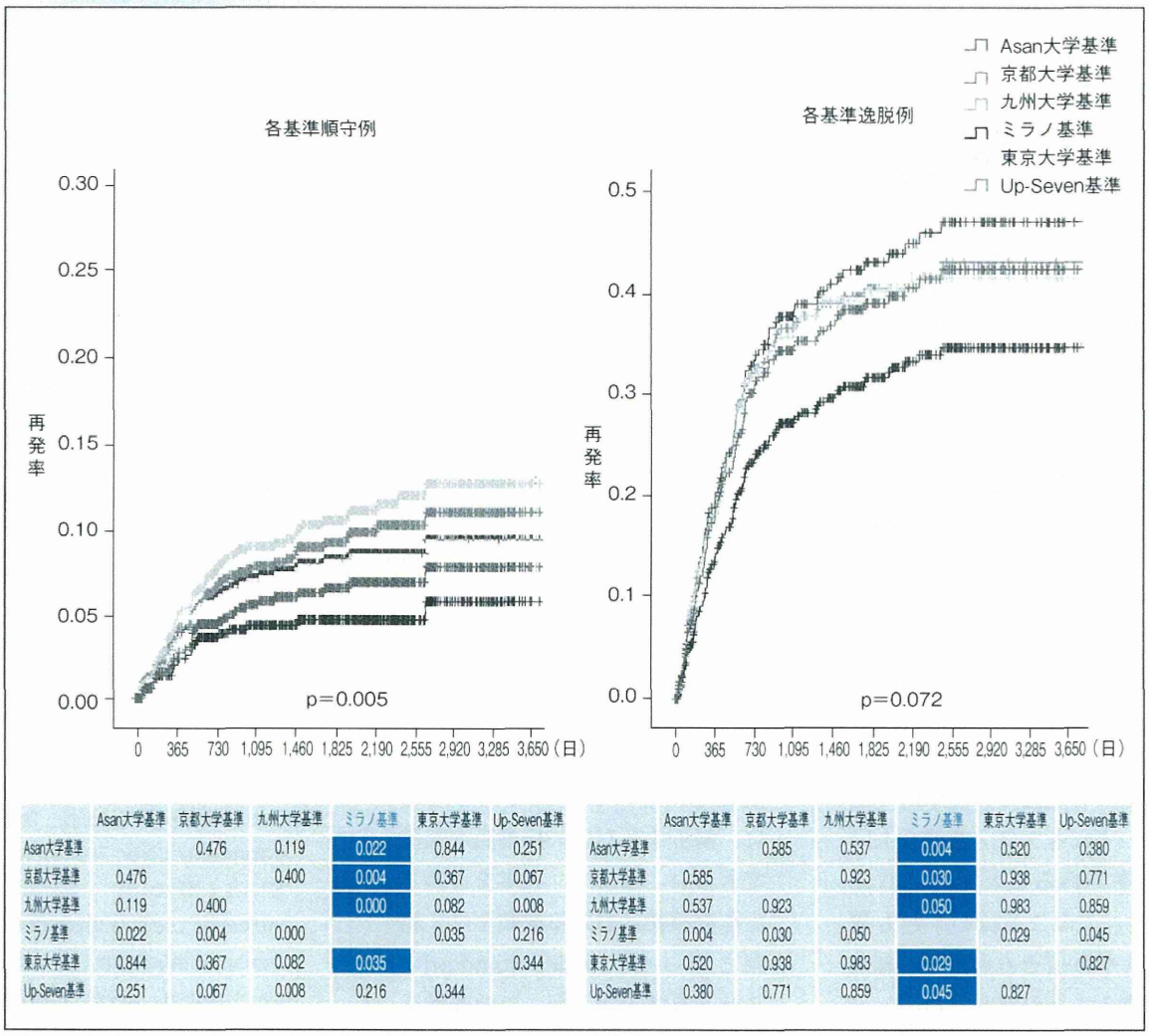

	Asan大学基準	京都大学基準	九州大学基準	ミラノ基準	東京大学基準	Up-Seven基準
Asan大学基準		0.476	0.119	0.022	0.844	0.251
京都大学基準	0.476		0.400	0.004	0.367	0.067
九州大学基準	0.119	0.400		0.000	0.082	0.008
ミラノ基準	0.022	0.004	0.000		0.035	0.216
東京大学基準	0.844	0.367	0.082	0.035		0.344
Up-Seven基準	0.251	0.067	0.008	0.216	0.344	

	Asan大学基準	京都大学基準	九州大学基準	ミラノ基準	東京大学基準	Up-Seven基準
Asan大学基準		0.585	0.537	0.004	0.520	0.380
京都大学基準	0.585		0.923	0.030	0.938	0.771
九州大学基準	0.537	0.923		0.050	0.983	0.859
ミラノ基準	0.004	0.030	0.050		0.029	0.045
東京大学基準	0.520	0.938	0.983	0.029		0.827
Up-Seven基準	0.380	0.771	0.859	0.045	0.827	

図6．各施設における肝細胞癌に対する肝移植の適応基準別累積再発率(巻頭カラーグラビアp.6参照)
左：適応内症例，右：適応逸脱症例
文献3)より引用

機会を与えうる結果に繋がっている。しかしながら，これらはそれぞれの施設内での基準であり，他施設からのvalidationが必要となる。そこで全国調査を施行した肝細胞癌を用いて各基準のvalidationということで，ミラノ基準，MazzaferroのUp-Seven基準，韓国のAsan大学基準，京都大学基準，東京大学基準，九州大学基準のそれぞれの基準に合致した肝細胞癌の生存率を検討した。この分析は嶋村らが施行し，すでに論文[3]として詳細に報告している(表1)[3]。

それぞれの適応基準に合わせた累積生存率は図5[3]に示す。興味深いことにミラノ基準から九州大学基準までの適応内外での5年累積生存率に統計学的に有意な差は認めなかった。それぞれの基準に適合した5年累積生存率はミラノ基準(571例)で77.5％，Up-Seven基準(707例)で76.8％，Asan大学基準(783例)で75.5％，京都大学基準(776例)で75.2％，東京大学基準(752例)で75.9％，九州大学基準(811例)で73.7％であった。一方，各基準を逸脱している症例の5年累積生存率はミラノ基準(456例)で61.6％，Up-Seven基準(320例)で56.8％，Asan大学基準(54.7％)，京都大学基準(239例)で55.6％，東京大学基準(275例)で55.9％，九州大学基準(204例)で57.8％と分析され，これも有意

差を認めていない(図5)[3]。

この検討結果を引用すると，ミラノ基準と同等の予後でUp-Seven基準で13.3％，Asan大学基準で20.6％，京都大学基準で20.7％，東京大学基準で17.6％，九州大学基準で24.3％の適応患者数の拡大が見込まれることが判明している。

各適応別累積再発率

一方，興味深いことは各施設による適応基準による適応内，逸脱例での累積再発率である。

各基準を逸脱した症例の再発率はミラノ基準に比べてすべての基準で統計学的に有意に高率であった。さらに各施設での基準内の症例でもいずれもミラノ基準を上回る再発率であることが示された(図6)[3]。このことはいずれも適応を拡大すればその再発率が有意に上昇することが判明したが，一方で各基準を逸脱した症例でもその予後成績に差はなく，いずれの基準でも50％以上の5年生存率が得られている。

振り返って各基準を検討すると，腫瘍数では京都大学が10個以内とミラノ基準に比して多数の結節を基準に示しているが，バイオマーカーのPIVKA-Ⅱ 400IU/L未満という規制が無尽蔵に数を増加させているのではないことが理解できる。

同様に九州大学基準もPIVKA-Ⅱで規制し，東京大学基準の5cm以下の5結節以内もミラノ基準と大差がないとの判断で理解できるようである。

おわりに

わが国の肝臓疾患の大半を占める肝細胞癌に対する生体肝移植の成績を示した。脳死肝移植例は今まで約180例であり，いずれも非代償性肝硬変に伴うミラノ基準を逸脱していない肝細胞癌という保険診療に沿った症例であるために，解析するだけの症例数が集計できない。そこで，大半を占める生体肝移植における成績を示す結果となった。Golden standardのミラノ基準であるが，この基準を逸脱している肝細胞癌でも十分な治療成績が得られていることを示す結果が得られた以上，基準逸脱で保険適応とならない症例の救済を真剣に考えなければならない時期に来ていると考える。多方面からのデータの集積で，肝細胞癌に対する肝移植の適応基準の拡大を考えるべき時期が来たと思う。

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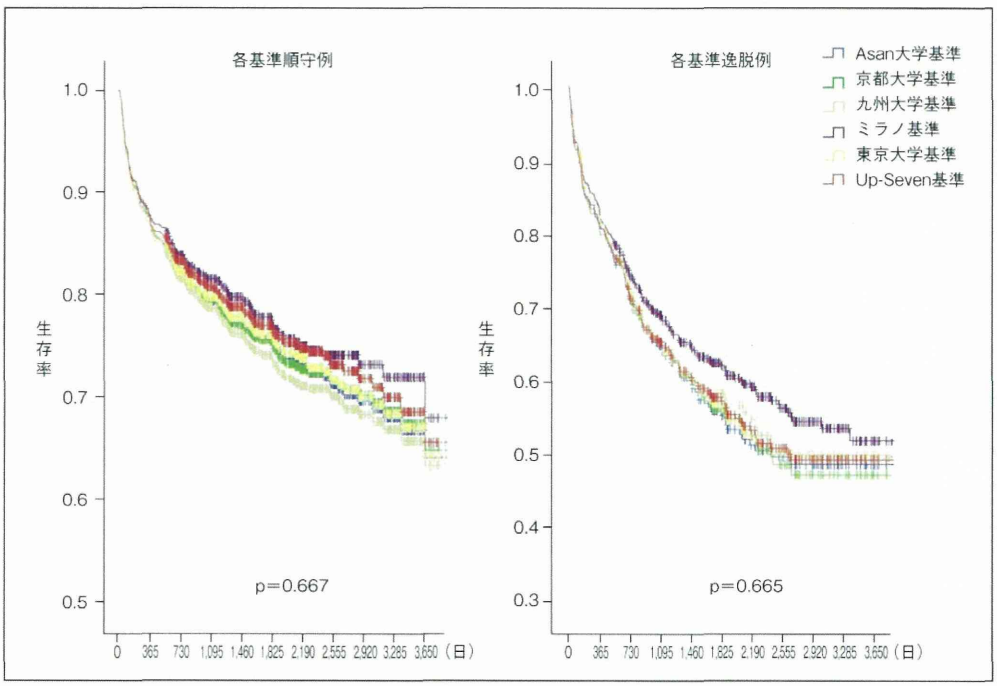
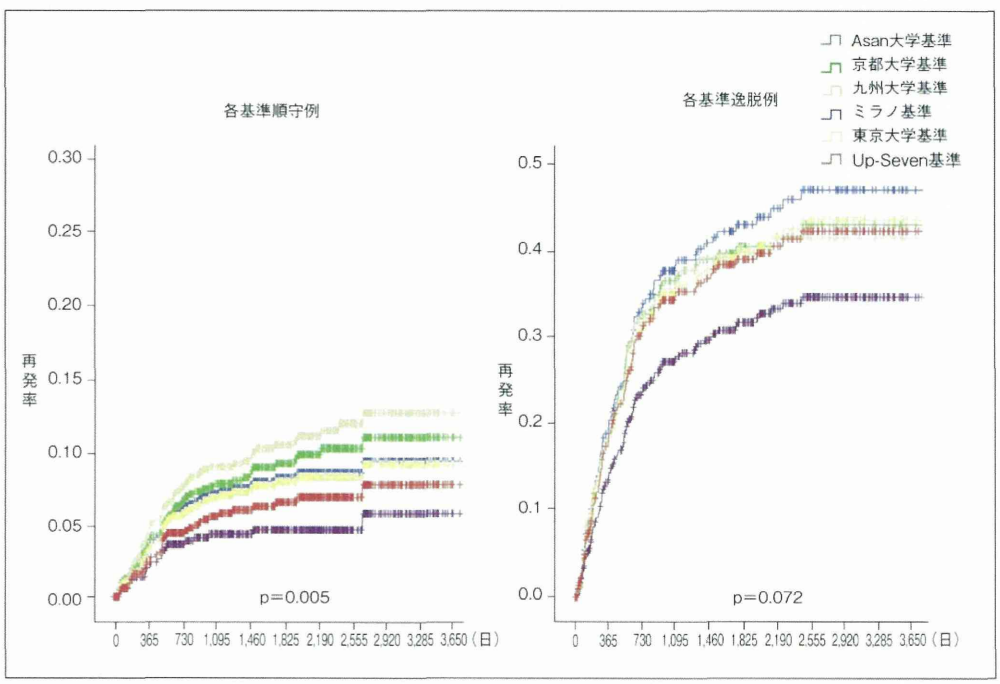


[7] 各施設における肝細胞癌に対する肝移植の適応基準別累積生存率

(本文 p.41, 図 5 参照)



[8] 各施設における肝細胞癌に対する肝移植の適応基準別累積再発率

(本文 p.42, 図 6 参照)

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HEPATOLOGY

Prediction of liver stiffness hepatocellular carcinoma in chronic hepatitis C patients on interferon-based anti-viral therapy

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Key words
chronic hepatitis C, hepatocellular carcinoma, liver stiffness, risk factor.

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Abstract

Background and Aim: The purpose of this study was to evaluate the usefulness of liver stiffness measurement (LSM) for assessing the risk of hepatocellular carcinoma (HCC) in chronic hepatitis C (CHC) patients receiving interferon (IFN) therapy.

Methods: One hundred fifty-one CHC patients who underwent LSM and received IFN therapy were included in the estimation cohort, and 56 were included in the validation study. The cumulative HCC incidences were evaluated using Kaplan–Meier plot analysis and the log-rank test. Multivariate Cox proportional hazard analyses were used to estimate the hazard ratios (HRs) of variables for HCC.

Results: In the estimation cohort, 9 of 151 patients developed HCC during the median follow-up time of 722 days. Multivariate analysis identified three independent risk factors for HCC: LSM (≥ 14.0 kPa, HR 5.58, $P = 0.020$), platelet count ($< 14.1 \times 10^4/\mu L$, HR 5.59, $P = 0.034$), and non-sustained virological response (HR 8.28, $P = 0.049$). The cumulative incidence of HCC development at 3 years was 59.6%, 8.2%, and 0.0% in patients with all three risk factors, one to two risk factors, and none of these risk factors, respectively. The incidence of HCC was significantly different between these groups ($P < 0.001$). In the validation cohort, HCC incidence was also significantly different with respect to these risk factors ($P = 0.037$).

Conclusion: LSM, platelet count, and IFN-therapeutic effect could be used to successfully stratify the risk of HCC in patients receiving IFN therapy and demonstrate the usefulness of LSM before IFN therapy for the management of CHC patients.

Introduction

Persistent hepatitis C virus (HCV) infection is one of the major causes of chronic liver disease leading to the development of HCC, the fifth most common cancer, and the third most common cause of cancer-related death worldwide.[1] HCV is responsible for 27–75% of the HCC cases in Europe and the United States and > 80% of the HCC cases in Japan.[2,3] In fact, HCV-positive patients have a 20-fold higher risk of developing HCC than HCV-negative patients,[4] indicating a significant carcinogenic role for persistent HCV infection. Because of this connection, many chronic hepatitis C (CHC) patients are treated with interferon (IFN)-based antiviral therapy because it not only eradicates HCV but also reduces the rate of HCC development. IFN therapy is most effective at decreasing the risk of developing HCC in patients that achieve a sustained virological response (SVR);[5–7] however, the risk of HCC development persists after IFN therapy even in patients who do achieve SVR.[8] HCC might develop immediately after IFN therapy in some cases, or during long-term IFN therapy in others.[9,10] Because assessing the risk of developing HCC is clinically important in the management of CHC patients, it is necessary to establish predictors for HCC development in patients who receive IFN therapy.

Some factors reported to predict the risk of HCC development after IFN therapy are older age, male gender, and severe fibrosis,[11,12] with advanced fibrosis and cirrhosis significantly correlating with the risk of HCC development.[13] To date, liver biopsy has been the gold standard for assessing the severity of liver fibrosis and cirrhosis,[14] although sampling errors and intraobserver and interobserver variability can lead to understaging.[15,16] In addition, it is difficult to perform liver biopsy for all patients because of its invasiveness and rare but potentially life-threatening complications.[14] As a result, liver stiffness measurement (LSM), a type of transient elastography, has become a reliable alternative for assessing hepatic fibrosis and cirrhosis mainly in patients with CHC.[17,18] LSM is non-invasive, reproducible, can be expressed numerically as continuous values, and has a wide dynamic range in the evaluation of hepatic fibrosis. These advantages over liver biopsy

suggest the clinical usefulness of LSM for predicting HCC development. Here, we evaluated factors that affect the occurrence of HCC in CHC patients receiving IFN therapy, with a special focus on the predictive value of LSM.

Methods

Patients. Between October 2007 and April 2011, a total of 207 consecutive CHC patients who underwent a successful LSM and then received IFN-based antiviral therapy at the Department of Gastroenterology and Hepatology, Juntendo University Shizuoka Hospital, Shizuoka, Japan, were retrospectively enrolled in this study. CHC diagnosis was based on serum HCV-RNA positivity. Exclusion criteria were as follows: (i) hepatitis B surface antigen positivity; (ii) other causes of liver disease of mixed etiologies, including autoimmune hepatitis, primary biliary cirrhosis, hemochromatosis, and Wilson's disease; (iii) evidence of hepatocellular carcinoma (HCC) on ultrasonography or computed tomography; (iv) previous history of liver transplantation; and (v) treatment for HCC. This study was approved by the Ethics Committee of Juntendo University Shizuoka Hospital in accordance with the Helsinki Declaration, and all patients provided written informed consent.

Of these 207 patients, 151 underwent ultrasonography-guided percutaneous liver biopsy within a week before treatment initiation. Liver biopsy specimens were embedded in paraffin and stained with hematoxylin-eosin, Azan-Mallory, and reticulin silver impregnation. The specimens were evaluated by an experienced pathologist who was blinded to the patients' clinical data. Histological evaluation was based on the METAVIR criteria.[19] Hepatic fibrosis was defined as follows: F0, no fibrosis; F1, periportal fibrous expansion; F2, portal fibrous widening with bridging fibrosis; F3, bridging fibrosis with lobular distortion; and F4, liver cirrhosis. On the basis of the degree of lymphocyte infiltration and hepatocyte necrosis, inflammation was scored from A0 to A3, with higher scores indicating more severe inflammation. The 151 patients who underwent liver biopsy were enrolled into the estimation group for the identification of risk factors for HCC development, and the remaining 56 patients who did not undergo liver biopsy were enrolled into a group for the validation of these identified risk factors.

All laboratory tests were performed for each patient just before initiation of IFN therapy. Blood cell counts, serum alanine transaminase, gamma-glutamyl transpeptidase, hemoglobin A1c, total bilirubin, albumin, prothrombin time, and alpha-fetoprotein (AFP) were measured using commercially available assays. The HCV genotype was determined using polymerase chain reaction with the HCV Genotype Primer Kit (Institute of Immunology Co., Ltd., Tokyo, Japan) and classified as genotype 1, genotype 2, or other, according to Simmonds' classification system. Serum HCV viral load was determined using quantitative reverse transcription polymerase chain reaction using the COBAS TaqMan HCV Test (Roche Diagnostics, Branchburg, NJ, USA).

Treatment protocol. The treatment protocol for CHC patients consisted of 1.5 μg/kg of pegylated IFN-α-2b or 180 μg of pegylated IFN-α-2a once a week, combined with ribavirin at an oral dose of 600–1000 mg/day. Duration of the treatment was 48–72 weeks for those with HCV genotype 1 and a serum HCV viral load > 5 log IU/mL. For all other patients, treatment lasted for 24 weeks. SVR was defined as undetectable serum HCV-RNA at 24 weeks after the end of treatment.

Measurement of liver stiffness. Measurement of liver stiffness by transient elastography was performed using FibroScan (Echosens, Paris, France) within a week before treatment initiation. Technical details of the examination and procedure have been reported previously.[17] Ten validated measurements were made on each patient, and results were expressed in kilopascals (kPa). Only procedures with 10 validated measurements and a success rate of at least 60% were considered reliable, and the median value was considered representative of the liver elastic modulus.

Patient follow-up and HCC diagnosis. Serum AFP was measured every month, and ultrasonography or computed tomography were performed at least every 3–6 months for HCC surveillance during and after treatment, with a minimum follow-up duration of 6 months after the initiation of IFN therapy. HCC was diagnosed by histological examination and/or triphasic computerized tomography, in which hyperattenuation in the arterial phase with washout in the late phase is pathognomonic for HCC.[20] The status of patients enrolled in this study was confirmed as of March 2012.

Statistical analyses. All analyses were conducted using IBM SPSS version 19 (IBM SPSS, Chicago, IL, USA), and P values less than 0.05 were considered statistically significant. Continuous variables and categorical variables were summarized as median (range) and percentage, respectively. Mann–Whitney U and chi-square tests were used when appropriate. The strength of the association between LSM and the histological fibrosis stage was estimated using the Spearman's rank correlation coefficient. Cumulative incidences of HCC development were estimated by Kaplan–Meier analysis and compared using the log-rank test. Cox logistic regression analysis was used for multivariate analysis to identify factors that were independently associated with HCC development. The cut-off value of each factor for predicting the development of HCC was determined using receiver operator characteristics analysis.

Results

Patient characteristics. A total of 229 patients received LSM followed by IFN-based antiviral therapy at Juntendo Shizuoka Hospital during the study period. Twenty-two patients (9.6%) were excluded because of LSM failure and/or an invalid LSM. Of the remaining 207 patients, 151 underwent liver biopsy prior to IFN therapy and together formed the risk factor-estimation cohort. The clinical, anthropometric, and laboratory data of the estimation cohort are summarized in Table 1. The 151 patients (83 male and 68 female) had a median age of 62 years (range 22–82 years) and a median LSM of 8.8 kPa (range 2.8–45.7 kPa). There was a significant positive association between LSM and histological fibrosis stage ($r = 0.59$, $P < 0.001$). The prevalence of genotype

Table 1 Baseline characteristics of the estimation cohort

Variables	All	HCC development (+)	HCC development (–)	*P*-value
Number of patients	151	9	142	
Age (years)	62 (22–82)	67 (60–82)	61 (22–80)	0.010†
Male (%)	55	55.6	54.9	1.000‡
BMI (kg/m^2)	23.5 (18.1–36.8)	23.8 (23.3–25.7)	23.4 (18.1–36.8)	0.217†
Habitual drinker (%)	10.6	11.1	10.6	1.000‡
Fibrosis stage (F0–2/F3–4)	115/36	5/4	110/32	0.048‡
Inflammatory grade (A0–1/A2–3)	33/118	0/9	33/109	0.101‡
LSM (kPa)	8.8 (2.8–45.7)	14.8 (9.8–45.7)	8.7 (2.8–34.8)	0.002†
Observation period (days)	722 (189–1378)	688 (189–1217)	733 (190–1378)	0.467†
Genotype 1 (%)	56.3	100	53.5	0.065‡
HCV-RNA (log IU/mL)	6.4 (0.0–7.7)	6.5 (2.9–7.2)	6.3 (0.0–7.7)	0.168†
Albumin (g/dL)	4.1 (3.4–4.8)	4.1 (3.5–4.6)	4.1 (3.4–4.8)	0.390†
ALT (IU/L)	59 (10–410)	75 (27–181)	57 (10–410)	0.467†
Total bilirubin (mg/dL)	0.7 (0.3–1.8)	0.8 (0.5–1.3)	0.7 (0.3–1.8)	0.070†
γGTP (IU/L)	44 (4–517)	75 (31–129)	41 (4–517)	0.120†
Hemoglobin A1c (%)	5.1 (3.7–8.2)	5.1 (3.7–6.1)	5.1 (4.2–8.2)	0.561†
Ferritin (ng/mL)	134 (8–2096)	215 (8–1026)	134 (9–2096)	0.675†
White blood cell count (× 10^3/μL)	4.9 (2.0–10.3)	4.3 (3.0–7.3)	4.9 (2.0–10.3)	0.496†
Hemoglobin (g/dL)	13.8 (8.9–17.5)	13.3 (9.9–17.5)	13.8 (8.9–17.1)	0.376†
Platelet count (× 10^4/μL)	16.3 (5.2–37.0)	9.6 (5.2–19.4)	16.5 (5.8–37.0)	0.004†
Prothrombin time (%)	100 (70–157)	93 (79–120)	102 (70–157)	0.185†
AFP (ng/mL)	6 (1–306)	14 (4–109)	6 (1–306)	0.004†
SVR rate (%)	55	11.1	57.7	0.011‡

Scale data are shown as median (range). *P* values are for comparisons between patients with and without HCC development.
†Mann–Whitney *U* test.
‡Chi-square test.
γGTP, γ-glutamyl transpeptidase; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; BMI, body mass index; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LSM, liver stiffness measurement; SVR, sustained virological response.

1 HCV infection was 56.3%. Following IFN-based antiviral therapy, SVR was obtained in 83 of the 151 patients (55%). During the median follow-up period of 722 days (range 189–1378 days), nine patients (6.0%) developed HCC. The cumulative incidence of HCC estimated using the Kaplan–Meier method was 1.3%, 4.5%, and 9.0% at 1, 2, and 3 years, respectively (Fig. 1). Compared with patients who had not developed HCC, HCC patients were of advanced age and had a high LSM, a high fibrosis stage, a low platelet count, and a low SVR rate (Table 1).

Risk analyses. Univariate analysis revealed that age ($P = 0.029$), LSM ($P = 0.005$), platelet count ($P = 0.002$), AFP ($P = 0.003$), and non-SVR ($P = 0.011$) were associated with HCC development (Table 2). Multivariate Cox logistic regression analysis identified three independent risk factors: LSM ≥ 14.0 kPa (hazard ratio [HR] 5.58, 95% confidence interval [CI] 1.32–23.64, $P = 0.02$), non-SVR (HR 8.28, 95% CI 1.01–68.05, $P = 0.049$), and platelet count < 14.1 × 10^4/μL (HR 5.59, 95% CI 1.14–27.53, $P = 0.034$), Table 3. The 1-, 2-, and 3-year cumulative incidence rates of HCC development in patients with LSM < 14.0 kPa were 0.8%, 2.3%, and 4.6%, respectively, whereas those with LSM ≥ 14.0 kPa were 3.2%, 12.0%, and 22.2%, respectively ($P = 0.005$) (Fig. 2a). The cumulative incidence rates of HCC development in patients with SVR were 0.0%, 2.0%, and 2.0%, respectively, whereas those without SVR were 3.0%, 7.4%, and 17.1%, respectively ($P = 0.011$) (Fig. 2b). The cumulative incidence rates of HCC development in patients with a platelet count ≥ 14.1 × 10^4/μL were 0.0%, 0.0%, and 4.2%, respectively, whereas those with a platelet count < 14.1 × 10^4/μL were 4.0%, 13.4%, and 19.1%, respectively ($P = 0.002$) (Fig. 2c).

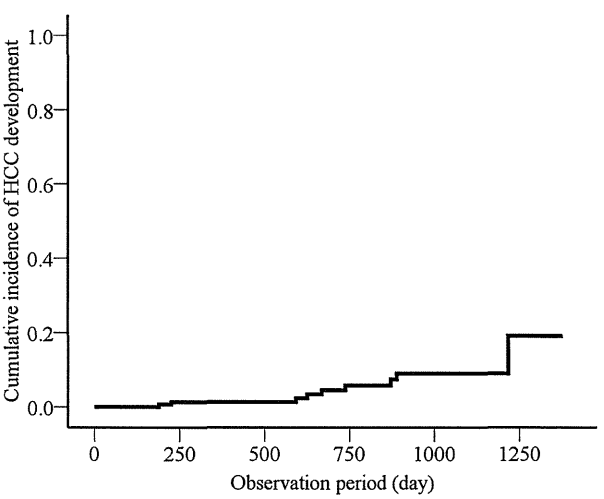

Figure 1 Incidence of hepatocellular carcinoma (HCC) in 151 patients with chronic hepatitis C receiving interferon-based anti-viral therapy estimated using the Kaplan–Meier method.

Table 2 Univariate analysis of factors associated with hepatocellular carcinoma development

Variables	*n*	Cumulative incidence of HCC (%)		*P*-value
		1 year	3 years	
Age (years)				
< 60	63	0.0	0.0	0.029
≥ 60	88	2.3	13.6	
Sex				
Female	68	1.5	12.1	0.910
Male	83	1.2	6.7	
BMI† (kg/m²)				
< 23.8	50	0.0	5.3	0.250
≥ 23.8	42	2.4	6.0	
Habitual drinker				
No	135	0.8	9.6	0.905
Yes	16	6.2	6.2	
Fibrosis stage				
F0–2	115	0.9	6.7	0.228
F3–4	36	2.9	15.0	
LSM (kPa)				
< 14	119	0.8	4.6	0.005
≥ 14	32	3.2	22.2	
ALT (IU/L)				
< 55	71	0.0	4.9	0.123
≥ 55	80	2.5	12.9	
γGTP† (IU/L)				
< 55	83	0.0	5.2	0.057
≥ 55	67	3.0	13.5	
Hemoglobin A1c† (%)				
< 5.5	109	0.9	6.8	0.219
≥ 5.5	25	0.0	18.8	
Ferritin† (ng/mL)				
< 210	74	1.4	10.0	0.175
≥ 210	43	2.3	16.3	
Platelet count (× 10^4/μL)				
≥ 14.1	101	0.0	4.2	0.002
< 14.1	50	4.0	19.1	
AFP† (ng/mL)				
< 10	95	0.0	5.6	0.003
≥ 10	38	4.9	22.3	
SVR				
Yes	83	0.0	2.0	0.011
No	68	3.0	17.1	

†Data not available for all patients.
AFP, alpha-fetoprotein; ALT, alanine aminotransferase; BMI, body mass index; γGTP, γ-glutamyl transpeptidase; HCC, hepatocellular carcinoma; LSM, liver stiffness measurement; SVR, sustained virological response.

Number of risk factors and HCC development. The number of risk factors varied between patients: 12 patients (7.9%) had all three risk factors, 32 patients (21.2%) had two, 50 patients (33.1%) had one, and 57 patients (37.7%) had none of these risk factors (Fig. 3). Patients without these risk factors did not develop HCC during the study period. In patients with 1 or 2 risk factors, the cumulative incidence rates at 1, 2, and 3 years were 1.2%, 3.1%, and 8.2%, respectively, whereas patients with all three risk

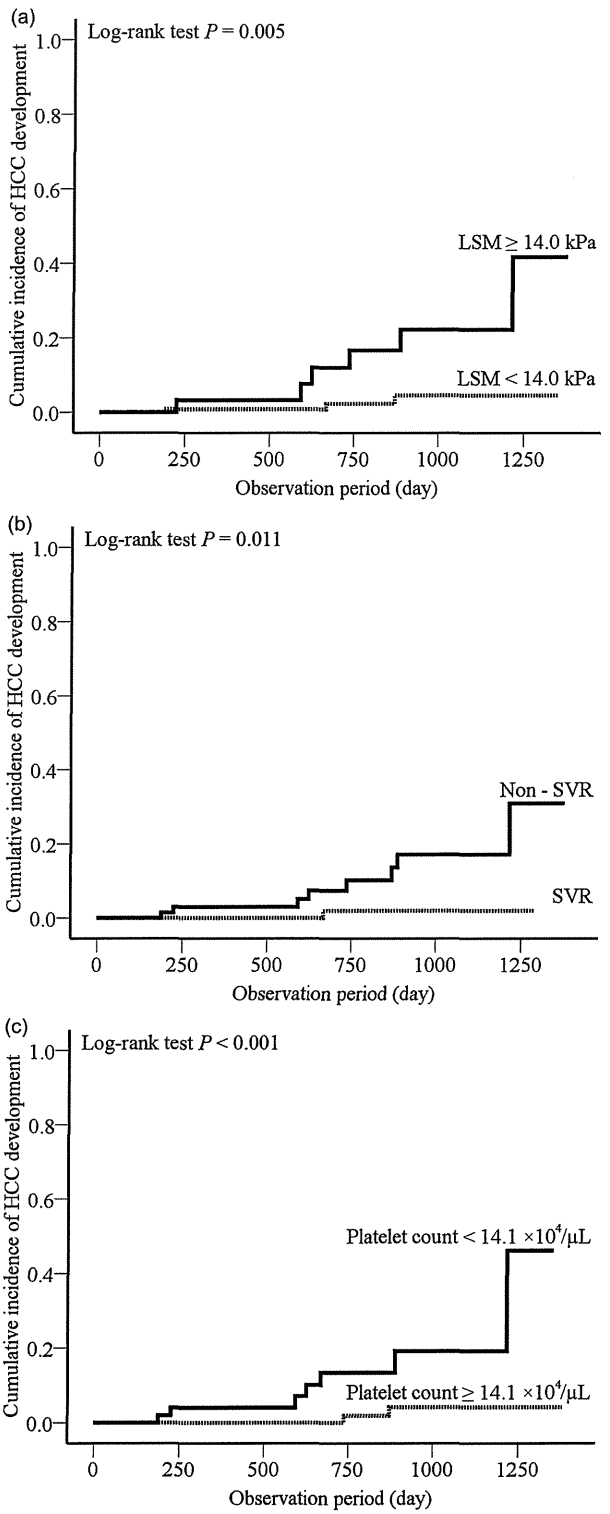

Figure 2 Kaplan–Meier curves comparing the cumulative incidence of hepatocellular carcinoma (HCC) development. Patients were stratified according to liver stiffness measurement (LSM) (a), sustained virological response (SVR) (b), and platelet count (c).

Table 3 Multivariate analysis of factors associated with hepatocellular carcinoma development

Variable		Hazard ratio (95% CI)	*P*-value
LSM (kPa)	< 14.0	1.00	0.020
	≥ 14.0	5.58 (1.32–23.64)	
SVR	SVR	1.00	0.049
	Non-SVR	8.28 (1.01–68.05)	
Platelet count (× 10^4/μL)	> 14.1	1.00	0.034
	≤ 14.1	5.59 (1.14–27.53)	

CI, confidence interval; LSM, liver stiffness measurement; SVR, sustained virological response.

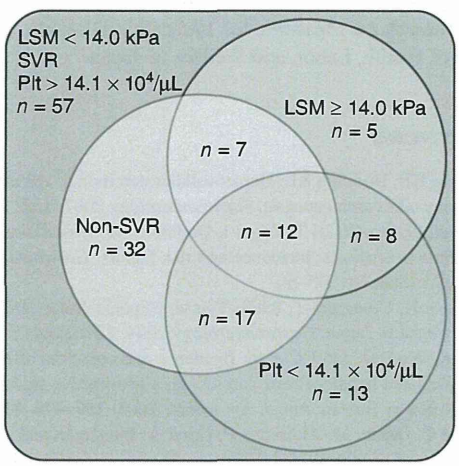

Figure 3 Patient distribution at each risk factor. LSM, liver stiffness measurement; Plt, platelet count; SVR, sustained virological response.

factors had significantly higher cumulative incidence rates (9.1%, 39.4%, and 59.6% at 1, 2, and 3 years, respectively; log-rank test, $P < 0.001$) (Fig. 4).

The relationship between the number of risk factors and HCC development in the validation cohort. Fifty-six patients who received IFN therapy without liver biopsy were enrolled into the validation group for analysis of these three risk factors. The 56 patients (33 male and 23 female) had a median age of 65 years (range 35–79 years) and a median LSM of 8.0 kPa (range 2.6–32.0 kPa). There were no significant differences in clinical, anthropometric, and laboratory findings between the validation and estimation cohorts (data not shown). In the validation cohort, seven patients (12.5%) had all three risk factors, 25 patients (44.6%) had one or two risk factors, and 24 patients (42.9%) had none of these risk factors. Patients without these risk factors did not develop HCC during the study period. In patients with one or two risk factors, and patients with all three risk factors, the cumulative incidence rates at 3 years were 12.7% and 28.6%, respectively. There was also a significant difference in the cumulative incidences of HCC development according to the number of risk factors ($P = 0.037$, Fig. 5).

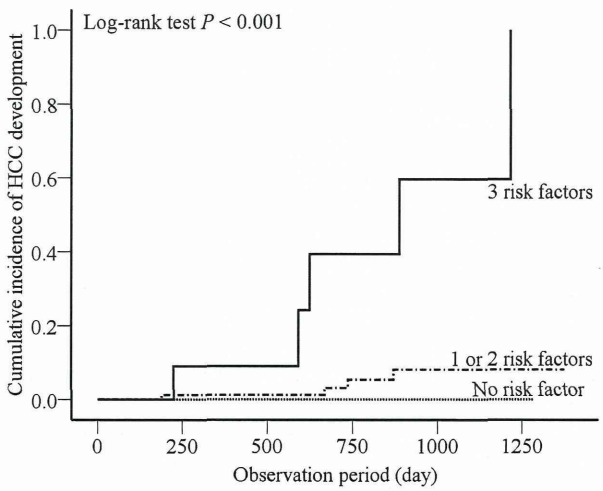

Figure 4 Kaplan–Meier curves comparing the cumulative incidence of hepatocellular carcinoma (HCC) development. Patients were stratified according to the number of risk factors.

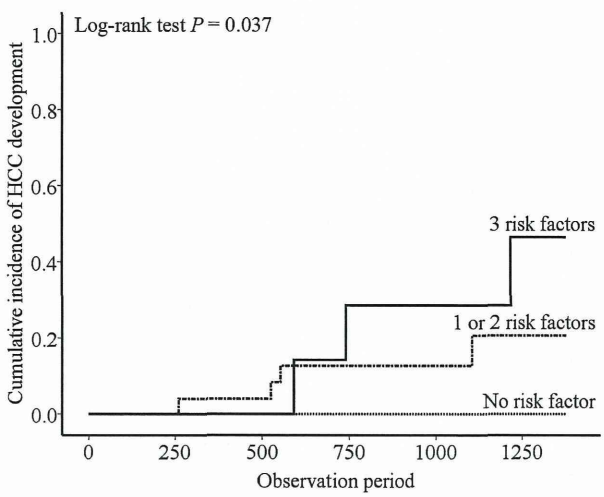

Figure 5 Kaplan–Meier curves comparing the cumulative incidence of hepatocellular carcinoma (HCC) development in the validation cohort. Patients were stratified according to the number of risk factors they had.

Discussion

Patients with liver cirrhosis or pre-existing severe hepatic fibrosis have a higher risk of developing HCC,[2] even after IFN-based therapy with SVR.[9,10] Clinical diagnosis of liver cirrhosis can be easily made in cases showing stigmata of end-stage liver disease, such as ascites, jaundice, variceal bleeding, and hepatic encephalopathy; however, diagnosis becomes difficult if the liver shows compensation, and normal or near-normal laboratory findings. Liver biopsy has been considered the only diagnostic method for the assessment of early compensated cirrhosis, although

several studies have pointed out sampling variability as a potential limitation of biopsy to diagnose cirrhosis.[21,22] Given the importance of assessing the HCC risk factors in managing CHC patients, we evaluated factors that affect the occurrence of HCC in CHC patients receiving IFN therapy, with a special focus on the predictive value of LSM as an alternative to liver biopsy.

Our data identified three risk factors for developing HCC after IFN therapy. Consistent with previous reports,[5–7] we found that failure to achieve SVR was a significant predictor of HCC development among patients receiving IFN therapy. Although it is possible that IFN therapy itself reduces the risk of HCC,[6,7] non-SVR patients had an approximately eightfold higher risk of developing HCC than SVR patients. In addition, we identified both high LSM and low platelet count as significant predictors of HCC development independently of non-SVR. The LSM threshold ≥ 14.0 kPa identified here as a risk factor for HCC is in agreement with previously reported cut-off values for liver cirrhosis,[15,16] further supporting the idea that pre-existing liver cirrhosis increases the risk of HCC development. Similar to LSM, the platelet count reflects the severity of CHC[21] and is used to estimate the degree of fibrosis.[23–25] Previous reports have also shown low platelet counts to represent a risk of HCC.[23,24] Our cohort showed that LSM was sometimes high even in patients without a low platelet count, whereas other patients had a low platelet count without LSM elevation. Such patients are nevertheless at risk of HCC, suggesting that LSM and platelet count indicate advanced fibrosis or compensated cirrhosis in a complementary manner.

In agreement with a previous report, our findings indicate that LSM could be used to stratify the risk of HCC development in CHC patients.[26] Moreover, combination of LSM with platelet count and the IFN-therapeutic effect could be used to stratify the risk of HCC in patients receiving IFN therapy. Patients without all three risk factors had a very low risk of HCC development, and patients with 1 or 2 risk factors had a moderate risk. Conversely, patients with all three risks had an extremely high risk. In clinical practice, frequency of HCC surveillance should be decided based on HCC risk. Indeed, each of these three factors has previously been shown to be associated with the risk of developing HCC. However, here, we have proposed a new, non-invasive risk assessment based on the combination of LSM and two other factors. In the present study, we did not identify advanced histological fibrosis stage F3–4 as a risk factor for HCC likely because of liver biopsy sampling variability because patients were not excluded based on the length of liver biopsy samples, an important factor affecting variability in histological assessment of liver fibrosis.[15] Taken together, these findings suggest that LSM would be more useful than liver biopsy for diagnosis of patients with liver cirrhosis who are at high risk of HCC, especially those with compensated cirrhosis.

Our data indicate patients with all of the three risk factors require the most intensive HCC surveillance; however, this study does have a few limitations. One drawback is that LSM failure and unreliable results occur in some patients. In our cohort, 9.0% of patients who received LSM did not yield reliable results. Because subcutaneous fat attenuates the transmission of share waves and the ultrasonic signals into the liver used to determine LSM, obesity is the principal reason for LSM failure.[27] In addition, it is likely that obesity itself is associated with an increased risk of HCC.[28] As a result, our findings might not reflect the risk of HCC in obese patients. Another recent report demonstrated that a new FibroScan XL probe, designated for use in obese patients, could reduce LSM failure and facilitate reliable results.[29] A study using this new probe will more accurately evaluate the predictive value of LSM for the risk of HCC development.

In conclusion, our findings indicate that LSM, platelet count, and IFN-therapeutic effect could be used to successfully stratify the risk for HCC development in patients receiving IFN-based antiviral therapy and demonstrate the usefulness of LSM before IFN therapy for the management of CHC patients.

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