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Combined impact of myosteatosis and liver steatosis on prognosis in stage I–III colorectal cancer patients

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Abstract

Background Myosteatosis and liver steatosis (LS) have been recognized as patient-derived image biomarkers that correlate with prognosis in colorectal cancer (CRC) patients. However, the significance of considering fat deposition in multiple body areas simultaneously has been underestimated. This study aimed to investigate the combined effect of myosteatosis and LS in stage I-III CRC patients.

Methods A total of 616 stage I-III CRC patients were included in the study. Myosteatosis was assessed using skeletal muscle radiodensity (SMD), and LS was estimated by calculating the Hounsfield unit of the liver and spleen ratio (LSR). Cox proportional hazard models were utilized to evaluate disease-free survival (DFS). A combination of myosteatosis and LS was proposed, and its discriminatory performance was compared using the C-index.

Results Among the 616 participants, the median (interquartile) age was 64 (55–72) years, and 240 (38.9%) were female. The median and interquartile range of LSR were determined as 1.106 (0.967–1.225). The optimal cutoff value for LSR was identified as 1.181, leading to the classification of patients into low (410, 66.5%) and high LSR (206, 33.4%) groups. Among the patients, 200 were categorized into the low SMD group, while 416 were allocated to the high SMD group. Both myosteatosis and LS were identified as independent prognostic factors in the multivariable analysis. The combination of these two variables resulted in a three-group classification: high SMD with low LSR group, high SMD with high LSR group, and low SMD group. When comparing the C-index values, the three-group classification exhibited superior discriminatory performance compared with considering myosteatosis and LS separately.

Conclusions Myosteatosis was associated with poorer survival, while the presence of LS was linked to a better prognosis in non-metastatic CRC patients. Simultaneously considering fat infiltration can serve as a more effective prognosticator in non-metastatic CRC patients.

Keywords Colorectal cancer; HU; Liver fat infiltration; Myosteatosis

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Introduction

Colorectal cancer (CRC) ranks third among the most prevalent cancers globally and is the second leading cause of cancer-related deaths worldwide.[1] Thanks to advancements in early cancer detection and collaborative approaches, the 5-year survival rate for CRC has consistently improved.[2,3] In South Korea, CRC is projected to be the fourth most common cancer among men and the third most fatal, while among women it ranks second in terms of mortality.[4]

Myosteatosis, characterized by the accumulation of fat in skeletal muscles, is a commonly observed phenomenon that tends to increase with age and was recognized to negatively related with muscle mass, mobility, strength and metabolism

that cause to insulin resistance or diabetes.[5] Researchers have explored the prognostic significance of myosteatosis in cancer patients and found that its correlation varied depending on factors such as race, cancer location, and place of residence.[5] Overall, individuals classified as belonging to the myosteatosis group, as determined by skeletal muscle radiodensity (SMD), exhibited a 75% higher risk of mortality [hazard ratio (HR) 1.75, 95% confidence interval (CI), 1.60–1.92] compared with those in the non-myosteatosis group.[6]

A previous study demonstrated that the presence of ectopic fat accumulation in the liver is independently associated with poorer overall survival (OS) in patients with colorectal liver metastasis (CRLM).[7] Prolonged storage of lipids in the liver can lead to liver dysfunction and inflammation, which play a crucial role in creating a metastatic-friendly environment that facilitates cancer seeding and colonization.[8] Moreover, CRLM patients with liver steatosis exhibit significantly shorter OS and hepatic recurrence-free survival.[9] To date, the correlation between liver steatosis and prognosis has mainly been analysed in patients with stage IV CRC with liver metastasis. The clinical significance of liver steatosis in non-metastatic CRC patients has not been extensively explored. A recent study reported a 22% higher skeletal muscle fat infiltration in patients with high liver stiffness compared with those with low liver stiffness ($P < 0.001$), indicating a possible association between liver fat infiltration and skeletal muscle fat infiltration.[10] However, the combined impact or association of liver steatosis and myosteatosis has not been thoroughly investigated in non-metastatic CRC patients.

Thus, the aim of this study was to investigate the association and prognostic significance of liver and skeletal muscle fat infiltration in patients with stage I–III CRC patients.

Methods

Patients and treatment

This study is a single-centre based retrospective cohort study. CRC patients on pathologic diagnosis of colorectal adenocarcinoma without distant metastasis who underwent resection of primary tumour site with curative intent in the Gangnam Severance Hospital, Yonsei University College of Medicine from January 2004 and April 2014 were initially enrolled. Exclusion criteria were as below: (1) emergency operation; (2) receiving preoperative chemoradiotherapy or radiotherapy only; (3) tumour location in appendix or anus; (4) distant other organ metastasis; (5) double primary cancer; (6) Crohn's disease, familiar adenomatous polyposis, and hereditary non-polyposis syndrome; (7) unavailable to extract liver Hounsfield unit (HU), spleen HU, and SMD and (8) duration between computed tomography (CT) to surgery is exceeding 60 days. After excluding above patients, this study included 616 patients. (Figure S1).

Our study protocol adhered to the ethical standards of the institutional and/or national research committees and 1964 Declaration of Helsinki and its later amendments. The study was approved by Gangnam Severance Hospital Institutional Review Board. The institutional review board waived the requirement for informed consent owing to the retrospective study nature.

Measurement of computed tomography attenuation of muscle, liver and spleen

Myosteatosis was estimated by SMD, and liver steatosis was estimated by ratio of liver and spleen HU calculated using CT images. CT images of skeletal muscle were gained at the level of third lumbar vertebra. SMD was measured by the '3DSlicer', which is an open-source software package for image analysis and scientific visualization, and this program handle digital imaging and communications in medicine (DICOM) images of CT, show interactive visualization of volumetric voxel images, volume renderings.[11] In addition, we used LIFEx program to estimate HU value of region of interest (ROI) of liver and spleen in CT images.[12]

Gold standard for diagnosis and grading of liver steatosis is biopsy, but it is invasive procedure.[13] In contrast, CT provides a relatively accurate liver fat infiltration quantification and also is non-invasive.[14] In our study, we used non-contrast CT liver and spleen ratio (LSR) to distinguish liver steatosis or not. CT images taken before surgery was extracted from picture archiving and communication system. Patients who had not images of non-contrast CT alternatively used non-contrast CT image in positron emission tomography-computed tomography (PET-CT) scan, if available. The ROI was two same size area (1 cm circle) in different segment of liver and spleen (separately upper and lower portion of liver and spleen) respectively. ROI was selected avoiding vessels, bile ducts, and focal lesions. Each HU of liver and spleen was defined as the average HU of two ROIs. LSR was calculated by mean value of liver attenuation (HU)/mean value of spleen attenuation (HU).[14,15]

One investigator (D. H. L.) extracted the mean CT attenuation values both in liver and spleen using LIFEx program. Another investigator (I. J.) also estimate data about a small sampling group according to same method. After checking accordance of data tendency (Table S1), one investigator (D. H. L.) estimates remnant data.

Definition of myosteatosis and liver steatosis

In our study, myosteatosis was defined as the recommended criteria of previous study. In that study myosteatosis was

defined as <41HU in patients with low body mass index (BMI) (<25 kg/m^2) and <33HU in patients with high BMI (≥25 kg/m^2).[16] Patients were allocated into low and high SMD groups according to this definition.

The tertile value of LSR was set as 1.029 and 1.181, respectively (Table S2). When we divided patients into three groups according to the tertile of LSR, first and second tertile group showed similar survival outcomes, whereas third tertile LSR group (range 1.181 to 2.287) showed worse survival in the Kaplan–Meier survival curve (Figure S2). Thus, we defined cut-off value of LSR as 1.181, and patients were divided into presence of liver steatosis or absence of liver steatosis according to cut-off value of LSR.

Statistical analysis

Pearson's chi square test has been used in testing for association between two categorical differences. Kaplan–Meier curve and log-rank test was used to compare survival difference between groups. Disease-free survival (DFS) was defined as time from surgery to first event (local or systemic recurrence or death). Patients with no event were censored at the time of last follow-up. Univariable and multivariable analysis using Cox proportional hazard models were used to evaluate DFS rate. Factors with P value <0.05 in the univariable analysis were entered into the multivariable analysis with backward selection.

The concordance index (C-index) is usually used to measure how well a factor predicts time to an event.[17] We use the C-index to compare accuracy of prediction according to single or multiple variables.

All statistical analysis was done using R program 4.2.0 (R-project, Institute for Statistics and Mathematics, Vienna, Austria). All tests were two sided, and 95% CIs were used. Statistical significance was set as $P < 0.05$.

Table 1 Comparison of liver Hounsfield unit, spleen Hounsfield unit and liver spleen ratio according to SMD status

	Low SMD (n = 200)	High SMD (n = 416)	P
Liver HU (median, IQR)	54.5 (49.7–61.3)	57.2 (51.5–63.2)	0.010
Spleen HU (median, IQR)	47.1 (42.8–55.2)	49.8 (45.8–62.2)	<0.001
LSR (median, IQR)	1.1 (1.0–1.2)	1.1 (0.9–1.2)	0.103

HU, Hounsfield unit; IQR, interquartile range; LSR, liver spleen ration of HU; SMD, skeletal muscle radiodensity.

Table 2 Patient characteristics according to low and high LSR

		Low LSR (n = 410)	High LSR (n = 206)	
		N (%)	N (%)	P
Sex	Female	135 (32.9)	105 (51.0)	
	Male	275 (67.1)	101 (49.0)	<0.001
Age (years)	<60	155 (37.8)	74 (35.9)	
	≥60	255 (62.2)	132 (64.1)	0.713
BMI (kg/m^2)	<25	282 (68.8)	150 (72.8)	
	≥25	128 (31.2)	56 (27.2)	0.348
CEA (ng/mL)	<5	289 (70.5)	123 (59.7)	
	≥5	111 (27.1)	71 (34.5)	
	Unknown	10 (2.4)	12 (5.8)	0.009
Tumour location	Colon	291 (71.0)	158 (76.7)	
	Rectum	119 (29.0)	48 (23.3)	0.158
Histologic grade	G1 and G2	374 (91.2)	192 (93.2)	
	G3, MC and SRC	36 (8.8)	14 (6.8)	0.487
LVI	Absent	282 (68.8)	130 (63.1)	
	Present	82 (20.0)	45 (21.8)	
	Unknown	46 (11.2)	31 (15.0)	0.287
Stage	I	95 (21.6)	30 (16.9)	
	II	155 (35.3)	59 (33.3)	
	III	189 (43.1)	88 (49.7)	0.252
Complications	No	315 (76.8)	159 (77.2)	
	Yes	95 (23.2)	47 (22.8)	>0.99
Chemotherapy	No	148 (36.1)	71 (34.5)	
	Yes	262 (63.9)	135 (65.5)	0.757
SMD (HU)	Mean (SD)	41.9 (8.7)	41.3 (9.1)	0.393

BMI, body mass index; CEA, carcinoembryonic antigen; HU, Hounsfield unit; LVI, lymphovascular invasion; MC, mucinous adenocarcinoma; SD, standard deviation; SMD, skeletal muscle radiodensity; SRC, signet-ring cell.

Results

A total of 616 patients was finally eligible for this study. Patients was classified into low SMD group (200, 32.4%) and high SMD group (416, 67.5%) respectively. Median liver and spleen HU in patients with high SMD were significantly higher than that of the patients with low SMD (57.2 vs. 54.5, P = 0.001, 49.8 vs. 47.1, $P < 0.001$) respectively. However, there was no significant difference of LSR between the two groups (P = 0.103) (Table 1). Additionally, LSR was not associated with skeletal muscle radiodensity (SMD), and further analysis after dividing men and women, specific correlation was also not found (Figure S3).

According to cut-off value of LSR, patients who showed low LSR (n = 410) was defined as the liver steatosis group and the others was defined as non-liver steatosis group (n = 206).

When we compared clinicopathological difference of tertile group of LSR, sex and BMI showed statistical difference (Table S3). When classified into using cut-off value of LSR, there was significant difference of rate of sex between the low and high LSR groups and low LSR group included more male patients (P = 0.001). There was no significant difference of age, BMI, tumour location, histologic grade, lymphovascular invasion, stage, complications, chemotherapy, and SMD according to LSR (Table 2).

Kaplan–Meier survival curve revealed that high SMD was associated with better DFS compared with low SMD group ($P < 0.0001$). Whereas high LSR (non-liver steatosis group)

showed poor prognosis than low LSR group (liver steatosis group) (P = 0.0092) (Figure 1).

In the univariable analysis, age (<60 years vs. ≥60 years, P = 0.001), BMI (<25 kg/m^2 vs. ≥25 kg/m^2, P = 0.004), CEA (<5 ng/mL vs. ≥5 ng/mL, $P < 0.001$), histologic grade (P = 0.030), LVI (absent vs. present, P = 0.046), stage (I vs. III, $P < 0.001$), complications (P = 0.010), SMD ($P < 0.001$) and LSR (P = 0.009) were identified as significant prognostic factors of DFS. In the multivariable analysis, BMI (<25 kg/m^2 vs. ≥25 kg/m^2, HR 0.618; 95% CI 0.425–0.899; P = 0.011), CEA (<5 ng/mL vs. ≥5 ng/mL, HR 1.505; 95% CI 1.087–2.084; P = 0.013), stage (I vs. III, HR 2.153; 95% CI 1.304–3.555; P = 0.002), SMD (low vs. high, HR 0.543; 95% CI 0.392–0.753; $P < 0.001$) and LSR (low vs. high, HR 1.388; 95% CI 1.016–1.897; P = 0.039) were statistically significantly associated with DFS (Table 3).

Using two by two combination of SMD and LSR, patients could be classified into four groups. Kaplan–Meier survival curve of these four groups showed different survival outcomes. However, there was similar survival rates between low LSR with low SMD group and high LSR with low SMD group (Figure S4). Thus, these patients were grouped together in further analysis. Finally, combination of myosteatosis and liver steatosis enable three group stratifications as group 1: high SMD with low LSR, group 2: high SMD with high LSR and group 3: low SMD. A total of 280 (45.4%), 136 (22.0%) and 200 (32.4%) patients were allocated into group 1, group 2 and group 3 respectively. Kaplan–Meier survival curve showed survival difference between the three groups ($P < 0.0001$) (Figure 2). Multivariable analysis revealed that three group classification is as an independent prognostic factor (group 1 vs. group 2, HR 1.705; 95% CI 1.105–2.630; P = 0.015, group 1 vs. group 3, HR 2.293; 95% CI 1.556–3.379; $P < 0.001$) (Table S4). When we divided the patient cohort into groups based on colon cancer and rectal cancer, we observed similar trends in survival for each of the three groups (Figure S5).

C-index was used to confirm the stratification power of combined model. We compared combined model with SMD or LSR single model. The C-index in the combined model was 0.632 (95% CI 0.590–0.670), which was higher than that of the SMD (0.604, 95% CI 0.565–0.639) [estimated difference 0.029 (0.008–0.048)] and LSR (0.547, 95% CI 0.509–0.586) [estimated difference 0.085 (0.041–0.132)] (Table 4).

Discussion

Our study demonstrated a significant connection between the accumulation of fat in skeletal muscles (known as myosteatosis) and a poor prognosis, while the presence of fat in the liver (liver steatosis) was associated with improved survival rates in patients with non-metastatic colorectal cancer (CRC). The extent of liver steatosis did not show a correlation with the density of skeletal muscle, but the combined

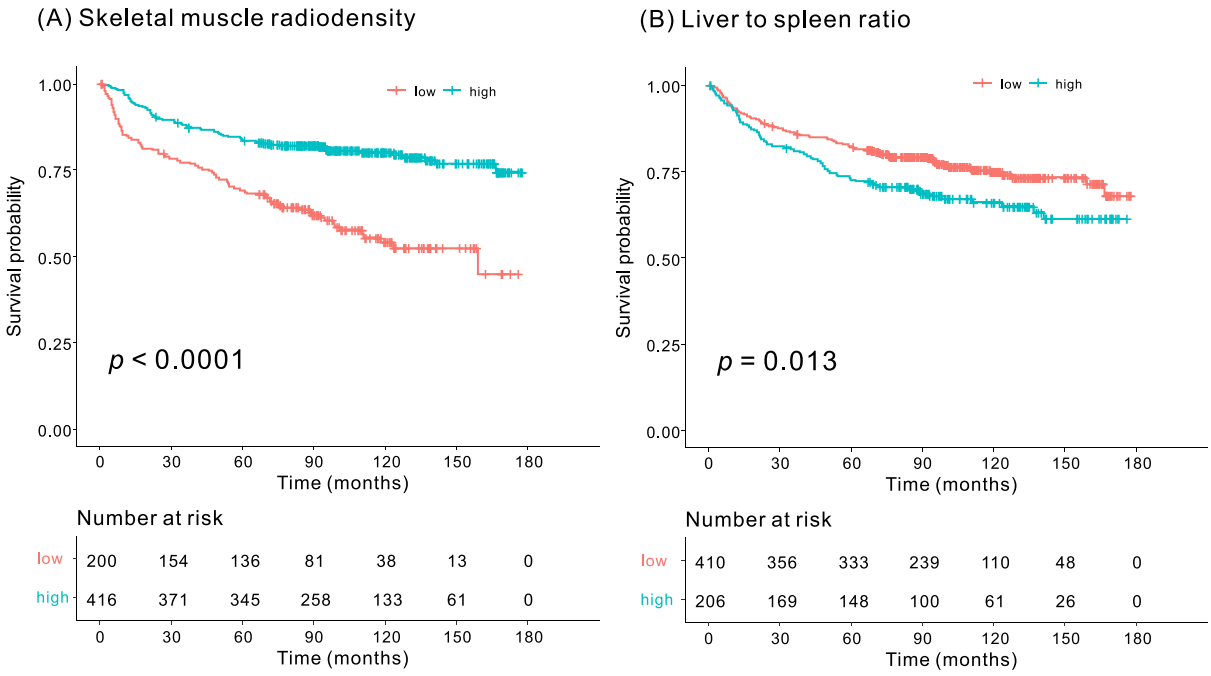

Figure 1 Kaplan–Meier survival curve according to the myosteatosis and liver steatosis. Kaplan–Meier survival curve revealed that non myosteatosis group was associated with better DFS compared with myosteatosis group ($P < 0.0001$) (A). Whereas non-liver steatosis group showed poor prognosis than liver steatosis group (P = 0.0092) (B).

Table 3 Univariable and multivariable analyses of factors associated with disease-free survival

		Univariable analysis		Multivariable analysis	
		HR (95% CI)	*P*	HR (95% CI)	*P*
Sex	Female	1			
	Male	1.194 (0.868–1.642)	0.275		
Age (years)	<60	1		1	
	≥60	1.766 (1.251–2.492)	0.001	1.408 (0.980–2.022)	0.063
BMI (kg/m^2)	<25	1		1	
	≥25	0.586 (0.405–0.847)	0.004	0.618 (0.425–0.899)	0.011
CEA (ng/mL)	<5	1		1	
	≥5	1.878 (1.375–2.565)	<0.001	1.505 (1.087–2.084)	0.013
	Unknown	1.109 (0.450–2.728)	0.822	1.106 (0.442–2.768)	0.829
Tumour location	Colon	1			
	Rectum	0.937 (0.664–1.323)	0.713		
Histologic grade	G1 and G2	1		1	
	G3, MC and SRC	1.693 (1.05–2.729)	0.030	1.521 (0.934–2.475)	0.091
LVI	Absent	1			
	Present	1.439 (1.005–2.059)	0.046		
	Unknown	0.851 (0.522–1.388)	0.518		
Stage	I	1		1	
	II	1.486 (0.873–2.529)	0.144	1.127 (0.655–1.938)	0.665
	III	2.808 (1.719–4.587)	<0.001	2.153 (1.304–3.555)	0.002
Complications	No	1		1	
	Yes	1.545 (1.109–2.153)	0.010	1.601 (1.143–2.243)	0.006
Chemotherapy	No	1			
	Yes	0.900 (0.655–1.237)	0.517		
SMD	Low	1		1	
	High	0.402 (0.296–0.545)	<0.001	0.543 (0.392–0.753)	<0.001
LSR	Low	1		1	
	High	1.476 (1.084–2.009)	0.013	1.388 (1.016–1.897)	0.039

BMI, body mass index; CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazard ratio; LSR, liver to spleen ratio; LVI, lymphovascular invasion; MC, mucinous adenocarcinoma; SMD, skeletal muscle radiodensity; SRC, signet-ring cell.

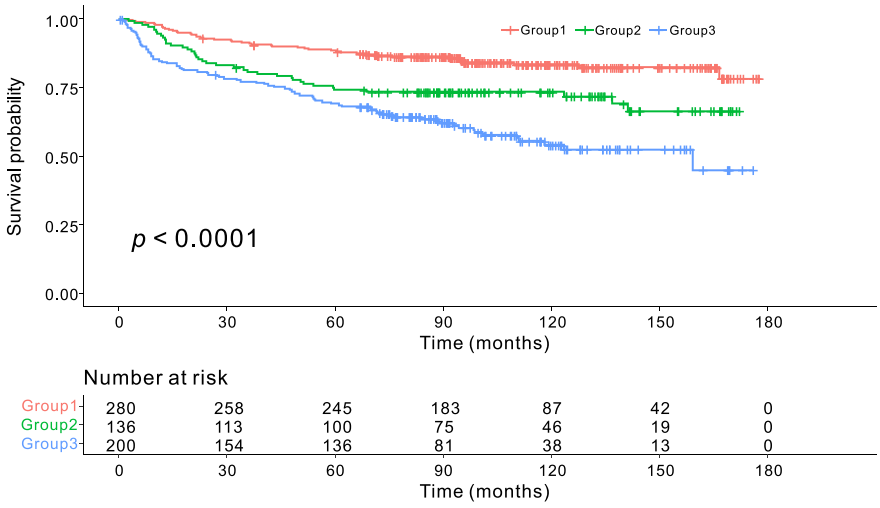

Figure 2 Kaplan–Meier survival curve according to the three groups. Kaplan–Meier survival curve showed survival difference between the three groups ($P < 0.0001$).

presence of liver steatosis and myosteatosis could offer better risk stratification for disease-free survival compared with either myosteatosis or liver steatosis alone. Therefore, liver steatosis holds potential as a valuable biomarker based on body composition, enabling the estimation of prognosis in non-metastatic CRC patients.

Liver biopsy, although considered the most accurate method for measuring liver steatosis, is highly invasive and carries the risk of various complications. Additionally, it can only assess a small portion of the entire liver.[18] In this study, we employed the LSR as a means to evaluate the degree of liver steatosis. Typically, the Hounsfield unit (HU) attenuation

Table 4 Comparison of C-index between LSR combined model versus SMD

Included variables	LSR-SMD combined model	SMD	LSR-SMD combined model	LSR
C-index (95% CI) (bootstrapped)	0.632 (0.590–0.670)	0.604 (0.565–0.639)	0.632 (0.590–0.670)	0.547 (0.509–0.586)
Estimated difference	0.029 (0.008–0.048)		0.085 (0.041–0.132)	

C-index, Harrell's concordance index; CI, confidence interval.

of the liver in CT images is higher than that of the spleen. Previous research defined a lower LSR (<1.1) as an indication of liver steatosis.[19] Despite having lower sensitivity, LSR has been utilized as an alternative non-invasive method for diagnosing liver steatosis due to its convenience.[20] Moreover, LSR enables the evaluation of a larger volume of liver parenchyma compared with biopsy.[21]

There is conflicting evidence regarding the clinical significance of liver steatosis in patients with CRC. In a study involving 195 patients with CRLM, it was observed that patients with liver steatosis had significantly worse overall survival and hepatic recurrence-free survival.[9] The presence of liver steatosis was determined by a computed tomography (CT) measurement of LSR lower than 1.1. The study proposed that liver steatosis creates a favourable microenvironment for tumour seeding by regulating cytokines, immune cells (such as IL-1, IL-6 and tumour necrosis factor-α), and natural killer T cells.[9] In a recent meta-analysis involving 14 197 patients, liver steatosis was found to be statistically associated with reduced disease-free survival (HR 1.32; 95% CI 1.08–1.62; I^2 = 67%, P = 0.007) in patients with CRLM. However, the same study reported that liver steatosis did not have a statistically significant impact on patient survival (HR 0.92; 95% CI 0.82–1.04; I^2 = 82%, P = 0.18).[22] The authors suggested that further prospective studies should investigate this discrepancy in patients with CRLM. Another study involving 283 patients with stage II to IV rectal cancer found no difference in terms of overall survival between patients with and without liver steatosis.[23]

Whereas, several studies support our findings. In patients with stage I–III CRC who underwent curative surgery, the presence of liver steatosis was associated with better liver-specific DFS (HR 7.81; 95% CI 1.72–138.0; P = 0.003).[24] The authors of this study suggested that fat accumulation in the liver creates an unfavourable environment for the invasion and growth of metastatic tumour cells.[24] In another study involving 5853 patients who underwent liver resection for CRLM without preoperative chemotherapy, liver steatosis was associated with improved 5-year OS (47.4% vs. 43.0%, P = 0.0017) and cancer-specific survival (56.1% vs. 50.3%, P = 0.002) compared with a normal background liver. This trend persisted even after adjusting for confounding factors.[25] In this study, liver steatosis was defined based on liver biopsy results, specifically the presence of pathological changes in the liver parenchyma. Furthermore, an in vivo study using a mouse model of nonalcoholic steatohepatitis induced by a western diet demonstrated that liver steatosis, as assessed by liver biopsy, had an inhibitory effect on colorectal cancer liver metastasis. This effect was attributed to the suppression of IL-6/STAT3 signalling and the facilitation of SAA/MMP9 expression, indirectly supporting our results.[26]

The reason for the conflicting prognostic impact of liver steatosis in patients with CRC remains uncertain. One factor contributing to this uncertainty is the diverse methodologies used to estimate liver steatosis, making it challenging to define liver steatosis using the LSR in CT examinations. Kan et al. conducted a study comparing four grades of pathologic liver steatosis with LSR in 67 biopsy-proven non-alcoholic fatty liver disease patients and suggested a cut-off value of 1.1 as optimal for excluding steatosis.[13] Since then, many studies have utilized LSR to assess liver steatosis, often employing a similar cut-off value. However, this criterion has not been thoroughly investigated in predicting patient prognosis, particularly in CRC patients. In our study, we initially categorized patients' LSR into three different groups and discovered that one group exhibited worse survival outcomes than the others. Therefore, we adopted this criterion to evaluate patient prognosis, despite the cut-off value being similar to previous studies. One potential confounding factor that could contribute to conflicting outcomes is the stage of the disease at presentation. It can be hypothesized that in CRC patients without liver metastasis, liver steatosis exerts a protective effect through a different mechanism within the cancer microenvironment, which may not apply to patients with CRLM. However, this hypothesis lacks reliable evidence as it has not been thoroughly investigated. Further research is necessary to determine whether these differences can fully explain the conflicting outcomes observed.

Certainly, our study had several limitations. Firstly, it was a retrospective cohort study conducted at a single centre, which inherently presents limitations in terms of sample size and potential biases. We did not initially determine an adequate sample size in advance. Instead, we utilized patient data that was readily accessible within the clinical setting. During our literature review, we encountered challenges in identifying prior studies that addressed a similar issue, which may have contributed to our decision not to conduct a sample size calculation. Nevertheless, we acknowledge that this could be considered a weakness of our study. Secondly, the use of LSR for diagnosing liver steatosis is not considered the gold standard method. Therefore, the suggested cut-off value we proposed in our study should be further investi-

gated and validated in independent groups or through prospective studies.

In summary, our study revealed that the absence of myosteatosis and the presence of liver steatosis were both independently associated with improved survival outcomes. Notably, patients who lacked myosteatosis and had liver steatosis exhibited the most favourable prognosis. We observed that myosteatosis and liver steatosis were not correlated, suggesting that fat deposition occurs independently of the body site. Nevertheless, considering both liver steatosis and myosteatosis could enhance the stratification of survival in non-metastatic CRC patients.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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