

# Proposal of a New Preoperative Prognostic Model for Solitary Hepatocellular Carcinoma Incorporating $^{18}\text{F}$ -FDG-PET Imaging with the ALBI Grade

Tomoaki Yoh, MD<sup>1</sup>, Satoru Seo, MD, PhD<sup>1</sup>, Satoshi Ogiso, MD, PhD<sup>1</sup>, Takayuki Kawai, MD, PhD<sup>1</sup>, Yukihiro Okuda, MD, PhD<sup>1</sup>, Takamichi Ishii, MD, PhD<sup>1</sup>, Kojiro Taura, MD, PhD<sup>1</sup>, Tatsuya Higashi, MD, PhD<sup>2</sup>, Yuji Nakamoto, MD, PhD<sup>3</sup>, Etsuro Hatano, MD, PhD<sup>4</sup>, Toshimi Kaido, MD, PhD<sup>1</sup>, and Shinji Uemoto, MD, PhD<sup>1</sup>

<sup>1</sup>Department of Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan; <sup>2</sup>National Institute of Radiological Sciences, National Institutes of Quantum and Radiological Science and Technology, Chiba, Japan; <sup>3</sup>Department of Diagnostic Imaging and Nuclear Medicine, Kyoto University, Kyoto, Japan; <sup>4</sup>Department of Surgery, Hyogo College of Medicine, Nishinomiya, Japan

## ABSTRACT

**Background.** Existing prognostic systems were not developed using only objective variables available preoperatively, and therefore do not provide ideal prognostication for patients undergoing hepatectomy for hepatocellular carcinoma (HCC). We aimed to develop a preoperative prognostic model using objective variables involving two parameters:  $^{18}\text{F}$ -fluorodeoxyglucose-positron emission tomography ( $^{18}\text{F}$ -FDG-PET) and the albumin-bilirubin (ALBI) grade.

**Methods.** This study included 207 consecutive patients with solitary HCC who underwent  $^{18}\text{F}$ -FDG-PET prior to hepatectomy. The tumor to non-tumor maximum standardized uptake value ratio (TNR) was used as an  $^{18}\text{F}$ -FDG PET imaging parameter.

**Results.** The 5-year overall survival (OS) and disease-free survival (DFS) rates were 58.6% and 28.8%, respectively. Multivariate analysis of OS identified TNR  $\geq 2$  (hazard ratio [HR] 1.743, 95% confidence interval [CI]

1.114–2.648,  $p = 0.016$ ) and ALBI grade 2 (HR 1.966, 95% CI 1.349–2.884,  $p < 0.001$ ) as the only significant prognostic factors; tumor diameter and tumor markers were not significant. Patients were divided into low- (TNR  $< 2$  and ALBI grade 1), intermediate- (TNR  $< 2$  and ALBI grade 2, or TNR  $\geq 2$  and ALBI grade 1), and high-risk (TNR  $\geq 2$  and ALBI grade 2) groups, which differed significantly in terms of survival (5-year OS: 75.7, 49.6, and 27.3%, respectively,  $p < 0.001$ ; 5-year DFS: 37.0, 24.9, and 13.6%, respectively,  $p < 0.001$ ). Compared with other staging systems, our model had the best discriminatory ability (corrected Akaike information criteria 1054.8,  $p < 0.001$ ) and homogeneity (likelihood ratio Chi square value 27.6,  $p < 0.001$ ).

**Conclusion.** A preoperative prognostic model incorporating  $^{18}\text{F}$ -FDG-PET imaging with the ALBI grade may be useful for estimating the prognosis of selected patients with solitary HCC.

Several factors related to tumor characteristics, underlying liver disease, and estimated hepatic reserves are comprehensively used to determine the prognosis of and therapeutic strategies for patients with hepatocellular carcinoma (HCC).<sup>1</sup> Of the various treatment options available, hepatectomy offers long-term survival and potential cure; patients with solitary HCC with good hepatic reserve are widely considered the best candidates for hepatectomy.<sup>2,3</sup>

In recent years, multidisciplinary approaches for the surgical management of patients with HCC have increasingly been adopted.<sup>4–7</sup> Preoperative prognostic information may play a pivotal role in achieving long-term survival. To

This paper has not been presented at any international meetings.

**Electronic supplementary material** The online version of this article (<https://doi.org/10.1245/s10434-017-6262-z>) contains supplementary material, which is available to authorized users.

© Society of Surgical Oncology 2017

First Received: 10 July 2017;

Published Online: 22 November 2017

S. Seo, MD, PhD

e-mail: [rutosa@kuhp.kyoto-u.ac.jp](mailto:rutosa@kuhp.kyoto-u.ac.jp)

date, a number of HCC staging systems integrating both tumor characteristics and hepatic reserve estimation have been developed;<sup>8–10</sup> however, the reliability and objectivity of various staging systems are compromised by the subjective nature of certain variables (e.g. radiographic findings or the Child–Pugh grade). Moreover, for patients who have undergone hepatectomy, these staging systems are difficult to interpret, therefore a refined prognostic model is needed.

Recently, the albumin-bilirubin (ALBI) grade was established by Johnson et al. as a novel parameter for estimating hepatic reserves;<sup>11</sup> it uses two commonly measured variables (serum bilirubin and albumin) and allows reliable prognostication for patients who have undergone hepatectomy. Moreover, it is more objective than the Child–Pugh grade.<sup>12</sup> Therefore, the ALBI grade is expected to contribute to the development of new preoperative prognostic models for patients undergoing hepatectomy for HCC.

As a candidate marker that can be incorporated with the ALBI grade in a preoperative prognostic model, we focused on <sup>18</sup>F-fluorodeoxyglucose-positron emission tomography (<sup>18</sup>F-FDG-PET)<sup>13–15</sup> imaging, which visualizes tumor glucose metabolism. The malignant potential of primary tumors can be determined and quantified by <sup>18</sup>F-FDG uptake. We have previously reported that high <sup>18</sup>F-FDG uptake correlates with the aggressiveness of primary tumors,<sup>13–15</sup> suggesting the feasibility of <sup>18</sup>F-FDG-PET as a prognostic indicator.<sup>14</sup>

The purpose of this study was to develop a preoperative prognostic model using clinical parameters involving <sup>18</sup>F-FDG-PET imaging findings and the ALBI grade. We explored whether this model could provide more reliable prognostication than is provided by the currently available staging systems.

## METHODS

### Study Design

This was a single-center, observational study. The protocol was approved by the Ethical Committee of the Graduate School of Medicine, Kyoto University, and written informed consent was obtained from all study participants (approval code: R1007).

### Patients

We retrospectively reviewed a prospectively maintained institutional database of consecutive patients who underwent hepatectomy with curative intent at the Department of

Surgery, Kyoto University, between September 2003 and December 2013. The inclusion criteria were (1) patients with solitary HCC diagnosed on computed tomography (CT) and magnetic resonance imaging (MRI); and (2) patients who underwent hepatectomy within 2 weeks of the <sup>18</sup>F-FDG-PET study being performed. Exclusion criteria were (1) patients with distant metastasis detected on CT, MRI, or <sup>18</sup>F-FDG-PET scans; and (2) patients with histologically unrelated diseases. Clinicopathologic data, including sex, age, hepatitis virus markers, primary tumor characteristics, treatment-related variables, and survival were retrieved. The follow-up protocol and recurrence criteria have been previously reported.<sup>16,17</sup> The follow-up data were last updated in January 2017.

### <sup>18</sup>F-Fluorodeoxyglucose-Positron Emission Tomography (<sup>18</sup>F-FDG-PET) Imaging Parameters and the Albumin-Bilirubin (ALBI) Grade

All <sup>18</sup>F-FDG-PET imaging procedures were performed as previously described,<sup>13–15,18</sup> and PET images were interpreted by at least two experienced nuclear medicine physicians. For quantitative analysis of <sup>18</sup>F-FDG uptake, regions of interest were manually defined on transaxial tomograms. In patients for whom no significant high uptake was detectable by PET, the regions of interest were drawn based on abdominal CT scans.<sup>14</sup> The maximum standardized uptake value (SUV) was calculated for quantitative analysis of tumor <sup>18</sup>F-FDG uptake as follows:  $SUV = C \text{ (kBq/mL)} / ID \text{ (kBq/body weight (kg))}$ , where C represents the tissue activity concentration measured by PET, and ID represents the injected dose. The tumor to non-tumor ratio (TNR) was calculated as follows:  $TNR = \text{tumor SUV} / \text{non-tumor SUV}$ , where the non-tumor SUV was defined as the average of the SUVs measured at five randomly chosen points in tumor-free liver tissue.

The ALBI grade is a simple and objective measurement of liver function that uses only serum albumin and bilirubin levels.<sup>11,19</sup> It can be applied to HCC at all stages of chronic liver disease, unlike the Child–Pugh grade, which is conventionally restricted to patients with cirrhosis. The ALBI grade was derived from and subsequently validated by a statistical analysis of more than 6000 patients with HCC.<sup>11</sup> The ALBI grade formula is as follows:  $ALBI \text{ grade} = 0.66 \times \log_{10} (\text{total bilirubin } [\mu\text{mol/L}]) - 0.085 (\text{albumin } [\text{g/L}])$ . The ALBI grade is stratified as grade 1 ( $\leq -2.60$  or less), grade 2 ( $-2.59$  to  $-1.39$ ), and grade 3 ( $> -1.39$ ). As noted above, <sup>18</sup>F-FDG-PET imaging stratifies tumor aggressiveness,<sup>13–15</sup> while the ALBI grade stratifies hepatic reserves.<sup>11,19</sup>

## Surgical Strategy

The indications for hepatectomy included Child–Pugh grade A or B and a future remnant liver volume > 25% of the liver volume, as previously reported.<sup>17</sup> Anatomic resections were planned if possible, and the hepatectomy technique was standardized. Transection of the liver parenchyma was performed using an ultrasonic surgical aspirator and bipolar irrigation forceps. For the laparoscopic procedure, a combination of an ultrasonic surgical aspirator, coagulation shears, and bipolar radiofrequency coagulation forceps was used. Postoperative hepatic arterial infusion therapy (HAIC) was administered for patients with major portal vein tumor thrombosis.<sup>16</sup>

## Statistical Analysis

Categorical variables, expressed as numbers and percentages, were compared using the Chi square test or Fisher's exact test, as appropriate, while continuous variables were expressed as median values (range). Overall survival (OS) was calculated from the date of surgery to the date of death or the end of the follow-up period, while disease-free survival (DFS) was calculated from the date of surgery to the date of death or recurrence. Survival outcomes, estimated using the Kaplan–Meier method and compared using the generalized Wilcoxon test, were expressed as actuarial values. Independent prognostic factors for OS were identified using multivariate Cox proportional hazards models with stepwise selection according to the minimally corrected Akaike information criterion (AICc) method. The performance of prognostic models was compared by assessing their homogeneity (likelihood ratio Chi square test, related to the generalized Wilcoxon test) and discriminatory ability (AICc). More accurate models exhibited higher likelihood ratio Chi square values and lower AICc values than less accurate models. Differences were considered significant at a *p* value < 0.05. Statistical analyses were performed using JMP version 12.1 software (SAS Institute, Cary, NC, USA).

## RESULTS

### Baseline Patient Characteristics

During the study period, 419 patients with radiologically ascertained solitary HCCs underwent hepatectomy with curative intent at our institution, of whom 208 underwent <sup>18</sup>F-FDG-PET prior to hepatectomy; the remaining 211 did not undergo imaging because of difficulties with surgical schedule adjustments or refusal to consent to the procedure. One of the 208 patients had an ALBI grade of 3 and was

excluded from the analysis as the statistical power for this patient group is very weak and the resultant data would not be reliable. Finally, 207 patients were enrolled; their demographic and clinical characteristics are shown in Table 1.

Before referral to our department, 44 (21.3%) patients had undergone preoperative transcatheter arterial chemoembolization (TACE) in accordance with the Japanese consensus-based treatment algorithm,<sup>20</sup> and 19 (9.2%) patients had previously undergone hepatectomy. Postoperatively, nine (4.3%) patients received adjuvant HAIC. Ninety-one (44.0%) patients experienced at least one

**TABLE 1** Clinicopathological characteristics and surgical outcomes of 207 patients with solitary HCC

| Variable                                 | N = 207          |
|------------------------------------------|------------------|
| Preoperative findings                    |                  |
| Age, years (range)                       | 69 (26–84)       |
| Male sex                                 | 158 (76.3)       |
| HBsAg [+]                                | 40 (19.3)        |
| HCV Ab [+]                               | 103 (49.8)       |
| AFP levels, ng/ml                        | 19.1 (0–167,928) |
| DCP levels, mAU/ml                       | 245 (8–267,000)  |
| Child–Pugh grade B                       | 18 (8.7)         |
| ALBI grade 2                             | 98 (47.3)        |
| TNR                                      | 1.29 (0.54–13.3) |
| Tumor diameter, cm                       | 4.0 (1.0–17.0)   |
| Tumor thrombosis                         | 14 (6.8)         |
| Macrovascular invasion                   | 19 (9.2)         |
| Preoperative TACE                        | 44 (21.3)        |
| Previous hepatectomy                     | 19 (9.2)         |
| Pathological findings                    |                  |
| Microvascular invasion                   | 68 (32.9)        |
| Satellite nodule                         | 11 (5.3)         |
| Poorly differentiation/undifferentiation | 45 (21.7)        |
| Surgical outcomes                        |                  |
| R0 resection                             | 197 (95.2)       |
| Anatomical resection                     | 131 (63.3)       |
| Laparoscopic hepatectomy                 | 22 (10.6)        |
| Major hepatectomy, ≥ 3 segments          | 75 (36.2)        |
| Morbidity                                | 91 (44.0)        |
| Post-hepatectomy liver failure grade B/C | 21 (10.1)        |
| Clavien–Dindo grade III/IV complication  | 18 (8.7)         |
| Postoperative mortality, < 30 days       | 2 (1.0)          |
| Postoperative HAIC                       | 9 (4.3)          |

Data are expressed as *n* (%) unless otherwise specified

HCC hepatocellular carcinoma, HBsAg hepatitis B surface antigen, HCV Ab hepatitis C surface antibody, AFP  $\alpha$ -fetoprotein, DCP des-gamma carboxyprothrombin, TNR tumor to non-tumor ratio, ALBI grade albumin-bilirubin grade, TACE transarterial chemoembolization, R0 no residual tumor, HAIC hepatic arterial infusion chemotherapy

complication, and 18 (8.7%) patients experienced Clavien–Dindo grade III/IV complications.<sup>21</sup> Twenty-one patients (10.1%) experienced post-hepatectomy liver failure grade B/C, as defined by the International Study Group of Liver Surgery.<sup>22</sup> Postoperative mortality (< 30 days) was 1.0% ( $n = 2$ ), and the median follow-up duration was 58.8 months (range 0.2–112 months). The median OS duration and 5-year OS rates were 84.5 months and 58.6%, respectively, while the median DFS duration and 5-year DFS rates were 19.5 months and 28.8%, respectively.

#### *The Combined Tumor to Non-tumor Ratio (TNR) and ALBI Grade Model Yields the Best Fit for Survival Prediction*

First, we developed a prognostic model using objective preoperative factors—nine potential prognostic indicators were selected for evaluation. The best TNR cut-off value was 2, based on our previous studies;<sup>13–15,18</sup> the cut-off values of the other continuous variables have also been previously determined.<sup>2,3,9,20,23–25</sup> Univariate analysis identified TNR, ALBI grade and serum  $\alpha$ -fetoprotein levels as significant prognostic factors for OS. Other variables, including tumor size and tumor markers, were not significant. Multivariate analysis revealed that a combination of the TNR and the ALBI grade was the best-fit predictive model for OS statistically, with the following hazard ratios (HRs): for  $\text{TNR} \geq 2$ , HR 1.739, 95% confidence interval [CI] 1.112–2.642,  $p = 0.016$ ; and for ALBI grade 2, HR 1.965, 95% CI 1.349–2.883,  $p < 0.001$  (Table 2).

#### *Patient Characteristics According to the TNR and the ALBI Grade*

Next, we assessed associations between patient characteristics and the TNR and the ALBI grade (electronic supplementary Table S1). Features of tumor aggressiveness, including high tumor marker levels, large tumor size, tumor thrombosis, macro- and microvascular invasion, and poorly differentiated/undifferentiated tumors, were more frequently observed in patients with a  $\text{TNR} \geq 2$ . Additionally, anatomical resection, major hepatectomy ( $\geq 3$  segments)<sup>26</sup> and postoperative HAIC were performed more frequently in patients with a  $\text{TNR} \geq 2$ . Furthermore, poor liver function-related variables, including hepatitis C virus positivity or Child–Pugh grade B, were more frequently observed in patients with an ALBI grade of 2. Preoperative TACE was also more frequently performed in patients with an ALBI grade of 2, and these patients also had a higher proportion of poorly differentiated/undifferentiated tumors. Morbidity and mortality were comparable between the groups.

#### *Prognostic Model Incorporating the TNR and the ALBI Grade*

Patients were divided into three groups based on the results of the multivariate analysis (Table 2): low-risk ( $\text{TNR} < 2$  and ALBI grade 1), intermediate-risk ( $\text{TNR} < 2$  and ALBI grade 2, or  $\text{TNR} \geq 2$  and ALBI grade 1), and high-risk ( $\text{TNR} \geq 2$  and ALBI grade 2). In the low-, intermediate-, and high-risk groups, the median OS duration and 5-year OS rates were 115.9, 55.9, and 24.4 months, respectively, and 75.7, 49.6, and 27.3%, respectively ( $p < 0.001$ ) (Fig. 1a). The difference in OS between each risk group was significant. Similar results were obtained for DFS, with median DFS and 5-year DFS rates of 29.1, 16.2, and 7.2 months, respectively, and 37.0, 24.9, and 13.6%, respectively ( $p < 0.001$ ) (Fig. 1b). The differences in DFS between each risk group were significant.

#### *Recurrence Patterns According to the TNR and the ALBI Grade*

Associations between the TNR and the ALBI grade and the patterns of recurrence were examined. Recurrence occurred in 140 (68.3%) patients during the follow-up period (excluding two patients who died within 30 days of undergoing surgery). The patterns of recurrence and subsequent treatments are listed in Electronic Supplementary Table S2; none of the patients underwent liver transplantation after recurrence. Eighty-six (61.4%) patients developed intrahepatic recurrence, 13 (9.3%) developed extrahepatic recurrence, and 41 (29.3%) developed intra- and extrahepatic recurrence. The overall recurrence rates were not significantly associated with the TNR or the ALBI grade; however, patients with a  $\text{TNR} \geq 2$  had a significantly higher incidence of extrahepatic ( $p = 0.006$ ) and both intra- and extrahepatic ( $p = 0.038$ ) recurrence, but a lower incidence of intrahepatic recurrence ( $p < 0.001$ ) than those with a  $\text{TNR} < 2$ . The ALBI grade was not associated with the pattern of recurrence (Table 3).

#### *Preoperative Prognostic Efficacy of the Model Combining <sup>18</sup>F-FDG-PET and ALBI Grade Versus Other Tumor Staging Systems*

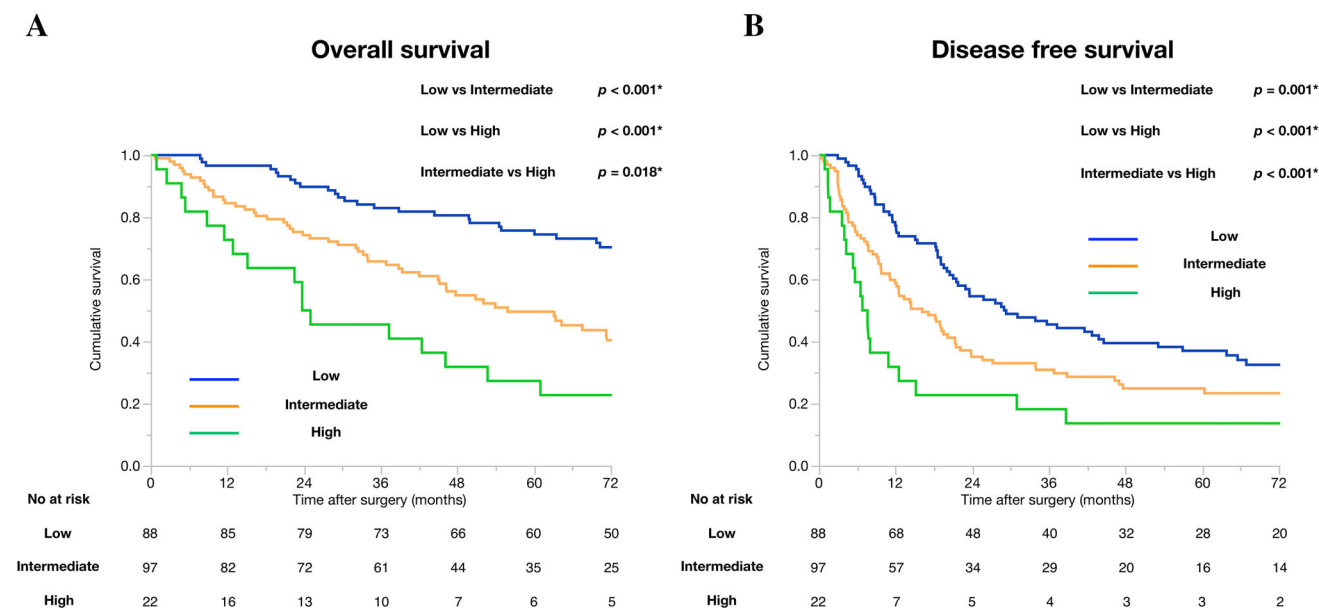
We compared the preoperative prognostic power of the model combining <sup>18</sup>F-FDG-PET and ALBI grade with three conventional integrated staging systems: The Barcelona Clinic Liver Cancer staging system,<sup>3</sup> the Cancer of the Liver Italian Program score,<sup>1</sup> and the Japan Integrated Staging score<sup>9</sup> (survival curves are shown in Electronic Supplementary Fig. S1). Table 4 shows the homogeneity (likelihood ratio Chi square test) and discriminatory ability

**TABLE 2** Univariate and multivariate analyses of overall survival after hepatectomy in patients with solitary hepatocellular carcinoma with respect to selected objective preoperative variables

| Variable           | Category | N   | Univariate analysis (generalized Wilcoxon test) |                | Multivariate analysis (Cox model) |                |
|--------------------|----------|-----|-------------------------------------------------|----------------|-----------------------------------|----------------|
|                    |          |     | MST (months)                                    | p-value        | HR (95% CI)                       | p-value        |
| Age (years)        | ≥ 70     | 91  | 64.3                                            | 0.414          | —                                 | —              |
|                    | < 70     | 116 | 96.8                                            |                |                                   |                |
| Sex                | Male     | 158 | 87.9                                            | 0.667          | —                                 | —              |
|                    | Female   | 49  | 71.3                                            |                |                                   |                |
| HBV                | Positive | 40  | NR                                              | 0.999          | —                                 | —              |
|                    | Negative | 167 | 81.6                                            |                |                                   |                |
| HCV                | Positive | 103 | 64.3                                            | 0.224          | —                                 | —              |
|                    | Negative | 104 | 96.8                                            |                |                                   |                |
| TNR                | ≥ 2      | 43  | 42.0                                            | < <b>0.001</b> | 1.743 (1.114–2.648)               | <b>0.016</b>   |
|                    | < 2      | 146 | 94.0                                            |                | Reference                         |                |
| ALBI grade         | 1        | 109 | 115.9                                           | < <b>0.001</b> | 1.966 (1.349–2.884)               | < <b>0.001</b> |
|                    | 2        | 98  | 50.8                                            |                | Reference                         |                |
| Serum AFP (ng/mL)  | ≥ 200    | 49  | 38.8                                            | <b>0.003</b>   | —                                 | —              |
|                    | < 200    | 158 | 89.7                                            |                |                                   |                |
| Serum DCP (mAU/mL) | ≥ 100    | 129 | 63.5                                            | 0.102          | —                                 | —              |
|                    | < 100    | 78  | 94.0                                            |                |                                   |                |
| Tumor size (cm)    | ≤ 2      | 39  | NR                                              | 0.066          | —                                 | —              |
|                    | 2–5      | 103 | 86.5                                            |                |                                   |                |
|                    | > 5      | 71  | 63.1                                            |                |                                   |                |

Bolded values indicate statistical significance ( $p < 0.05$ )

MST median survival time, HR hazard ratio, CI confidence interval, HBV hepatitis B virus, HCV hepatitis C virus, TNR tumor to non-tumor ratio, ALBI grade albumin-bilirubin grade, AFP  $\alpha$ -fetoprotein, DCP des-gamma carboxyprothrombin, NR not reached



**FIG. 1** (a) Overall survival and (b) disease-free survival of patients with solitary hepatocellular carcinoma stratified according to our prognostic model that combined  $^{18}\text{F}$ -FDG-PET imaging parameters with the ALBI grade. Low-risk: TNR < 2 and ALBI grade 1;

intermediate-risk: TNR ≥ 2 and ALBI grade 1, or TNR < 2 and ALBI grade 2; and high-risk: TNR ≥ 2 and ALBI grade 2.  $^{18}\text{F}$ -FDG-PET  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography, ALBI grade albumin-bilirubin grade, TNR tumor to non-tumor ratio

**TABLE 3** Patterns of recurrence observed in 140 patients with initial solitary hepatocellular carcinoma according to  $^{18}\text{F}$ -FDG-PET imaging parameters and ALBI grade

|                                      | $^{18}\text{F}$ -FDG-PET imaging parameter |              |                 | ALBI grade   |              |                 |
|--------------------------------------|--------------------------------------------|--------------|-----------------|--------------|--------------|-----------------|
|                                      | TNR < 2                                    | TNR $\geq$ 2 | <i>p</i> -Value | ALBI grade 1 | ALBI grade 2 | <i>p</i> -Value |
| Overall recurrence                   | 111 (68.1)                                 | 29 (69.1)    | 0.906           | 70 (64.2)    | 70 (72.9)    | 0.182           |
| Intrahepatic recurrence              | 77 (69.4)                                  | 9 (31.0)     | < <b>0.001</b>  | 44 (62.9)    | 42 (60.0)    | 0.728           |
| Extrahepatic recurrence <sup>a</sup> | 6 (5.4)                                    | 7 (24.1)     | <b>0.006</b>    | 6 (8.6)      | 7 (10.0)     | 1.000           |
| Intra- and extrahepatic recurrence   | 28 (25.2)                                  | 13 (44.8)    | <b>0.039</b>    | 20 (28.6)    | 21 (30.0)    | 0.853           |

Data are expressed as *n* (%)

Bolded values indicate significant difference ( $p < 0.05$ )

<sup>a</sup>Fisher's exact test; Chi square test used for all other analyses

$^{18}\text{F}$ -FDG-PET  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography, ALBI grade albumin-bilirubin grade, TNR tumor to non-tumor ratio

**TABLE 4** Preoperative prognostic efficacy of a model incorporating  $^{18}\text{F}$ -FDG-PET imaging and ALBI grade compared with those of other tumor staging systems in patients with solitary hepatocellular carcinoma

| Staging system                                         | Likelihood ratio (Chi square value) | <i>p</i> -Value | AICc   | <i>p</i> -Value |
|--------------------------------------------------------|-------------------------------------|-----------------|--------|-----------------|
| $^{18}\text{F}$ -FDG-PET imaging plus ALBI grade model | 27.6                                | < <b>0.001</b>  | 1054.8 | < <b>0.001</b>  |
| BCLC staging system                                    | 22.4                                | < <b>0.001</b>  | 1060.6 | <b>0.001</b>    |
| CLIP score                                             | 18.4                                | < <b>0.001</b>  | 1061.8 | <b>0.002</b>    |
| JIS score                                              | 13.3                                | <b>0.001</b>    | 1065.3 | <b>0.013</b>    |

Bolded values indicate significant difference ( $p < 0.05$ )

$^{18}\text{F}$ -FDG-PET  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography, ALBI grade albumin-bilirubin grade, BCLC Barcelona Clinic Liver Cancer, CLIP Cancer of the Liver Italian Program, JIS Japan Integrated Staging, AICc corrected Akaike information criterion

(AICc) of our model versus the other tumor staging systems. Notably, our prognostic model had the best discriminatory ability (AICc 1054.8,  $p < 0.001$ ) and homogeneity (likelihood ratio Chi square test value 27.6,  $p < 0.001$ ).

## DISCUSSION

Patients with solitary HCC are currently considered the best candidates for hepatectomy. In this study, we developed a new preoperative prognostic model for such patients, incorporating  $^{18}\text{F}$ -FDG-PET imaging findings and the ALBI grade. A predictive model should be straightforward and should clearly discriminate between and stratify patients. Our  $^{18}\text{F}$ -FDG-PET and ALBI grade combination model clearly met these parameters and predicted OS more accurately than the currently available staging systems. Therefore, our findings have significant implications in this era of multidisciplinary surgical approaches to HCC.

With this study, we primarily aimed to develop an objective prognostic model based on parameters related to tumor characteristics and estimated hepatic reserves.

Therefore, for our model, we focused on the ALBI grade, which is a more objective evaluation than the Child–Pugh grade, and  $^{18}\text{F}$ -FDG-PET, which is predictive of tumor aggressiveness,<sup>13–15</sup> while excluding relatively subjective radiographic variables (e.g. vascular invasion) and the Child–Pugh grade. Specifically, we selected the TNR as the  $^{18}\text{F}$ -FDG PET imaging parameter for our model. Although the maximum SUV of the primary tumor is commonly used in this context, SUV measurements are influenced by physiologic noise (e.g. liver background); therefore, we have suggested the TNR instead of the maximum SUV as a prognosticator for HCC.<sup>13,14</sup> As expected, we found that the combination of the TNR and the ALBI grade yielded the best-fit model for predicting OS and, subsequently, DFS among patients with solitary HCC after hepatectomy. Moreover, our prognostic model yielded more accurate predictions of OS than the currently available staging systems.

Our study further demonstrated that a high TNR was significantly associated with extrahepatic recurrence patterns. Patients with extrahepatic HCC recurrence generally have poor 5-year postoperative survival rates (16.1–24.0%);<sup>27–29</sup> however, Uchino et al.<sup>30</sup> reported that

the prognosis of patients with extrahepatic metastasis was partly determined by the controllability of intrahepatic lesions. These reports suggest that, even though the tumor itself is aggressive (i.e. has a high TNR), better hepatic reserve (i.e. ALBI grade 1) may provide multiple treatment choices and improve survival rates (as shown in the intermediate-risk group). Moreover, we reported that patients with a high TNR showed recurrence beyond the Milan criteria, depriving them of a chance to undergo liver transplantation.<sup>18</sup> Our model may therefore have implications in terms of expected patterns of recurrence and consequent treatment planning.

Our study has some limitations. First, it was conducted retrospectively, using data from a single-center Japanese cohort, and certain biases in patient selection could not be avoided (e.g. etiology, previous therapy, and applied treatment variables, including preoperative treatments). Second, one patient with ALBI grade 3 was excluded from the analysis; however, such patients are expected to have an extremely poor prognosis.<sup>11,19</sup> Moreover, Wang et al. stated that ALBI grade 3 may be a contraindication to hepatectomy.<sup>12</sup> Third, we compared the prognostic value of our model with that of established staging systems; however, such comparisons should be externally validated prospectively to confirm the true efficacy of our model.

## CONCLUSION

We propose a new preoperative prognostic model for patients with solitary HCC incorporating <sup>18</sup>F-FDG-PET and ALBI grade. In the era of multidisciplinary strategies for HCC treatment, preoperative assessment of prognosis plays an increasingly pivotal role. In the future, we hope to adopt a multidisciplinary strategy based on our prognostic model.

**DISCLOSURES** Tomoaki Yoh, Satoru Seo, Satoshi Ogiso, Takayuki Kawai, Yukihiro Okuda, Takamichi Ishii, Kojiro Taura, Tatsuya Higashi, Yuji Nakamoto, Etsuro Hatano, Toshimi Kaido, and Shinji Uemoto have no conflicts of interest to declare in relation to this article.

**FUNDING** No financial support was received for this work.

## REFERENCES

1. Capuano G, Daniele B, Gaeta GB, Gallo C, Perrone F. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients: the Cancer of the Liver Italian Program (CLIP) investigators. *Hepatology*. 1998;28:751–55.
2. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology*. 2011;53:1020–22.
3. European Association for the Study of the Liver, European Organisation For Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2012;56:908–43.
4. Dhir M, Melin AA, Douaiher J, et al. A review and update of treatment options and controversies in the management of hepatocellular carcinoma. *Ann Surg*. 2016;263:1112–25.
5. Barone C, Koeberle D, Metselaar H, et al. Multidisciplinary approach for HCC patients: hepatology for the oncologists. *Ann Oncol*. 2013;24 Suppl 2:i15–23.
6. Allard MA, Sebah M, Ruiz A, et al. Does pathological response after transarterial chemoembolization for hepatocellular carcinoma in cirrhotic patients with cirrhosis predict outcome. *J Hepatol*. 2015;63:83–92.
7. Kim BK, Kim SU, Kim KA, et al. Complete response at first chemoembolization is still the most robust predictor for favorable outcome in hepatocellular carcinoma. *J Hepatol*. 2015;62:1304–10.
8. Kinoshita A, Onoda H, Fushiya N, et al. Staging systems for hepatocellular carcinoma: current status and future perspectives. *World J Hepatol*. 2015;7:406–24.
9. Kudo M, Chung H, Haji S, et al. Validation of a new prognostic staging system for hepatocellular carcinoma: the JIS score compared with the CLIP score. *Hepatology*. 2004;40:1396–05.
10. Hsu CY, Hsia CY, Huang YH, et al. Selecting an optimal staging system for hepatocellular carcinoma: comparison of 5 currently used prognostic models. *Cancer*. 2010;116:3006–14.
11. Johnson PJ, Berhane S, Kagebayashi C, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach—the ALBI grade. *J Clin Oncol*. 2015;33:550–58.
12. Wang YY, Zhong JH, Su ZY, et al. Albumin–bilirubin versus Child–Pugh score as a predictor of outcome after liver resection for hepatocellular carcinoma. *Br J Surg*. 2016;103:725–34.
13. Kitamura K, Hatano E, Higashi T, et al. Proliferative activity in hepatocellular carcinoma is closely correlated with glucose metabolism but not angiogenesis. *J Hepatol*. 2011;55:846–57.
14. Seo S, Hatano E, Higashi T, et al. Fluorine-18 fluorodeoxyglucose positron emission tomography predicts tumor differentiation, P-glycoprotein expression, and outcome after resection in hepatocellular carcinoma. *Clin Cancer Res*. 2007;13:427–33.
15. Kawai T, Yasuchika K, Seo S, et al. Identification of keratin19-positive cancer stem cells associating human hepatocellular carcinoma using 18F-fluorodeoxyglucose positron emission tomography. *Clin Cancer Res*. 2017;23:1450–60.
16. Kojima H, Hatano E, Taura K, et al. Hepatic resection for hepatocellular carcinoma with tumor thrombus in the major portal vein. *Dig Surg*. 2015;32:413–20.
17. Nishio T, Taura K, Koyama Y, et al. Prediction of posthepatectomy liver failure based on liver stiffness measurement in patients with hepatocellular carcinoma. *Surgery*. 2016;159:399–408.
18. Kitamura K, Hatano E, Higashi T, et al. Preoperative FDG-PET predicts recurrence patterns in hepatocellular carcinoma. *Ann Surg Oncol*. 2012;19:156–62.
19. Toyoda H, Lai PB, O’Beirne J, et al. Long-term impact of liver function on curative therapy for hepatocellular carcinoma: application of the ALBI grade. *Br J Cancer*. 2016;114:744–50.
20. Kudo M, Matsui O, Izumi N, et al. JSH Consensus-based clinical practice guidelines for the management of hepatocellular carcinoma: 2014 Update by the Liver Cancer Study Group of Japan. *Liver Cancer*. 2014;3:458–68.
21. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;40:205–13.
22. Rahbari NN, Garden OJ, Padbury R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery*. 2011;149:713–24.
23. Yamashita Y, Tsujita E, Takeishi K, et al. Predictors for microinvasion of small hepatocellular carcinoma  $\leq 2$  cm. *Ann Surg Oncol*. 2012;19:2027–34.

24. Hong G, Suh KS, Suh SW, et al. Alpha-fetoprotein and 18F-FDG positron emission tomography predict tumor recurrence better than Milan criteria in living donor liver transplantation. *J Hepatol*. 2016;64:852–922.
25. Bruix J, Sherman M: Practice Guidelines Committee, American Association for the Study of Liver Diseases Management of hepatocellular carcinoma. *Hepatology*. 2005;42:1208–36.
26. Strasberg SM. Nomenclature of hepatic anatomy and resections: a review of the Brisbane 2000 system. *J Hepatobiliary Pancreat Surg*. 2005;12:351–55.
27. Taketomi A, Toshima T, Kitagawa D et al. Predictors of extrahepatic recurrence after curative hepatectomy for hepatocellular carcinoma. *Ann Surg Oncol*. 2010;17:2740–46.
28. Yang Y, Nagano H, Ota H, Morimoto O, Nakamura M, Wada H, et al. Patterns and clinicopathologic features of extrahepatic recurrence of hepatocellular carcinoma after curative resection. *Surgery*. 2007;141:196–202.
29. Ochiai T, Ikoma H, Okamoto K, et al. Clinicopathologic features and risk factors for extrahepatic recurrences of hepatocellular carcinoma after curative resection. *World J Surg*. 2012;36:136–143.
30. Uchino K, Tateishi R, Shiina S, et al. Hepatocellular carcinoma with extrahepatic metastasis: clinical features and prognostic factors. *Cancer*. 2011;117:4475–83.