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ORIGINAL ARTICLE

A novel combined C-reactive protein-albumin ratio and modified albumin-bilirubin score can predict long-term outcomes in patients with hepatocellular carcinoma after hepatic resection

Takashi Aida[1] | Koichiro Haruki[1] | Munetoshi Akaoka[1] | Kenei Furukawa[1] | Shinji Onda[1] | Yoshihiro Shirai[1] | Hironori Shiozaki[1] | Keita Takahashi[1] | Tsunekazu Oikawa[2] | Toru Ikegami[1]

[1]Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, The Jikei University School of Medicine, Tokyo, Japan

[2]Division of Gastroenterology and Hepatology, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan

Correspondence
Koichiro Haruki, Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, The Jikei University School of Medicine, 3-25-8, Nishi-Shinbashi, Minato-ku, Tokyo 105-8461, Japan.
Email: haruki@jikei.ac.jp

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Abstract

Background: Systemic inflammatory response represented by C-reactive protein and albumin ratio (CAR) and modified albumin-bilirubin (mALBI) grade both have been associated with long-term outcome in patients with hepatocellular carcinoma (HCC). In this study, we investigated the prognostic utility of combined score of CAR and mALBI score to predict the prognosis of HCC patients after hepatic resection.

Methods: This study included 214 patients who had undergone primary hepatic resection for HCC between 2008 and 2018. Systemic inflammatory response and mALBI were evaluated preoperatively and patients were classified into three groups based on the combination of CAR and mALBI score: low CAR and low mALBI grade (score 0), either high CAR or high mALBI grade (score 1), and both high CAR and high mALBI grade ≥2b (score 2). Multivariate Cox proportional hazard models were conducted to assess disease-free and overall survival.

Results: In multivariate analysis, sex ($p < 0.01$), HBsAg positivity ($p < 0.01$), serum AFP level ≥20 ng/mL ($p < 0.01$), microvascular invasion ($p = 0.02$), multiple tumors ($p < 0.01$), type of resection ($p < 0.01$), and CAR-mALBI score ≥2 (HR 2.19, 95% CI 1.39–3.44, $p < 0.01$) were independent prognostic factors of disease-free survival, while sex ($p = 0.01$), HBsAg positivity ($p < 0.01$), poor tumor differentiation ($p = 0.03$), multiple tumors ($p < 0.01$), CAR-mALBI score ≥2 (HR 2.70, 95% CI 1.51–4.83, $p < 0.01$) were independent prognostic factors of overall survival.

Conclusions: CAR-mALBI score is associated with disease-free and overall survival in patients with HCC after hepatic resection, suggesting the importance of evaluating both hepatic functional reserve and host-inflammatory state in the risk assessment of HCC patients.

KEYWORDS
ALBI, hepatic functional reserve, hepatic resection, hepatocellular carcinoma, systemic inflammatory response

1 | INTRODUCTION

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related death worldwide.[1] Although surgical resection is a potentially curative treatment, a high recurrence rate of the HCC after liver resection is the main cause of impairing long-term survival.[2] Prognosis of HCC depends on not only tumor stage but also underlying liver function. Hepatic functional reserve represented by ALBI is one of the important factors that influence the clinical decision-making as well as survival in patients with HCC.[3]

Previous studies suggest that the albumin-bilirubin (ALBI) grade and modified ALBI (mALBI) grade have been considered as more objective markers of liver function compared to Child–Pugh score in patients with HCC.[4] ALBI grade has more sensitively stratified outcomes of HCC patients.[5] A growing body of evidence suggests that the systemic inflammatory response including neutrophil-lymphocyte ratio (NLR),[6] platelet-lymphocyte ratio (PLR),[7] lymphocyte-monocyte ratio (LMR),[8] C-reactive protein-albumin ratio (CAR)[9] has been associated with long-term outcomes in cancer patients including HCC.

Given that both hepatic functional reserve and systemic inflammatory response might be important in the prediction of survival in patients with HCC, we here proposed a novel combined CAR and mALBI score and investigated the prognostic value of this biomarker in patients with HCC after liver resection.

2 | PATIENTS AND METHODS

2.1 | Patient selection

This retrospective study included HCC patients who underwent primary hepatic resection at the Department of Surgery, Jikei University Hospital, Tokyo, Japan between January 2008 to December 2018. Patients with other malignancies, postoperative mortality, and unavailable data on preoperative systemic inflammatory response were excluded. We included 214 patients for this study. We collected data on clinical information, operative and pathological findings, and postoperative course from medical records. We pursued patients until death or the end of follow-up. This study was approved by the Ethics Committee of the Jikei University School of Medicine (#27–177).

2.2 | Treatment and follow-up

We determined the extent and type of hepatic resection on the basis of preoperative tumor staging, retention rate of indocyanine green at 15 min (ICG_{R15}) before surgery, and hepatic reserve, mentioned by Miyagawa et al.[10] and defined the segment and types of operations according to the Brisbane 2000 terminology.[11] Liver resection was classified into two types: anatomical resection (hemi-hepatectomy, sectionectomy, or segmentectomy) and non-anatomical limited partial resection.[12] We used Tumor-Nodes-Metastasis (TNM) classification for HCC staging by reference to tumor pathology and the General Rules for the Clinical and Pathological Study of Primary Liver Cancer by the Liver Cancer Study Group of Japan.[13]

The definition of the relapse of HCC was newly detected hypervascular hepatic or extrahepatic tumors by ultrasonography, computed tomography, or magnetic resonance image regardless of the elevated serum α-fetoprotein (AFP) or protein induced by vitamin K absence or antagonist-II (PIVKA-II).

Reiterate hepatectomy, local ablation therapy, or transarterial chemoembolization was selected for the treatment of recurrence lesion considering hepatic functional reserve evaluated mainly by retention rate of indocyanine green at 15 min (ICG_{R15}) and extrahepatic recurrence was mainly treated with systemic chemotherapy.

2.3 | Definition of parameters

Each patient was routinely measured hemogram and biochemical examination preoperatively. ALBI score was calculated (log10 bilirubin × 17.1 × 0.66) + (albumin × 10 × −0.085) and, mALBI grades were defined as grade 1 (≤−2.60), grade 2a (≥2.60 to ≤2.27), grade 2b (≥2.27 to ≤1.39), grade 3 (≥1.39).[4] mALBI grade ≥2b was considered as low hepatic functional reserve (score 1), while mALBI grade ≤2a as preserved hepatic functional reserve (score 0). NLR, PLR, LMR, and CAR were evaluated within 7 days before surgery. NLR was calculated as absolute neutrophil count divided by absolute lymphocyte count. PLR was calculated as absolute platelet count divided by absolute lymphocyte count.[7] LMR was calculated as absolute lymphocyte count divided by absolute monocyte count.[8] CAR was calculated as serum C-reactive protein (CRP) level (mg/dl) divided by serum albumin (g/dl).[9] The cut-off values of NLR, PLR, LMR, and CAR were determined by a receiver operating characteristics (ROC) analysis using survival status at the 5-year follow-up (Figure S1). Elevated CAR was scored as 1, while normal CAR was scored as 0. The combination of the CAR-mALBI score was calculated as the sum of the CAR score and the mALBI score. Patients were classified into three groups based on the CAR-mALBI score: low CAR and low mALBI grade (score 0), either high CAR or high mALBI grade (score 1), and both high CAR and high mALBI grade ≥2b (score 2).

2.4 | Statistical analysis

All statistical analyses were performed using EZR version 1.54, and *p*-values <0.05 was considered statistical significant. Data are expressed as a median, interquartile range, or ratio. Continuous and categorical variables were compared using the Mann–Whitney *U*-test or chi-square test as appropriate and data are expressed as a median, interquartile range, or ratio.

Univariate and multivariate Cox proportional hazards regression models were used to estimate the hazard ratios (HRs) for disease-free and overall survival. The multivariate Cox regression model initially included age (≥65 vs. <65 years), sex (female vs. male), HBsAg status (positive vs. negative), HCV-Ab status (positive vs. negative), ICG_{R15} (≥15 vs. <15%), Child–Pugh grade (B vs. A), serum AFP level (≥20 vs. <20 ng/mL), serum PIVKA-II level (≥200 vs. <200 mAU/mL), tumor differentiation (poor vs. well or moderate), duration of operation (≥360 vs. <360 min), microvascular invasion (yes vs. no), tumor size (>5 vs. ≤5 cm), number of tumors (multiple vs. solitary) intraoperative blood loss (≥1000 vs. <1000 g), type of resection (anatomical vs. partial), NLR (high vs. low), PLR (high vs. low), LMR (low vs. high), CAR (high vs. low), mALBI grade (≥2b vs. ≤2a), and CAR-mALBI score (2 vs. 0–1). A backward elimination was conducted with a threshold *p* of 0.05 to select variables for the final models. Cumulative survival probabilities were estimated by the Kaplan–Meier method and a linear trend in survival probabilities across the groups was assessed using the log-rank test for trend.

3 | RESULTS

3.1 | Patient clinicopathological characteristics

Patients clinicopathological characteristics are summarized in Table 1, S1, and S2 with a median, interquartile range (IQR), or ratio. CAR-mALBI score 2 was observed in 47 patients (22%), score 1 was observed in 82 patients (38%), and score 0 was observed in 85 patients (40%). The distribution of all patients of CAR and mALBI grade was shown in Figure 1. The median follow-up of the entire study population was 5.6 years (IQR, 3.5–7.4 years). During follow-up, 125 of 214 patients experienced tumor recurrence (58.4%) and the median time to recurrence after hepatectomy was 3.6 years (IQR, 1.0–5.4 years). The recurrence rate of CAR-mALBI score 1 or 0 was 53.9% (90 of 167 patients), while that of CAR-mALBI score 2 was 74.5% (35 of 47 patients). Fifty-one of 125 patients underwent local treatment including hepatic resection or radiofrequency ablation (RFA). The patients who underwent local therapies included 45 patients of score 1 or 0 and six patients of score 2. Local therapies were more frequently performed in patients with CAR-mALBI score 1 or 0 than in patients with score 2 ($p<0.01$). Elevated serum AFP and PIVKA-II levels and greater tumor size were significantly associated with CAR and mALBI score. LMR was negatively associated with CAR and mALBI score (Tables S1 and S2). CAR-mALBI score 2 patients included nine patients of Child–Pugh grade B (19%). Serum AFP ($p=0.01$) and PIVKA-II level ($p<0.01$), and tumor size ($p<0.01$) were significantly greater in patients with score 2 than those in patients with score 1 or 0. Patients with score 2 had more anatomical resection ($p=0.04$) and greater intraoperative bleeding ($p<0.01$). NLR ($p<0.01$), PLR ($p<0.01$), and CAR ($p<0.01$) level were positively associated with CAR-mALBI score, while LMR ($p<0.01$) was negatively associated with CAR-mALBI score.

3.2 | Univariate and multivariate analyses of prognostic factors for disease-free and overall survival in patients with hepatocellular carcinoma after hepatic resection

Table 2 showed the association of the clinical variables with disease-free survival after hepatic resection for HCC. In univariate analysis, the disease-free survival was significantly associated with sex ($p<0.01$), HBsAg positivity ($p<0.01$), serum PIVKA-II level ≥200 ng/mL ($p=0.02$), tumor size >5 cm ($p<0.01$), multiple tumors ($p<0.01$), microvascular invasion ($p=0.02$), intraoperative blood loss ≥1000 g ($p=0.02$), CAR high ($p<0.01$), mALBI grade ≥ 2b ($p<0.01$), and CAR-mALBI score ≥2 ($p<0.01$). High CAR and mALBI grade ≥2b was significantly associated with worse disease-free survival ($p<0.001$, $p<0.01$ by the log-rank test, Figure S2A, B). In multivariate analysis, sex ($p<0.01$), HBsAg positivity ($p<0.01$), serum AFP level ≥20 ng/mL ($p<0.01$), microvascular invasion ($p=0.02$), multiple tumors ($p<0.01$), type of resection ($p<0.01$), and CAR-mALBI score ≥2 [HR 2.19, 95% confidence interval (CI) 1.39–3.44, $p<0.01$)] were independent prognostic factors of disease-free survival. CAR-mALBI score was associated with worse disease-free survival ($p<0.001$ by the log-rank test for trend, Figure 2A).

Table 3 showed the association of the clinical variables with overall survival after hepatic resection for HCC. In univariate analysis, overall survival was significantly associated with HBsAg positivity ($p<0.01$), ICG_{R15} ≥15% ($p=0.03$), tumor size >5 cm ($p<0.01$), multiple tumors ($p=0.04$), CAR high ($p=0.02$), mALBI grade ≥2b ($p<0.01$), and CAR-mALBI score ≥2 ($p<0.01$). High CAR and mALBI grade ≥2b was significantly associated with worse overall survival ($p=0.01$, $p<0.01$ by the log-rank test, Figure S2C,D). In multivariate analysis, sex ($p=0.01$), HbsAg positivity ($p<0.01$), poor tumor differentiation ($p=0.03$), multiple tumors ($p<0.01$), and CAR-mALBI score ≥2 (HR 2.70, 95% CI 1.51–4.83, $p<0.01$) were independent prognostic factors of overall survival. CAR-mALBI score was associated with worse overall survival ($p<0.001$ by the log-rank test for trend, Figure 2B).

4 | DISCUSSION

In this study, we found that the combined CAR and mALBI score was associated with poor disease-free and overall survival in patients with HCC after hepatic resection. Our finding highlighted the

TABLE 1 Clinicopathological characteristics of enrolled patients and univariate analysis of clinicopathologic variables in relation to the CAR-mALBI score.

Variables	Total ($n=214$)	CAR-mALBI		p-Value
		Score 2 ($n=47$)	Score 0 or 1 ($n=167$)	
Age (years)	68 (61–74)	71 (62–77)	67 (61–74)	0.16
Sex, female	42 (20%)	7 (15%)	35 (21%)	0.41
BMI	24 (21–27)	23 (21–27)	24 (21–26)	0.74
HBsAg, positive	45 (21%)	5 (11%)	40 (24%)	0.07
HCV-Ab, positive	64 (30%)	15 (32%)	49 (29%)	0.72
ICG_{R15} (%)	14 (9–21)	13 (9–22)	15 (10–21)	0.83
Child–Pugh grade, B	20 (8.9%)	9 (19%)	11 (7%)	0.02
Serum AFP level (ng/mL)	8 (4–46)	26 (6–428)	12 (4–31)	0.01
Serum PIVKA-II level (mAU/mL)	64 (22–830)	802 (37–7040)	45 (20–279)	<0.01
Tumor differentiation, poor	31 (14%)	11 (23%)	20 (12%)	0.05
Tumor size (cm)	3.4 (2.1–5.5)	7.0 (3.3–10.0)	3.0 (2.0–4.9)	<0.01
Tumor number, multiple	43 (20%)	9 (19%)	34 (20%)	1.00
Microvascular invasion, yes	34 (16%)	9 (19%)	25 (15%)	0.50
Type of resection, anatomical	136 (64%)	36 (77%)	100 (60%)	0.04
Duration of operation (min)	384 (300–517)	430 (298–546)	369 (301–511)	0.16
Intraoperative blood loss (g)	470 (200–1040)	610 (393–1495)	428 (180–938)	<0.01
ALBI	−2.4 (−2.6–−2.1)	−1.9 (−2.1–−1.6)	−2.5 (−2.7–−2.3)	<0.01
NLR	2.1 (1.6–3.0)	3.2 (1.9–4.9)	1.9 (1.5–2.7)	<0.01
PLR	105 (80–151)	161 (96–266)	101 (80–135)	<0.01
LMR	5.0 (3.4–6.3)	3.0 (2.6–5.0)	5.0 (3.8–6.5)	<0.01
CAR	0.02 (0.01–0.09)	0.19 (0.06–1.01)	0.13 (0.01–0.03)	<0.01

Abbreviations: AFP, alpha-fetoprotein; BMI, body mass index; CAR, C-reactive protein-albumin ratio CI, confidence interval; HBsAg, hepatitis B surface antigen; HCV-Ab, hepatitis C virus antibody; HR, hazard ratio; ICG_{R15}, retention rate of indocyanine green at 15 min; LMR, lymphocyte-monocyte ratio; mALBI, modified albumin-bilirubin; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; PIVKA-II, protein induced by vitamin K absence or antagonist-II.

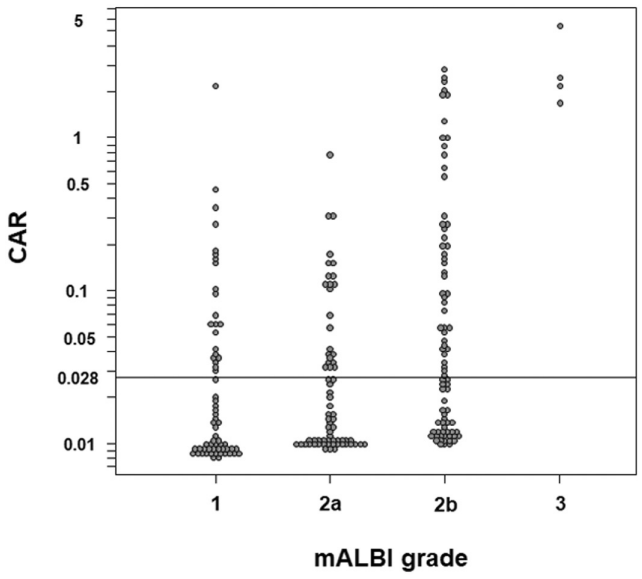

FIGURE 1 The distribution of CAR and modified albumin-bilirubin (ALBI) grade of all patients. The black dot represents each patient and the transverse line demonstrates the cut-off value of CAR (0.028).

importance of evaluating both hepatic functional reserve and systematic inflammatory response in the risk prediction of HCC.

ALBI score, calculated using two objective factors of total bilirubin and serum albumin, was proposed as the indicator of liver function by Johnson et al. in 2015.[14] Several studies suggested that low hepatic reserve has been associated with a high incidence of postoperative complications and impaired long-term survival in HCC patients.[5] Therefore, the evaluation of postoperative liver function is essential to predict patient's prognosis and clinical decision-making to select the treatment option if the tumor recurs. ALBI score may be superior to the Child–Pugh score in terms of assessment of hepatic functional reserve because it does not include subjective indexes, such as the grading of ascites and encephalopathy.[15] In fact, a large multi-institution study suggested that ALBI score for the assessment of patient liver function showed a better prediction of the hepatic functional reserve as well as prognosis than that of Child–Pugh grade in HCC patients.[16] Therapeutic options, including surgical resection, radiofrequency ablation (RFA), transarterial chemoembolization (TACE), or systemic chemotherapy, are chosen considering tumor factor as well as underlying liver function. Liver resection is considered one of the most

TABLE 2 Univariate and multivariate analyses of prognostic factors for disease-free survival in patients with hepatocellular carcinoma after hepatic resection.

	Univariate analysis		Multivariate analysis	
Variables	**HR (95% CI)**	***p*-Value**	**HR (95% CI)**	***p*-Value[a]**
Age ≥65 years	1.21 (0.84–1.75)	0.31		NS
Sex, female	0.48 (0.28–0.82)	<0.01	0.34 (0.19–0.61)	<0.01
HBsAg, positive	0.50 (0.30–0.83)	<0.01	0.45 (0.27–0.76)	<0.01
HCV-Ab, positive	1.08 (0.90–1.31)	0.42		NS
ICG_{R15} ≥15%	1.42 (1.00–2.02)	0.05		NS
Child–Pugh grade, grade B	1.00 (0.55–1.82)	0.99		NS
Serum AFP level, ≥20 ng/mL	1.34 (0.94–1.93)	0.11	1.83 (1.21–2.77)	<0.01
Serum PIVKA-II level, ≥200 mAU/mL	1.56 (1.09–2.25)	0.02		NS
Tumor differentiation, poor	1.59 (1.00–2.53)	0.05		NS
Microvascular invasion, yes	1.57 (0.99–2.48)	0.06	1.73 (1.08–2.80)	0.02
Tumor size, >5 cm	1.71 (1.18–2.49)	<0.01		NS
Tumor number, multiple	2.42 (1.64–3.57)	<0.01	3.63 (2.30–5.73)	<0.01
Duration of operation, ≥360 min	1.09 (0.76–1.55)	0.65		NS
Intraoperative blood loss, ≥1000 g	1.58 (1.09–2.29)	0.02		NS
Type of resection, anatomical	0.85 (0.60–1.22)	0.39	0.58 (0.38–0.87)	<0.01
NLR, high	1.15 (0.81–1.63)	0.45		NS
PLR, high	1.16 (0.79–1.70)	0.45		NS
LMR, low	1.17 (0.74–1.84)	0.51		NS
CAR, high	1.81 (1.27–2.57)	<0.01		NS
mALBI grade, ≥2b	1.63 (1.15–2.32)	<0.01		NS
CAR-mALBI, score 2	1.95 (1.31–2.89)	<0.01	2.19 (1.39–3.44)	<0.01

Abbreviations: AFP, alpha-fetoprotein; CAR, C-reactive protein-albumin ratio CI, confidence interval; HBsAg, hepatitis B surface antigen; HCV-Ab, hepatitis C virus antibody; HR, hazard ratio; ICG_{R15}, retention rate of indocyanine green at 15 min; LMR, lymphocyte-monocyte ratio; mALBI grade, modified albumin-bilirubin grade; NLR, neutrophil-lymphocyte ratio. NS, not significant (did not remain in the final model); PLR, platelet-lymphocyte ratio; PIVKA-II, protein induced by vitamin K absence or antagonist-II.

[a]The multivariate Cox regression model initially included age (≥65 vs. <65 years), sex (female vs. male), HBsAg status (positive vs. negative), HCV-Ab status (positive vs. negative), ICG_{R15} (≥15 vs. <15%), Child–Pugh grade (B vs. A), serum AFP level (≥20 vs. <20 ng/mL), serum PIVKA-II level (≥200 vs. <200 mAU/mL), tumor differentiation (poor vs. well or moderate), duration of operation (≥360 vs. <360 min), microvascular invasion (yes vs. no), tumor size (>5 vs. ≤5 cm), number of tumors (multiple vs. solitary) intraoperative blood loss (≥1000 vs. <1000 g), type of resection (anatomical vs. partial), NLR (high vs. low), PLR (high vs. low), LMR (low vs. high), CAR (high vs. low), mALBI grade (≥2b vs. ≤2a), and CAR-mALBI score (2 vs. 1 or 0). A backward elimination was conducted with a threshold p of 0.05 to select variables for the final models.

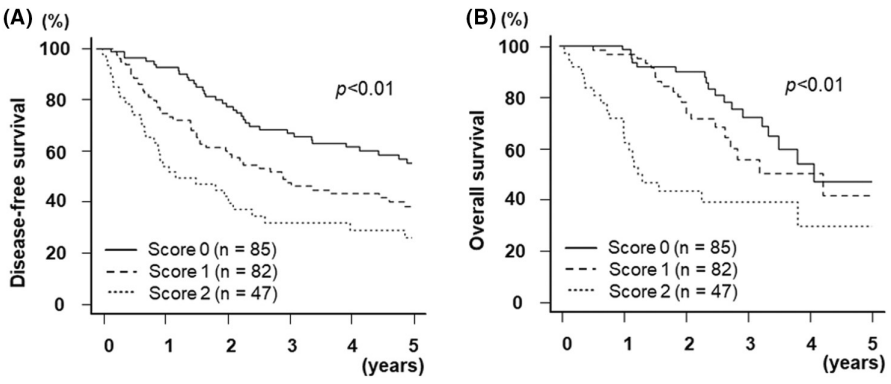

FIGURE 2 Kaplan–Meier curves of disease-free (A) and overall survival (B) according to the status of CAR-mALBI score after hepatic resection for HCC.

curative treatment options for HCC, and better hepatic functional reserve allows surgical resection. Therefore, patients with good hepatic functional reserve has better survival.[17] Furthermore, high ALBI score is likely to be concomitant with liver cirrhosis which has a higher hepatocarcinogenic potential state, and liver cirrhosis is also a well-known risk factor for HCC relapse.[18] A recent study

TABLE 3 Univariate and multivariate analyses of prognostic factors for overall survival in patients with hepatocellular carcinoma after hepatic resection.

	Univariate analysis		Multivariate analysis	
Variables	**HR (95% CI)**	***p*-Value**	**HR (95% CI)**	***p*-Value[a]**
Age ≥65 years	1.08 (0.64–1.81)	0.79		NS
Sex, female	0.47 (0.20–1.08)	0.08	0.30 (0.12–0.78)	0.01
HBsAg, positive	0.43 (0.21–0.92)	0.03	0.34 (0.15–0.77)	<0.01
HCV-Ab, positive	1.16 (0.89–1.51)	0.29		NS
ICG_{R15} ≥15%	1.77 (1.05–2.98)	0.03		NS
Child–Pugh grade, grade B	1.74 (0.86–3.55)	0.12		NS
Serum AFP level, ≥20 ng/mL	1.68 (1.01–2.81)	0.05		NS
Serum PIVKA-II level, ≥200 mAU/mL	1.25 (0.74–2.12)	0.40		NS
Tumor differentiation, poor	1.88 (1.00–3.55)	0.05	2.00 (1.04–3.87)	0.03
Microvascular invasion, yes	2.06 (1.22–3.47)	<0.01		NS
Tumor size, >5 cm	2.09 (1.21–3.60)	<0.01	2.38 (1.34–4.21)	<0.01
Tumor number, multiple	1.64 (0.87–3.10)	0.12		NS
Duration of operation, ≥360 min	1.01 (0.61–1.68)	0.97		NS
Intraoperative blood loss, ≥1000 g	1.55 (0.91–2.63)	0.10		NS
Type of resection, anatomical	0.78 (0.47–1.30)	0.34		NS
NLR, high	1.12 (0.68–1.87)	0.65		NS
PLR, high	1.48 (0.87–2.51)	0.15		NS
LMR, low	1.31 (0.68–2.54)	0.42		NS
CAR, high	1.88 (1.13–3.12)	0.02		NS
mALBI grade, ≥2b	2.05 (1.23–3.41)	<0.01		NS
CAR-mALBI, score 2	2.57 (1.51–4.37)	<0.01	2.70 (1.51–4.83)	<0.01

Abbreviations: AFP, alpha-fetoprotein; CAR, C-reactive protein-albumin ratio CI, confidence interval; HBsAg, hepatitis B surface antigen; HCV-Ab, hepatitis C virus antibody; HR, hazard ratio; ICG_{R15}, retention rate of indocyanine green at 15 min; LMR, lymphocyte-monocyte ratio; mALBI grade, modified albumin-bilirubin grade; NLR, neutrophil-lymphocyte ratio; NS, not significant (Did not remain in the final model); PLR, platelet-lymphocyte ratio; PIVKA-II, protein induced by vitamin K absence or antagonist-II.

[a]The multivariate Cox regression model initially included age (≥65 vs. <65 years), sex (female vs. male), HBsAg status (positive vs. negative), HCV-Ab status (positive vs. negative), ICG_{R15} (≥15 vs. <15%), Child–Pugh grade (B vs. A), serum AFP level (≥20 vs. <20 ng/mL), serum PIVKA-II level (≥200 vs. <200 mAU/mL), tumor differentiation (poor vs. well or moderate), duration of operation (≥360 vs. <360 min), microvascular invasion (yes vs. no), tumor size (>5 vs. ≤5 cm), number of tumors (multiple vs. solitary) intraoperative blood loss (≥1000 vs. <1000 g), type of resection (anatomical vs. partial), NLR (high vs. low), PLR (high vs. low), LMR (low vs. high), CAR (high vs. low), mALBI grade (≥ 2b vs. ≤2a), and CAR-mALBI score (2 vs. 1 or 0). A backward elimination was conducted with a threshold p of 0.05 to select variables for the final models.

stated that liver cirrhosis may be subsequently occurred by highly increasing rate of random mutations and promotion.[19] Taken together, ALBI score can be closely connected with HCC recurrence after hepatic resection.

Systemic inflammatory response includes host and tumor-related inflammation and elevated host inflammatory states develop immunosuppressive actions and angiogenesis in the tumor microenvironment.[20] Sustained inflammatory state promotes cancer cell proliferation and metastasis by synthesizing many proinflammatory cytokines.[21,22] The high concentration of CRP, which is promoted by IL-6 due to local tissue injury, is related to serum levels of vascular endothelial growth factors which enhance angiogenesis in the tumor microenvironment.[23] Angiogenesis is widely recognized as a key factor of tumor progression as well as antitumor immunity in HCC patients.[24] In this study, CAR was the only significant predictor of long-term outcomes among inflammation-based biomarkers. Our previous study suggested the superior prognostic value of CAR compared with other inflammatory biomarkers.[9] The possible reason is that CAR consists of the serum levels of CRP and albumin. Although other blood cell-based biomarkers only represent inflammatory states, CAR can reflect both host inflammatory and malnutritional states.[8]

There have been some studies on the utility of the combination score including ALBI and other predictors such as aspartate aminotransferase to platelet ratio index (APRI)[25,26] or fibrosis-4 (FIB-4) index.[27] APRI can evaluate underlying liver disease, especially to have good power in the detection of chemotherapy-associated liver injury.[25] Whereas, FIB-4 is the marker that can assess the severity of fibrosis. As well as liver function, liver fibrosis also strongly influences HCC patient survival after liver resection.[28] Similar to our study, these combination scores have been able to better predict HCC patient prognosis than each score alone. Given that clinical outcomes of HCC mainly depend on host factors including hepatic

functional reserve and tumor factor, combined evaluation of these factors would provide better prediction rather than evaluation of each factor alone. In the present study, we focused on hepatic functional reserve and systemic inflammatory response represented by CAR. Hepatic functional reserve can affect the selection of treatment strategy, which has been associated with the patient's prognosis and recurrence of HCC.[15,16] Recent studies suggested that inflammatory markers have also been strong predictors of long-term outcomes in several kinds of cancer including HCC. Although tumor-related factors have been key factors in terms of the prediction of survival, studies suggested that inflammatory markers may have better prediction of survival.[20] Thus, in this study, we attempted to utilize inflammatory markers and an indicator of hepatic functional reserve, and our findings suggested that this novel combined marker can provide more sensitive prediction of outcomes. Although CAR and mALBI were significant predictors of long-term outcomes in the univariate analysis, multivariate analysis using the backward elimination method showed the combined score was the only independent prognostic factor with the highest HR in overall survival. Low liver function and high inflammatory state may not only independently affect patient prognosis, but also complicatedly influence each other in the host and may cause a more comfortable environment for cancer cell promotion. In our study, CAR-mALBI score was associated with not only overall survival but also disease-free survival. Early recurrence can occur from circulating tumor cells (CTCs), micrometastasis, host immunosuppression due to surgical stress, and dissemination of tumor cells due to surgical procedures.[29] The systemic inflammatory state promotes the adhesion of CTCs to vascular endothelial cells and leads to constitute distant metastasis. Malnutrition and systemic inflammatory state have been associated with a decrease in host immune response.[30] Tumor cell proliferation can be accelerated under such conditions. Moreover, low liver function patients have a high carcinogenic potential for de novo recurrence because of underlying liver disease.[18] Given inflammation and malnutrition and liver reserve are deeply committed to the mechanism of early relapse, the CAR-mALBI score can also predict disease recurrence and provide better stratification in disease-free survival as well.

This study has potential limitations. The study design was retrospective and included a single institution with limited sample size. Thus, potential bias could not be completely eliminated. Further study is needed to validate our finding in larger cohorts.

5 | CONCLUSION

We have shown that the CAR-mALBI score was significantly associated with disease-free and overall survival in patients with HCC. Our finding gives new insight into the interaction of liver function and host-inflammatory state for the risk prediction of HCC patients.

AUTHOR CONTRIBUTIONS

TA, KH, and MA developed the main concept and designed the study. KF, SO, YS, HS, KT, and TO were responsible for acquisition of clinicopathological data. TA, KH, and MA performed data analysis and interpretation. TA, KH, and TI drafted the manuscript. KF, SO, YS, HS, KT, and TO contributed to editing and critical revision for important intellectual content.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

ETHICS STATEMENT

Approval of the research protocol: This study protocol was approved by the Ethics Committee of Jikei University School of Medicine (#27–177).

Informed Consent: Patients were given an opportunity to optout of this study through public announcements.

Registry and the Registration No. of the study/trial: Not applicable.

Animal Studies: Not applicable.

ORCID

Koichiro Haruki https://orcid.org/0000-0002-1686-3228
Kenei Furukawa https://orcid.org/0000-0002-5081-6417
Yoshihiro Shirai https://orcid.org/0000-0002-4907-0101
Keita Takahashi https://orcid.org/0000-0003-0149-3401
Toru Ikegami https://orcid.org/0000-0001-5792-5045

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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