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ORIGINAL ARTICLE

Body fat composition determines outcomes before and after liver transplantation in patients with cirrhosis

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Abstract

Cachexia occurs in late stages of liver cirrhosis, and a low-fat mass is potentially associated with poor outcome. This study compared different computed tomography (CT)–derived fat parameters with respect to its prognostic impact on the development of complications and death before and after liver transplantation. Between 2001 and 2014, 612 patients with liver cirrhosis without hepatocellular carcinoma listed for liver transplantation met the inclusion criteria, including abdominal CT scan (±200 days to listing). A total of 109 patients without cirrhosis served as controls. The subcutaneous fat index (SCFI), the paraspinal muscle fat index, and the visceral fat index were assessed at L3/L4 level and normalized to the height (cm^2/m^2). Data were collected and analyzed retrospectively. Low SCFI was associated with a higher rate of ascites and increased C-reactive protein levels ($p < 0.001$). In addition, multivariate Cox regression analysis adjusting for sex, age, body mass index (BMI), and Model for End-Stage Liver Disease showed that decreasing SCFI was also associated with an increased risk of cirrhosis-related complications ($p = 0.003$) and death on the transplant wait list ($p = 0.013$). Increased paraspinal and visceral fat were not only positively correlated with creatinine levels ($p < 0.001$), BMI, and metabolic comorbidities (all $p < 0.001$) before transplantation, but also predictive for 1-year mortality after transplantation. *Conclusion:* The distribution of body fat is a major determinant for complications and outcome in cirrhosis before and after liver transplantation.

INTRODUCTION

Liver cirrhosis is a major chronic disease that ranges among the 10 most important causes of death in Europe.[1–3] The treatment of underlying liver diseases effectively prevents the development of complications in a proportion of patients, but some progress to later disease stages in which liver transplantation is the only

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therapeutic option.[4] To reduce the number of deaths and to tailor individual management strategies, it is essential to identify patients at high risk for fatal outcomes and disease-related complications among a cohort with very heterogeneous clinical phenotype, ranging from well-compensated mild cirrhosis to severely decompensated patients with additional organ failures, so-called acute-on-chronic liver failure (ACLF).

The indication and urgency for liver transplantation depends on multiple aspects, of which the severity of liver disease is one major criterion. In late stages of cirrhosis, liver dysfunction develops with high Model for End-Stage Liver Disease (MELD) score and other disease-related complications such as hepatorenal syndrome (HRS), ascites or hepatic encephalopathy (HE), indicating an elevated likelihood of death.[5,6] However, the current MELD-based allocation system does not reflect the true survival probability in some subgroups such as patients with refractory ascites or ACLF, in whom the MELD score is less predictive.[7] The second aspect that needs to be considered during assessment for liver transplantation strongly relates to the likelihood of success after transplantation, which is majorly defined by the risk of posttransplant complication.[4] However, its prediction remains inaccurate also because its genesis is less well defined. Therefore, new prognostic markers might help to prioritize patients on the wait list and to avoid fatal complications before and after liver transplantation.

Chronic liver disease and cirrhosis are associated with alterations in body composition and cachexia. Muscle wasting is a well-known phenomenon associated with late stages of liver disease,[8] but the body fat distribution might also be a marker for disease severity and outcome in patients with liver cirrhosis. Indirect impedance-based techniques revealed that wasting and loss of body fat is a typical feature of liver cirrhosis.[9,10] Computed tomography (CT) or magnetic resonance imaging–based techniques have been allocating a high risk of liver-related complications to those with low muscle fat or subcutaneous fat mass, especially in female patients.[11,12] However, the link between body fat composition and occurrence of individual complications tends to be more controversial, as individual fat compartments might impact differently on the development of disease-related complications.[11,13,14]

Alterations in body fat composition might also have a persisting impact on patients' disease course even beyond the time point of liver transplantation. Metabolic complications become more prevalent during maintenance after transplantation,[15] and, indeed, it has been shown that obesity and a metabolic syndrome is a negative predictor for complications and outcome after liver transplantation.[16]

These observations emphasize the complexity of mechanisms linking body fat composition with disease severity in liver cirrhosis and success after liver transplantation,[17] and making high demands on body fat composition as a prognostic marker in this cohort. Therefore, we performed a retrospective study assessing the nutritional status of patients listed for liver transplantation by measuring three CT-derived fat parameters to evaluate its impact on clinical outcomes before and after liver transplantation. Herein, we could show that a decreased subcutaneous fat is associated with the development of disease-related complications and death in patients with liver cirrhosis before transplantation, whereas an increased muscle fat mass and visceral fat mass enhances the likelihood of death after transplantation.

METHODS

Study design and population

Between March 2001 and September 2014, a total of 1326 patients were evaluated for liver transplantation in the University Hospital Leipzig. Of those, 612 patients with cirrhosis and without hepatocellular carcinoma who received an abdominal CT scan at the time of transplant assessment ± 200 days were included. Patients younger than 18 years, with previous liver transplantation and those with insufficient data were excluded (Figure S1). A total of 109 patients without liver diseases with CT scan as part of their diagnostic work-up after polytrauma served as a control cohort. Clinical data including age, gender, causes of cirrhosis, history of cirrhosis–associated complications and co-morbidities at baseline, as well as the development of cirrhosis-associated complications, biochemistry data and patients' survival status during follow-up, were retrieved retrospectively from patients' records.

Assessment of body fat content by CT

The body fat content was determined using CT scans. Two trained observers (interrater agreement: Cohen's Kappa coefficient of 0.89; $p < 0.001$) analyzed the CT images. SliceOmatic V 5.0 software (Tomovision, Montréal, Canada) was used to analyze an axial section of the abdomen at the level of the spinal segment L3/L4. SliceOmatic uses previously reported Hounsfield unit (HU) thresholds to quantify different tissue compartments in cross-sectional images. The subcutaneous fat index (SCFI), paraspinal intramuscular fat index (PSFI), and visceral fat index (VFI) was identified and quantified using HU thresholds of −150 to −30. The SliceOmatic V4.3 software automatically calculated the cross-sectional areas (cm^2). Normalization to body height was performed by dividing the fat area by body height in square meters.

Statistical analysis

Statistical analysis was performed using SPSS 22 software (SPSS Inc., Chicago, IL). Categorical variables were displayed as frequency (%), continuous variables as mean ± SD, or median (range), as appropriate. A two-sided *p*-value of $p \leq 0.05$ implicated statistical significance. Group comparisons for categorical variables were performed using the χ^2-test and for metric variables using the Mann-Whitney U test. For more than two groups, data were analyzed by one-way analysis of variance followed by a Dunnett's *post hoc* analysis for unequal variances. About one third of patients was transplanted within 1 year after listing. We used Cox regression analysis adjusting for age, body mass index [BMI], and MELD score to assess factors modifying the cause-specific hazard functions, censoring time-to-event endpoints at the time of transplant, including transplantation itself.

To define patients with high-fat and low-fat mass indices, the cohort was divided based on tertiles. As calculated by Cox regression modeling based on the metric variable, a decreased SCFI was associated with an increased risk for complications and death before transplantation; therefore the lower tertile was chosen as the cutoff. VFI and PSFI showed higher values associated with worsened outcome after liver transplantation. Therefore, the upper tertile was chosen as the cutoff. Taking into account that there are gender-related fat mass differences, we defined cutoffs individually for men and women as follows: PSFI male, 4.04 cm²/m²; PSFI female, 4.93 cm²/m²; SCFI male, 38.44 cm²/m²; SCFI female, 39.58 cm²/m²; VFI male, 58.61 cm²/m²; and VFI female, 49.97 cm²/m².

RESULTS

Patients' baseline characteristics

The mean age of patients with liver cirrhosis was 52 years, which was significantly younger than the control group (61.7 years; $p < 0.001$). Of 612 patients with liver cirrhosis, 63.6% had alcohol-associated liver disease and 66.7% were male (Tables 1 and 2). There was no significant difference in terms of gender or BMI between patients with cirrhosis and the control group. Patients with cirrhosis were primarily Child Pugh B (51.2%), the mean MELD score was 17 ± 7.1. Further baseline clinical and biochemical data are provided in Table 2. Out of 612 patients, 264 patients received liver transplantation. In total, 67% of patients suffered from ascites, 80.8% from gastric and/or esophageal varices, and 27.7% had a history of variceal bleeding. Transjugular intrahepatic portosystemic shunt (TIPS) was implanted in 6.7%. At least one episode of HE occurred in 83.2% in their past medical history; 18.6% were at least once treated for spontaneous bacterial peritonitis (SBP); and 20% had a history of bacterial infections.

TABLE 1 Demographics for patients with cirrhosis (derivation cohort) on the wait list for transplantation and for patients after polytraumatic accidents (group comparison with Mann-Whitney U test)

Parameter	Cirrhosis n = 612	Polytrauma n = 109	Level of significance
Age (years)	52 ± 9.1	61.7 ±18	$p < 0.001$
Gender	♂ 408 (66.7%) ♀ 204 (33.3%)	♂ 75 (68.8%) ♀ 34 (31.2%)	$p = 0.661$
Body height (cm)	171.7 ± 9.1	171.8 ± 9.1	$p = 0.998$
Body weight (kg)	78 ± 16.8	79.2 ± 15.4	$p = 0.535$
BMI (kg/m^2)	26.3 ± 4.8	26.9 ± 4.5	$p = 0.226$

Fat indices and severity of liver disease

PSFI, SCFI, and VFI were significantly lower in patients with cirrhosis compared to controls (PSFI: 3.9 ± 2.3 cm²/m² vs. 5.3 ± 3.5 cm²/m² [$p = 0.002$]; SCFI: 56.7 ± 32.2 cm²/m² vs. 69.2 ± 35.4 cm²/m² [$p = 0.002$]; and VFI: 47.6 ± 24 cm²/m² vs. 61.3 ± 33.8 cm²/m² [$p < 0.001$]) (Figure 1; Table S1). Patients with liver cirrhosis who suffered from refractory ascites or who had a history of SBP showed lower SCFI values (refractory ascites: 45 ± 29.3 cm²/m² vs. no ascites 67.2 ± 32.3 cm²/m² [$p < 0.001$]; SBP: 49.3 ± 30.7 cm²/m² vs. no SBP 58.7 ± 31.2 cm²/m² [$p = 0.008$]), whereas the PSFI and VFI were no different.

In contrast, patients with Child-Pugh score C had a higher PSFI than patients with Child Pugh Score A (3.3 ± 1.8 cm²/m² vs. 4.3 ± 2.6 cm²/m² [$p = 0.028$]). There was neither a significant difference between Child Pugh A and B nor between Child Pugh B and C. Neither a history of HE nor TIPS was associated with alterations of fat indices. However, there were slight differences of fat indices between genders (Figures S2–S4, Table S1A–C).

Fat indices and development of complications or death before liver transplantation

Univariate Cox regression analysis showed a decreased risk of death within 1 year after listing with a higher SCFI (hazard ratio [HR] = 0.992 [0.985–1.000], $p = 0.043$), whereas an increased PSFI was associated with higher risk (HR = 1.081 [1.001–1.167], $p = 0.046$) (Table S2). Multivariate Cox regression analysis adjusted to age, BMI, MELD score, white blood count, and gender revealed that the SCFI remained as an independent predictor of death before liver transplantation with a HR of 0.984 (0.971–0.997; $p = 0.013$) (Table

TABLE 2 Baseline characteristics of patients with liver cirrhosis in this study

Etiology of liver disease (n = 612)	
• ALD	389 (63.6%)
• Viral (hepatitis B and C)	50 (8.2%)
• NASH	30 (4.9%)
• Others	143 (23.4%)
MELD score (n = 595)	17 ± 7.1
• 6–11 points	136 (22.9.0%)
• 12–24 points	375 (63%)
• 25–40 points	84 (14.1%)
Child-Pugh classification (n = 410)	
• Class A	52 (12.7%)
• Class B	210 (51.2%)
• Class C	148 (36.1%)
Bilirubin (μmol/l)	48.9 (4.6–887.8)
Creatinine (μmol/l)	82 (32–868)
GFR (ml/min) (MDRD-Formel)	82.4 (6.4–251.6)
INR	1.45 (0.9–5.1)
Albumin (g/l)	32.9 (12.6–52.8)
WBC (exp9/l)	6.1 (1.2–45.2)
CRP (mg/dl)	9.7 (0.2–218.5)
Platelet count (exp9/l)	102.5 (12–1180)
Ascites (n = 555)	
• No ascites	183 (33%)
• Mild to moderate ascites	144 (25.9%)
• Massive	228 (41.1%)
TIPS at evaluation	
Yes/No	41 (6.7%)/571 (93.3%)
History of bacterial Infections (n = 643)	
Yes/No	99 (20%)/395 (80%)
History of SBP (n = 643)	
Yes/No	92 (18.6%)/403 (81.4%)
History of HE (n = 333)	
Yes/No	252 (83.2%)/51 (16.8%)
History of hepatorenal syndrome (n = 650)	
Yes/No	109 (17.8%)/393 (78.3%)
Varices (n = 724)	
Yes/No	449 (80.8%)/107 (19.2%)
History of variceal bleeding (n = 664)	
Yes/No	142 (27.7%)/371 (72.3%)
Diabetes mellitus (n = 556)	
Yes/No	187 (33.6%)/369 (66.4%)
Arterial hypertension (n = 536)	
Yes/No	219 (40.9%)/317 (59.1%)
Obesity (n = 524)	
Yes/No	107 (20.4%)/417 (79.6%)
Coronary heart disease (n = 537)	
Yes/No	31 (5.8%)/506 (94.2%)

Note: Values are displayed as median (range) or number (%), respectively. The numbers in brackets represent the number of patients providing information.

Abbreviations: ALD, alcohol-associated liver disease; CRP, C-reactive protein; GFR, glomerular filtration rate; HE, hepatic encephalopathy; INR, international normalized ratio; NASH, nonalcoholic steatohepatitis.

S2; Figure 2). This result was also confirmed after exclusion of patients with nonalcoholic steatohepatitis (NASH) cirrhosis (n = 30) or patients with TIPS (n = 41) (Table S2). After including the paraspinal muscle index (as published by Engelmann et al.[8]) into the multivariate regression model, only the paraspinal muscle index remained as an independent predictor of 1-year mortality, whereas the SCFI cost its significance (Figure S5).

Furthermore, the association between fat indices and occurrence of cirrhosis-associated complications within 1 year after listing for liver transplantation was calculated by univariate Cox regression analysis. Accordingly, higher SCFI values were associated with a reduced risk of developing any complication (HR = 0.993 [0.989–0.998], $p = 0.005$), bacterial infection (HR = 0.989 [0.983–0.995], $p < 0.001$), SBP (HR = 0.988 [0.979–0.998], $p = 0.015$), and variceal bleedings (HR = 0.983 [0.970–0.995], $p = 0.007$) but not with the development of HRS or HE episodes. The PSFI showed an opposite risk correlation with complications being higher with increased PSFI values for any complication (HR = 1.080 [1.024–1.140], $p = 0.005$) and HE (HR = 1.117 [1.043–1.197], $p = 0.002$). After multivariate analysis adjusted to age, BMI, MELD score and gender, only the SCFI remained as independent predictor for any complication (HR = 0.989 [0.981–0.996], $p = 0.003$), bacterial infection (0.984 [0.974–0.994], $p = 0.001$), and SBP (0.970 [0.955–0.984], $p < 0.001$) (Table S3; Figure 2).

To define patients with low-fat and high-fat mass indices, the cohort was divided based on index's tertiles. A decreasing SCFI was associated with an increasing risk of complication and death before liver transplantation. Therefore, the lower SCFI tertile was chosen as the cutoff (male: 38.44 cm²/m²; female: 39.58 cm²/m²). Patients with a low SCFI had an increased risk of death on the wait list (HR = 1.490 [0.966, 2.300], $p = 0.072$) and an increased risk of developing complications before liver transplantation (HR = 1.403 [1.057, 1.862], $p = 0.019$) (Figure 3). They suffered more often from ascites (80.4% vs. 62% [$p < 0.001$]) and had higher C-reactive protein (CRP) levels (14 vs. 7.2 mg/dl [$p < 0.001$]). The subgroup of patients with a high SCFI suffered more often from diabetes mellitus (35.3% vs. 22%; $p < 0.001$) and had a higher BMI (26.7 vs. 22.4 kg/m²; Table 3).

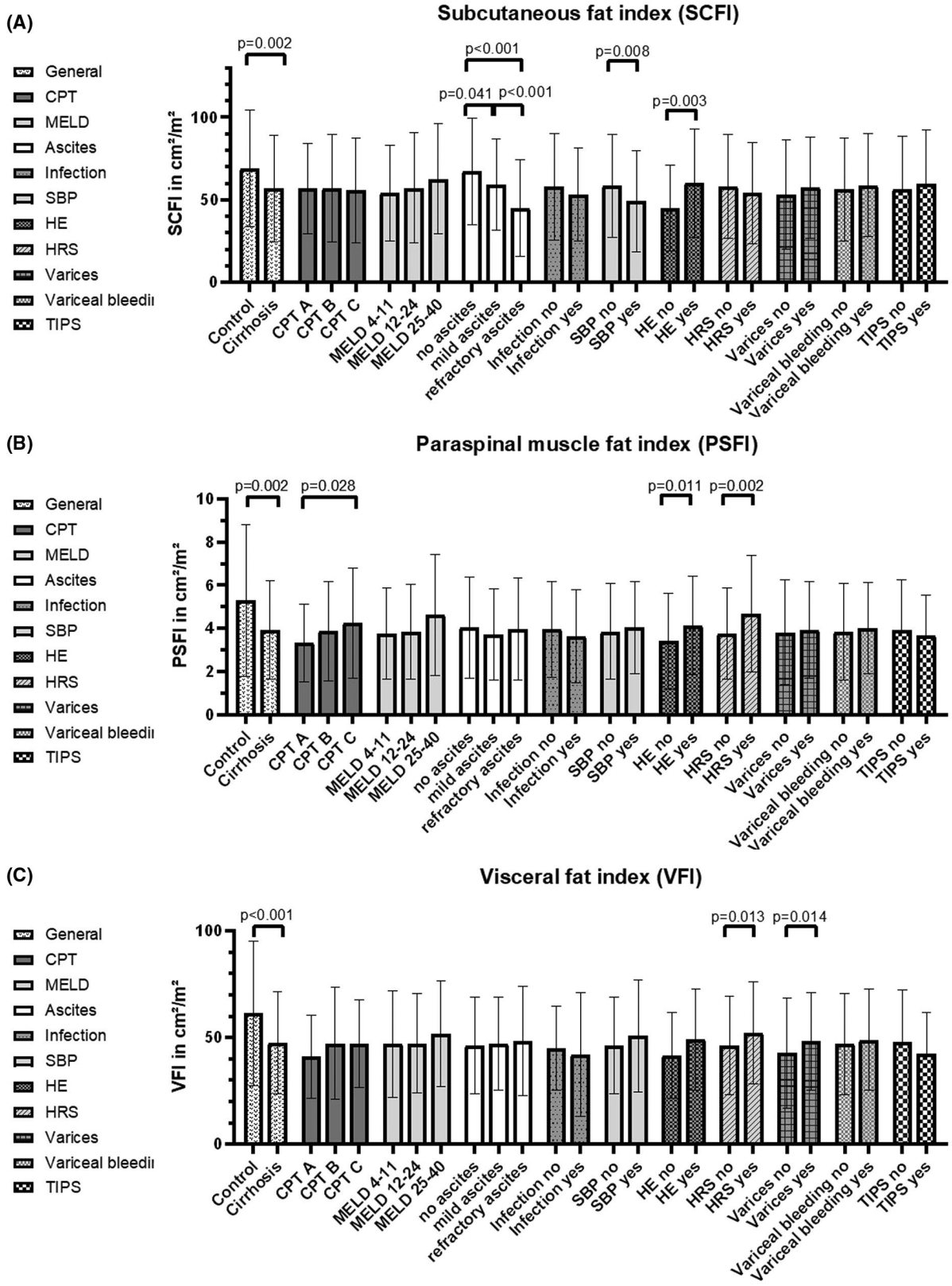

FIGURE 1 According to Table S1C, different computed tomography (CT)–derived fat parameters were obtained at baseline. Groups were compared by Mann-Whitney U test or one-way analysis of variance and *post hoc* Dunnett's test (unequal variances), depending on the number of groups according to subcutaneous fat index (SCFI) (A), paraspinal muscle fat index (PSFI) (B), and visceral fat index (VFI) (C). CPT, Child-Pugh Turcotte; HE, hepatic encephalopathy; HRS, hepatorenal syndrome; MELD: Model for End-Stage Liver Disease; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt

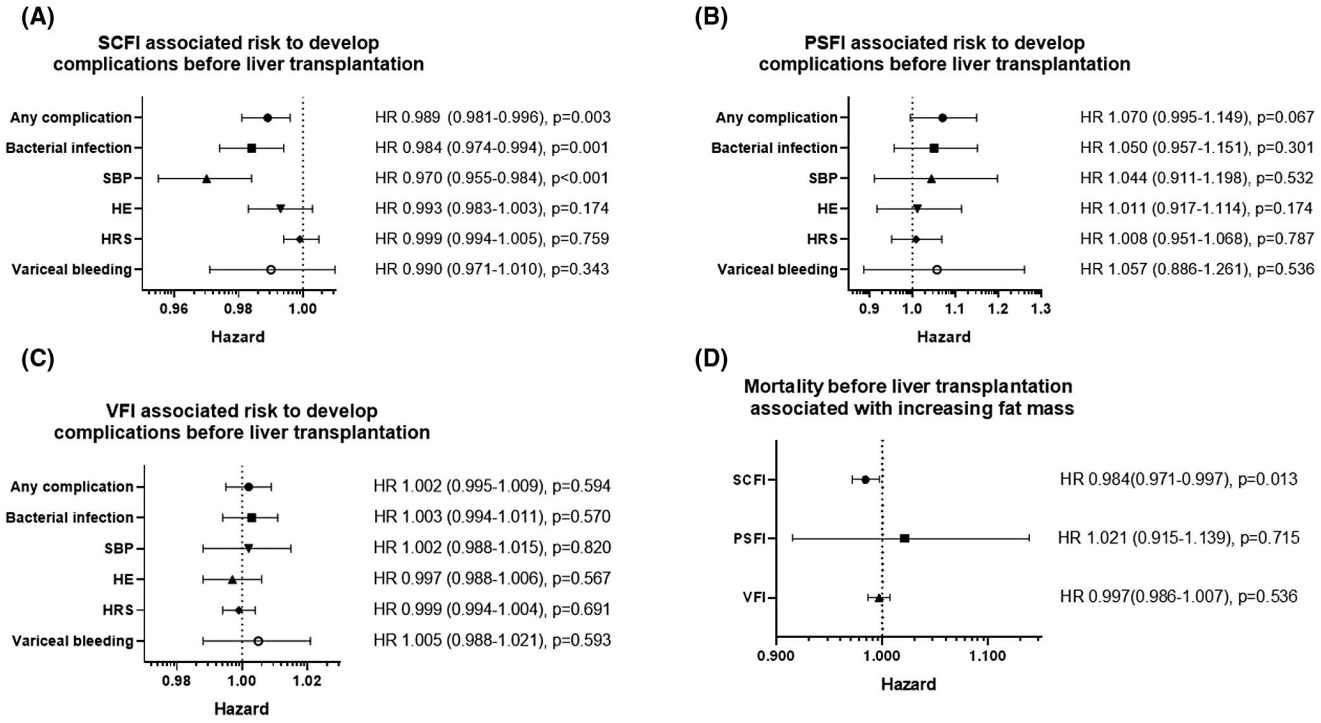

FIGURE 2 Multivariate Cox regression analysis of complications and 1-year-mortality before liver transplantation. (A–C) After multivariate Cox regression analysis, adjusting fat parameters to age, body mass index (BMI), MELD and gender, the SCFI remained as an independent predictor for complications, particularly bacterial infections and SBP. All other parameters were not associated with the development of cirrhosis-related complications before liver transplantation. (D) After multivariate Cox regression analysis, adjusting fat parameters to age, BMI, MELD, white blood count (WBC) and gender, the SCFI remained as independent predictor for death within 1 year before liver transplantation (Table S2). HR, hazard ratio

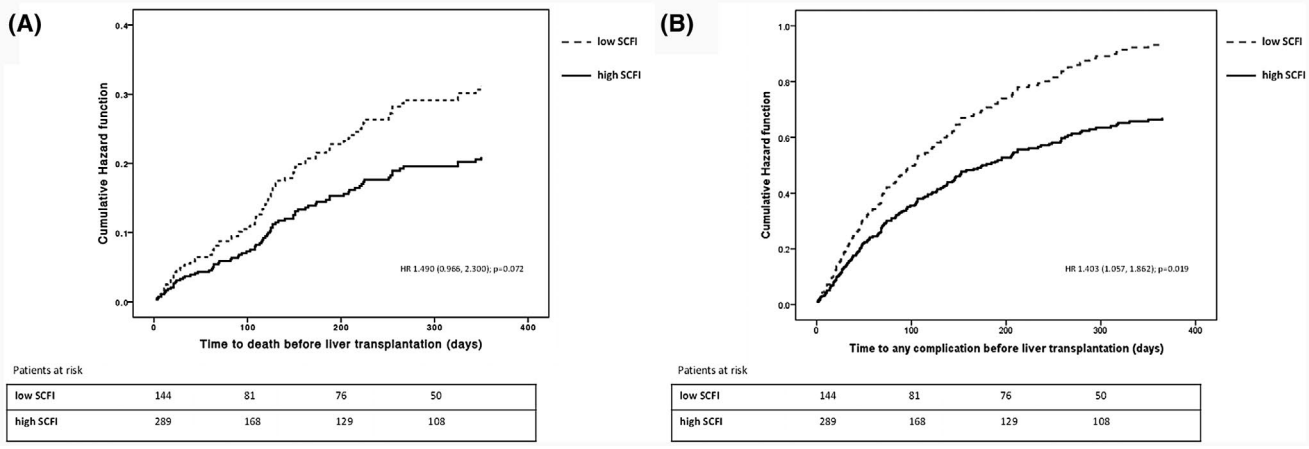

FIGURE 3 One-year mortality and development of complications before liver transplantation of patients with a high or low SCFI. Patients were divided into a cohort of low-fat and high-fat mass according to the gender-dependent, individual lower tertile (SCFI male: 38.44; SCFI female: 39.58). A lower SCFI was associated with a higher risk for death (A) and particularly complication (B) before live transplantation

Fat indices and the risk of death after liver transplantation

Univariate Cox regression model showed a higher risk of death within 1 year with an increased PSFI (HR = 1.141 [1.029–1.264], p = 0.012) and VFI (HR = 1.011 [1.001–1.020], p = 0.031). Multivariate Cox regression adjusting to age, BMI, MELD score, and gender also showed that a higher PSFI or VFI was associated with an increased risk of death after liver transplantation (PSFI HR = 1.188 [1.032–1.368], p = 0.017; VFI HR = 1.014 [1.001–1.027], p = 0.037) (Figure 4). After

TABLE 3 Patients were divided into a cohort of low-fat and high-fat mass according to the gender-dependent, individual high-risk tertile (PSFI male: 4.04 cm²/m²; PSFI female: 4.93 cm²/m²; SCFI male: 38.44 cm²/m²; SCFI female: 39.58 cm²/m²; VFI male: 58.61 cm²/m²; VFI female: 49.97 cm²/m²)

Baseline	**SCFI**			**PSFI**			**VFI**		
Subgroup	**Low**	**High**	***p***	**Low**	**High**	***p***	**Low**	**High**	***p***
MELD	15 (6–40)	15 (6–40)	0.232	15 (6–40)	17 (5–39)	0.101	15 (6–40)	16.5 (7–40)	0.128
Ascites	**119 (80.4%)**	**184 (62%)**	**<0.001**	253 (68.9%)	133 (66.5%)	0.552	254 (68.3%)	129 (67.2%)	0.792
HE	33 (24.1%)	84 (29.9%)	0.215	100 (29.3%)	64 (35%)	0.184	96 (28.3%)	66 (36.3%)	0.062
Varices	108 (75.5%)	242 (82.6%)	0.082	293 (80.5%)	154 (81.1%)	0.875	288 (78.9%)	156 (93.9%)	0.163
Bilirubin (µmol/l)	44.2 (4.6–649.5)	45.3 (5.5–887.8)	0.146	48 (4.6–887.8)	52.8 (4.6–688.8)	0.759	50.7 (4.6–887.8)	46.8 (5.5–688.8)	0.665
Creatinine (µmol/l)	84.5 (34–509)	79 (32–868)	0.563	**76 (32–868)**	**96 (45–577)**	**<0.001**	**76 (32–868)**	**93.5 (41–739)**	**<0.001**
INR	1.4 (0.9–3.86)	1.4 (0.93–5.09)	0.227	1.4 (0.93–5.09)	1.38 (0.9–3.5)	0.615	1.4 (0.9–5.09)	1.36 (0.93–3.5)	0.554
WBC ($\times 10^9$/l)	6.1 (1.2–20.3)	5.8 (1.3–36)	0.330	**5.8 (1.2–36)**	**6.4 (1.3–25.5)**	**0.023**	**5.8 (1.2–20.8)**	**6.5 (1.3–36)**	**0.007**
CRP (mg/l)	**14 (0.72–218.5)**	**7.2 (0.15–144-6)**	**<0.001**	9.2 (0.15–218.5)	9.6 (0.47–127.8)	0.096	9.24 (0.15–218.5)	8.4 (0.47–127.8)	0.122
Diabetes mellitus	**31 (22%)**	**103 (35.3%)**	**0.005**	**101 (28.1%)**	**84 (43.3%)**	**<0.001**	**97 (27%)**	**89 (46.6%)**	**<0.001**
AHT	47 (34.1%)	112 (39.3%)	0.297	**122 (34.9%)**	**96 (51.9%)**	**<0.001**	**118 (34%)**	**100 (54.3%)**	**<0.001**
CKD	41 (28.5%)	100 (33.4%)	0.293	**105 (28.4%)**	**81 (41.5%)**	**0.002**	**104 (28.3%)**	**81 (42%)**	**0.001**
BMI (kg/m²)	**22.4 (15.4–33.8)**	**26.7 (17.4–49)**	**<0.001**	**24.4 (15.4–37)**	**27.7 (20.9–49)**	**<0.001**	**24.4 (15.4–41.7)**	**27.8 (21.2–49)**	**<0.001**
Age (years)	**50 (21–71)**	**54 (27–71)**	**0.001**	**50 (21–70)**	**57 (27–71)**	**<0.001**	**51 (21–71)**	**54.5 (27–71)**	**<0.001**

Note: Groups were compared by Mann-Whitney U test or one-way analysis of variance and *post hoc* Dunnett's test (unequal variances), depending on the number of groups. *p*-Values are displayed if significant in comparison to the control group.

Abbreviations: AHT, arterial hypertension; CKD, chronic kidney disease.

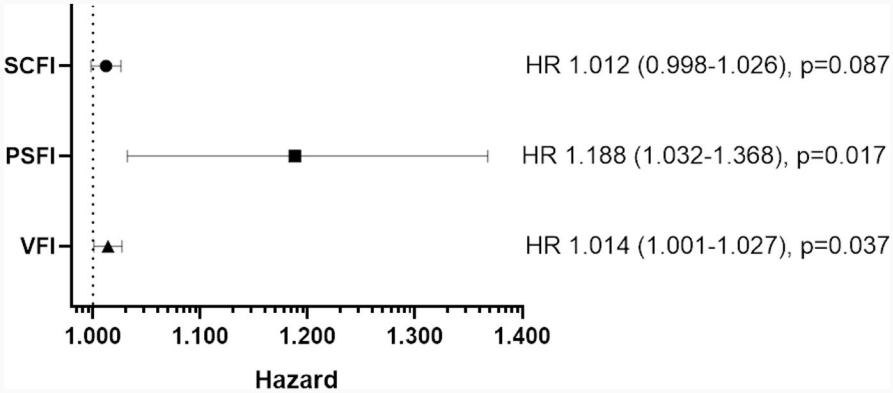

FIGURE 4 Mortality after liver transplantation according to different CT-derived fat parameters. After multivariate Cox regression analysis, adjusting fat parameters to age, BMI, MELD and gender, the VFI and PSFI could be identified as an independent predictor for the occurrence of death within 1 year after liver transplantation (Table S2)

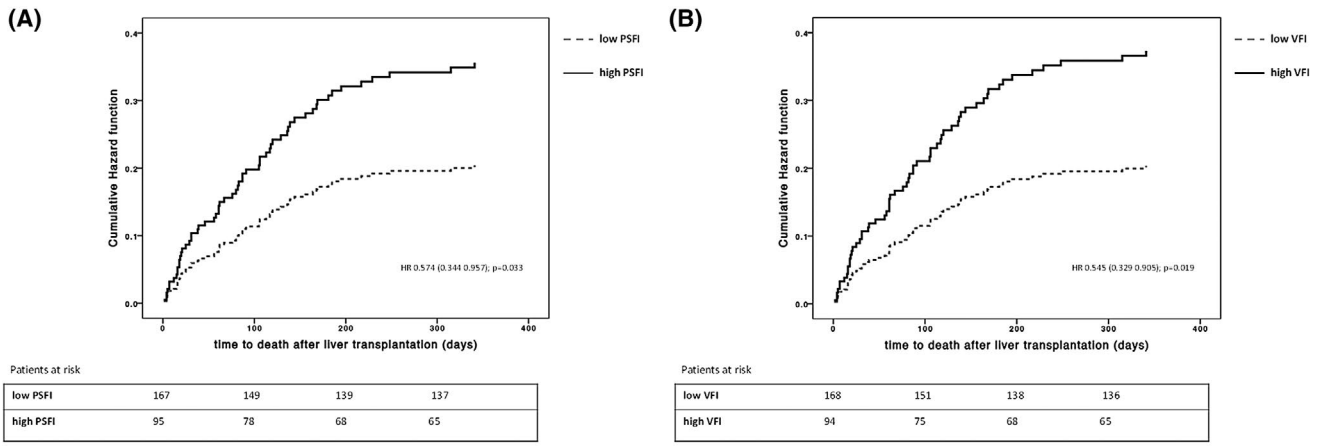

FIGURE 5 One-year mortality of patients with a high or low PSFI and VFI. Patients were divided into a cohort of low-fat and high-fat mass according to the gender-dependent, individual upper tertile (PSFI male: 4.04; PSFI female: 4.93; VFI male: 58.61; FRI female: 49.97). The PSFI (A) and VFI (B) inversely correlated with the posttransplant 1-year-survival

exclusion of patients with NASH (n = 30) or patients with TIPS (n = 41), the PSFI remained as independent prognosticator, whereas the VFI was lacking significance (Table S2).

Due to the positive correlation between risk of complications and PSFI and VFI values, the upper tertile was chosen as the cutoff to define high and low fatty indices (PSFI male: 4.04 cm^2/m^2; PSFI female: 4.93 cm^2/m^2; VFI male: 58.61 cm^2/m^2; and VFI female: 49.97 cm^2/m^2). Patients with high PSFI (HR = 1.743 [1.045, 2.905], p = 0.033) and high VFI (1.834 [1.105, 3.043], p = 0.019) were more likely to die after liver transplantation (Figure 5). Patients with a high PSFI suffered more often from diabetes mellitus (43.3% vs. 28.1%, p < 0.001), arterial hypertension (51.9% vs. 34.9%, p < 0.001), and chronic kidney disease (41.5% vs. 28.4%, p = 0.002). In addition, they had a higher BMI (27.7 kg/m^2 vs. 24.4 kg/m^2, p < 0.001), and they were older (57 years vs. 50 years, p < 0.001). Likewise, patients with a high VFI suffered more often from diabetes mellitus (46.6% vs. 27%, p < 0.001), arterial hypertension (54.3 vs. 34%, p < 0.001), and chronic kidney disease (42% vs. 28.3%, p = 0.001). They also had a higher BMI (27.8 kg/m^2 vs. 24.4 kg/m^2, p < 0.001), and they were also older (54.5 years vs. 51 years, p < 0.001) (Table 3).

A difference in severity of liver disease at transplantation between patients with high and low fat at evaluation might explain the effect on posttransplant outcome. Therefore, patient characteristics were calculated at the time point of liver transplantation and compared between groups. Patients with high PSFI had increased creatinine levels, whereas all other organ function parameters were not different between cohorts with high-fat and low-fat indices (Table S4).

DISCUSSION

Liver cirrhosis accelerates wasting, as exaggerated energy consumption requires amino acids and lipids

as additional energy sources,[18] and wasting is associated with poor outcome.[8] The CT scan is a widespread and reliable technique to determine body composition. CT-derived fat mass parameters serve to identify subgroups of patients with cirrhosis with high risks of complications before and after liver transplantation. This is a large retrospective study in patients with end-stage liver disease using three different CT-derived fat parameters to explore their impact on developing cirrhosis-associated complications and on mortality before and after liver transplantation.

Although patients with cirrhosis had lower fatty indices compared with liver-healthy control patients, there was a great heterogeneity among individual fat compartments to predict patients' outcome, and only the SCFI but not the other parameters was associated with the development of complications such as bacterial infections, ascites, SBP, or death before transplantation. The lower the subcutaneous fat mass, the higher the risk of complications. Data emphasize that wasting in end-stage liver disease goes beyond sarcopenia as an indicator of disease severity,[8] and suggest that adipose tissue composition has the potential to serve as an alternative or additional marker for outcome in cirrhosis. To date there are several relevant studies evaluating the prognostic role of adipose tissue in liver disease. Ebadi et al.[11] showed in a large retrospective cohort of 677 patients that a decreased SCFI was associated with a higher mortality in female patients with cirrhosis awaiting liver transplantation. However, the impact of body fat composition after transplantation was not explored. The second study presented by Tapper et al.[19] investigated the influence of fat and muscle density on mortality in a prospective cohort (n = 274). This study showed that a decreased density of fatty tissue was associated with increased mortality and risk for decompensation. However, this analysis was performed in a univariate manner only, which in combination with the low sample size certainly questions the robustness of these results. The third study enrolled 104 patients with cirrhosis due to alcohol-associated liver disease and showed a shorter survival in patients with increased subcutaneous fat mass.[20] Finally, a fourth study evaluated sarcopenia in 109 patients with CT who underwent hepatic vein pressure gradient measurement, and revealed sarcopenia as an independent risk factor for increased mortality.[21] Recently two other studies evaluated fat mass and myosteatosis at L3 in especially the perioperative setting, implying that at the timepoint of transplantation, body composition acts as a prognostic factor.[22,23] Herein, the authors describe a poorer outcome and increased hospital and intensive-care-unit stay with a higher myosteatosis at the time point of transplantation. However, there was no differentiation of compartments.

In light of the results presented here, it might be tempting to add CT-derived fat parameters to already established prognostic markers for cirrhosis, to increase their prognostic accuracy. Ebadi et al. introduced the MELD-SATI, a combination of MELD and the SCFI, and it showed an increased c-index compared with MELD only (0.93 [0.87–0.99] vs. 0.85 [0.75–0.96]). However, data used to calculate the MELD-SATI were collected only in female patients,[11] questioning the generalizability of these data especially as the gender did not play a role in our cohort. Previous attempts to add nutritional parameter to prognostic score, especially for sarcopenia, were of limited success.[24] Therefore, it might be necessary to validate such scores in a large-scale, multicenter setting.

It would be interesting to understand whether a reduced fat mass actively contributes to a progression of liver cirrhosis, thereby explaining its prognostic relevance. To answer this, it is important to note that CRP values as a marker of inflammatory response were increased in patients with low SCFI. Lipids are strong signals for intercellular communication, and a loss of fat mass in cirrhosis is associated with increased levels and impaired composition of circulating lipids.[18,25] In cirrhosis, lipids are inflammatory cues enhancing inflammation through alterations of toll-like receptor signaling.[26] Therefore, a loss of adipose tissue might enhance inflammation and organ injury in decompensated liver cirrhosis.

Interestingly, the interplay between body fat composition and patients' outcome appears to be complex. A low SCFI increased the risk of complications, whereas patients suffering from HRS and varices were characterized by higher PSFI and VFI values. Although it remains speculative, previous observations in obese patients might provide one explanatory approach. The presence of the metabolic syndrome was associated with an elevated sympathetic nerve activity in both muscles as in kidneys,[27] leading to a "sympathetic overdrive."[28] This overdrive initiated an activation of the so-called hepatorenal reflex, leading to decreased renal blood flow, sodium retention, and increased portal vein pressure.[29] Therefore, it might be possible that an increase in visceral and paraspinal adipose tissue could enhance renal sympathetic activity. In addition, there were gender differences of fat composition, which prompted us to include gender as a co-founder in the multivariate regression model. Results did not provide evidence of a gender-related effect of fat composition on patient's outcome.

It is intriguing that while cachexia generally predicts outcome before transplantation, there is an opposite relationship between fat parameters and death after liver transplantation. Patients with high visceral and paraspinal muscle fat mass were more likely to die after transplantation. Therefore, a HR of 1.188 for PSFI translates into a risk increase to die after transplantation of about 19% with every point of PSFI elevation. In addition to patient's age, this was associated with

the presence of diabetes mellitus, arterial hypertension and chronic renal insufficiency, implying that the presence of other diseases in general and the metabolic syndrome in particular significantly contribute to this observation. This is well in line with studies evaluating the outcome of obese patients who underwent liver transplantation. These patients were more likely to develop wound complications, postoperative infections, metabolic syndrome–related complications, and death.[16,30,31] Further studies also describe an increased risk of death after transplantation for patients with an increased visceral-subcutaneous fat tissue ratio,[32] an increased visceral fat area,[33] and with myosteatosis.[22,23,34] However, there are also contrary data showing that obesity does not affect survival after liver transplantation,[35,36] suggesting that the distinction between different fat compartments might be the clue to reliably predict patients' outcome in different disease scenarios.

Indeed, several observations highlighted especially visceral adipose tissue being associated with the development of NASH, arteriosclerosis, and increasing insulin resistance.[37–39] However, there was no difference between patients with low and high PSFI and SCFI concerning their cause of death (Table S5). The rather large number of unknown causes of death might influence the lack of significance.

There are several limitations to that study. The retrospective design might question the quality of data retrieval, especially if there are a considerable number of censored data included in the analysis. It might be arguable that there is a significant difference in age between patients with cirrhosis and controls included in this study. Assuming that older muscle mass decreases and fatty tissue increases with age, this might interfere with the difference in fatty indices in this study. However, it appears unlikely, as multivariate analysis did not reveal age or gender as a significant factor. Furthermore, it might be argued that patients with NASH-related cirrhosis or patients with TIPS might have a significant influence on the prognostic impact of fat parameters in patients with cirrhosis. However, these subgroups represented only a minority in our cohort (NASH 4.9%, TIPS 6.7%), and the multivariate analysis in a cohort without patients with NASH confirmed the results from the overall cohort regarding mortality before and after liver transplantation, although the VFI was lacking significance for predicting death after transplantation. Finally, the categorized SCFI provided a HR for the risk of death before transplantation with borderline significance, while the metric SCFI variable proved to be a significant independent risk factor. Generally, metric variables provide statistically more robust results for this type of regression analysis. Adding the paraspinal muscle index as a confounder for 1-year mortality before liver transplantation, the SCFI loses significance, which emphasizes the potential complex interplay between muscle and fat composition in the context of liver cirrhosis, and further studies are needed to evaluate the interplay between fatty and muscle tissue.

CONCLUSIONS

Distinct fat compartments impacted differently on patients' outcome in cirrhosis. Although a low subcutaneous fat mass increased the risk of death and complications in patients with cirrhosis on the wait list, the risk of complications after liver transplantation was associated with high muscle and visceral fat. Therefore, it appears worthwhile to consider the nutritional state of patients awaiting liver transplantation as an important determinant of potential complications in relation to this intervention, and future risk indices may include fat indices as an essential confounder.

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CONFLICT OF INTEREST

R.J. owns stock in, is an employee of, consults, advises, received grants, and holds intellectual property rights with Yaqrit Ltd. He consults, advises, and received grants from Grifols. C.E. own stock in and holds intellectual property rights with Hepyx. D.S. advises Sirtex and is on the speaker's bureau of Astelas, Bayer, Eisai, and MSD/Merck. He advises and is on the speaker's bureau of BTG, Johnson & Johnson, Novartis, and Olympus.

ETHICS, CONSENT, AND PERMISSION

Due to this retrospective, non-interventional, observational study design, patients' informed consent was not required. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the ethics committee of the University of Leipzig (No. 356-10-13122010). Data shown in this manuscript can be requested from the corresponding author. The manuscript was compiled according to the STROBE guidelines.

AUTHOR CONTRIBUTIONS

Cornelius Engelmann: Study concept and design, analysis, interpretation of data, draft of the manuscript; Niklas F. Aehling: Analysis, interpretation, draft of the manuscript; Stefan Schob, Ines Nonnenmacher, Luise Handmann: data collection, interpretation of data, critical revision of the manuscript; Jane Macnaughtan, Adam Herber, Alexey Surov, Thorsten Kaiser, Timm Denecke, Rajiv Jalan, Daniel Seehofer, Michael Moche, Thomas Berg: interpretation of data, critical revision of the manuscript.

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SUPPORTING INFORMATION

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