ORIGINAL ARTICLE

Journal of Cachexia, Sarcopenia and Muscle 2015; **6**: 155–163
Published online 28 April 2015 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/jcsm.12018

Sarcopenia, obesity and sarcopenic obesity: effects on liver function and volume in patients scheduled for major liver resection

Toine M. Lodewick[1,2,3]*, Anjali A.J. Roeth[1,3], Steven W.M. Olde Damink[2,3,4], Patrick H. Alizai[1,3], Ronald M. van Dam[2,3], Nikolaus Gassler[5], Mark Schneider[1,3], Simon A.W.G. Dello[2], Maximilian Schmeding[1,3], Cornelis H.C. Dejong[2,3] & Ulf P. Neumann[1,3]

[1]*Department of Surgery, Division of General, Visceral and Transplantation Surgery, RWTH Aachen University, Aachen, Germany;* [2]*Department of Surgery, Maastricht University Medical Centre & Nutrim School for Nutrition, Toxicology and Metabolism, Maastricht University, Maastricht, The Netherlands;* [3]*Euregional HPB collaboration Aachen–Maastricht, Aachen–Maastricht, Germany–The Netherlands;* [4]*Department of Surgery, Division of Surgery and Interventional Science, Royal Free Hospital, and University College London, London, United Kingdom;* [5]*Institute of Pathology, RWTH Aachen University, Aachen, Germany*

Abstract

Background Sarcopenia, obesity and sarcopenic obesity have been linked to impaired outcome after liver surgery. Preoperative liver function of sarcopenic, obese and sarcopenic-obese patients might be reduced, possibly leading to more post-operative morbidity. The aim of this study was to explore whether liver function and volume were influenced by body composition in patients undergoing liver resection.

Methods In 2011 and 2012, all consecutive patients undergoing the methacetin breath liver function test were included. Liver volumetry and muscle mass analysis were performed using preoperative CT scans and Osirix® software. Muscle mass and body-fat% were calculated. Predefined cut-off values for sarcopenia and the top two body-fat% quintiles were used to identify sarcopenia and obesity, respectively. Histologic assessment of the resected liver gave insight in background liver disease.

Results A total number of 80 patients were included. Liver function and volume were comparable in sarcopenic(-obese) and non-sarcopenic(-obese) patients. Obese patients showed significantly reduced liver function [295 (95–508) vs. 358 (96–684) μg/kg/h, $P = 0.018$] and a trend towards larger liver size [1694 (1116–2685) vs. 1533 (869–2852) mL, $P = 0.079$] compared with non-obese patients. Weight ($r = -0.40$), body surface area ($r = -0.32$), estimated body-fat% ($r = -0.43$) and body mass index ($r = -0.47$) showed a weak but significant negative (all $P < 0.05$) correlation with liver function. Moreover, body-fat% was identified as an independent factor negatively affecting the liver function.

Conclusion Sarcopenia and sarcopenic obesity did not seem to influence liver size and function negatively. However, obese patients had larger, although less functional, livers, indicating dissociation of liver function and volume in these patients.

Keywords Sarcopenia; Obesity; L3 skeletal muscle index; Body fat percentage; Liver function; LiMAx; Volumetry

Received: 3 August 2014; Revised: 8 December 2014; Accepted: 5 January 2015
**Correspondence to: Toine M. Lodewick, MD, Department of Surgery, Maastricht University Medical Centre, P. Debyelaan 25, 6229 HX Maastricht, The Netherlands: Tel: +31 43 388 1501. Email: t.lodewick@maastrichtuniversity.nl*

Introduction

In the past decade, indications for liver surgery have changed dramatically. This was mainly due to improvements in surgical technique and new insights in the field of oncology and chemotherapy, which led to larger liver resections.[1,2] Despite more extensive preoperative assessment of patients undergoing major liver surgery, post-resectional liver failure still occurs and it remains the most frequent cause of death following major liver surgery.[3–5] Today, preoperative volumetric and, if needed, functional assessment of the liver are the cornerstones in the pursuit of safe resection liver surgery.[6–9]

As primary or secondary liver tumours often are accompanied by weight loss and cachexia, disturbances in body

composition and metabolic state are now suggested to be risk factors for the development of major post-operative morbidity and post-resectional liver failure.[10] Recently, our group showed that depletion of muscle mass (i.e. sarcopenia) negatively influences total liver volume in patients undergoing liver surgery.[11] Several other studies have indicated that disturbances in body composition possibly have negative effects on outcome after liver surgery.[10,12–16] The increased complication rates in patients with body composition disturbances (i.e. sarcopenia, obesity and sarcopenic obesity) might well be partially caused by impaired liver function.

Therefore, the aim of the present study was to explore whether total liver function and volume are influenced by sarcopenia, obesity and sarcopenic obesity in patients undergoing extensive preoperative assessment prior to potential liver surgery.

Materials and methods

Patients

This study was conducted according to the revised version of the Declaration of Helsinki (October 2008, Seoul). From January 2011 to December 2012, all consecutive patients undergoing a LiMAx[6,7] liver function breath test and a CT scan as part of regular preoperative assessment in the Aachen University Hospital were included. Informed consent was obtained in every patient. The decision for LiMAx evaluation was based on clinical indications (such as resection of four or more liver segments and known or suspected fibrosis or cirrhosis) and was made by the responsible surgeons. Patients underwent extensive preoperative laboratory testing, and Child–Pugh[17] and model for end-stage liver disease (MELD)[18] scores were calculated. Jaundice was defined as a serum bilirubin level greater than 2.5 per decilitre.[19] Patients who underwent portal vein embolization (PVE) prior to resection were studied before the PVE procedure.

Methods

Liver function test

The LiMAx test was used to assess hepatocyte-specific metabolic function. This test is based on metabolization of ^{13}C-labelled methacetin (Euriso-top, Saint-Aubin Cedex, France) by the cytochrome P450 1A2 enzyme in the liver.[6,7] After intravenous injection, ^{13}C-labelled methacetin is instantly metabolized, and the ratio between exhaled $^{13}CO_2$ and normal non-enriched background $^{12}CO_2$ is registered over a period of 60 min.[7]

Liver volumetry

A 2.4 GHz Intel Core 2 Duo MacBook (Apple Inc., Cupertino, CA, USA) with Osirix® software version 4.1.1 (http://www.osirix-viewer.com) was used for volumetric analysis of the liver. Liver contour was manually outlined by one researcher (T.M.L.) on transverse slices of the venous phase of routinely performed preoperative contrast-enhanced CT scans. Total liver volume (TLV) and tumour volume were measured as described earlier.[20] The non-tumour total liver volume (ntTLV) was calculated by subtracting tumour volume from TLV.

Body composition

Presence of sarcopenia was assessed through measurements of skeletal muscle areas by one single researcher (T.M.L.) with the use of the Osirix® programme on contrast-enhanced preoperative (or pre-PVE in case of a PVE) CT scans. A threshold range between −30 and 110 Hounsfield units was set to semi-automatically outline muscle areas at the transversal level of the third lumbar vertebra (L3) as recently described.[11] The mean of measurements on two adjacent CT slices at L3 level was used to calculate the L3 skeletal muscle index (L3 MI) by correcting it for height. Sarcopenia was defined as a L3 MI $< 41\,cm^2/m^2$ in women, $< 43\,cm^2/m^2$ in men with a body mass index (BMI) of <25 and $< 53\,cm^2/m^2$ in men with a BMI of >25 as these cut-off values showed an association with mortality.[21] The ntTLV–bodyweight ratio (%) was calculated using the following formula: [ntTLV (mL)/bodyweight (g)] * 100%. Body surface area was estimated using the Mosteller formula,[22] $\{[\text{height (cm)} * \text{weight (kg)}]/3600\}^{0.5}$. Total fat-free body mass (kg) was estimated as $0 \cdot 30 * (\text{skeletal muscle surface area at L3 in } cm^2) + 6.06$.[23] Body-fat% was calculated as [body weight (kg) − fat-free body mass (kg)]/body weight (kg). Obesity was based on body-fat%; cut-off values for obesity were >49.6% for women and >37.5% for men, based on the top two body-fat% quintiles in our study as is conventional for studies evaluating sarcopenic obesity.[24–26] Sarcopenic obesity was defined as the presence of both sarcopenia and obesity according to our definitions.

Histopathology

One pathologist (N.G.) performed all pathologic examinations. Fibrosis of background liver tissue was classified using the Metavir score, which among others consists of a five-point fibrotic scale.[27] The degree of non-alcoholic steatohepatitis (NASH) was analysed using the NASH scoring system (NAS score).[28] Finally, sinusoidal dilatation was scored as a four-point scale as a measure of sinusoidal obstruction syndrome.[29]

Outcome after surgery

Post-operative morbidity was graded according to the Dindo–Clavien classification.[30] Complications with a grade ≥3a were considered major complications. Thirty-day and 90-day mortality were scored.

Statistical analysis

Data were analysed with SPSS version 18.0 (SPSS Inc., Chicago, IL) and Prism 5.0 for Macintosh (Graphpad software, Inc, San Diego, CA, USA). The data were expressed as median (range). Chi-square tests were used to analyse categorical

data while continuous data were analysed with Mann–Whitney *U* tests. A level of $P < 0.05$ was considered statistically significant. Correlations between body composition factors and liver function or ntTLV were performed in patients with relatively healthy livers, that is, livers without cirrhosis (Metavir fibrotic scale Stage 4[27]), NASH (NAS score ≥ 5[28]) or severe sinusoidal dilatation (sinusoidal dilatation score = 3[29]). Also, patients without pathologic examination of liver tissue were excluded for correlation analysis. Correlations were calculated with Pearson's test. The resulting regression line was described as a linear equation, and the correlation coefficient (*r*) was calculated. Relevant clinicopathologic variables associated with liver function were examined using univariable and, where applicable, multivariable linear regression. For the multivariable models, a univariable inclusion criterion of $P \leq 0.15$ was used.

Results

Patients

A total of 80 patients were included in the present study. The patient characteristics, body composition and liver-related measurements are presented in detail in *Tables* 1 and 2. Indications for potential liver resection were mostly cholangiocarcinoma ($n = 28$, 35.0%), colorectal liver metastases ($n = 24$, 30.0%) and hepatocellular carcinoma ($n = 15$, 18.8%).

Influence of sarcopenia on liver volume and function

The median L3 MI was 50.7 (31.9–68.3) cm^2/m^2 in men and 41.6 (28.7–71.9) cm^2/m^2 in women. Based on the predefined criteria, 18 (35.3%) men and 13 (44.8%) women were sarcopenic (*Table* 2). *Table* 3 shows the features associated with sarcopenia, obesity and sarcopenic obesity. The median preoperative LiMAx value and non-tumour TLV were 326 (95–684) μg/kg/h and 1571 (869–2852) mL, respectively (*Table* 2). No statistically significant difference in liver function was observed between patients with or without sarcopenia [327 (95–684) μg/kg/h and 324 (125-594) μg/kg/h, respectively, $P = 0.917$]. Sarcopenic patients also had a comparable ntTLV compared with patients without sarcopenia [1518 (869–2581) vs. 1678 (1052–2852) mL, $P = 0.215$] (*Table* 3).

Influence of obesity on liver volume and function

According to our cut-off body-fat% values for obesity, 11 (37.9%) women and 21 (41.2%) men were obese (*Table* 2). The L3 MI in women was comparable between the two groups. On the contrary, in obese men, the L3 MI was significantly smaller compared to that of non-obese men [42.9 (31.9–68.3) cm^2/m^2 vs. 53.4 (41.3–67.7) cm^2/m^2, $P < 0.001$]. There was a trend towards larger liver volume in obese patients, with an ntTLV of 1694 (1116–2685) mL in obese and 1533 (869–2852) mL in non-obese patients ($P = 0.079$). Median liver function, as determined by LiMAx, was reduced in obese patients [295 (95–508) vs. 358 (96-684) μg/kg/h, $P = 0.018$]. Moreover, the median liver function per millilitre ntTLV was significantly smaller in obese patients [0.17 (0.07–0.32) vs. 0.22 (0.06–0.47), $P = 0.004$] (*Table* 3).

Influence of sarcopenic obesity on liver volume and function

Eighteen (22.5%) patients met the criteria for sarcopenic obesity, and sarcopenic-obese patients were predominantly male (83.3%) (*Table* 2). Sarcopenic-obese patients were older than patients without sarcopenic obesity [72 (43–82) vs. 65 (28–80), $P = 0.029$]. NtTLV and LiMAx values were comparable between patients with and without sarcopenic obesity (*Table* 3).

Table 1 Patient characteristics

Variables, median (range)	All $n = 80$	Male $n = 51$	Female $n = 29$	*P*
Patient characteristics				
Median age (years)	66 (28–82)	67 (28–82)	64 (29–76)	0.289
Percentage with ASA 3/4	53.9	51.1	58.6	0.521
Patients with PVE (%)	34 (42.5)	19 (37.3)	15 (51.7)	0.208
Weight (kg)	80 (47–134)	82 (52-109)	72 (47–134)	0.032
Height (cm)	174 (155–205)	176 (160–205)	165 (155–180)	<0.001
BMI (kg/m^2)	24.9 (18.7–46.4)	24.6 (20.2–37.7)	27.3 (18.7–46.4)	0.837
BMI >30 kg/m^2 (%)	14 (17.5)	5 (9.8)	9 (31.0)	0.016
Child–Pugh grade				
Percentage with A	82.1	83.7	79.3	0.627
Percentage with B	17.9	16.3	20.7	0.627
MELD score	7 (6–20)	7 (6–20)	7 (6–19)	0.758
Indication (%)				
Colorectal liver metastases	24 (30.0)	15 (29.4)	9 (31.0)	0.879
Other metastases	6 (7.5)	3 (5.9)	3 (10.3)	—
Hepatocellular carcinoma	15 (18.8)	14 (27.5)	1 (3.4)	0.008
Cholangiocarcinoma	28 (35.0)	16 (31.4)	12 (41.4)	0.367
Gallbladder carcinoma	1 (1.3)	0 (0.0)	1 (3.4)	—
Benign lesion	5 (6.3)	2 (3.9)	3 (10.3)	—
Living donor liver transplant	1 (1.3)	1 (2.0)	0 (0.0)	—

ASA, American society of anesthesiologists; PVE, portal vein embolization; BMI, body mass index.

Table 2 Body composition and liver-related measurements

Variables, median (range)	All $n = 80$	Men $n = 51$	Women $n = 29$	P
Body composition				
L3 MI (cm^2/m^2)	45.3 (28.7–71.9)	50.7 (31.9–68.3)	41.6 (28.7–71.9)	<0.001
Sarcopenia (%)	31 (38.8)	18 (35.3)	13 (44.8)	0.400
Fat-free body mass (kg)	47.3 (31.7–75.9)	54.2 (37.7–67.4)	39.8 (31.7–75.9)	<0.001
Fat mass (kg)	29.0 (1.9–86.0)	28.6 (1.9–45.6)	29.2 (8.3–86.0)	0.296
Body fat (%)	36.5 (2.9–64.2)	34.8 (2.9–49.7)	43.5 (17.5–64.2)	0.001
Obesity (%)	32 (40.0)	21 (41.2)	11 (37.9)	0.776
Sarcopenic obesity	18 (22.5)	15 (29.4)	3 (10.3)	0.050
Body surface area (m^2)	1.9 (1.4–2.5)	2.0 (1.5–2.4)	1.81 (1.42–2.52)	0.001
Liver volume				
Total liver volume (mL)	1680 (1067–3883)	1844 (1142–3883)	1537 (1067–2871)	0.003
Tumour volume (mL)	59 (0–2002)	67 (0–2002)	30 (0–290)	0.159
Non-tumour TLV (mL)	1571 (869–2852)	1721 (1052–2708)	1477 (869–2852)	0.017
Liver function				
LiMAx value (μg/kg/h)	326 (95–684)	337 (188–594)	301 (95–684)	0.086
LiMAx/ntTLV (μg/kg/h/mL)	0.20 (0.06–0.47)	0.19 (0.10–0.47)	0.20 (0.06–0.44)	0.908
Laboratory testing (normal)				
Bilirubin (mg/dL) (1.2)	0.7 (0.2–14.3)	0.7 (0.2–5.6)	0.7 (0.3–14.3)	0.540
ALT (U/L) (50)	32 (15–358)	34 (15–164)	32 (16–358)	0.829
AST (U/L) (38)	46 (14–224)	43 (16–211)	49 (14–224)	0.423
INR (ratio)	1.04 (0.82–1.45)	1.05 (0.82–1.45)	1.04 (0.90–1.24)	0.338
C-reactive protein (mg/L) (<5)	10 (1–187)	9 (1–187)	11 (1–172)	0.208
Creatinin (mg/dL) (0.6–1.1)	0.9 (0.5–3.8)	0.9 (0.5–3.8)	0.7 (0.5–1.5)	<0.001
Albumin (g/L) (35–52)	36.0 (19.5–45.8)	36.5 (19.5–45.8)	35.8 (22.6–42.7)	0.379
Background liver				
Metavir	1 (0–6)	1 (0–6)	1 (0–4)	0.242
Percentage cirrhosis (fibrosis score = 4)	8.3	13.2	0.0	—
NAS	1 (0–4)	1 (0–4)	1 (0–4)	0.435
Percentage severe steatosis (NAS ≥ 5)	0.0	0.0	0.0	—
Sinusoidal dilatation score	0 (0–3)	0 (0–3)	0 (0–3)	—
Percentage severe dilatation (Grade 3)	5.3	5.7	4.5	0.663
Percentage with severe background liver disease (Cirrhosis or NAS ≥ 5 or dilatation Grade 3)	10.5	14.3	4.5	0.243

L3 MI, L3 skeletal muscle index; AST, aspartate transaminase; ALT, alanine transaminase; ntTLV, non-tumour total liver volume; NAS, non-alcoholic fatty liver disease (NAFLD) activity score.

Correlations between liver function, liver volume and body composition

Because of irresectable disease, histopathologic examination was not performed in 23 (28.8%) patients. Another six (10.5) patients had severe background liver disease and were also excluded for assessing possible correlations between liver volume, liver function and body composition (*Figures* 1 and 2). Therefore, 51 (63.8%) patients without severe background liver disease were analysed. We found no correlation between the LiMAx test and ntTLV ($r = 0.06$, $P = 0.679$) (*Figure* 1). Weight ($r = -0.40$, $P = 0.003$), body surface area ($r = -0.32$, $P = 0.023$), estimated body-fat% ($r = -0.43$, $P < 0.002$) and BMI ($r = -0.47$, $P < 0.001$) showed a weak but significant negative correlation with the LiMAx test outcome. No correlation was found between the LiMAx test and L3 MI ($r = 0.09$, $P = 0.550$) or fat-free body mass ($r = 0.09$, $P = 0.538$) (*Figure* 2). A significant but weak correlation between the L3 MI and ntTLV was found ($r = 0.41$, $P = 0.003$). Moreover, fat-free body mass ($r = 0.60$, $P < 0.001$), body surface area ($r = 0.66$, $P < 0.001$), weight ($r = 0.58$, $P < 0.001$), height ($P = 0.60$, $r < 0.001$) and BMI ($r = 0.29$, P = 0.042) were all weak but significantly correlated with ntTLV (*Figure* 2).

Histology

Cirrhosis was present in 8.3% of all patients, and all were men. None of the patients had NASH (*Table* 2). However, 21.1% of the patients had borderline NASH (NAS = 3–4). Of the non-obese and obese, 13.9% and 38.1% were considered as having borderline NASH ($P = 0.036$). Obese patients also showed a significantly higher preoperative C-reactive protein level [19 (1–187) vs. 8 (1–95) mg/L, $P = 0.007$] (*Table* 3). Severe sinusoidal dilatation as an indication for sinusoidal obstruction syndrome was present in 5.3% of the patients.

Predictors of decreased liver function LiMAx value

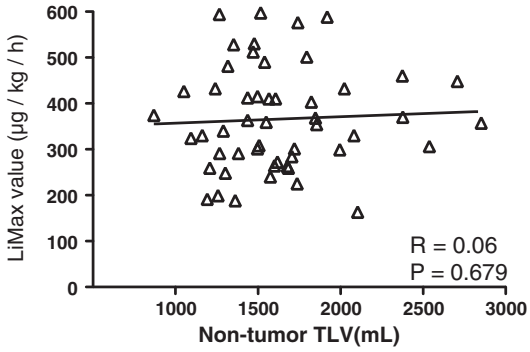
After univariable analysis, seven variables were considered significant negative prognostic factors for LiMAx liver function values, namely BMI ($P = 0.001$), obesity ($P = 0.013$), fat mass ($P < 0.001$), body-fat% ($P < 0.001$), body surface area ($P = 0.022$), INR (International Normalized Ratio) ($P = 0.012$)

Table 3 Features associated with sarcopenia, obesity and sarcopenic obesity

Patient characteristics	Sarcopenia			Obesity			Sarcopenic obesity		
	No ($n = 49$)	Yes ($n = 31$)	P	No ($n = 48$)	Yes ($n = 32$)	P	No ($n = 62$)	Yes ($n = 18$)	P
Median age (years)	65 (28–80)	67 (34–82)	0.277	65 (28–80)	66 (37–82)	0.180	65 (28–80)	72 (43–82)	0.029
Sex, number of men (%)	33 (67.3)	18 (58.1)	0.400	30 (62.5)	21 (65.6)	0.776	36 (58.1)	15 (83.3)	0.050
BMI (kg/m^2)	26.0 (19.6–46.4)	24.2 (18.7–33.0)	0.016	23.6 (18.7–32.1)	28.6 (21.8–46.4)	<0.001	24.3 (18.7–46.4–	26.6 (21.8–33.0)	0.324
Child–Pugh Grade A	83.7	79.3	0.627	85.4	76.7	0.327	85.5	68.8	0.120
Child–Pugh Grade B	16.3	20.7	0.627	14.6	23.3	0.327	14.5	31.3	0.120
MELD score	7 (6–20)	7 (6–19)	0.648	7 (6–20)	9 (6–19)	0.015	7 (6–20)	8 (6–19)	0.093
Liver volume									
Total liver volume (mL)	1762 (1111–3883)	1578 (1067–3290)	0.127	1592 (1067–3883)	1831 (1142–3290)	0.084	1656 (1067–3883)	1768 (1142–3290)	0.637
Tumour volume (mL)	28 (0–2002)	63 (0–709)	0.659	50 (0–2002)	72 (0–709)	0.481	50 (0–2002)	72 (0–709)	0.627
Non-tumour TLV (mL)	1678 (1052–2852)	1518 (869–2581)	0.215	1533 (869–2852)	1694 (1116–2685)	0.079	1562 (869–2852)	1638 (1116–2581)	0.541
Non-tumour TLV–body weight ratio (%)	2.02 (1.31–3.22)	2.28 (1.34–3.19)	0.181	2.24 (1.43–3.22)	1.97 (1.31–3.19)	0.062	2.06 (1.31–3.22)	2.16 (1.34–3.19)	1.000
Liver function									
LiMAx value (μg/kg/h)	324 (125–594)	327 (95–684)	0.917	358 (96–684)	295 (95–508)	0.018	333 (96–684)	313 (95–490)	0.378
LiMAx/ntTLV (μg/kg/h/mL)	0.19 (0.06–0.47)	0.21 (0.07–0.44)	0.707	0.22 (0.06–0.47)	0.17 (0.07–0.32)	0.004	0.20 (0.06–0.47)	0.18 (0.07–0.32)	0.246
Laboratory testing (normal)									
Bilirubin (mg/dL) (<1.2)	0.6 (0.2–14.3)	0.8 (0.3–5.6)	0.356	0.6 (0.2–4.3)	0.8 (0.3–14.3)	0.140	0.6 (0.2–14.3)	0.8 (0.3–5.6)	0.162
ALT (U/L) (<50)	35 (15–358)	32 (15–234)	0.615	32 (15–234)	39 (15–358)	0.516	36 (15–358)	29 (15–121)	0.341
AST (U/L) (<38)	45 (14–224)	46 (15–150)	0.311	45 (19–211)	49 (14–224)	0.965	46 (14–224)	40 (15–150)	0.313
INR (ratio)	1.06 (0.82–1.24)	1.04 (0.90–1.45)	0.700	1.03 (0.82–1.19)	1.06 (0.90–1.45)	0.038	1.04 (0.82–1.24)	1.05 (0.90–1.45)	0.190
C-reactive protein (mg/L) (<5)	9 (1–172)	11 (1–187)	0.107	8 (1–95)	19 (1–187)	0.007	9 (1–172)	14 (1–187)	0.034
Creatinine (mg/dL) (0.6–1.1)	0.9 (0.6–3.8)	0.8 (0.5–2.3)	0.130	0.8 (0.5–3.8)	0.9 (0.5–2.3)	0.623	0.8 (0.5–3.8)	0.9 (0.5–2.3)	0.373
Albumin (g/L) (35–52)	36.7 (24.3–45.8)	35.1 (19.5–45.8)	0.138	36.3 (22.6–45.8)	35.7 (19.5–43.1)	0.693	36.6 (22.6–45.8)	35.1 (19.5–41.7)	0.313

BMI, body mass index; ntTLV, non-tumour total liver volume.

Figure 1 Correlation between non-tumour total liver volume (TLV) and liver function (LiMAx).



and sinusoidal dilatation ($P = 0.019$). One additional borderline significant ($P \leq 0.15$) variable was selected for multivariable analysis, namely female sex ($P = 0.118$) (*Table* 4). Because of possible collinearity with body-fat%, five (borderline) significant negative prognostic factors were excluded for multivariable analysis, that is, BMI, obesity, fat mass, body surface area and NAS score. Using multivariable analysis, only body-fat% was identified as an independent negative prognostic factor influencing the liver function with a regression coefficient (standard error) of −3.2 (1.2), $P = 0.011$. Presence of chemotherapy-induced sinusoidal dilatation also showed a tendency to decrease liver function with a regression coefficient of −34.4 (17.7), $P = 0.057$.

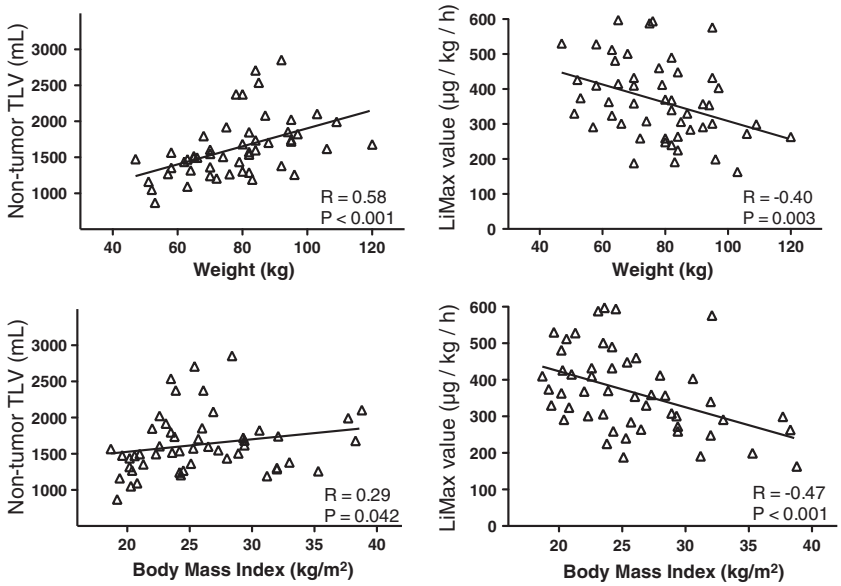
Outcome after liver resection

Complications and survival were evaluated in 57 (71.2%) patients who had undergone liver resection. Complications and major complications occurred in 19 (33.3%) and 17 (29.8%) patients, respectively. Most frequent complications were intra-abdominal abscess ($n = 8$, 14.0%), bile leakage ($n = 7$, 12.3%), biloma ($n = 4$, 7.0%), sepsis ($n = 4$, 7.0%) and intra-abdominal haemorrhage ($n = 3$, 5.3%). One patient developed post-resectional liver failure (1.8%), and another patient developed hepatic encephalopathy (1.8%). There were no differences in major complication rates between sarcopenic and non-sarcopenic patients ($P = 0.392$), obese and non-obese ($P = 0.530$) and patients with and without sarcopenic obesity ($P = 0.765$). Thirty-day and 90-day mortality rates were 3.5% ($n = 2$) and 10.5% ($n = 6$). There were also no significant differences in 90-day mortality rates between patients with and without sarcopenia ($P = 0.624$), obesity ($P = 0.486$) or sarcopenic obesity ($P = 0.487$).

Discussion

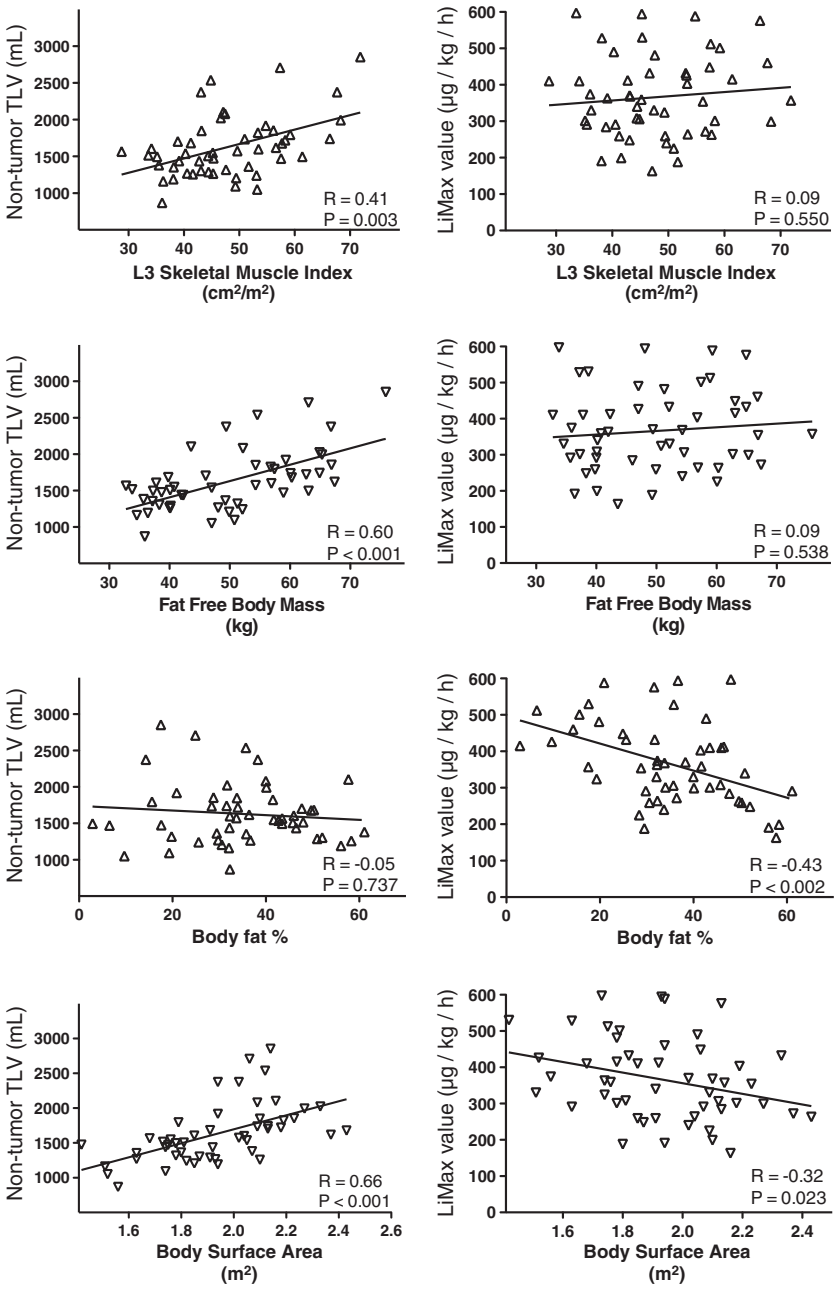
This study aimed to assess how liver function and volume relate to sarcopenia, obesity and sarcopenic obesity in patients undergoing extensive preoperative assessment prior to potential liver surgery. We showed that sarcopenic and sarcopenic-obese patients did not have diminished liver function compared with patients without sarcopenia or sarcopenic obesity, evidenced by comparable LiMAx values prior to surgery. Obese patients however showed significantly reduced LiMAx values compared with patients without obesity, and body-fat% was identified as an independent negative factor affecting liver function. Moreover, there were significant negative correlations between the LiMAx values and body-fat%,

Figure 2 Correlation between, on one hand, non-tumour total liver volume (TLV) (left) and, on the other hand, LiMAx values (right) and L3 skeletal muscle index, fat-free body mass, body-fat%, body surface area, weight and body mass index.



DOI: 10.1002/jcsm.12018

Figure 2. Continued.



body surface area, weight and BMI, which confirmed that obesity influenced liver function. Differences in ntTLV between sarcopenic and non-sarcopenic, obese and non-obese and sarcopenic-obese and patients without sarcopenic obesity did not reach statistical significance.

Recently, we demonstrated that liver volume was associated with the L3 MI, whereby sarcopenic patients had smaller ntTLVs compared with patients without sarcopenia.[11] In the present study, we found comparable ntTLVs in patients with and without sarcopenia. Nevertheless, the L3 MI was correlated with ntTLV, indicating that muscle wasting is somehow associated with smaller livers. As only patients at risk of developing postoperative liver failure (i.e. large resections) underwent a LiMAx test, a selection bias may have influenced our findings. Whereas the majority of patients in our previous study suffered from colorectal cancer liver metastases, more patients with intrahepatic cholangiocarcinoma or Klatskin tumours were included in the present study. The difference in metabolic behaviour could explain the

Table 4 Univariable and multivariable analysis of factors influencing LiMAx liver function values

	Univariable		Multivariable	
Prognostic factor	S (SE)	*P*	S (SE)	*P*
Age (years)	−0.1 (1.1)	0.952		
Female sex	−43.6 (27.6)	0.118	−19.0 (31.0)	0.543
Liver volume (100 mL)	−1.1 (3.1)	0.730		
Body mass index[a]	−8.3 (2.4)	0.001		
Obesity[a]	−67.0 (26.5)	0.013		
Fat-free body mass (kg)	1.3 (1.3)	0.330		
Fat mass (kg)[a]	−3.7 (0.9)	<0.001		
Body-fat%	−4.0 (1.0)	<0.001	−3.2 (1.2)	0.011
Body surface area (m^2)[a]	−139.8 (59.8)	0.022		
Sarcopenia	−6.2 (27.7)	0.823		
L3 index (cm^2/m^2)	1.4 (1.5)	0.357		
Sarcopenic obesity	−38.8 (32.0)	0.229		
AST (U/L)	0.1 (0.3)	0.659		
ALT (U/L)	0.1 (0.2)	0.691		
Bili (mg/dL)	−6.1 (7.6)	0.422		
INR (ratio)	−366.3 (142.7)	0.012	−53.9 (177.5)	0.763
Albumin (g/L)	−0.2 (2.5)	0.936		
Child–Pugh grade	1.9 (16.9)	0.909		
MELD score	−3.9 (4.5)	0.388		
Metavir score	−1.7 (8.9)	0.846		
NAS score[a]	−22.7 (11.4)	0.053		
Sinusoidal dilatation	−44.9 (18.5)	0.019	−34.4 (17.7)	0.057

SE, standard error; NAS, non-alcoholic steatohepatitis.
[a]Excluded from multivariable analysis due to possible collinearity.

absence of a significant difference between the ntTLVs of sarcopenic and non-sarcopenic patients and lower correlation coefficient between L3 MI and liver volume in the present study ($r = 0.41$ vs. $r = 0.64$ in the previous study). This study also assessed (LiMAx) liver function values in relation with sarcopenia. The present data do not support the idea that the increased post-operative morbidity, earlier recurrence and shorter survival in sarcopenic patients[10,12,16] could be explained by a decline in preoperative liver function. However, sarcopenia or muscle wasting remains an important factor negatively influencing outcome through hypercatabolism, hypoanabolism and, as a result, reduced reserves.

Only few studies have been performed on the effect of obesity on morbidity, overall survival and disease-free survival in the surgical treatment of primary or secondary liver tumours. Recently, Cauchy *et al.* showed that the metabolic syndrome even in absence of overt steatosis adversely affected outcome.[14] Also, in other fields of oncologic surgery, obesity has been identified as an important factor affecting outcome.[31–34] In the present study, body-fat%, body surface area, BMI and weight all showed a significant negative correlation with liver function LiMAx values. Moreover, body-fat% was identified as an independent factor negatively affecting the liver function. The significantly decreased LiMAx values in obese patients were accompanied by an increase in borderline NASH as could be expected.[35,36] We showed a trend that obese patients had larger livers and a positive correlation between liver volume and bodyweight, BMI and body surface area. Thus, obese patients have larger, although less functioning, livers probably due to deposition of fat, presumably increasing the risk of developing morbidity.

We found no disadvantageous consequences of sarcopenic obesity on liver volume or function. This is probably due to the small number of sarcopenic-obese patients and the heterogeneity of the indications for liver resection. However, it may be that sarcopenic-obese patients have an increased risk of post-operative morbidity as sarcopenia and obesity independently of one another proved to be risk factors for post-operative complications.[10,14,16] Differences in complication and mortality could however not be confirmed in this study, but this may relate to the sample size.

Body composition features have been calculated based on preoperative CT scans, body weight and length, and CT scanning is considered the gold standard for estimating muscle mass or lean body mass.[37] The use of body-fat% instead of BMI might be a better method of defining obesity as it prevents that muscular patients (with a BMI of >30) are incorrectly indicated as obese. Moreover, body-fat% is able to identify obesity in thin patients. The sample size and heterogeneity of our population are relative drawbacks of our study. Therefore, further investigations of the influence of body composition on short-term and long-term outcome after liver surgery are of major importance.

In conclusion, sarcopenia and sarcopenic obesity did not seem to influence liver volume or function negatively. However, obese patients have larger but less functional livers compared with those of non-obese patients. This indicates dissociation of function and volume most likely due to deposition of fat. Moreover, body-fat% seemed to be an independent factor affecting liver function negatively. The influence of obesity on morbidity after liver resection should therefore be taken into account as a part of routine preoperative assessment to prevent post-resectional liver failure especially in centres were no standard liver function evaluation is performed before major liver surgery.

Acknowledgements

The authors certify that they comply with the ethical guidelines for authorship and publishing of the Journal of Cachexia, Sarcopenia and Muscle (von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for authorship and publishing in the Journal of Cachexia, Sarcopenia and Muscle. *J Cachexia Sarcopenia Muscle* 2010;1:7–8.).

Conflict of interest

None declared.

References

1. de Haas RJ, Wicherts DA, Andreani P, Pascal G, Saliba F, Ichai P, *et al.* Impact of expanding criteria for resectability of colorectal metastases on short- and long-term outcomes after hepatic resection. *Ann Surg* 2011; **253**:1069–1079.
2. van der Pool AE, Lalmahomed ZS, de Wilt JH, Eggermont AM, Ijzermans JN, Verhoef C. Trends in treatment for synchronous colorectal liver metastases: differences in outcome before and after 2000. *J Surg Oncol* 2010; **102**:413–418.
3. Schreckenbach T, Liese J, Bechstein WO, Moench C. Posthepatectomy liver failure. *Dig Surg* 2012; **29**:79–85.
4. van den Broek MA, Olde Damink SW, Dejong CH, Lang H, Malago M, Jalan R, *et al.* Liver failure after partial hepatic resection: definition, pathophysiology, risk factors and treatment. *Liver Int : Off J Int Assoc Study Liver.* 2008; **28**:767–780.
5. Simmonds PC, Primrose JN, Colquitt JL, Garden OJ, Poston GJ, Rees M. Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. *Br J Cancer* 2006; **94**:982–999.
6. Stockmann M, Lock JF, Malinowski M, Niehues SM, Seehofer D, Neuhaus P. The LiMAx test: a new liver function test for predicting postoperative outcome in liver surgery. *HPB* (Oxford) 2010; **12**:139–146.
7. Stockmann M, Lock JF, Riecke B, Heyne K, Martus P, Fricke M, *et al.* Prediction of postoperative outcome after hepatectomy with a new bedside test for maximal liver function capacity. *Ann Surg* 2009; **250**: 119–125.
8. Schindl MJ, Redhead DN, Fearon KC, Garden OJ, Wigmore SJ. The value of residual liver volume as a predictor of hepatic dysfunction and infection after major liver resection. *Gut* 2005; **54**:289–296.
9. Ferrero A, Vigano L, Polastri R, Muratore A, Eminefendic H, Regge D, *et al.* Postoperative liver dysfunction and future remnant liver: where is the limit? Results of a prospective study. *World J Surg* 2007; **31**: 1643–1651.
10. Peng PD, van Vledder MG, Tsai S, de Jong MC, Makary M, Ng J, *et al.* Sarcopenia negatively impacts short-term outcomes in patients undergoing hepatic resection for colorectal liver metastasis. *HPB* (Oxford) 2011; **13**:439–446.
11. Dello SA, Lodewick TM, van Dam RM, Reisinger KW, van den Broek MA, von Meyenfeldt MF, *et al.* Sarcopenia negatively affects preoperative total functional liver volume in patients undergoing liver resection. *HPB* (Oxford) 2012.
12. Harimoto N, Shirabe K, Yamashita YI, Ikegami T, Yoshizumi T, Soejima Y, *et al.* Sarcopenia as a predictor of prognosis in patients following hepatectomy for hepatocellular carcinoma. *Br J Surg* 2013; **100**: 1523–1530.
13. Tan BH, Birdsell LA, Martin L, Baracos VE, Fearon KC. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. *Clin Cancer Res : Off J AmerAssoc Cancer Res* 2009; **15**:6973–6979.
14. Cauchy F, Zalinski S, Dokmak S, Fuks D, Farges O, Castera L, *et al.* Surgical treatment of hepatocellular carcinoma associated with the metabolic syndrome. *Br J Surg* 2013; **100**:113–121.
15. Visser M, van Venrooij LM, Vulperhorst L, de Vos R, Wisselink W, van Leeuwen PA, *et al.* Sarcopenic obesity is associated with adverse clinical outcome after cardiac surgery. *Nutr, Metab, Cardiovasc Dis : NMCD* 2012.
16. van Vledder MG, Levolger S, Ayez N, Verhoef C, Tran TC, Ijzermans JN. Body composition and outcome in patients undergoing resection of colorectal liver metastases. *Br J Surg* 2012; **99**:550–557.
17. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973;**60**:646–649.
18. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, *et al.* A model to predict survival in patients with end-stage liver disease. *Hepatology* (Baltimore, Md) 2001; **33**:464–470.
19. Roche SP, Kobos R. Jaundice in the adult patient. *Am Fam Physician* 2004; **69**: 299–304.
20. van der Vorst JR, van Dam RM, van Stiphout RS, van den Broek MA, Hollander IH, Kessels AG, *et al.* Virtual liver resection and volumetric analysis of the future liver remnant using open source image processing software. *World J Surg* 2010; **34**: 2426–2433.
21. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, *et al.* Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol* 2013;**31**:1539–1547.
22. Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med* 1987; **317**:1098.
23. Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, *et al.* Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol* 2008; **9**:629–635.
24. Baumgartner RN, Wayne SJ, Waters DL, Janssen I, Gallagher D, Morley JE. Sarcopenic obesity predicts instrumental activities of daily living disability in the elderly. *Obes Res* 2004; **12**:1995–2004.
25. Davison KK, Ford ES, Cogswell ME, Dietz WH. Percentage of body fat and body mass index are associated with mobility limitations in people aged 70 and older from NHANES III. *J Am Geriatr Soc* 2002; **50**:1802–1809.
26. Prado CM, Wells JC, Smith SR, Stephan BC, Siervo M. Sarcopenic obesity: a Critical appraisal of the current evidence. *Clin Nutr* (Edinburgh, Scotland) 2012; **31**: 583–601.
27. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. *Hepatology* (Baltimore, Md) 1996; **24**:289–293.
28. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, *et al.* Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology* (Baltimore, Md) 2005; **41**:1313–1321.
29. Rubbia-Brandt L, Audard V, Sartoretti P, Roth AD, Brezault C, Le Charpentier M, *et al.* Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. *Ann Oncol* 2004; **15**:460–466.
30. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;**240**:205–213.
31. Moon HG, Ju YT, Jeong CY, Jung EJ, Lee YJ, Hong SC, *et al.* Visceral obesity may affect oncologic outcome in patients with colorectal cancer. *Ann Surg Oncol* 2008; **15**:1918–1922.
32. Ojima T, Iwahashi M, Nakamori M, Nakamura M, Naka T, Ishida K, *et al.* Influence of overweight on patients with gastric cancer after undergoing curative gastrectomy: an analysis of 689 consecutive cases managed by a single center. *Arch Surg* 2009; **144**:351–358; discussion 8.
33. Benns M, Woodall C, Scoggins C, McMasters K, Martin R. The impact of obesity on outcomes following pancreatectomy for malignancy. *Ann Surg Oncol* 2009; **16**:2565–2569.
34. van Roermund JG, van Basten JP, Kiemeney LA, Karthaus HF, Witjes JA. Impact of obesity on surgical outcomes following open radical prostatectomy. *Urol Int* 2009; **82**:256–261.
35. Bedogni G, Miglioli L, Masutti F, Tiribelli C, Marchesini G, Bellentani S. Prevalence of and risk factors for nonalcoholic fatty liver disease: the Dionysos nutrition and liver study. *Hepatology* 2005; **42**:44–52.
36. Kim HK, Park JY, Lee KU, Lee GE, Jeon SH, Kim JH, *et al.* Effect of body weight and lifestyle changes on long-term course of nonalcoholic fatty liver disease in Koreans. *Am J Med Sci* 2009; **337**:98–102.
37. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, *et al.* Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. *Age Ageing* 2010; **39**:412–423.