Elevated serum IP-10/CXCL10 levels are associated with sarcopenia development, a prognostic factor, in patients with primary hepatocellular carcinoma

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Abstract

Sarcopenia is a prognostic factor in patients with hepatocellular carcinoma (HCC). However, the mechanism underlying sarcopenia development in patients with HCC remains unclear. The chemokine interferon-gamma-induced protein 10/C-X-C motif chemokine ligand 10 (IP-10/CXCL10) has emerged as one of the mechanisms in previous studies. Therefore, we aimed to elucidate the significance of sarcopenia, and investigate the association between serum IP-10/CXCL10 levels and sarcopenia development. This retrospective study included 738 patients with primary HCC, and among these patients, serum IP-10/CXCL10 levels were measured both at baseline and after 1–3 years in a subset of 135 patients. Among patients with primary HCC, those with sarcopenia at baseline had a poorer prognosis than those without, and patients with sarcopenia at 1, 3, and 5 years after the first occurrence of HCC had a poorer prognosis. Furthermore, serum IP-10/CXCL10 ratios were found to be higher in patients with sarcopenia at baseline and those who developed sarcopenia during the observation period than in those without sarcopenia ($p = 0.0016$). This study revealed that the significance of sarcopenia as a prognostic factor in patients with HCC, and the changes in serum IP-10/CXCL10 levels appear to be associated with the development of sarcopenia following the first occurrence of HCC.

Introduction

Sarcopenia is characterized by low skeletal muscle mass, skeletal muscle weakness, and decreased physical performance [1]. It has been reported as a poor prognostic factor in patients with hepatocellular carcinoma (HCC) [2–6]. Therefore, sarcopenia has received increasing attention in recent years among patients with chronic liver disease.

According to the assessment criteria for sarcopenia in liver disease established by the Japan Society of Hepatology, patients with chronic liver disease who exhibit low grip strength and muscle mass, as determined by computed tomography (CT) or bioelectrical impedance analysis, are considered to have sarcopenia [7]. Recently, there has been a growing emphasis on evaluating sarcopenia in terms of muscle quality, especially focusing on decreased grip strength and increased intramuscular fat mass [8, 9]. The correlation between CT values of the skeletal muscles at the L3 level and triglyceride content in muscle biopsy specimens has been an interesting topic of study [10]. Furthermore, the association between CT values of skeletal muscles and prognosis in patients with unresectable HCC, as well as the development of adverse effects in patients undergoing systemic therapy for ovarian cancer, have also been reported [9, 11, 12].

Although several theories have been proposed, the exact mechanism underlying the development of sarcopenia in patients with HCC remains unclear. Reduced amino acids, hyperammonemia, hypermetabolic state, low testosterone levels, and inhibition of the mammalian target of rapamycin pathway due to physical inactivity and systemic therapy are all considered potential contributors to the development of sarcopenia [13]. Among these potential mechanisms, the chemokine interferon-gamma (IFN-γ)-induced protein 10/C-X-C motif chemokine ligand 10 (IP-10/CXCL10), a downstream molecule of

IFN-γ, has emerged as a particularly interesting candidate [14, 15]. Interestingly, IP-10/CXCL10 levels may have opposing effects on muscle regeneration in the elderly and young, as well as in patients with cancer, depending on the stage of the disease [16, 17]. Therefore, in this study, we aimed to elucidate the significance of sarcopenia in patients with primary HCC and investigate the association between serum IP-10/CXCL10 levels and sarcopenia development.

Methods

Patients

From January 2008 to January 2021, a total of 738 patients diagnosed with primary HCC at our hospital were enrolled in this study. Among these patients, serum IP-10/CXCL10 levels were measured both at baseline and after 1–3 years in a subset of 135 patients (Supplementary Fig. 1).

In this study, cases with adequate imaging at baseline and who were over 20 years old were included, while cases from which data could not be collected precisely or cases that were followed up for a short period (< 4 weeks) were excluded. In this study, HCC was defined pathologically. However, classical HCC findings, i.e., contrast enhancement in the arterial phase and presence of portal vein phase washout, determined using dynamic CT, gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-magnetic resonance imaging, or contrast-enhanced ultrasonography and intrahepatic tumors with elevated alpha-fetoprotein (AFP), AFP-L3 index, and des-gamma-carboxy prothrombin (DCP) levels were clinically strongly suggestive of HCC. In addition, cirrhosis was defined as a platelet count less than 150,000/μL, Type IV collagen 7S of 4.4 mg/dL or greater, and hyaluronic acid of 50 ng/mL or greater [18, 19]. Radical cure was defined as the absence of recurrence one year after treatment for HCC. Overall survival (OS) was defined as the time between treatment initiation and the date of death.

This study was conducted in accordance with the principles of the Helsinki Declaration and received approval from the Human Ethics Review Committee of the University of Yamanashi.

Diagnosis of sarcopenia

According to the assessment criteria for sarcopenia in liver disease established by the Japan Society of Hepatology, the presence of decreased grip strength and low muscle mass in patients with chronic liver disease indicates sarcopenia. However, due to the retrospective nature of this study, adequate grip strength measurements were not available. Therefore, CT values were used instead of grip strength as an indicator of skeletal muscle quality in this study.

Psoas muscle mass index (PMI) at the level of the third lumbar vertebra, as determined by CT scan imaging, was used as an indicator of muscle mass volume. CT scan images taken at the time of the primary HCC diagnosis served as the baseline. The cross-sectional areas of the bilateral psoas muscles were measured by manual tracing, and PMI was calculated by normalizing these areas to the square of the patient's height in meters. The cutoff value for PMI was identified as 6.36 cm^2/m^2 for males and 3.92

cm^2/m^2 for females according to the assessment criteria for sarcopenia in liver disease established by the Japan Society of Hepatology [20]. CT values of the multifidus muscle at the level of the third lumbar vertebra were used as an indicator of skeletal muscle quality [21–23]. The cutoff value for low CT values was identified as 44.4 Hounsfield Unit (HU) for males and 39.3 HU for females [8, 9].

In the present study, sarcopenia was defined as the presence of both low PMI and low CT values. The measurement of muscle mass volume and CT values was conducted by two hepatology specialists with expertise in this field.

Measurement of serum IP-10/CXCL10 levels

Serum samples were obtained from 9 mL of blood collected at baseline and 1–3 years after the first occurrence of HCC. These samples were divided into aliquots and stored at − 80°C until further analysis. Serum IP-10/CXCL10 levels were measured using an enzyme-linked immunosorbent assay kit, following the manufacturer's instructions. The levels were calculated using standard calibration curves and expressed in pg/mL. The IP-10/CXCL10 ratio was defined as the ratio of IP-10 levels between baseline and 1–3 years after the first occurrence of HCC.

Statistical analysis

All experimental data were expressed as medians (ranges). Between-group comparisons were conducted using the Mann-Whitney U test, Kruskal-Wallis test, Friedman test, and nonparametric analysis of variance. If the one-way analysis of variance yielded significant results, differences between individual groups were assessed using Fisher's exact test. The receiver operating characteristic analysis was performed, and the optimal cutoff values were determined using Youden's index. A $p < 0.05$ was considered statistically significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). Specifically, EZR is a modified version of the R commander designed to include statistical functions frequently used in biostatistics [24].

Results

Patient characteristics

A total of 738 patients were enrolled in this study, with a median age of 72 years (range: 21–93 years), out of which 530 were male. The etiologies of HCC were hepatitis B virus infection in 76 cases, hepatitis C virus infection in 414 cases, and non-B non-C in 248 cases. In terms of the Child–Pugh grading, 561 cases had grade A, 161 had grade B, and 16 had grade C. Regarding the Tumor-Node-Metastasis (TNM) staging, 212 cases were classified as Stage 1, 299 cases as Stage 2, 162 cases as Stage 3, and 65 cases as Stage 4. In terms of the Barcelona Clinic Liver Cancer (BCLC) staging, 455 cases were classified as Stage A, 199 cases as Stage B, 72 cases as Stage C, and 12 cases as Stage D. The maximum

intrahepatic tumor diameter was 23 mm (range: 6–200 mm), and the number of intrahepatic tumors was 1 (range: 1–24). A portal venous invasion was observed in 60 cases, whereas distant metastasis was detected in 50 cases. The treatment modalities for primary HCC included resection alone or in combination, percutaneous puncture treatment alone or in combination, transarterial chemoembolization alone or in combination, systemic therapy or in combination, radiotherapy, and best supportive care in 229, 287, 170, 13, 26, and 13 cases, respectively. At baseline, 214 patients (29%) were diagnosed with sarcopenia. The median observation period for the study was 55 months (range: 50–61 months).

Meanwhile, the cohort of 135 patients who had their serum IP-10/CXCL10 levels measured had a median age of 71 years (range: 51–87 years), with 87 of them being male. The Child–Pugh scores were 5, 6, and 7 in 94, 22, and 19 cases, respectively. In terms of the TNM staging, there were 35 cases classified as Stage 1, 52 cases as Stage 2, 34 cases as Stage 3, and 14 cases as Stage 4. Regarding the BCLC staging, there were 64 cases classified as Stage A, 50 cases as Stage B, and 21 cases as Stage C. At the time of the first occurrence of HCC, 95 cases (70%) had achieved a radical cure. Among the 135 patients who had their serum IP-10/CXCL10 levels measured, 45 patients did not experience sarcopenia during the observation period, 45 patients developed sarcopenia during the observation period, and 45 patients had sarcopenia at baseline. The characteristics of these patients are summarized in Table 1 and Supplementary Table 1.

Table 1
Patient characteristics

	Patients diagnosed with primary HCC (n = 738)	Patients whose IP-10/CXCL10 levels were measured (n = 135)
Age, years old	72 (21–93)	71 (51–87)
Male, n	530 (72%)	87 (64%)
Body mass index	23 (14–40)	23 (15–40)
PMI < men 6.36, women 3.92 cm^2/m^2	303 (41%)	63 (47%)
CT value < men 44.4, women 39.3 HU	520 (71%)	47 (67%)
Sarcopenia at baseline, n	214 (29%)	45 (33%)
Etiology (HBV/HCV/nonBnonC), n	76/414/248 (10/56/34%)	44/51/40 (33/38/29%)
Child-Pugh grade (A/B/C), n	561/161/16 (76/22/2%)	116/19/0 (86/14/0%)
Alpha-fetoprotein, ng/ml	11 (1.0-623027)	7.0 (1.2-307313)
Des-γ-carboxy prothrombin, mAU/ml	31 (5.0-636373)	26 (8.0-261987)
Tumor size, maximum, mm	23 (6-200)	24 (8.0-200)
The number of intrahepatic tumors, n	1 (1–24)	1 (1–10)
Portal vein invasion, n	60 (8.1%)	16 (12%)
Extrahepatic metastasis, n	50 (6.8%)	10 (7.4%)
TNM stage (1/2/3/4), n	212/299/162/65 (29/41/22/8%)	35/52/34/14 (26/39/25/10%)
BCLC stage (A/B/C/D), n	455/199/72/12 (62/27/10/1%)	64/50/21/0 (47/37/16%)
Therapy for primary HCC (resection alone or in combination / percutaneous puncture treatment alone or in combination / transarterial chemoembolization alone or in combination / systemic therapy or in combination / radiotherapy / best supportive care), n	229/287/170/13/26/13 (31/39/23/2/3/2%)	33/38/61/1/2/0 (24/29/46/1/0%)
Radical cure at the time of the first occurrence of HCC, n	525 (71%)	95 (70%)

Prognostic factors in patients with primary hepatocellular carcinoma

Among patients with primary HCC (n = 738), those with sarcopenia at baseline had a poorer prognosis than those without (p = 0.046) (Figure.1a). Several prognostic factors were identified for shorter survival in patients with primary HCC, including sarcopenia, age over 78 years old, a body mass index < 18.5, Child–Pugh grades B/C, TNM Stages 3/4, DCP levels of 150 mAU/mL or higher, and the absence of radical cure at the time of the first occurrence of HCC (Table 2). Similarly, even among patients who achieved radical cure at the time of the first occurrence of HCC (n = 525), those with sarcopenia at baseline had a poorer prognosis than those without (p = 0.029) (Figure.1b).

Table 2
Prognostic factors for shorter survival in patients with primary hepatocellular carcinoma

	Univariate		Multivariate	
	HR	p value	HR	p value
Age, years old	1.02 (1.01–1.04)	< 0.001		
over 78 years old	2.0 (1.5–2.5)	< 0.001	2.0 (1.5–2.7)	< 0.001
Male	1.1 (0.87–1.4)	0.40		
Body mass index	0.95 (0.92–0.99)	0.0065		
<18.5	1.8 (1.2–2.7)	0.0059	2.4 (1.4–4.1)	< 0.001
Sarcopenia at baseline, n	1.3 (1.003-1.6)	0.047	1.3 (1.004-1.8)	0.046
Etiology: nonBnonC	1.5 (1.2–1.9)	< 0.001	1.2 (0.86–1.5)	0.34
Child–Pugh grades B/C	2.5 (2.0-3.2)	< 0.001	3.1 (2.3–4.2)	< 0.001
Alpha-fetoprotein, ng/ml	1 (1–1)	< 0.001		
20 ng/mL or higher	2.0 (1.6–2.5)	< 0.001	1.0 (0.76–1.4)	0.88
Des-γ-carboxy prothrombin, mAU/mL	1 (1–1)	< 0.001		
150 mAU/mL or higher	3.9 (3.1–4.9)	< 0.001	2.3 (1.7–3.1)	< 0.001
Ammonia, μg/dL	1.005 (1.002–1.008)	< 0.001		
73 μg/dL or higher	1.7 (1.4–2.3)	< 0.001	1.1 (0.85–1.5)	0.39
TNM Stages 3/4	2.4 (2.1–2.7)	< 0.001	2.3 (1.7–3.1)	< 0.001
Tumor size, maximum, mm	1.02 (1.02–1.03)	< 0.001		
The number of intrahepatic tumors, n	1.3 (1.3–1.4)	< 0.001		

	Univariate		Multivariate	
Portal vein invasion, n	6.8 (4.9–9.5)	< 0.001		
Extrahepatic metastasis, n	5.5 (3.9–7.6)	< 0.001		
Absence of radical cure at the time of the first occurrence of HCC	4.8 (3.8–6.1)	< 0.001	2.1 (1.5–2.9)	< 0.001

Association between sarcopenia development and prognosis in patients with primary hepatocellular carcinoma

Following the first occurrence of HCC, the PMI and CT values of the multifidus muscle exhibited a gradual decrease over time (Figures.2a,b). The frequency of survival without sarcopenia decreased gradually at 1, 3, and 5 years after the first occurrence of HCC (49%, 30%, and 16%). Notably, patients with sarcopenia at these time points had a poorer prognosis than those without (Figures.3a–c). Similarly, even among patients who achieved radical cure at the time of the first occurrence of HCC (n = 525), those with sarcopenia had a poorer prognosis than those without (Figures.3d–f). In contrast, sarcopenia did not emerge as a significant prognostic factor in patients who did not achieve radical cure at the time of the first occurrence of HCC (n = 213).

Association between IP-10/CXCL10 levels and sarcopenia at baseline and second measurement timing

IP-10/CXCL10 levels at baseline were found to be higher in the Child-Pugh score worsening and TNM-stage worsening groups, but were not significantly associated with the presence of sarcopenia (p = 0.43) (Figure.4a). At the second measurement timing, there was a trend toward higher IP-10/CXCL10 levels in patients who developed sarcopenia during the observation period compared to those who did not (p = 0.089) (Figure.4b). Similar findings on IP-10/CXCL10 levels at baseline were observed among patients who achieved radical cure at the time of the first occurrence of HCC (n = 95) (p = 0.35). In radical cure group, there was a trend toward higher IP-10/CXCL10 levels at the second measurement timing in patients who developed sarcopenia compared to those who did not (p = 0.10).

Association between the IP-10/CXCL10 ratio and sarcopenia development

IP-10/CXCL10 ratios were found to be higher in patients with sarcopenia at baseline and those who developed sarcopenia during the observation period than in those without sarcopenia (p = 0.0016) (Figure.5a). Similar findings were observed among patients who achieved radical cure at the time of the first occurrence of HCC (n = 95) (p = 0.0069) (Figure.5b).

Characteristics of patients with high IP-10/CXCL10 ratios

Patients with high IP-10/CXCL10 ratios exhibited several characteristics compared to those with low ratios. They were found to be older, had a lower prevalence of cirrhosis, and were more likely to exceed

the up to seven criteria at baseline and second measurement timing (Table 3). Similarly, even among patients who achieved radical cure at the time of the first occurrence of HCC (*n* = 95), those with high IP-10/CXCL10 ratios were older, had a lower prevalence of cirrhosis, and were more likely to exceed the up to seven criteria at baseline and second measurement timing.

Table 3
Characteristics of patients with high IP-10/CXCL10 ratios

	Patients with high IP-10/CXCL10 ratios (n = 71)	**Patients with high IP-10/CXCL10 ratios (n = 64)**	**p value**
Age, years old	73 (52–86)	68 (51–87)	0.017
Male	46 (65%)	41 (64%)	1.0
Body mass index	23 (17–40)	24 (15–31)	0.57
Etiology: HBV/HCV/nonBnonC, n	20/27/24 (28/38/34%)	24/24/16 (38/38/24%)	0.41
Cirrhosis, n	57 (80%)	61 (95%)	0.009
Child–Pugh grade A/B, n	64/7 (90/10%)	52/12 (81/19%)	0.19
Alpha-fetoprotein, ng/ml	5.4 (1.2-80484)	8.3 (1.4-307313)	0.098
Des-γ-carboxy prothrombin, mAU/mL	26 (12-143672)	24 (8.0-261987)	0.39
Tumor size, maximum, mm	27 (8-150)	22 (9-200)	0.62
The number of intrahepatic tumors, n	1 (1–10)	1 (1–10)	0.63
Portal vein invasion, n	7 (10%)	9 (14%)	0.33
Extrahepatic metastasis, n	3 (4.2%)	7 (11%)	0.19
TNM Stage 1/2/3/4, n	23/20/21/7 (32/28/30/10%)	12/32/13/7 (19/50/20/11%)	0.051
Up to seven beyond at baseline, n	26 (37%)	6 (9.4%)	< 0.001
Absence of radical cure at the time of the first occurrence of HCC	51 (72%)	44 (69%)	0.71
Up to seven beyond at second measurement timing, n	37 (52%)	12 (19%)	< 0.001
Transition of sarcopenia, n Without sarcopenia/Developed sarcopenia/With sarcopenia at baseline	14/29/28 (20/41/39%)	31/16/17 (48/25/27%)	0.002
Supplementary Table 1. Characteristics of patients whose IP-10/CXCL10 levels were measured.			

Discussion

In the first part of this study, we assessed the significance of sarcopenia in patients with primary HCC. Our findings revealed that patients with sarcopenia at baseline had a poorer OS than those without, regardless of the HCC stage or the achievement of a radical cure. Sarcopenia at baseline was identified as an independent prognostic factor for patients with primary HCC. Similarly, our analysis demonstrated that patients with sarcopenia had a poorer prognosis at 1, 3, and 5 years following the first occurrence of HCC than those without. These findings underscore the importance of diagnosis of sarcopenia at any time following the first occurrence of HCC.

Sarcopenia was first proposed in 1989, and since then, several diagnostic criteria have been developed [1, 7, 25, 26]. According to the assessment criteria for sarcopenia in liver disease established by the Japan Society of Hepatology, patients with chronic liver disease who exhibit low grip strength and muscle mass are considered to have sarcopenia. While grip strength measurement is considered essential for evaluating muscle quality in Japan, our study lacked sufficient grip strength measurements due to its retrospective nature. However, a correlation was observed between CT values of the multifidus muscle and grip strength (Spearman correlation coefficient, $r = 0.40$, $p < 0.001$). Therefore, CT values were used instead of grip strength as an indicator of skeletal muscle quality in this study.

Numerous recent studies have investigated the correlation between sarcopenia and prognosis in patients with HCC [3, 4, 6, 27]. However, few studies have examined a large number of cases over a long period of time, as conducted in the present study. We identified several independent prognostic factors associated with shorter survival in patients with primary HCC, including sarcopenia, age over 78 years old, a body mass index less than 18.5, Child–Pugh grades B/C, TNM Stages 3/4, DCP levels of 150 mAU/mL or higher, and the absence of radical cure at the time of the first occurrence of HCC.

Unfortunately, the development of sarcopenia following the first occurrence of HCC and its impact on prognosis at different time points have not been reported in previous reports [28]. This study is the first to demonstrate a gradual decrease in both PMI and CT values of the multifidus muscle following the first occurrence of HCC. Similar to the baseline assessment, patients with sarcopenia had a poorer prognosis at 1, 3, and 5 years following the first occurrence of HCC than those without. While early detection and treatment of primary HCC are crucial for improving patient prognosis, our findings suggest that it is also equally important to diagnose and intervene sarcopenia at any timing.

Furthermore, this study delved into changes in serum IP-10/CXCL10 levels as a potential molecular mechanism underlying sarcopenia development. Our findings revealed that IP-10/CXCL10 ratios were higher in patients with sarcopenia at baseline and those who developed sarcopenia during the observation period than in those without sarcopenia. This study suggests, for the first time, a potential association between elevated IP-10/CXCL10 levels and sarcopenia development in patients with primary HCC, implying the importance of measuring serum IP-10/CXCL10 levels in these patients.

The molecular mechanisms underlying the development of sarcopenia in patients with HCC are complex and not yet fully understood. In particular, the relationship between IP-10/CXCL10 levels and sarcopenia development in patients with HCC has not been thoroughly analyzed. Previous studies have indicated an association between IP-10/CXCL10 levels and cancer stage, demonstrating higher levels in patients with advanced HCC. Furthermore, IP-10/CXCL10 overexpression has been observed in HCC tissues compared to nontumorous tissues, with significant associations with serum AFP levels, tumor size, tumor number, and TNM stage [29]. Patients with elevated IP-10/CXCL10 expression levels also had significantly poorer overall and disease-free survival rates [30]. In the present study, we found that patients with high IP-10/CXCL10 ratios had a higher frequency of high intrahepatic tumor volume, as indicated to be up to seven beyond. They also had shorter survival than those with low IP-10/CXCL10 ratios (82 *vs.* NA months, $p = 0.034$). It has been reported that downregulation of IP-10/CXCL10 can suppress metastasis and invasion in patients with HCC. Accordingly, further studies are needed to determine the prognostic impact of therapeutic intervention on IP-10/CXCL10 levels in patients with HCC [29].

Previous studies have reported higher peripheral IP-10/CXCL10 concentrations in the elderly than in the young [31]. It has been suggested that IFN-γ may contribute to muscle damage by suppressing M2 macrophage activation and inhibiting muscle cell proliferation in a mouse model of muscular dystrophy [32]. However, gene expression patterns associated with responses to IFN-γ were significantly downregulated during muscle regeneration in aged mice, which is thought to contribute to satellite cell dysfunctions in aged skeletal muscles [17]. Therefore, IP-10/CXCL10 levels may have opposing effects on muscle regeneration in the elderly and young populations. While no age-related difference was observed in baseline IP-10/CXCL10 levels, our study revealed a higher prevalence of cases with high IP-10/CXCL10 ratios in the elderly group. This suggests that increased IP-10/CXCL10 levels in elderly patients may be associated with the development of sarcopenia in patients with HCC.

There are some limitations to this study. First, it was a single-facility retrospective study and lacked grip strength measurements. Therefore, incorporating grip strength measurements, which are required by the currently widely used guidelines for diagnosing sarcopenia in Japan, is a future challenge. Second, patient selection bias exists in studies of IP-10/CXCL10 levels. Reexamination is necessary after increasing the number of cases in the future. Third, the relationship between etiology and IP-10/CXCL10 levels was not fully investigated. Previous studies have reported associations between IP-10/CXCL10 levels and cirrhosis, liver function, and hepatitis activity. For instance, IP-10/CXCL10 has been found to play a key role in the development of inflammation and fibrosis in chronic hepatitis C, with elevated blood levels observed in patients with severe fibrosis [33–37]. In patients with hepatitis C, higher levels of IP-10/CXCL10 were observed in those with Child–Pugh B cirrhosis compared to those with Child–Pugh A cirrhosis [37]. Furthermore, in patients with hepatitis B, IP-10/CXCL10 levels were found to be lower in those with mild fibrosis than in those with severe fibrosis [38, 39]. In contrast, our study found that patients with high IP-10/CXCL10 ratios had a lower prevalence of cirrhosis. However, the large number of elderly patients in the noncirrhotic group, compared to the cirrhotic group, may have influenced our results (78 *vs.* 71 years old, $p < 0.001$). Further investigations are warranted to explore the association between etiology and IP-10/CXCL10 levels.

The findings of this study underscore the significance of sarcopenia as a prognostic factor in patients with primary HCC, both at baseline and at 1, 3, and 5 years following the first occurrence of HCC. Therefore, the diagnosis of sarcopenia at any time after the first occurrence of HCC is important. Furthermore, elevated levels of IP-10/CXCL10 after the first occurrence of HCC may be associated with the development of sarcopenia in patients with HCC. By analyzing changes in IP-10/CXCL10 levels, this study not only aids in identifying high-risk groups for sarcopenia development but also deepens our understanding of the underlying mechanisms implicated in sarcopenia development in patients with primary HCC.

Conclusion

The changes in serum IP-10/CXCL10 levels appear to be associated with the development of sarcopenia following the first occurrence of HCC. Therefore, monitoring these changes may serve as a valuable tool for identifying high-risk groups who are prone to developing sarcopenia, which is a significant prognostic factor for patients with primary HCC.

Declarations

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Author contributions (names must be given as initials)

Study concept and design: H.T. Acquisition of data: H.T., K.Y., L.O., Y.K., M.M., Y.S., M.S., S.K., T.Y, S.T., S.M. Analysis and interpretation of data: H.T. Writing the manuscript: H.T. Critical revision: S.M., N.E. Study supervision: S.M., N.E. All authors reviewed the manuscript.

Data availability statement

Research data obtained in this study are not shared.

Competing interests

The authors declare no competing interests.

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Figures

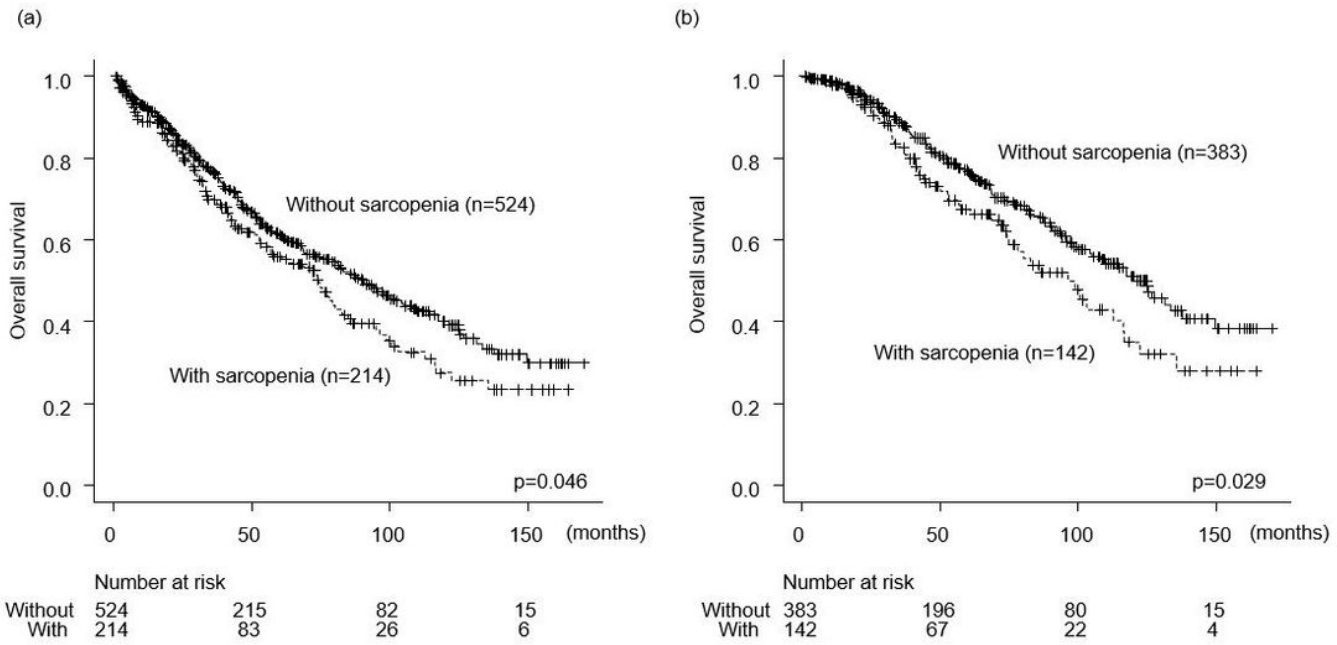

Figure 1

(a) Overall survival in patients with primary HCC (*n* = 738), (b) Overall survival in patients who achieved radical cure at the time of the first occurrence of HCC (*n* = 525); those with sarcopenia at baseline versus those without sarcopenia.

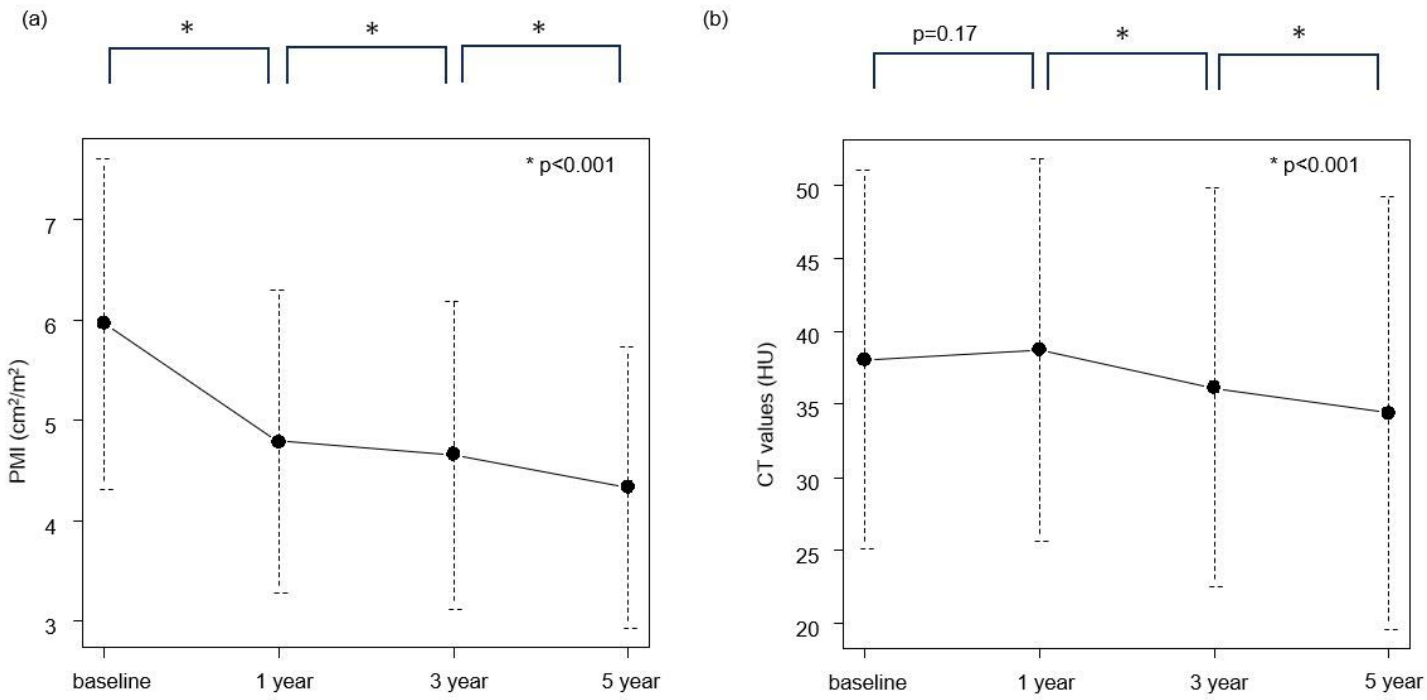

Figure 2

(a) Psoas muscle mass index (PMI) trends following the first occurrence of HCC, (b) transition of CT values of the multifidus muscle following the first occurrence of HCC.

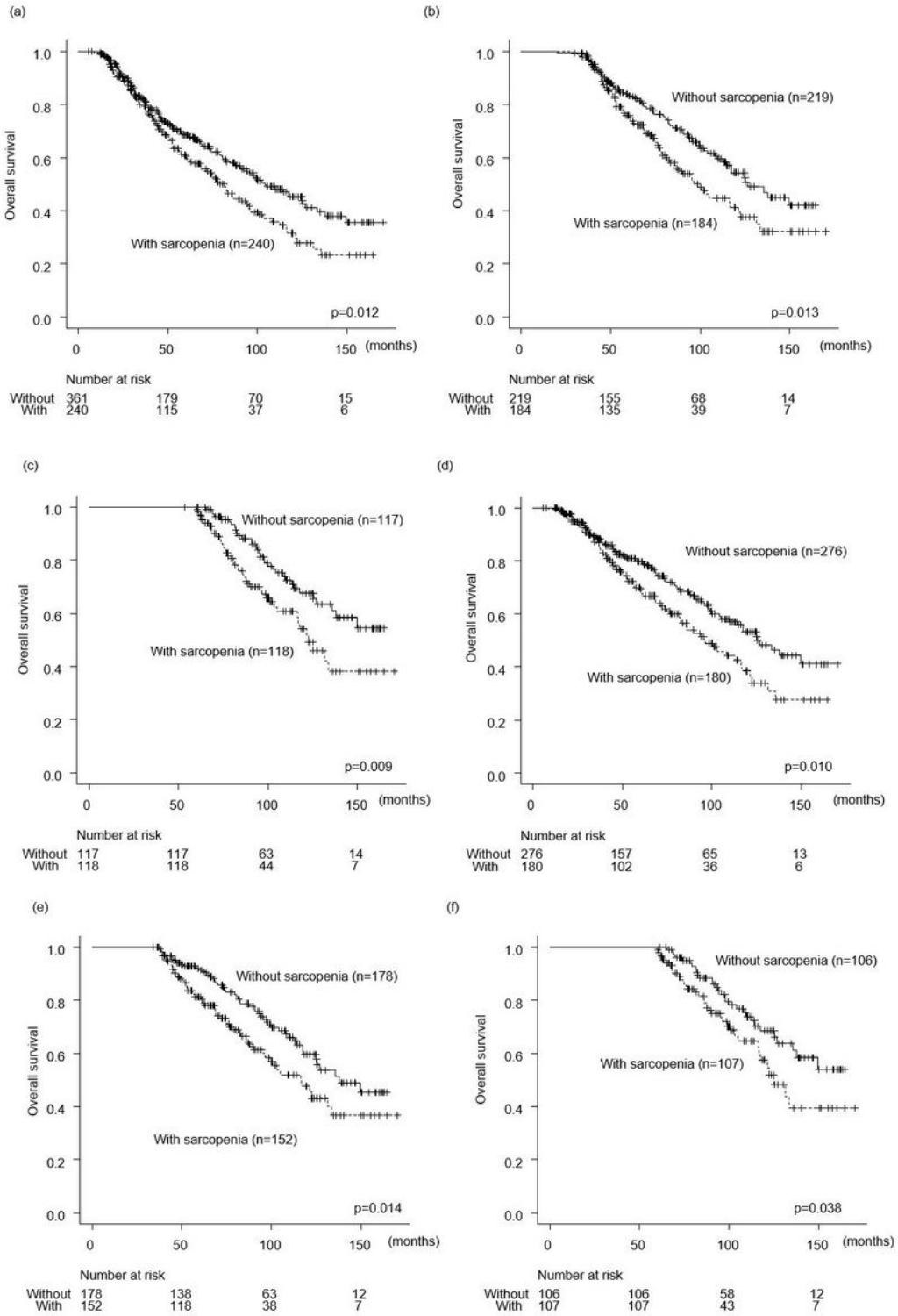

Figure 3

(a-c) Overall survival in patients with primary HCC (*n* = 738); those with sarcopenia at (a) 1, (b) 3, and (c) 5 years after the first occurrence of HCC versus those without sarcopenia. (d-f) Overall survival in patients who achieved radical cure at the time of the first occurrence of HCC (*n* = 525); those with sarcopenia at (d) 1, (e) 3, and (f) 5 years after the first occurrence of HCCversus those without sarcopenia.

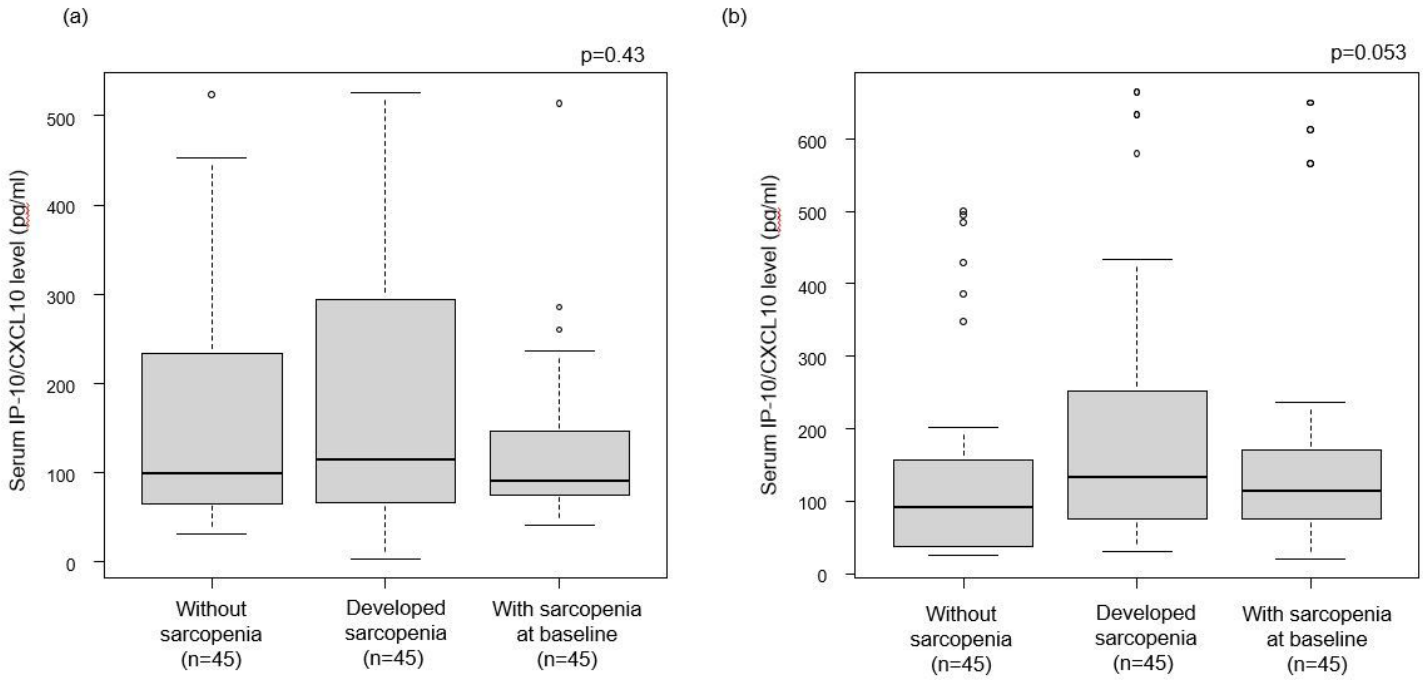

Figure 4

(a) The association between serum IP-10/CXCL10 levels at baseline and the presence of sarcopenia, (b) The association between serum IP-10/CXCL10 levels at the second measurement timing and the presence of sarcopenia.

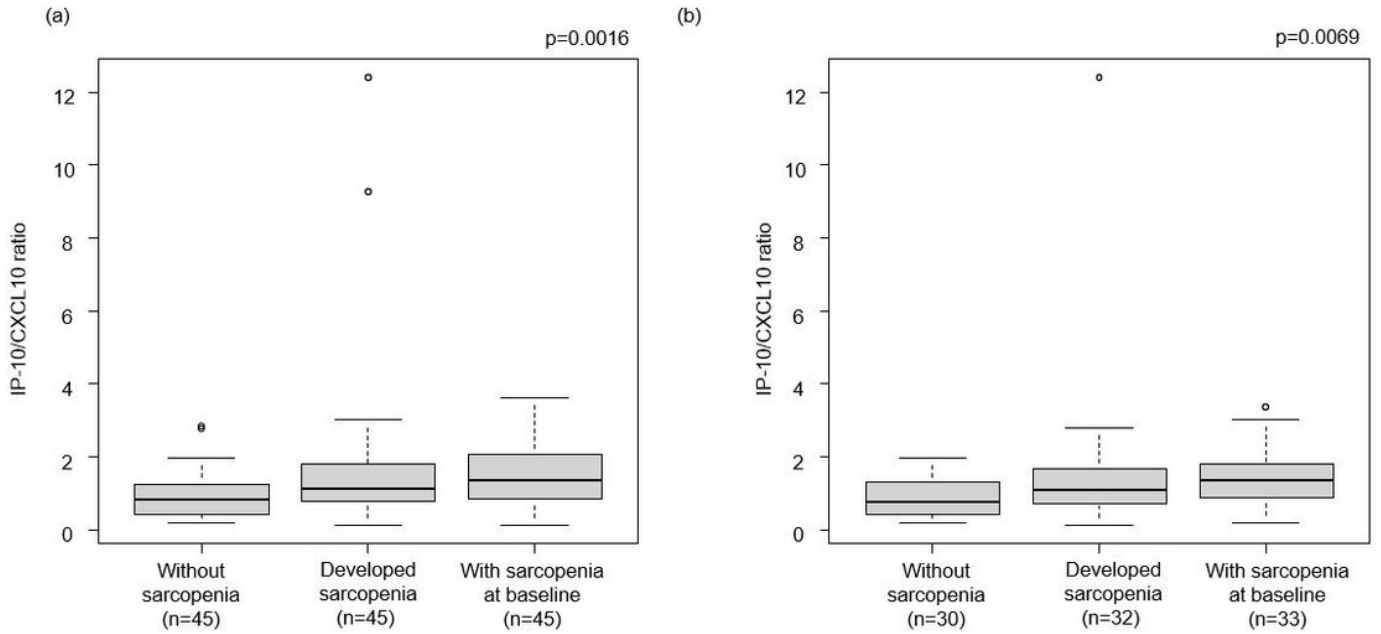

Figure 5

The association between IP-10/CXCL10 ratios and sarcopenia development, (a) in patients with primary HCC (*n* = 135), (b) in patients who achieved radical cure at the time of the first occurrence of HCC (n = 95).

Supplementary Figure 1. Flowchart of patient enrollment.

Supplementary Files

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- SupplementaryFigure1.pptx