

CT-Based Skeletal Muscle Loss for Predicting Poor Survival in Patients With Hepatocellular Carcinoma Experiencing Curative Hepatectomy Plus Adjuvant Transarterial Chemoembolization: a Preliminary Retrospective Study

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Research Article

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Abstract

Background To evaluate the prognostic value of skeletal muscle index (SMI) and its change in patients with hepatocellular carcinoma (HCC) experiencing curative hepatectomy plus adjuvant transarterial chemoembolization (TACE).

Methods and Methods A total of 62 patients with HCC who underwent adjuvant TACE after curative hepatectomy were analysed retrospectively. Skeletal muscle area at the third lumbar level was quantitated using computed tomography images and was normalized for height squared to obtain skeletal muscle index (SMI). Skeletal muscle loss (SML) over six months was computed with two SMIs before and after hepatectomy plus adjuvant TACE. Correlation analyses were performed to investigate factors associated with SML. The curves of cause-specific survival (CSS) were analysed using the Kaplan-Meier method. A Cox proportional hazards model was used to assess prognostic factors.

Results Low SMI was diagnosed in 23(37.1%) patients preoperatively. The median SML standardized by 6 months was -1.6% in the entire cohort. Liver cirrhosis and microvascular invasion correlated negatively with SML respectively ($r=-0.320$, $P=0.002$; $r=-0.243$, $P=0.021$). Higher SML ($<-2.42\%$) predicted a significant reduction in CSS ($P=0.001$), whereas low SMI did not ($P=0.687$). Following the multivariate analysis for CSS, AFP > 400 ng/ml (HR, 5.643; 95%CI, 3.608-17.833; $P<0.001$) and SML $<-2.42\%$ (HR, 6.586; 95%CI, 3.610-22.210; $P<0.001$) were independent predictors for poor CSS.

Conclusions Skeletal muscle loss during hepatectomy plus adjuvant TACE was remarkable. Higher SML was an independent risk factor for CSS in patients with HCC, especially those with liver cirrhosis.

Introduction

Malnutrition is usually observed in patients with chronic liver disease (CLD) and is caused by an imbalance of protein synthesis and breakdown resulting from abnormal liver synthesis, metabolism, detoxification and immune function[1]. However, due to fluid overload or obesity, malnutrition risk evaluation is often overlooked. In fact, malnutrition has recently been highlighted in clinical practice for CLD patients. As a new entity in the International Classification of Diseases, sarcopenia evaluated by low skeletal muscle index (SMI) at radiologic images and grip strength loss has become of increasing importance in clinical management and survival assessment for patients with hepatocellular carcinoma (HCC)[2, 3].

Currently, only performance status and serum albumin contribute to Child-Pugh and MELD scoring as indicators of nutritional condition for HCC patients with CLD, especially in the context of cirrhosis. Since patients with resectable HCC in the real world prone to be classified as having no or low risk owing to well liver function reserve, the differentiation value of some malnutrition screening tools, such as the NRS-2002 or royal-free hospital nutritional prioritization tool, is limited.

SMI measured by radiologic images reflecting skeletal muscle mass has superior accessibility and repeatability in evaluating the quantity of skeletal muscle for HCC patients[4]. Computed tomography (CT) and magnetic resonance imaging were routinely used in the diagnosis of HCC and tumor surveillance in follow-up. The latest review summarized that low SMI or sarcopenia was associated with a poor prognosis for HCC patients in different tumor stages who received liver resection or systemic therapy[5]. As noted, the HCC patients at early stage tend to have better liver function reserve, lower tumor burden and nonsignificant weight loss during treatment, and they recovered

their weight quickly after diet adjustment. Therefore, the occurrence of sarcopenia and the loss of skeletal muscle mass during treatment in such patients may be overlooked extensively.

In the light of positive impact of postoperative adjuvant transarterial chemoembolization (TACE) on prognosis of HCC patients received curative hepatectomy, which was validated in two randomized controlled trials[6, 7], this combined therapy was recommended for the HCC patients at high risk of recurrence in the latest guidelines of primary liver cancer in China[8]. However, Kobayashi, A.et al.[9] showed the skeletal muscle mass is depleted significantly after hepatectomy, and repetitive platinum-based chemotherapy may also yield a negative impact[10-12]. To date, little is known about the prognostic value of SMI or related measurements for patients with HCC experiencing curative hepatectomy plus adjuvant TACE. Herein, this study retrospectively investigated whether the stratification of these HCC patients using skeletal muscle index or related parameters could identify subgroups with different survival risks.

Materials And Methods

Patients Selection

Patients with HCC who underwent adjuvant TACE after curative hepatectomy from January 2015 to December 2020 were consecutively and retrospectively analysed. The presence of at least one high risk characteristic including maximum tumor diameter >5 cm, tumor microvascular invasion (MVI), multiply tumors and liver cirrhosis was indication to perform adjuvant TACE since 2014 in our institution. Inclusion criteria were as follows: curative hepatectomy performed as initial treatment and HCC diagnosed pathologically; the presence of at least one high risk characteristic of poor prognosis; postoperative adjuvant TACE conducted at least once. Exclusion criteria were as follows: abdominal CT images not available within 2 weeks before and 5-8 months after hepatectomy; tumor recurrence found between two CT examinations; a history of other malignancies; patients with missing data or loss of follow-up. The flowchart of this study is shown in Figure 1. The study procedures conformed to the ethical guidelines of the Declaration of Helsinki, and the institutional review board approved this retrospective study. The requirement for informed consent of recruitment was waived.

Hepatectomy and Postoperative Adjuvant TACE

Patients with Barcelona Clinic Liver Cancer Group (BCLC) 0 or A and selective BCLC B stage HCC were candidates for curative hepatectomy referring to all tumor lesions found by preoperative imaging and intraoperative exploration. R0 resection (negative tumor involvement of margin in specimen) was confirmed histologically. Patients with BCLC B stage HCC, whose lesions were located at the same segment or lobe of liver and residual liver volume was sufficient, were considered to be eligible for surgery.

The first TACE was performed 3-4 weeks after hepatectomy. According to the laboratory results and performance status, TACE was conducted again after 4 weeks. Considering that Chinese guideline recommendation and protection of liver function reserve, no more than 3 times TACE sessions were conducted. Hepatic angiography was performed to clarify the liver feeding artery. Chemoembolization, including infusion of 50 mg/m² oxaliplatin, 250 mg/m² fluorouracil, 100 mg/m² calcium leucovorin and embolization of 2-5ml iodized oil, was performed through the left and right hepatic arteries unselectively.

SMI Quantitation

Mimics Research software (Version 19.0, Materialise NV, Leuven, Belgium) was applied to calculate the targeted skeletal muscle area on preoperative and postoperative CT cross-sectional images at the level of the third lumbar

vertebra level (L3), including psoas major, erector spinae, quadratus lumborum, transverse abdominis, internal and external oblique and rectus abdominis. The standard Hounsfield units-derived measurement on CT image as reference methods for quantifying skeletal muscle was proposed by Mitsiopoulos, N. et al[13]. Accordingly, the CT images were segmented by density thresholds ranging from -29 to 150 Hounsfield units, and boundaries of the targeted area were manually adjusted as needed (Figure 2). SMI was derived from the formula: skeletal muscle area(cm²)/height²(m²).

Definitions and Follow-ups

Liver cirrhosis was confirmed by histopathology of the liver parenchyma adjacent to the tumor. Major and minor hepatectomy were defined as the resection of ≥ 1 or < 1 hepatic segments, respectively. The adverse events were categorized as minor and major classifications according to whether the presence of additional therapy, prolonged hospitalization and severe consequences or not[14]. The criteria of low SMI were 42 cm²/m² for men and 38 cm²/m² for women recommended by the working group for creation of sarcopenia assessment criteria of Japan Society of Hepatology[15]. Multiphase CT and laboratory tests were performed 1 month after resection, every 3 months thereafter. The quantitative assessment of SMI change was obtained using the following formula: SML = [(postoperative SMI – preoperative SMI) × 180 / interval days between CT examinations] / pre-operative SMI × 100%. The endpoint was cause-specific survival (CSS), defined as the interval between hepatectomy and the date of the last follow-up (30th April, 2021) or death. The cause of death was HCC or liver disease-related events (i.e., liver failure, variceal bleeding or hepatic encephalopathy).

Statistical Analysis

Continuous variables expressed as the mean \pm standard deviation or median (interquartile range) were compared by two-sample *t* tests or Mann–Whitney *U* tests, and categorical variables expressed as number (percentage) were compared by χ^2 test or Fisher's exact tests. Correlation analyses were performed using the Spearman or Kendall's tau-b analysis. The optimal cut-off value of SML was obtained by the receiver operating characteristic (ROC) curve according to the Youden index related to the endpoints. Survival curves were generated by using the Kaplan–Meier method and analysed with the log-rank test. A Cox proportional hazard model was used to analyse prognostic factors of CSS. Univariable analyses were performed after proportional hazard verification, and variables with *P* < 0.1 were included in multivariate analysis. *P* < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS statistics software (Version 26.0; IBM Corp., Armonk, NY) and R software (version 4.0.3.; [http:// www.r-project.org/](http://www.r-project.org/))

Results

Patient Demographics

A total of 62 HCC patients were eligible to be reviewed in this study. The baseline demographic and clinical characteristics of all patients are listed in Table 1 and Appendix Table 1 according to different SML groups and SMI groups respectively. The optimal cut-off value of SML was -2.42%, as determined by ROC curve analysis. Compared with the lower SML group, patients in the higher SML group (SML < -2.42%) had a higher frequency of liver cirrhosis (*P* = 0.005), tumor MVI (*P* = 0.048) and neutrophil to lymphocyte ratio (NLR) level (*P* = 0.026), but fewer TACE sessions (*P* = 0.031). Additionally, male patients with a higher baseline SMI had more skeletal muscle loss (*P* = 0.021). In the entire cohort, liver cirrhosis was identified in 36 (58.1%) patients. Low SMI was diagnosed in 23 (37.1%) patients preoperatively. The median time between two CT examinations was 188 (164–218) days. A total of 164 adjuvant TACE

sessions were administrated and all adverse events related to interventional procedures were nonsignificant, mainly including embolism syndrome and mild decreasing appetite. Baseline Child-Pugh A class was observed in all participants, and there was no deterioration of Child-Pugh class after combined treatment.

The impacts of SMI and SML on CSS

The cumulative CSS at 1, 3 and 5 years was 100.0%, 85.8% and 67.0%, respectively. Baseline SMI based on Japanese criteria was unable to stratify the liver-related mortality risk of patients ($P=0.687$, Figure 3a).

The follow-up times in lower and higher SML groups were 36.1(19.2-45.1) months and 21.6(17.4-32.8) months, respectively. During the follow-up, Four (10.0%) out of the 40 patients in the lower SML group died, and the cumulative CSS at 1, 3 and 5 years was 100%, 93.6% and 82.6%, respectively. Nine (40.9%) out of the 22 patients in the higher SML group died, and the cumulative CSS at 1, 3 and 5 years was 100%, 71.4% and 38.1%, respectively. The difference in CSSs between the two groups was statistically significant (median CSS: NA vs. 911.0 days, $P=0.001$, Figure 3b).

Features of SML between patient subgroups

The median SML standardized by 6 months was -1.6% in the entire cohort. Correlation analyses were used to further clarify the potential relationship between SML and other characteristics, including clinical variables (sex, age, BMI, BCLC class, tumor number, maximum tumor diameter, tumor differentiation, MVI, cirrhosis and TACE sessions) as well as routine laboratory values (TBIL, ALT, AST, PLT, AFP and NLR). Only two factors, the presence of cirrhosis ($r=-0.320$, $P=0.002$) and MVI ($r=-0.243$, $P=0.021$), were negatively correlated with SML. Besides, patients with cirrhosis had a higher SML than those without cirrhosis (median SML: -2.52 % vs 0.69%, $P=0.003$, Figure 4a). Likewise, a higher SML was seen in the patients with MVI than those without MVI (median SML: -3.32 % vs -0.90%, $P=0.016$, Figure 4b). When the cohort was divided into different subgroups according to NLR level categorized by median value or TACE sessions (>2), there was no significant differences in SML between different subgroups, respectively ($P=0.746$; $P=0.081$).

Association between lower SML and poor CSS

Subgroups analyses were performed as per imbalanced variables between lower and higher SML groups, thereby minimizing the effects of confounding factors. As exploratory analyses showed, the higher SML was associated with reduced CSS in all subgroups stratified by the presence of cirrhosis or MVI (cirrhosis subgroup: $P=0.016$, Figure 5a; non-MVI subgroup: $P=0.005$, Figure 5d), despite with an equivocal difference in the non-cirrhosis subgroup and MVI subgroup ($P=0.319$, Figure 5b; $P=0.110$, Figure 5c).

Multivariate analysis for CSS identified AFP >400 ng/mL (HR:5.643, 95%CI:3.608–17.833, $P<0.001$) and SML $<-2.42\%$ (HR:6.586,95%CI:3.610-22.210, $P<0.001$) were independently predictive of poor CSS (Table 2).

Discussion

In this retrospective study, the skeletal muscle index of HCC patients experiencing curative hepatectomy plus adjuvant TACE significantly decreased over 6 months. More skeletal muscle mass loss served as an independent predictor of poor survival for HCC patients.

In advanced HCC patients, low SMI or sarcopenia was more common and proved to have a negative impact on these patients undergoing systemic therapy or intra-arterial therapy[16-18]. Indeed, the incidence of low SMI or sarcopenia

in HCC patients who received curative treatments was also high and worthy of attention. In this study, low SMI patients accounted for 37.1% of study subjects, which was similar to 14.0-40.3% reported in previous studies[19-22]. Comparing to distribution of age or sex and the frequency of liver cirrhosis or chronic liver disease among these studies, it seems that the prevalence of low SMI was in accordance with liver disease progression. Besides, the effect of tumor burden led to reduced SMI due to decreasing appetite, increasing protein decomposition and aggravation of systemic inflammatory response[18, 23].

In addition, some prior studies also identified either low SMI or sarcopenia as indicative of recurrence and reduced survival for HCC patients undergoing hepatectomy[19, 24-26]. However, this study indicated that preoperative SMI did not stratify liver-related mortality risk, which could be a result of different endpoint and additional adjuvant TACE treatment.

When the presence of risk factors determined after curative hepatectomy for HCC patients, the combined therapy, namely curative hepatectomy plus adjuvant TACE, is an appropriate therapy. However, there were no studies elucidating the impact of skeletal muscle loss on such patients previously. As an integrated course of treatment aiming to achieve curative effect, skeletal muscle mass depletion should be quantified during a period of combined treatment rather than hepatectomy alone. Hence, the potential impact of TACE on skeletal muscle mass was considered in our study.

Our data showed that the median SML over 6 months was -1.6% in the cohort of patients with Child-Pugh A class. A study found that the annual change rate in skeletal muscle mass at the level of L3 in counterparts was -1.3%[27]. This demonstrated that SML during hepatectomy plus adjuvant TACE was also significant. In a study concerning changes in body composition for HCC patients underwent hepatectomy, the psoas muscle index was measured at different time points after surgery and measurements failed to exceed preoperative level in the following two years[9]. It is surmised that the loss of skeletal muscle mass caused by hepatectomy could last for a quite long time. Notably, skeletal muscle loss varied individually in this study. This could be attributed to the heterogeneity of individual liver function reserve and adjuvant TACE treatment.

Increasing evidence has demonstrated that more skeletal muscle loss may be related to poor tumor characteristics, such as MVI, larger tumor size and worse liver function, but not the treatment itself. Our results showed more skeletal muscle mass loss during treatment was associated with cirrhosis, MVI and inflammatory status, which is in line with the findings of other studies, and a negative correlation was observed between SML and liver cirrhosis as well as MVI. Recently, researchers have found that there was a distinct decrease in skeletal muscle mass per TACE cycle, and the degree of skeletal muscle mass depletion was a risk factor for overall survival[10, 11]. They further proposed that the SML after the first TACE largely reflected worse tumor characteristics, and the liver function reserve was the main factor affecting SML in subsequent TACE cycles. Similarly, a study enrolling HCC patients who underwent radiotherapy to the liver demonstrated that HCC patients newly diagnosed with sarcopenia after radiotherapy had more Child-Pugh B or C as well as a larger tumor burden[28]. Another report including 603 patients with cirrhosis identified a higher NLR level in patients with severe sarcopenia than those in non- and sarcopenic groups[29]. In addition, Voron, T. et al.[19] thought sarcopenia was associated with HCC satellite lesions and MVI.

This study revealed that SML could evidently differentiate survival stratification. In spite of no statistical significance in some subgroups, it is probably related to the limited sample size. In the comparison of SMI, skeletal muscle mass loss and its rate may be more likely to reflect the response of patient's condition to therapeutic intervention. A cohort study also showed that the rate of muscle loss was a robust predictor for mortality in patients with cirrhosis instead of other single muscle mass-related measurements[30].

Our results showed that SML < -2.42% remained a significant independent risk factor for reduced CSS, indicating that the effect of skeletal muscle loss on prognosis was not the result of concomitant presence of adverse factors but rather the progression of liver dysfunction and worse general clinical condition. A mounting number of studies have unveiled that skeletal muscle mass loss was associated with pathophysiological alternations in the body, including decreased hepatic glycogen synthesis, hyperammonemia, glycogenolysis, myostatin, autophagy, and proinflammatory cytokines as well as endocrine changes[1, 31, 32]. However, more explorations are required in the underlying mechanisms.

To date, there is only general guidance for the prevention and treatment of sarcopenia without a distinct role on decision-making in clinical settings. Our study suggested individual skeletal muscle loss and its rate were quite remarkable, especially for HCC patients with cirrhosis. Accordingly, it is necessary to increase awareness of declining skeletal muscle index during radiologic follow-up. If obvious skeletal muscle loss is observed, nutrition- supporting interventions, such as late evening snack, branched-chain amino acid supplementation and in-hospital exercise, should be considered[33-35].

The limitation of this study should be recognized. First, the data were retrospectively collected and analysed from a single center. Second, due to a lack of skeletal muscle function evaluation, sarcopenia could not be defined strictly, but the loss of skeletal muscle mass could be precisely quantified[36]. Third, because of the limited sample size of certain subgroup, some conclusions need to be further validated.

Conclusion

In conclusion, skeletal muscle loss during curative hepatectomy and adjuvant therapy has a detrimental impact on liver-related survival for patients with HCC, and seems to indicate poor liver and tumor characteristics.

Abbreviations

skeletal muscle index (SMI); skeletal muscle loss (SML); hepatocellular carcinoma (HCC); chronic liver disease (CLD); transarterial chemoembolization (TACE); cause-specific survival (CSS); Computed tomography (CT); microvascular invasion (MVI); Barcelona Clinic Liver Cancer Group (BCLC); receiver operating characteristic (ROC); neutrophil to lymphocyte ratio (NLR); the third lumbar vertebra level (L3)

Declarations

Ethics approval and consent: this retrospective study gained the approval from Capital Medical University affiliated Beijing Friendship Hospital's institutional review board in China. The registration number is 2021-P2-272-01.

Consent for publication: not applicable.

Data availability statement: The datasets generated or analyzed during the study are not publicly available due to the data of DICOM including patients' intimate information but are available from the corresponding author on reasonable request.

Competing interests: none.

Funding: none.

Author contributions

Siwei Yang, Zhiyuan Zhang proposed the conception and design; Siwei Yang, Zhiyuan Zhang, Tianhao Su conducted the development of methodology; Siwei Yang, Jianan Yu, Shasha Cao, Haochen Wang performed the analysis and interpretation of data; Siwei Yang, Zhiyuan Zhang, Long Jin performed the writing, review, and revision of the manuscript; Long jin assisted in the administration, or material support.

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Tables

Figures

Figure 1

Flowchat shows patient selection.

Figure 2

Skeletal muscle loss marked by green mask over 171 days in a 52-year-old man with a single moderate differentiated HCC lesion. (a) Preoperative skeletal muscle index (SMI) on axial CT image at the L3 level was 46.97 cm²/m². (b) postoperative SMI at the same plane on CT image was 40.82 cm²/m².

Figure 3

Table 1 Baseline demographic and clinical characteristics in higher and lower SML groups

variable	Total (n=62)	higher SML (n=22)	lower SML (n=40)	<i>P</i> value	
Sex (male)	49(79.0)	17(77.3)	32(80.0)	0.801	
Age (year)	59.39±10.6	57.3±11.2	60.5±10.2	0.258	
BMI (kg/m ²)	male	24.1±3.4	24.8±3.2	23.7±3.5	0.291
	female	22.5±3.2	21.8±1.7	23.0±3.9	0.557
SMI (kg ² /m ²)	male	45.0±6.9	48.0±8.1	43.3±5.6	0.021
	female	39.0±5.5	39.5±8.4	38.6±3.2	0.820
SML (%)	male	-1.5±3.2	-4.9±1.5	0.38±2.1	<0.001
	female	-1.4±3.2	-4.9±1.3	0.60±1.8	0.002
Aetiology (HBV/HCV/others)	49(79.0)/3(4.8)/10(16.1)	19(86.4)/0/3(13.6)	30(75.0)/3(7.5)/7(17.5)	0.473	
BCLC (0/A/B)	6(9.7)/53(85.5)/3(4.8)	4(18.2)/16(72.7)/2(9.1)	2(5.0)/37(92.5)/1(2.5)	0.109	
Tumor number (solitary/multiple)	54(87.1)/8(12.9)	19(86.4)/3(13.6)	35(87.5)/5(12.5)	0.898	
Maximum tumor diameter (cm)	4.3±2.1	3.9±2.3	4.5±1.9	0.278	
Differentiation(well or moderate/poor)	54(87.1)/8(12.9)	18(81.8)/4(18.2)	36(90.0)/4(10.0)	0.438	
Hepatectomy (major/minor)	49(79.0)/13(21.0)	18(81.8)/4(18.2)	31(77.5)/9(22.5)	0.756	
MVI (presence/absence)	13(21.0)/49(79.0)	8(36.4)/14(63.6)	5(12.5)/35(87.5)	0.048	
Cirrhosis (presence/absence)	36(58.1)/26(41.9)	18(81.8)/4(18.2)	18(45.0)/22(55.0)	0.005	
TACE sessions (1/2/3)	5(8.1)/12(19.4)/45(72.6)	1(4.5)/8(36.4)/13(59.1)	4(10.0)/4(10.0)/32(80.0)	0.031	
Child-Pugh class (A/B)	62(100.0)	22(100.0)/0	40(100.0)/0	-	
MELD-Na score	7.0(6.0~9.0)	7.0(6.0~8.0)	7.0(6.0~9.0)	0.359	
ALB (g/L)	40.0±3.8	39.8±4.2	39.7±3.6	0.878	
TBIL (umol/L)	15.5(11.9~22.6)	14.3(11.6~17.0)	16.8(13.1~24.7)	0.064	
ALT (U/L)	23.0(17.0~31.3)	24.5(15.0~30.3)	22.0(18.0~39.3)	0.466	
AST (U/L)	29.2(22.6~36.6)	26.5(21.0~32.5)	30.7(23.1~36.9)	0.406	
PLT (10 ⁹ /L)	159.4±59.4	153.6±62.8	162.3±58.0	0.573	
AFP (ng/ml)	20.7(2.7~305.9)	53.6(2.6~325.4)	15.0(2.8~297.9)	0.953	
NLR	1.9±1.0	2.3±1.1	1.7±0.9	0.026	

Table 2 Univariate and multivariate analysis using Cox proportional hazards model for cause-specific survival				
Variables	Univariate analysis		Multivariate analysis	
	HR[95%CI]	P value	HR[95%CI]	P value
Age (>60y)	0.384 (0.122~1.202)	0.288		
Sex (male)	2.053 (0.453~9.308)	0.351		
SML (<-2.42%)	5.761 (1.761~18.848)	0.004	6.586 (3.610~22.210)	<0.001
BMI (>23 kg/m ²)	3.316 (1.018~10.802)	0.147		
Maximum tumor diameter (>5 cm)	1.429 (0.466~4.384)	0.532		
tumor number (multiple)	1.871 (0.513~6.826)	0.343		
MVI	1.163 (0.319~4.238)	0.819		
Cirrhosis	2.158 (0.593~7.845)	0.243		
BCLC (B)	2.582 (0.571~11.688)	0.218		
TBIL (>17.1ummol/L)	0.724 (0.233~2.355)	0.591		
ALB (<35 g/L)	3.333 (0.730~15.212)	0.120		
ALT (>40 U/L)	0.330 (0.043~2.541)	0.287		
PLT (<100×10 ⁹ /L)	2.364 (0.648~8.626)	0.193		
AFP (>400 ng/ml)	4.478 (1.494~13.419)	0.007	5.643 (3.608~17.833)	<0.001
TACE (>2 sessions)	0.561 (0.172~1.822)	0.336		
NLR (>1.83*)	1.127 (0.378~3.364)	0.830		
*median value;				

Comparisons of Survival curves in different SMI or SML subgroups. (a) Cumulative CSS curves between the baseline low and high SMI groups. (b) Cumulative CSS curves between the lower and higher SML groups.

Figure 4

(a) Boxplot diagram showed patients with cirrhosis had higher SML than those without cirrhosis (median SML: -2.52 % vs 0.69%, P=0.003). (b) higher SML was observed in patients with MVI than those without MVI (median SML: -3.32 % vs -0.90%, P=0.016).

Figure 5

Subgroup analyses for CSS between lower and higher SML groups. (a) Patients with higher SML had a reduced CSS in the patients with cirrhosis. (b) No significant difference was found in CSS between patients with lower and higher

SML subgroups in non-cirrhosis patients. (c) A trend towards an impaired CSS was observed in patients with higher SML in patients with MVI.(d) Patients with higher SML had a reduced CSS in the patients with non-MVI.

Supplementary Files

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