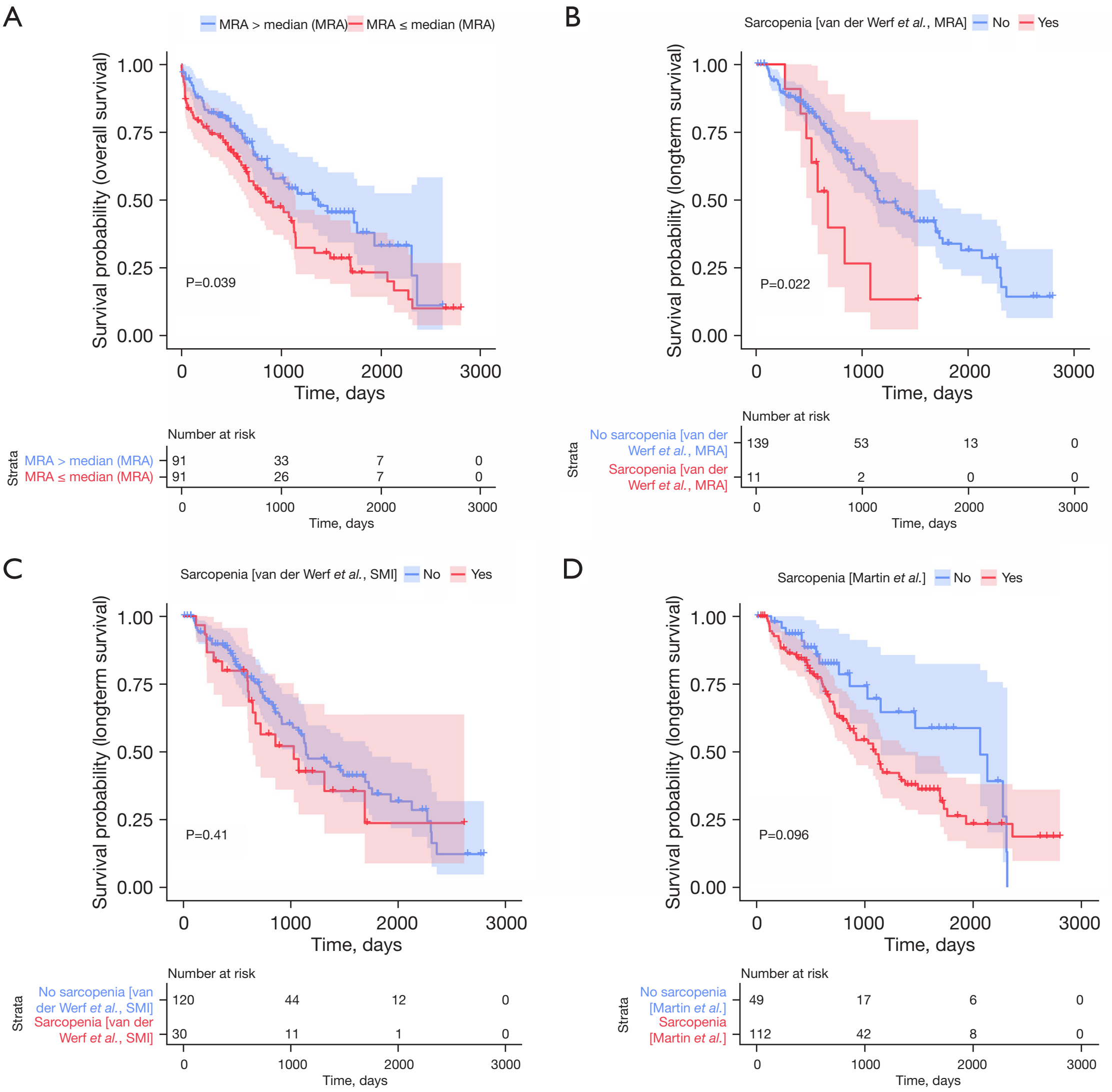

Figure 4 Kaplan-Meier plot for overall survival of patients below and above the median MRA (A), for long-term survival of patients below the age, sex, and body mass index-specific 5th percentile of van der Werf *et al.* for the MRA (B) and the SMI (C), and below the SMI cut-off of Martin *et al.* (D) with corresponding P values. MRA, muscle radiodensity attenuation; SMI, skeletal muscle index.

Prediction of survival based on CT body composition and cut-off-based sarcopenia

An increase of the MRA was associated with lower hazard ratios and thus a higher probability of overall survival [0.75 per MRA increase of 10 HU (95% CI: 0.58–0.97), P=0.029] (*Figure 4A*, *Table 5*) and long-term survival [0.78 per 10 HU (95% CI: 0.58–1.05), P=0.096] (Table S1). The same trend was observed for an increase of the SMI for overall survival [0.82 per SMI increase of 10 cm^2/m^2 (95% CI: 0.60–1.11), P=0.203] and long-term survival [0.68 per 10 cm^2/m^2 (95% CI: 0.47–0.96), P=0.031].

However, only a rise in the MRA and thus higher muscle quality resulted in lower odds of short-term (90-day) mortality [0.63 (95% CI: 0.36–1.12), P=0.104], while patients with a higher SMI, indicating more muscle mass showed a slightly higher 90-day mortality [1.41 (95% CI: 0.74–2.74), P=0.297] (Table S2).

Correspondingly, according to cut-off-based sarcopenia detection, only patients below van der Werf's 5th percentiles of the MRA showed higher odds of short-term death [1.52 (95% CI: 0.22–6.60), P=0.615]. Also, only for this group the probability of both overall (*Table 5*) and long-term survival

Table 5 Cox proportional hazards regression modeling overall survival using either continuous CT body composition results or cut-off-based sarcopenia results together with adjusting variables as independent variables.

Adjusting variables	Overall survival																	
	Predictors																	
	MRA (per 10 units)			SMI (per 10 units)			Sarcopenia (Prado *et al.*)			Sarcopenia (Martin *et al.*)			SMI <5th percentile (van der Werf *et al.*)			MRA <5th percentile (van der Werf *et al.*)		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
	0.75	0.58–0.97	0.029	0.82	0.60–1.11	0.203	0.90	0.50–1.60	0.710	1.19	0.72–1.97	0.492	1.10	0.67–1.79	0.712	2.32	1.18–4.54	0.015
Malignancy	14.61	1.97–108.46	0.009	13.59	1.84–100.41	0.011	13.62	1.86–99.82	0.010	13.76	1.88–100.90	0.010	10.45	1.43–76.55	0.021	11.27	1.54–82.44	0.017
Extended hemihepatectomy	1.35	0.86–2.12	0.194	1.46	0.92–2.30	0.106	1.37	0.87–2.17	0.173	1.41	0.90–2.21	0.130	1.52	0.96–2.41	0.072	1.52	0.96–2.40	0.072
Surgery time (hours)	1.04	0.94–1.15	0.479	1.04	0.94–1.15	0.445	1.04	0.94–1.15	0.439	1.04	0.94–1.16	0.402	1.01	0.91–1.12	0.887	1.01	0.91–1.11	0.907
Liver tissue quality	0.99	0.64–1.55	0.975	1.12	0.73–1.72	0.596	1.13	0.74–1.73	0.562	1.13	0.74–1.72	0.586	1.10	0.72–1.68	0.664	1.05	0.69–1.61	0.824
Age (per 10 years)	1.19	0.98–1.44	0.075	1.28	1.07–1.54	0.007	1.30	1.08–1.56	0.005	1.28	1.07–1.54	0.006	–	–	–	–	–	–
BMI (per 10 units)	0.80	0.50–1.29	0.364	1.14	0.66–1.97	0.629	0.88	0.53–1.45	0.620	0.98	0.62–1.56	0.945	–	–	–	–	–	–
Gender male	1.00	0.66–1.53	0.985	1.12	0.70–1.79	0.631	–	–	–	–	–	–	–	–	–	–	–	–

HR, hazard ratio; CI, confidence interval; MRA, muscle radiodensity attenuation; SMI, skeletal muscle index; BMI, body mass index.

(*Figure 4B*) was reduced as indicated by the increased hazard ratios [2.32 (95% CI: 1.18–4.54), P=0.015; 2.68 (95% CI: 1.25–5.74), P=0.011].

For patients below van der Werf's 5th percentiles for the SMI hazard ratios of overall and long-term survival (*Figure 4C*) were slightly increased with however large confidence intervals [1.10 (95% CI: 0.67–1.79), P=0.712; 1.20 (95% CI: 0.68–2.09), P=0.530]. Similarly, for sarcopenic patients according to the SMI cut-off of Martin *et al*. hazard ratios for overall and long-term survival (*Figure 4D*) were slightly increased and confidence intervals were large [1.19 (95% CI: 0.72–1.97), P=0.492; 1.44 (95% CI: 0.78–2.64), P=0.245]. For patients defined as sarcopenic by the SMI cut-off of Prado *et al.* the hazard ratio for overall survival was 0.9 with however again a large confidence interval (95% CI: 0.50–1.60, P=0.710).

Discussion

This study analyzed the influence of the CT-derived SMI and MRA on survival and postoperative complications after major hepatectomy by using both the Clavien-Dindo classification and the liver surgery-specific FABIB score.

The main results were (I) a lower MRA and thus higher muscle fat amounts and a lower muscle quality were associated with more severe postoperative complications after hepatectomy according to both the Clavien-Dindo and the FABIB score; (II) there was no relevant relation of the SMI and of cut-off-based sarcopenia detection to postoperative complications. Concerning survival, (III) patients with a higher MRA and higher SMI, indicating better muscle quality and higher muscle mass had a higher probability of overall and long-term survival. Of all cut-off-based systems, only patients below the 5th percentiles of van der Werf *et al.* for the MRA showed a lower probability of overall and long-term survival.

Compared to the SMI, reports about the MRA in surgical patients are rare. Still, an important influence of the MRA and thus muscle quality on the outcome after surgery, as found in this study, has been suggested for other entities before. Carvalho *et al.* found that after surgery for gastric and colorectal carcinoma, the SMI and MRA were both associated with postoperative complications according to the Clavien-Dindo score, but only the MRA was of significant influence for major complications (score > III) (26). By van Dijik *et al.* it was described that the MRA was associated with low survival after periampullary surgery in patients with pancreatic cancer (27). This study however is the first which evaluated the association of the MRA to postoperative complications after hemihepatectomy. In the only other related study, an index of the radiodensity within the posterior paraspinal muscle divided by the radiodensity of subcutaneous fat was calculated and found to be a significant prognostic factor on survival for patients with hepatocellular carcinoma and hemihepatectomy (15). However, the recommended approach on how to measure the MRA is to employ a muscle-specific threshold and to include the whole abdominal muscle area, because muscle density varies between different muscle groups (16). In this study, the MRA was measured correspondingly and demonstrated to be associated with postoperative complications and survival after hemihepatectomy. Indeed, only the MRA showed a clear association with survival and postoperative complications in both the Clavien-Dindo classification and the FABIB score.

One should note that independent of surgery, a low MRA is known to be an unfavorable influence on survival in a variety of different cancer entities, e.g., malignant melanoma (28), lung cancer (24), renal cell carcinoma (29), lymphoma (30), or colorectal carcinoma (31). That is why in this study, statistical analyses were adjusted for the variable "malignancy" to define the true impact of the MRA on clinical outcome after hemihepatectomy.

The SMI was found to be associated with overall and long-term survival but not with short-term survival or postoperative complications in neither the Clavien-Dindo nor the FABIB score. In contrast to the MRA, several articles have already been published about the impact of the SMI on the outcome after hemihepatectomy. Interestingly, the results of these publications are contradictory, as well. Takagi *et al.* found the SMI to be predictive for lower overall survival (32), as did Harimoto *et al.* and Kobayashi *et al.* for overall survival and recurrence-free survival (8,33). On the other hand, Yabusaki *et al.* only described a relation to tumor recurrence and did not find an association to overall survival (11). The results of the only two other studies on Caucasian populations concerning the influence of the SMI on survival after hemihepatectomy were contradictory as well (10,12). There is thus good agreement between the literature and the findings in this study, indicating that the SMI and thus muscle mass is not a sufficient parameter to predict survival or complications after hemihepatectomy and that the MRA as a parameter of muscle quality should be considered, as well.

Moreover, all these studies used varying cut-off values to assign patients to a sarcopenic and non-sarcopenic group. As discussed before (34), using a cut-off system on continuous data results in loss of information. It is thus a strength of this study that not only cut-off-based classification systems as that of Prado *et al.*, Martin *et al.*, and van der Werf *et al.* were used but analyses of continuous non-categoric MRA and SMI data were also included. As the association of the cut-off-based sarcopenia results to postoperative complications and survival was indeed minor and not consistent, the results of this study confirm that hard cut-off values are disadvantageous. An individual's MRA and SMI values should rather be considered as part of a continuum and if feasible continuous data analyses should be included in future studies. As both approaches, cut-off-based and continuous analyses, were evaluated in this study validity and generalizability of this study's results for similar patient collectives with major hepatic surgery can be assumed.

A limitation of this study is the heterogeneity of the study collective. The patients received hemihepatectomy of different extent and the underlying diseases varied. However, the vast majority were cancer patients, and the analyses were adjusted for the variables "malignancy" and "surgery type" ("regular" *vs.* "extended hemihepatectomy") to reduce the impact of patient heterogeneity on the study results. While the analyses were adjusted for neoadjuvant chemotherapy as well, this was not feasible for adjuvant therapy, as the overall patient number was too small to consider the large variety of individual treatments based on, e.g., histological cancer subtypes and further predictors.

In future studies, as done in this work, care should be taken to only include CT scans within the same contrast phase for MRA measurements, as the MRA changes between non-contrast-enhanced and contrast-enhanced scans. So far, many articles vary in their approach or do not provide information on the contrast phase at all, which hinders comparability of study results (16). Also, new techniques on how to measure muscle quality are expected to gain importance (1) and a contrast media independent approach by using material decomposition in dual-energy CT has recently been proposed (35), which warrants further investigation.

Conclusions

In conclusion, this study found the MRA as a parameter of muscle quality to be of higher predictive value than the SMI as a parameter of muscle quantity and continuous non-categoric analyses of the MRA and SMI superior to cut-off-based systems in prediction of survival and postoperative complications after hemihepatectomy as measured by the Clavien-Dindo classification and the liver-specific FABIB score.

In future, both parameters, the SMI and the MRA, should be assessed in patients who receive CT scans before hemihepatectomy to estimate an individual's risk profile and initiate appropriate nutritional regimes and physiotherapy. It is also advisable to consider SMI and MRA measurement results as part of a spectrum between sarcopenic and non-sarcopenic patients rather than strictly distinguishing between values below and above defined cut-offs.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-21-5948/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-21-5948/coif). MK was supported with a partial exemption from his clinical duties by the Clinician Scientist Program of the University Medical Center Hamburg-Eppendorf. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. For this retrospective study, which was conducted in accordance with the Declaration of Helsinki (as revised in 2013), a waiver was obtained from the local ethics committee

(Ärztekammer Hamburg, Germany). Informed, written consent was retrospectively available from all participants.

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Supplementary

Table S1 Cox proportional hazards regression modeling long-term survival (>90 days) with continuous CT body composition results or sarcopenia classification results and adjusting variables as independent variables

Adjusting variables	Long-term survival (>90 days)																	
	Predictors																	
	MRA (per 10 units)			SMI (per 10 units)			Sarcopenia (Prado *et al.*)			Sarcopenia (Martin *et al.*)			SMI <5th percentile (van der Werf *et al.*)			MRA <5th percentile (van der Werf *et al.*)		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
	0.78	0.58–1.05	0.096	0.68	0.47–0.96	0.031	1.01	0.50–2.04	0.983	1.44	0.78–2.64	0.245	1.20	0.68–2.09	0.530	2.68	1.25–5.74	0.011
Malignancy	10.36	1.38–78.04	0.023	9.75	1.30–73.28	0.027	9.83	1.33–72.96	0.025	10.21	1.37–76.00	0.023	7.39	1.00–54.80	0.051	8.39	1.13–62.27	0.038
Extended hemihepatectomy	1.44	0.86–2.42	0.168	1.66	0.98–2.79	0.057	1.51	0.90–2.55	0.119	1.54	0.92–2.56	0.098	1.78	1.05–3.03	0.032	1.73	1.03–2.93	0.040
Surgery time (hours)	1.01	0.90–1.13	0.905	1.01	0.90–1.14	0.830	1.01	0.90–1.14	0.847	1.02	0.91–1.14	0.755	0.97	0.86–1.09	0.601	0.97	0.86–1.09	0.599
Liver tissue quality	1.21	0.74–1.97	0.456	1.34	0.83–2.14	0.228	1.35	0.85–2.15	0.207	1.33	0.83–2.12	0.231	1.32	0.82–2.12	0.249	1.25	0.78–2.00	0.349
Age (per 10 years)	1.17	0.95–1.45	0.144	1.25	1.03–1.53	0.025	1.26	1.03–1.54	0.025	1.25	1.02–1.52	0.028	–	–	–	–	–	–
BMI (per 10 units)	0.68	0.39–1.18	0.171	1.17	0.62–2.20	0.627	0.79	0.44–1.42	0.428	0.90	0.52–1.54	0.693	–	–	–	–	–	–
Gender male	1.02	0.63–1.65	0.948	1.30	0.76–2.21	0.335	–	–	–	–	–	–	–	–	–	–	–	–

HR, hazard ratio; CI, confidence interval; MRA, muscle radiodensity attenuation; SMI, skeletal muscle index; BMI, body mass index.

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Table S2 Logistic regression modelling 90-day mortality with continuous CT body composition results or sarcopenia classification results and adjusting variables as independent variables

Adjusting variables	90-day mortality																	
	Predictors																	
	MRA (per 10 units)			SMI (per 10 units)			Sarcopenia (Prado *et al.*)			Sarcopenia (Martin *et al.*)			SMI <5th percentile (van der Werf *et al.*)			MRA <5th percentile (van der Werf *et al.*)		
	Est.	95% CI	P value	Est.	95% CI	P value	Est.	95% CI	P value	Est.	95% CI	P value	Est.	95% CI	P value	Est.	95% CI	P value
	0.63	0.36–1.12	0.104	1.41	0.74–2.74	0.297	0.63	0.21–2.03	0.425	0.67	0.24–1.91	0.435	0.93	0.25–2.79	0.908	1.52	0.22–6.60	0.615
Malignancy	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Extended hemihepatectomy	1.38	0.50–4.11	0.538	1.22	0.45–3.58	0.700	1.20	0.44–3.50	0.729	1.21	0.45–3.51	0.719	1.09	0.41–3.14	0.866	1.12	0.41–3.23	0.829
Surgery time (hours)	1.11	0.88–1.40	0.382	1.13	0.89–1.44	0.309	1.13	0.89–1.43	0.311	1.13	0.89–1.43	0.315	1.12	0.89–1.41	0.342	1.12	0.88–1.41	0.348
Liver tissue quality	0.41	0.11–1.27	0.153	0.54	0.15–1.63	0.311	0.51	0.14–1.51	0.258	0.52	0.14–1.55	0.277	0.53	0.15–1.53	0.275	0.51	0.14–1.49	0.254
Age (per 10 years)	1.23	0.77–2.05	0.407	1.53	1.00–2.50	0.066	1.51	0.98–2.45	0.074	1.49	0.98–2.41	0.080	–	–	–	–	–	–
BMI (per 10 units)	1.36	0.45–3.80	0.569	1.12	0.31–3.61	0.856	1.31	0.41–3.89	0.637	1.40	0.47–3.95	0.527	–	–	–	–	–	–
Gender male	1.50	0.57–4.18	0.421	0.96	0.31–2.98	0.939	–	–	–	–	–	–	–	–	–	–	–	–

Est., regression estimates; CI, confidence interval; MRA, muscle radiodensity attenuation; SMI, skeletal muscle index; BMI, body mass index.

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