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# Laparoscopic liver resection is associated with less significant muscle loss than the conventional open approach

Ruoh-Yun Gau<sup>1</sup>, Hsin-I Tsai<sup>2,3,4</sup>, Ming-Chin Yu<sup>4,5</sup>, Kun-Ming Chan<sup>1,3</sup>, Wei-Chen Lee<sup>1,3</sup>, Haw-En Wang<sup>6</sup>, Sheng-Fu Wang<sup>6</sup>, Mei-Ling Cheng<sup>7,8,9</sup>, Chien-Chih Chiu<sup>10</sup>, Hsin-Yi Chen<sup>3,10,11</sup> and Chao-Wei Lee<sup>1,2,3\*</sup>

## Abstract

**Background:** Laparoscopic liver resections (LLR) have been shown a treatment approach comparable to open liver resections (OLR) in hepatocellular carcinoma (HCC). However, the influence of procedural type on body composition has not been investigated. The aim of the current study was to compare the degree of skeletal muscle loss between LLR and OLR for HCC.

**Methods:** By using propensity score matching (PSM) analysis, 64 pairs of patients were enrolled. The change of psoas muscle index (PMI) after the operation was compared between the matched patients in the LLR and OLR. Risk factors for significant muscle loss (defined as change in PMI > mean change minus one standard deviation) were further investigated by multivariate analysis.

**Results:** Among patients enrolled, there was no significant difference in baseline characteristics between the two groups. The PMI was significantly decreased in the OLR group ( $P = 0.003$ ). There were also more patients in the OLR group who developed significant muscle loss after the operations ( $P = 0.008$ ). Multivariate analysis revealed OLR ( $P = 0.023$ ), type 2 diabetes mellitus, indocyanine green retention rate at 15 min (ICG-15) > 10%, and cancer stage  $\geq 3$  were independent risk factors for significant muscle loss. In addition, significant muscle loss was associated with early HCC recurrence ( $P = 0.006$ ). Metabolomic analysis demonstrated that the urea cycle may be decreased in patients with significant muscle loss.

**Conclusion:** LLR for HCC was associated with less significant muscle loss than OLR. Since significant muscle loss was a predictive factor for early tumor recurrence and associated with impaired liver metabolism, LLR may subsequently result in a more favorable outcome.

**Keywords:** Laparoscopic, Liver resection, Hepatectomy, Hepatocellular carcinoma, Sarcopenia, Muscle loss

## Background

Liver resection remains one of the major curative treatments for hepatocellular carcinoma (HCC) [1]. With the improvement in surgical technique and instruments,

laparoscopic liver resection (LLR) has gradually become an acceptable approach for surgical resection of HCC. The surgical outcome between laparoscopic and conventional open liver resection (OLR) for HCC had been widely investigated. In addition to comparable oncological outcome, the potential benefits of LLR also included shorter postoperative hospital stay, reduced blood loss, and less occurrence of postoperative complications [2–7]. LLR, as a result, has been endorsed by many experts

\*Correspondence: alanchaoweilee@hotmail.com

<sup>1</sup> Division of General Surgery, Department of Surgery, Linkou Chang Gung Memorial Hospital, Guishan, Taoyuan 33305, Taiwan  
Full list of author information is available at the end of the article



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and consensus to be a justified treatment approach for the management of HCC.

Sarcopenia, initially described and noticed in elderly people with a negative impact on health, is a syndrome characterized by physical frailty, malnutrition, and loss in muscle volume and strength [8, 9]. It is recognized nowadays that not only people with aging or disability but also those suffering from diseases, metabolic disorders, or stress events are also at risk of developing sarcopenia [10, 11]. In the meanwhile, the significant role of sarcopenia in various clinical conditions including cancers, critical illness, trauma, and major surgery has also been demonstrated [12–16]. For example, studies have shown that preoperative sarcopenia could independently predict adverse outcomes following major abdominal operations [14, 17–19]. For patients undergoing liver resection, preoperative sarcopenia significantly increased postoperative complications and impaired long-term survival [15, 20, 21]. Moreover, loss of skeletal muscle mass was found associated with all-cause mortality and tumor recurrence in patients with HCC [21]. In addition to baseline body composition, there were other studies reporting the negative impact of dynamic change, i.e., treatment-related accelerated muscle loss, on the surgical outcome of various cancers [22–26].

Although sarcopenia was significantly correlated with an adverse outcome following liver resections, the influence of procedural type on body composition in patients with HCC has not been fully investigated. Compared to the open procedure, it is widely accepted that the smaller incisions inherent to LLR may contribute to less wound pain, earlier ambulation, and shorter hospital stay after the surgery [4, 5, 27, 28]. In addition, the systemic stress response produced by the laparoscopic approach was also less than the conventional open approach [29, 30]. Consequently, we theoretically hypothesized that these intrinsic advantages would reduce the adverse effect of surgery on body composition and further improve treatment outcome. The aim of the current study was thus to compare the degree of skeletal muscle loss between LLR and OLR for HCC. The influence of skeletal muscle loss on serum metabolome and survival outcome was also investigated.

## Materials and methods

### Patients

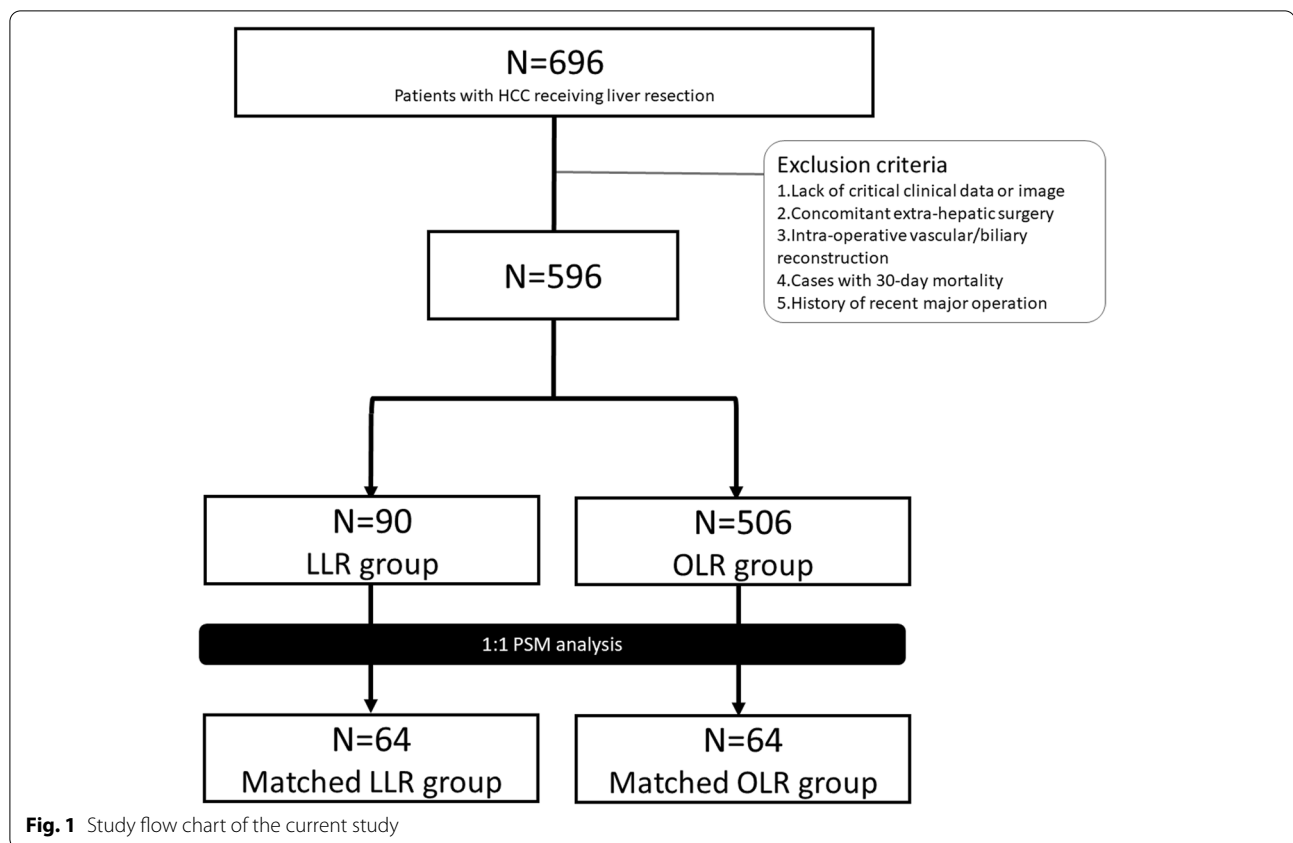
Under the approval of the Institutional Review Boards (IRB) of Chang Gung Memorial Hospital (CGMH) (Nos. 201600940B0, 201602025B0, and 202100068B0), a total of 696 patients who received liver resection for primary HCC in Linkou CGMH from 2012 to 2019 were reviewed. The exclusion criteria were as follows (1) patients who lacked critical clinical data or image, (2)

who received concomitant extrahepatic surgery except cholecystectomy, (3) who underwent intraoperative vascular/biliary reconstruction, (4) who died within 30 days of surgery, and (5) who had history of major operations or trauma within 3 months of liver surgery. Five-hundred and ninety-six patients, of whom 90 received LLR and 506 underwent OLR, remained and were enrolled for further analysis.

Demographic data including age, gender, cigarette smoking, alcohol consumption, hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, serum bilirubin, albumin, prothrombin time, international normalized ratio (INR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), platelet count, platelet-to-lymphocyte ratio (PLR), prognostic nutritional index (PNI = serum albumin level (in grams per liter) + 0.005 × lymphocyte count (in per mm<sup>3</sup>)) [31, 32], cholesterol, and alpha-fetoprotein (AFP) were recorded from the prospectively established database. The surgical variables, pathological factors, and oncological outcome including tumor size, American Joint Committee on Cancer (AJCC) stage, history of previous abdominal surgery, extent of liver resection, tumor encapsulation, histological grade, vascular invasion, daughter nodules, resection margin, liver cirrhosis, hepatitis activity index (HAI), tumor recurrence, and long-term survival were also recorded. The demographic characteristics of the entire cohort were summarized in Supplementary Table S1. A 1:1 propensity score matching (PSM) analysis between the LLR and OLR groups was then adopted. The variables employed for PSM included tumor size, AJCC cancer stage, previous abdominal surgery, IWATE difficulty score, and extent of liver resection. Sixty-four matched pairs were finally identified and analyzed in the current study (Fig. 1). Tumor was staged by the 7th edition of AJCC TNM staging system for HCC in the current study [33, 34].

### Assessment of muscle

For preoperative staging workup and postoperative follow-up, all patients recruited had undergone computed tomography (CT) scans both before and around 1 month after liver resections. The median interval between liver resections and the first postoperative CT scan was 38 days (interquartile range 26) in the current study. The time intervals were also comparable between the LLR and OLR groups. The cross-sectional area of psoas muscles at the level of the inferior end plate of the third lumbar vertebrae was obtained from the CT scans. The areas (cm<sup>2</sup>) of bilateral psoas muscles were measured by a picture processing and analyzing software and further normalized by patients' height squared (psoas muscle index (PMI) (cm<sup>2</sup>/m<sup>2</sup>) = total



psoas muscle area ( $\text{cm}^2$ )/height<sup>2</sup> ( $\text{m}^2$ ) [20, 35]. Both the preoperative and postoperative PMI were obtained, and PMI change was calculated by subtracting the preoperative PMI from the postoperative one. The change of PMI was further divided by preoperative PMI to yield the percentage change in PMI (percentage change in PMI (%) = (postoperative PMI – preoperative PMI)/preoperative PMI  $\times$  100%). All of the measurements and calculations were performed by the same research team who was blinded to the patient information.

#### Metabolomic studies regarding significant muscle loss

For serum metabolomic analysis, we collected the patient's serums at 1 month after the operation. The serum was processed and subjected to liquid chromatography-mass spectrometry (LC-MS) metabolomic analysis [36]. Since the current study aimed to investigate the degree of skeletal muscle loss after liver resection, the metabolomic study would preferentially focus on the major component of skeletal muscle, namely, amino acids. For statistical analysis, the patients were divided into three groups according to their decrease in PMI:  $\leq 5\%$ , 5–11.5%, and  $> 11.5\%$ .

#### Definition and statistical analysis

The preoperative preparation, operative procedures, and postoperative care had been described in our previous studies [6, 7]. Major liver resection was defined as liver resection of three or more segments according to the Brisbane 2000 terminology [37]. The difficulty levels were classified according to the 4-level IWATE criteria [38]. Surgical duration was defined as the time period elapsing from the induction of general anesthesia to endotracheal extubation. The severity of postoperative complications was graded according to the Clavien-Dindo classification [39]. Significant muscle loss was defined as percentage change in PMI (%) more than “mean PMI change (%) – one standard deviation (%)”. The sex-specific cutoff value for sarcopenia was defined as  $6.36 \text{ cm}^2/\text{m}^2$  for men and  $3.92 \text{ cm}^2/\text{m}^2$  for women in the current study [40]. The recurrence of HCC was determined by the emergence of image findings characteristic of HCC with or without elevated tumor markers during routine postoperative follow-up. Disease-free survival (DFS) was defined as the time interval from the date of surgery to the date of first documented disease recurrence. Tumor recurred within 2 years of liver resection was defined as early recurrence. The overall survival (OS) was defined as the time period

spanning from the date of surgery to either the date of death or the date of last follow-up.

Continuous variables were expressed as mean  $\pm$  standard deviation (SD) or median (interquartile range (IQR)) whenever appropriate and analyzed by Student's *t*-test or Mann-Whitney *U*-test. Categorical variables were described by number and frequency (%) and analyzed by Pearson chi-square test. Kaplan-Meier method and long-rank test were adopted to analyze DFS and OS. Logistic regression analysis was employed to identify independent risk factors associated with significant muscle loss after liver resection. Cox proportional hazard model was

adopted to explore prognostic factors predictive of early recurrence. Statistical significance was defined as *P*-value  $< 0.05$ . The statistical analysis was performed by IBM SPSS Statistics 22 (IBM Corporation, Software Group, Somers, NY, USA).

## Results

### Demographic characteristic of LLR and OLR for HCC

The patient demographics and clinical characteristics were similar between the OLR and LLR groups (all *P*  $> 0.05$ ) (Table 1). The mean age of diagnosis was around 60 years, and the majority of patients were male. The mean

**Table 1** Patient characteristics

	LLR <sup>a</sup> (n = 64 (100%))	OLR <sup>b</sup> (n = 64 (100%))	p-value
Age (years) (mean $\pm$ SD <sup>c</sup> (range))	60.2 $\pm$ 11.2	59.5 $\pm$ 11.8	0.729
Male gender, n(%)	49 (76.6)	52 (81.3)	0.516
DM <sup>d</sup> , n(%)	13 (20.3)	16 (25.0)	0.526
Hypertension, n(%)	17 (26.6)	22 (34.4)	0.337
ESRD <sup>e</sup> , n(%)	0 (0.0)	0 (0.0)	1.000
CCI <sup>f</sup> score, median (IQR <sup>g</sup> )	5 (2.7)	6 (2.7)	0.162
ECOG <sup>h</sup> $\geq 2$	5 (7.8)	3 (4.7)	0.718
Smoking, n(%)	16 (25.0)	24 (37.5)	0.127
Alcohol, n(%)	13 (20.3)	18 (28.1)	0.302
BMI (kg/m <sup>2</sup> ) <sup>i</sup> (mean $\pm$ SD <sup>c</sup> )	24.9 $\pm$ 3.5	24.4 $\pm$ 3.3	0.441
Obesity, n(%)	15 (23.4)	15 (23.4)	1.000
Sarcopenia (pre-operative), n(%)	24 (37.5)	23 (35.9)	0.855
Previous abdominal surgery, n(%)	6 (9.4)	8 (12.5)	0.571
Preoperative treatment to HCC, n(%)	5 (7.8)	11 (17.2)	0.180
Child-Pugh class, n(%)			
Class A	64 (100)	64 (100)	1.000
BCLC stage, n(%)			1.000
Stage 0	11 (17.2)	12 (18.8)	
Stage A	51 (79.7)	51 (79.7)	
Stage B	2 (3.1)	1 (1.6)	
Preoperative ascites (n(%))	3 (4.7)	2 (3.1)	1.000
HBV infection, n(%)	37 (57.8)	43 (67.2)	0.273
HCV infection, n(%)	19 (29.7)	18 (28.1)	0.845
Liver cirrhosis, n(%)	27 (42.2)	36 (56.3)	0.157
Fatty liver, n(%)	31 (48.4)	27 (42.2)	0.478
Albumin (g/dL) (mean $\pm$ SD <sup>c</sup> )	4.20 $\pm$ 0.40	4.19 $\pm$ 0.41	0.533
Hemoglobin (gm/dL) (mean $\pm$ SD <sup>c</sup> )	13.7 $\pm$ 1.6	13.9 $\pm$ 1.7	0.503
NLR <sup>j</sup> , median (IQR <sup>g</sup> )	1.83 (0.98)	1.88 (0.85)	0.898
Platelet count (K/uL) (mean $\pm$ SD <sup>c</sup> )	174.7 $\pm$ 48.3	160.7 $\pm$ 53.8	0.121
T-bil (mg/dL), median (IQR <sup>g</sup> )	0.6 (0.5)	0.6 (0.5)	0.266
INR <sup>k</sup> (mean $\pm$ SD <sup>c</sup> )	1.1 (0.1)	1.1 (0.11)	0.370
ICG-15 <sup>l</sup> $> 10\%$ , n(%)	20 (32.3)	21 (32.8)	0.947
$\alpha$ -Fetoprotein $> 200$ ng/mL, n(%)	15 (24.6)	11 (17.2)	0.308

<sup>a</sup>Laparoscopic liver resection, <sup>b</sup>open liver resection, <sup>c</sup>standard deviation, <sup>d</sup>diabetes mellitus, <sup>e</sup>end-stage renal disease, <sup>f</sup>Charlson Comorbidity Index, <sup>g</sup>interquartile range, <sup>h</sup>Eastern Cooperative Oncology Group, <sup>i</sup>body mass index, <sup>j</sup>neutrophil-to-lymphocyte ratio, <sup>k</sup>international normalized ratio, <sup>l</sup>indocyanine green retention rate at 15 min

BMI was 24 kg/m<sup>2</sup>, and about 36% of patients were categorized as sarcopenia before the operation. HBV infection was the most common etiology, and more than 40% of patients had liver cirrhosis. Laboratory parameters including hemoglobin, albumin, bilirubin, prothrombin time, neutrophil-to-lymphocyte ratio, and liver reserve were all comparable between the two groups.

Supplementary Table S2 summarized the pathological features and surgical outcome of the current cohort. The tumor characteristics were essentially comparable between the LLR and OLR groups (all  $P > 0.05$ ). The mean tumor size was around 3 cm, and more than 75% of tumors were encapsulated. Microscopic vascular invasion was identified in about 20%, and around 40% of tumors are categorized as Edmondson-Steiner grades 3 or 4. Stages 1 and 2 tumors comprised more than 90% of cases, and no patients enrolled had extrahepatic metastasis before the operation. Major liver resection accounted for 15% of procedures, and more than 50% of operations were classified as IWATE intermediate difficulty group.

The surgical outcome including surgical time, blood loss, and postoperative major complications, likewise, was comparable between the two groups. The length of postoperative hospital stay, on the other hand, was significantly shorter in the LLR group (9 days in the OLR and 7.5 days in the LLR,  $P < 0.001$ ). While the preoperative albumin level was not different between the LLR and OLR, a significantly lower albumin level was found in the OLR group after the operation (3.46 g/dL in the OLR and 3.63 g/dL in the LLR,  $P < 0.001$ ).

#### Change of PMI in LLR and OLR groups

The mean PMI change of the entire cohort was  $-5.0\%$  with a standard deviation of  $6.5\%$  (Fig. 2A). Significant muscle loss was thus defined as more than  $-5.0\text{--}6.5\%$ , which implied a reduction of more than  $11.5\%$  from the preoperative baseline PMI. Seventeen patients (13.3%) were found to have significant muscle loss after the operation. The PMI and muscle mass status both before and after surgery were summarized in Table 2. Although the perioperative PMI was similar between the two groups, OLR led to a more significant reduction in the PMI than the laparoscopic approach (mean change,  $-6.61\%$  in the OLR group and  $-3.37\%$  in the LLR group,  $P = 0.003$ ) (Fig. 2B). The OLR group also had remarkably more significant muscle loss after surgery than the LLR group (21.9% vs. 4.7%,  $P = 0.008$ ), which further impacted the prevalence of sarcopenia. Before liver resection, the prevalence of sarcopenia was comparable between the LLR and OLR groups. However, ten (15.4%) non-sarcopenic patients in the OLR group developed sarcopenia after surgery, in contrast to only 3 (4.7%) patients in the LLR group ( $P = 0.041$ ).

#### Predisposing factors of significant muscle loss

Univariate analysis was conducted to identify potential factors related to significant muscle loss following liver resection (Supplementary Tables S3 and S4). Laparoscopic approach was found to be associated with less significant muscle loss than the conventional open approach ( $P = 0.008$ ). In addition, larger tumor size ( $P = 0.094$ ),  $AFP > 200$  ng/mL ( $P = 0.024$ ), and tumor rupture ( $P = 0.017$ ) were also correlated with significant muscle loss. Moreover, patients who experienced any grade of postoperative complications ( $P = 0.098$ ) or major complications ( $P = 0.001$ ) were more likely to have significant muscle loss after surgery. The length of postoperative hospital stay was longer among patients who developed significant muscle loss (11 vs. 8 days,  $P = 0.004$ ). Other factors such as age, gender, comorbidity, performance status, body habitus, previous abdominal surgery, liver cirrhosis, liver biochemical function, tumor grade, tumor stage, extent of liver resection, and blood loss, on the other hand, were not related to the occurrence of significant muscle loss after surgery.

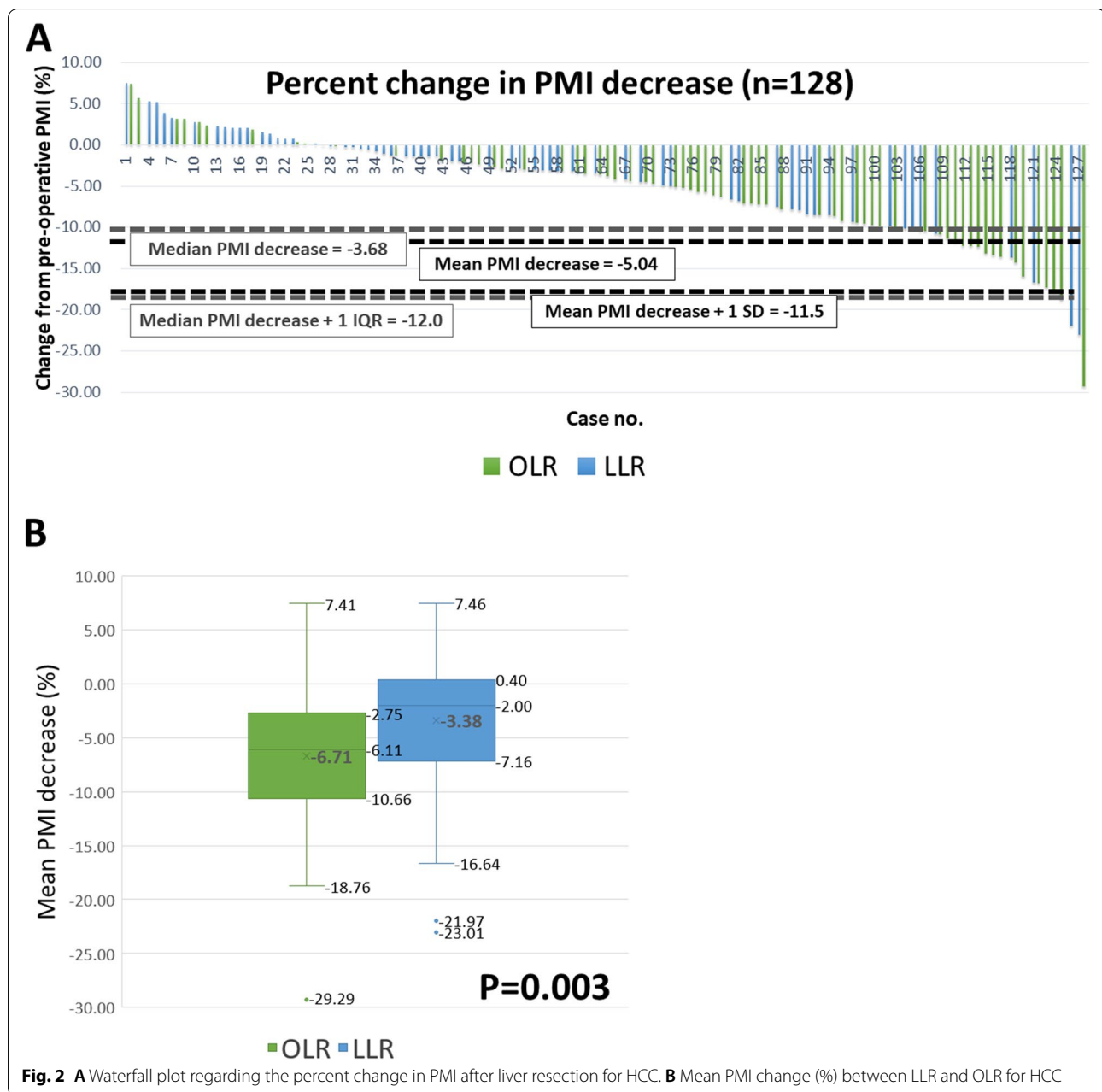
After logistic regression multivariate analysis, conventional open procedure, tumor rupture,  $AFP > 200$  ng/mL, and occurrence of postoperative major complications were independent predisposing factors for the development of postoperative significant muscle loss ( $P = 0.01$ , 0.036, 0.004, and 0.003, respectively) (Table 3).

#### Impact of significant muscle loss on the oncological outcome

The Kaplan-Meier DFS and OS curves of the entire HCC cohort before PSM were shown in Fig. 3A, B. The median DFS of the entire cohort was 38.0 months, and more than 50% of the patients were still alive at the end of this study. As for different surgical approach, the DFS of patients receiving LLR was significantly better than that of OLR ( $P = 0.007$ ), and the OS of patients receiving LLR was marginally superior to that of OLR ( $P = 0.078$ ) (Fig. 4A, B). Regarding the impact of muscle loss, Kaplan-Meier survival analysis demonstrated that the DFS and OS were comparable between patients with and without significant muscle loss ( $P = 0.111$ ,  $P = 0.212$ , respectively) (Fig. 5A, B). However, there was a still trend toward favorable OS in patients without significant muscle loss. Moreover, the rate of early recurrence was significantly higher in patients suffering from significant muscle loss (37.8% vs. 13.7%,  $P = 0.006$ ) (Fig. 3C).

The potential risk factors for early recurrence were further investigated and presented in Table 4. After analyzed by COX proportional hazards models with stepwise backward selection, type 2 diabetes mellitus (DM) ( $HR$  3.05,  $CI$  1.15–8.13,  $P = 0.025$ ), ICG-15  $> 10\%$





**Fig. 2** **A** Waterfall plot regarding the percent change in PMI after liver resection for HCC. **B** Mean PMI change (%) between LLR and OLR for HCC

(*HR* 4.48, *CI* 1.74–11.49, *P* = 0.002), significant muscle loss (*HR* 3.22, *CI* 1.17–8.84, *P* = 0.023), and AJCC cancer stage  $\geq 3$  (*HR* 7.41, *CI* 1.81–30.30, *P* = 0.005) were significantly related to early HCC recurrence.

#### Metabolomic profiles of significant muscle loss

For metabolomic analysis, a total of 58 patients were finally enrolled. After LC-MS study, the concentrations of amino acids were compared between patients with the least and most PMI loss ( $\leq 5\%$  vs.  $> 11.5\%$ ). As shown in

Table 5, serum concentrations of ornithine and citrulline were significantly decreased in patients with PMI loss  $> 11.5\%$ , while those of other amino acids were essentially comparable between patients with the least and most PMI loss.

#### Discussion

Surgical intervention can lead to loss of body skeletal muscle mass and strength due to many physiological perturbations including decreased physical activity,

**Table 2** Change in psoas muscle after liver section for hepatocellular carcinoma

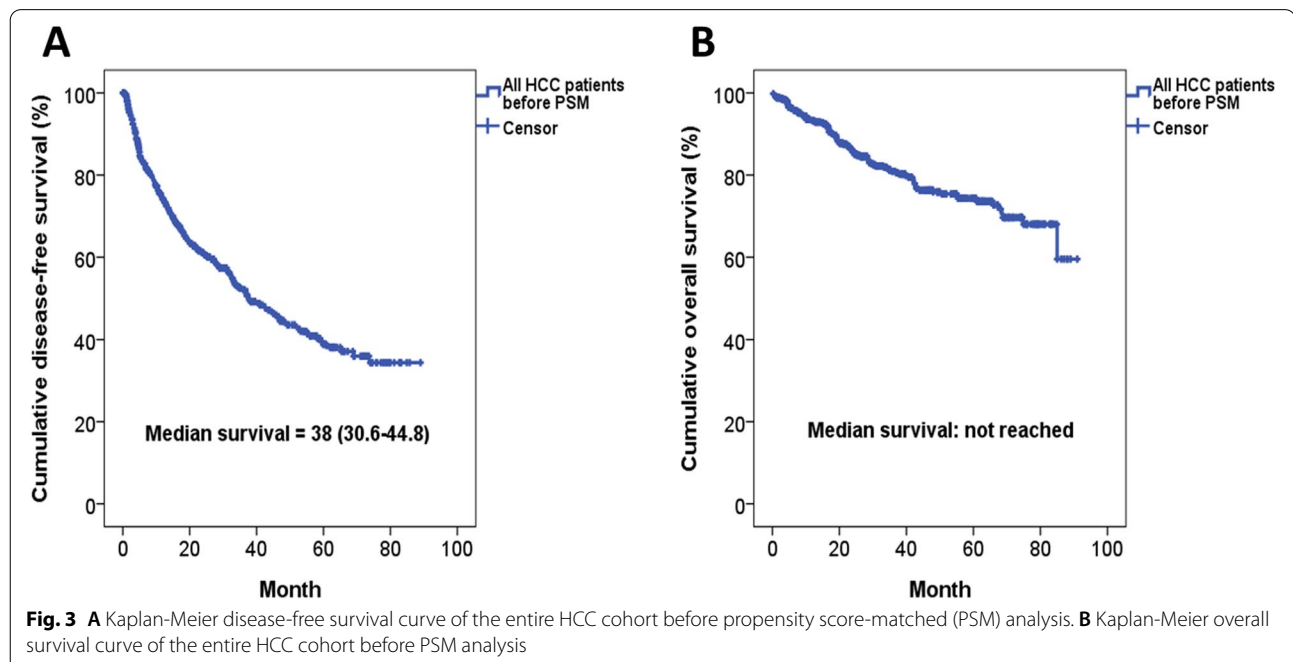
	LLR <sup>a</sup> (n = 64 (100%))	OLR <sup>b</sup> (n = 64 (100%))	p-value
PMI <sup>c</sup> (pre-operative) (mean ± SD <sup>d</sup> )	6.50 ± 2.03	6.36 ± 1.55	0.663
PMI <sup>c</sup> (post-operative) (mean ± SD <sup>d</sup> )	6.24 ± 1.87	5.93 ± 1.49	0.300
Change of PMI <sup>c</sup> % (mean ± SD <sup>d</sup> )	−3.37 ± 5.92	−6.71 ± 6.50	0.003
Median (IQR <sup>e</sup> )	−1.98 ± 7.2	−5.92 ± 7.5	0.001
Significant muscle loss (> 11.5%), n(%)	3 (4.7%)	14 (21.9)	0.008
Sarcopenia (pre-operative), n(%)	24 (37.5)	23 (35.9)	0.855
Sarcopenia (post-operative), n(%)	26 (40.6)	31 (48.4)	0.374
De novo sarcopenia after operation, n(%)	3 (4.7)	10 (15.4)	0.041

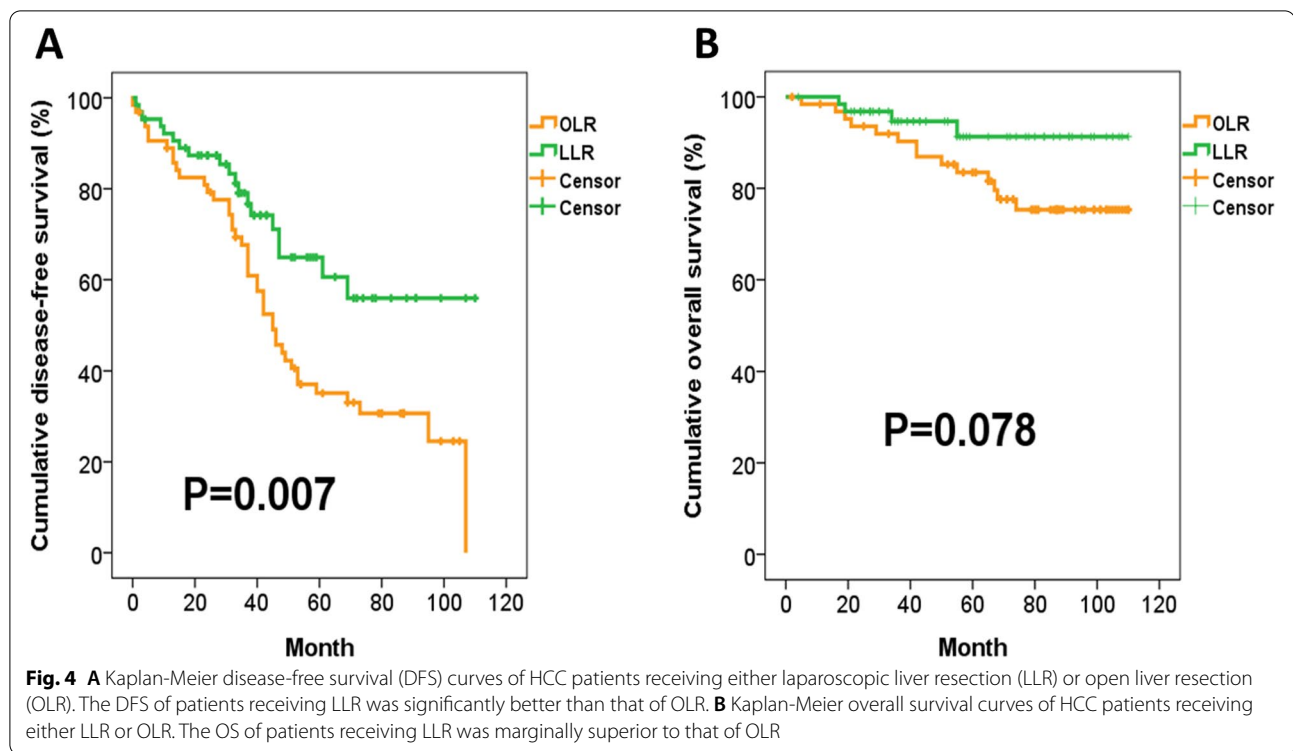
<sup>a</sup> Laparoscopic liver resection, <sup>b</sup>open liver resection, <sup>c</sup>psoas muscle index (cm<sup>2</sup>/m<sup>2</sup>), <sup>d</sup>standard deviation, <sup>e</sup>interquartile range

**Table 3** Univariate and multivariate analysis of risks factors for significant muscle loss

Variables	Univariate analysis		Multivariate analysis	
	Odds ratio	p-value	Hazard ratio (95% CI <sup>a</sup> )	p-value
Operation approach (OLR vs LLR)	5.68	0.008	8.1 (1.6–39.0)	0.010
Tumor rupture (yes vs. no)	11.6	0.017	8.9 (1.15–66.6)	0.036
AFP <sup>b</sup> > 200 ng/mL (yes vs. no)	3.27	0.026	7.4 (1.89–29.4)	0.004
Postoperative complication <sup>c</sup> (any grade vs. none)	2.41	0.098	-	0.820
Grade ≥ III major complication <sup>c</sup> (yes vs. no)	16.7	0.003	18.5 (2.73–125)	0.003
Postoperative length of stay (per day)	1.23	0.002	-	0.110
Tumor size (per cm)	1.34	0.082	-	0.901

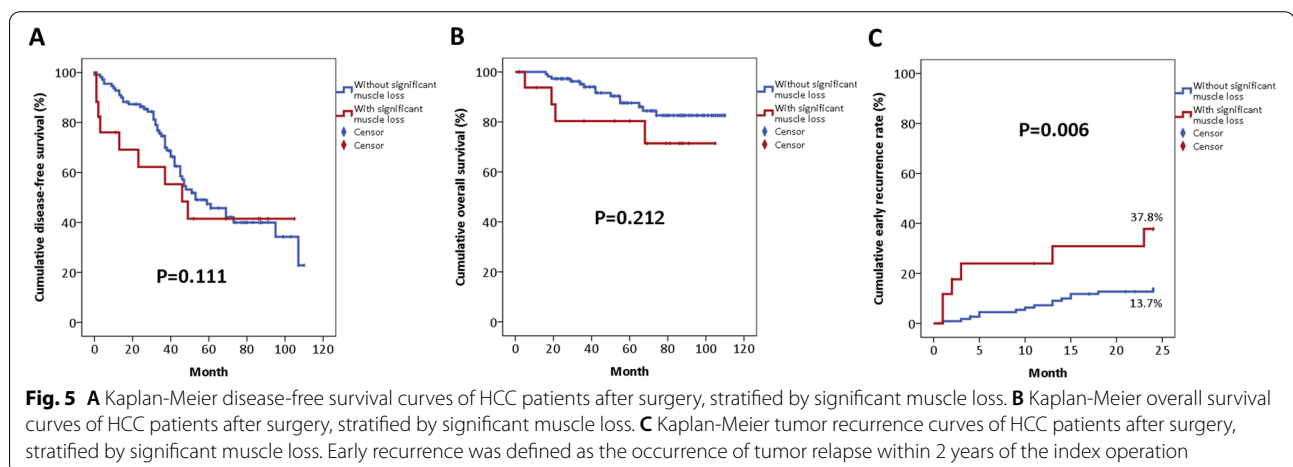
<sup>a</sup> Confidence interval, <sup>b</sup>α-fetoprotein, <sup>c</sup>Clavien-Dindo classification





augmented stress response, increased metabolism, and interruption of essential nutritional support. Moreover, chronic liver disease or liver dysfunction would lead to altered protein turnover, malnutrition, deranged energy disposal, increased inflammation, and hormonal change, which in turn result in muscle depletion and occurrence of sarcopenia [41, 42]. Therefore, development of muscle loss following liver resection seemed inevitable and had been documented [26, 43, 44]. In addition to studies assessing muscle wasting following conventional open liver surgery, Himura et al. revealed that patients receiving laparoscopic liver resection would also experience

muscle loss and deteriorated nutritional status, even in those without preoperative sarcopenia or severe post-operative complications [43]. There have also been other studies investigating the impact of surgery on skeletal muscle mass and subsequent survival in patients with different types of cancers [44] (Supplementary Table S5). However, the impact of different surgical approach on muscle change after liver resection remained undetermined. The present study is by far the first one in the English literature which compared the extent of muscle loss between conventional open and laparoscopic liver resection for HCC. According to the current study, the





**Table 4** Univariate and multivariate analysis of risks factors for early recurrence

Variables	Univariate analysis		Multivariate analysis		Stepwise backward selection	
	Odds ratio (95% CI <sup>a</sup> )	p-value	Hazard ratio (95% CI <sup>a</sup> )	p-value	Hazard ratio (95%CI <sup>a</sup> )	P value
Age > 65 year	1.02 (0.41–2.53)	0.963	-	-	-	-
DM <sup>b</sup>	2.03 (0.78–4.80)	0.153	2.82 (7.51–1.06)	0.038	3.05 (1.15-8.13)	0.025
HBV <sup>c</sup>	1.21 (0.75–1.94)	0.431	-	-	-	-
HCV <sup>d</sup>	1.04 (0.62–1.61)	0.986	-	-	-	-
Liver cirrhosis	2.09 (0.84–5.17)	0.111	1.56 (0.58–4.16)	0.375	-	-
ICG-15 <sup>e</sup> > 10%	3.31 (1.39–7.87)	0.007	4.28 (1.62–11.30)	0.003	4.48 (1.74-11.49)	0.002
AFP <sup>f</sup> > 200 ng/mL	2.28 (0.92–5.67)	0.074	1.83 (0.67–4.98)	0.231	-	-
Significant muscle loss	3.45 (1.33–8.91)	0.010	3.13 (1.08–9.02)	0.034	3.22 (1.17-8.84)	0.023
Pre-op sarcopenia	1.23 (0.49–3.04)	0.654	-	-	-	-
Laparoscopic procedure	0.59 (0.24–1.43)	0.246	-	-	-	-
Tumor rupture	3.58 (0.83–15.43)	0.086	1.16 (0.09–1.42)	0.905	-	-
Resection margin < 0.5 cm	1.42 (0.60–3.34)	0.421	-	-	-	-
Vessel invasion	1.82 (0.73–4.52)	0.194	-	-	-	-
AJCC <sup>g</sup> cancer stage $\geq$ III	3.85 (1.13–13.11)	0.031	6.29 (0.71–55.21)	0.097	7.41 (1.81-30.30)	0.005
Major postoperative complication <sup>h</sup>	1.18 (0.15–8.85)	0.867	-	-	-	-

<sup>a</sup> Confidence interval, <sup>b</sup>diabetes mellitus, <sup>c</sup>hepatitis B virus, <sup>d</sup>hepatitis C virus, <sup>e</sup>indocyanine green retention rate at 15 min, <sup>f</sup> $\alpha$ -fetoprotein, <sup>g</sup>American Joint Committee on Cancer, <sup>h</sup>Clavien-Dindo classification

**Table 5** Serum amino acid profiles between patients with PMI<sup>a</sup> decrease  $\leq$  5% and > 11.5%

Metabolites	PMI <sup>a</sup> decrease $\leq$ 5%	PMI <sup>a</sup> decrease > 11.5%	p-value
Ornithine	143.22 $\pm$ 42.92	103.48 $\pm$ 34.5	0.017
Citrulline	51.44 $\pm$ 28.22	37.62 $\pm$ 11.78	0.048
Threonine	130.18 $\pm$ 32.86	113.00 $\pm$ 29.41	0.173
Tyrosine	89.54 $\pm$ 23.64	78.62 $\pm$ 14.83	0.204
Glycine	216.47 $\pm$ 77.26	191.91 $\pm$ 54.58	0.386
Serine	128.94 $\pm$ 24.76	121.27 $\pm$ 22.76	0.418
Isoleucine	67.53 $\pm$ 22.59	74.04 $\pm$ 19.39	0.444
Tryptophan	36.80 $\pm$ 9.67	34.51 $\pm$ 10.79	0.554
Glutamine	446.48 $\pm$ 132.11	415.31 $\pm$ 146.42	0.554
Histidine	92.30 $\pm$ 14.23	89.29 $\pm$ 16.84	0.603
Asparagine	52.93 $\pm$ 13.73	50.08 $\pm$ 15.24	0.603

<sup>a</sup> Psoas muscle index

PMI decreased more significantly in patients receiving OLR than LLR. Given inherent merits of minimally invasive procedure, laparoscopic approach was expected to produce less stress response and better postoperative physical activity, thus subsequently reducing surgery-related muscle loss.

In the current study, we have demonstrated that conventional open procedure was an independent risk factor for the development of significant muscle loss. Laparoscopic liver resection for HCC, on the other hand, was associated with less significant muscle loss. The advantage of laparoscopic approach in preventing muscle

wasting has also been reported in patients with gastric cancer. Compared to open gastrectomy, laparoscopic gastrectomy was associated with enhanced recovery of muscle mass at 6 months after surgery [45]. In addition, there were other studies revealing the protective effect of laparoscopic procedure on surgery-related muscle loss [26, 46]. Furthermore, the current study found that serum albumin level on the 7th postoperative day was significantly lower in patients receiving open surgery. Our finding paralleled a previous report that laparoscopic procedure may reduce the development of hypoalbuminemia and ascites by protecting the collateral vein circulation of the abdominal wall [47]. Since albumin is known to indicate the global nutritional status, and hypoalbuminemia, similar to sarcopenia, has been found to be predictive of early postoperative outcome after liver resection and its drop is also a marker of stress response, laparoscopic liver resection thus can maintain a better nutritional profile and produce less surgery-related stress response [48, 49]. As a result, the benefits of laparoscopic surgery for HCC could include not only smaller wounds, earlier recovery, less pain, and shorter hospital stay but also more favorable body composition!

In addition to surgical approach, the current study revealed that tumor rupture, larger tumor, AFP > 200 ng/mL, and major complications also predisposed to the development of significant muscle loss. Similar to pancreatic cancer, in which a higher preoperative CA 19-9 was associated with surgical-related muscle loss [22], we have discovered that a more advanced HCC in terms of

AFP or tumor size could also result in more pronounced muscle loss after surgery. Since disease severity is intrinsic to tumors and can hardly be altered, we should thus try to optimize the modifiable variables, i.e., adoption of laparoscopic approach and avoidance of major complications, to minimize skeletal muscle loss after surgery [24, 26, 46].

From the current study, significant muscle loss could impact not only the perioperative recovery but also the oncological outcome. Early recurrence, according to our analysis, was remarkably more likely to occur in patients suffering from significant muscle loss. Since it has been demonstrated that early recurrence was closely related to OS in HCC, clinicians therefore should extreme their efforts to prevent the development of early recurrence in order to prolong OS [50, 51]. Laparoscopic liver resection for HCC, as a result, could be a more favorable surgical approach to reduce the risk of early recurrence by avoiding significant skeletal muscle loss. The mechanism underlying early tumor recurrence, on the other hand, remained undetermined. Whether occult tumor metastasis or impaired immunity may play a role deserves further investigation.

In addition to early tumor recurrence, the current study also discovered that patients having significant muscle loss had considerably lower serum concentrations of ornithine and citrulline after surgery. Both ornithine and citrulline are intermediate metabolites of the urea cycle. This cycle converts highly toxic ammonia to urea for excretion and primarily takes place in the liver [52, 53]. The reduction of ornithine and citrulline after surgery indicated reduced urea cycle, which might represent declined liver function [54]. Furthermore, studies have shown that citrulline was capable of protecting against skeletal muscle wasting by activating the machinery of muscle protein synthesis [55, 56]. Supplementation of citrulline in aged malnourished rats could promote skeletal muscle protein synthesis during periods of malnourishment or low protein intake [57]. The reduced uremic metabolites in human blood were also prominent feature of sarcopenia [58]. As a result, it is speculated that the significant muscle loss after surgery may partly be attributed to diminished citrulline. Whether this citrulline reduction was related to impaired liver ureotelic function remains uncertain and mandates further investigation.

Despite remarking findings, the present study still had several limitations. First, the definition of significant muscle loss was not well established. A 10% decrease in PMI was regarded significant in several cancers including esophageal cancer, pancreatic cancer, and colorectal cancer [22, 23, 25, 59]. In patients with end-stage liver disease receiving living donor liver transplantation, a decrease in  $PMI \geq 11.7\%$  was classified as high muscle

loss [60]. The current study, in which significant muscle loss was defined as percentage change in PMI (%) more than “mean PMI change (%) - one standard deviation (%) = 11.5%,” was similar to previous reports. However, further study is still warranted to precisely define the cut-off for significant muscle loss. Secondly, although PSM has been adopted, selection bias was still inevitable in a retrospective study. Patients who lacked critical clinical data were also unavoidably excluded. The relatively small sample size similarly rendered our findings less convincing. Moreover, the present study examined muscle quantity in terms of psoas muscle area. The quality of skeletal muscle, on the other hand, was not investigated. Future larger scale prospective randomized studies investigating both muscle mass, strength, and quality thus are mandatory to validate our findings. Furthermore, the current study only adopted the IWATE difficulty score to assess the complexity of liver tumors. Other promising and validated scoring systems, for example, the IMM score [61, 62], were not considered. We believe these novel systems should be incorporated in the future studies to precisely describe the difficulty of liver resections. Last but not the least, the clinical significance of decreased citrulline and ornithine in patients with significant muscle loss remained undetermined. The efficacy of citrulline/ornithine supplementation in preventing or restoring muscle loss after surgery also deserves further investigation. Future trials are therefore required to answer these questions.

## Conclusion

In conclusion, our study demonstrated that laparoscopic liver resection was associated with less significant muscle loss than the conventional open approach for HCC patients undergoing liver resection. Significant muscle loss, on the other hand, was a predictive factor for early tumor recurrence after surgery. In addition, it was associated with deranged metabolism of certain amino acids. As a result, laparoscopic HCC resection should lead to a more favorable outcome and must be considered for patients eligible for LLR. Future studies are warranted to validate our findings.

## Abbreviations

AFP:  $\alpha$ -Fetoprotein; AJCC: American Joint Committee on Cancer; BMI: Body mass index; CCI: Charlson Comorbidity Index; CGMH: Chang Gung Memorial Hospital; CI: Confidence interval; DFS: Disease-free survival; DM: Diabetes mellitus; DS: Difficulty score; ECOG: Eastern Cooperative Oncology Group; ESRD: End-stage renal disease; Hb: Hemoglobin; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma; ICG-15: Indocyanine green retention rate at 15 min; IQR: Interquartile range; IRB: Institutional review board; LLR: Laparoscopic liver resection; LOS: Length of stay; NLR: Neutrophil-to-lymphocyte ratio; OLR: Open liver resection; OS: Overall survival; PMI: Psoas muscle index; POD: Postoperative day; PSM: Propensity score matching; SD: Standard deviation.

## Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12957-022-02854-1>.

**Additional file 1: Supplementary Table S1.** The clinicopathological data of the entire cohort.

**Additional file 2: Supplementary Table S2.** Surgical and pathological characteristics.

**Additional file 3: Supplementary Table S3.** Clinical characteristics of patients with significant muscle loss after liver resection.

**Additional file 4: Supplementary Table S4.** Surgical and pathological characteristics of patients with significant muscle loss after liver resection.

**Additional file 5: Supplementary Table S5.** Summary of studies regarding muscle loss after surgery.

## Acknowledgements

We are grateful to all our colleagues in the Division of General Surgery, Department of Surgery, Department of Cancer Center, and Department of Pathology, Linkou Chang Gung Memorial Hospital, and Graduate Institute of Clinical Medical Sciences, Chang Gung University, for their technical assistance. We also appreciate Yi-Ping Liu and Chi-Jen Lo for their assistance in data retrieval and processing.

## Authors' contributions

Conceptualization, RYG, HIT, and CWL; data curation, RYG, CWL, and MCY; formal analysis, RYG, HIT, and KMC; funding acquisition, CWL; methodology, MCY, WCL, and KMC; project administration, CWL; resources, HEW, SFW, and MLC; software, MLC, CCC, and HYC; supervision, CWL, MCY, and WCL; validation, MCY, HIT, WCL, and KMC; visualization, HEW, SFW, and HIT; writing — original draft, RYG; writing — review and editing, HIT and CWL. The authors read and approved the final manuscript.

## Funding

This study was supported by Chang Gung Memorial Hospital (CMRPG3L1641 and CMRPG3L1831).

## Availability of data and materials

All data generated or analyzed during the study are included in this published article. Raw data may be requested from the authors with the permission of the institution.

## Declarations

### Ethics approval and consent to participate

This study was approved by the Institutional Review Boards (CGMH IRB No: 201600940B0, 201602025B0, and 202100068B0) of CGMH. For retrospective study, informed consent was waived according to our institutional guideline.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

### Author details

<sup>1</sup>Division of General Surgery, Department of Surgery, Linkou Chang Gung Memorial Hospital, Guishan, Taoyuan 33305, Taiwan. <sup>2</sup>Graduate Institute of Clinical Medical Sciences, Chang Gung University, Guishan, Taoyuan, Taiwan. <sup>3</sup>College of Medicine, Chang Gung University, Guishan, Taoyuan, Taiwan. <sup>4</sup>Department of Anesthesiology, Linkou Chang Gung Memorial Hospital, Guishan, Taoyuan, Taiwan. <sup>5</sup>Division of General Surgery, Department of Surgery, New Taipei Municipal Tu-Cheng Hospital (built and operated by Chang Gung Medical Foundation), Tu-Cheng, New Taipei City, Taiwan. <sup>6</sup>Department of Gastroenterology and Hepatology, Linkou Chang Gung Memorial Hospital, Guishan, Taoyuan, Taiwan. <sup>7</sup>Metabolomics Core Laboratory, Healthy Aging Research Center, Chang Gung University, Guishan, Taoyuan, Taiwan.

<sup>8</sup>Department of Biomedical Sciences, Chang Gung University, Guishan, Taoyuan, Taiwan. <sup>9</sup>Clinical Metabolomics Core Laboratory, Linkou Chang Gung Memorial Hospital, Guishan, Taoyuan, Taiwan. <sup>10</sup>Department of Nursing, Linkou Chang Gung Memorial Hospital, Guishan, Taoyuan, Taiwan. <sup>11</sup>Department of Cancer Center, Linkou Chang Gung Memorial Hospital, Guishan, Taoyuan, Taiwan.

Received: 27 August 2022 Accepted: 24 November 2022

Published online: 04 December 2022

## References

- He J, Amini N, Spolverato G, Hirose K, Makary M, Wolfgang CL, et al. National trends with a laparoscopic liver resection: results from a population-based analysis. *HPB (Oxford)*. 2015;17:919–26.
- Chen J, Li H, Liu F, Li B, Wei Y. Surgical outcomes of laparoscopic versus open liver resection for hepatocellular carcinoma for various resection extent. *Medicine (Baltimore)*. 2017;96:e6460.
- Kim H, Suh KS, Lee KW, Yi NJ, Hong G, Suh SW, et al. Long-term outcome of laparoscopic versus open liver resection for hepatocellular carcinoma: a case-controlled study with propensity score matching. *Surg Endosc*. 2014;28:950–60.
- Lee JJ, Conneely JB, Smoot RL, Gallinger S, Greig PD, Moulton CA, et al. Laparoscopic versus open liver resection for hepatocellular carcinoma at a North-American Centre: a 2-to-1 matched pair analysis. *HPB (Oxford)*. 2015;17:304–10.
- Di Sandro S, Bagnardi V, Najjar M, Buscemi V, Lauterio A, De Carlis R, et al. Minor laparoscopic liver resection for hepatocellular carcinoma is safer than minor open resection, especially for less compensated cirrhotic patients: propensity score analysis. *Surg Oncol*. 2018;27:722–9.
- Lee CW, Tsai HI, Cheng HT, Chen WT, Hsu HY, Chiu CC, et al. Stapleless laparoscopic left lateral sectionectomy for hepatocellular carcinoma: reappraisal of the Louisville statement by a young liver surgeon. *BMC Gastroenterol*. 2018;18:178.
- Gau RY, Yu MC, Tsai HI, Lee CH, Kuo T, Lee KC, et al. Laparoscopic liver resection should be a standard procedure for hepatocellular carcinoma with low or intermediate difficulty. *J Pers Med*. 2021;11(4):266.
- 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;39:412–23.
- Metter EJ, Talbot LA, Schrager M, Conwit R. Skeletal muscle strength as a predictor of all-cause mortality in healthy men. *J Gerontol A Biol Sci Med Sci*. 2002;57:B359–65.
- Meng SJ, Yu LJ. Oxidative stress, molecular inflammation and sarcopenia. *Int J Mol Sci*. 2010;11:1509–26.
- Stefanaki C, Pervanidou P, Boschiero D, Chrousos GP. Chronic stress and body composition disorders: implications for health and disease. *Hormones (Athens)*. 2018;17:33–43.
- Kou HW, Yeh CH, Tsai HI, Hsu CC, Hsieh YC, Chen WT, et al. Sarcopenia is an effective predictor of difficult-to-wean and mortality among critically ill surgical patients. *PLoS One*. 2019;14:e0220699.
- Makiura D, Ono R, Inoue J, Fukuta A, Kashiwa M, Miura Y, et al. Impact of sarcopenia on unplanned readmission and survival after esophagectomy in patients with esophageal cancer. *Ann Surg Oncol*. 2018;25:456–64.
- Francomacaro LM, Walker C, Jaap K, Dove J, Hunsinger M, Widom K, et al. Sarcopenia predicts poor outcomes in urgent exploratory laparotomy. *Am J Surg*. 2018;216:1107–13.
- Cornet M, Lim C, Salloum C, Lazzati A, Compagnon P, Pascal G, et al. Prognostic value of sarcopenia in liver surgery. *J Visc Surg*. 2015;152:297–304.
- Marasco G, Serenari M, Renzulli M, Alemanni LV, Rossini B, Pettinari I, et al. Clinical impact of sarcopenia assessment in patients with hepatocellular carcinoma undergoing treatments. *J Gastroenterol*. 2020;55:927–43.
- Elliott JA, Doyle SL, Murphy CF, King S, Guinan EM, Beddy P, et al. Sarcopenia: prevalence, and impact on operative and oncologic outcomes in the multimodal management of locally advanced esophageal cancer. *Ann Surg*. 2017;266:822–30.

18. Xu JY, Li C, Zhang H, Liu Y, Wei JM. Total psoas area index is valuable to assess sarcopenia, sarcopenic overweight/obesity and predict outcomes in patients undergoing open pancreatoduodenectomy. *Risk Manag Healthc Policy*. 2020;13:761–70.
19. Zhang Y, Wang JP, Wang XL, Tian H, Gao TT, Tang LM, et al. Computed tomography-quantified body composition predicts short-term outcomes after gastrectomy in gastric cancer. *Curr Oncol*. 2018;25:e411–22.
20. Cao Q, Xiong Y, Zhong Z, Ye Q. Computed tomography-assessed sarcopenia indexes predict major complications following surgery for hepatopancreatobiliary malignancy: a meta-analysis. *Ann Nutr Metab*. 2019;74:24–34.
21. Chang KV, Chen JD, Wu WT, Huang KC, Hsu CT, Han DS. Association between loss of skeletal muscle mass and mortality and tumor recurrence in hepatocellular carcinoma: a systematic review and meta-analysis. *Liver Cancer*. 2018;7:90–103.
22. Choi MH, Yoon SB, Lee K, Song M, Lee IS, Lee MA, et al. Preoperative sarcopenia and post-operative accelerated muscle loss negatively impact survival after resection of pancreatic cancer. *J Cachexia Sarcopenia Muscle*. 2018;9:326–34.
23. Fukuoka T, Maeda K, Nagahara H, Shibutani M, Iseki Y, Matsutani S, et al. Change in PMI during neoadjuvant therapy is a predictive prognostic marker in rectal cancer. *Anticancer Res*. 2019;39:5157–63.
24. Kawakita Y, Motoyama S, Sato Y, Wakita A, Nagaki Y, Imai K, et al. Decreases in the psoas muscle index correlate more strongly with survival than other prognostic markers in esophageal cancer after neoadjuvant chemoradiotherapy plus esophagectomy. *World J Surg*. 2020;44:1559–68.
25. Park SY, Yoon JK, Lee SJ, Haam S, Jung J. Postoperative change of the psoas muscle area as a predictor of survival in surgically treated esophageal cancer patients. *J Thorac Dis*. 2017;9:355–61.
26. van Wijk L, van Duinhoven S, Liem MSL, Bouman DE, Viddeleer AR, Klaase JM. Risk factors for surgery-related muscle quantity and muscle quality loss and their impact on outcome. *Eur J Med Res*. 2021;26:36.
27. Kaneko H, Takagi S, Otsuka Y, Tsuchiya M, Tamura A, Katagiri T, et al. Laparoscopic liver resection of hepatocellular carcinoma. *Am J Surg*. 2005;189:190–4.
28. Mala T, Edwin B, Gladhaug I, Fosse E, Soreide O, Bergan A, et al. A comparative study of the short-term outcome following open and laparoscopic liver resection of colorectal metastases. *Surg Endosc*. 2002;16:1059–63.
29. Buunen M, Gholghesaei M, Veldkamp R, Meijer DW, Bonjer HJ, Bouvy ND. Stress response to laparoscopic surgery: a review. *Surg Endosc*. 2004;18:1022–8.
30. Arsalani-Zadeh R, Ullah S, Khan S, MacFie J. Oxidative stress in laparoscopic versus open abdominal surgery: a systematic review. *J Surg Res*. 2011;169:e59–68.
31. Tohme S, Chidi AP, Sud V, Tsung A. Prognostic nutritional index is associated with survival in patients with unresectable hepatocellular carcinoma treated with radioembolization. *J Vasc Interv Radiol*. 2017;28:470–2.
32. Pinato DJ, North BV, Sharma R. A novel, externally validated inflammation-based prognostic algorithm in hepatocellular carcinoma: the prognostic nutritional index (PNI). *Br J Cancer*. 2012;106:1439–45.
33. Sobin LHGM, Wittekind C. International Union Against Cancer (UICC): TNM Classification of Malignant Tumours. 7th ed. Hoboken: Wiley-Blackwell; 2009.
34. Greene FL, Sobin LH. A worldwide approach to the TNM staging system: collaborative efforts of the AJCC and UICC. *J Surg Oncol*. 2009;99:269–72.
35. Jones KI, Doleman B, Scott S, Lund JN, Williams JP. Simple psoas cross-sectional area measurement is a quick and easy method to assess sarcopenia and predicts major surgical complications. *Colorectal Dis*. 2015;17:O20–6.
36. Tsai HI, Lo CJ, Lee CW, Lin JR, Lee WC, Ho HY, et al. A panel of biomarkers in the prediction for early allograft dysfunction and mortality after living donor liver transplantation. *Am J Transl Res*. 2021;13:372–82.
37. Pang YY. The Brisbane 2000 terminology of liver anatomy and resections. HPB 2000; 2:333–39. HPB (Oxford). 2002;4:99 author reply 99–100.
38. Krenzien F, Wabitsch S, Haber P, Kamali C, Brunnbauer P, Benzing C, et al. Validity of the Iwate criteria for patients with hepatocellular carcinoma undergoing minimally invasive liver resection. *J Hepatobiliary Pancreat Sci*. 2018;25:403–11.
39. Ishii M, Mizuguchi T, Harada K, Ota S, Meguro M, Ueki T, et al. Comprehensive review of post-liver resection surgical complications and a new universal classification and grading system. *World J Hepatol*. 2014;6:745–51.
40. Hamaguchi Y, Kaido T, Okumura S, Kobayashi A, Hammad A, Tamai Y, et al. Proposal for new diagnostic criteria for low skeletal muscle mass based on computed tomography imaging in Asian adults. *Nutrition*. 2016;32:1200–5.
41. Bojko M. Causes of sarcopenia in liver cirrhosis. *Clin Liver Dis (Hoboken)*. 2019;14:167–70.
42. Dasarthy S. Cause and management of muscle wasting in chronic liver disease. *Curr Opin Gastroenterol*. 2016;32:159–65.
43. Hoshi H, Ogawa H, Maeda S, Nakahira S, Osaki M, Kono S, et al. The Influence of Preoperative Sarcopenia on Perioperative Nutritional Status Changes in Laparoscopic Liver Resection: A Single-Institution Retrospective Analysis. *Clin Surg*. 2020;5:2834.
44. Argillander TE, Spek D, van der Zaag-Loonen HJ, van Raamt AF, van Duijvendijk P, van Munster BC. Association between postoperative muscle wasting and survival in older patients undergoing surgery for non-metastatic colorectal cancer. *J Geriatr Oncol*. 2021;12:1052–8.
45. Abdiev S, Kadera Y, Fujiwara M, Koike M, Nakayama G, Ohashi N, et al. Nutritional recovery after open and laparoscopic gastrectomies. *Gastric Cancer*. 2011;14:144–9.
46. Maeda N, Shirakawa Y, Tanabe S, Sakurama K, Noma K, Fujiwara T. Skeletal muscle loss in the postoperative acute phase after esophageal cancer surgery as a new prognostic factor. *World J Surg Oncol*. 2020;18:143.
47. Jiang S, Wang Z, Ou M, Pang Q, Fan D, Cui P. Laparoscopic versus open hepatectomy in short- and long-term outcomes of the hepatocellular carcinoma patients with cirrhosis: a systematic review and meta-analysis. *J Laparoendosc Adv Surg Tech A*. 2019;29:643–54.
48. Hübner M, Mantziari S, Demartines N, Pralong F, Coti-Bertrand P, Schäfer M. Postoperative albumin drop is a marker for surgical stress and a predictor for clinical outcome: a pilot study. *Gastroenterol Res Pract*. 2016;2016:8743187.
49. Golse N, Nunez J, Mazzotta A, Cano L, Bergeat D, Sulpice L, et al. Personalized preoperative nomograms predicting postoperative risks after resection of perihilar cholangiocarcinoma. *World J Surg*. 2020;44:3449–60.
50. Yamamoto Y, Ikoma H, Morimura R, Konishi H, Murayama Y, Komatsu S, et al. Optimal duration of the early and late recurrence of hepatocellular carcinoma after hepatectomy. *World J Gastroenterol*. 2015;21:1207–15.
51. Hsu HY, Yu MC, Lee CW, Tsai HI, Sung CM, Chen CW, et al. RAM score is an effective predictor for early mortality and recurrence after hepatectomy for hepatocellular carcinoma. *BMC Cancer*. 2017;17:742.
52. Mew NA, Pappa MB, Gropman AL. Chapter 57 - Urea cycle disorders. In: Rosenberg RN, Pascual JM, editors. *Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease (Fifth Edition)*. Boston: Academic Press; 2015. p. 633–47.
53. Walker V. Chapter three - Ammonia metabolism and hyperammonemic disorders. In: Makowski GS, editor. *Advances in Clinical Chemistry*. Amsterdam: Elsevier; vol. 67: 2014. p. 73–150.
54. Moretto J, Girard C, Demougeot C. The role of arginase in aging: a systematic review. *Exp Gerontol*. 2019;116:54–73.
55. Ham DJ, Gleeson BG, Chee A, Baum DM, Caldwell MK, Lynch GS, et al. L-Citrulline protects skeletal muscle cells from cachectic stimuli through an iNOS-dependent mechanism. *PLoS One*. 2015;10:e0141572.
56. Allerton TD, Proctor DN, Stephens JM, Dugas TR, Spielmann G, Irving BA. L-Citrulline supplementation: impact on cardiometabolic health. *Nutrients*. 2018;10(7):921.
57. Osowska S, Duchemann T, Walrand S, Paillard A, Boirie Y, Cynober L, et al. Citrulline modulates muscle protein metabolism in old malnourished rats. *Am J Physiol Endocrinol Metab*. 2006;291:E582–6.
58. Kameda M, Teruya T, Yanagida M, Kondoh H. Reduced uremic metabolites are prominent feature of sarcopenia, distinct from antioxidative markers for frailty. *Aging (Albany NY)*. 2021;13:20915–34.
59. Yamazaki Y, Kanaji S, Takiguchi G, Urakawa N, Hasegawa H, Yamamoto M, et al. Skeletal muscle loss after laparoscopic gastrectomy assessed by measuring the total psoas area. *Surg Today*. 2020;50:693–702.
60. Chae MS, Moon KU, Jung JY, Choi HJ, Chung HS, Park CS, et al. Perioperative loss of psoas muscle is associated with patient survival in living donor liver transplantation. *Liver Transpl*. 2018;24:623–33.

61. Goh BKP, Prieto M, Syn N, Koh YX, Teo JY, Lee SY, et al. Validation and comparison of the Iwate, IMM, Southampton and Hasegawa difficulty scoring systems for primary laparoscopic hepatectomies. *HPB (Oxford)*. 2021;23:770–6.
62. Kawaguchi Y, Tanaka S, Fuks D, Kanazawa A, Takeda Y, Hirokawa F, et al. Validation and performance of three-level procedure-based classification for laparoscopic liver resection. *Surg Endosc*. 2020;34:2056–66.

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