Original Article

Prognostic Model for Hepatocellular Carcinoma with Time-Dependent Factors

Kenji Kuwaki[a]*, Kazuhiro Nouso[a,b], Yoshiyuki Kobayashi[a], Shinichiro Nakamura[a], Yoichi M. Ito[c], Shouta Iwadou[a], Hiroaki Hagihara[a], Tetsuya Yasunaka[a], Junichi Toshimori[a], Hirokazu Miyatake[a], Kenji Miyoshi[a], Hideki Onishi[a], Yasuhiro Miyake[a,b], Bon Shoji[a], Akinobu Takaki[a], Hidenori Shiraha[a], Yoshiaki Iwasaki[a], Haruhiko Kobashi[a], and Kazuhide Yamamoto[a]

Departments of [a]Gastroenterology and Hepatology, [b]Molecular Hepatology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700–8558, Japan, and [c]Hokkaido Organization for Translational Research, Hokkaido University Graduate School of Medicine, Sapporo 060–8638, Japan

The purpose of this study was to build a prognostic model of hepatocellular carcinoma (HCC) using time-dependent covariates to re-evaluate the prognosis at any stage of the disease. The subjects were consecutive HCC patients who were treated at our institute between 1995 and 2007. We constructed time-fixed and time-dependent prognostic models with a training group (n = 336) and compared the prognostic abilities between conventional Cancer of the Liver Italian Program (CLIP) scores, Japan Integrated Staging (JIS) scores, an Okuda classification, and our prognostic models in the testing group (n = 227) with the c-index. The time-dependent prognostic model consisted of main tumor size, tumor number, portal vein invasion, distant metastasis, alpha-fetoprotein, des-gamma-carboxy prothrombin (DCP), bilirubin, and albumin and the weighted scores were set for each factor depending on the hazard ratio for the prognosis. The prognostic index was determined by summing the scores. The c-index values for the CLIP scores, JIS scores, Okuda classification, and our time-dependent model were 0.741, 0.727, 0.609, and 0.870, respectively. These results indicate that our time-dependent model can estimate the prognosis of HCC more precisely than traditional time-fixed models and can be used to re-predict the prognosis of HCC.

Key words: hepatocellular carcinoma, humans, prognosis, proportional hazards models, time factors

H epatocellular carcinoma (HCC) is the fifth most common cancer and is one of the leading causes of cancer death in the world [1]. In Japan, approximately 35,000 people die of HCC every year, and 90% of patients suffer from persistent infection of hepatitis B virus (HBV) or hepatitis C virus (HCV) [2].

The prognosis is affected by both the tumor sever-ity, as indicated by factors such as size and the number or levels of alpha-fetoproteins (AFP), and the degree of pre-existing liver damage, as indicated by serum albumin or serum bilirubin levels [3]. Many prognostic models of HCC using Cox regression models have been described. As for unification scores to estimate prognosis, the Child-Pugh stage [4], the Cancer of the Liver Italian Program (CLIP) score [5], the Japan Integrated Staging (JIS) score [6], and the Barcelona Clinic and Liver Cancer (BCLC) classification [7] have been reported. However, most of these prognostic models are based on tumor-related

factors and background factors at the initial treatment of HCC.

Recently, time-dependent analyses using repetitively measured prognostic variables have been reported and their usefulness has been suggested [8–11]. Boberg et al. have reported that the prediction of prognosis improves when the change in a covariate over time is included in the prognostic index of primary sclerosing cholangitis [8]. Murtaugh et al. have developed an updated model for primary biliary cirrhosis that can be used to predict short-term survival at any time in the course of the disease [11].

HCC frequently recurs even after curative treatments such as hepatectomy or radiofrequency ablation (RFA). Stage and the liver residual function at recurrence of tumor may often vary in patients whose prognoses have been predicted to be the same by conventional methods. Therefore, re-evaluation of prognosis after initial treatment is a rational way of achieving a better prediction of survival.

The purpose of this study was to build a prognostic model of HCC using time-dependent covariates, which we can then use to re-evaluate the prognosis at any stage of the disease.

Materials and Methods

Patients.   We examined 563 consecutive patients who were newly diagnosed as having HCC and received initial treatment of HCC at Okayama University Hospital from January, 1995 to June, 2007. We divided the patients into a training group (n = 336) and a testing group (n = 227). Patients for whom the last digit of their identification data (ID) number was 0–5 were assigned to the training group, regardless of condition, and those for whom the last digit was 6–9 was assigned to the testing group. We built prognostic models with the training group and validated them with the testing group. The patients who were alive at the end of June, 2007 were no longer followed in the study and were assumed considered to be "censored". The average observation period was 3.0 years. Informed consent was obtained from patients for the use of their clinical data. The study protocol conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki, and was approved by the ethical committee of the institute.

Diagnosis.   HCC was diagnosed by abdominal ultrasonography, abdominal computerized tomography (CT), magnetic resonance imaging (MRI), abdominal angiography or tumor biopsy. The diagnostic criteria for HCC via imaging were based on previous reports of hyperattenuation at the arterial phase, hypoattenuation at the portal phase in dynamic CT or MRI, and tumor staining on angiography [12]. The patients with hepatic masses who did not satisfy the above criteria underwent ultrasound-guided fine-needle biopsy with histologically confirmed HCC. We classified HCC morphologically according to the criteria outlined by the Liver Cancer Study Group of Japan [13].

Treatments.   The selection of therapies was performed in accordance with the evidence-based clinical practice guidelines for HCC in Japan [14].

For the initial treatment of HCC, 150 (27%), 129 (23%), and 73 patients (13%) received RFA, hepatectomy, and percutaneous ethanol injection therapy (PEIT), respectively (Table 1). One hundred and thirty-one people (23%) underwent transcatheter arterial chemoembolization (TACE)/transcatheter arterial infusion (TAI) without local ablation therapies. TACE/TAI was performed before PEIT and RFA in 36% (26/73) and 66% (99/150) of the patients, respectively.

Follow-up.   We performed blood tests at every outpatient visit (at least once every 3 months). The examined factors were as follows: bilirubin, serum albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum creatinine, platelet count, prothrombin time and tumor markers (AFP and des-gamma-carboxy prothrombin, DCP). Ultrasound, dynamic CT, or MRI were also performed every 3–4 months. When HCC recurred, re-treatment was performed depending on patient conditions, tumor stage and background liver function, according to the same clinical indications as for the first intervention.

Time-fixed model construction.   Survival duration was calculated from the date of initial treatment to the date of liver-related death. Examined covariates were as follows: nine background factors (presence of ascites, age, bilirubin, albumin, AST, ALT, creatinine, platelet count, and prothrombin time) and six tumor-related factors (main tumor size, tumor number, presence of portal vein invasion or distant metastasis, AFP, and DCP). We conducted univariate survival analysis using a Cox proportional

Table 1   Baseline characteristics of 563 patients with HCC

	Total	Training Group (n = 336)	Testing Group (n = 227)	p-value
Male (%)	407 (72%)	241 (72%)	166 (73%)	0.72
Etiology (B/C/B+C/other)	82/413/14/54	49/245/9/33	33/168/5/21	1.00
Child-Pugh grade (A/B/C)	395/142/26	240/82/14	155/60/12	0.68
Age at treatment (years)[†]	65 (23–85)	65 (23–83)	65 (28–85)	0.73
Tumor number (single)	306 (54%)	183 (54%)	123 (54%)	0.95
Main tumor size (mm)[†]	25 (8–160)	25 (9–160)	25 (8–160)	0.91
Tumor stage (I / II / III / IV)	145/185/167/65	91/107/98/40	54/78/69/25	0.80
AFP (ng/ml)[†]	23 (0.5–455,560)	22 (0.5–455,560)	25 (1.4–116,870)	0.76
DCP (mAU/ml)[†]	23 (0–455,560)	44 (0–410,500)	56 (0–317,000)	0.46
Number of hospitalization[†]	1 (1–12)	2 (1–12)	1 (1–8)	0.44
Number of liver-related death	218 (38.8%)	123 (36.6%)	95 (41.9%)	0.15
Histologic differentiation				
Well differentiated	95 (17%)	55 (16%)	40 (18%)	
Moderately differentiated	97 (17%)	57 (17%)	40 (18%)	
Poorly differentiated	15 (3%)	9 (3%)	6 (3%)	0.97
Not examined	356 (63%)	215 (64%)	141 (61%)	
Treatment of HCC				
RFA	150 (27%)	94 (28%)	56 (25%)	
MCT	13 (2%)	8 (2%)	5 (2%)	
PEIT	73 (13%)	49 (15%)	24 (11%)	
Liver resection	129 (23%)	72 (21%)	57 (25%)	
TACE/TAI	131 (23%)	75 (22%)	56 (25%)	0.80
Chemotherapy	49 (8%)	28 (8%)	21 (9%)	
Liver transplantation	8 (1%)	4 (1%)	4 (2%)	
Others	10 (2%)	6 (2%)	4 (2%)	

[†]Data are shown as median (range). AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin; RFA, radiofrequency ablation; MCT, microwave coagulation therapy; PEIT, percutaneous ethanol injection therapy; TACE, transcatheter arterial chemoembolization; TAI, transcatheter arterial infusion.

hazards model [15] with these covariates at the initial treatment. For continuous variables or category variables with 3 values or more, we prepared multiple cut-off values for each factor and adopted the one with the highest likelihood.

Factors exhibiting significant values in univariate analysis were selected to build the model and were used for time-fixed multivariate Cox regression analysis. We built the model consisting of 8 factors where the goodness of fit of the model was optimized with the best option of the PHREG procedure of SAS 9.1.3. We assumed the value of the logarithm hazard corresponding to each factor rounded to 0.5 units as the "weighted score (WS)" and summed the score. The integer part of the total score was defined as the prognostic index (PI). When the score was more than 5, we considered it to be PI 5.

Time-dependent model construction.   We adopted the method of Murtaugh *et al.* to incorporate the change in the covariate over time in the model. In

this way, 721 survival data points were generated for the training group and 465 for the testing group. Missing values were estimated from the previously recorded value of the variable [16]. The same 9 background factors and 6 tumor-related factors that we adopted in the time-fixed model construction were examined.

The cut-off values of each covariate were determined and used to build a model by the same method as that for the time-fixed model construction.

Validation.   To evaluate the validity of the time-fixed and time-dependent models that we built, we applied these models to the testing group. We examined conformity between observed prognosis and PI of all patients in the testing group and calculated the c-index [17]. The c-index is defined as the proportion of all usable patient pairs in which the predictions and outcome are concordant.

The c-indexes and the 95% confidence intervals of CLIP scores, JIS scores, and Okuda classification

[18] were calculated in the testing group, and the precision of the prognostic values was compared with that obtained with our models. SAS 9.1.3 and JMP 7.0.2 (SAS Institute) were used for all analyses.

Results

Patient background.   The background factors of 563 patients are shown in Table 1. The average age was 64.4 years old. Four hundred and thirteen patients (73%) were positive for hepatitis C virus antibody, and 82 patients (15%) were positive for hepatitis B virus antigen. No difference in values was observed between the training and testing groups. The 1-year, 3-year, and 5-year survival rates were 88%, 67%, and 52%, respectively.

Time-fixed model.   Based on the univariate analysis, the presence of ascites, bilirubin, albumin, AST, ALT, prothrombin time, main tumor size, tumor number, portal vein invasion, distant metastasis, AFP, and DCP were closely related to survival. The 8 selected factors and WS values were as follows: main tumor size (WS = 1), portal vein invasion (WS = 1.5), tumor number (WS = 1), distant metastasis (WS = 2), AFP (WS = 0.5), bilirubin (WS = 0.5), albumin (WS = 0.5), and prothrombin time (WS = 1) (Table 2). The 1-year survival rates in PI 0, 1, 2, 3, 4, and 5 of the training group were 100%, 97%, 96%, 75%, 20%, and 10%, and the 5-year survival rates were 69%, 70%, 43%, 19%, 0%, and 0%, respectively. The survival curves for each PI are shown in Fig. 1. With the exception of that between PI0 and PI1, statistically significant differences were found between each survival period.

Time-dependent model.   Based on the univariate analysis, the factors related to survival were the presence of ascites, bilirubin, albumin, AST, prothrombin time, main tumor size, tumor number, portal vein invasion, distant metastasis, AFP, and DCP. From the results of the multivariable analysis, a prognosis model consisting of main tumor size (WS = 0.5), portal vein invasion (WS = 0.5), tumor number (WS = 1.5), distant metastasis (WS = 1.5), AFP (WS = 0.5), DCP (WS = 1), bilirubin (WS = 0.5), and albumin (WS = 0.5) was made (Table 3). The 1-year survival rates in PI 0, 1, 2, 3, 4, and 5 of the training group were 99%, 92%, 76%, 39%, 15%, and 0%, and the 5-year survival rates were 84%, 75%, 31%, 0%, 10%, and 0%, respectively. The survival curves for each PI are shown in Fig. 2. Between all pairs of 2 adjacent prognostic indices, statistically significant differences of survival were observed. Median survival times (MST) and 95% confidence intervals of survival duration of PI 1, 2, 3, 4, and 5 were 7.9 years (5.0–18.0 years), 2.5 years (1.6–4.9 years), 0.7 years (0.4–1.4 years), 0.4 years (0.1–0.6 year), and 0.2 years (0.1–0.4 year), respectively.

Model fitness.   We applied conventional CLIP scores, JIS scores, Okuda classifications, and our prognostic models to the testing group, and compared the goodness of fit of the models in terms of the c-index. Regarding our time-fixed and time-dependent model, CLIP scores, JIS scores, the Okuda classification, and survival curves in the testing group are shown in Fig. 3(A)–(E). The c-indexes and the 95% confidence intervals of our time-fixed and time-dependent model, CLIP scores, JIS scores, and Okuda

Table 2   Time-fixed model

| Factor	β	SE	RR	95%CI	p-value	Weighted score
Main tumor size (30 mm <)	0.79	0.24	2.20	1.39–3.50	<0.001	1
Portal vein invasion (vp2<)	1.65	0.33	5.19	2.75–9.80	<0.001	1.5
Tumor number (3<)	1.24	0.23	3.45	2.18–5.46	<0.001	1
Distant metastasis (present)	1.78	0.43	5.92	2.55–13.71	<0.001	2
AFP (400 ng/ml<)	0.53	0.27	1.70	1.01–2.86	0.045	0.5
Serum bilirubin (1.0 mg/dl<)	0.12	0.22	1.13	0.73–1.74	0.587	0.5 [†]
Serum albumin (<3.5 g/dl)	0.61	0.22	1.84	1.19–2.83	0.006	0.5
Prothrombin time (<80%)	0.86	0.23	2.34	1.51–3.71	<0.001	1

[†] Because the logarithm hazard of the serum bilirubin was less than 0.25, we defined 0.5, which was the minimum of the score, as the weighted score of serum bilirubin.
β, parameter of each factor; SE, standard error of β; RR, risk ratio; 95%CI, 95% confidence interval of RR.
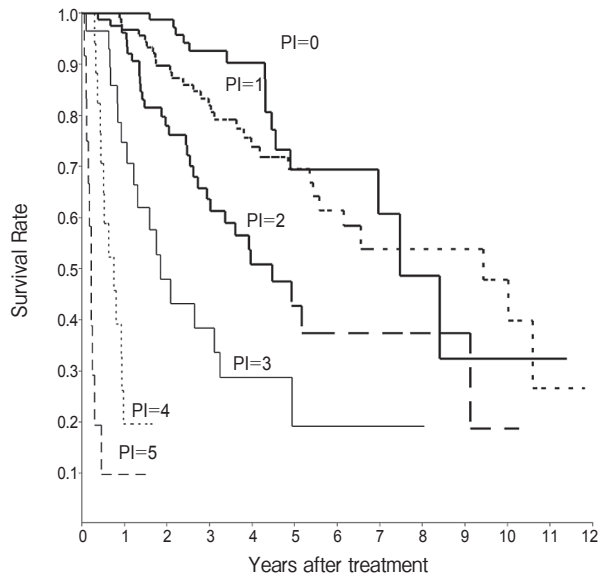
Fig. 1   Survival rate in each PI of the time-fixed model for the training group. The 1-year survival rates in PI 0, 1, 2, 3, 4, and 5 of the training group were 100%, 97%, 96%, 75%, 20%, and 10%, and the 5-year survival rates were 69%, 70%, 43%, 19%, 0%, and 0%, respectively. With the exception of that between PI0 and PI1, statistically significant differences were found between each survival period.
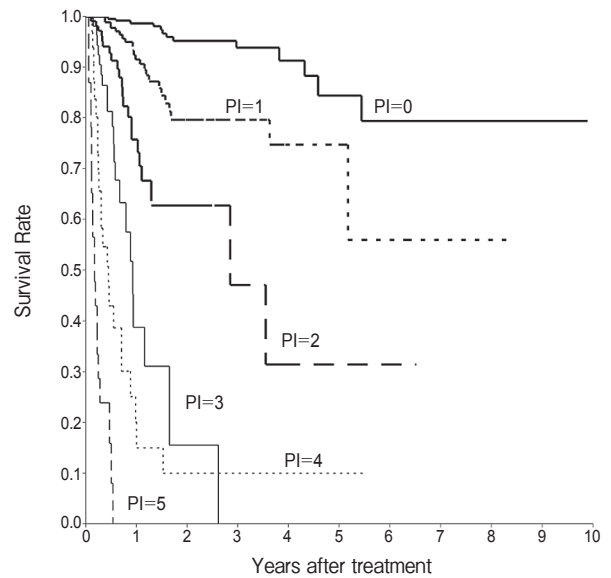
Fig. 2   Survival rates in each PI of the time-dependent model for the training group. The 1-year survival rates in PI 0, 1, 2, 3, 4, and 5 of the training group were 99%, 92%, 76%, 39%, 15%, and 0%, and the 5-year survival rates were 84%, 75%, 31%, 0%, 10%, and 0%, respectively. Between all pairs of two adjacent prognostic indices, statistically significant differences of survival were observed.

Table 3   Time-dependent model

| Factor	β	SE	RR	95%CI	p-value	Weighted score
Main tumor size (30 mm <)	0.48	0.24	1.62	1.01–2.59	0.045	0.5
Portal vein invasion (vp1 <)	0.46	0.26	1.58	0.95–2.65	0.080	0.5
Tumor number (3 <)	1.61	0.23	5.00	3.21–7.78	<0.001	1.5
Distant metastasis (present)	1.39	0.28	4.02	2.35–6.89	<0.001	1.5
AFP (1,000 ng/ml <)	0.63	0.23	1.88	1.20–2.95	0.006	0.5
DCP (1,000 ng/ml <)	0.94	0.25	2.56	1.57–4.16	<0.001	1
Serum bilirubin (1.0 mg/dl <)	0.70	0.22	2.00	1.31–3.06	0.001	0.5
Serum albumin (<3.5 g/dl)	0.67	0.24	1.96	1.24–3.11	0.004	0.5

β, parameter of each factor; SE, standard error of β; RR, risk ratio; 95%CI, 95% confidence interval of RR.

classification are shown in Table 4. The c-index of our time-dependent model was higher than that of all of the time-fixed prognostic models, indicating that the prognostic estimation of the time-dependent model was the best.
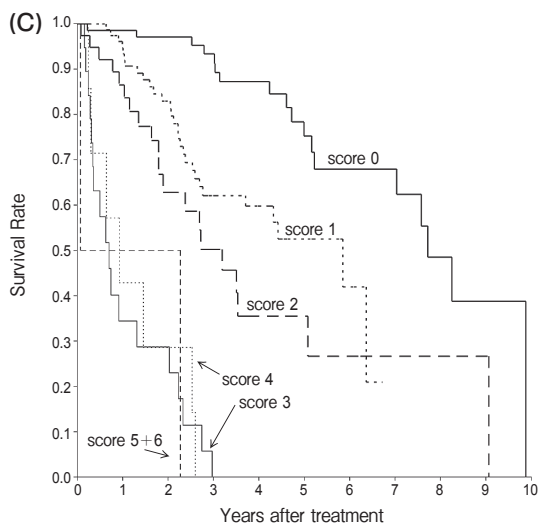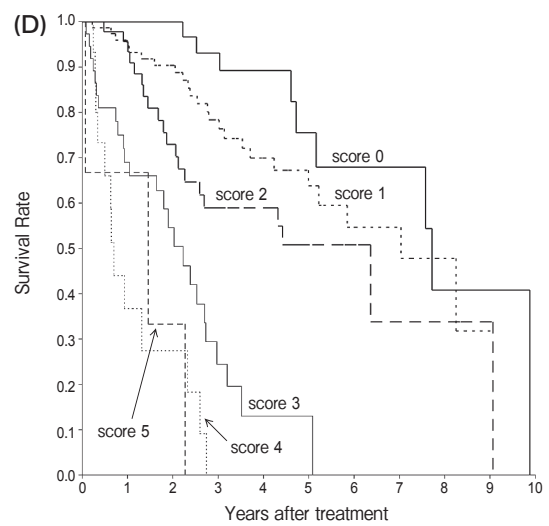
(A)
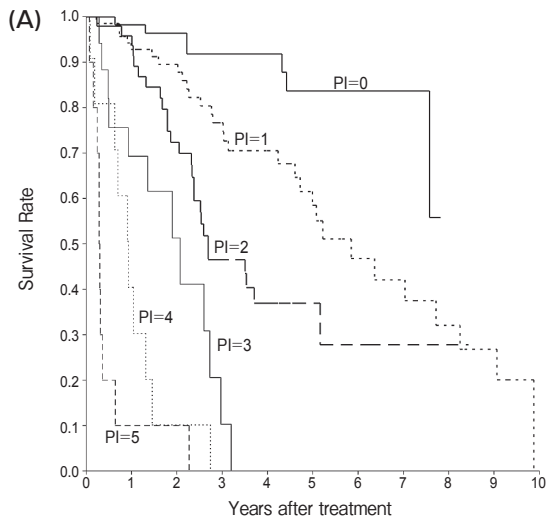
PI	Patients at risk					
	0	2	4	6	8	10
0	60	44	26	10	0	
1	72	51	27	11	6	0
2	40	29	8	2	1	0
3	19	5	0			
4	11	1	0			
5	10	1	0			

(B)
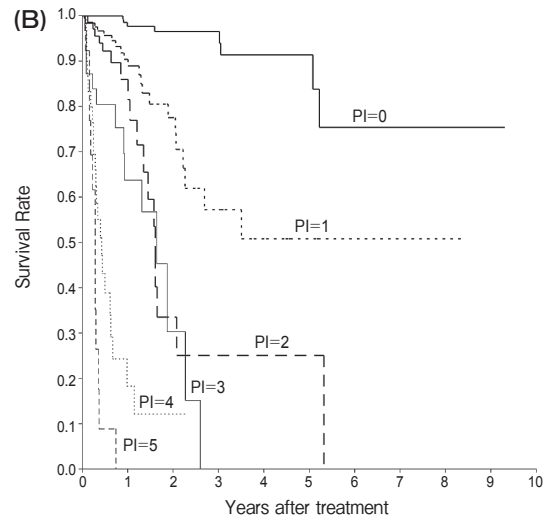
PI	Patients at risk					
	0	2	4	6	8	10
0	184	71	22	6	3	0
1	127	23	7	1	1	0
2	76	5	2	0		
3	31	2	0			
4	30	1	0			
5	13	0				

(C)

PI	Patients at risk					
	0	2	4	6	8	10
0	71	57	34	16	5	0
1	82	51	21	11	6	0
2	40	15	6	3	2	0
3	20	5	0			
4	8	2	0			
5+6	2	0				

(D)

PI	Patients at risk					
	0	2	4	6	8	10
0	38	31	16	9	2	0
1	79	57	28	10	3	0
2	49	27	17	5	2	0
3	38	13	1	0		
4	17	3	0			
5	3	1	0			

Fig. 3   Survival rate in each prognostic score of the time-fixed model and our time-dependent model for the testing group. Our time-fixed model (**A**), our time-dependent model (**B**), CLIP scores (**C**), JIS scores (**D**), and Okuda classification (**E**) are shown.
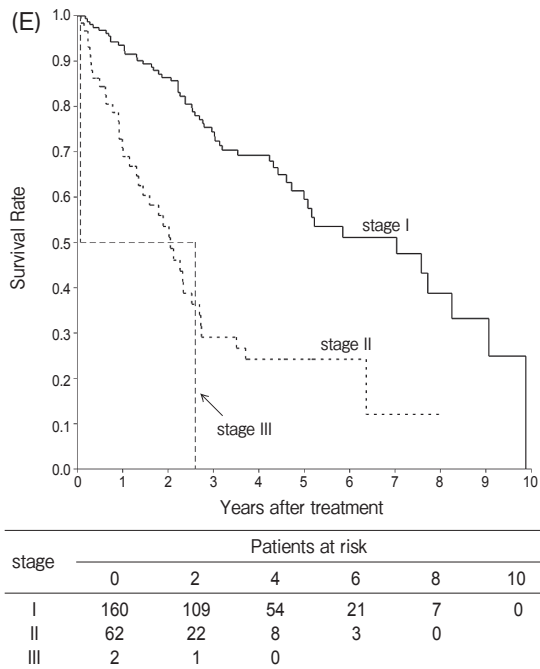
Fig. 3 Survival rate in each prognostic score of the time-fixed model and our time-dependent model for the testing group. Okuda classification (**E**) are shown.

Table 4   C-index of models

	c-index (95%CI)	
	Time-fixed	Time-dependent
Our model	0.775 (0.477–0.990)	0.870 (0.603–1.000)
CLIP	0.741 (0.432–0.975)	—
JIS	0.727 (0.418–0.966)	—
Okuda	0.609 (0.226–0.946)	—

CLIP, Cancer of the Liver Italian Program; JIS, Japan Integrated Staging Score; Okuda, Okuda staging system; 95%CI, 95% confidence interval.

Discussion

The utilization of time-dependent covariates has been shown to help in predicting the prognosis of several diseases. We used time-dependent covariates for constructing a prognostic model of HCC and demonstrated its superiority in this study. The c-indexes of our time-dependent model and the time-fixed model were higher than those of pre-existing time-fixed scores such as CLIP scores, JIS scores, and Okuda stage.

One of the characteristics of our time-dependent model is that the weight of tumor-related factors is higher than that in other models, including our time-fixed model. Among the eight factors constituting the time-dependent model, 6 are tumor-related. Of the 6.5 total points for the total weighted score, 5.5 are for tumor-related factors.

The weights of tumor-related factors in 3 conventional prognostic models were different. The tumor-related factors in the CLIP scoring system are tumor morphology, AFP and portal vein thrombus, so the weight is 4 of 6. There is only one tumor-related factor, tumor size, in the Okuda staging system out of four covariates. The JIS scoring system consists of 2 equally weighted factors, which are the TNM classification and Child-Pugh grade, meaning that half of the score is from tumor-related factors. Among the 3 conventional prognostic models, the CLIP score was superior to the 2 other models in terms of its ability to estimate prognosis. Our time-fixed model consists of 5 tumor-related factors out of 8 total factors, and the c-index is very similar to that of the CLIP score.

These results indicate that a higher weight of tumor-related factors in prognostic models may increase the ability to predict prognosis in this study population and might be one of the reasons for the striking superiority of our time-dependent model.

Liao *et al.* [10] investigated 108 patients with HCC smaller than 5 cm and built a time-dependent prognostic model with a time-dependent Cox regression model. The method used was very similar to that used in the present study and also suggested the superiority of the adoption of time-dependent factors for predicting prognosis. The prognostic model in this previous study consists of 6 factors: AFP, serum albumin, AST, serum bilirubin, alkaline phosphatase (ALP), and prothrombin time. They selected only AFP as a tumor-related factor. They considered other tumor-related factors such as tumor number and diameter only as baseline parameters and did not examine change over time. One of the possible explanations for the difference in covariates between their study and our model is the difference in the study population. They dealt with only HCC treated with PEIT, meaning that they seemed to treat HCC curatively and that the effects of tumor factors such as tumor size decreased and were excluded from the

model. In contrast, the patients in our study were not limited to those with small HCC.

The superiority of the time-dependent model for prediction of the prognosis of HCC was clearly demonstrated; however, there were some limitations to this study. There are several other factors associated with prognosis of HCC such as lens culinaris agglutinin-reactive fraction of alpha-fetoprotein (AFP-L3). The adoption of these factors may result in the construction of a better model.

The hepatitis C virus is a maximal pathogenesis factor of HCC, and the most of patients of this study are transmitted to the virus. The contribution of mutations in the hepatitis C virus core gene has been reported to be a virus side factor associated with liver carcinogenesis [19]. Also, single nucleotide polymorphisms (SNPs) of IL28B have been reported as a host factor involved in the treatment of chronic hepatitis C [20]. The adoption of genetic information from the virus and the host may result in the construction of a more correct model in the future.

Because this was a study based at a single institution, it has not been shown that we can extrapolate our results to other institutions or countries. The skill in RFA and selective TACE differ, and patient backgrounds also differ. The index might be too precise to apply to all cases. But there is also merit in the study being limited to a single institution. Because blood tests and imaging studies were performed according to the same surveillance algorithm, the lead-time bias that influenced the model was minimized. As for all the prognostic factors, minor modifications depending on individual clinical circumstances are advisable for obtaining better predictive ability.

The original point in this study is that we used time-dependent covariates in a model based on the premise that prognosis changes drastically with the state at recurrence. We can predict prognosis even if HCC recurs and tumor stage and liver residual function change using this time-dependent model. The potential to estimate the prognosis of HCC is better than that of the traditional time-fixed models. More studies to verify its effectiveness for different populations are needed to confirm that the index can be widely used.

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