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Visceral Fat Accumulation Is Associated with Increased Mortality Rate after Transcatheter Arterial Chemoembolization in Patients with Hepatocellular Carcinoma

Masaya Saito[1*], Yoshihiko Yano[1,2], Hirotaka Hirano[1], Kenji Momose[1], Yuki Kawano[1], Masaru Yoshida[1,3], Takeshi Azuma[1]

[1]Division of Gastroenterology, Department of Internal Medicine, Graduate School of Medicine, Kobe University, Kobe, Japan
[2]Center for Infectious Diseases, Graduate School of Medicine, Kobe University, Kobe, Japan
[3]Division of Metabolomics Research, Department of Internal Medicine, Graduate School of Medicine, Kobe University, Kobe, Japan
Email: *masaya@med.kobe-u.ac.jp

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Abstract

Aim: Transcatheter arterial chemoembolization (TACE) is thought to be a safe and effective treatment for hepatocellular carcinoma (HCC). However, in some HCC patients, it potentially shortens survival due to liver damage. We aimed to identify independent factors to predict overall survival of HCC after TACE. Methods: We included a total of 96 consecutive HCC patients who underwent TACE at Kobe University Hospital. Areas of skeletal muscle and fat tissue were measured by computed tomography (CT) scan before TACE. We divided the patients into two groups in terms of the presence or absence of 1-year mortality after TACE. Factors associated with 1-year mortality after TACE were assessed by multivariate analyses, and the optimal cut-off values were evaluated using a propensity score. Results: Multivariate analyses showed that visceral fat accumulation on CT was an independent factor associated with 1-year mortality after TACE (p = 0.033). There were no differences in skeletal muscle area and subcutaneous and intermuscular fat area between the two groups. Cut-off values for visceral fat area associated with 1-year mortality after TACE were defined as 33.3 cm^2/m^2 for males and 24.4 cm^2/m^2 for females. Conclusions: High visceral fat area was a prognostic factor associated with increased mortality rate in HCC patients undergoing TACE. Using this value, 1-year mortality risk after TACE would be better estimated before the day TACE was performed.

*Corresponding author.

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Keywords

Glucose Metabolism, Liver Cirrhosis, Obesity, Overall Survival, Sarcopenia

1. Introduction

Transcatheter arterial chemoembolization (TACE) is the most widely used first-line treatment in the western world and Asia for patients with unresectable hepatocellular carcinoma (HCC). TACE displays a tumor-response rate of 30% - 60% [1]-[3] and shows a survival benefit compared with that in controls [4]-[6]. However, TACE against HCC sometimes worsens liver parenchymal function. The deterioration of liver function due to ischemia of the non-tumoral liver following TACE can occasionally lead to the shortening of life expectancy [7]-[9]. Current guidelines for HCC management recommend mortality risk estimates as a decision-making support [10].

Several staging systems before HCC treatment have been developed for mortality risk estimates. The best known systems are Child's score [11], Model for End-stage Liver Disease (MELD) score [12], and Tumor Node Metastasis (TNM) stage [13]. Moreover, previous studies showed that obesity influenced the prognosis of HCC [14] [15]. In addition, we previously reported that energy metabolism could be associated with overall survival in HCC patients after TACE [16]. Visceral fat is a metabolically active component, and is reported to be a prognostic marker of other tumors [17]. Visceral fat can be measured by computed tomography (CT) scan [18], which is routinely used to screen for HCC lesions in cirrhotic patients, and provides precise, objective, and reproducible quantification of visceral fat mass.

In the present study, we aimed to identify independent factors to predict overall survival of HCC after TACE. The pre-therapeutic prediction of overall survival after TACE would help in improving awareness of the development of jaundice, as cites and encephalopathy. To our knowledge, there have been no studies that examine whether visceral fat determined by CT scan can become a new prognostic model after any HCC treatment.

2. Patients and Methods

2.1. Ethics Statement

All patients provided written consent to participate in the study, and the protocol was approved by the institutional ethics review board at Kobe University. This study complies with the standards of the Declaration of Helsinki and current ethical guidelines.

2.2. Patients

We included a total of 96 consecutive patients (mean age: 70.2 years, range: 41 - 87 years; male: female ratio: 61:35) who underwent TACE for HCC between July 2009 and October 2010 at Kobe University Hospital. All patients were Japanese and had liver cirrhosis that had been diagnosed on the basis of laboratory data, ultrasonography, and CT scan. According to the modified Child's classification [11], 52 patients were classified into Child's grade A and 44 were classified into grade B. The etiology of cirrhosis was as follows: hepatitis B in 12 patients, hepatitis C in 66, alcoholic liver dysfunction in 31, primary biliary cirrhosis in 2, autoimmune hepatitis in 1, non-alcoholic fatty liver disease (NAFLD) in 4, and unknown in 1, although each category overlaps with others (**Table 1**). The diagnosis of HCC was based on findings obtained from contrast-enhanced X-ray CT scans. As cites was confirmed by ultrasonography and CT.

In Japan, a consensus-based clinical practice manual proposed by the Japan Society of Hepatology is widely used for the management of HCC [19]. Those who had 4 or more lesions, those who had 3 or fewer lesions and tumor of 3 cm or more in size, and those who had mild portal invasion without an extra-hepatic lesion were eligible for this study. In addition, those who did not consent to a liver resection, difficult cases in terms of undertaking radiofrequency ablation (RFA) and percutaneous ethanol injection (PEI), and those who were elderly, that is, over 80 years old, were also eligible. Those who had refractory as cites, overt encephalopathy, uncontrolled esophageal varices, severe jaundice, Child's grade C, portal vein trunk thrombosis, or poor performance status (PS) of more than 2 were excluded from the study. In addition, those who used intravenous albumin regu-

Table 1. The background clinical characteristics of the 96 HCC patients who underwent TACE.

Age (years)	70.2 ± 9.2 (41 - 87)
Sex (male/female)	61/35
Child's grade A/B	52/44
Cause of liver cirrhosis	
Hepatitis B	12
Hepatitis C	66
Alcoholic liver dysfunction	31
Primary biliary cirrhosis	2
Autoimmune hepatitis	1
Non-alcoholic fatty liver disease	4
Unknown	1

Data are n or mean ± SD (range). Each category overlaps with others.

larly, those who were given a branched-chain amino acid preparation, and those who had dialysis were also excluded. Liver function of these cases was limited to Child's grade A or B.

The follow-up time was defined as the number of months from TACE to last contact with the patient or death. All patients were periodically seen as outpatients at our hospital. The follow-up protocol included clinical assessment by physical examination and biochemistry every month and the use of ultrasonography or contrast-enhanced CT scan every 3 months. In our study, TACE-related mortality was defined as death from a complication within 2 weeks of each session of TACE.

2.3. Clinical Evaluation

The clinical evaluation before treatment was performed on the basis of the results of physical examination and laboratory measurements. All patients were analyzed by the Child's score, MELD score, and TNM stage. The duration (days) of febrile episodes (over 37˚C) after TACE was recorded, and the therapeutic volume (cm^3) in TACE was evaluated by observing Lipiodol deposits on a liver CT scan following TACE. Past TACE treatment frequency (number of times) and other treatments (surgical resection, RFA, and PEI) were also documented. Laboratory measurements including prothrombin time, aspartate aminotransferase, alanine aminotransferase, γ-glutamyltranspeptidase, total bilirubin, cholinesterase, albumin (Alb), prealbumin (preAlb), the branched-chain amino acid/tyrosine ratio, C-reactive protein (CRP), creatinine, fasting plasma glucose, immunoreactive insulin, homeostasis model assessment of insulin resistance, hemoglobin A1c (HbA1c), the indocyanine green dye clearance test (ICG test) retention rate at 15 min, type 4 collagen 7S, hyaluronic acid, alpha fetoprotein (AFP), and des-γ-carboxy prothrombin (DCP) were assessed before TACE.

2.4. Protocol for TACE

TACE for HCC was performed by catheterization via the femoral artery under local anesthesia, with super-selective catheterization of the hepatic artery feeding the tumor, unless bilobar tumors were involved, in which case chemoembolization was performed in the appropriate hepatic artery. Depending on the tumor size, various amounts of an emulsion of 20 mg of Farmorubicin (epirubicin hydrochloride; Pfizer, USA) and 3 ml of Lipiodol (the iodine addition products of the ethyl esters of fatty acids obtained from poppy seed oil; Mitsui, Japan) at a 1:1 volume ratio were injected under fluoroscopic monitoring. This was followed by embolization with gelatin (Gelpart; Yamanouchi, Japan). Following TACE, a liver CT scan was performed to calculate the therapeutic volume from the distribution of Lipiodol deposits.

2.5. CT Analyses of Body Composition Variables

CT scans used for analyses were performed solely for the purpose of diagnosing and staging HCC. A transverse

CT image from L3 in the inferior direction was assessed from each scan. Images were analyzed with Slice Omantic V5.0 software (Tomo Vision, Montreal, Quebec, Canada), which enables specific tissue demarcation by using previously reported Hounsfield unit (HU) thresholds. Skeletal muscle is identified and qualified by HU thresholds of −29 to +150 [20]. Muscles in the L3 region encompass psoas, erector, spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis. The following HU thresholds were used for fat tissues: −190 to −30 for subcutaneous and intermuscular fat tissues [21], and −150 to −50 for visceral fat tissues [22]. With these specific HU thresholds, measurements of the skeletal muscle are not influenced by the presence of ascites in patients with cirrhosis. Cross-sectional areas (cm^2) were automatically computed by summing tissue pixels and multiplying by pixel surface area. All CT images were analyzed by two trained observers. Cross-sectional area of muscle and fat tissue was normalized for stature (cm^2/m^2), as reported elsewhere [23]. The L3 skeletal muscle was expressed as cross-sectional muscle area/height, and cut-offs for sarcopenia were based on a CT-based sarcopenic study (L3 skeletal muscle area/ height, ≤38.5 cm^2/m^2 for females and ≤52.4 cm^2/m^2 for males) [24] [25].

2.6. Statistical Analysis

Statistical analyses were conducted using SPSS Statistics 18.0 (SPSS Inc., Chicago, IL, USA). Univariate analyses of demographic factors were performed to investigate the difference between two groups. Multivariate analyses were constructed using backward stepwise logistic regression. The predictive ability of the model was quantified using each significant multivariate factor and 1-year mortality (area under ROC, AUC). An optimal cut-off point was a propensity score on the maximal sum of sensitivity and specificity. The relationship between two variables was investigated by Spearman's correlation coefficient test. Log-rank test was performed to compare the survival distributions. Values of $p < 0.05$ were considered significant.

3. Results

3.1. Factor Analyses Associated with 1-Year Mortality after TACE

One-year mortality after TACE was found in 32 patients out of 96 (1-year mortality group), and 1-year survival was detected in 64 patients (1-year survival group). **Table 2** shows the results of univariate analyses comparing several factors before TACE between the two groups. Body mass index (BMI), Child's score, TNM stage, past treatment frequency of TACE, visceral fat area, CRP, ICG test retention rate at 15 min, AFP, and DCP were significantly higher in the 1-year mortality group than in the survival group (p = 0.002, 0.009, 0.001, 0.000, 0.016, 0.023, 0.005, 0.004, and 0.000, respectively). Alb and preAlb were significantly lower in the 1-year mortality group than in the survival group (p = 0.016 and 0.044, respectively). Skeletal muscle area and subcutaneous and intermuscular fat area showed no significant differences between the two groups (p = 0.051 and 0.105, respectively). **Table 3** shows the results of univariate analyses comparing several factors after TACE between the two groups. Therapeutic volume and febrile duration were significantly higher in the 1-year mortality group than in the survival group (p = 0.001 and 0.000, respectively).

We found a significant positive correlation between visceral fat area and BMI (p = 0.000, r = 0.423) (**Figure 1**). Multicollinearity was also detected between Alb and preAlb, so BMI and preAlb were not introduced into the multivariate logistic regression analyses. The 9 significant univariate factors other than them were introduced into a multivariable logistic model. Backward stepwise multivariate regression analyses showed that visceral fat, ICG test retention rate at 15 min, DCP, and past treatment frequency of TACE were independent factors associated with 1-year mortality after TACE (p = 0.033, 0.001, 0.009, and 0.007, respectively) (**Table 4**).

3.2. Evaluation of Cut-Off Values of Visceral Fat Area

The median visceral fat area of all patients was 34.3 cm^2/m^2 (range 2.3 - 111.3 cm^2/m^2) and, in male patients, it was 35.9 cm^2/m^2 (range 2.3 - 111.3 cm^2/m^2), which was greater than that in female patients (median 26.1 cm^2/m^2, range 4.9 - 69.8 cm^2/m^2; p = 0.029) (**Figure 2**). Using propensity score, cut-off values for visceral fat area associated with 1-year mortality after TACE were defined as 33.3 cm^2/m^2 for males and 24.4 cm^2/m^2 for females, which is recognized as a measure of metabolic abnormalities in Japan [26]. We divided the study population into two groups: high visceral fat area (H-VFA) or low visceral fat area (L-VFA).

Table 2. Univariate analyses comparing several factors (before TACE) between 1-year mortality group and survival group (n = 96).

Factor	1-year mortality group		1-year survival group		*p* value
(before TACE)	n = 32		n = 64		
Age (years)	71	(56 - 86)	71	(41 - 87)	0.669†
Sex (male/female)	20/12		41/23		0.881§
Height (cm)	158.4 ± 8.0	(144.0 - 174.5)	161.0 ± 9.3	(138.5 - 179.0)	0.088*
Body weight (kg)	62.1	(48.0 - 91.5)	59.8	(37.0 - 93.6)	0.280†
BMI (kg/m^2)	24.8 ± 2.7	(19.0 - 30.0)	22.9 ± 2.8	(15.6 - 30.2)	**0.002***
HBs Ag (+/−)	4/28		8/56		1.000¶
HCV Ab (+/−)	22/10		44/20		1.000§
Alcohol (over 20 g/day) (+/−)	9/23		22/42		0.537§
Child's score (5, 6, 7, 8, 9)	7 (5 - 9)		6 (5 - 9)		**0.009†**
MELD score	7.3 (6.0 - 11.9)		7.1 (6.0 - 20.7)		0.465†
TNM stage of HCC (I, II, III, IVa, IVb)	0/8/20/2/2		8/23/32/1		**0.001***
Past treatment frequency of TACE (times)	3 (0 - 11)		1 (0 - 10)		**0.000†**
Past treatments other than TACE (+/−)	15/17		25/39		0.464§
Visceral fat area (cm^2/m^2)	39.9 (12.2 - 111.3)		30.7 (2.3 - 93.0)		**0.016†**
Subcutaneous and intermuscular fat area (cm^2/m^2)	57.9 ± 20.9 (7.9 - 96.8)		51.6 ± 24.2 (2.8 - 101.0)		0.105*
Skeletal muscle area (cm^2/m^2)	44.5 ± 6.9 (27.1 - 57.6)		41.6 ± 8.6 (20.5 - 70.8)		0.051*
PT (%)	77.1	(67.1 - 100.0)	83.2	(57.6 - 100.0)	0.133†
AST (IU/L)	47	(19 - 165)	49	(18 - 141)	0.920†
ALT (IU/L)	35	(11 - 111)	37	(13 - 130)	0.388†
γ-GTP (IU/L)	52	(10 - 857)	49	(13 - 1188)	0.594†
T-Bil (mg/dL)	0.9	(0.4 - 2.5)	0.9	(0.3 - 2.1)	0.935†
ChE (IU/L)	130	(81 - 348)	168	(47 - 327)	0.062†
Alb (g/dL)	3.2	(2.4 - 4.3)	3.7	(2.4 - 4.8)	**0.016†**
Prealbumin (mg/dL)	9.6	(4.5 - 28.2)	12.4	(4.2 - 33.1)	**0.044†**
BTR	3.4	(1.7 - 7.3)	4.0	(1.5 - 8.0)	0.076†
CRP	0.1	(0.1 - 3.5)	0.1	(0.1 - 6.1)	**0.023†**
Crn	0.77	(0.46 - 1.93)	0.75	(0.44 - 4.91)	0.616†
FPG (mg/dL)	100	(71 - 207)	101	(74 - 351)	0.834†
IRI (μU/mL)	14	(4 - 40)	11	(1 - 84)	0.243†
HOMA-IR	3.01	(0.81 - 12.10)	2.58	(0.19 - 43.30)	0.310†
HbA1c (%)	5.3	(4.4 - 6.9)	5.4	(4.3 - 10.2)	0.112†
ICG test retention rate at 15 min (%)	31.6	(8.5 - 75.6)	21.9	(3.5 - 59.5)	**0.005†**
Type 4 collagen 7S (ng/mL)	7.3	(5.0 - 11.0)	6.5	(3.0 - 16.0)	0.091†
HA (ng/mL)	286.9	(53.8 - 1483.6)	299	(12.4 - 1237.8)	0.841†
AFP (ng/mL)	80	(6 - 94260)	17	(2 - 14183)	**0.004†**
DCP	1249	(16 - 688500)	90	(14 - 7138)	**0.000†**

Data represent n, mean ± SD (range), or median (range). The data were evaluated with the §Chi-square test, *two-sample t-test, †Wilcoxon rank sum test, or ¶Fisher's exact test as appropriate.

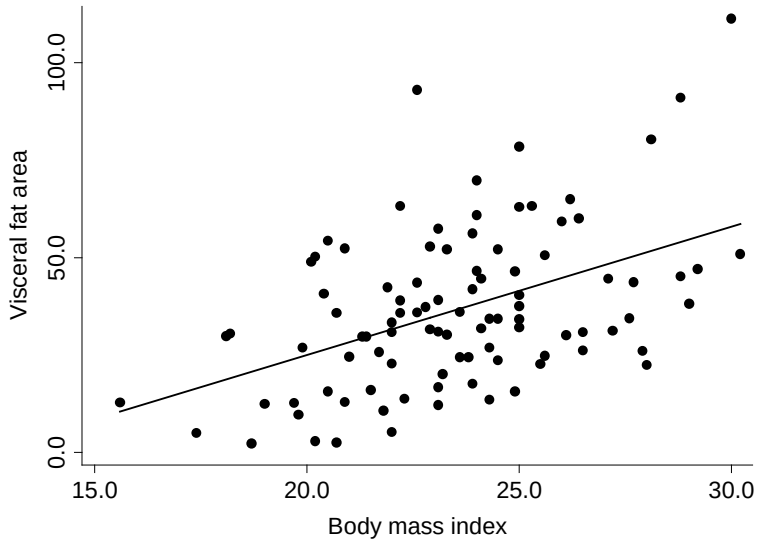

Figure 1. The correlation between visceral fat area and body mass index (BMI) in hepatocellular carcinoma (HCC) patients undergoing transcatheter arterial chemoembolization (TACE). Before TACE, visceral fat area was positively related to BMI by Spearman's correlation coefficient test (p = 0.000, r = 0.423).

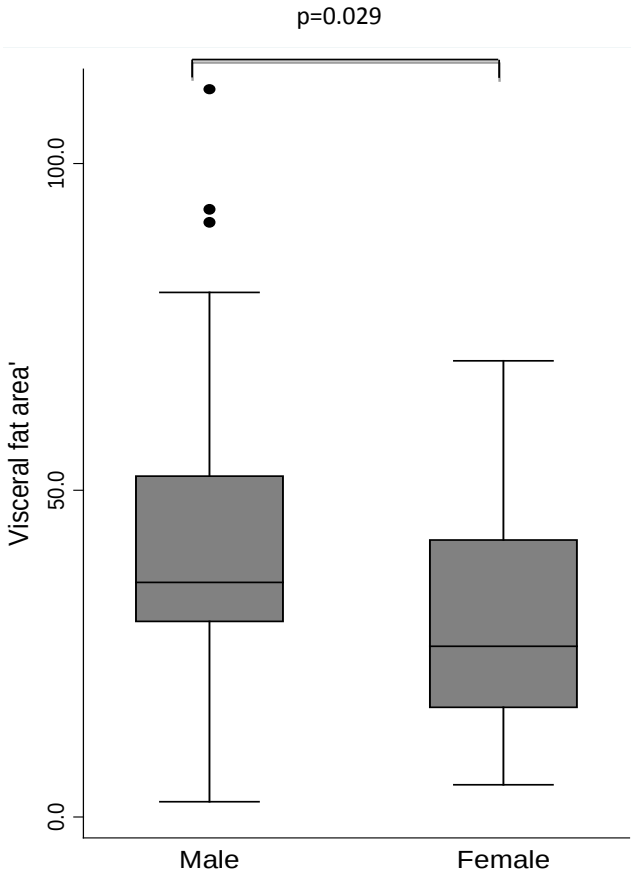

Figure 2. Comparison of visceral fat area between males and females. The median visceral fat area of all patients was 34.3 cm^2/m^2 (range 2.3 - 111.3 cm^2/m^2); in male patients, it was 35.9 cm^2/m^2 (range 2.3 - 111.3 cm^2/m^2), which was more than that in female patients (median 26.1 cm^2/m^2, range 4.9 - 69.8 cm^2/m^2; p = 0.029).

Table 3. Univariate analyses comparing several factors (after TACE) between 1-year mortality group and survival group (n = 96).

Factor	1-year mortality group	1-year survival group	*p* value
(after TACE)	n = 32	n = 64	
Therapeutic volume (cm^3)	110.1 (11.9 - 527.2)	50.7 (2.0 - 291.4)	**0.001**†
Febrile duration (days)	7 (1 - 7)	3 (0 - 7)	**0.000**†

Data represent median (range). The data were evaluated with the †Wilcoxon rank sum test.

Table 4. Multivariate logistic regression analyses comparing the significant univariate factors associated with 1-year mortality after TACE (n = 96).

Factor	B	SE	*p* value	Exp(B)	95% CI of EXP(B)	
					Upper limit	Lower limit
Visceral fat area	2.13	0.005	**0.033**	1.012	1.001	1.022
ICG test retention rate at 15 min (%)	3.22	0.033	**0.001**	1.102	1.039	1.169
DCP	2.63	0.000	**0.009**	1.001	1.000	1.001
Past treatment frequency of TACE	2.70	0.196	**0.007**	1.442	1.106	1.882

B: regression coefficient; CI: confidence interval; Exp(B): odds ratio; SE: standard error. Multicollinearity was detected between visceral fat area and BMI and between Alb and preAlb, so BMI and preAlb were not introduced into the multivariate logistic regression analyses.

3.3. Factor Analyses Associated with Visceral Fat Area

H-VFA was found in 58 out of 96 patients (H-VFA group), and L-VFA was detected in 38 patients (L-VFA group). **Table 5** shows the results of univariate analyses comparing several factors before TACE between the two groups. Body weight, BMI, TNM stage, subcutaneous and intermuscular fat area, and HbA1c were significantly higher in the H-VFA group than in the L-VFA group (p = 0.003, 0.000, 0.003, 0.001, and 0.017, respectively). T-Bil was significantly lower in the H-VFA group than in the L-VFA group (p = 0.044). Skeletal muscle area and presence or absence of sarcopenia did not differ between the two groups (p = 0.232 and 0.904, respectively). **Table 6** shows the results of univariate analyses comparing several factors after TACE between the two groups. One-year mortality after TACE was significantly higher in the H-VFA group than in the L-VFA group (p = 0.003).Before the analyses, this study showed that visceral fat area had significantly positive relationships to BMI and 1-year mortality after TACE. Multicollinearity was also detected between body weight and BMI, so they were not introduced into the multivariate logistic regression analyses. The 4 significant univariate factors other than them were introduced into a multivariable logistic model. Backward stepwise multivariate regression analyses showed that TNM stage, subcutaneous and intermuscular fat area, and HbA1c were independent factors associated with visceral fat area (p = 0.007, 0.001, and 0.028, respectively) (**Table 7**).

3.4. Follow-Up

All of the 96 patients were completely followed up. During the follow-up, 56 patients died, whereas 40 patients were alive at the end of the study. Out of the 56 dead patients, 36 patients died of liver failure and the other 20 patients died of HCC progression. TACE- and/or sepsis-related mortality was not observed in this study. The median follow-up period was 24 months (2 - 41 months). The median survival time was 27.0 months (95% CI 16.146 - 31.854). The overall survival rates were 66.7% and 49.0% at 12 and 24 months, respectively. Using the Kaplan-Meier method, the distribution of the 96 patients between H-VFA and L-VFA associated with 1-year mortality after TACE is described in **Figure 3**. Overall survival was significantly shorter in the H-VFA group than in the L-VFA group (p = 0.017).

4. Discussion

Coinciding with the rising incidence of HCC, the prevalence of obesity has increased rapidly over the past two

Table 5. Univariate analyses comparing several factors (before TACE) between H-VFA group and L-VFA group (n = 96).

Factor	H-VFA group		L-VFA group		*p* value
(Before TACE)	n = 58		n = 38		
Age (years)	71	(41 - 87)	71	(55 - 83)	0.784[†]
Sex (male/female)	37/21		24/14		0.950[§]
Height (cm)	160.0 ± 9.8	(138.5 - 179.0)	160.2 ± 7.6	(147.7 - 176.9)	0.452[*]
Body weight (kg)	63.1	(40.2 - 93.6)	56.8	(37.0 - 73.6)	**0.003**[†]
BMI (kg/m^2)	24.4 ± 2.6	(20.1 - 30.2)	22.2 ± 2.8	(15.6 - 28.0)	**0.000**[*]
HBs Ag (+/−)	7/51		5/33		1.000[¶]
HCV Ab (+/−)	36/22		30/8		0.081[§]
Alcohol (over 20 g/day)(+/−)	20/38		11/27		0.571[§]
Child's score (5, 6, 7, 8, 9)	6 (5 - 9)		7 (5 - 9)		0.390[†]
MELD score	7.0 (6.0 - 12.3)		7.3 (6.0 - 20.7)		0.227[†]
TNM stage of HCC (I, II, III, IVa, IVb)	5/11/37/3/2		3/20/15/0/0		**0.003**[*]
Past treatment frequency of TACE (times)	1 (0 - 11)		1 (0 - 10)		0.283[†]
Past treatments other than TACE (+/−)	24/34		16/22		0.944[§]
Subcutaneous and intermuscular fat area (cm^2/m^2)	59.8 ± 18.1 (33.6 - 97.8)		44.4 ± 27.1 (2.8 - 101.4)		**0.001**[*]
Skeletal muscle area (cm^2/m^2)	43.0 ± 8.7 (20.5 - 70.8)		41.8 ± 7.2 (21.7 - 57.6)		0.232[*]
Sarcopenia (+/−)	39/19		26/12		0.904[§]
PT (%)	80.3	(58.5 - 100.0)	82.4	(57.6 - 100.0)	0.827[†]
AST (IU/L)	48	(19 - 165)	49	(18 - 141)	0.412[†]
ALT (IU/L)	36	(11 - 111)	37	(13 - 130)	0.875[†]
γ-GTP (IU/L)	51	(20 - 857)	47	(10 - 1188)	0.436[†]
T-Bil (mg/dL)	0.8	(0.3 - 2.5)	1.0	(0.3 - 2.5)	**0.044**[†]
ChE (IU/L)	161	(81 - 348)	145	(47 - 327)	0.123[†]
Alb (g/dL)	3.6	(2.4 - 4.8)	3.4	(2.4 - 4.5)	0.346[†]
Prealbumin (mg/dL)	11.5	(4.2 - 28.2)	10.9	(4.5 - 33.1)	0.479[†]
BTR	3.9	(1.5 - 7.4)	4.0	(1.9 - 8.0)	0.691[†]
CRP	0.1	(0.1 - 6.1)	0.1	(0.1 - 2.9)	0.401[†]
Crn	0.77	(0.44 - 1.93)	0.72	(0.45 - 4.91)	0.514[†]
FPG (mg/dL)	104	(71 - 234)	98	(74 - 351)	0.142[†]
IRI (μU/mL)	11	(4 - 84)	11	(1 - 40)	0.280[†]
HOMA-IR	2.8	(0.81 - 43.30)	2.64	(0.19 - 20.80)	0.310[†]
HbA1c (%)	5.6	(4.4 - 8.2)	5.1	(4.3 - 10.2)	**0.017**[†]
ICG test retention rate at 15 min (%)	25.4	(5.5 - 59.5)	23.4	(3.5 - 75.6)	0.919[†]
Type 4 collagen 7S (ng/mL)	6.5	(3.0 - 14.0)	7.8	(3.6 - 16.0)	0.132[†]
HA (ng/mL)	229	(12.4 - 1483.6)	332.9	(48.1 - 1237.8)	0.074[†]
AFP (ng/mL)	36	(2 - 94260)	26	(5 - 14183)	0.694[†]
DCP	250	(14 - 688500)	93	(14 - 12749)	0.076[†]

Data represent n, mean ± SD (range), or median (range). The data were evaluated with the [§]Chi-square test, [*]two-sample t-test, [†]Wilcoxon rank sum test, or [¶]Fisher's exact test as appropriate.

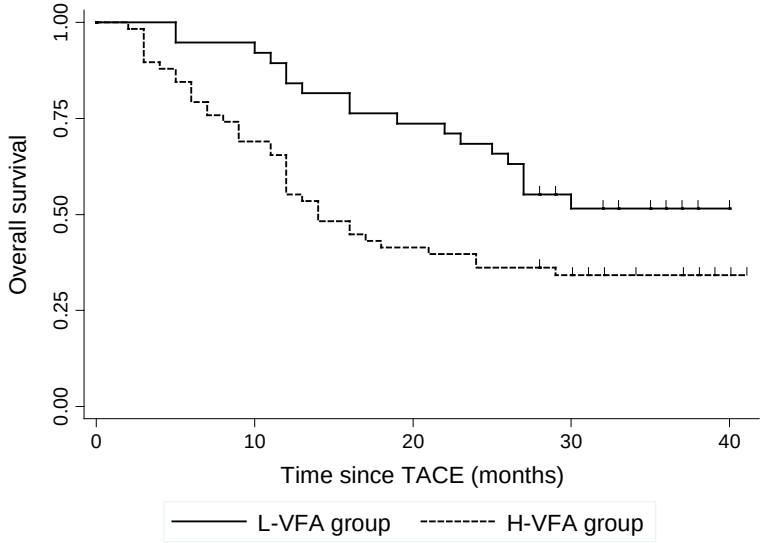

Figure 3. Overall survival according to visceral fat area in 96 patients with HCC after TACE. All of the 96 patients were completely followed up. During follow-up, 56 patients died, whereas 40 patients were alive at the end of the study. TACE-related mortality was not observed in this study. The median follow-up period was 24 months (2 - 41 months). The median survival time was 27.0 months (95% CI 16.146 - 31.854). The overall survival rates were 66.7% and 49.0% at 12 and 24 months, respectively. Overall survival was significantly shorter in the high-VFA (H-VFA) group than in the low-VFA (L-VFA) group (p = 0.017). The H-VFA group is designated by a dotted line and the L-VFA group by a solid line.

Table 6. Univariate analyses comparing several factors (after TACE) between H-VFA group and L-VFA group (n = 96).

Factor	H-VFA group	L-VFA group	*p* value
(After TACE)	n = 58	n = 38	
Therapeutic volume (cm^3)	78.4 (2.0 - 527.2)	52.1 (3.1 - 316.0)	0.120[†]
Febrile duration (days)	5 (0 - 7)	5 (0 - 7)	0.924[†]
1-year mortality after TACE (dead/alive)	26/32	6/32	**0.003**[§]

Data represent nor median (range). The data were evaluated with the [§]Chi-square test or [†]Wilcoxon rank sum test as appropriate.

Table 7. Multivariate logistic regression analyses comparing the significant univariate factors associated with H-VFA or L-VFA (n = 96).

Factor	B	SE	*p* value	Exp(B)	95% CI of EXP(B)	
					Upper limit	Lower limit
TNM stage	2.68	0.852	**0.007**	2.495	1.277	4.873
Subcutaneous and intermuscular fat area	3.26	0.013	**0.001**	1.043	1.017	1.070
HbA1c	2.19	0.54	**0.028**	1.878	1.069	3.299

B: regression coefficient; CI: confidence interval; Exp (B): odds ratio; SE: standard error. Before the analyses, this study showed that visceral fat area had significantly positive relationships to BMI and 1-year mortality after TACE. Multicollinearity was also detected between body weight and BMI, so they were not introduced into the multivariate logistic regression analyses.

decades [14] [27]-[31]. Obesity is now recognized as one of the most challenging public health issues worldwide. Calle *et al.* reported that obesity was related to increased mortality from HCC [14]. To elucidate the impact of the type of obesity further, we measured both visceral fat tissue and subcutaneous and intermuscular fat tissue. Our study showed that high visceral fat tissue, but not subcutaneous and intermuscular fat tissue, was an independent factor associated with 1-year mortality of HCC patients after TACE. Moreover, our study showed that the HCC patients with H-VFA had significantly worse overall survival after TACE than those with L-VFA. It

was considered that visceral fat tissue is the metabolically active component, whereas subcutaneous and intermuscular fat tissue is the inactive component [17]. Our findings suggest that the distribution of fat tissue is a major determinant of the prognosis of HCC patients after TACE.

The extent of visceral fat has been reported to differ between males and females [32]. Indeed, in the present study, visceral fat area differed between males (median, 97.2 cm^2) and females (median, 62.6 cm^2) ($p = 0.001$). Therefore, the optimal cut-off values for visceral fat area were analyzed in males and females separately. These values of our study were lower than those of the previous studies for metabolic syndrome in the Japanese population [33]. This might be due to the fact that our study sample was biased towards older patients, although the previous study sample was limited to middle-aged patients. Indeed, Hayashi *et al.* have reported that the visceral fat area differed by generation [34]. Moreover, the NAFLD patients in our study numbered only 4 (4.2%) out of 96 patients.

Visceral fat tissue is no longer classified as an inert site solely for energy homeostasis. In fact, it is now characterized as the largest multifunctional endocrine organ that participates in the regulation of hormonal balance of the body in patients with not only NAFLD, but also viral cirrhosis [35]-[37]. Our study showed that high visceral fat was associated with poor HbA1c. Previous studies showed that visceral fat has been reported to be associated with negative effects against glucose metabolism [38]. Visceral fat tissue controls the function of the pancreas by secreting adipokines [39]. The disturbance of adipokine balance by excessive visceral fat tissue could play a role in worsening glucose metabolism. Our study also showed that high visceral fat was associated with the TNM stage of HCC. A situation of worse glucose metabolism promotes cellular growth and increases free insulin-like growth factor levels, which plays an important role in tumor growth and differentiation [40] [41]. Visceral fat accumulation may be involved in both tumor initiation and promotion or progression steps through these mechanisms.

In our study, sarcopenia as defined previously [24] [25] was not associated with 1-year mortality and overall survival after TACE. In general, sarcopenia associated with mortality has progressive functional impairment, mainly Child's grade C. For example, these patients were waiting for liver transplantation [42] [43]. In our study, all of the HCC patients retained their liver function, namely, Child's grade A and B, not grade C. Sarcopenia associated with mortality has also been related to low quality of life (QOL) [44]. In our study, all patients had PS 0 or 1 and retained good QOL. Moreover, sarcopenia associated with mortality was reported to increase the risk of sepsis-related death in cirrhotic patients, suggesting impaired immunity [45]. In our study, liver failure and HCC progression after TACE, but not sepsis, were the causes of death in all of the patients. Therefore, it is considered that sarcopenia would not be necessarily related to mortality in cirrhotic patients.

Many hepatologists have needed new prognostic models after HCC treatment [46]. We considered that the prognosis of patients after TACE would be better evaluated by visceral fat area. Using the value of visceral fat area, patients who have a potentially high risk of 1-year mortality after TACE could be detected. This value is not available for the selection of HCC patients for whom TACE would not be recommended. However, for early detection and prevention of 1-year mortality risk after TACE, this value is available. To prevent 1-year mortality risk after TACE, nutritional support is thought to be necessary in cirrhotic patients with advanced HCC undergoing TACE. L-carnitine is an essential cofactor in the transport of long-chain fatty acids, such as acylcarnitine esters, across the inner mitochondrial membrane for subsequent fat degradation [47]. Previous studies have shown that visceral steatosis was found in the loss of L-carnitine transport activity [48]. In addition, the administration of L-carnitine reduced the accumulation of visceral fat mass [49]. Nutritional supplementation with oral L-carnitine might be beneficial in reducing visceral fat, and in improving the mortality rate in HCC patients undergoing TACE. Our predictive model was established by the value of visceral fat area without a secondary effect by L-carnitine supplementation. Therefore, using the value of visceral fat area, appropriate nutritional support could be administered to HCC patients undergoing TACE while avoiding the provision of unnecessary nutritional support to patients with a low risk of 1-year mortality after TACE.

Our study has several limitations. First, it is a single institutional study with a relatively small sample size of HCC patients undergoing TACE. Second, the study is observational, so we could not infer causality between visceral fat accumulation and mortality. Third, the cut-off value of visceral fat area might differ in patients with liver disease. Finally, we have not yet validated predictive factors associated with 1-year mortality after TACE. At present, we are recruiting a different cohort to validate its ability, which we will report on in the near future.

5. Conclusion

In conclusion, our study showed that H-VFA was a prognostic factor associated with survival in HCC patients

undergoing TACE. Using the value of visceral fat area, 1-year mortality risk after TACE would be better estimated before the day TACE was performed.

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Conflict of Interest

We, the authors, declare that we have no conflicts of interest.

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