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Visceral Fat Associated with Worsening of Recurrent Esophageal Varices in Alcoholic/Nonalcoholic Steatohepatitis-Related Liver Cirrhosis

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Background: Alcoholic steatohepatitis and nonalcoholic steatohepatitis-related liver cirrhosis (ASH/NASH-LC) are major causes of esophageal varices (EVs). However, the association between high visceral fat and exacerbation of EVs remains unclear. The aim of this study was to clarify the association of visceral fat and recurrence rate of EVs in ASH/NASH-LC and to identify independent predictors associated with recurrence.

Methods: We retrospectively evaluated data from 94 patients who underwent endoscopic injection sclerotherapy for EVs with ASH/NASH-LC. Using the receiver operating characteristic curve for the cut-off value of visceral fat index (VFI; 46.4 cm^2/m^2), we classified patients as having a high VFI (n = 53) or low VFI (n = 41). Propensity score matching was used to align for background factors, and the recurrence rate of EVs was compared between the two groups. Predictors associated with esophageal variceal recurrence were identified by multivariate analysis. The recurrence rate in patients with viral LC was also investigated.

Results: In the overall analysis, the recurrence rate was significantly higher in the high VFI group than in the low VFI group ($P = 0.023$). The recurrence rate was also higher in the high VFI group than in the low VFI group after propensity score matching, in which 19 patients were matched in each group ($P = 0.048$). VFI and Child-Pugh score were independently associated with recurrence. Recurrence rates were comparable between the two groups in viral LC patients.

Conclusions: Worsening of variceal recurrence was observed in high visceral fat patients in ASH/NASH-LC but not in viral LC. Furthermore, high visceral fat was an independent predictor associated with variceal recurrence. (J Nippon Med Sch 2024; 91: 362–370)

Key words: alcoholic steatohepatitis-related liver cirrhosis, nonalcoholic steatohepatitis-related liver cirrhosis, endoscopic injection sclerotherapy, visceral fat

Introduction

The recent decrease in the number of patients with chronic hepatitis C is attributable to the high therapeutic response rate to direct-acting antiviral agents for hepatitis C virus (HCV) infection[1]. However, there is a worldwide surge in cases of alcoholic steatohepatitis (ASH) and nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH), and a resulting increase in ASH/NASH-related liver cirrhosis (LC). In addition, the prevalence rate of NAFLD is increasing because of rising rates of overweight/obesity, currently 75% in Western countries and 30% in Japan[2]. This has resulted in increased incidences of portal hypertension (PH) and esophageal varices (EVs) caused by NASH-related LC. Furthermore,

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PH elevation is associated with a variety of symptoms, including EVs, and is a risk factor for bleeding EVs[3,4].

High visceral fat area (VFA) in patients with LC and EVs is a primary predictor of liver dysfunction, leading to increased incidence of hepatocellular carcinoma (HCC) and worse outcomes[5]. In addition, the incidence of EVs was significantly higher in patients with high body mass index (BMI) and HCV-related LC[6]. Excessive visceral fat could possibly exacerbate liver dysfunction in patients with LC complicated by PH. However, previous findings are unclear on whether high BMI and excessive visceral fat are indicators of worsening of incident or recurrent EVs due to ASH/NASH-related LC. In this study, we retrospectively examined the association between high VFA and recurrence rate of EVs after endoscopic injection sclerotherapy (EIS) in patients with ASH/NASH-LC and those with viral LC.

Materials and Methods

Study Design

The primary endpoint in this retrospective study was the association of high VFA with the recurrence rate of EVs before and after propensity score matching. The secondary endpoint was identifying independent predictors associated with the recurrence rate by using multivariate analysis.

This study was performed in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was approved by the institutional review board of Tokyo Women's Medical University (Approval No. 2022-0135). The need for written informed consent was waived by the Ethics Committee of Tokyo Women's Medical University and opt-out consent was approved instead. This was obtained via the institutional websites where permission was requested for use of participants' personal information in this study.

Patient Selection

The inclusion criteria were as follows: (1) age older than 20 years; (2) diagnosis of LC related to ASH and NASH; (3) had undergone EIS between March 2008 and June 2022; (4) had undergone computed tomography (CT) scanning before treatment; and (5) had been observed for longer than 1 year. Patients were excluded if they (1) were cases of emergency rupture of EVs, since these cases were treated with endoscopic variceal ligation (EVL); (2) had hyperbilirubinemia (>4 mg/dL); (3) had portal vein thrombosis; (4) had uncontrolled HCC; (5) had not undergone CT scanning; and (6) were taking concomitant antihypertensive medication. Clinical data from 94 patients with life-threatening EVs [F2, F3, or any form with positive red color sign (RCS)], treated with EIS were included in the analysis. Diagnosis of ASH-related LC was based on a self-reported past and/or current history of alcohol abuse (over 60 g/day) without evidence of another cause of liver insult such as viral or autoimmune hepatitis, Wilson's disease, or idiopathic PH. NASH-related LC was diagnosed based on (1) presence of metabolic risk factors, namely diabetes mellitus, dyslipidemia, hypertension, and obesity; (2) a threshold of alcohol intake of 30 g/day in males and 20 g/day in females; (3) hepatic fibrosis based on platelet count, fibrosis-4 (FIB-4) index [based on aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, platelet count, and age], NAFLD fibrosis score [based on age, hyperglycemia, BMI, platelet count, albumin level, and AST/ALT ratio]; (4) fatty liver diagnosed using CT/ultrasonography; and (5) exclusion of ASH, viral hepatitis, autoimmune hepatitis, Wilson's disease, and idiopathic PH.

Body Composition Measurements

Body composition measurements were performed as previously described[7]. All preoperative CT scans were obtained with a 64-row or 16-row multidetector CT scanner (GE HealthCare, Hino, Japan) at 1 to 2 months before EIS. Digital Imaging and Communication in Medicine images were imported into a computer and ImageJ software ver. 1.52i (National Institutes of Health, Bethesda, MD, USA) was used to measure VFA and subcutaneous fat area on a cross-sectional plain CT scan at the level of the third lumbar vertebra. VFA and subcutaneous fat area were identified and expressed at thresholds ranging from −190 to −30 Hounsfield units (HU) (**Fig. 1A, 1B**)[8,9]. Similarly, skeletal muscle mass area, comprising the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis, was identified and expressed at thresholds from −29 to 150 HU (**Fig. 1C**)[10]. To correct for bias in VFA, subcutaneous fat area, and skeletal muscle mass measurements due to body size differences, each index [visceral fat index (VFI, cm^2/m^2), subcutaneous fat index (SFI, cm^2/m^2), and skeletal muscle index (cm^2/m^2)] was divided by the square of the height e.g., VFI (cm^2/m^2) = VFA (cm^2)/height^2 (m^2).

EV Recurrence Rate before and after Propensity Score Matching

Using the receiver operating characteristic (ROC) curve modulated by the presence/absence of variceal recurrence, the cut-off value of the VFI before EIS in all pa-

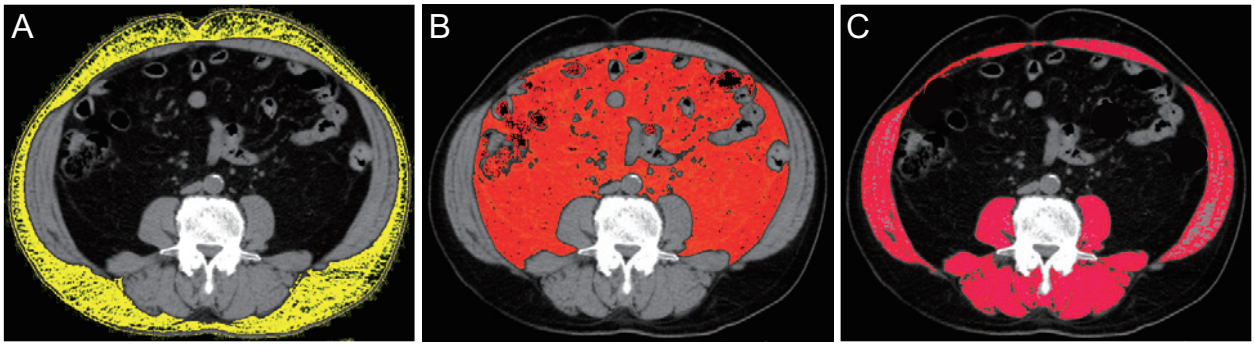

Fig. 1 Cross-sectional computed tomography images at the level of the third lumbar vertebra. (**A**) Subcutaneous fat area and (**B**) visceral fat area, both quantified with thresholds ranging from −190 to −30 HU. (**C**) Skeletal muscle area, including the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis, quantified with thresholds ranging from −29 to 150 HU. HU indicates Hounsfield units.

tients was set as 46.4 cm^2/m^2 [area under the curve (AUC); 0.732]. The patients were classified as having a high VFI (≥46.4 cm^2/m^2; n = 53) or low VFI (<46.4 cm^2/m^2; n = 41).

Next, we investigated the recurrence rate of EVs after EIS by propensity score matching using JMP Pro Software ver. 15 (SAS Institute, Cary, NC, USA). Patients in the high and low VFI groups were compared in relation to the background factors age, sex, platelet count, liver function indices (prothrombin time-international normalized ratio, AST, ALT, total bilirubin, and albumin), cause of LC, and form of varices. In total, data from 38 patients were extracted (high VFI group, n = 19; low VFI group, n = 19) after propensity score matching.

Independent Predictors Associated with EV Recurrence

Univariate and multivariate logistic regression analysis were used to identify predictive factors relative to recurrence of EVs in all 94 patients. The variables included in the analysis were age, sex, BMI, skeletal muscle index, VFI, SFI, serum albumin levels, cause of LC, absence/presence of ascites, and Child-Pugh score. Regarding age, BMI, skeletal muscle index, VFI, SFI, serum albumin levels, and Child-Pugh score, the cut-off values and AUC were analyzed based on the ROC curve modulated by the presence/absence of variceal recurrence (**Table 3**).

Patients with Viral LC

Patients with hepatitis B virus (HBV)/HCV-related LC (n = 48) were classified into a high VFI group (n = 24) and low VFI group (n = 24), using the same cut-off value, and the recurrence rate of EVs was compared between the two groups.

EIS Protocol

A GIF-Q260 or Q260J endoscope (Olympus, Tokyo, Japan) and the EVIS LUCERA CV-260SL light source device (Olympus) were used for the EIS procedure. Endoscopic findings of EVs (L, location; F, form; and C, color) and RCS were classified by using the general rules for documenting endoscopic findings of EVs in Japan[11]. EIS was performed by seven operators with more than 10 years of experience as endoscopists. EIS puncture, using a 23-gauge needle, was performed repeatedly with a 5% ethanolamine oleate iopamidol mixture as sclerosant. Intravariceal and paravariceal injections were confirmed by fluoroscopy. Patients were discharged 1 week after the first session of EIS if the EVs were deemed eradicated. Otherwise, an additional session of EIS was performed. An appropriate dose of sedative was administered intravenously to maintain conscious sedation during EIS. Recurrence of EVs was defined as life-threatening EVs of (1) F2 or F3 and/or (2) any form with a positive RCS during follow-up endoscopy, every 3-6 months after the initial EIS. Additional EIS was repeated until complete remission of EVs (F0/F1 and negative RCS) was achieved.

Statistical Analysis

Continuous data are presented as the median or mean ± SD. Continuous variables were analyzed nonparametrically with the Mann-Whitney *U* test. Categorical variables were compared with the χ^2 test when appropriate. Correlations between continuous variables were assessed by using Spearman correlation coefficients. Cut-off and AUC values for each predictive factor were computed using the ROC curve, which was adjusted for the presence/absence of variceal recurrence. Univariate and multivariate logistic regression analysis were used to identify predictive factors relative to recurrence of EVs. In univariate analysis, variables with a *P* value less than 0.05 were selected as candidates for multivariate analysis. Propensity score was calculated by using logistic regression, and one-to-one and nearest neighbor or within-

Table 1 Patient characteristics

	All (n = 94)	High VFI (n = 53)	Low VFI (n = 41)	*P* value
Age, median (range)	64 (32-89)	64 (32-89)	61 (40-85)	0.393
Sex, n (%)				0.563
Male	73 (77.7)	40 (75.5)	33 (80.5)	
Female	21 (22.3)	13 (24.5)	8 (19.5)	
BMI, kg/m^2, median (range)	23.4 (14.3-34.6)	25.2 (17.5-34.6)	22.1 (14.3-28.1)	<0.001
Skeletal muscle mass index, cm^2/m^2, median (range)	52.1 (35.1-69.4)	52.7 (40.7-69.4)	50 (35.1-64.4)	0.011
VFI, cm^2/m^2, median (range)	50.1 (13.9-120.4)	62.9 (48-120.4)	38.5 (13.9-46.4)	<0.001
SFI, cm^2/m^2, median (range)	46.1 (13.2-167.3)	60.5 (15.8-167.3)	35.9 (13.2-124.1)	<0.001
Concomitant diabetes mellitus, n (%)	36 (38.3)	21 (39.6)	15 (36.6)	0.764
Cause of liver cirrhosis, n (%)				0.194
Alcoholic	62 (66.0)	32 (60.4)	30 (73.2)	
NASH	32 (34.0)	21 (39.6)	11 (26.8)	
Ascites, n (%)	31 (33.0)	19 (35.9)	12 (29.3)	0.501
Classification of varices, n (%)				
Form (F1/F2/F3)	15 (16.0)/74 (78.7)/5 (5.3)	7 (13.2)/43 (81.1)/3 (5.7)	8 (19.5)/31 (75.6)/2 (4.9)	0.708
Color (Cw/Cb)	20 (21.3)/74 (78.7)	12 (22.6)/41 (77.4)	8 (19.5)/33 (80.5)	0.713
Red color sign (No/Yes)	8 (8.5)/86 (91.5)	4 (7.6)/49 (92.4)	4 (9.8)/37 (90.2)	0.704
Lg (No/Yes)	74 (78.7)/20 (21.3)	42 (79.3)/11 (20.7)	32 (78.1)/9 (21.9)	0.888
Variceal recurrence rate, n (%)	81 (86.2)	47 (88.7)	34 (82.9)	0.423
Operators (A/B/C/D/E/F/G)	12/9/13/14/18/23/5	10/5/6/7/10/11/4	2/4/7/7/8/12/1	0.406
Blood test results, median (range)				
PT-INR	1.15 (0.88-1.63)	1.15 (0.88-1.62)	1.14 (0.91-1.63)	0.527
Platelets ×10^4/uL	8.8 (2.7-22.7)	8.8 (2.7-22.7)	8.6 (2.9-17.3)	0.942
AST, IU/L	36.5 (14-313)	34 (14-313)	40 (14-124)	0.664
ALT, IU/L	24 (6-218)	23 (6-218)	24 (7-70)	0.694
Total bilirubin, mg/dL	1.2 (0.3-4.6)	1.3 (0.3-4.6)	1.1 (0.5-2.8)	0.674
Albumin, g/dL	3.4 (2.2-4.7)	3.4 (2.2-4.7)	3.5 (2.3-4.3)	0.562
Creatinine, mg/dL	0.77 (0.30-6.89)	0.77 (0.39-2.18)	0.72 (0.30-6.89)	0.289
Ammonia, ug/dL	47 (12-194)	46 (14-194)	47 (12-183)	0.954
FIB-4 index, median (range)	4.94 (1.92-14.15)	5.42 (1.92-14.15)	4.55 (2.31-10.06)	0.243
Child-Pugh score, median (range)	6 (5-9)	7 (5-9)	6 (5-8)	0.048
Child-Pugh classification (A/B), n (%)	55 (58.5)/39 (41.5)	26 (49.1)/27 (50.9)	29 (70.7)/12 (29.3)	0.034
Follow-up period, days, median (range)	1,067 (10-6,484)	1,056 (115-4,723)	1,207 (10-6,484)	0.462

BMI, Body mass index; VFI, Visceral fat index; SFI, Subcutaneous fat index; NASH, Non-alcoholic steatohepatitis; PT-INR, Prothrombin time-International Normalized Ratio; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; FIB-4, Fibrosis-4.

caliper matching was performed. The narrow caliper value was set as 0.05 to obtain an exact match. After propensity score matching, the recurrence rate curve was generated using the Kaplan-Meier method and was analyzed with the log-rank test. A *P* value less than 0.05 was considered to indicate statistical significance. All statistical data were analyzed with JMP Pro 15 software (SAS Institute).

Results

Patient Characteristics

Patient characteristics in the high VFI and low VFI groups before propensity score matching are shown in **Table 1**. BMI ($P < 0.0001$), skeletal muscle mass index ($P = 0.011$), VFI ($P < 0.0001$), and SFI ($P < 0.0001$) were significantly higher in the high VFI group than in the low VFI group. Child-Pugh score was worse in the high VFI group than in the low VFI group ($P = 0.048$).

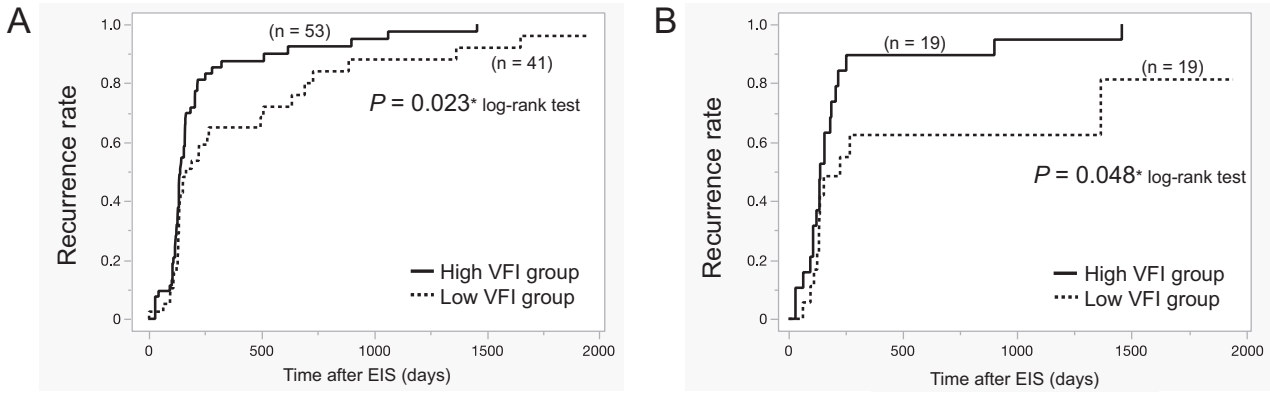

Fig. 2 Recurrence rate of esophageal varices in patients with ASH/NASH-related liver cirrhosis with high VFI or low VFI. Recurrence rate curve generated using the Kaplan-Meier method, analyzed with the log-rank test showing (**A**) significantly higher recurrence rate (P = 0.023) in the high VFI group (n = 53) than in the low VFI group (n = 41). (**B**) Significantly higher recurrence rate in the high VFI group (n = 19) (P = 0.048) than in the low VFI group (n = 19) after propensity score matching. ASH/NASH indicates alcoholic steatohepatitis and non-alcoholic steatohepatitis. VFI, visceral fat index.

EV Recurrence Rates in the High and Low VFI Groups

In all patients before propensity score matching, the cumulative recurrence rate of EVs after EIS was significantly higher in the high VFI group than that in the low VFI group (P = 0.023; **Fig. 2A**). After propensity score matching (**Table 2**), the recurrence rate was also significantly higher in the high VFI group than in the low VFI group (P = 0.048; **Fig. 2B**).

Independent Predictors Associated with Recurrence Rate of EVs

Univariate analysis using the logistic regression model showed that VFI and Child-Pugh score were significantly associated with recurrence rate (**Table 3**). Even after multivariate analysis, both factors [VFI (odds ratio; 11.84; P = 0.003) and Child-Pugh score (Odds ratio; 10.95; P = 0.031)] were extracted as independent predictors of recurrence rate.

Recurrence Rate of EVs in Patients with HCV/HBV-Related LC

The correlation between VFA and EVs in patients with HCV/HBV-related LC was a novel investigation. In contrast to the findings for patients with ASH/NASH, no significant difference between the high VFI and low VFI groups was noted in the recurrence rate of EVs in patients with HCV/HBV-LC (P = 0.482; **Fig. 3**).

Discussion

This study highlights three important findings. First, VFI and Child-Pugh score were identified as predictors of EV recurrence in patients with ASH/NASH-LC. Second, in patients with ASH/NASH-LC, the recurrence rate was significantly higher for those with a high VFI than for those with a low VFI. Third, in contrast to the findings for ASH/NASH-LC, VFI was not associated with EV recurrence rate in patients with HCV/HBV-LC only.

Several studies have implicated Child-Pugh score as a risk factor for EV exacerbation. Zheng et al.[12] reported that Child-Pugh score was a risk factor for variceal recurrence after EIS or endoscopic variceal ligation during a 3-year follow-up. Amitrano et al.[13] reported that a Child-Pugh score of C was a risk factor for mortality, uncontrolled bleeding, and rebleeding within 5 days after treatment of EVs. Past and present evidence suggests that Child-Pugh score is an appropriate predictive factor for EV recurrence. However, no study has shown that VFI is a predictor for variceal recurrence in ASH/NASH-related LC. The European Association for the Study of the Liver (EASL) guidelines for alcoholic-related liver disease state that excessive BW and severe obesity are important risk factors for progression of liver fibrosis in ASH[14]. The EASL further defines NAFLD as being characterized by "excessive hepatic fat accumulation associated with insulin resistance", in terms of NAFLD and NASH[15]. We hypothesized that in patients with high VFI this factor induces progression of liver fibrosis, leading to PH and exacerbation of recurrence of EVs in ASH/NASH-related LC.

To understand the higher recurrence rate of EVs in patients with high VFI, we focused on the pathophysiology of VFA and liver fibrosis in ASH/NASH-related LC. In ASH-related LC, alcohol alters the gut microbiota, causing overgrowth of gram-negative flora and elevated portal blood lipopolysaccharide level, which activates

Table 2 Patient characteristics after propensity score matching

	High VFI (n = 19)	Low VFI (n = 19)	*P* value
Age, median (range)	69 (41-89)	65 (40-83)	0.267
Sex, n (%)			0.485
Male	12 (63.2)	14 (73.7)	
Female	7 (36.8)	5 (26.3)	
BMI, kg/m^2, median (range)	23.7 (21-34.6)	22.5 (14.3-25.2)	0.015
Skeletal muscle mass index, cm^2/m^2, median (range)	49.3 (41.9-69.4)	51.8 (41.1-64.4)	0.599
VFI, cm^2/m^2, median (range)	53.6 (49.2-120.4)	38.5 (13.9-46.4)	<0.001
SFI, cm^2/m^2, median (range)	60.5 (15.8-125)	33.7 (13.2-104.8)	0.007
Concomitant diabetes mellitus, n (%)	9 (47.4)	7 (36.8)	0.511
Cause of liver cirrhosis, n (%)			0.461
Alcoholic	13 (68.4)	15 (78.9)	
NASH	6 (31.6)	4 (21.1)	
Ascites, n (%)	7 (36.8)	6 (31.6)	0.732
Classification of varices, n (%)			
Form (F1/F2/F3)	2 (10.5)/16 (84.2)/1 (5.3)	5 (26.3)/14 (73.7)/0 (0.0)	0.298
Color (Cw/Cb)	5 (26.3)/14 (73.7)	5 (26.3)/14 (73.7)	1.000
Red color sign (No/Yes)	3 (15.8)/16 (84.2)	4 (21.1)/15 (78.9)	0.676
Lg (No/Yes)	14 (73.7)/5 (26.3)	17 (89.5)/2 (10.5)	0.209
Variceal recurrence rate, n (%)	17 (89.5)	15 (79.0)	0.374
Operators (A/B/C/D/E/F/G)	3/3/2/2/3/4/2	2/2/1/4/5/5/0	0.675
Blood test results, median (range)			
PT-INR	1.15 (0.88-1.61)	1.14 (0.95-1.63)	0.715
Platelets ×10^4/uL	8.1 (3.8-19.8)	8.5 (2.9-15.7)	0.849
AST, IU/L	38 (21-313)	42 (14-64)	0.640
ALT, IU/L	28 (10-110)	36 (7-70)	0.715
Total bilirubin, mg/dL	1 (0.5-3.8)	1.2 (0.6-2.8)	0.198
Albumin, g/dL	3.4 (2.9-4.2)	3.3 (2.3-4.3)	0.747
Creatinine, mg/dL	0.8 (0.39-1.17)	0.78 (0.3-6.89)	0.977
Ammonia, ug/dL	46 (16-104)	41 (12-183)	0.838
FIB-4 index, median (range)	5.51 (2.24-11.36)	4.76 (2.54-10.06)	0.439
Child-Pugh score, median (range)	6 (5-8)	6 (5-8)	0.692
Child-Pugh classification (A/B), n (%)	11 (57.9)/8 (42.1)	12 (63.2)/7 (36.8)	0.740
Follow-up period, days, median (range)	1,200 (252-4,723)	907 (10-6,484)	0.335

BMI, Body mass index; VFI, Visceral fat index; SFI, Subcutaneous fat index; NASH, Non-alcoholic steatohepatitis; PT-INR, Prothrombin time-International Normalized Ratio; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; FIB-4, Fibrosis-4.

Kupffer cells through the CD14/Toll-like receptor-4 complex. This then produces reactive oxygen species (ROS) via nicotinamide adenine dinucleotide phosphate oxidase, which causes liver damage[16]. Additionally, acetaldehyde, the primary product of alcohol metabolism, and ROS activate hepatic stellate cells to stimulate inflammatory and fibrogenic signals, which then causes liver fibrosis[17]. In NASH-related LC, adipose tissue dysfunction, gut dysbiosis, and genetic factors influence the development of NAFLD. The inflammatory process in the liver is activated by proinflammatory cytokines and chemokines produced by adipocytes, liver macrophages, and lipid-laden hepatocytes that facilitate activation of stellate cells, thereby resulting in hepatic fibrogenesis[18]. Further, VFA was significantly higher in patients with non-cirrhotic NAFLD and PH than in those without PH, and waist circumference and insulin resistance were independent predictors of PH[19]. Taken together, excessive visceral fat may cause adipocyte dysfunction and potentially modulates the gut microbiota with stellate cell activation, resulting in liver fibrosis and PH in ASH/NASH-related LC.

EV recurrence rate was higher in patients with high VFI and ASH/NASH-related LC; thus, the recurrence rate in HCV/HBV-related LC patients was investigated for comparison. We previously reported that the EV recurrence rate of patients with ASH-related LC who continued to consume alcohol was comparable to that of patients with HCV/HBV-related LC without viral control[20]. Remarkably, high VFI did not affect the recurrence rate

Table 3 Univariate and multivariate analysis of recurrence rate

Variables	AUC	Cut-off value	n	Univariate		Multivariate	
				Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Age, years	0.571	< 60	36	9.98 (0.87-115.11)	0.065		
		≥ 60	58	1.00			
Sex	NA	Male	73	1.69 (0.21-13.42)	0.620		
		Female	21	1.00			
BMI, kg/m^2	0.753	< 23.8	49	1.00	0.436		
		≥ 23.8	45	3.52 (0.15-83.76)			
Skeletal muscle mass index, cm^2/m^2	0.644	< 42.3	11	1.00	0.145		
		≥ 42.3	83	5.01 (0.57-43.95)			
VFI, cm^2/m^2	0.732	< 46.4	41	1.00	0.048	1.00	0.003
		≥ 46.4	53	9.37 (0.99-88.35)		11.84 (2.27-61.71)	
SFI, cm^2/m^2	0.760	< 37.1	33	1.00	0.603		
		≥ 37.1	61	2.01 (0.14-27.96)			
Albumin, g/dL	0.670	< 3.4	43	1.00	0.787		
		≥ 3.4	51	1.27 (0.22-7.34)			
Cause of liver cirrhosis		Alcoholic	62	1.00	0.495		
		NASH	32	2.13 (0.24-18.53)			
Ascites		Yes	31	1.11 (0.19-6.48)	0.904		
		No	63	1.00			
Child-Pugh score	0.626	< 6	27	1.00	0.040	1.00	0.031
		≥ 6	67	14.92 (1.12-197.80)		10.95 (1.25-95.97)	

BMI, Body mass index; VFI, Visceral fat index; SFI, Subcutaneous fat index; NASH, Non-alcoholic steatohepatitis.

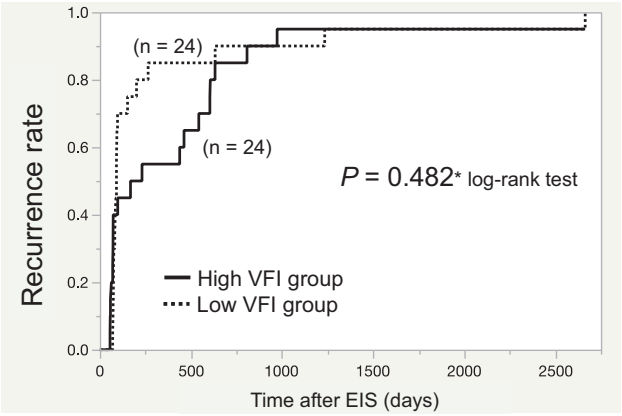

Fig. 3 Recurrence rate of esophageal varices in patients with HCV/HBV-related liver cirrhosis with high VFI or low VFI. Recurrence rate curve generated using the Kaplan-Meier method and analyzed with the log-rank test showed no difference (P = 0.482) in recurrence rate between the high VFI group (n = 24) and low VFI group (n = 24). HCV/HBV indicates hepatitis C virus/hepatitis B virus. VFI, visceral fat index.

in patients with HCV/HBV-related LC, as shown in **Fig. 3**. To understand this contradictory finding, we focused on pathophysiological differences between ASH/NASH and HCV/HBV-related LC. The pathophysiology of ASH/NASH-related LC is described above. In HCV-related LC, HCV directly modulates signaling and metabolic pathways by viral proteins. Moreover, it indirectly induces host antiviral immune responses, leading to chronic inflammation. Together, these events promote liver fibrosis[21]. Regarding HBV-related LC, HBV infection mostly causes acute hepatitis, which progresses to chronic hepatitis in 10% of cases[22]. In this context, Th2-type cytokines such as IL-4 and IL-10 are associated with persistent HBV infection resulting in chronic liver damage[23]. As mentioned above, high VFA is involved in gut dysbiosis, adipocyte dysfunction, and stellate cell activation, which results in liver fibrosis and PH in ASH/NASH-related LC. Nevertheless, the effect of excessive visceral fat in HCV/HBV-related LC patients is negligible because direct viral infection modulates liver damage leading to liver fibrosis and PH.

Several studies have reported an association between NAFLD/NASH and fructose consumption[24,25]. Dietary fructose, which is mainly consumed in the form of sucrose and high-fructose corn syrup, is catabolized by the small intestine and then the liver. However, excess fructose consumption overwhelms small intestinal clearance, causing fatty deposition in the liver, resulting in NAFLD and NASH[26]. We previously reported that modulating

nutritional components of dietary fructose affected experimental colitis and colitis-associated colonic tumor formation by altering the gut microbiota[27,28]. Moreover, Yin et al.[29] reported that aerobic exercise enhanced endothelial function in rats on a high-fat diet by altering the gut microbiota composition. These studies suggest that appropriate nutritional therapy, including exercise therapy and avoidance of a high-fructose/high-fat diet, may improve NAFLD/NASH and excessive visceral fat, which could be helpful in preventing EV recurrence in NASH-related LC patients with excessive visceral fat.

Despite these robust findings, there are limitations in this study to be considered. First, it was a single-center retrospective study with limited follow-up. Observation was limited to short-term outcomes that developed during the 1-year follow-up period, which may preclude potential observation of findings that develop over a longer term. Additionally, follow-up of ongoing drinking history was not recorded. Second, the number of patients was small, and so our findings may not be generalizable to a broader population. Third, definitive diagnosis of NASH was not obtained by liver biopsy, which is considered the gold standard. These limitations notwithstanding, to our knowledge no study has demonstrated the utility of VFI evaluation for recurrence of EVs in patients with LC. Thus, we think our study constitutes useful clinical research, as it quantifies VFI and other conventional predictive factors.

Conclusion

Our results suggest that high VFI exacerbates the recurrence rate of EVs, perhaps by exacerbating LC and PH, with consequent worsening of EVs in ASH/NASH-related LC but not in HCV/HBV-related LC. In addition, high VFI, along with Child-Pugh score, was an independent predictor associated with EV recurrence in ASH/NASH-related LC.

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References

1. Drafting Committee for Hepatitis Management Guidelines, the Japan Society of Hepatology. Japan Society of Hepatology guidelines for the management of hepatitis C virus infection: 2019 update. Hepatol Res [Internet]. 2020 Jul;50(7):791–816. Available from: https://www.ncbi.nlm.nih.gov/pubmed/32343477
2. Tokushige K, Ikejima K, Ono M, et al. Evidence-based clinical practice guidelines for nonalcoholic fatty liver disease/nonalcoholic steatohepatitis 2020. J Gastroenterol [Internet]. 2021 Nov;56(11):951–63. Available from: https://www.ncbi.nlm.nih.gov/pubmed/34533632
3. Yoshida H, Mamada Y, Taniai N, et al. Risk factors for bleeding esophagogastric varices. J Nippon Med Sch [Internet]. 2013;80(4):252–9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23995567
4. Yoshida H, Shimizu T, Yoshioka M, et al. The Role of the Spleen in Portal Hypertension. J Nippon Med Sch [Internet]. 2023;90(1):20–5. Available from: https://www.ncbi.nlm.nih.gov/pubmed/36908126
5. Kimura N, Tsuchiya A, Oda C, et al. Visceral adipose tissue index and hepatocellular carcinoma are independent predictors of outcome in patients with cirrhosis having endoscopic treatment for esophageal varices. Dig Dis [Internet]. 2021;39(1):58–65. Available from: https://www.ncbi.nlm.nih.gov/pubmed/32450556
6. Enomoto H, Aizawa N, Ikeda N, et al. Association of the body mass index with the presence of gastroesophageal varices in compensated cirrhotic patients with hepatitis C viral infection. Ann Clin Lab Sci [Internet]. 2018 Nov;48(6):801–4. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30610054
7. Nishiguchi R, Asaka S, Shimakawa T, et al. Preoperative subcutaneous fat is an useful indicator for learning totally extraperitoneal repair. J Nippon Med Sch [Internet]. 2023 Mar 11;90(1):33–40. Available from: https://www.ncbi.nlm.nih.gov/pubmed/36273904
8. Irving BA, Weltman JY, Brock DW, Davis CK, Gaesser GA, Weltman A. NIH ImageJ and Slice-O-Matic computed tomography imaging software to quantify soft tissue. Obesity (Silver Spring) [Internet]. 2007 Feb;15(2):370–6. Available from: https://www.ncbi.nlm.nih.gov/pubmed/17299110
9. Kvist H, Chowdhury B, Grangard U, Tylen U, Sjostrom L. Total and visceral adipose-tissue volumes derived from measurements with computed tomography in adult men and women: predictive equations. Am J Clin Nutr [Internet]. 1988 Dec;48(6):1351–61. Available from: https://www.ncbi.nlm.nih.gov/pubmed/3202084
10. Gomez-Perez SL, Haus JM, Sheean P, et al. Measuring abdominal circumference and skeletal muscle from a single cross-sectional computed tomography image: A step-by-step guide for clinicians using National Institutes of Health ImageJ. JPEN J Parenter Enteral Nutr [Internet]. 2016 Mar;40(3):308–18. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26392166
11. Tajiri T, Yoshida H, Obara K, et al. General rules for recording endoscopic findings of esophagogastric varices (2nd edition). Dig Endosc [Internet]. 2010 Jan;22(1):1–9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20078657
12. Zheng J, Zhang Y, Li P, et al. The endoscopic ultrasound probe findings in prediction of esophageal variceal recurrence after endoscopic variceal eradication therapies in

cirrhotic patients: a cohort prospective study. BMC Gastroenterol [Internet]. 2019 Feb 19;19(1):32. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30782139
13. Amitrano L, Guardascione MA, Manguso F, et al. The effectiveness of current acute variceal bleed treatments in unselected cirrhotic patients: refining short-term prognosis and risk factors. Am J Gastroenterol [Internet]. 2012 Dec;107(12):1872–8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23007003
14. European Association for the Study of the Liver. EASL clinical practice guidelines: Management of alcohol-related liver disease. J Hepatol [Internet]. 2018 Jul;69(1):154–81. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29628280
15. European Association for the Study of the Liver, European Association for the Study of Diabetes, European Association for the Study of Obesity. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. Diabetologia [Internet]. 2016 Jun;59(6):1121–40. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27053230
16. Wheeler MD, Kono H, Yin M, et al. The role of Kupffer cell oxidant production in early ethanol-induced liver disease. Free Radic Biol Med [Internet]. 2001 Dec 15;31(12):1544–9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/11744328
17. Maher JJ, Zia S, Tzagarakis C. Acetaldehyde-induced stimulation of collagen synthesis and gene expression is dependent on conditions of cell culture: studies with rat lipocytes and fibroblasts. Alcohol Clin Exp Res [Internet]. 1994 Apr;18(2):403–9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/8048746
18. Manne V, Handa P, Kowdley KV. Pathophysiology of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. Clin Liver Dis [Internet]. 2018 Feb;22(1):23–37. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29128059
19. Francque S, Verrijken A, Mertens I, et al. Visceral adiposity and insulin resistance are independent predictors of the presence of non-cirrhotic NAFLD-related portal hypertension. Int J Obes (Lond) [Internet]. 2011 Feb;35(2):270–8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20661251
20. Furuichi Y, Nishiguchi R, Shimakawa T, Fujiwara T, Sato K, Kato H. Outcomes and recurrence rate of esophageal varices after endoscopic treatment in patients with alcoholic cirrhosis and viral cirrhosis. J Nippon Med Sch. 2024;91(2):180–9.
21. Friedman SL. Evolving challenges in hepatic fibrosis. Nat Rev Gastroenterol Hepatol [Internet]. 2010 Aug;7(8):425–36. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20585339
22. McKeating C, Cadden I, McDougall N, et al. Progression from acute to chronic hepatitis B is more common in older adults. Ulster Med J [Internet]. 2018 Oct;87(3):177–80. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30559541
23. Lee M, Lee M, Lee SK, et al. Expression of Th1 and Th2 type cytokines responding to HBsAg and HBxAg in chronic hepatitis B patients. J Korean Med Sci [Internet]. 1999 Apr;14(2):175–81. Available from: https://www.ncbi.nlm.nih.gov/pubmed/10331564
24. Abdelmalek MF, Suzuki A, Guy C, et al. Increased fructose consumption is associated with fibrosis severity in patients with nonalcoholic fatty liver disease. Hepatology [Internet]. 2010 Jun;51(6):1961–71. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20301112
25. Ouyang X, Cirillo P, Sautin Y, et al. Fructose consumption as a risk factor for non-alcoholic fatty liver disease. J Hepatol [Internet]. 2008 Jun;48(6):993–9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/18395287
26. Jang C, Hui S, Lu W, et al. The small intestine converts dietary fructose into glucose and organic acids. Cell Metab [Internet]. 2018 Feb 6;27(2):351–61.e3. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29414685
27. Nishiguchi R, Basu S, Staab HA, et al. Dietary interventions to prevent high-fructose diet-associated worsening of colitis and colitis-associated tumorigenesis in mice. Carcinogenesis [Internet]. 2021 Jun 21;42(6):842–52. Available from: https://www.ncbi.nlm.nih.gov/pubmed/33513602
28. Montrose DC, Nishiguchi R, Basu S, et al. Dietary fructose alters the composition, localization, and metabolism of gut microbiota in association with worsening colitis. Cell Mol Gastroenterol Hepatol [Internet]. 2021;11(2):525–50. Available from: https://www.ncbi.nlm.nih.gov/pubmed/32961355
29. Yin H, Huang J, Hu M. Moderate-intensity exercise improves endothelial function by altering gut microbiome composition in rats fed a high-fat diet. J Nippon Med Sch [Internet]. 2022;89(3):316–27. Available from: https://www.ncbi.nlm.nih.gov/pubmed/35768269

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