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Figure Legends

Figure 1. Association between pretreatment liver fibrosis as assessed by pathological evaluation of liver biopsy specimens and FIB-4 index at SVR 24. The liver fibrosis grade was based on the METAVIR score (25). FIB-4 index at SVR 24 was 1.52 ± 1.10 in patients with F0, 1.81 ± 1.17 in F1, 2.36 ± 1.89 in F2, and 3.59 ± 2.66 in F3.

Figure 2. The incidence of hepatocellular carcinoma after SVR according to the FIB-4 index at SVR24. The incidences of HCC at five and ten years were 0 % and 2.0 %, respectively, in patients with FIB-4 index at SVR 24 <2.0, and were 3.4 % and 9.2 %, respectively, in patients with FIB-4 index at SVR 24 ≥ 2.0.

Table 1. Baseline characteristics of the study patients before antiviral therapy (n = 522).

Age (years)*	50.6 ± 11.8
Sex (female/ male)	230 (44.1) / 292 (55.9)
Habitual alcohol intake (no/ yes)	322 (79.9) / 81 (20.1)
Diabetes mellitus (no/ yes)	448 (91.8) / 40 (8.2)
Treatment when SVR was achieved (naïve/ retreatment)	410 (78.5) / 112 (21.5)
Ribavirin use (no/ yes)	267 (51.1) / 255 (48.9)
Peginterferon use (no/ yes)	282 (54.0) / 240 (46.0)
Body mass index	23.2 ± 9.2
Baseline ALT (IU/L)	96.5 ± 93.8
Baseline AST (IU/L)	65.2 ± 57.3
Baseline GGTP (IU)	54.8 ± 73.5
Baseline albumin (g/dL)	4.16 ± 0.33
Baseline total bilirubin (mg/dL)	0.72 ± 0.65
Baseline AFP (ng/dL)	4.16 ± 6.68
Baseline platelet counts (x $10^3/\mu L$)	187 ± 58
HCV genotype (1b/ 2a or 2b)	227 (44.6)/ 282 (55.4)
Pretreatment HCV RNA levels ($log_{10}IU/mL$)	5.25 ± 1.47
Pretreatment liver activity (A0/ A1/ A2/ A3)	31 (6.3)/ 296 (59.9)/ 150 (30.4) 17 (3.4)
Pretreatment liver fibrosis (F0/ F1/ F2/ F3)	83 (16.8)/ 263 (53.2)/ 121 (24.5)/ 27 (5.5)

SVR, sustained virologic response; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGTP, gamma-glutamyl

transpeptidase; AFP, alpha-fetoprotein; HCV, hepatitis C virus.

*At 24weeks after the end of antiviral therapy when SVR was documented (i.e., SVR24).

Table 2. Univariate and multivariate analysis of factors associated with the development of HCC after SVR (n = 522).

A) Univariate analysis

		Parameter estimate	Standard error	X	Risk ratio (95% confidence interval)	*P* value
Age (years) at SVR24		0.0591	0.0280	5.19	1.0609 (1.0077-1.1247)	0.0228
Sex	Female				1	
	Male	0.6271	0.3165	5.02	1.8721 (1.0747-3.8910)	0.0250
Habitual alcohol intake	No				1	
	Yes	0.5450	0.2593	3.90	1.7246 (1.0042-2.8366)	0.0484
Diabetes mellitus	No				1	
	Yes	0.6488	0.2635	4.85	1.9132 (1.0830-3.1181)	0.0277
Treatment that achieved SVR	Naïve				1	
	Retreatment	0.1985	0.2642	0.53	1.2195 (0.6897-1.9906)	0.4664
Ribavirin use	No				1	
	Yes	-0.0444	0.2800	0.03	0.9565 (0.5284-1.6235)	0.8734
Peginterferon use	No				1	
	Yes	-0.0837	0.3024	0.08	0.9197 (0.4766-1.6090)	0.7797
Body mass index		-0.0547	0.0736	0.60	0.9468 (0.8384-1.0184)	0.4377
Baseline ALT (IU/L)		-0.0009	0.0029	0.12	0.9991 (0.9902-1.0022)	0.7312
Baseline AST (IU/L)		-0.0033	0.0035	1.45	0.9967 (0.9882-1.0010)	0.2287

Baseline GGTP (IU)		0.0032	0.0021	1.62	1.0033 (0.9977-1.0066)	0.2033
Baseline albumin (g/dL)		-2.0868	0.7299	8.05	0.1241 (0.0295-0.5220)	0.0045
Baseline total bilirubin (md/dL)		-0.1743	0.5316	0.14	0.8400 (0.1760-1.5222)	0.7116
Baseline AFP (ng/dL)		-0.0031	0.0215	0.03	0.9969 (0.8847-1.0113)	0.8641
Baseline platelet count (x $10^3/\mu L$)		-0.1953	0.0589	13.53	0.8226 (0.7281-0.9176)	0.0002
HCV genotype	2a/2b				1	
	1b	-0.2449	0.2539	0.97	0.7828 (0.4594-1.2694)	0.3254
Pretreatment HCV level		-0.1841	0.1436	1.56	0.8319 (0.6328-1.1153)	0.2114
Pretreatment Liver activity	A0/A1				1	
	A2/A3	0.1766	0.2521	0.48	1.1931 (0.7132-1.9549)	0.4879
Pretreatment Liver fibrosis	F0/F1				1	
	F2/F3	0.8549	0.2634	12.18	2.3511 (1.4429-4.1526)	0.0005
FIB-4 index at SVR24		0.4095	0.0728	18.21	1.5060 (1.2841-1.7207)	<0.0001
APRI at SVR24		0.7139	0.1832	8.76	2.0419 (1.3326-2.8052)	0.0031

B) Multivariate analysis

		Parameter estimate	Standard error	X	Risk ratio (95% confidence interval)	*p*-value
Age (years) at SVR24		0.0031	0.0448	0.005	1.0031 (0.9209-1.0992)	0.9442
Sex	Female				1	
	Male	0.6372	0.4373	2.48	1.8911 (0.8657-5.0473)	0.1151
Habitual alcohol intake	No				1	
	Yes	0.4572	0.3038	2.18	1.5797 (0.8543-2.8814)	0.1402
Diabetes mellitus	No				1	
	Yes	0.7318	0.3418	4.01	2.0788 (1.0170-4.0133)	0.0453
Baseline albumin (g/dL)		-1.7984	0.9374	3.70	0.1656 (0.0252-1.0343)	0.0544
Baseline platelet counts (X 10^3/μL)		-0.0108	0.0084	1.90	0.9893 (0.9712-1.0041)	0.1679
Liver fibrosis	F0/F1				1	
	F2/F3	-0.1384	0.3373	0.17	0.8708 (0.4494-1.7262)	0.6829
FIB-4 index at SVR24		0.5474	0.2387	5.43	1.7288 (1.0927-2.8570)	0.0198
APRI at SVR24		0.0318	0.6396	0.002	1.0323 (0.2436-3.2694)	0.9604

HCC, hepatocellular carcinoma; SVR, sustained virologic response; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGTP, gamma-glutamyl transpeptidase; AFP, alpha-fetoprotein; HCV, hepatitis C virus.

Table 3. Characteristics of patients who developed HCC after SVR (n = 18).

Age at SVR24 (years)	58.7 ± 5.6
Age at HCC development (years)	65.5 ± 5.2
Sex (female/ male)	3 (44.1) / 15 (55.9)
Habitual alcohol intake (no/ yes)	11 (79.9) / 7 (20.1)
Diabetes mellitus (no/ yes)	10 (91.8) / 8 (8.2)
Treatment when SVR was achieved (naïve/ retreatment)	13 (78.5) / 5 (21.5)
Ribavirin use (no/ yes)	12 (51.1) / 6 (48.9)
Peginterferon use (no/ yes)	11 (54.0) / 7 (46.0)
HCV genotype (1b/ 2a or 2b)	7 (44.6)/ 11 (55.4)
Pretreatment HCV RNA levels (log_{10}IU/mL)	4.61 ± 1.52
Pretreatment AFP (ng/dL)	4.17 ± 2.02
AFP at HCC development (ng/dL)	44.3 ± 79.0
Pretreatment liver fibrosis (F0/ F1/ F2/ F3/ F4)	1 (5.5)/ 5 (27.8)/ 7 (38.9)/ 5 (27.8)/ 0
Liver fibrosis at HCC development (F0/ F1/ F2/ F3/ F4)*	0/ 1 (6.7)/ 3 (20.0)/ 5 (33.3)/ 6 (40.0)
FIB-4 index at SVR24	4.01 ± 2.98
FIB-4 index at HCC development	3.57 ± 2.73
APRI at SVR24	1.02 ± 1.04
APRI at HCC development	0.76 ± 0.69
Interval between SVR24 and HCC development (years)	6.76 ± 4.19

HCC, hepatocellular carcinoma; SVR, sustained virologic response; HCV, hepatitis C virus; AFP, alpha-fetoprotein.

*Among 15 patients who underwent surgical resection and liver specimen was available.

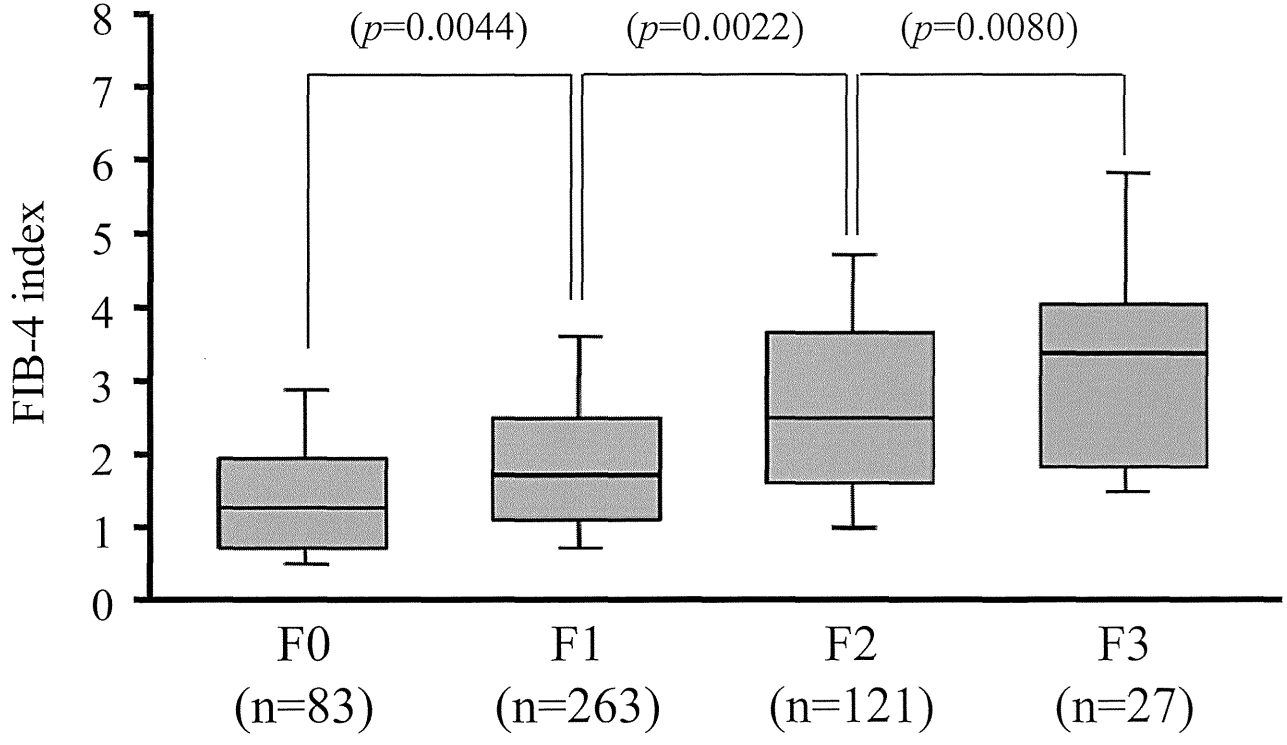
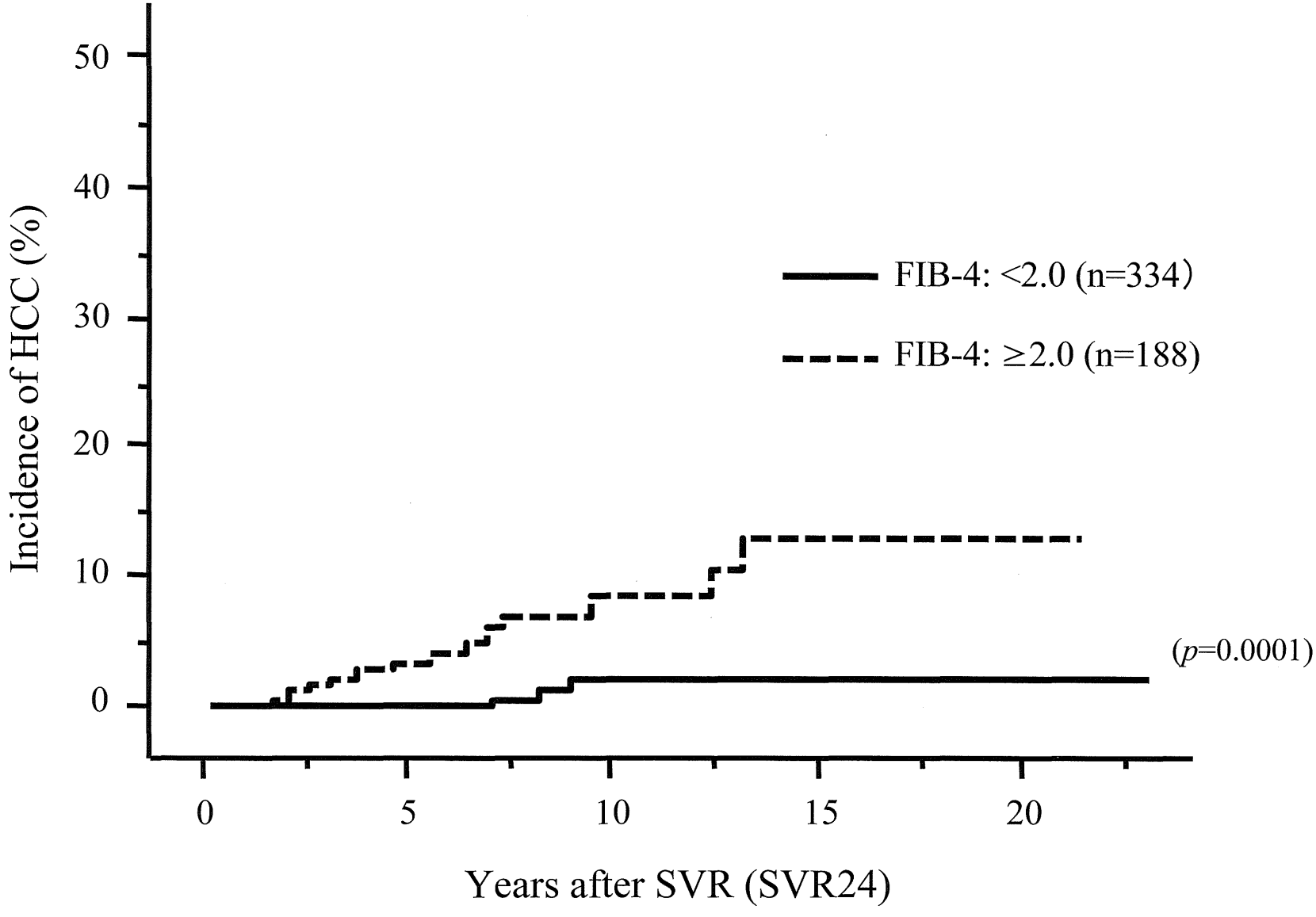

FIB-4 index
8
7
6
5
4
3
2
1
0
(p=0.0044)
(p=0.0022)
(p=0.0080)
F0
(n=83)
F1
(n=263)
F2
(n=121)
F3
(n=27)

Figure 1



Patients at risk

FIB-4: <2.0	334	241	111	79	20
FIB-4: ≥2.0	188	148	54	31	5

Figure 2

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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

FIB-4 index for assessing the prognosis of hepatocellular carcinoma in patients with Child-Pugh class A liver function

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Abstract
Purpose We evaluated the prognosis of hepatocellular carcinoma (HCC) patients with Child-Pugh (C-P) class A based on FIB-4 index, which is a liver fibrosis marker.
Patients and methods A total of 915 HCC patients with C-P class A were investigated. We assessed the prognosis using FIB-4 index, and factors associated with survival rates were analyzed in these patients.
Results When patients were categorized according to FIB-4 index as <2.0 ($n = 93$), ≥2.0 and <4.0 ($n = 311$), and ≥4.0 ($n = 511$), survival rates at 5 years were 70.5 % [95 % confidence interval (CI) 59.0–79.9], 56.4 % (95 % CI 50.1–62.5), and 47.1 % (95 % CI 42.2–52.1), respectively. Patients with FIB-4 index <2.0 had a higher survival rate than the other groups (≥4.0 vs ≥2.0 and <4.0, $p = 0.010$; ≥2.0 and <4.0 vs <2.0, $p = 0.028$). We were able to predict prognosis in patients with C-P score 5 by FIB-4 index, but survival rate did not significantly differ in patients with C-P score 6. Multivariate analysis identified C-P score, FIB-4 index [≥2.0 and <4.0; hazard ratios (HRs) 1.638 (95 % CI 1.084–2.474); $p = 0.019$/≥4.0; HR 1.828 (95 % CI 1.217–2.744); $p = 0.004$], *Lens culinaris* agglutinin-reactive α-fetoprotein, tumor size, number, vascular invasion, antiviral therapy, and hepatectomy as independent predictive factors for survival.
Conclusions The FIB-4 index is useful for assessing prognosis in HCC patients with C-P class A, especially those with C-P score 5.

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Keywords FIB-4 index · Noninvasive fibrosis marker · Prognosis · Hepatocellular carcinoma · Child-Pugh classification

Abbreviations

HCC	Hepatocellular carcinoma
C-P	Child-Pugh
SVR	Sustained virological response
HCV	Hepatitis C virus
HBV	Hepatitis B virus
EASL	European Association for the Study of the Liver
AFP	α-Fetoprotein
AFP-L3	*Lens culinaris* agglutinin-reactive α-fetoprotein
DCP	Des-γ-carboxy prothrombin
US	Ultrasonography
CT	Computed tomography
MRI	Magnetic resonance imaging
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
HR	Hazard ratio
LAT	Locoregional ablative therapy
RFA	Radiofrequency ablation
TACE	Transcatheter arterial chemoembolization
CI	Confidence interval

Introduction

The incidence of hepatocellular carcinoma (HCC) has rapidly increased worldwide. HCC is the sixth most common malignancy and the third most common cause of cancer-related death (El-Serag and Rudolph 2007; Jemal et al. 2011). Since HCC usually develops in a damaged liver, the prognosis of HCC depends not only on tumor progression

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