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ORIGINAL ARTICLE

Sarcopenia predicts reduced liver growth and reduced resectability in patients undergoing portal vein embolization before liver resection - A DRAGON collaborative analysis of 306 patients

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Abstract

Background: After portal vein embolization (PVE) 30% fail to achieve liver resection. Malnutrition is a modifiable risk factor and can be assessed by radiological indices. This study investigates, if sarcopenia affects resectability and kinetic growth rate (KGR) after PVE.

Methods: A retrospective study was performed of the outcome of PVE at 8 centres of the DRAGON collaborative from 2010 to 2019. All malignant tumour types were included. Sarcopenia was defined using gender, body mass and skeletal muscle index. First imaging after PVE was used for liver volumetry. Primary and secondary endpoints were resectability and KGR. Risk factors impacting liver growth were assessed in a multivariable analysis.

Results: Eight centres identified 368 patients undergoing PVE. 62 patients (17%) had to be excluded due to unavailability of data. Among the 306 included patients, 112 (37%) were non-sarcopenic and 194 (63%) were sarcopenic. Sarcopenic patients had a 21% lower resectability rate (87% *vs.* 66%, $p < 0.001$) and a 23% reduced KGR ($p = 0.02$) after PVE. In a multivariable model dichotomized for KGR $\geq$2.3% standardized FLR (sFLR)/week, only sarcopenia and sFLR before embolization correlated with KGR.

Conclusion: In this largest study of risk factors, sarcopenia was associated with reduced resectability and KGR in patients undergoing PVE.

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Introduction

Regenerative liver surgery expands the limitations of technical resectability by increasing the size of the future liver remnant (FLR) prior to resection to prevent post-hepatectomy liver failure (PHLF).[1]

For a more accurate estimation of the volume requirement to prevent PHLF, the MD Anderson group proposed the metrics "standardized FLR" (sFLR), which is based on an ideal total liver volume for each patient based on biometric data.[2] The sFLR allows to exclude confounders as tumour volumes or dilated bile ducts and keeps the denominator stable when liver growth is measured over multiple time points. A minimal required sFLR of 20–30% for healthy livers and >40% in patients with abnormal histology like cirrhosis has become the generally accepted cut-off for extensive liver resections.[2–5] To estimate the speed of liver growth after regenerative manoeuvres, the metrics kinetic growth rate (KGR) is routinely used and is defined as the difference between the sFLR after and before embolization divided by the elapsed time in weeks between embolization and volumetric assessment.[6]

Portal vein embolization (PVE) by interventional radiology is the gold standard procedure to induce liver regeneration of the FLR prior to resection. However, hypertrophy induced by PVE is limited and takes several weeks until sufficient liver growth is achieved.[7,8] According to a frequently cited systematic review,[7] based on 44 reported studies, a mean FLR increase of 38% can be observed after a mean of 37 days. In 20–30% of patients curative liver resection cannot be performed due to tumour progression in the waiting interval and/or insufficient liver growth.[7,8] In two-stage hepatectomies (TSH) with PVE or portal vein ligation between the stages, dropout rates of up to 43% have been reported.[9]

Multivariable analyses show that factors as sex (male),[10] diabetes,[6,10] cirrhosis,[7] elevated bilirubin,[10] or platinum-based chemotherapies[11] influence liver growth. A recent single centre analysis demonstrated in patients with colorectal liver metastasis (CRLM) that sarcopenia as assessed by computer tomography (CT) also impairs liver growth after PVE,[12] but could not assess whether the lower growth rate had an impact on resectability due to the small study size.

This retrospective international multi-centre study investigates, if sarcopenia has an impact on resectability and KGR after PVE.

Methods

Study design and setting

This study was designed as a multi-centre retrospective cohort study of 8 international liver resection centres participating in the DRAGON collaborative to investigate outcomes in regenerative liver surgery. All patients in participating centres that required PVE for planned liver resection between Jan. 2010 and Dec. 2019 were retrospectively analysed. Participating centres contributed their anonymized data to a central data repository. All malignant tumour types were included (Table 1). Reporting of data was performed according to the STROBE (strengthening the reporting of observational studies in epidemiology) guidelines.[13]

Participants

A comprehensive dataset of all patients who underwent PVE in 9 years was requested from participating centres and entered a database sourcing data from local hepato-pancreatic-biliary (HPB) databases, multidisciplinary tumour board records, planning logs, operating logs, and embolization records.

Variables

The primary endpoint of this study was resectability. While the decision to resect was not based on prospectively defined criteria, however, general accepted volume cut-offs of sFLR of 30% for normal livers and 40% for livers with histological damage were used by each participating centre over the respective 9-year period. Secondary endpoint was KGR. A biometric formula based on the body weight (18.51 x body weight (kg) + 191.8),[14] which has shown to provide the most accurate prediction,[15] was used to calculate the standardized total liver volume (sTLV) and the sFLR. KGR was defined as the difference between the sFLR after and before embolization divided by the elapsed time in weeks between intervention and the first volume assessment after intervention: $KGR = (sFLR_{after\ embolization} - sFLR_{before\ embolization})/time\ in\ weeks$.[6]

To determine sarcopenia for each patient, skeletal muscle area, subcutaneous adipose area and the visceral adipose area were measured at the third lumbar vertebra (L3) using CT before PVE. Dividing by patient's height square (m^2), the anthropometric measures were standardized to skeletal muscle index (SMI), visceral adipose index (VAI) and subcutaneous adipose index (SAI), as reported before.[12,16] Following generally accepted sex-specific conventions, sarcopenia was defined in women as a SMI <41 cm^2/m^2, in men as a SMI <43 cm^2/m^2 with a BMI <25 or a SMI <53 cm^2/m^2 with a BMI >25.[12,16]

Volume changes were described by the degree of hypertrophy (DH) and percent hypertrophy (%HT). DH was defined as the difference between the sFLR after and before embolization ($DH = sFLR_{after\ embolization} - sFLR_{before\ embolization}$).[17] %HT was calculated by the sFLR after embolization divided by the sFLR before embolization minus 1 $((sFLR_{after\ embolization}/sFLR_{before\ embolization})-1) * 100)$.

While time between embolization and imaging was analysed to describe growth kinetics, time between embolization and liver resection was additionally assessed.

Clinical and pathological data include demographics, concomitant diseases, tumour type based on the final pathology report, operative details, extent of the liver resection according to the Brisbane terminology,[18] pre- and post-interventional lab values, length of hospital stay in days, complication rate

Table 1 Demographics

Variates	Non-sarcopenic n = 112	Sarcopenic n = 194	*p* value
Age in years, median (IQR)	62 (55–71)	64 (57–71)	0.34
Sex - female/male, number (%)	48/64 (43%/57%)	75/119 (38%/62%)	0.47
Weight (kg), median (IQR)	75.5 (69–88)	76 (65–87)	0.61
Height (m), median (IQR)	1.73 (1.7–1.8)	1.73 (1.7–1.8)	0.42
Body mass index (kg/m^2), median (IQR)	25.3 (24–29)	25.7 (22–29)	0.42
Body surface area (m^2), median (IQR)	1.9 (1.8–2.1)	1.9 (1.8–2.1)	0.81
Type of tumour, number (%)			0.61
CRLM	59 (53%)	113 (58%)	
HCC	8 (7%)	12 (6%)	
IHCC	17 (15%)	20 (10%)	
PHCC	16 (14%)	30 (16%)	
GBC	8 (7%)	11 (6%)	
Other	4 (4%)	8 (4%)	
Cirrhosis, number (%)	8 (7%)	8 (4%)	0.25
Diabetes, number (%)	15 (13%)	25 (13%)	0.89
Chemotherapy, number (%)	61 (52%)	95 (49%)	0.80
Platinum-based chemotherapy, number (%)	38 (62%)	77 (81%)	0.09
Blood values			
Haemoglobin baseline (mmol/l), median (IQR)	7.9 (7.4–8.7)	7.6 (7.1–8.4)	**0.03**
Albumin baseline (g/l), median (IQR)	38 (35–42)	37 (33–41)	**0.03**
Creatinine baseline in μmol/L, median (IQR)	72 (62–86)	72 (59–85)	0.46
Bilirubin baseline in μmol/L), median (IQR)	10 (7–16)	10.7 (6–20)	0.53
INR baseline, median (IQR)	1 (0.9–1.1)	1 (1–1.1)	**0.03**
Body composition			
Skeletal muscle area (cm^2), median (IQR)	146 (129–163)	108.9 (96–131)	**<0.001**
Subcutaneous adipose area (cm^2), median (IQR)	156.5 (116–201)	164.9 (117–216)	0.73
Visceral adipose area (cm^2), median (IQR)	171.9 (119–254)	160.2 (107–230)	0.23
Skeletal muscle index (cm^2/m^2), median (IQR) (SMI)	48 (44–54)	38 (33–42)	**<0.001**
Subcutaneous adipose index (cm^2/m^2), median (IQR) (SAI)	54.4 (38–78)	53.6 (39–76)	0.79
Visceral adipose index (cm^2/m^2), median (IQR) (VAI)	59.2 (41–84)	55.6 (36–73)	0.16
Embolization technique			
Segment 4 embolization, number (%)	14 (13%)	23 (12%)	0.87
Embolic agents, number (%)			0.23
N-butyl-cyanoacrylate (NBCA)	44 (39%)	52 (27%)	
Coils	2 (2%)	9 (5%)	
Plugs	0	4 (2%)	
Microspheres	0	0	
Coils + microspheres	40 (36%)	88 (45%)	
Coils + plugs	8 (7%)	17 (9%)	
NBCA + plugs	11 (10%)	0	
Other	7 (6%)	24 (12%)	

CRLM: colorectal liver metastasis; GBC: gallbladder carcinoma; HCC: hepatocellular carcinoma; IHCC: intrahepatic cholangiocarcinoma; IQR: interquartile ranges; NBCA: n-butyl-cyanoacrylate; PHCC: perihilar cholangiocarcinoma.
Bold means $p < 0.05$.

according to the Dindo-Clavien classification (major complications, grade $\geq$ IIIA),[19] and PHLF according to the criteria of the International Study Group of Liver Surgery (ISGLS).[20]

Data sources and management

Patient's demographics were retrieved from prospectively maintained databases, electronic health records and clinical source documents. Body composition and liver volumetry were assessed by one radiologist (JoHo) and one surgeon (JaHe) using OsiriX MD Version 11.0.2 (Pixmeo SARL, Switzerland) in consensus. Tumour volume was subtracted from the FLR volume to calculate volumetry. Anthropometric measures were based on segmentation of a single 5 mm CT slice at the L3 level before embolization. The segmentation was performed in semi-automated fashion by outlining the border and setting the threshold range of Hounsfield units between −30 and +150 for the skeletal muscle area, −190 to −30 for the visceral adipose area and −190 to −30 for the subcutaneous adipose.

Bias

Data reporting bias was reduced by systematic comparison with source files in electronic health records, tumour board records, pathology reports as well as procedure and operative reports.

The decision to perform PVE was generally based on sFLR <30% for normal liver and <40% for histologically damaged livers with judgement by respective clinicians. In one centre, liver function test was additionally used to assess resectability using technetium-99m mebrofenin hepatobiliary scintigraphy (HIDA) and their cut-off for resection was 2.7%/min/m^2.[21]

Due to a lack of a prospective study design, a selection bias cannot be excluded. Due to the long study period study period over 9 years, an era bias cannot be excluded either.

Statistics

Descriptive data are given as means with standard deviation (SD) for parametric and medians with interquartile ranges (IQR) for non-parametric data. Kolmogorov–Smirnov test was used to test distribution of data. Categorical variables are reported in numbers and proportions. For comparisons, t-test was used for parametric, Mann-Whitney-test for non-parametric data, and Fischer's exact test for categorical variables. $P < 0.05$ was considered significant. All dichotomizations are based on medians, except for bilirubin where a C-statistic was performed. Stepwise regression was performed for multivariable analysis. Analyses and graphics were made with JMP 15.0 (SAS Institute, Cary, USA) and Graph Pad Prism 8.4.3 (Graph Pad Software, La Jolla, CA, USA).

Ethical approval

The study was approved by the Cantonal Ethics Commission Zurich (approval number: 2020-00571) and conducted in accordance with the declaration of Helsinki of 1996.

Results

Participants

A total of 368 patients underwent PVE before liver resection in 8 centres between Jan. 2010 and Dec. 2019, Fig. 1. In 62 patients (17%) cross sectional imaging at the level of the third lumbar vertebrae before embolization was not available for measuring the body compositions. These patients were excluded. The analysis cohort contains 306 patients.

Among these, 112 (37%) patients were not sarcopenic and 194 patients (63%) met the criteria for sarcopenia.

Descriptive data

Demographics and body compositions are shown in Table 1. Sarcopenic patients demonstrated a reduced haemoglobin ($p = 0.03$) and albumin ($p = 0.03$). Since SMI determines sarcopenia based in conjunction with gender and BMI, skeletal muscle area ($p < 0.001$) and SMI ($p < 0.001$) were lower in sarcopenic patients. Embolic agents used for PVE did not differ between the groups and also the number of segment 4 embolizations performed were similar in the groups.

Missing data

Among the 8 participating centres, 3 centres did not contribute their cases for the whole study period. One centre contributed cases between 2013 and 2017, another between 2010 and 2017, and one centre between 2016 and 2019.

In the pre-interventional course, albumin and bilirubin were not available in 35 and 11 patients, respectively, while INR and bilirubin at post-operative day 5 were not available in 12 and 10 patients, respectively, and creatinine at post-operative day 2 was not available in 7 patients. 90-day mortality was not available in 25 patients.

Outcome data

Outcome data are shown in Table 2. sTLV and sFLR before embolization did not differ between sarcopenic and non-

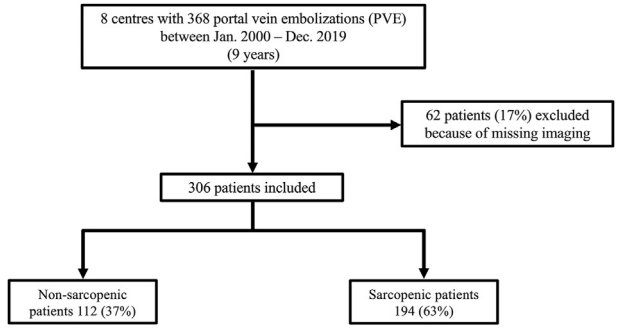

Figure 1 Flowchart of patients screened and included. Eight centres identified 368 patients undergoing PVE prior to liver resection. Due to unavailability of data 62 patients (17%) had to be excluded. Among the 306 included patients, 112 (37%) were non-sarcopenic and 194 (63%) were sarcopenic

Table 2 Volumetry, operative and outcome data

Variates	Non-sarcopenic n = 112	Sarcopenic n = 194	*p* value
Liver volume before intervention			
Standardized total liver volume, median (IQR) (sTLV)	1636 (1456–1858)	1589 (1376–1803)	0.07
sFLR (%), median (IQR)	24 (18–30)	21 (15–28)	0.06
Liver volume after intervention			
Time intervention to first volumetry in days, median (IQR)	25 (21–30)	26 (21–30)	0.66
sFLR (%), median (IQR)	36 (27–46)	30 (22–41)	**0.003**
Degree of hypertrophy (%), median (IQR) (DH)	11 (6–16)	8 (5–13)	**0.003**
Percent hypertrophy (%), median (IQR) (%HT)	45.8 (25–69)	39.7 (24–63)	0.25
Kinetic growth rate (sFLR/week), median (IQR) (KGR)	2.6 (1.6–4.5)	2.0 (1.2–3.5)	**0.02**
Resection			
Feasibility of resection, number (%)	97 (87%)	127 (66%)	**<0.001**
Time intervention to resection in days, median (IQR)	49 (40–72)	49 (40–64)	0.79
Type of resection, number (%)			0.68
Right hepatectomy	40 (41%)	59 (46%)	
Extended right hepatectomy	55 (57%)	62 (49%)	
Left hepatectomy	0	1 (1%)	
Extended left hepatectomy	1 (1%)	1 (1%)	
Other	1 (1%)	4 (3%)	
Post-operative course			
Bilirubin post op day 5 in μmol/L, median (IQR)	19 (14–34)	17 (14–28)	**0.04**
INR post op day 5, median (IQR)	1.2 (1.1–1.5)	1.2 (1.1–1.4)	0.21
Creatinine post op day 2 in μmol/L, median (IQR)	66 (51–78)	69 (52–91)	0.96
PHLF per ISGLS criteria, number (%)	21 (22%)	20 (16%)	0.20
Hospital stay in days, median (IQR)	8 (6–17)	10 (8–16)	0.23
Complications			
Major complications (≥IIIA Dindo-Clavien), number (%)	32 (33%)	39 (31%)	0.75
90-day mortality, number (%)	6 (6%)	9 (7%)	0.70

IQR: interquartile ranges; ISGLS: international study group of liver surgery; PHLF: post-hepatectomy liver failure; sFLR: standardized future liver remnant.
Bold means $p < 0.05$.

sarcopenic patients. Following PVE, after a median of 25 and 26 days ($p = 0.66$), respectively, sarcopenic patients demonstrated a significantly reduced sFLR compared to non-sarcopenic patients (36% *vs.* 30%, $p = 0.003$). Sarcopenic patients had a reduced DH (11% *vs.* 8%, $p = 0.003$) and a reduced KGR (2.6% *vs.* 2.0%, $p = 0.02$) compared to non-sarcopenic patients.

Supplementary Fig. 1 shows that among the 3 described radiological body composition tools only SMI significantly correlated with KGR ($p = 0.007$).

Surgery was performed after a median of 49 days in both groups, however, sarcopenic patients were 21% less likely to be resected compared to non-sarcopenic patients (87% *vs.* 66%, $p < 0.001$). There was no difference in the post-operative outcomes between sarcopenic and non-sarcopenic patients (Table 2).

Multivariable analysis for KGR ≥2.3% sFLR/week

A multivariable analysis is given in Table 3 and shown in a forest plot in Fig. 2 with respective odds ratios of factors impacting KGR ≥2.3% sFLR/week (median). Of the 9 variables, sarcopenia and size of the sFLR before embolization (dichotomized as sFLR <20%) remained significant in the multivariable analysis. Sex, age, diabetes, cirrhosis, kidney function or chemotherapy prior to PVE had no impact on KGR. Hyperbilirubinemia (dichotomized as bilirubin ≥50 μmol) only correlated with KGR in the univariable analysis and had a positive correlation with kinetic growth.

Discussion

This study shows that sarcopenia prior to PVE is associated with a significantly reduced resection rate and KGR prior to liver

Table 3 Uni- and multivariable analysis for KGR ≥2.3% sFLR/week

Variables	univariable		multivariable	
	OR (CI)	p-value	OR (CI)	p-value
Sex -female/male	0.75 (0.47–1.19)	0.22	0.67 (0.4–1.13)	0.13
Age >60 years (y/n)	0.91 (0.58–1.44)	0.69	0.93 (0.54–1.6)	0.79
Diabetes (y/n)	1.27 (0.65–2.48)	0.48	1.34 (0.65–2.77)	0.43
Cirrhosis (y/n)	1.36 (0.49–3.75)	0.55	1.14 (0.36–3.68)	0.28
Creatinine ≥88 μmol/L (y/n)	0.81 (0.47–1.42)	0.47	0.59 (0.31–1.12)	0.10
Bilirubin ≥50 μmol/L (y/n)	3.03 (1.14–8.04)	**0.019**	2.02 (0.7–5.84)	0.18
Chemotherapy before PVE (y/n)	0.81 (0.52–1.27)	0.36	0.87 (0.51–1.48)	0.61
Sarcopenia (y/n)	0.60 (0.37–0.96)	**0.031**	0.52 (0.32–0.89)	**0.02**
sFLR before embolization <20% (y/n)	0.40 (0.25–0.65)	**<0.001**	0.40 (0.24–0.69)	**<0.001**

CI: confidence interval; KGR: kinetic growth rate; OR: odds ratio; PVE: portal vein embolization; sFLR: standardized future liver remnant.
Bold means $p < 0.05$.

resection. Despite a comparable sFLR before embolization and comparable time interval between embolization and first volumetry assessment after PVE, sarcopenic patients had a 21% lower chance to achieve curative liver resection after PVE, likely due to a 23% reduced KGR and a 17% smaller sFLR after embolization compared to non-sarcopenic patients. These findings suggest the importance of nutritional support prior to PVE to improve the resection rate, which remains the Achilles tendon of PVE as a regenerative strategy. Among the 9 factors impacting kinetic growth, only sarcopenia and sFLR size before embolization correlated with kinetic growth after PVE in the multivariable analysis.

The importance of a higher feasibility of resection was recently shown by the LIGRO trial, the first randomized controlled trial for ALPPS. In LIGRO, patients underwent either ALPPS or TSH with PVE or PVL between the stages.[9] Patients who underwent ALPPS had a 33% higher chance to undergo curative liver resection ($p < 0.001$). A follow-up evaluation of the LIGRO cohort yielded a translation of the increased resectability after ALPPS into an improved median overall survival.[22] It is possible that a pre-operative improvement of sarcopenia could have a similar effect on survival via resectability as demonstrated in LIGRO for the ALPPS technique. Sarcopenia may be the only modifiable risk factor prior to PVE in patients suffering from malignancies. Therefore, routinely assessment of malnutrition should be recommended prior to PVE to identify patients at risk for an impaired liver growth.

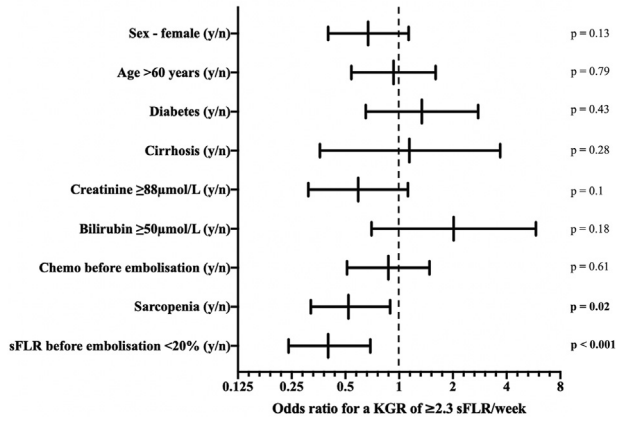

Figure 2 Forest plot to show odds ratios to achieve KGR ≥2.3% sFLR/week in multivariable analysis. Among the 9 described risk factors for liver growth after PVE only sarcopenia and sFLR before embolization (dichotomized as sFLR <20%) correlated with kinetic growth in the multivariable analysis

How to approach and treat sarcopenia in patients that have a significant cancer burden and require regenerative liver surgery? A large number of patients will receive neoadjuvant therapy and therefore have time for preoperative interventions. There is a broad consensus that moderate aerobic endurance exercising[23] and muscle training[24] ("prehabilitation") improve outcomes after liver surgery in general. Standardized implementation of such training programs has to be studied in the future to provide evidence of their efficacy in regenerative liver surgery. Additionally, intervention with a protein enriched supplementary nutrition is recommended by guidelines and has been implemented widely in bundles with other interventions, such as in ERAS (enhanced recovery after surgery) process,[25] but not specifically in sarcopenic populations.

The MD Anderson group first described the negative impact of sarcopenia on liver growth after PVE in a small cohort of 45 patients with CRLM.[12] The study did not provide data about the sFLR size after embolization. In contrast to our results, the MD Anderson study showed a reduced VAI in sarcopenic patients, VAI did not differ in our analysis.

Two studies from the University of Aachen analysed sarcopenic patients undergoing liver surgery. In the first study, 80

patients underwent LiMAx liver function breath test and volumetric CT scan for pre-operative assessment prior to liver resection and showed no difference of total liver volume or total liver function between sarcopenic and non-sarcopenic patients.[16] Although 34 patients (43%) had PVE prior to surgery, the article did not provide information about the FLR size before and after intervention.

A further study from Aachen analysed the relationship between liver growth and psoas muscle volume, psoas muscle cross-sectional area at the largest diameter and SMI at the third lumbar vertebrae in patients undergoing PVE before liver resection.[26] While the psoas volume and the largest psoas plane correlated with KGR, SMI did not correlate neither with KGR nor DH, in marked contrast to our findings. PVE in Aachen was performed in patients with larger starting FLRs (34% FLR) than typically considered to be cut-offs to indicate regenerative manoeuvres.[26] Using PVE in patients with larger starting sFLRs may not allow to detect the effect of sarcopenia on KGR.

In this study, post-operative outcome and 90-day mortality did not differ between sarcopenic and non-sarcopenic patients. The largest study about the effect of sarcopenia on outcomes of liver surgery (non-sarcopenic: 72 vs. sarcopenic: 72) showed that sarcopenic patients had more major complications (Dindo-Clavien $\geq$ III, $p = 0.046$) and a 4.3 higher 90-day mortality ($p = 0.002$).[27] Especially, elderly sarcopenic patients (>70 years) had a 6.54 increased mortality risk. This negative impact of sarcopenia on outcomes after major liver resections has been confirmed by others.[28] Interestingly, only 30% of patients studied underwent PVE prior to resection.[27] The difference to our study may be explained by the fact that all patients with sarcopenia here underwent PVE. Pre-operative volume enhancement may be the reason why this study did not find worse outcomes in sarcopenic patients after liver resection. Indeed, PVE may be protective to avoid bad post-operative outcomes in sarcopenic patients after extensive liver resection, similarly to the improved outcomes shown in the cirrhotic subgroup in a trial of PVE *vs.* no PVE prior to major liver reactions.[29] Another explanation is selection in that PVE provides a biological test, allowing surgeons to avoid surgery in patients with insufficient regenerative capacity.

The current study is the largest multivariable analysis on factors impacting KGR after PVE performed so far and does not confirm any associations between sex,[10] diabetes,[6,10] cirrhosis,[7] or chemotherapy[11] that have been previously described as negative prognostic factors. Additionally, an inverse correlation has been described between small FLRs size before embolization and %HT.[11] In this study, KGR was chosen as secondary endpoint in contrast to %HT since it is a time dependent variable and therefore a more precise metrics than %HT. Interestingly, smaller sFLRs before embolization *did not* growth faster in this multivariable analysis.

This study has several limitations. First, a reporting bias cannot be excluded due to the retrospective design and the lack of an independent monitoring. However, we attempted to minimize this bias through a close collaboration between participating centres in the DRAGON collaborative.

Second, the retrospective design may introduce a selection bias since not all participating centres were able to provide data of the entire study period. Nevertheless, this bias was reduced by a large study size and performing a multivariable analysis.

Third, an era bias cannot be excluded. Paradigm regarding the technical resectability and the indication for regenerative liver surgery have changed during the study period. While a sFLR of 20% was initially accepted as a cut-off for resection,[3] a cut-off of 25–30% became more widely used in the following years.[2,4] However, the sFLR in the non-sarcopenic and sarcopenic group before embolization reported here clearly demonstrates the indication for regenerative liver surgery in these patients.

Fourth, due to the retrospective and multi-centric design technical aspect of PVE were not entirely homogenous. However, growth metrics of PVE (DH, %HT and KGR) in the current study compare favourably with published series so far since grow metrics are in the expected range.[6]

Fifth, due to the retrospective study design imaging protocols were not standardized for measuring the body compositions. The use of contrast media, different amount of contrast media and the contrast phase may result in a slight overestimation of the skeletal muscle area and SMI, respectively, compared to non-enhanced scans.[30] However, the overall effect will be small.

Sixth, various definitions of sarcopenia do exist and different definitions are used by other studies.[26,27] This may explain the different findings of the impact of sarcopenia on liver regeneration and outcome after liver resection. Standardization will be obligatory to achieve progress in further studies. We chose a most widely used definition of sarcopenia also used in recently published series about liver surgery.[12,16] The advantage of the definition in this study is that different cut-offs do exist for male and female, and for normal-weighted and obese male. The SMI of obese patients tends to be overestimated without taking the BMI into account, while the SMI in female patients tends to be underestimated using a sex-independent cut-off for SMI.

Conclusion

This is the largest study to date to systematically examine factors affecting resectability and kinetic growth in regenerative liver surgery. We found that sarcopenia is associated with decreased resectability and an impaired liver growth after PVE. A prospective trial may be warranted to confirm if nutritional intervention before or in conjunction with PVE may improve the resectability and long-term oncologic outcome in patients with small future liver remnants.

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Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2021.08.818.