



Sarcopenia with systemic inflammation can predict survival in patients with hepatocellular carcinoma undergoing curative resection

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Background: This study aimed to examine the prognostic significance of sarcopenia combined with systemic inflammation in patients who underwent curative hepatectomy for hepatocellular carcinoma (HCC).

Methods: Between January 2010 and July 2019, we identified 159 patients with HCC who underwent curative hepatectomy at three institutional centers. We retrospectively analyzed clinicopathological outcomes, surgical outcomes, platelet lymphocyte ratio (PLR) as a systemic inflammatory marker, and computed tomography (CT)-assessed sarcopenia at the third lumbar vertebra level (L3).

Results: Sarcopenia was noted in 74 (46.5%) of 159 patients and was significantly associated with male sex, low body mass index (BMI), and high PLR. In the multivariate analysis, sarcopenia [hazard ratio (HR): 2.127, P=0.026] and high PLR (HR: 1.971, P=0.038) were associated with a decrease in overall survival (OS) but not in recurrence-free survival (RFS). The combination of sarcopenia and PLR status stratified the 5-year OS into 82.0% (non-sarcopenia and a low PLR), 68.3% (sarcopenia or a high PLR), and 44.4% (sarcopenia and a high PLR) (P=0.001). In the multivariate analysis, “sarcopenia and a high PLR” and “sarcopenia or a high PLR” were revealed to be significant predictors of OS (HR: 4.300, P=0.001 and HR: 2.723, P=0.010, respectively).

Conclusions: Sarcopenia and high PLR were significantly associated with poor OS. The combination of these two factors may be useful for predicting survival of patients with HCC undergoing curative hepatectomy.

Keywords: Sarcopenia; hepatocellular carcinoma (HCC); survival; prognosis; inflammation

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Introduction

Hepatocellular carcinoma (HCC) is one of the most frequent cancers in the world, accounting for approximately 600,000–700,000 deaths per year (1). The prognosis of HCC patients has improved considerably in recent years as a result of the advancements in therapeutic options, such as surgical resection, transarterial chemoembolization (TACE), radiofrequency ablation (RFA), and liver transplantation. However, owing to the high rate of recurrence after curative therapy, the overall prognosis for HCC continues to be poor (2).

Sarcopenia is defined as the decrease of skeletal muscle mass, strength, and function. It has been demonstrated to reduce survival in various clinical conditions, such as cancer, and it diminishes physical ability and survival in elderly, non-cancerous populations (3-5). Sarcopenia is also a significant predictor of poor overall survival (OS) and recurrence-free survival (RFS) in patients undergoing hepatectomy for HCC (6,7).

Carcinogenesis and cancer progression are both influenced by inflammation (8). Systemic inflammation has been found to be an important determinant of disease progression and OS in patients with HCC in a number of studies (9,10). The platelet lymphocyte ratio (PLR) is a frequently used systemic inflammatory marker, and a high PLR is associated with poor prognosis in patients with HCC (11).

Furthermore, the role of systemic inflammation in sarcopenia has been demonstrated in a number of studies (12,13). Systemic inflammation leads to skeletal muscle atrophy, and eventually, cachexia (14). Based on this point, many studies have reported that sarcopenia accompanied by systemic inflammation is associated with poor prognosis in various cancers, including colorectal cancer, head and neck cancers, and esophageal cancer (15-17). However, to the best of our knowledge, no study has examined the impact of sarcopenia combined with systemic inflammation on the prognosis of patients with HCC who underwent curative resection. We hypothesized that sarcopenia in combination with systemic inflammation plays a key role in predicting survival in patients undergoing curative resection for HCC. We present the following article in accordance with the STROBE reporting checklist (available at <https://jgo.amegroups.com/article/view/10.21037/jgo-21-802/rc>).

Methods

Patient selection

We retrospectively examined HCC patients who underwent liver resection at three institutional centers (Hallym, Kang-Nam, and Chun-Cheon Sacred Heart Hospital) between January 2010 and July 2019. During the study period, 254 patients underwent liver resection for HCC. A total of 47 individuals were excluded because they had undergone liver resections for ruptured HCC (n=8), had HCC with additional malignancies (n=13), or had HCC and had undergone prior treatments involving TACE or RFA (n=26). Owing to lack of follow-up, 48 patients were excluded.

The final analysis included 159 patients (*Figure 1*). Postoperative pathological examination confirmed the HCC diagnosis. Demographic information [age, sex, body mass index (BMI), underlying illnesses, and the American Society of Anesthesiologists (ASA) categorization] was collected from electronic medical records. Blood samples were taken from patients before surgery and admission date as part of the standard preoperative workup. The following parameters were obtained: complete blood count results, liver function, hepatitis B and C status, serum alpha-fetoprotein (AFP) level, and the Child-Pugh score. Pathologic data regarding factors such as tumor size, liver cirrhosis, number of tumors, tumor grade, and lymphovascular invasion (LVI) were gathered. Intraoperative data, including surgical procedures [minor hepatectomy (< segmentectomy) *vs.* major hepatectomy (\geq lobectomy)], estimated blood loss, and transfusion, were collected. Estimated blood loss was calculated using the weight of the gauze plus the blood extracted during surgery. The Clavien-Dindo classification was used to grade postoperative complications (18). The study was approved by institutional review board of Chuncheon Sacred Heart Hospital (No. Hallym 2021-10-018). Because of the retrospective nature of the study, the requirement for informed consent was waived. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Treatment and follow-up

The need for hepatectomy and extent of hepatic resection were determined by the size, number, and location of

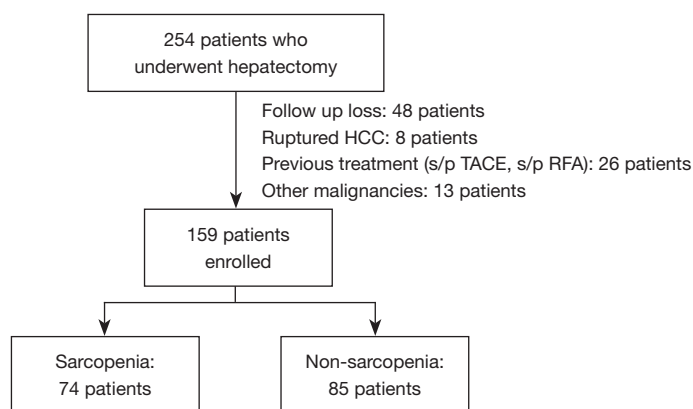


Figure 1 Flow chart for the study. HCC, hepatocellular carcinoma; s/p, status post; TACE, transarterial chemoembolization; RFA, radiofrequency ablation.

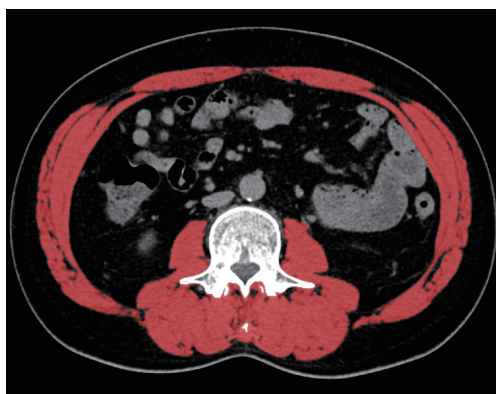


Figure 2 Cross-sectional CT images at the lumbar level. Skeletal muscles (red shadows) were identified and measured from -29 to $+150$ HU. CT, computed tomography.

tumors, as well as liver function and the Child-Pugh score. All patients were routinely followed up after surgical therapy. After discharge, patients were followed up with computed tomography (CT) and magnetic resonance imaging examinations in the third month and at 3–6-month intervals thereafter. RFS was calculated as the duration between surgery and recurrence. The time from surgery to death from any cause or the last follow-up was referred to as OS. Clinical records were used to gather recurrence data. Survival data were obtained from the national register.

Body composition measurement and sarcopenia definition

Skeletal muscles were identified and measured from -29 to $+150$ HU using OsiriX software. In the third lumbar (L3)

area, muscles such as the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis were included (Figure 2). Skeletal muscle index (SMI) (cm^2/m^2) was calculated at the L3 level based on the cross-sectional area of the muscle measured from each image and corrected for height (m^2) to obtain the L3 SMI (cm^2/m^2). According to earlier reports (19), the cut-off values for L3 SMI were defined as $52.4 \text{ cm}^2/\text{m}^2$ for men and $38.5 \text{ cm}^2/\text{m}^2$ for women; sarcopenia was diagnosed when L3 SMI values were less than the cut-off value. Based on the L3 SMI cut-off value, patients were divided into two groups (sarcopenia and non-sarcopenia).

Cut-off value of PLR

PLR was obtained by dividing the platelet count by the absolute lymphocyte count. Preoperative PLR was calculated on the day of admission for liver surgery. The cut-off value for PLR was established to be >132 with an area under the curve of 0.647 using time-dependent receiver operating curves based on prognostic outcomes for OS rates. The Youden index (sensitivity + specificity $- 1$) was used to establish the optimal cut-off value for balancing sensitivity and specificity. The optimal PLR cut-off value of 132 had a sensitivity of 53.2% and a specificity of 82.2%. A high PLR was defined as a PLR greater than 132.

Statistical analysis

The chi-square test and Fisher's exact test were used to compare categorical variables. To compare differences in

continuous variables between patients with and without sarcopenia, the Mann-Whitney U-test was used. The Kaplan-Meier technique was used to estimate survival, and the differences were assessed using the log-rank test. All variables with a P value of 0.05 were included in the multivariate analysis using a Cox proportional hazards model. The statistical significance level was set at $P < 0.05$. SPSS version 21.0 software (SPSS, Chicago, IL, USA) was used for all statistical analyses.

Results

Clinical characteristics

This population comprised 133 men (83.6%) and 26 women (16.4%); their mean age was 59.3 years. A total of 120 patients (75.5%) were positive for antibodies against hepatitis B surface antigen or hepatitis C virus (HCV). The mean tumor size was 4.12 cm (standard deviation, 3.46), and 136 patients (85.5%) had a single tumor. Pathological reports also showed liver cirrhosis in 99 patients (62.3%), LVI in 39 patients (24.5%), and high histological grades [3–4] in 94 patients (59.1%). A total of 116 patients (73.0%) underwent major hepatectomy, and the median estimated blood loss was 788 (range, 395–1,395) mL. Median SMI was 51.08 (range, 44.44–56.78) cm^2/m^2 . *Table 1* shows the characteristics of the patients in the sarcopenia ($n=74$) and non-sarcopenia ($n=86$) groups. Patients in the sarcopenia group had a lower BMI, 91.9% of whom were men. They also had a higher PLR than those in the non-sarcopenia group (median, 106, range, 73–151; and median, 88, range, 64–112; $P=0.004$). The median SMIs were 45.97 (range, 42.55–49.64) and 56.65 (range, 52.86–61.09) cm^2/m^2 in the sarcopenia and non-sarcopenia groups, respectively. The other variables did not differ significantly between the two groups.

Survival analysis

Over a median follow-up period of 45 (range, 31–65) months, 43 patients died, and 89 experienced recurrence. The 5-year OS and RFS rates for the entire cohort were 70.2% and 41.5%, respectively.

In the univariate analysis, tumor size >3 cm, multiple tumors, histology grade 3–4, and a high PLR were significantly associated with RFS. In the multivariate analysis, multiple tumors [hazard ratio (HR): 2.512, 95% confidence interval (CI): 1.467–4.302, $P=0.001$], and

histology grade 3–4 (HR: 2.56, 95% CI: 1.043–2.631, $P=0.033$) were significantly associated with poor RFS. Sarcopenia and a high PLR were not associated with poor RFS (*Table 2*). However, patients with sarcopenia and a high PLR had a reduced OS compared to non-sarcopenic patients with a low PLR. The Kaplan-Meier curve is shown in *Figure 3*. In the univariate analysis, tumor size >3 cm, histology grade 3–4, LVI positivity, sarcopenia, and a high PLR were significantly associated with OS. As shown in *Table 3*, LVI (HR: 2.162, 95% CI: 1.162–4.021, $P=0.015$), sarcopenia (HR: 0.026, 95% CI: 1.092–4.142, $P=0.026$), and a high PLR were associated with a reduction in OS in the multivariate analysis.

Influence of “sarcopenia and PLR status” on survival

Sarcopenia and a high PLR were the only significant prognostic factors for OS in patients with HCC who underwent hepatectomy. We combined these two factors to derive “sarcopenia and PLR status”. Survival was compared between “non-sarcopenia and a low PLR”, “sarcopenia or a high PLR”, and “sarcopenia and a high PLR”. According to sarcopenia and PLR status, the Kaplan-Meier curves were divided into three groups for 5-year OS (non-sarcopenia and a low PLR: 82.0%, sarcopenia or a high PLR: 68.3%, sarcopenia and a high PLR 44.4%; log-rank test: $P=0.001$; *Figure 4*). As sarcopenia and a high PLR are strongly correlated with “sarcopenia and a high PLR status”, we performed a multivariate analysis using the variable “sarcopenia and PLR status” excluding sarcopenia and a high PLR. This analysis showed that “sarcopenia and a high PLR” and “sarcopenia or a high PLR” were significant prognostic factors for OS (HR: 4.300, 95% CI: 1.880–9.834, $P=0.001$; HR: 2.723, 95% CI: 1.271–5.837, $P=0.010$, respectively) (*Table 4*).

Discussion

We investigated the effects of sarcopenia and systemic inflammation on survival after curative hepatectomy in patients with HCC in this study. Our results showed that the presence of sarcopenia and a high PLR were associated with poor OS, but not RFS. The combination of sarcopenia and a high PLR was also found to have a stronger effect on poor survival. To our knowledge, this is the first clinical study to assess the relationship between sarcopenia accompanied by systemic inflammation and survival in patients with HCC who underwent hepatectomy.

Table 1 Baseline characteristics

Variables	Total (n=159)	Sarcopenia (n=74)	Non-sarcopenia (n=85)	P value
Age in years, mean (SD)	59.3 (9.7)	59.7 (9.1)	59.0 (10.3)	0.654
Sex, n (%)				0.009
Male	133 (83.6)	68 (91.9)	65 (76.5)	
Female	26 (16.4)	6 (8.1)	20 (23.5)	
BMI, kg/m ² , mean (SD)	24.80 (3.62)	22.84 (2.85)	26.50 (3.36)	<0.001
Original disease, n (%)				0.155
HBV or HCV	120 (75.5)	52 (70.3)	68 (80.0)	
Others	39 (24.5)	22 (29.7)	17 (20.0)	
Child-Pugh score, n (%)				0.897
A	150 (94.3)	70 (94.6)	80 (94.1)	
B	9 (5.7)	1 (5.4)	5 (5.9)	
Diabetes mellitus, n (%)	52 (32.7)	27 (36.5)	25 (29.4)	0.343
ASA, n (%)				0.165
I/II	105 (66.0)	53 (71.6)	52 (61.2)	
III/IV	54 (34.0)	21 (28.4)	33 (38.8)	
AFP, ng/dL, median [range]	13.0 [4.0–133.5]	14.0 [4.0–188.0]	12.0 [4.0–117.0]	0.894
Liver cirrhosis, n (%)	99 (62.3)	41 (55.4)	58 (68.2)	0.096
Tumor size, cm, mean (SD)	4.12 (3.46)	4.63 (4.03)	3.67 (2.83)	0.082
Tumors number, n (%)				0.750
Single	136 (85.5)	64 (86.5)	72 (84.7)	
Multiple	23 (14.5)	10 (13.5)	13 (15.3)	
Histology grade, n (%)				0.225
1–2	65 (40.9)	34 (45.9)	31 (36.5)	
3–4	94 (59.1)	40 (54.1)	54 (63.5)	
LVI, n (%)	39 (24.5)	19 (25.7)	20 (23.5)	0.754
Major hepatectomy, n (%)	116 (73.0)	52 (70.3)	64 (75.3)	0.477
Transfusion, n (%)	59 (37.1)	32 (43.2)	27 (31.8)	0.135
Estimated blood loss, mL, median [range]	788 [395–1,395]	788 [419–1,408]	799 [350–1,410]	0.804
Clavien–Dindo classification >IIIa, n (%)	19 (12.0)	8 (10.9)	11 (13.0)	0.893
PLR, median [range]	93 [69–126]	106 [73–151]	88 [64–112]	0.004
SMI, cm ² /kg ² , median [range]	51.08 [44.44–56.78]	45.97 [42.55–49.64]	56.65 [52.86–61.09]	<0.001

SD, standard deviation; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; ASA, American society of anesthesiologists; AFP, Alpha-fetoprotein; LVI, lympho-vascular invasion; PLR, platelet lymphocyte ratio; SMI, skeletal muscle index.

Table 2 Prognostic factors for RFS in the univariate and multivariate analyses

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age >60 years	1.262 (0.830–1.918)	0.277		
Male	1.078 (0.617–1.883)	0.792		
BMI <25 kg/m ²	1.189 (0.779–1.814)	0.421		
HBV or HCV	1.235 (0.777–1.963)	0.372		
Child-Pugh score, B	1.054 (0.427–2.601)	0.908		
Diabetes mellitus	1.163 (0.739–1.831)	0.513		
ASA III/IV	0.990 (0.631–1.552)	0.963		
AFP >40 ng/mL	1.496 (0.979–2.84)	0.063		
Liver cirrhosis	1.309 (0.857–1.999)	0.212		
Tumor size >3 cm	1.672 (1.099–2.544)	0.016	1.481 (0.956–2.294)	0.079
Multiple tumor	2.476 (1.453–4.219)	0.001	2.512 (1.467–4.302)	0.001
Histology grade 3–4	1.881 (1.206–2.933)	0.005	2.656 (1.043–2.631)	0.033
LVI, positive	1.441 (0.901–2.306)	0.128		
Major hepatectomy	0.836 (0.522–1.337)	0.454		
Transfusion	1.476 (0.968–2.252)	0.071		
Estimated blood loss >700 mL	1.478 (0.960–2.276)	0.076		
Clavien-Dindo classification >IIIa	1.056 (0.598–1.867)	0.850		
Sarcopenia	1.291 (0.850–1.962)	0.231		
High PLR	1.674 (1.056–2.653)	0.028	1.529 (0.958–2.441)	0.075

RFS, recurrence-free survival; HR, hazard ratio; CI, confidence interval; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; ASA, American Society of Anesthesiologists; AFP, alpha-fetoprotein; LVI, lymphovascular invasion; PLR, platelet-lymphocyte ratio.

Several studies showed that sarcopenia was an independent prognostic factor for both RFS and OS in patients with HCC who underwent surgical resection with curative intent (20,21). Harimoto *et al.* reported that the 5-year OS rates for patients with and without sarcopenia were 71% and 83.7%, respectively, whereas the 5-year RFS rates for patients with and without sarcopenia were 13% and 33.2%, respectively (20). Voron *et al.* observed that sarcopenia was a significant predictor of death (HR: 3.19, 95% CI: 1.28–7.96, P=0.013) and recurrence (HR: 3.03, 95% CI: 1.67–5.49, P=0.001) after liver resection in 198 patients with HCC (21). However, other studies have shown that sarcopenia is related to OS, but not RFS (22–24). Sarcopenia was not related to recurrence in the 120 cases of curative treatment of HCC investigated by Iritani *et al.*, and body fat-free mass did not correlate with

any of the tumor-specific variables, including AFP and protein induced by vitamin K absence-II levels in the blood (22). They concluded that the impact of sarcopenia on HCC development remains debatable. Similarly, in our study, RFS was associated with multiple tumors and histological grade, but not with sarcopenia. Thus, the role of sarcopenia in HCC recurrence remains controversial, and further studies are required.

Inflammation is an important element of tumor development, invasion, and metastasis (8). The prognosis of various cancers, including HCC, has been linked to a systemic inflammatory response. Many factors, such as neutrophil-lymphocyte ratio and PLR, have been developed to predict survival and recurrence in postoperative patients with HCC. In a recent meta-analysis, it was discovered that a high PLR was significantly associated with a worse

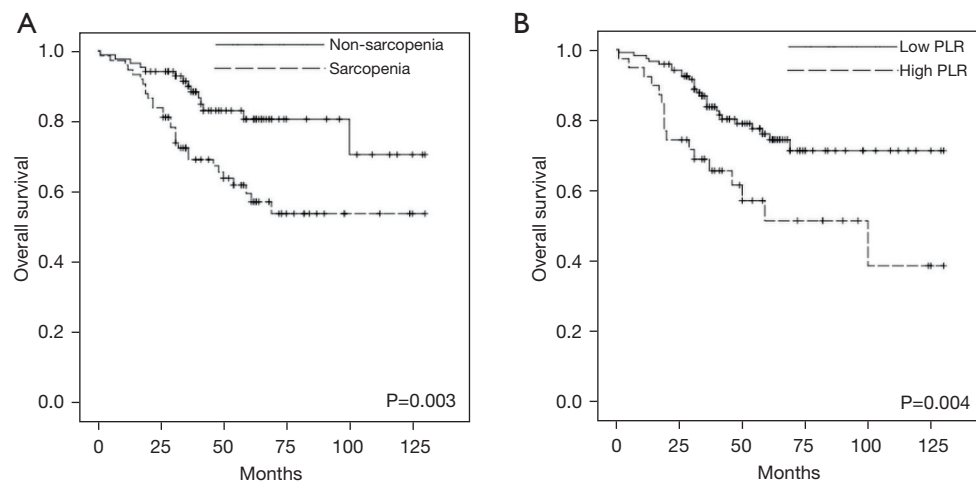


Figure 3 OS curve after curative hepatectomy of patients (A) with or without sarcopenia and (B) with a low PLR or high PLR. PLR, platelet lymphocyte ratio; OS, overall survival.

Table 3 Prognostic factors for OS in the univariate and multivariate analyses

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age >60 years	1.345 (0.738–2.451)	0.333		
Male	0.849 (0.357–2.016)	0.711		
BMI <25 kg/m ²	1.502 (0.801–2.816)	0.205		
HBV or HCV	1.653 (0.870–3.140)	0.125		
Child-Pugh score, B	1.271 (0.307–5.263)	0.741		
Diabetes mellitus	0.985 (0.512–1.893)	0.963		
ASA III/IV	1.597 (0.762–3.346)	0.215		
AFP >40 ng/mL	1.076 (0.580–1.997)	0.816		
Liver cirrhosis	1.249 (0.681–2.291)	0.472		
Tumor size >3 cm	1.916 (1.048–3.504)	0.035		
Multiple tumor	1.633 (0.782–3.410)	0.192		
Histology grade 3–4	1.980 (1.042–3.765)	0.037		
LVI, positive	2.155 (1.160–4.004)	0.015	2.162 (1.162–4.021)	0.015
Major hepatectomy	1.489 (0.786–2.821)	0.222		
Transfusion	1.657 (0.908–3.021)	0.100		
Estimated blood loss >700 mL	1.363 (0.734–2.530)	0.327		
Clavien-Dindo classification >IIIa	1.998 (0.888–4.496)	0.094		
Sarcopenia	2.541 (1.341–4.813)	0.004	2.127 (1.092–4.142)	0.026
High PLR	2.392 (1.296–4.417)	0.005	1.971 (1.039–3.744)	0.038

OS, overall survival; HR, hazard ratio; CI, confidence interval; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; ASA, American Society of Anesthesiologists; AFP, alpha-fetoprotein; LVI, lymphovascular invasion; PLR, platelet-lymphocyte ratio.

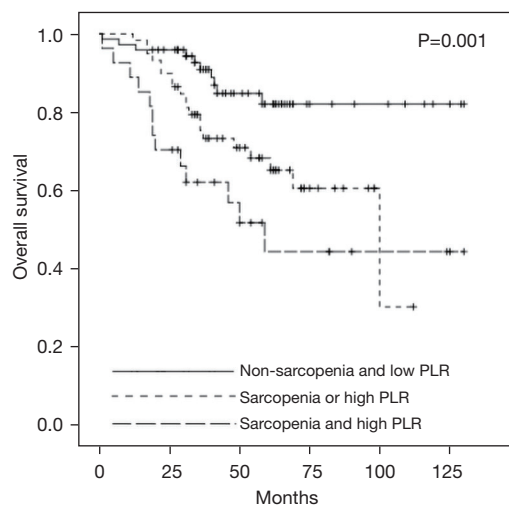


Figure 4 OS curve according to sarcopenia and PLR status. PLR, platelet lymphocyte ratio; OS, overall survival.

Table 4 Multivariate analysis for OS including sarcopenia and PLR status

Variables	Multivariate	
	HR (95% CI)	P value
LVI	2.232 (1.196–4.167)	0.012
Sarcopenia and PLR status		0.001
Non-sarcopenia and a low PLR	Ref.	
Sarcopenia or a high PLR	2.723 (1.271–5.837)	0.010
Sarcopenia and a high PLR	4.300 (1.880–9.834)	0.001

OS, overall survival; PLR, platelet lymphocyte ratio; HR, hazard ratio; CI, confidence interval; LVI, lymphovascular invasion.

OS (HR: 1.60, 95% CI: 1.23–2.08, $P=0.0005$) compared to a low PLR. Additionally, they discovered no obvious correlation between PLR and RFS in patients with HCC (HR: 1.21, 95% CI: 0.87–1.67, $P=0.26$) (11). However, Ji *et al.* reported that a low PLR was a positive predictive factor for disease-free survival in HCC (25). Because of these disputes, further studies investigating the effects of PLR on RFS in patients with HCC are needed.

Many studies have found that systemic inflammation is closely associated with sarcopenia. Systemic inflammation can have a negative impact on skeletal muscle through direct catabolic effects or indirect mechanisms, resulting in muscle breakdown (12). Muscle atrophy caused by such inflammation exacerbates systemic inflammation, which is detrimental to the inflammation-myopenia cycle (26). This

negative cycle may accelerate tumor growth, leading to poor oncological outcomes. As mentioned in the Introduction section, sarcopenia accompanied by inflammation influences the prognosis of various cancers. However, there are few studies on the effect of the combination of inflammation and sarcopenia on the prognosis of patients undergoing liver resection for HCC. We found that a high PLR was significantly associated with sarcopenia. In a large cohort study, Liaw *et al.* found that a high PLR was associated with a higher incidence of sarcopenia in older populations. They concluded that PLR, as a simple parameter, can be used as an inflammatory biomarker for sarcopenia (27). In the present study, when PLR and sarcopenia were combined, the survival curve was stratified, and the multivariate analysis revealed that the combinations of these parameters were independent factors affecting OS. Our findings suggest that sarcopenia with systemic inflammation may be an independent prognostic indicator in patients with HCC undergoing hepatectomy with curative intent.

The retrospective design and limited sample size limit the generalizability of our study findings. Cho *et al.* established SMI cut-off values of $49 \text{ cm}^2/\text{m}^2$ for men and $31 \text{ cm}^2/\text{m}^2$ for women in studies of Korean patients (28). However, the L3 SMI cut-off values utilized in the present study have already been used in many studies, including Asian populations (29). Because of the debate over the prevalence of sarcopenia using CT and the cutoff value of skeletal muscle mass, the definition of sarcopenia used in this study may be inappropriate for Korean patients.

In conclusion, sarcopenia and a high PLR were both significantly associated with poor OS. The combination of these two measures may be beneficial in predicting the survival of patients with HCC undergoing curative resection.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://jgo.amegroupp.com/article/view/10.21037/jgo-21-802/rc>

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Conflicts of Interest: All authors have completed the ICMJE

uniform disclosure form (available at <https://jgo.amegroups.com/article/view/10.21037/jgo-21-802/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by institutional review board of Chuncheon Sacred Heart Hospital (No. Hallym 2021-10-018). Because of the retrospective nature of the study, the requirement for informed consent was waived. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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