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ORIGINAL ARTICLE

Albumin-indocyanine green evaluation of future liver remnant predicts liver failure after anatomical hepatectomy for hepatocellular carcinoma: A dual-center retrospective study

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Abstract

Aim: The albumin-indocyanine green evaluation (ALICE) score is a useful predictor of post-hepatectomy liver failure (PHLF); however, its usefulness in combination with future liver remnant (FLR), measured by 3-D volumetry, has not been investigated. This study aimed to investigate the relationship between the ALICE of the FLR (ALICE-FLR) score and severe PHLF.

Methods: The clinical data of 215 patients who underwent anatomical hepatectomy for hepatocellular carcinoma without portal vein embolization at two institutes between January 2010 and December 2021 were analyzed retrospectively. PHLF occurrence and severity were determined according to the International Study Group of Liver Surgery's definition. Grades B and C PHLF were defined as severe PHLF. The ALICE-FLR, ALICE scores, and indocyanine green clearance of FLR (ICGK-FLR) were evaluated for severe PHLF prediction.

Results: Severe PHLF was observed in 40 patients (18.6%). The areas under the curve (AUCs) for the ALICE-FLR, ALICE scores, ICGK-FLR, and FLR were 0.76, 0.64, 0.73, and 0.69, respectively. The AUC of the ALICE-FLR score was significantly higher than that of the ALICE score. The ALICE-FLR score was identified as an independent predictor of severe PHLF (the odds ratio for every 0.01 increment in the ALICE-FLR score was 1.24; 95% confidence interval, 1.070–1.453; $p = 0.004$). Among patients with severe PHLF, the ALICE-FLR score was significantly higher in the grade C than in the grade B PHLF group.

Conclusion: The combination of liver function models, including indocyanine green, albumin, and FLR is considered compatible for predicting severe PHLF.

KEYWORDS
albumin, hepatectomy, hepatocellular carcinoma, indocyanine green, liver failure

1 | INTRODUCTION

Hepatectomy is a complex gastroenterological surgical procedure with a high risk of complications.[1] Post-hepatectomy liver failure (PHLF) is the main cause of morbidity and mortality after hepatectomy. Despite major improvements in surgical techniques and perioperative management, PHLF remains the most serious complication of liver surgery.[2] Therefore, the preoperative prediction of severe PHLF occurrence is beneficial.

Indocyanine green (ICG), a cyanine dye, is selectively taken up by the liver and excreted in the bile; therefore, liver function can be assessed directly by measuring serum ICG level.[3] Especially in Asian countries, the ICG test is regarded as a reliable preoperative assessment tool of liver function. Makuuchi et al.[4] have reported a criterion for the surgical limit of remnant liver volume based on preoperative serum ICG retention rate at 15 min (ICG-R15) values to reduce postoperative mortality due to severe PHLF. Recently, Kokudo et al.[5] proposed a new model of liver function estimation using serum albumin and ICG-R15 levels. They reported that the albumin-ICG evaluation (ALICE) score is a good predictor of PHLF and post-hepatectomy mortality in patients with hepatocellular carcinoma (HCC).

Preoperative 3-D volumetry enables liver surgeons to understand complicated liver structures and calculate the future liver remnant (FLR).[6] When scheduling excessive hepatectomy, portal vein embolization is performed with the aim of increasing the FLR and improving postoperative outcome.[7,8] ICG clearance of the FLR (ICGK-FLR), which comprises the serum ICG clearance (ICG-K) value and FLR, is a better predictor of severe PHLF occurrence than ICG-K alone.[9,10] We hypothesized that the combination of the ALICE score and FLR is a more powerful predictive model for severe PHLF occurrence than the ALICE score alone. Therefore, we investigated the relationship between the ALICE of the FLR (ALICE-FLR) score and PHLF occurrence after hepatectomy for HCC and compared it with ALICE score and other preoperative factors. To determine the exact total functional and remnant liver volume using 3-D volumetry, this study included only patients who underwent anatomical hepatectomy without portal vein embolization.

2 | METHODS

2.1 | Patients and data collection

This was a dual-center, retrospective cohort study. Between January 2010 and December 2021, 332 patients underwent hepatectomy for HCC at Ehime University Hospital and its affiliated Uwajima City Hospital. Of those, six patients who received portal vein embolization preoperatively and 109 who underwent partial hepatectomy were excluded. Of the remaining 217 patients, two were excluded because of insufficient medical records for analysis. Finally, 215 patients were included in the study. To clarify the differences in factors related to the presence or absence of severe PHLF and assess the ALICE-FLR score as a severe PHLF predictor, we collected clinical and pathological data, including pre-, intra-, and postoperative and tumor-related factors. This study was approved by the Institutional Review Board of each institution (No. 2102011), with a waiver of written informed consent from the patients and was conducted in accordance with the ethical guidelines of the 2013 Declaration of Helsinki. The protocol was described on Ehime University Hospital's website, and the participants had the opportunity to opt out of the study. All patient records were anonymized and de-identified before analysis.

2.2 | FLR measurement

Abdominal computed tomography performed within 2 months before surgery was used for image analysis. To calculate future liver volume, contrast-enhanced computed tomography images with a triphasic liver protocol were analyzed using 3D simulation software (SYNAPSE VINCENT®; FUJIFILM, Tokyo, Japan). FLR was defined as the ratio of future liver volume to total functional liver volume, which was calculated by subtracting the tumor volume from the total liver volume.

2.3 | ICG-K and ICG-R 15 measurement

The ICG test was performed in all patients within 4 weeks before hepatectomy. After resting in the recumbent position for >30 min, an intravenous bolus of 0.5 mg/kg ICG was injected into the peripheral vein, and a blood sample was drawn from another site 5, 10, and 15 min later. ICG-K values were automatically calculated by plotting the decay curve of serum ICG concentration over time. ICG-R 15 values were expressed as the percentage of serum ICG level remaining 15 min post-injection.

2.4 | Definition

The ALICE score was calculated according to a previous report as follows: $0.663 \times \log_{10}$ICG-R 15 (%) $- 0.718 \times$ albumin (g/dL).[5] ICGK-FLR and ALICE-FLR scores were obtained by multiplying the ICG-K and ALICE scores with FLR, respectively. To calculate the ALICE and ALICE-FLR scores, we obtained the preoperative albumin value from the blood test on the same day as or the closest day to the ICG test. PHLF occurrence and severity were determined according to the International Study Group of Liver Surgery in 2011.[11] In this study, grade B and C PHLF were defined as severe PHLF. Macrovascular invasion is defined as Vv2-4 and/or Vp2-4 according to the Liver Cancer Study Group of Japan's proposed classification.[12] Ninety-day mortality was defined as all deaths within 90 days after surgery. All patients were followed up for at least 90 days postoperatively.

2.5 | Surgical procedure

In principle, ICGK-FLR of 0.05 or higher is considered an indication for anatomical hepatectomy at our hospitals. If ICGK-FLR is less than 0.05, percutaneous transhepatic portal vein embolization is performed, if possible. Anatomical hepatectomy was performed according to the Brisbane 2000 Terminology of Liver Anatomy and Resections.[13] Both hospitals used the same parenchymal transection method. A Cavitron ultrasonic surgical aspirator and electrical cautery with water irrigation were used to perform liver parenchymal dissection. All the procedures were performed and/or supervised by expert surgeons, accredited by the Japanese Society of Hepato-Biliary-Pancreatic Surgery.[14]

2.6 | Statistical analysis

Continuous variables are presented as median (range) and were analyzed non-parametrically using the Mann–Whitney U test. Categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate. The receiver operating characteristic (ROC) curve was calculated to evaluate the predictive ability of the model, and the Youden index was used to determine the optimal cutoff value of the continuous variables. Statistical significance was set at $p < 0.05$, and the factors with $p < 0.05$ in the univariate analysis were subjected to multivariate analysis using logistic regression analysis. JMP version 12.2 software (SAS Institute) was used for all analyses.

3 | RESULTS

3.1 | Univariate analysis of factors associated with severe PHLF

A univariate analysis was performed to investigate the preoperative, intra-operative, postoperative, and tumor-related factors associated with severe PHLF, as shown in Table 1. Of 215 patients,

TABLE 1 Univariate analysis of factors associated with severe PHLF.

Factors	Total $N = 215$	Severe PHLF group $N = 40$	Non-severe PHLF group $N = 175$	p-Value
Preoperative				
Sex, male	170 (79.7)	30 (75.0)	140 (80.0)	0.483
Age, years	72 (41, 86)	69 (41,85)	72 (42, 86)	0.076
BMI, kg/m^2	23.6 (15.4, 35.6)	24.0 (17.6, 35.6)	23.4 (15.4, 35.3)	0.489
Diabetes mellitus	81 (37.6)	18 (45.0)	63 (36.0)	0.289
Hepatitis virus infection				0.551
Hepatitis B virus	50 (23.3)	9 (22.5)	41 (23.4)	0.900
Hepatitis C virus	70 (32.6)	12 (30.0)	58 (33.1)	0.702
ICG-K	0.146 (0.041, 0.376)	0.138 (0.055, 0.292)	0.148 (0.041, 0.376)	0.218
ALICE score	−2.11 (−3.13, −0.91)	−1.93 (−3.13, −1.13)	−2.13 (−3.10, −0.91)	0.007
MELD score	6 (6–13)	6 (6, 12)	6 (6, 13)	0.336
Child–Pugh grade A/B	207 (96,3) /8 (3.7)	37 (92.5) / 3 (7.5)	170 (97.1) / 5 (2.9)	0.162
Tumor-related				
Multifocality	67 (31.2)	12 (30.0)	55 (31.4)	0.860
Maximum size of tumor, ≥2 cm	184 (85.6)	35 (87.5)	149 (85.1)	0.702
Macrovascular invasion	21 (9.8)	9 (22.5)	12 (6.9)	0.003
Intraoperative				
Open approach	197 (91.6)	39 (97.5)	158 (90.3)	0.137
Operation time, min	401 (170, 1009)	484 (245, 925)	367 (170, 1009)	<0.001
Blood loss volume, mL	520 (5, 10000)	957 (130, 10000)	501 (5, 7050)	0.003
Red blood cell transfusion	45 (20.9)	15 (37.5)	30 (17.1)	0.004
Postoperative				
Postoperative hospital stays, days	15 (6, 123)	28 (13, 121)	14 (6, 123)	<0.001
PHLF grade B/C	35 (16.3)/5 (2.3)	35 (87.5)/5 (12.5)	0/0	
90-day mortality	3 (1.4)	3 (7.5)	0	0.006[a]

Note: Categorical and continuous variables are presented as patient numbers with ratios (%) and medians with ranges, respectively.

Abbreviations: ALICE, albumin-indocyanine green evaluation; BMI, body mass index; ICG-K, indocyanine green clearance; MELD, model for end-stage liver disease; PHLF, post-hepatectomy liver failure.

[a]Fisher's exact test.

TABLE 2 Univariate analysis of volumetry-related factors associated with severe PHLF.

Factors	Total $N=215$	Severe PHLF group $N=40$	Non-severe PHLF group $N=175$	p-Value
FLR, %	70.0 (27.8, 95.1)	61.8 (30.1, 85.9)	71.7 (27.8, 95.1)	<0.001
Planned procedure				0.177
Trisectionectomy	3 (1.4)	1 (2.5)	2 (1.1)	
Bisectionectomy	82 (38.2)	20 (50.0)	62 (35.4)	
Sectionectomy	102 (47.4)	17 (42.5)	85 (48.6)	
Segmentectomy	28 (13.0)	2 (5.0)	26 (14.9)	
ICGK-FLR	0.097 (0.032, 0.201)	0.071 (0.032, 0.176)	0.103 (0.037, 0.201)	<0.001
ALICE-FLR score	−1.40 (−2.56, −0.56)	−1.11 (−2.04, −0.57)	−1.48 (−2.56, −0.56)	<0.001

Note: Categorical and continuous variables are presented as patient numbers with ratios (%) and medians with ranges, respectively.

Abbreviations: ALICE-FLR, albumin-indocyanine green evaluation of future liver remnant; FLR, future liver remnant; ICG-FLR, indocyanine green clearance of future liver remnant; PHLF, post-hepatectomy liver failure.

severe PHLF occurred in 40 patients (18.6%): grades B and C in 35 (16.3%) and five (2.3%) patients, respectively. Regarding preoperative and tumor-related factors, the median ALICE score (−1.93 vs. −2.13, $p<0.001$) and the incidence of macrovascular invasion (22.5% vs. 6.9%, $p=0.003$) were significantly higher in the severe PHLF group than in the non-severe PHLF group. Regarding intraoperative factors, the median operation time (484 min vs. 367 min, $p<0.001$), blood loss volume (957 vs. 501 mL, $p<0.003$), and incidence of red blood cell transfusion (37.5% vs. 17.1%, $p=0.004$) were significantly higher in the severe PHLF group than in the non-severe PHLF group. Regarding postoperative factors, the median length of postoperative hospital stays (28 vs. 14 days, $p<0.001$) was significantly longer in the severe PHLF group than in the non-severe PHLF group. The incidence of 90-day mortality (7.6% vs. 0%, $p=0.006$) was significantly higher in the severe PHLF group than in the non-severe PHLF group. In contrast, no significant differences between the severe PHLF and non-severe PHLF groups were observed for the ICG-K ($p=0.218$), Child–Pugh grade ($p=0.1616$), and MELD score ($p=0.336$). Table 2 shows the results of the univariate analysis of the relationship between volumetry-related factors and severe PHLF occurrence. The median FLR (61.8% vs. 71.7%, $p<0.001$) and ICGK-FLR (0.071 vs. 0.103, $p<0.001$) were significantly lower in the severe PHLF group than in the non-severe PHLF group. The median ALICE-FLR score (−1.11 vs. −1.48, $p<0.001$) was significantly higher in the severe PHLF group than in the non-severe PHLF group.

3.2 | ROC curve analysis for severe PHLF

Figure 1 shows the results of ROC curve analysis of preoperative predictors with a p-value <0.05 by univariate analysis for severe PHLF. The areas under the curve (AUCs) of the ALICE-FLR, ALICE scores, ICGK-FLR, and FLR were 0.76, 0.64, 0.73, and 0.69, respectively. The AUC of the ALICE-FLR scores was significantly higher than that of the ALICE scores ($p=0.020$), whereas no significant difference was observed between the AUCs of the ALICE-FLR scores and those of the ICGK-FLR ($p=0.415$) and FLR ($p=0.109$). The optimal cut-off value of the ALICE-FLR score for severe PHLF prediction was −1.19, with a sensitivity of 0.63 and specificity of 0.78.

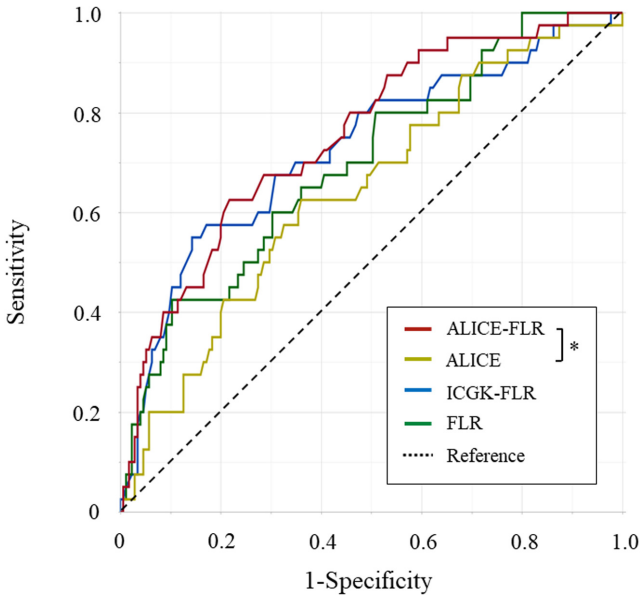

FIGURE 1 Receiver-operating characteristic (ROC) curve of preoperative predictors for severe post-hepatectomy liver failure. The areas under the curve of the albumin-indocyanine green evaluation of future liver remnant (ALICE-FLR), albumin-indocyanine green evaluation (ALICE), and indocyanine green clearance of future liver remnant (ICGK-FLR) are 0.76, 0.64, 0.73, and 0.69, respectively. *$p<0.05$.

3.3 | Multivariate analysis for severe PHLF

Multivariate logistic regression analyses for severe PHLF were performed. To avoid multicollinearity, FLR was excluded such that the variance inflation factor for each factor subjected to multivariate analysis was less than 5.[15] The ALICE-FLR score was identified as an independent risk factor for severe PHLF, as shown in Table 3.

TABLE 3 Multivariate analysis of preoperative risk factors for severe PHLF.

Factors	Odds ratio	95% CI lower	95% CI upper	*p*-Value
Macrovascular invasion, yes vs. no[a]	2.89	0.990	8.276	0.052
ICGK-FLR	1.05	0.874	1.264	0.636
ALICE score	1.00	0.901	1.110	0.982
ALICE-FLR score	1.24	1.070	1.453	0.004

Abbreviations: ALICE, albumin-indocyanine green evaluation; ALICE-FLR, albumin-indocyanine green evaluation of future liver remnant; CI, confidence interval; ICG-FLR, indocyanine green clearance of future liver remnant.

[a]Reference. The odds ratio in ICGK-FLR is given for each decrement of 0.01. The odds ratios in ALICE and ALICE-FLR scores are given for each increment of 0.1.

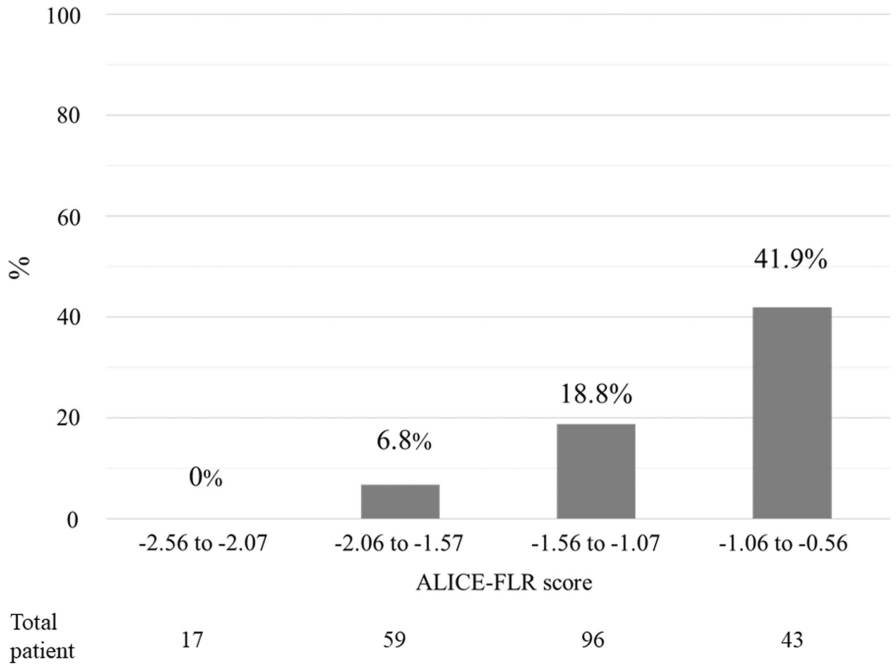

FIGURE 2 Relationship between albumin-indocyanine green evaluation of future liver remnant (ALICE-FLR) score and severe post-hepatectomy liver failure occurrence.

The odds ratio for severe PHLF for every 0.01 increment in ALICE-FLR score was 1.24 (95% confidence interval (CI), 1.070–1.453; $p=0.004$). There was a marginally significant correlation between macrovascular invasion and severe PHLF (odds ratio, 2.89; 95% CI, 0.990–8.276; $p=0.052$). Figure 2 shows that the incidence of severe PHLF increases with increasing ALICE-FLR score. Additionally, to determine whether the planned procedure was influenced by the ALICE score, we also examined the relationship between ALICE score and FLR for each type of hepatectomy, but there was no correlation between them (Figure S1).

3.4 | Relationship between ALICE and ALICE-FLR scores and PHLF severity

We investigated the relationship between the ALICE and ALICE-FLR scores and PHLF severity in 40 patients with severe PHLF. The median ALICE-FLR score was significantly higher in grade C than in grade B PHLF (−0.74 vs. −1.16, $p<0.001$) (Figure 3A). In contrast, the median ALICE score was not significantly different between grade B and C PHLF (−1.74 vs. −1.94, $p=0.117$) (Figure 3B).

4 | DISCUSSION

This study demonstrated that the ALICE-FLR score is a significantly more reliable predictor of severe PHLF occurrence and severity than the ALICE score alone. Furthermore, the ALICE-FLR score showed the highest AUC over other preoperative predictors of PHLF. To our knowledge, this is the first study to examine the relationship between the ALICE-FLR score and PHLF.

The ICG test is a dynamic liver function test that can evaluate the actual liver function at the time of evaluation.[16] The Makuuchi criteria, which include the ICG-R 15 value, allow the indication for safe hepatectomy to reflect the patient's liver function in more detail than the Child–Pugh grade.[17] Kokudo et al.[5] reported that the ALICE grade can be regarded as a combination of the Makuuchi criteria and the Child–Pugh grading system. The ALICE score was classified into grades 1, 2, and 3 as normal, impaired, and poor liver function, respectively, and a range of possible hepatectomy procedures was proposed according to the grades. Shirata et al.[18] also reported that patients with HCC who underwent sectionectomy or more extensive resections had poor postoperative outcomes in an ALICE grade 2 group. Even for hepatectomy in

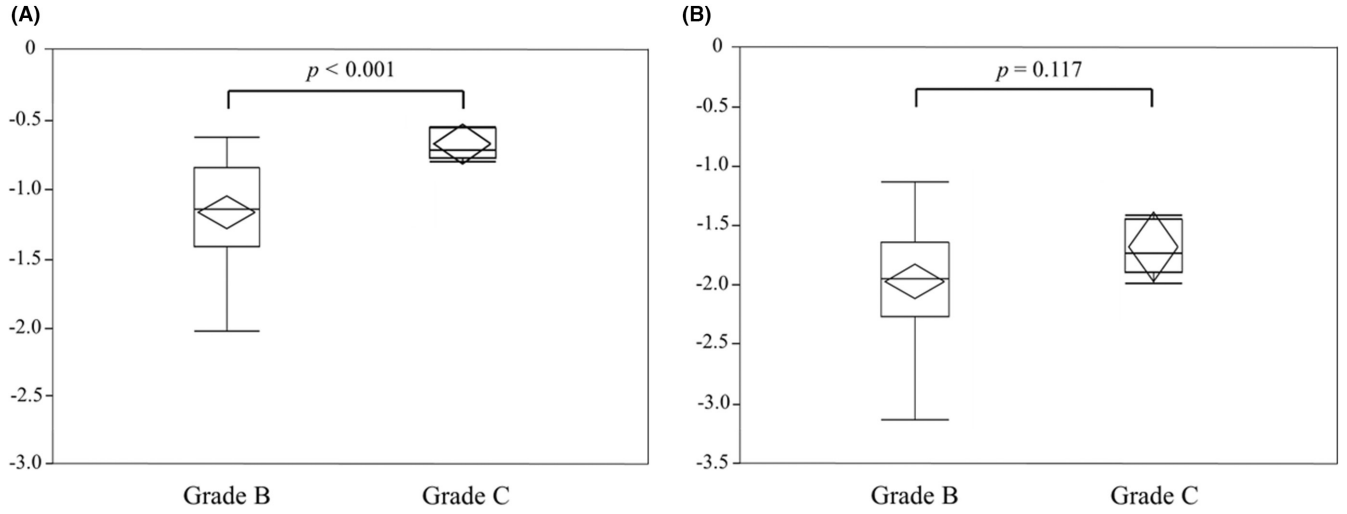

FIGURE 3 Relationship between the liver function model score and severity of post-hepatectomy liver failure (PHLF). (A) Severe PHLF and albumin-indocyanine green evaluation of future liver remnant (ALICE-FLR) score; (B) severe PHLF and albumin-indocyanine green evaluation (ALICE) score.

patients with biliary tract cancer, the ALICE grading system effectively stratifies the risk of PHLF.[19]

FLR is strongly associated with the development of PHLF[20] and was a significant predictor of severe PHLF in our study. Guglielmi et al.[21] proposed that in patients with hepatic impairment, preoperative assessment of severe PHLF risk should include FLR and accurate liver function evaluation. Particularly in HCC, liver function varies greatly among individuals owing to the progression of liver fibrosis.[22] Therefore, it is preferable to clinically use an accurate liver function model, including ICG-R15 and FLR, for safe hepatectomy. The ICGK-FLR is a useful predictive score for severe PHLF and mortality, with a reported criterion of 0.05 for safe hepatectomy.[9,10,23] Iguchi et al.[24] reported that the ICGK-FLR was correlated with PHLF occurrence and severity. In our study, the ICGK-FLR showed the second highest AUC for severe PHLF prediction after the ALICE-FLR score, and was correlated with severity of PHLF ($p = 0.031$, data not shown). By contrast, because the ALICE-FLR score formula includes serum albumin—an important liver function variable—in addition to ICG-R15 and FLR, the ALICE-FLR score may be a more valuable predictor of severe PHLF than the ICGK-FLR. We found it to be an independent predictor of severe PHLF in multivariate analysis and suggest that when the ALICE-FLR score is −1.2 or higher, the type of hepatectomy should be carefully selected, including parenchymal-sparing hepatectomy, which can achieve radical resection of the tumor and increase the FLR more. Additionally, in the severe PHLF group, the ALICE-FLR score predicted PHLF severity, and the score was significantly higher in grade C than in grade B PHLF, although grade C PHLF occurred in only five patients. In this study, there were three deaths within 90 days after surgery and one of the patients developed grade C PHLF with an ALICE-FLR score of −0.72, which was considered to have a strong influence on mortality. Although our study is inappropriate to examine the relationship between the ALICE-FLR score and post-hepatectomy mortality due to the small number of deaths, the ALICE-FLR score is considered a possible predictor for post-hepatectomy mortality similar to the ICGK-FLR. Thus, the ALICE-FLR score may be a more accurate model for remnant liver function estimation and a reliable preoperative predictor of severe PHLF. The efficacy and appropriate cut-off value of the ALICE-FLR score for severe PHLF and limit of surgical safety need to be investigated further.

4.1 | Limitations

This study had some limitations. First, this was a retrospective analysis of a relatively small number of patients at a dual center. Second, this study included only patients who had undergone anatomical hepatectomy, that is, those with relatively preserved liver function. Therefore, the results may differ in a cohort that includes patients with poor liver function who can only undergo non-anatomical hepatectomy. Despite these limitations, this study examined a new predictor of severe PHLF using a combination of preoperative conventional and dynamic liver function test results and 3-D volumetry; this noninvasive risk model may contribute to safe hepatectomy.

5 | CONCLUSIONS

The ALICE-FLR score showed a superior predictive value compared with the ALICE score alone for the occurrence and severity of PHLF. The combination of liver function models, including ICG, albumin, and FLR, measured by 3-D volumetry, is considered compatible for predicting severe PHLF.

AUTHOR CONTRIBUTIONS

Tomoyuki Nagaoka, Kohei Ogawa, and Katsunori Sakamoto conceived the study. Taro Nakamura, Yoshinori Imai, and Yusuke Nishi

collected the data. Katsunori Sakamoto and Yasutsugu Takada supervised the conduct of the study. Kohei Ogawa, Katsunori Sakamoto, Masahiko Honjo, Kei Tamura, Naotake Funamizu, and Yasutsugu Takada provided statistical advice on the study design and analyzed the data. Tomoyuki Nagaoka and Kohei Ogawa drafted the article and managed the data. Katsunori Sakamoto, Taro Nakamura, Yoshinori Imai, Yusuke Nishi, Masahiko Honjo, Kei Tamura, Naotake Funamizu, and Yasutsugu Takada revised the manuscript. Tomoyuki Nagaoka and Kohei Ogawa take responsibility for the paper as a whole. All authors are in agreement with the content of the manuscript.

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CONFLICT OF INTEREST STATEMENT

All authors have no related conflicts of interest to declare.

ETHICS STATEMENT

This study was approved by the Institutional Review Board of Ehime University Hospital and Uwajima City Hospital in February 2023 (No. 2102011) with a waiver of informed consent from patients and was conducted in accordance with the ethical guidelines of the 2013 Declaration of Helsinki. The protocol was described on Ehime University Hospital's website, and the participants had the opportunity to opt out of the study.

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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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