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【 ORIGINAL ARTICLE 】

Pemafibrate Reduced Liver Stiffness in Patients with Metabolic Dysfunction-associated Steatotic Liver Disease Complicated with Hyperlipidemia and Liver Fibrosis with a Fibrosis-4 Index Above 1.3

Tatsuki Ichikawa[1-3], Mio Yamashima[1], Shinobu Yamamichi[1], Makiko Koike[3], Yusuke Nakano[3], Hiroyuki Yajima[1], Osamu Miyazaki[1], Tomonari Ikeda[1], Takuma Okamura[1,2], Naohiro Komatsu[1], Sayuri Sugio[1], Miruki Yoshino[1] and Hisamitsu Miyaaki[4]

Abstract:

Objective To evaluate the effect of pemafibrate (PEM) on metabolic dysfunction-associated steatotic liver disease (MASLD).

Methods We retrospectively evaluated 43 patients with hyperlipidemia and MASLD to determine changes in clinical factors between the start of PEM treatment and 0.5 years later. Using FibroScan, 39 of 43 patients were evaluated for liver stiffness (LS; kPa) and controlled attenuation parameter (CAP; dB/m). None of the patients had decompensated cirrhosis.

Results Thirty patients were women, the median age was 66 years old, the median fibrosis-4 (FIB-4) score was 2.52, the median LS was 8.05 kPa, and the median CAP was 280.5 dB/m at the start of PEM treatment. AST, ALT, ALP, γGTP, and triglyceride levels decreased 0.5 years after starting PEM treatment, but FIB-4, LS, and CAP values did not decrease. However, LS decreased in patients with a FIB-4 index ≥1.3 at the start of PEM treatment, whereas it did not change in patients with a FIB-4 index <1.3. Similarly, LS decreased in patients with a value ≥8 kPa at the start of treatment and did not change in those with <8 kPa. The decreased LS group had higher baseline ALT and LS levels and lower ALT levels during 0.5 years of follow-up than the increased LS group.

Conclusion At the initiation of PEM treatment, the LS decreased in patients with MASLD complicated by hyperlipidemia and moderate LS (FIB-4>1.3 or LS >8 kPa). Although there is currently no approved treatment for MASLD, PEM may be a viable treatment option for MASLD with mild LS.

Key words: liver stiffness, MASLD, pemafibrate

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Introduction

The frequency of non-alcoholic fatty liver disease (NAFLD) is increasing globally in all age groups, with over 80% of countries experiencing an increase in NAFLD and NAFLD-related mortality (1). Although viral hepatitis remains the leading cause of cirrhosis worldwide, the prevalence of NAFLD and alcohol-associated cirrhosis is increasing in several regions (2). With the obesity pandemic in full swing, NAFLD-related hepatocellular carcinoma has contributed exponentially to the burden of disease (3). To combat this, many pharmacological agents are being developed as monotherapies (4).

[1]Department of Gastroenterology, Nagasaki Harbor Medical Center, Japan, [2]Department of Comprehensive Community Care Systems, Graduate School of Biomedical Sciences, Nagasaki University, Japan, [3]Innovation and Translational Research Center, Nagasaki Harbor Medical Center, Japan and [4]Department of Gastroenterology and Hepatology, Graduate School of Biomedical Sciences, Nagasaki University, Japan
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Correspondence to Dr. Tatsuki Ichikawa, ichikawa@nagasaki-u.ac.jp

NAFLD previously referred to fatty liver disease not associated with excess alcohol intake. However, with the deepening of our understanding of NAFLD's pathogenesis and its increasing prevalence, the need for specific diagnostic criteria has emerged. Consequently, NAFLD has been renamed "metabolic dysfunction-associated fatty liver disease" (MAFLD) (5). This term is considered more appropriate for fatty liver conditions in the Asia-Pacific region (6) and Japan (7). The main limitations of the terms NAFLD and nonalcoholic steatohepatitis (NASH) are their reliance on exclusionary criteria and potentially stigmatizing language (8). Furthermore, steatohepatitis is a significant pathophysiological entity (8). To address these issues, "metabolic dysfunction-associated steatotic liver disease"(MASLD) was introduced as a replacement term for NAFLD (8). It is noted that 99% of patients with NAFLD in Asia meet the criteria for MASLD (9), and the prevalence and progression of atherosclerotic cardiovascular disease risks are comparable in these patients (10). Recent findings suggest that alanine aminotransferase (ALT) levels >30 U/L in conjunction with MASLD may play a role in the development of significant hepatic fibrosis in patients ≥65 years old (11).

The selective thyroid hormone receptor β agonist (resmetirom) was shown to be superior to placebo in resolving the primary endpoints of NASH without worsening fibrosis and improving fibrosis by at least one stage with no worsening of NASH (12). The 52-week histological data met the early approval requirements of the Food and Drug Administration and European Medicines Agency, based on the reasonable likelihood that these surrogate outcomes predict clinical benefit. Although encouraging, the phase III research results raise pertinent questions, the foremost perhaps being uncertainties around the overall risk and benefit of resmetirom (or any putative NASH drug). Such an appraisal must balance effectiveness, safety, tolerability, and drug costs, given the need for long-term treatment (13). In addition, this research has not yet been approved in Japan. Under these circumstances, hepatologists must choose among drugs with even slight efficacy that are not approved for NASH.

Pemafibrate (PEM), a novel selective peroxisome proliferator (PPAR)-α-activated receptor modulator, is superior to fenofibrate in terms of lowering serum triglyceride (TG) levels and hepatic and renal safety (14). ALT and γ-glutamyltranspeptidase (γGTP) levels were significantly decreased in PEM-treated patients (14). To evaluate the efficacy and safety of PEM in patients with a high risk of NAFLD, a phase 2 trial was conducted with 118 patients randomized (1:1) to either 0.2 mg PEM or placebo, orally, twice daily for 72 weeks. Consequently, PEM did not decrease liver fat content but significantly reduced magnetic resonance elastography (MRE)-based liver stiffness (LS) (15). In another double-blind controlled study, PEM was associated with a reduced incidence of NAFLD (16). In another small study, PEM improved LS [shear wave velocity (SWV) (17), vibration-controlled transient elastography (18), MRE (19)], autotoxin (20), and Mac-2-binding protein (M2BPGi) (21), but fatty liver did not change (18-22). These studies revealed that PEM is effective for fibrosis in NASH-complicated hyperlipidemia.

Currently, as no drugs have been approved for NASH, those used for patients complicated with steatotic liver disease (SLD) must be as effective as possible for liver disease. Therefore, we considered PEM a promising candidate for SLD treatment and retrospectively analyzed the use of PEM in hyperlipidemia-related MASLD (8).

Materials and Methods

Patients

In total, 43 patients with MASLD and hyperlipidemia who visited Nagasaki Harbor Medical Center between February 2019 and September 2023 were enrolled and evaluated at the beginning of PEM treatment and 0.5 years after treatment initiation (Table 1 and Supplementary material 1). Cases of liver cirrhosis with Child-Pugh grades B and C were excluded from PEM treatment because of contraindications. The median patient age was 66 years old, and the median body mass index was 25.19 at the start of PEM. Thirty patients were women, 16 patients had diabetes (sodium glucose cotransporter 2 inhibitors, 13 patients; glucagon-like peptide-1 receptor agonist, 3 patients; and pioglitazone, 0), 4 were prior vitamin E users, 3 were prior bezafibrate users, and 8 were prior ursodeoxycholic acid (UDCA) users (Supplementary material 2). Patients were prescribed PEM (oral, 0.1 mg, twice a day) and instructed to visit the outpatient clinic every 4-12 weeks. Hyperlipidemia was defined as either a fasting low-density lipoprotein (LDL) cholesterol level ≥140 mg/dL or a TG level ≥150 mg/dL. Patients were excluded if their LDL levels were elevated or if they had not undergone any prior treatment for hyperlipidemia. TG values immediately before the start of PAL were <150 mg/dL in some cases, but the values ≥1 month before the start of PAL, when the decision was made to start PAL, were ≥ 150 mg/dL in all cases.

The medical records of the 43 patients were retrospectively reviewed. All laboratory measurements were obtained from medical records. Informed consent was obtained from each patient included in the study, and they were guaranteed the right to leave the study, if desired. The study protocol conformed to the 1975 Declaration of Helsinki guidelines (23) and was approved by the Human Research Ethics Committee of Nagasaki Harbor Medical Center (approval no. H30-031).

Laboratory measurements

At the start of PEM treatment (time 0) and 0.5 years later (time 0.5), the values for total bilirubin (normal range; 0.3-1.2 mg/dL), albumin (3.8-5.2 g/dL), creatinine [men (M): 0.61-1.04, women (F): 0.47-0.79 mg/dL], cystatin C (M: 0.63-0.95, F: 0.56-0.87 mg/L), platelet count (PLT; M: 13.1-26.2, F: 13-36.9×10^4/μL), aspartate aminotransferase (AST;

Table 1. Differences in Clinical Factors.

Factors	Number at start	Number at 0.5Y	Median at start	Median at 0.5Y	p value
TB	43	43	0.8	0.7	0.06922
ALB	43	43	4.3	4.4	0.24714
Cr	43	43	0.72	0.66	0.48402
CysC	43	42	1.03	1.075	0.52657
BW	43	43	60.5	61.0	0.86283
PLT	43	43	19.0	20.9	0.39729
AST	43	43	53.0	32.0	0.00036
ALT	43	43	55.0	30.0	0.00006
ALP	43	42	138.0	99.0	0.00399
γGTP	43	43	60.0	34.0	0.00017
HbA1c	37	37	6.3	6.2	0.57320
TG	43	43	155.0	105.0	0.00014
LDL	42	41	113.0	89.0	0.12818
HDL	43	42	58.0	60.0	0.52950
FIB-4	43	43	2.5195	2.1013	0.19963
M2BPGI	43	41	1.26	0.97	0.28688
LS	40	39	8.05	7.50	0.30081
CAP	40	39	280.5	288.0	0.78362

Number is the number of patients at start and 0.5Y. Median is at start and 0.5Y. The p value is compared between the median at 0 and 0.5, using the Mann-Whitney U test.

TB: total bilirubin, ALB: albumin, Cr: creatinine, CysC: cystatin C, BW: body weight, PLT: platelet count, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γGTP: γ-glutamyltranspeptidase, HbA1c: hemoglobin A1c, TG: triglyceride, LDL: low-density lipoprotein choresterol, HDL: high-density lipoprotein choresterol, FIB-4: fibrosis-4 index, M2BPGI: macrophage galactose-specific lectin-2 binding protein glycosylation isomer, LS: liver stiffness, CAP: controlled attenuation parameter

10-40 U/L), ALT (5-40 U/L), alkaline phosphatase (ALP; 38-113 U/L), γGTP (M: <70 U/L, F; <30 U/L), hemoglobin A1c (4.8%-6%), triglyceride (TG; 50-149 mg/dL), and M2BPGi (<1 cutoff index) were evaluated. Fibrosis-4 (FIB-4) was calculated based on the age, AST, ALT, and PLT values (24). Overall, 39 patients were evaluated using FibroScan. LS (kPa) was evaluated using vibration-controlled transient elastography, and liver fat content (dB/m) was evaluated using the controlled attenuation parameter (CAP).

Statistical analyses

Data were analyzed using the StatFlex software program (version 6.0; Artech, Osaka, Japan) and are presented as the median and 95% confidence interval. Laboratory variables were compared using Mann-Whitney U tests (for differences between two groups) and χ^2 tests. The detection level was analyzed using a receiver operating characteristic curve. Statistical significance was set at $p<0.05$.

Results

PEM treatment reduced LS after 0.5 years in patients with MASLD complicated with hyperlipidemia and moderate LS (FIB-4 ≥1.3, LS ≥8 kPa or LS ≥12).

AST, ALT, ALP, γ-GTP, and TG levels decreased 0.5 years after starting PEM treatment, but FIB-4, LS, M2BPGi, and CAP values did not decrease (Table 1). We selected patients with an FIB-4 index ≥1.3 at the start, since the FIB-4 status category shifting from low risk (<1.3) to intermediate risk (1.3-2.67) to high risk (≥2.67) may be used to assess clinical progression (25, 26). The LS decreased from the start of treatment (start) in the FIB-4 ≥1.3 group after 0.5 years (0.5Y) (Fig. 1B) but did not change markedly in the FIB-4<1.3 group (Fig. 1B). CAP levels did not change in either group (data not shown).

Next, we divided the patients into those with LS ≥8 kPa (Fig. 1D) at the start and those with LS <8 kPa (Fig. 1C). LS ≥8 kPa indicates an intermediate risk (26). LS decreased after 0.5 years from baseline in the LS ≥8 kPa group but not in the <8 kPa group.

We then divided the patients into those with LS ≥12 kPa at the start (Fig. 1F) and those with LS <12 kPa (Fig. 1E). LS ≥12 kPa indicates a high risk (26). LS decreased from baseline after 0.5 years in the LS ≥12 kPa group but not in the <12 kPa group.

We evaluated changes in LS from treatment initiation to 0.5 years later. The LS decrease group (difference LS group: decrease) included 26 patients (Table 2). The difference factor (dfactor) was calculated as the value of a factor at 0.5, minus the value at 0. ALT and LS levels at 0 were higher in the LSG decrease group than in the LSG increase group. M2BPGi and FIB-4 levels at 0 did not change markedly in the LSG decrease group. However, dALT levels were higher in the LSG decrease group than in the LSG increase group. difference FIB-4 and difference M2BPGi levels did not

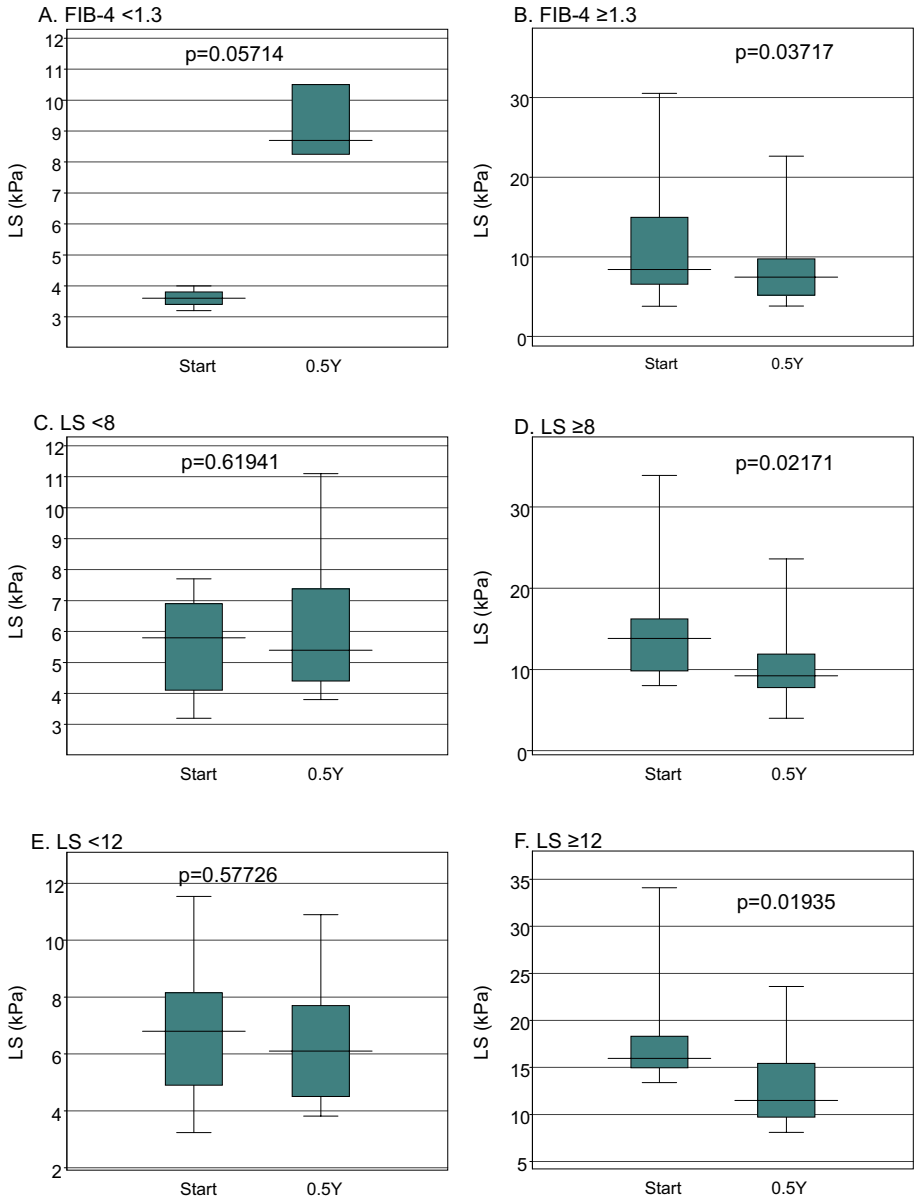

Figure 1. **Changes in LS. A: FIB-4 normal (<1.3) at start. Value of LS (kPa) at start (4 cases) and 0.5 years (3 cases). B: FIB-4 high (≥1.3) group at start. Value of LS (kPa) at start (36 cases) and 0.5 years (36 cases). C: LS normal (<8) at start. Value of LS (kPa) at start (19 cases) and 0.5 years (19 cases). D: LS high (≥8) group at start. Value of LS (kPa) at start (21 cases) and 0.5 years (21 cases). E: LS low (<12) at start. Value of LS (kPa) at start (28 cases) and 0.5 years (28 cases). F: LS High (≥12) at start. Value of LS (kPa) at start (12 cases) and 0.5 years (12 cases). LS: liver stiffness, FIB-4: fibrosis-4 index**

change. The detection levels for LS decrease were evaluated using an ROC analysis (Fig. 2). FIB-4, M2BPGi, and LS at 0 were analyzed using noninvasive tests. The cutoff value was a sensitivity equal to the 1-specificity point. The cutoff point of FIB-4 was 2.5195 [sensitivity: 0.46154 and area under the curve (AUC): 0.55621], that for M2BPGi was 1.2 (0.53846 and 0.60947), and that for LS was 7.3 (0.73077 and 0.83432). The AUC of LS was more significant than those of FIB-4 (p=0.00116) and M2BPGi (p=0.00513). ALT at 0 h and dALT levels were also analyzed using an ROC curve (Supplementary material 3). The cutoff value of ALT was 50.7 (sensitivity, 0.74359; AUC, 0.75888), and that of dALT was -18 (0.61538 and 0.74112). The differences in AUC between LS at 0, ALT at 0, and dALT were not significant.

Discussion

PEM treatment reduced LS after 0.5 years in patients with MASLD complicated with hyperlipidemia and moderate LS (FIB-4>1.3 or LS >8 kPa). As this study did not include decompensated cirrhosis, PEM may be a feasible treatment choice for MASLD with mild LS, given the current lack of approved treatments for MASLD.

Table 2. DLSG and Clinical Factors.

dLSG		Decrease	Increase	p value	dLSG		Decrease	Increase	p
Age	n	26	13	0.64389	dTB	n	26	13	0.77452
	Median	67	65			Median	-0.10	-0.10	
TB	n	26	13	0.17184	dALB	n	26	13	0.15718
	Median	0.8	0.7			Median	0.15	0.00	
ALB	n	26	13	0.44524	dPTINR	n	26	13	0.56916
	Median	4.3	4.3			Median	0.000	0.000	
PTINR	n	26	13	0.34740	dCr	n	26	13	0.95243
	Median	1.00	0.99			Median	-0.005	0.010	
Cr	n	26	13	0.41236	dCysC	n	25	13	0.45952
	Median	0.705	0.740			Median	0.060	0.010	
CysC	n	26	13	0.31060	dBW	n	26	13	0.49272
	Median	0.990	1.070			Median	-1.050	0.000	
BMI	n	26	13	0.69854	dPLT	n	26	13	0.09815
	Median	25.20	23.49			Median	1.55	0.40	
PLT	n	26	13	0.23334	dAST	n	26	13	0.09504
	Median	17.95	20.70			Median	-17.5	-9.0	
AST	n	26	13	0.06907	**dALT**	n	26	13	0.01513
	Median	61.5	44.0			Median	-33.5	-10.0	
ALT	n	26	13	0.00912	dALP	n	25	13	0.51795
	Median	70.0	43.0			Median	-30.0	-22.0	
					dGTP	n	26	13	0.65478
ALP	n	26	13	0.85812		Median	-22.5	-19.0	
	Median	137.5	138.0		dHbA1c	n	23	12	0.51813
γGTP	n	26	13	0.84644		Median	-0.20	0.05	
	Median	58.5	62.0		dTG	n	26	13	0.50256
HbA1c	n	23	12	0.65090		Median	-53.0	-35.0	
	Median	6.30	6.35		dFIB-4	n	26	13	0.18003
TG	n	26	13	0.73187		Median	-0.37785	-0.23915	
	Median	140.5	177.0		dAFP	n	26	13	0.33199
FIB-4	n	26	13	0.57136		Median	-0.25	0.20	
	Median	2.45595	2.5991		dPIVKA	n	26	13	0.81059
AFP	n	26	13	0.59157		Median	3.00	2.00	
	Median	5.45	4.30		dM2BPGI	n	26	12	0.90002
PIVKA	n	26	13	0.76514		Median	-0.175	-0.160	
	Median	25.0	25.0		dCAP	n	24	13	0.22658
M2BPGi	n	26	13	0.27018		Median	-1.0	20.0	
	Median	1.27	1.19						
CAP	n	25	13	0.57962					
	Median	281.0	280						
LS	n	26	13	0.00535					
	Median	10.25	5.8						

'n' is the number in each group. The p value was tested using the Mann-Whitney U test.

DLSG: decrease liver stiffness group, TB: total bilirubin, ALB: albumin, PTINR: prothronmin time international rate, Cr: creatinine, CysC: cystatin C, BMI: body mass index, PLT: platelet count, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkali phosphatase, γGTP: γ-glutamyltranspeptidase, HbA1c: hemoglobin A1c, TG: triglyceride, FIB-4: fibrosis-4 index, AFP: arufa fetoprotein, PIVKA: protein inudeuced vitamin K absence, M2BPGI: macrophage galactose-specific lectin-2 binding protein glycosylation isomer, LS: liver stiffness, CAP: controlled attenuation parameter d difference

Consistent with previous reports (15, 18-22), liver fibrosis, evaluated as LS and not FIB-4 or M2BPGi, was improved by PEM, while steatosis did not improve. Furthermore, combined treatment with PEM and a low-carbohydrate diet led to weight loss and improvements in ALT, MRE, and magnetic resonance imaging-proton density fat fraction in MAFLD patients (27). The administration of PEM has proven effective in primary biliary cholangitis patients with dyslipidemia who do not respond to UDCA monotherapy (28). Switching from bezafibrate to PEM was beneficial for patients on UDCA and bezafibrate (28, 29). PPAR-α agonists inhibit steatosis in fat-laden hepatocytes, while PPAR-δ and PPAR-γ agonists inhibit inflammation in infiltrating macrophages and fibrosis in activated stellate cells, respectively (30). In contrast, PPAR-α agonist improved the stress response and downregulated AST and ALT

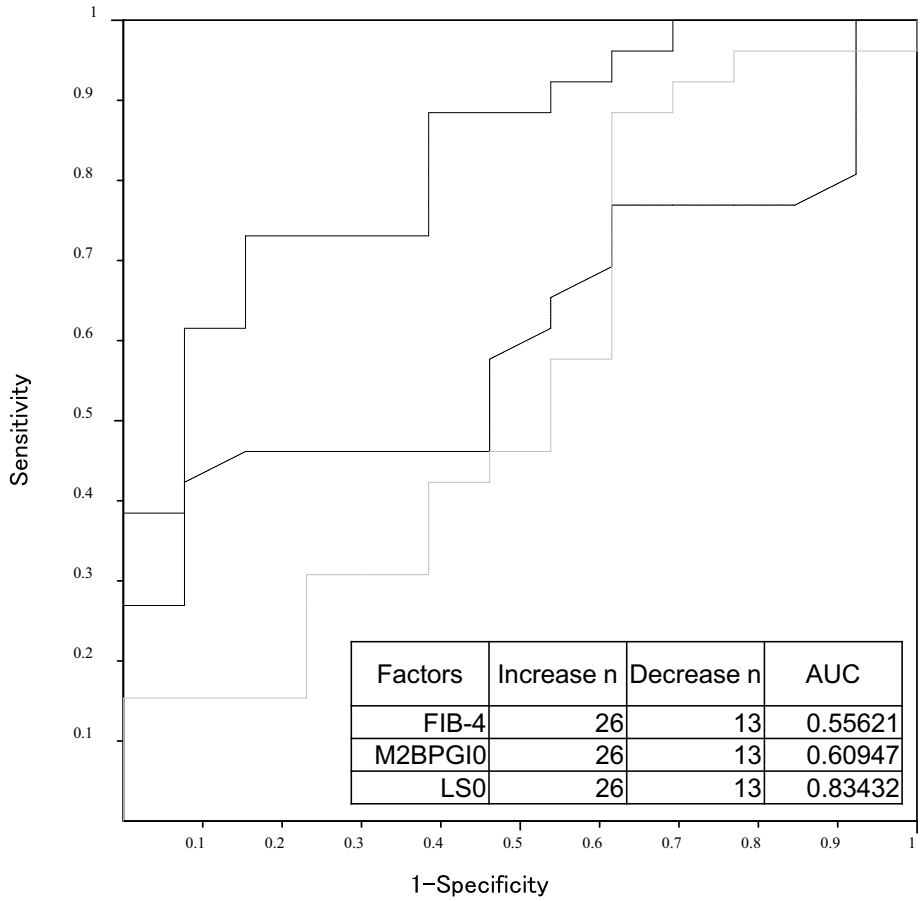

Figure 2. ROC curve for LS decrease. The X axis is sensitivity, and the Y axis is 1-specificity. The black line is LS, the dotted line is M2BPGi, and the gray line is FIB-4. FIB-4: fibrosis-4 index, M2BPGi0: macrophage galactose-specific lectin-2 binding protein glycosylation isomer, LS: liver stiffness

levels in a mouse model (31) while improving steatosis, fibrosis, and inflammation in another mouse model (32). Moreover, a PPAR-α agonist was effective for ameliorating liver damage in a mouse model of low- and late-occurring fat accumulation (31). Low levels of PPAR-α agonist did not decrease the liver TG content but inhibited inflammation and fibrosis in other mice (32). CAP and LS were independent risk factors for all-cause mortality (hazard ratios 1.01 and 1.06, respectively) (33). Changes in LS can predict clinical outcomes in patients with MASLD (34). A decrease in LS by PEM treatment might improve the long-term prognosis and requires follow-up.

The use of oral fibrates was recently reported to be associated with a reduced risk of advanced fibrosis (odds ratio 0.90, $p<0.05$) in 50,695 diabetic patients with NAFLD (35). No good prognostic factors for liver disease that can predict the effectiveness of PEM have been reported yet. In our study, the ALT, LS, and dALT levels were associated with decreased LS. In previous reports, a decrease in ALT levels at baseline was linked to SWV (17) and MRE-AST score (19). ALT levels at baseline and reduction during treatment may predict a good response. In addition, the LS at baseline may be evaluated as a predictive factor. However, TG levels were not related to changes in SWV (17) or MAST (19). Since steatosis did not vary with PEM (18-22), the association between the anti-hepatic fibrosis and TG-lowering effects of PEM may require reexamination.

This was a small retrospective single-center study. However, LS in patients with MASLD and moderate fibrosis without decompensated cirrhosis was decreased by PEM treatment for 0.5 years, and the decreased LS group had high ALT levels, high LS at baseline, and high dALT. PEM treatment may be considered for hyperlipidemic MASLD patients with elevated ALT levels and LS, although long-term follow-up is needed to evaluate the prognosis.

The authors state that they have no Conflict of Interest (COI).

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