Acta Medica et Biologica
Vol.56, No2, 73-84, 2008

A new scoring system for predicting survival in patients with hepatocellular carcinoma: The integration of the JIS and CLIP scoring systems

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Received January 4, 2008 ; accepted January 15, 2008

Summary. Several integrated scoring systems for hepatocellular carcinoma (HCC) have recently been proposed, but there is still no consensus regarding their validity. The present study developed a new scoring system to obtain a better model for predicting the survival of patients with HCC. Data obtained from 1,070 patients with HCC diagnosed at 31 hospitals affiliated with the Niigata Liver Disease Study Group from January 1993 through December 2003 were retrospectively analyzed. The significant factors, which affected the survival of the patients were analyzed, and the best fitting model for the patients' survival was constructed. Fourteen factors were identified based on a univariate analysis, and those factors were used in a multivariate analysis as the candidate prognostic factors. The first Cox's analysis revealed that the Cancer of the Liver Italian Program (CLIP) score, tumor diameter, metastasis (N factor and/or M factor) based on the Liver Cancer Study Group of Japan (LCSGJ), and Japan Integrated Staging (JIS) score were all significant factors. Since the results suggested that both the CLIP and JIS scores were insufficient for the prediction of survival, the Japan Integrated Triform system (JITs) score was designed by removing tumor morphology and portal vein thrombosis from the CLIP score and by adding T factor and metastasis of the LCSGJ. An evaluation by the Akaike information criteria (AIC) showed the JITs score to be a good-fitting model in the present study population. JITs score may hopefully be useful for physicians in determining the appropriate management options.

Key words— hepatocellular carcinoma, Japan Integrated Staging score, Cancer of the Liver Italian Program score, Akaike information criteria, Cox's proportional hazards regression model.

INTRODUCTION

The essential requirements of a scoring system, to obtain an accurate prognosis for each patient, to compare the results of treatments using different modalities or the results of treatments in different institutions or different counties, and to test the effectiveness of a new method of treatment for hepatocellular carcinoma (HCC), are interchangeability and universality. The prognostic assessment and the selection of treatment strategies for patients with HCC are important, but they are extremely complicated, unlike carcinomas arising in other organs. The reason for this complexity is that the prognosis of HCC depends not only on the degree of cancer spread but also on the hepatic functional reserve. Therefore, an accurate prognostic staging system is important for patients with HCC in order to provide appropriate treatment guidance. Such a system is also important to obtain better patient stratification when planning

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Abbreviations — HCC, hepatocellular carcinoma; CLIP score, Cancer of the Liver Italian Program score; JIS score, Japan Integrated Staging score; LCSGJ, Liver Cancer Study Group of Japan; AIC, Akaike information criteria; TNM classification, tumor node metastasis classification; AFP, alpha-fetoprotein; JITs score, Japan Integrated Triform system score.

controlled trials on locoregional treatment or for examining the results of open trials on new treatment methods.

The current classifications used for HCC include the Okuda stage,[1] the tumor node metastasis (TNM) classification according to International Union Against Cancer (UICC),[2] and staging system based on the Liver Cancer Study Group of Japan (LCSGJ).[3] The Cancer of the Liver Italian Program (CLIP) score,[4] which is used most commonly as an integrated staging score,[5-8] incorporates the Child-Pugh grade[9] as an index of the severity of liver dysfunction and three tumor-related factors: tumor morphology, serum alpha-fetoprotein (AFP) level, and portal vein thrombosis. Recently, Kudo et al. proposed the Japan Integrated Staging (JIS) score, which combines the Child-Pugh grade and the staging system of the LCSGJ, shows a higher predictive efficacy.[10,11] Although several integrated scoring systems for HCC have recently been proposed, there is still no worldwide consensus regarding which system is the best model for HCC.[12-20]

In the present study, the JIS and CLIP scores were evaluated in terms of predictive power for the prognosis of patients with HCC. Since the results indicated that both the CLIP and JIS scores include complementary factors, a new scoring system was thus developed to obtain a better fitting model for predicting the survival of patients with HCC.

METHODS

Patients and data collection

From January 1993 through December 2003, 1,070 patients were diagnosed as having HCC at 31 hospitals affiliated with the Niigata Liver Disease Study Group. Sixty-seven of those patients were diagnosed by pathological findings, and the others were diagnosed by reliable clinical criteria indicating the existence of a background chronic liver disorder with typical images of HCC and/or elevation of tumor markers. Typical images of HCC were defined as enhanced tumors in the arterial phase following washing-out in the portal phase. The study protocol was approved by the Institutional Ethics Review Board.

The 23 factors shown in Table 1 were collected from patient records and were analyzed to determine whether they are significant factors to predict the survival of patients. The maximum diameter of the tumor was measured on images of dynamic computed tomography (CT). The presence or absence of vascular invasion was determined by dynamic CT and/or angiography. The Child-Pugh grade determined by assessment of ascites, encephalopathy, serum total bilirubin, serum albumin, and prothrombin activity ratio (PT) and it is included in both the JIS and CLIP scores.[4]

The JIS score was calculated by the summation of scores according to the staging system of the LCSGJ (stages I, II, III, and IV allocated to scores 0, 1, 2, and 3, respectively) and Child-Pugh grade (Child-Pugh grade A, B, and C allocated to scores 0, 1, and 2, respectively).[10,11] In the JIS score, the staging system of the LCSGJ is composed of T factor (tumor morphology), N factor (lymph node metastasis), and M factor (distant metastasis). T factor includes three tumor-related factors: solitary, tumor diameter $\leq$ 2 cm, and the absence of vascular involvement; fulfilling 3 tumor-related factors is T1, fulfilling 2 is T2, fulfilling 1 is T3, and fulfilling 0 is T4. Metastasis (N factor and/or M factor) was assessed using ultrasonography, dynamic CT, and chest X-ray. If any symptoms associated with metastasis to the bone were suspected, then bone scintigraphy was conducted in this study group. The CLIP score was obtained by combining the scores of four factors: the Child-Pugh grade, tumor morphology, the AFP level, and portal vein thrombosis. Tumor morphology was determined based on the CT findings.

All of the patients were initially treated from 1993 through 2003. The initial treatments were a surgical resection, puncture-based therapies, transarterial chemoembolization, other treatments, and the best supportive care. The treatment factors were excluded from the candidate factors however, because the initial treatment for HCC depends mainly on the severity of the disease (i.e., the hepatic functional reserve and tumor extension).

Identification of mortality

The endpoint used in the analysis was the overall survival time, which was defined as the time from the date of diagnosis to either the date of death or the date when lost to follow-up.

Statistical analysis

The cumulative survival rates were estimated using the Kaplan-Meier method.[21] The log-rank test was used to test the equality of two survival curves. When the survival curves of more than two groups were compared, Bonferroni's correction method was used for multiple comparisons.

In order to clarify the factors which significantly affect the survival rate, a multivariate analysis was performed using a proportional hazards regression analysis.[22] The assumptions of the proportional hazards of each covariate were checked by the graph of the log [-log (cumulative survival rate)] versus log t. In order to evaluate the goodness-of-fit in the JIS and CLIP scores,

the AIC was calculated for Cox's proportional hazards model.[23] Model selection for identifying the factors with a significant effect on survival was based on a forward stepwise procedure with the entering and removing of criteria 0.05 and 0.06, respectively. In a proportional hazards regression analysis, the factors with more than two categories were converted into dummy factors. The most appropriate model was selected on the basis of the AIC. The difference in the AIC was evaluated by the Kishino-Hasegawa test.[24]

A two-tailed P value of < 0.05 was to be considered significant, except for multiple comparisons. All of the statistical analyses were performed using the SPSS Release 14.0J software program (SPSS Japan, Tokyo, Japan) in Windows XP.

RESULTS

Patients' characteristics

By December 2003, 583 (54.5%) of the patients had died while 487 (45.5%) of the patients were either lost to follow-up or were alive. The median follow-up period was 2.78 years, and the longest follow-up period was 10.5 years. Table 1 shows the distribution and survival of patients for each factor. The median age at diagnosis was 67 years (range of 28 to 91 years), and the patients were predominantly males (male/female ratio: 763:307). Antibodies against the hepatitis C virus were present in 730 patients (68.2%), antibodies against the hepatitis B virus were present in 236 patients (22.1%), and antibodies against both viruses were present in 38 patients (3.6%), almost the same rates as those obtained in a nationwide survey in Japan (70%, 23%, and 2%, respectively).[25] There was no statistically significant difference between these data and the nationwide data regarding the type of hepatitis virus markers ($P = 0.70$). The overall survival rates for 1 year, 3 years, 5 years, and 10 years were estimated to be 76.0%, 47.9%, 32.8%, and 12.2%, respectively. Most of the patients were in the early stages of the disease (JIS 0-1, 46.9%; CLIP 0-1, 65.9%), and 56.2% of the patients had a stage I or II based on the staging system of the LCSGJ and 69.6% had a Child-Pugh grade A.

Univariate analysis of factors that affect survival

The estimated survival rates for 1 year, 3 years, and 5 years and the results of the comparisons of the survival curves among several groups in each factor are shown in Table 1. Nineteen factors showed significant differences among the survival curves ($P < 0.05$) by the log-rank tests.

The estimated survival curves by the JIS and CLIP scores are shown in Figures 1 and 2, respectively. The log-rank tests with Bonferroni's correction revealed significant differences between all of the combinations of the two categories out of the six categories of the JIS score except the combination of JIS 4 and JIS 5 ($P = 0.028$; at Bonferroni's corrected level of significance of 0.0033). On the other hand, there were no significant differences between the survival curves of the CLIP 2 and CLIP 3 groups, the CLIP 4 and CLIP 5 groups, and the CLIP 5 and CLIP 6 groups ($P = 0.013$, 0.029, and 0.203, respectively; at Bonferroni's corrected level of significance of 0.0024).

Table 1. Factors influencing survival in 1,070 patients with HCC

Factor	No. of patients	Survival (%)			P value
		1-year	3-year	5-year	
Age					0.450
median	67				
range	28-91				
Sex					0.372
male	763	75.4	48.3	32.8	
female	307	77.4	47.1	33.0	
HCV					0.739
negative	340	72.5	48.4	33.0	
positive	730	77.6	47.7	32.7	
HBV					0.802
negative	834	77.3	46.5	31.6	
positive	236	71.4	53.0	36.9	
Modality of diagnosis					< 0.001
Histology	67	86.1	74.0	61.7	
MRI	70	82.1	49.7	31.4	
CTHA/CTAP	54	88.4	65.4	42.1	
Dynamic CT	381	71.6	37.0	25.4	
Conventional CT	140	69.9	49.0	34.0	
Ultrasoography	117	77.8	58.7	41.6	
Angiography	241	78.0	46.1	29.0	
Tumor enhancement on CT					< 0.001
no	69	92.3	79.2	57.7	
yes	1001	74.9	45.6	30.9	
Child-ascites					< 0.001
none	928	81.5	53.0	36.8	
mild	87	46.2	20.0	8.2	
$\geq$ moderate	55	31.1	5.8	–	
Child-encephalopathy					< 0.001
none	1027	77.1	49.2	33.8	
1 or 2	35	57.9	22.5	11.2	
3 or 4	8	12.5	–	–	
Child-total bilirubin (mg/dl)					< 0.001
<2	965	79.4	52.0	35.7	
2-3	73	50.4	14.9	7.7	
>3	32	34.4	9.5	–	
Child-albumin (g/dl)					< 0.001
>3.5	714	84.6	57.3	40.7	
2.8-3.5	306	61.9	31.3	18.8	
<2.8	50	45.7	19.2	7.7	
Child-PT (%)					< 0.001
>80	559	81.7	55.0	40.3	
50-80	397	72.9	43.4	25.9	
<50	114	58.7	29.3	20.5	

(to be continued)

Factor	No. of patients	Survival (%) 1-year	3-year	5-year	P value
Child-Pugh grade					< 0.001
A	715	85.5	58.0	41.2	
B	301	60.6	31.3	17.7	
C	54	36.7	9.8	6.5	
CLIP-tumor morphology (%)					< 0.001
uninodular and extension $\leq$ 50	628	86.3	60.6	43.9	
multinodular and extension $\leq$ 50	354	71.5	35.8	20.0	
massive or extension >50	88	18.8	5.9	3.0	
CLIP-AFP (ng/ml)					< 0.001
<400	814	83.6	55.1	38.8	
$\geq$ 400	256	51.4	24.6	12.7	
CLIP-portal vein thrombosis					< 0.001
no	887	33.2	15.9	10.2	
yes	183	84.6	54.2	37.2	
Number of tumor					< 0.001
solitary	424	62.4	30.8	17.0	
multiple	646	84.7	58.8	43.1	
Tumor diameter (cm)					< 0.001
$\leq$ 2	317	92.6	65.2	48.9	
>2	753	68.9	40.4	25.8	
Vascular involvement					< 0.001
no	855	85.5	55.0	37.9	
yes	215	37.4	18.2	10.9	
Metastasis†					< 0.001
no	1035	78.2	49.4	33.8	
yes	35	11.4	5.7	–	
T factor‡					< 0.001
T1	224	94.4	70.5	55.5	
T2	387	86.6	58.7	39.3	
T3	332	69.1	31.9	18.7	
T4	127	29.9	14.9	6.1	
Stage‡					< 0.001
I	224	94.3	70.5	55.5	
II	377	87.3	59.4	39.6	
III	322	72.4	33.5	19.6	
IV	147	26.0	14.1	7.2	
JIS score					< 0.001
0	155	99.3	78.0	63.6	
1	347	89.0	64.8	45.2	
2	291	82.2	40.6	24.6	
3	181	53.1	23.7	10.8	
4	81	16.5	3.0	–	
5	15	6.7	–	–	

(to be continued)

Factor	No. of patients	Survival (%)			P value
		1-year	3-year	5-year	
CLIP score					< 0.001
0	362	95.1	74.1	56.3	
1	343	87.2	49.7	31.8	
2	186	60.5	27.5	15.0	
3	93	48.9	16.8	7.0	
4	50	17.1	9.8	–	
5	32	3.3	–	–	
6	4	–	–	–	

† Metastasis includes N factor (lymph node metastasis) and/or M factor (distant metastasis) according to the staging system of the LCSGJ.[3)]

‡ According to the staging system of the LCSGJ.[3)]

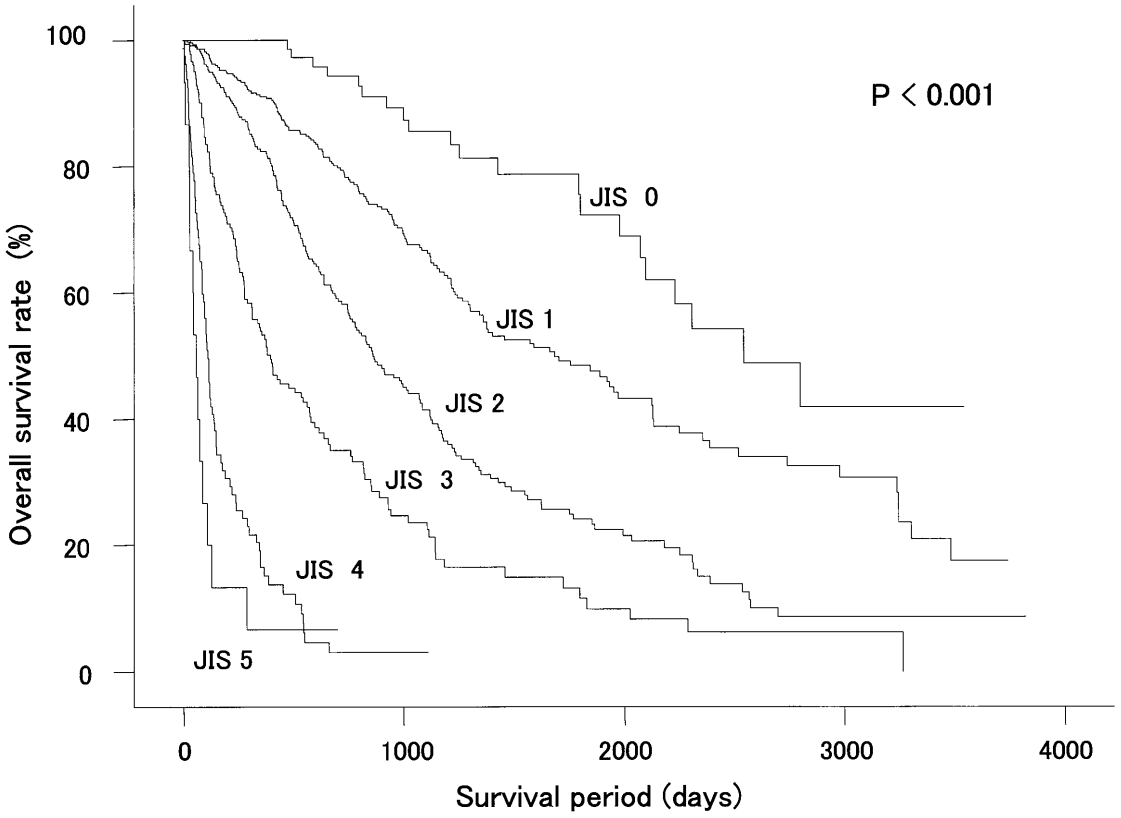

Figure 1. Kaplan-Meier estimated survival curves by the JIS score.

The median survival periods were 2, 310 days in JIS 0, 1,429 days in JIS 1, 833 days in JIS 2, 382 days in JIS 3, 111 days in JIS 4, and 58 days in JIS 5.

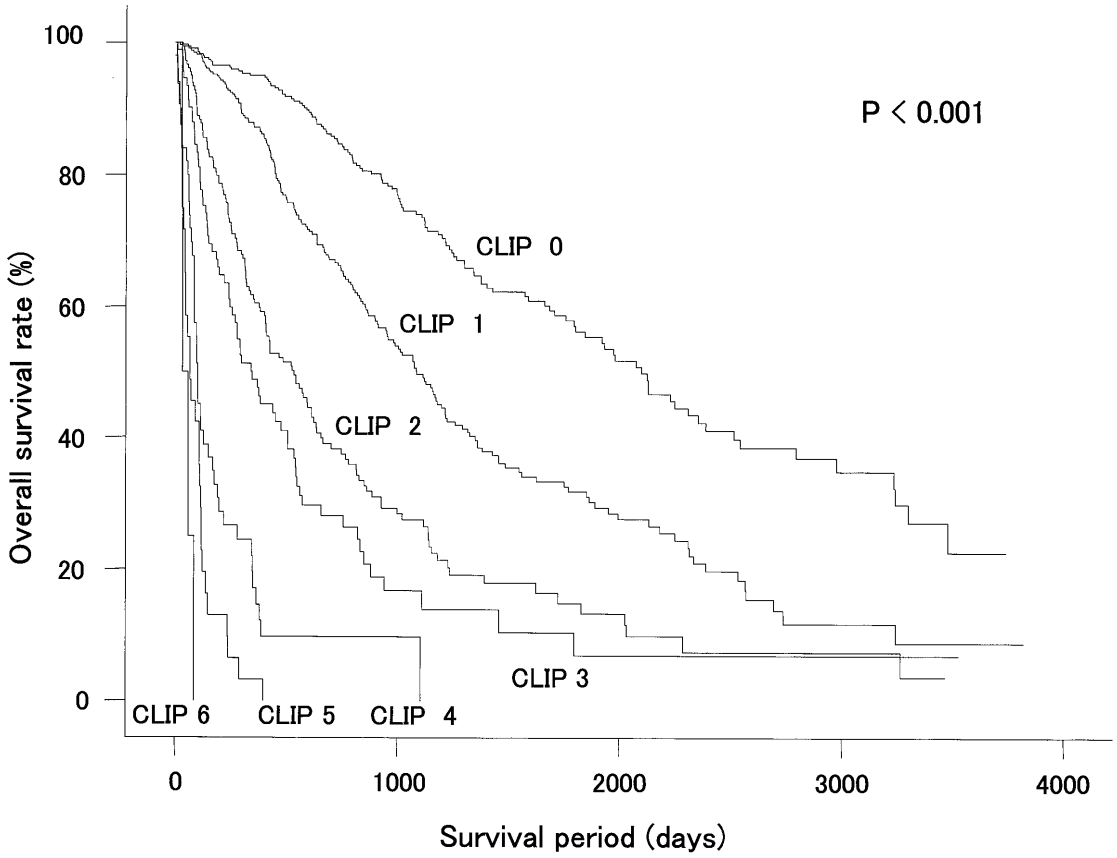

Figure 2. Kaplan-Meier estimated survival curves by the CLIP score.

The median survival periods were 2,100 days in CLIP 0, 1,086 days in CLIP 1, 536 days in CLIP 2, 346 days in CLIP 3, 102 days in CLIP 4, 65 days in CLIP 5, and 34 days in CLIP 6.

Multivariate analysis of the factors associated with survival

Before Cox's proportional hazards model was applied, the appropriateness of this model was evaluated using plots of log [-log (survivorship function)] versus log t. The plots indicated that there was no evidence of not following Cox's proportional hazards model.

The 19 factors that were significant in the previous univariate analyses were used as the candidate prognostic factors. The five factors of Child-ascites, Child-encephalopathy, Child-total bilirubin, Child-albumin and Child-PT (%) were combined with the Child-Pugh grade. Consequently, 14 factors were used as the candidate factors in the first Cox's analysis. The forward stepwise regression method in the proportional hazards regression model showed that the subset of significant prognostic factors consisted of the CLIP score, tumor diameter, metastasis (N factor and/or M factor), and JIS score (we called this subset the first Cox model, Table 2). The selection of both the JIS and CLIP scores in this analysis suggests that the two scoring systems are not really sufficient to accurately discriminate a favorable and unfavorable survival prognosis. Therefore, an alternative scoring system should be established to more accurately predict the prognosis.

We established a new complementary scoring system based on the first Cox model and named the Japan Integrated Triform system (JITs) score by removing the tumor morphology and portal vein thrombosis from the CLIP score and instead incorporating T factor including tumor diameter and metastasis (N factor and/or M factor) into the system (Table 3). The JITs score divides patients into six groups, from JITs 0 to JITs 5-7, based on the summation of the scores of these four factors ranging from 0 to 3. Figure 3 shows the survival curves of the JITs score. There were statistically significant

differences in survival between two of the groups at Bonferroni's corrected level of significance of 0.0018, except for comparisons between the high score groups, that is, the JITs 5 and JITs 6 groups, and the JITs 6 and JITs 7 groups (P = 0.40 and 0.27, respectively). Therefore, JITs 5, JITs 6, and JITs 7 were integrated into one group denoted by JITs 5-7. There were significant differences between all of the combinations of the two categories out of the six categories of the JITs score in the overall survival rates for 5 years.

When the CLIP 0 group was stratified according to the JIS score, it was found the CLIP 0 group included patients with JIS 0 to JIS 3. In these survival curves, JIS 1, JIS 2, and JIS 3 were integrated into one group denoted by JIS 1-3, because the number of cases was small: JIS 2 (n = 5), JIS 3 (n = 2). There was a statistically significant difference between the survival curves for the JIS 0 group and the JIS 1-3 group in the CLIP 0 group (P = 0.001; Figure 4), thus suggesting that the CLIP score lacks the ability to stratify the early stage group of HCC patients. The AIC statistic based on Cox's proportional hazards model with a single factor was calculated in order to compare the goodness-of-fit for prognosis. The AIC statistics of the JIS, CLIP, and JITs scores were 6818.8, 6785.8, and 6789.4, respectively. Kishino-Hasegawa tests suggested significant differences in the AIC statistics among the JIS, CLIP, and JITs scores (JIS vs. JITs; P < 0.001, CLIP vs. JITs; P < 0.001).

Table 2. Significant prognostic factors selected from 14 factors by Cox's analysis

Factor	Relative risk	95% confidence interval	P value
CLIP score			< 0.001
(0 vs. 1)	1.88	1.32-2.68	< 0.001
(0 vs. 2)	3.30	2.06-5.28	< 0.001
(0 vs. 3)	3.55	2.10-5.98	< 0.001
(0 vs. 4)	8.80	4.86-25.96	< 0.001
(0 vs. 5)	14.07	7.17-27.60	< 0.001
(0 vs. 6)	20.01	5.38-74.38	< 0.001
Tumor diameter			
($\leq$ 2 vs. >2)	1.49	1.01-2.21	0.045
Metastasis†			
(no vs. yes)	2.02	1.33-3.06	0.001
JIS score			< 0.001
(0 vs. 1)	1.34	0.75-2.40	0.330
(0 vs. 2)	1.43	0.67-3.03	0.353
(0 vs. 3)	1.67	0.72-3.84	0.230
(0 vs. 4)	3.75	1.55-9.11	0.003
(0 vs. 5)	4.02	1.39-11.68	0.010

†Metastasis includes N factor (lymph node metastasis) and/or M factor (distant metastasis) according to the staging system of the LCSGJ.[3)]

Table 3. Definitions of the JITs score

	Score			
Factors	0	1	2	3
Child-Pugh grade	A	B	C	–
CLIP-AFP (ng/ml)	<400	≥ 400	–	–
T factor†	T1	T2	T3	T4
Metastasis‡	No	Yes	–	–

†According to the staging system of the LCSGJ.[3)]
‡Metastasis includes N factor (lymph node metastasis) and/or M factor (distant metastasis) according to the staging system of the LCSGJ.[3)]

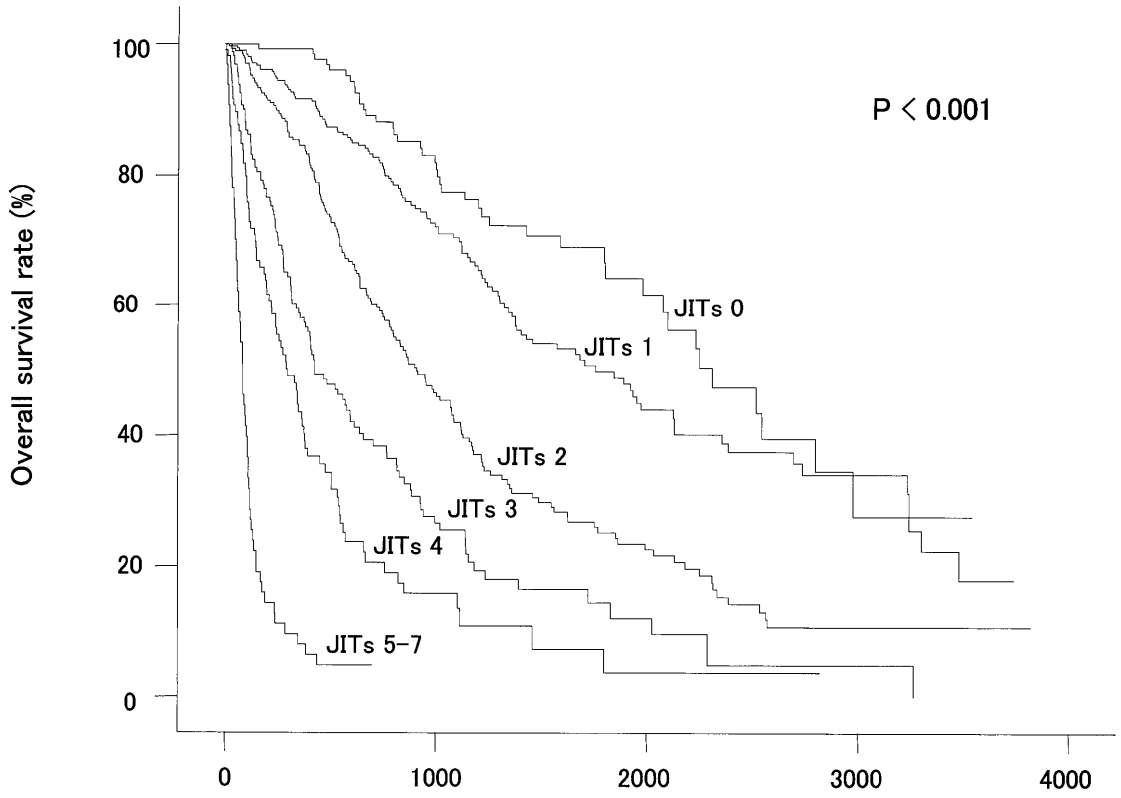

Figure 3. Kaplan-Meier estimated survival curves by the JITs score.

The median survival periods were 2,310 days in JITs 0, 1,758 days in JITs 1, 910 days in JITs 2, 426 days in JITs 3, 298 days in JITs 4, and 85 days in JITs 5-7.

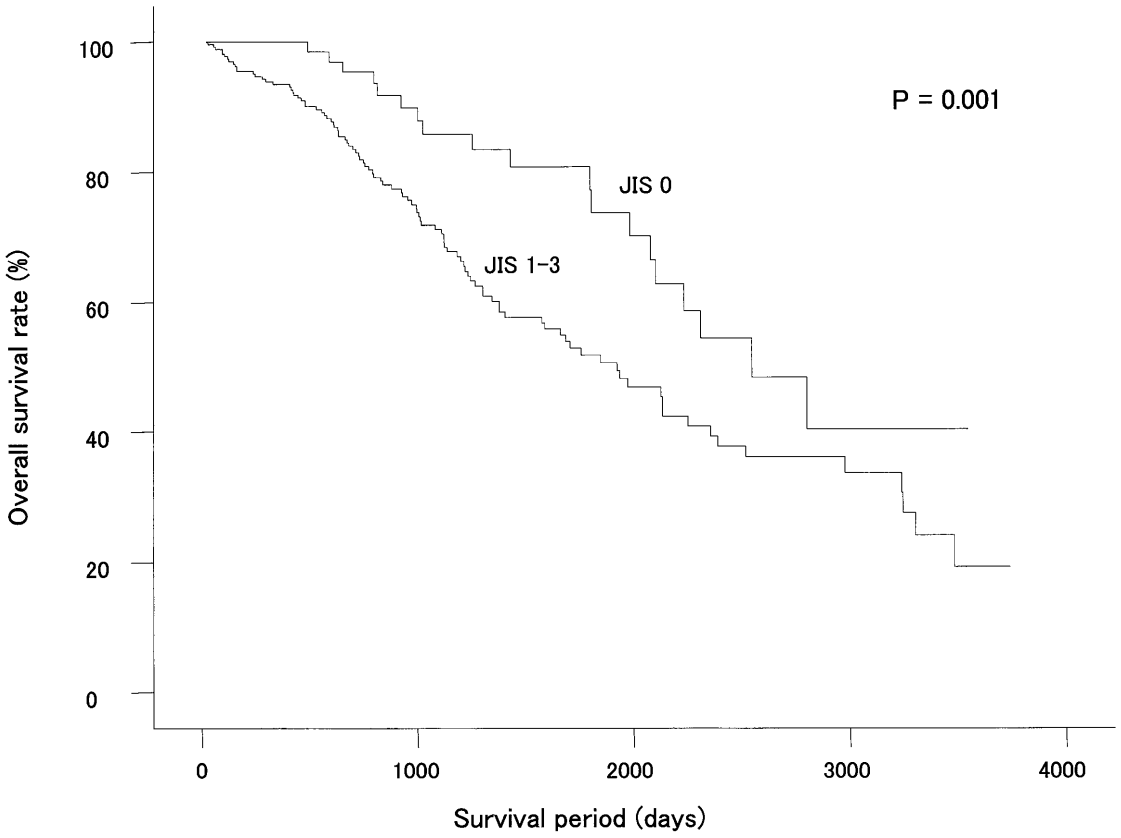

Figure 4. Kaplan-Meier estimated survival curves for patients with the CLIP 0 score, which were further categorized by the JIS score.

The median survival periods were 2,310 days in the JIS 0 group (n = 141) and 1,847 days in the JIS 1-3 group (n = 221).

DISCUSSION

The JITs score was constructed by compensating for the factors which have insufficient information in the current scoring systems. Furthermore, the goodness-of-fit of the survival models was evaluated by combining the JIS score, CLIP score, and other prognostic factors. Among the JIS, CLIP, and JITs scores, the CLIP score had the smallest AIC, namely, the CLIP score has the highest predictive power among three scores. However, it is likely that the CLIP score still has some drawbacks in practically predicting the survival of patients with HCC, based on the following reasons.

First of all, it can be difficult to discriminate patients at early stages by using the CLIP score because of the criteria of tumor morphology in the CLIP score. Patients with a fairly large tumor occupying nearly 50% of the liver volume are classified into the earliest tumor stage in CLIP, which is stage III according to the staging system based on the LCSGJ. In fact, it was clearly shown in this study that the CLIP 0 group included four different JIS groups with significant survival differences between the JIS 0 group and the JIS 1-3 groups. It may not be ideal that a small HCC belongs to the same tumor morphology group as a tumor occupying nearly 50% of the total liver volume. This assumption suggests that the tumor diameter was selected as an independent and significant factor besides the JIS and CLIP scores in the first Cox analysis of this study. Therefore, the tumor diameter and metastasis (N factor and/or M factor) were employed to distinguish different tumor morphology groups instead of the criteria used in the CLIP score.

Furthermore, although vascular involvement is one of prominent factors indicating tumor invasiveness in HCC, it is still difficult to accurately detect vascular

invasion even using the recently available higher resolution imaging modalities. Portal vein thrombosis is generally detected only at the stage of involvement of the main branches. In fact, the tumor was extended at least to the second branch of the portal vein in all of the cases that were judged to be positive for portal vein thrombosis in this study. It therefore does not seem practical to include vascular involvement as a factor of tumor morphology, especially in order to stratify patients with earlier stages. Fortunately, however, it has been reported that the frequency of microscopic vascular involvement is significantly different according to the size of HCC; HCC larger than 2 cm show a significantly higher frequency of microscopic vascular involvement than do those of 2 cm or less.[26] Consistent with this notion, a surgical resection has been reported to lead to more favourable results than percutaneous ablation therapy in cases with HCCs larger than 2 cm.[26] Therefore, the factor of tumor size appears to not only affect the tumor volume itself but also impacts the microscopic vessel invasion when the tumor diameter is employed as the factor of tumor morphology, which divides tumors into two groups by size: namely, larger than 2 cm and 2 cm or less.

One of the most important functions of a prognostic staging system is to provide appropriate treatment guidance. If the hepatic functional reserve is sufficient, a surgical resection results in the longest disease-free survival. Among other therapeutic options, puncture-based therapies such as radiofrequency ablation therapy (RFA) appear to be as safe and effective as a resection. The major drawback of RFA is the size limitation, which can be completed by an acceptable number of treatment sessions.[27,28] Although sequential or multiple sessions make it possible to ablate a larger area, it becomes difficult to achieve consistent results as the number of sessions is increased. An accurate 3-dimensional construction of an ablation area is very difficult in plural sessions. Therefore, the tumor size generally recommended for RFA is the size that can be ablated by a single session, which is approximately 2 cm. From these therapeutic points of view, it is also advantageous to employ the tumor diameter as a factor of tumor morphology.

Secondly, AFP was employed in the JITs score not only because the CLIP score includes AFP in its factors but also because it is well documented that tumor markers are independent prognostic markers in HCC by representing the biological behavior. Several studies have suggested that other tumor markers, such as des-γ-carboxy prothrombin or the degree of fucosylation of AFP, are better indicators of the tumor characteristics than AFP is.[29,30] Unfortunately, however, the efficacy of tumor markers other than AFP was not generally recognized when the patients enrolled in this study visited hospitals more than a decade ago. In addition, the measurements of plural tumor markers at the same time are not covered by the medical insurance system in Japan. As a result, tumor markers except for AFP were not evaluated in many cases of this study population. Although it is possible that other tumor markers have higher predictive values than AFP, it is desirable for a valuable prognostic scoring system to integrate three categories, hepatic functional reserve (Child-Pugh grade), tumor extension (morphology), and biological behavior, which is absent in the JIS system. Because the new scoring system presented herein integrates all of the three categories and differentiates the tumor morphology based on the staging system based on LCSGJ, this system was named the Japan Integrated Triform system (JITs) score.

The JITs score could therefore help to differentiate patients in earlier stages into several groups with significantly different prognoses and showed a good-fit AIC-value among the evaluated systems. Because all of the factors necessary to use this system are generally evaluated in the course of management of HCC, it is easy to introduce JITs in a clinical setting. Recent progress in new technologies has provided diagnostic and therapeutic modalities with higher resolution and local control capability, respectively. In this era, a scoring system with higher discrimination ability in the earlier stages is necessary. JITs may hopefully be useful for physicians in deciding appropriate management options both by both selecting adequate therapeutic strategies and by reducing excessive treatments.

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