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Original Article

Combination of systemic immune-inflammation index and albumin-bilirubin grade predict prognosis of regorafenib in unresectable hepatocellular carcinoma

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Abstract: Regorafenib improved prognosis for unresectable hepatocellular carcinoma (uHCC) after sorafenib treatment failure. We aimed to investigate prognostic value of combining systemic inflammatory markers with liver function evaluation in patients receiving sorafenib-regorafenib sequential therapy. A total of 122 uHCC patients who received sorafenib-regorafenib sequential therapy were retrospectively enrolled for analysis. The pre-treatment preserving liver function and six inflammatory indexes were collected. The Cox regression model was used to identify independent predictors of progression-free survival (PFS) and overall survival (OS). Baseline ALBI grade I (hazard ratio (HR) = 0.725, P = 0.040 for PFS; HR = 0.382, P = 0.012 for OS) and systemic inflammatory index (SII) ≤ 330 (HR = 0.341, P = 0.017 for OS; HR = 0.485, P = 0.037 for OS) were identified as independent prognostic factors in multivariable analysis and were used to develop the scoring system. Patients who fulfilled both criteria (2 points; score-high) had the longest median PFS (not-reached) and OS (not-reached), followed by fulfilling 1 criterion (1 point; score-intermediate; PFS: 3.7 months and OS: 17.9 months), and patients fulfilled no criterion (0 point; score-low; PFS: 2.9 months, overall log-rank P = 0.001 and OS: 7.5 months, overall log-rank P = 0.003). Additionally, best radiological response was significantly higher in patients with score-high (complete response/partial response/stable disease/progressive disease: score-high: 5.9%/5.9%/58.8%/29.4% vs. score-intermediate: 0%/14.0%/44.2%/41.9% vs. score-low: 0%/0%/25.0%/75.0%; P = 0.011). In conclusion, a combination of baseline ALBI grade and SII index can be used as a simple and powerful parameter to predict prognosis of uHCC patients receiving regorafenib after sorafenib-refractory treatment. The score may help with patient counseling but requires prospective validation.

Keywords: Hepatocellular carcinoma, sequential therapy, systemic inflammatory index, ALBI grade, prognosis

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths [1] worldwide and patients are often diagnosed at an advanced stage without the opportunity to receive curative treatments. Several systemic treatment options including tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors are available [2-5]. Patients with unresectable hepatocellular carcinoma (uHCC) have median overall survival (OS) increasing from 9 to 35 months after two or more lines of systemic therapy [6-8]. However, information about the survival benefit and the most optimal combination of sequential therapy is still under investigated. Regorafenib is an oral multikinase inhibitor that blocks the activity of protein kinases involved in angiogenesis, oncogenesis, metastasis, and tumor immunity [9, 10]. The results of RESORCE study demonstrated that regorafenib significantly improves OS compared with placebo in uHCC patients who had radiologic progression during sorafenib treatment [11]. However, the benefit for patients with uHCC following sorafenib-regorafenib sequential therapy varies greatly from person to person [12, 13].

Inflammation plays an essential role in tumor development and immune surveillance plays a crucial role in cancer elimination [14]. A series

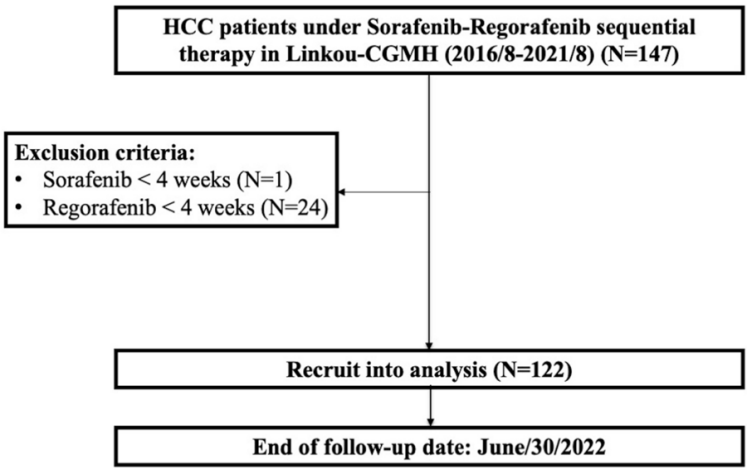

Figure 1. Flowchart of patients' enrollment.

of inflammation-based indexes (IBI) derived from peripheral inflammatory cells, including neutrophil to lymphocyte ratio (NLR) [15], platelet-to-lymphocyte ratio (PLR) [16], monocyte-to-lymphocyte ratio (MLR) [17], systemic immune-inflammation index (SII) [18], systemic inflammation response index (SIRI) [19], and integrated liver inflammatory score (ILIS) [20] are associated with prognosis in HCC patients. Besides, preserving liver function is essential to achieving favorable outcomes of sequential systemic therapy [21]. However, the role of inflammation, evaluated by simple peripheral blood immune cells, combining preserved liver function in predicting outcome of regorafenib treatment is still lacking. Therefore, we aimed to investigate issue in patients receiving regorafenib after sorafenib-refractory treatment.

Materials and methods

Patient recruitment

We reviewed all patients who received sorafenib-regorafenib sequential therapy from 2016 to 2021 at Chang Gung Memorial Hospital, Linkou branch, a medical referral center in Taiwan. A total of 122 patients who received regorafenib as second or beyond a second-line systemic therapy because their tumor burden fulfilled with Barcelona Clinic Liver Cancer (BCLC) stage C or not suitable for resection and locoregional therapy in BCLC stage B with Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 were included (**Figure 1**). Confirmation of radiological progression during sorafenib therapy and tolerability for sorafenib (sorafenib ≥ 400 mg/day for 20 or more days of the last 28 days) were strongly recommended for treatment conversion from sorafenib to regorafenib in accordance with the inclusion criteria of the RESORCE trial. The standard starting dose of regorafenib was 160 mg orally once a day for 3 weeks, followed by 1 week of no treatment in each cycle. Nevertheless, modification of the starting dose was allowed at the discretion of the attending physicians. Regorafenib therapy was continued until disease progression, death, or any intolerable adverse event. Patients who received sorafenib or regorafenib less than 4 weeks and lost to follow-up were excluded. This study was approved by Linkou Chang-Gung Memorial Hospital Institutional Review Board (IRB number: 202002147B0).

Laboratory examination

Biochemical tests were performed within 7 days before initiation of regorafenib therapy using automated techniques at the clinical pathology laboratories of the hospital. The albumin-bilirubin (ALBI) score was computed by the formula, -0.085 × (albumin g/l) + 0.66 × log (bilirubin μmol/l), HCC patients were stratified into 3 groups according to previously described cut-offs resulting in 3 grades: ALBI grade 1 (≤ -2.60), grade 2 (> -2.60 to -1.39) and grade 3 (> -1.39). The inflammatory markers were calculated by the following formula: NLR = neutrophil/lymphocyte, PLR = platelet/lymphocyte, MLR = monocyte/lymphocyte, SII = platelet × neutrophil/lymphocyte, SIRI = monocyte × neutrophil/lymphocyte, and ILIS = -0.057 × albumin (g/L) + 0.978 × log (bilirubin, mol/L) + 1.341 × log (ALP, IU/L) + 0.086 × neutrophil (10^9/L) + 0.301 × log (AFP, μg/L).

Diagnosis of hepatocellular carcinoma and follow-up protocol

HCC was diagnosed with hyperattenuation in the arterial phase and washout in the late phase [22] by multiphasic, contrast-enhanced

imaging (computed tomography (CT)/magnetic resonance imaging (MRI) scans) and/or histology according to European Association for the Study of the Liver/European Organization for Research and Treatment of Cancer (EASL/EORTC) diagnostic guideline [23]. We monitored HCC status by dynamic CT or MRI every 8-12 weeks intervals and measurement of serum AFP levels every 4-8 weeks.

Tumor response was assessed according to the revised Response Evaluation Criteria in Solid Tumors (RECIST) [24]: complete response (CR) defined as disappearance of all target lesions; partial response (PR) defined as at least a 30% decrease in the sum of diameters of target lesions; progressive disease (PD) defined as at least a 20% increase in the sum of diameters of target lesions and stable disease (SD) defined as neither PR nor PD. Patients were censored at the date of the last contact or cutoff for patients who were still alive without radiologically confirmed progression or until the date of death.

Statistical analysis and definitions

Descriptive data with normal distribution are reported as mean ± standard deviation (SD) or as percentage otherwise as median (range). The independent Student't test and Mann-Whitney U test were used to assess differences between groups in normal distributed and non-normal distributed variables respectively. Chi-square test was used for categorical variables between the 2 groups. A 2-tailed P value < 0.05 was considered as statistically significant.

Overall survival (OS) was defined as the time from start of drug until the date of death. Patients who were still alive were censored at the date of last contact or data cut-off. Progression-free survival (PFS) was defined as the time from the date of first drug administration until radiological disease progression or death, whatever came first. Patients who were still alive without radiologically confirmed progression were censored at the date of last contact or data cut-off. Survival curves were calculated using the Kaplan-Meier method and compared by means of the log-rank test. Cox regression model were used to determine the associations of the predictive factors to PFS and OS. The primary endpoint was overall survival. Secondary efficacy endpoints were progression-free survival, objective response rate (patients with complete or partial response), and disease control rate (patients with complete response, partial response, or stable disease).

Area under the receiver operating characteristic curve (AUROC) and Youden Index were applied for optimal cutoff value of each IBI for prediction of PFS and OS. DeLong's test was performed for the statistical comparison of each AUROC. Clinical usefulness and net benefit were estimated with decision curve analysis (DCA) [25]. Statistical analyses were performed using SAS version 9.4 and SPSS software, version 20.0 (SPSS, Inc., Chicago, IL).

Results

The baseline characteristics of enrolled patients

A total of 122 patients who received regorafenib therapy after sorafenib failure for unresectable HCC were evaluable. The main baseline characteristics are shown in **Table 1**. HBV infection was the most common etiology of HCC (n = 59, 48.4%), followed by HCV infection (n = 40, 32.8%) and non-B, non-C status (n = 23, 18.8%). One hundred and three patients (84.4%) were male gender and most patients still remained in Child-Pugh class A (n = 117, 95.9%) and nearly half of them were ALBI grade I (n = 59, 48.4%) liver reserve function when receiving regorafenib. Forty patients (32.8%) had AFP level ≥ 400 ng/ml. Forty patients (32.8%) encountered macrovascular invasion and sixty-three patients (51.6%) had extrahepatic metastasis. Regorafenib was used as the second and more than second lines of systemic therapy in 97 (79.5%) and 25 (20.5%) patients respectively. At the initiation of sorafenib administration, most patients had BCLC stage C (n = 85, 69.7%) and macrovascular invasion occurred in 40 patients (32.8%) as well as fifty-nine patients (48.4%) had extrahepatic metastasis. Seventy-one patients (58.2%) received combination therapy with transarterial chemoembolization (TACE) or radiofrequency ablation (RFA). All patients were confirmed to have radiological progression during sorafenib therapy and received ≥ 400 mg/day sorafenib at the time of sorafenib discontinuation. The median sorafenib treatment duration was 6.9 months and the median time between sorafenib

Table 1. Baseline characteristics of enrolled patients at initiation of regorafenib

Variables	Overall (N = 122)
Age (years-old)	65.7 (IQR 60.8-73.5)
Male gender	103 (84.4)
Etiology	
HBV/HCV/others	59/40/23 (48.4/32.8/18.8)
Child-Pugh A/B	116/6 (95.1/4.9)
ALBI grade I/II/III	59/62/1 (48.4/50.8/0.8)
BCLC stage B/C	33/89 (27.0/73.0)
Macrovascular invasion	40 (32.8)
Extra-hepatic metastasis	63 (51.6)
AFP ≥ 400 ng/ml	40 (32.8)
Prior lines of systemic therapy 0/1/≥ 2	0/97/25 (0/79.5/20.5)
Combination therapy	31 (25.4)
Loco-regional therapy	21 (17.2)
Immune checkpoint inhibitors	10 (8.2)
Systemic chemotherapy	3 (2.5)
Duration of therapy (months)	4.1 (IQR 2.6-8.0)
Follow-up duration since therapy start (months)	7.5 (IQR 4.2-13.7)

Abbreviations: AFP, alpha-fetoprotein; ALBI, albumin-bilirubin index; BCLC, Barcelona Clinic Liver Cancer.

discontinuation and regorafenib initiation was 0.5 months (Supplementary Table 1). The median OS was 39.4 months from initiation of sorafenib (**Figure 2A**).

In current study, regorafenib were initiated at 160 and < 160 mg/day in 15 (12.3%) and 107 (87.7%) patients, respectively. The median duration of regorafenib administration was 4.1 months. The median OS was 15.9 months (**Figure 2B**) while PFS were 3.4 months (**Figure 2C**) from initiation of regorafenib. Eighty-two (67.2%) patients experienced at least one adverse event (AE) (Supplementary Table 2). Most common adverse events were hand-foot-skin reaction (n = 46, 37.7%), fatigue (n = 21, 17.2%), diarrhea (n = 20, 16.4%), hypertension (n = 11, 9.0%), abdominal pain (n = 8, 6.6%) and muscle soreness (n = 3, 2.5%). Eight (6.6%) patients developed adverse events of higher grade (grade ≥ 3).

Efficacy of regorafenib

Among 119 patients receiving at least one tumor image assessment, CR, PR and SD were identified in 1 (0.8%), 8 (6.6%) and 48 (39.3%) patients as their best response, with an objective response rate (ORR) of 7.4% and a disease control rate (DCR) of 46.7%, respectively (Supplementary Table 3). Patients with good responder (CR+PR) or stable disease had better OS than those with disease progression (median OS: NR vs. 21.1 vs. 8.0 months, overall log-rank test, P < 0.001; Supplementary Figure 1A). There was no significant difference between patients treated with regorafenib as the second and more than second lines of systemic therapy including best response (6.3% vs. 12.5%, P = 0.306) and OS (median OS from initiation of regorafenib: 13.6 vs. 19.0 months, log-rank P = 0.240).

Seventy-eight patients showed disease progression on regorafenib and 35 patients received post-progression therapy including immune checkpoint inhibitor (n = 17, 48.6%), transarterial chemoembolization (TACE) (n = 7, 20.0%), other TKIs (n = 7, 20.0%), thalidomide or tegafur (n = 5, 14.3%) and systemic chemotherapy (n = 4, 11.4%). Patients treated with post-progression therapy had longer OS than those without post-progression therapy although not reaching statistical significance (median OS: 9.4 vs. 7.5 months, log-rank P = 0.150; Supplementary Figure 1B).

Furthermore, thirty-one patients received combination therapy during regorafenib treatment including loco-regional therapy (n = 21, 17.2%), immune checkpoint inhibitors (n = 10, 8.2%) and systemic chemotherapy (n = 3, 2.5%). Patients receiving combination therapy are prone to be younger (62.4 vs. 66.6 years-old, P

Table 2. Cox's proportional hazards model for predictors of progression-free survival

Variables	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age ≥ 65 years (vs. < 65 years)	1.163	0.742-1.824	0.510			
Male gender (vs. female)	0.966	0.522-1.787	0.911			
Viral etiology (vs. others)	0.793	0.463-1.357	0.397			
Child-Pugh A (vs. B)	0.639	0.232-1.757	0.385			
ALBI grade I (vs. II/III)	0.693	0.442-0.888	0.041	0.725	0.504-0.895	0.040
Macrovascular invasion (vs. no)	1.681	0.961-2.664	0.077			
Extrahepatic distant metastasis (vs. no)	0.676	0.432-1.058	0.087			
BCLC stage B (vs. C)	1.243	0.764-2.023	0.381			
AFP ≥ 400 ng/ml (vs. < 400)	1.338	0.847-2.113	0.092			
Combination therapy (vs. no)	0.562	0.327-0.967	0.037	0.734	0.380-1.421	0.359
SII < 330 (vs. ≥ 330)	0.255	0.119-0.543	< 0.001	0.341	0.141-0.828	0.017
AE (vs. no)	1.003	0.623-1.614	0.991			

Abbreviations: AE, adverse effect; AFP, alpha-fetoprotein; ALBI, Albumin-Bilirubin; BCLC, Barcelona Clinic Liver Cancer; SII, systemic inflammatory index.

= 0.049), better preserving liver function (ALBI grade I: 61.3% vs. 44.0%, P = 0.045) and less advantage tumor stage (BCLC stage C: 61.3% vs. 76.9%, P = 0.041) (Supplementary Table 4). After propensity score matching of age, gender, fibrosis status and tumor stage with a 1:1 ratio, totally 62 patients with 31 patients from each group were analyzed. The characteristics were comparable between these two groups as seen in Supplementary Table 5. Patients with combination therapy had longer OS and PFS than those without not only before matching (median OS: 17.1 vs. 13.2 months, log-rank P = 0.041, Supplementary Figure 2A; median PFS: 6.6 vs. 3.3 months, log-rank P = 0.016, Supplementary Figure 2B) but also after matching (median OS: 17.1 vs. 13.2 months, log-rank P = 0.049, Supplementary Figure 2C; median PFS: 6.6 vs. 3.7 months, log-rank P = 0.040, Supplementary Figure 2D).

Prognostic factors associated with OS and PFS for all patients

When compared with the different scoring systems or indices (NLR, PLR, MLR, SIRI and ILIS) at the time of initiation of regorafenib for predicting PFS, SII and SIRI showed better outperformed discriminatory power, with the receiver operating characteristic curves to determine the prediction are 0.744 (95% CI, 0.629-0.859, P < 0.001) and 0.738 (95% CI, 0.626-0.850, P = 0.001), respectively (Supplementary Figure 3). The prediction models significantly outperformed logistic regression models using either SII or SIRI (DeLong's test, P < 0.05) and was equally good as the others (Supplementary Table 6). When determining the predictors of OS, SII was the best outperformed discriminatory power, with the receiver operating characteristic curves to determine the prediction is 0.640 (95% CI, 0.518-0.762, P = 0.033; Supplementary Figure 4) although all DeLong's test *P* value > 0.05 (Supplementary Table 6).

Decision curve analysis (DCA) was used to facilitate the comparison between different prediction models. As seen in Supplementary Figure 5A, the decision curve analysis graphically shows the clinical usefulness of each model based on a continuum of potential thresholds (X axis) and the net benefit of using the model to risk stratify patients (Y axis) relative to assuming that no patient will have the episode. In this analysis, the SII score provided a larger net benefit across the range of PFS compared with other scores. As seen in Supplementary Figure 5B, the SII score provided a relative larger net benefit across the range of OS compared with some of the scores if not all of them.

We then used SII and other clinical characteristics to define the probable prognostic factors and the outcomes of the univariate and multivariate analyses of the relationship between PFS as well as OS are summarized in **Tables 2** and **3**. According to the univariate Cox regression analyses, ALBI grade, combination therapy

Table 3. Cox's proportional hazards model for predictors of overall survival

Variables	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age ≥ 65 years (vs. < 65 years)	1.161	0.661-2.038	0.604			
Male gender (vs. female)	0.886	0.375-2.095	0.783			
Viral etiology (vs. others)	0.516	0.270-1.086	0.075			
Child-Pugh A (vs. B)	0.671	0.150-1.083	0.065			
ALBI grade I (vs. II/III)	0.539	0.305-0.952	0.033	0.382	0.180-0.810	0.012
Macrovascular invasion (vs. no)	2.848	1.632-4.969	< 0.001	1.704	0.891-3.260	0.107
Extrahepatic distant metastasis (vs. no)	1.825	0.835-3.216	0.077			
BCLC stage B (vs. C)	0.808	0.422-1.548	0.521			
AFP ≥ 400 ng/ml (vs. < 400)	1.704	0.974-2.982	0.062			
Combination therapy (vs. no)	0.607	0.310-0.889	0.045	0.726	0.347-1.522	0.397
SII < 330 (vs. ≥ 330)	0.402	0.188-0.860	0.019	0.485	0.231-0.820	0.037
AE (vs. no)	0.862	0.484-1.537	0.615			
Post-progression therapy (vs. no)	0.481	0.243-0.955	0.037	0.613	0.286-1.313	0.208

Abbreviations: AE, adverse effect; AFP, alpha-fetoprotein; ALBI, Albumin-Bilirubin; BCLC, Barcelona Clinic Liver Cancer; SII, systemic inflammatory index.

and SII level were associated with PFS while ALBI grade, macrovascular invasion, combination therapy, SII level and post-progression therapy were associated with OS. In the multivariate analysis, ALBI grade I (aHR: 0.725, 95% CI 0.504-0.895, P = 0.040) and SII < 330 (aHR: 0.341, 95% CI 0.141-0.828, P = 0.017) were the protective predictors for PFS while ALBI grade I (aHR: 0.382, 95% CI 0.180-0.810, P = 0.012) and SII < 330 (aHR: 0.485, 95% CI 0.231-0.820, P = 0.037) were the protective predictors for OS.

Development of scoring system to predict outcome

Next, we aimed to develop an objective, lab-based score to predict outcome of patients with HCC undergoing sorafenib-regorafenib therapy. Given that both ALBI grade and SII were prognostic factors in multivariable analysis of OS and PFS, we developed a simple score based on those 2 variables and assigned 1 point for having ALBI grade I and 1 point for having SII < 330. Thus, a patient could achieve either 0 (ALBI grade II/III and SII ≥ 330), 1 (either ALBI grade I or SII < 330), or 2 (ALBI grade I and SII < 330) points. Among 88 patients with complete SII level and ALBI grade, median OS of patients with 2-points (score-high, n = 17), 1-point (score-intermediate, n = 43) and 0-point (score-low, n = 28) were not-reached (95% CI not-reached-not-reached) months, 17.9 (95% CI 12.3-23.4) months and 7.5 (95% CI 4.3-10.8) months, respectively (log-rank P = 0.003) (**Figure 3A**). On the other hand, median PFS of patients with 2-points, 1-point and 0-point were not-reached (95% CI not-reached-not-reached) months, 3.7 (95% CI 0-8.3) months and 2.9 (95% CI 2.5-5.1) months, respectively (log-rank P = 0.001) (**Figure 3B**).

In patients with at least one follow-up imaging assessment (n = 88), the score correlated with better best radiological response, as CR was n = 1/17 (5.9%) vs. n = 0/43 (0%) vs. n = 0/28 (0%), PR was n = 1/17 (5.9%) vs. n = 6/43 (14.0%) vs. n = 0/28 (0%), SD was n = 10/17 (58.8%) vs. n = 19/43 (44.2%) vs. n = 7/28 (25.0%), and PD was n = 5/17 (29.4%) vs. n = 18/43 (41.9%) vs. n = 21/28 (75.0%) for score-high vs. score-intermediate vs. score-low, respectively (P = 0.011). The DCR was 70.6% vs. 58.1% vs. 25.0% for score-high vs. score-intermediate vs. score-low, respectively (P < 0.001).

Discussion

Regorafenib has been approved as a second-line systemic therapy for advanced HCC after the failure of sorafenib in since 2017. However, patient who was beneficial from regorafenib therapy is still lack of good predictive biomarkers. In the current study, we evaluated the effi-

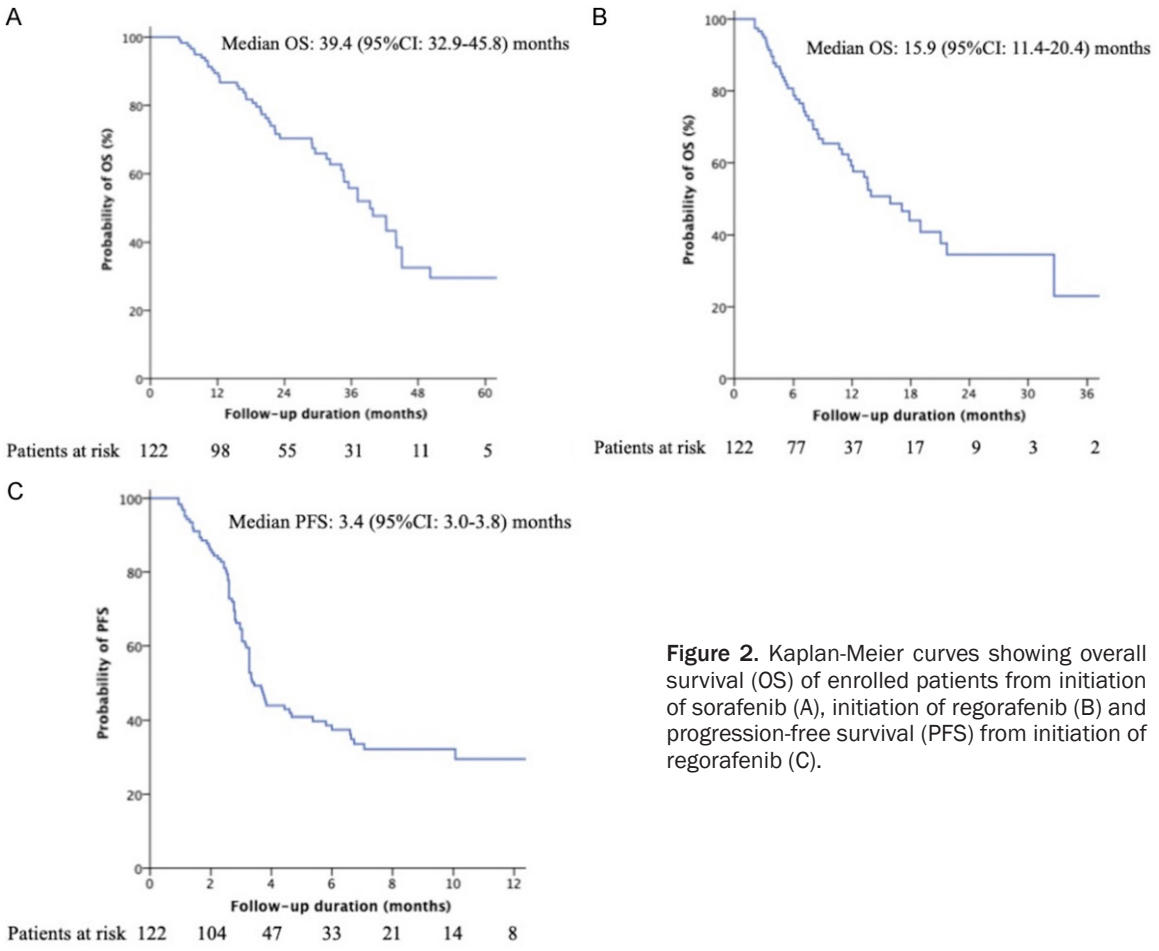

Figure 2. Kaplan-Meier curves showing overall survival (OS) of enrolled patients from initiation of sorafenib (A), initiation of regorafenib (B) and progression-free survival (PFS) from initiation of regorafenib (C).

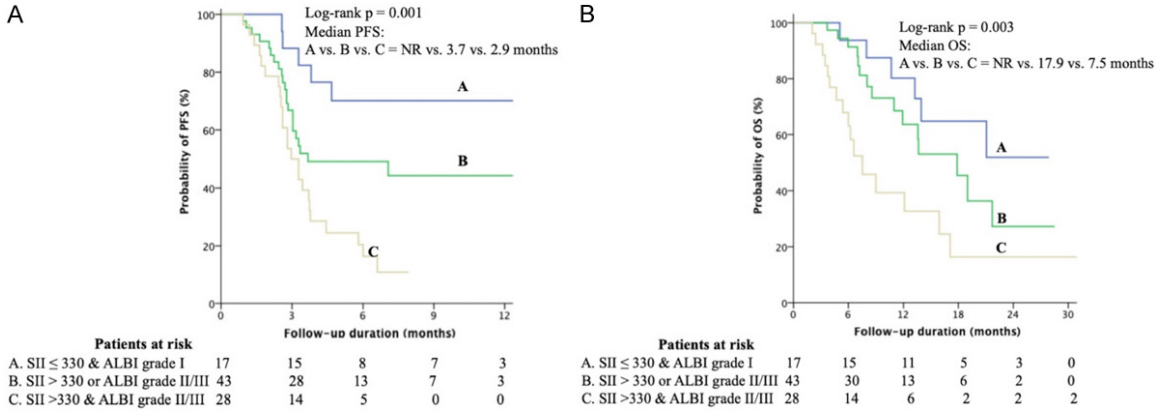

Figure 3. Kaplan-Meier curves showing overall survival (OS) (A) and progression-free survival (PFS) (B) of enrolled patients from initiation of regorafenib stratified by SII score and ALBI grade.

cacy and safety of regorafenib for patients whose HCC progressed during sorafenib treatment. We disclosed that the median OS and median PFS of regorafenib were 15.9 and 3.4 months, respectively, which were even better than the results of the phase III RESORCE trial and prior real-world reports [26-28]. In this retrospective study, SII showed the best outperformed discriminatory power both in prediction of PFS and OS compared with other inflamma-

tory indexes. Combining inflammatory markers including peripheral lymphocyte, neutrophil, as well as platelet count and preserved liver function based on ALBI grade showed good efficacy in discriminating between high, middle and low risk groups for uHCC patients receiving regorafenib after sorafenib-refractory treatment. Accordingly, patients who fulfilled all of these criteria had an excellent OS, PFS and response rate.

In current study, NLR based inflammatory indexes, including NLR, SII and SIRI, showed good efficacy in discriminating prognosis among uHCC patients receiving sorafenib-regorafenib therapy. Among them, SII score which is based on neutrophils, lymphocytes as well as peripheral platelet counts provided a larger net benefit and was proved to predict prognosis of patients treated with various treatments in HCC patients [29, 30]. High SII usually results from thrombocytosis, neutrophilia and lymphopenia, suggesting a deranged immune response. Inflammation plays an important role in the development of cancer and promotes all stage of tumor progression. Accumulated evidences had demonstrated that neutrophilia and thrombocytosis are associated with cancer progression in the tumor microenvironment [31, 32]. Platelets act as multifunctional cells participating in hemostasis, tissue generation and immune response as well as in cancer growth, invasion, and metastasis. Previous studies had demonstrated that platelets could facilitate cancer progression, invasion and metastasis [33, 34]. Neutrophils play protumoral roles through multiple mechanisms including enhancing cancer cell invasion, proliferation and metastasis by releasing inflammatory mediators such as neutrophil elastase, matrix metalloproteinase-9, and interleukin-8. Neutrophils also secrete the pro-inflammatory factors in the tumor microenvironment, resulting in lymphocyte apoptosis and immunosuppression [35]. On the contrary, lymphocytes are known to reflect the decreased immune surveillance against cancer and associated with poor survival in various solid tumors [36, 37]. Inflammation-based prognostic factor can reflect the immune microenvironment and the responses to cancer therapeutic agents. Therefore, a high SII with high platelets, high neutrophils while low lymphocytes level reflected a weak immune response in patients that favor pro-tumoral microenvironment [38].

Good liver reserve is associated with better prognosis. ALBI grade, which is based on only two factors with serum albumin and bilirubin level, is simple and more objective than the Child-Pugh classification [39]. It has recently attracted attention by serving as a useful parameter to predict the prognosis of HCC patients under different treatment modalities [40-43]. In the present study, we demonstrated that the baseline ALBI grade was a good predictor of PFS and OS after initiation of regorafenib therapy. Therefore, we combined the ALBI grade and SII level at the initiation of regorafenib therapy and further stratified our patients into three risks group. Patients with SII > 330 & ALBI grade II/III reflecting high tumor burden and poor preserved liver function before regorafenib may encounter worst outcome and should shift to other therapy as early as possible.

The median PFS of the current study with 3.4 months is comparable to those reported by the RESORCE trial [11] and reports from other Asia countries [26, 44], confirming the efficacy of regorafenib in patients with advanced HCC in real-world practice. However, the median OS in the current study were 15.9 months from initiation of regorafenib and 39.4 months from initiation of sorafenib which were markedly longer than that of the RESORCE trial [11, 13] and other reports [26-28]. Although the multivariate analysis did not find the combination therapy has an effect on the prognosis comparing with SII score and ALBI grade possibly due to limited case number (only one-fourth), patients receiving combination therapy had better OS and PFS than those without whether before or after matching confounding factors. Recent evidence had showed uHCC patients who can benefit from more aggressive therapies including locoregional therapies (LRTs) even in the presence of metastases or vascular invasion [45, 46]. Combined LRTs with sorafenib resulted in better OS compared with monotherapy in patients with high tumor burden [47]. According to previous study, TACE induces tumor hypoxia leading temporarily increase of angiogenic factors such as vascular endothelial growth factor (VEGF) [48] that combining an anti-angiogenic agent may provide complementary inhibition of neovascularization and tumor growth [49, 50]. On the other hand, sorafenib-mediated blockage of the Raf/MAPK and VEGF receptor pathways might enhance the efficacy of radiation [51].

The study still has some limitations. First, this was a retrospective study with median follow-up periods of 22.3 and 7.5 months for sorafenib-regorafenib sequential therapy and regorafenib therapy, respectively. A longer follow-up was needed to determine the median OS in our cohort. Second, we could not guarantee the daily dose of regorafenib during treatment because adjustments of the TKI dose by patients might not have been accurately documented in the medical records. Third, a validation cohort could not be set up because of the limited case number from a single institution. A validation cohort with a large population can be used in future studies. Fourth, the efficacy of combing with LRTs requires further verification using a prospective randomized controlled study, which can help in constructing a more convincing prognostic model for clinical guidance.

In conclusion, we developed a simple predicting score combining baseline SII score and ALBI grade that predicts outcome of uHCC patients undergoing regorafenib after sorafenib‐refractory treatment. If validated in a larger prospective study, the scoring system may provide a simple method for identifying patients with poor prognosis. Early identification of this poor prognosis group can provide an opportunity to change treatment strategies to improve patient outcomes.

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Disclosure of conflict of interest

None.

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Supplementary Table 1. Baseline characteristics of enrolled patients at initiation of sorafenib

Variables	Overall (N = 122)
Age (years-old)	64.0 (IQR 59.0-71.7)
Male gender	103 (84.4)
Etiology	
HBV/HCV/others	59/40/23 (48.4/32.8/18.8)
Child-Pugh A/B	117/5 (95.9/4.1)
ALBI grade I/II/III	65/57/0 (53.3/46.7/0)
BCLC stage B/C	37/85 (30.3/69.7)
Macrovascular invasion	40 (32.8)
Extra-hepatic metastasis	59 (48.4)
AFP ≥ 400 ng/ml	37 (30.3)
Prior lines of systemic therapy 0/1/≥ 2	0/0/0 (0/0/0)
Combination therapy	71 (58.2)
Loco-regional therapy	71 (58.2)
Immune checkpoint inhibitors	0 (0)
Systemic chemotherapy	0 (0)
Duration of therapy (months)	6.9 (IQR 4.2-17.7)
Follow-up duration since therapy start (months)	22.3 (IQR 14.8-36.8)

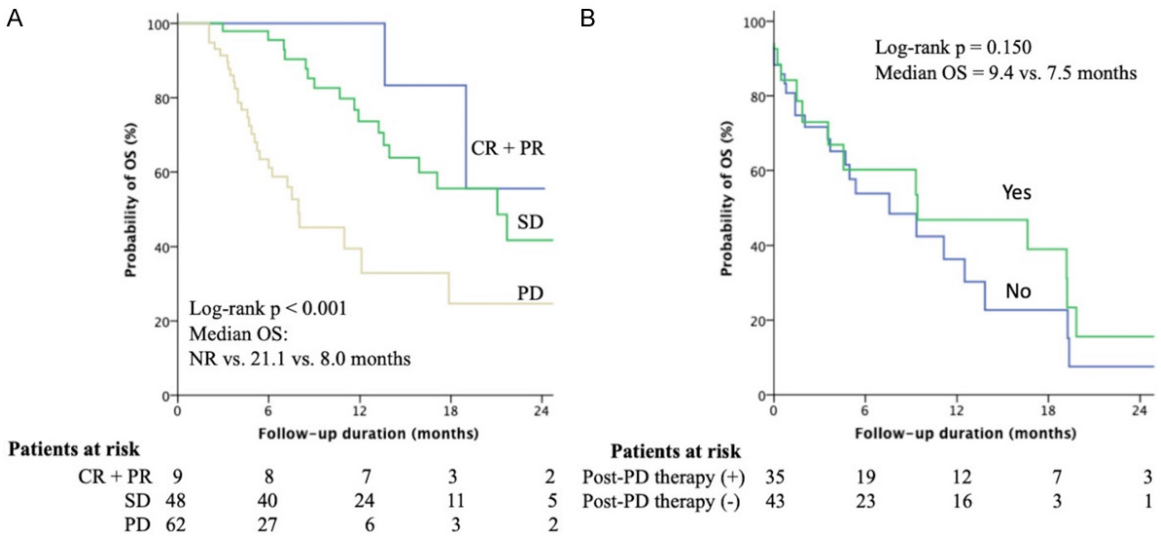
Abbreviations: AFP, alpha-fetoprotein; ALBI, albumin-bilirubin index; BCLC, Barcelona Clinic Liver Cancer.

Supplementary Table 2. Overview of SAE after initiation of regorafenib

Variables	Patients (N = 122)	
	Any grade	Grade ≥ 3
Hand-foot-skin reaction	46 (37.7)	7 (5.7)
Diarrhea	20 (16.4)	0 (0)
Fatigue	21 (17.2)	0 (0)
Hypertension	11 (9.0)	1 (0.8)
Abdominal pain	8 (6.6)	0 (0)
Muscle soreness	3 (2.5)	0 (0)

Supplementary Table 3. Tumor response

Variables	Patients (N = 122)
Best overall response	
Complete response	1 (0.8)
Partial response	8 (6.6)
Stable disease	48 (39.3)
Progressive disease	62 (50.8)
Not evaluable	3 (2.5)
Objective response	9 (7.4)
Disease control rate	57 (46.7)



Supplementary Figure 1. Kaplan-Meier curves showing overall survival (OS). A. Patients with good responder (CR+PR) or stable disease had better OS than those with disease progression. B. Patients treated with subsequent therapy had longer OS than those without post-disease progression although not reaching statistical significance.

Supplementary Table 4. Baseline characteristics of patients with and without combination therapy (before PSM)

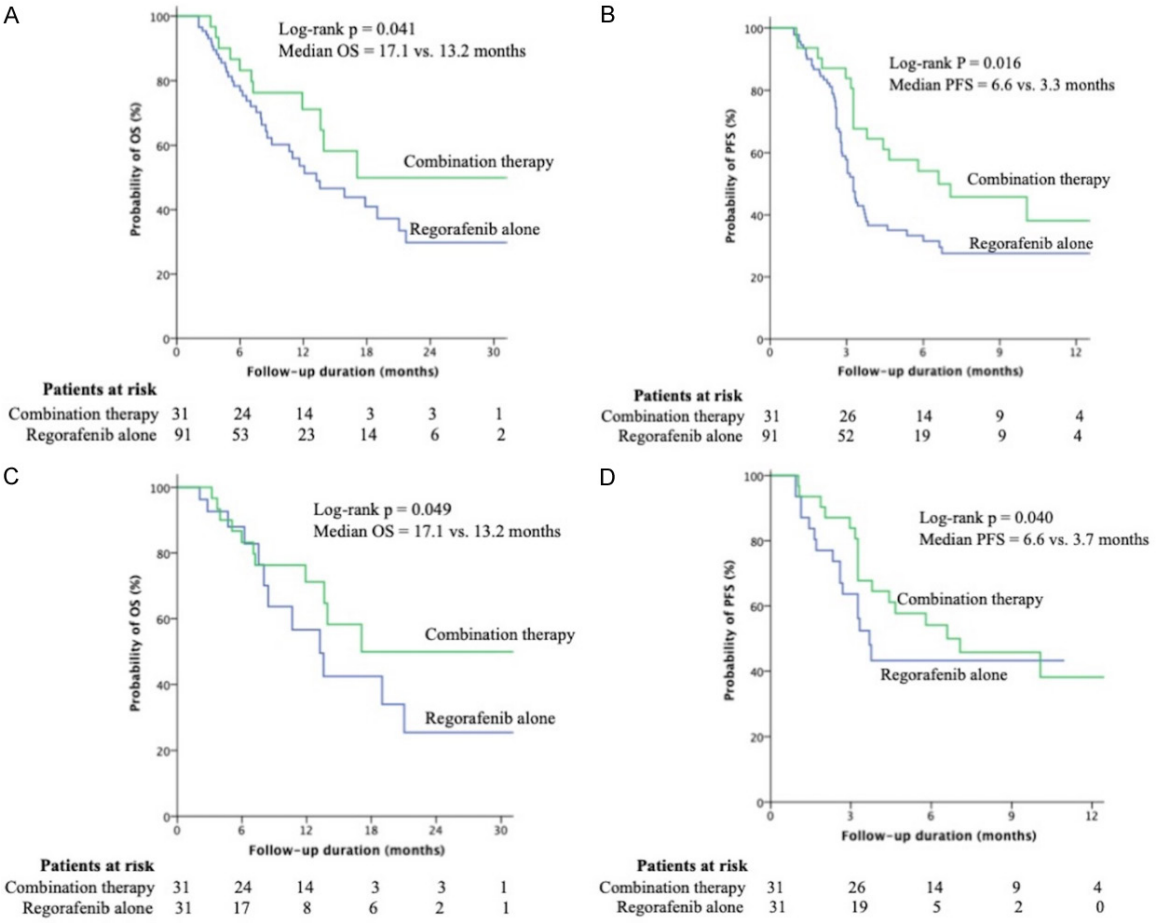
Variables	With combination therapy (n = 31)	Without combination therapy (n = 91)	*P*-value
Age (years-old)	62.4 (IQR 59.2-68.5)	66.6 (IQR 61.1-74.4)	0.049
Male gender	28 (90.3)	75 (82.4)	0.294
Etiology			0.176
HBV/HCV/others	19/9/3 (61.3/29.0/9.7)	40/31/20 (44.0/34.1/22.0)	
Child-Pugh A/B	31/0 (100/0)	85/6 (93.4/6.6)	0.143
ALBI grade I/II & III	19/12 (61.3/38.7)	40/51 (44.0/56.0)	0.045
Macrovascular invasion	8 (25.8)	32 (35.2)	0.338
Extra-hepatic metastasis	14 (45.2)	49 (53.8)	0.403
AFP ≥ 400 ng/ml	10 (25.0)	21 (25.6)	0.942
BCLC stage B/C	12/19 (38.7/61.3)	21/70 (23.1/76.9)	0.041
Follow-up since regorafenib start (months)	11.1 (IQR 7.1-16.4)	6.7 (IQR 3.9-12.1)	0.014

Abbreviations: AFP, alpha-fetoprotein; ALBI, Albumin-Bilirubin; BCLC, Barcelona Clinic Liver Cancer.

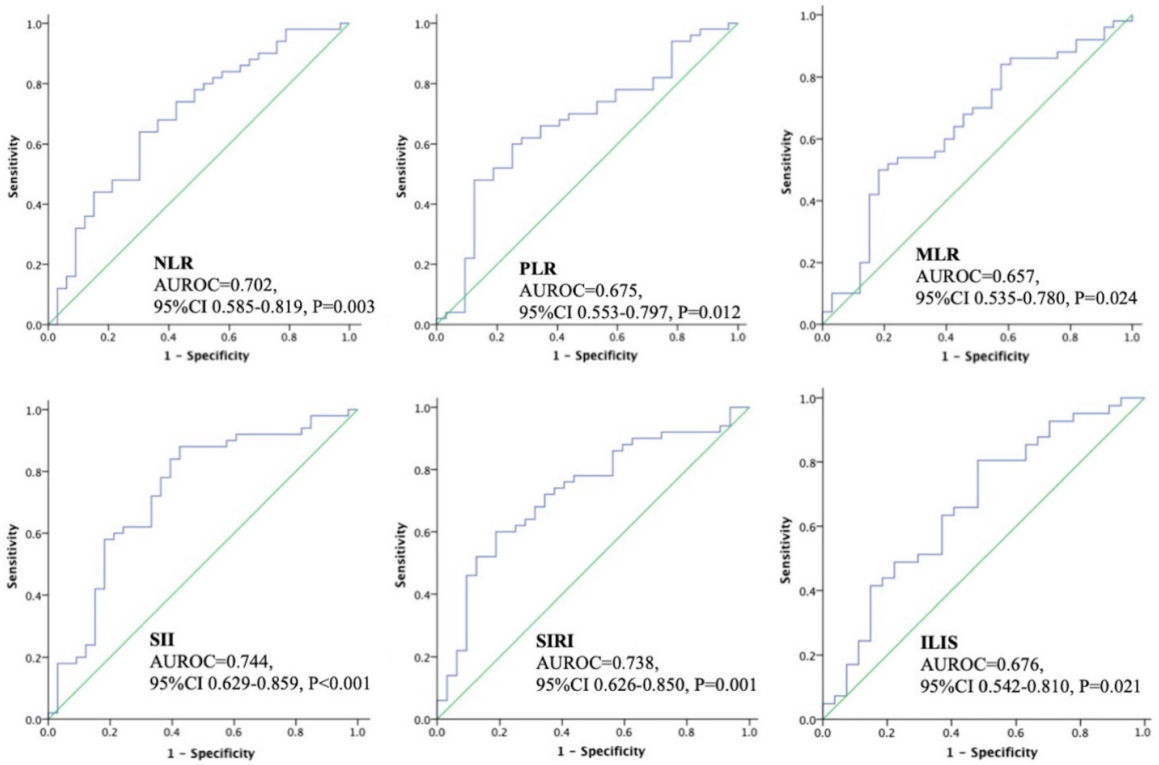
Supplementary Table 5. Baseline characteristics of patients with and without combination therapy (after PSM)

Variables	With combination therapy (n = 31)	Without combination therapy (n = 31)	*P*-value
Age (years-old)	62.4 (IQR 59.2-68.5)	65.0 (IQR 59.1-70.6)	0.709
Male gender	28 (90.3)	25 (80.6)	0.279
Etiology			0.533
HBV/HCV/others	19/9/3 (61.3/29.0/9.7)	16/9/6 (51.6/29.0/19.4)	
Child-Pugh A/B	31/0 (100/0)	29/2 (93.5/6.5)	0.239
ALBI grade I/II & III	19/12 (61.3/38.7)	16/15 (51.6/48.4)	0.303
Macrovascular invasion	8 (25.8)	13 (41.9)	0.180
Extra-hepatic metastasis	14 (45.2)	16 (51.6)	0.309
AFP ≥ 400 ng/ml	10 (55.6)	8 (44.4)	0.576
BCLC stage B/C	12/19 (38.7/61.3)	14/17 (45.2/54.8)	0.620
Follow-up since regorafenib start (months)	11.1 (IQR 7.1-16.4)	6.2 (IQR 3.1-11.6)	0.009

Abbreviations: AFP, alpha-fetoprotein; ALBI, Albumin-Bilirubin; BCLC, Barcelona Clinic Liver Cancer.



Supplementary Figure 2. Kaplan-Meier curves showing overall survival (OS) and progression-free survival (PFS). Patients with combination therapy had longer OS (A) and PFS (B) than those without. After matching with age, gender, fibrosis status and tumor stage, patients with combination therapy still had longer OS (C) and PFS (D).

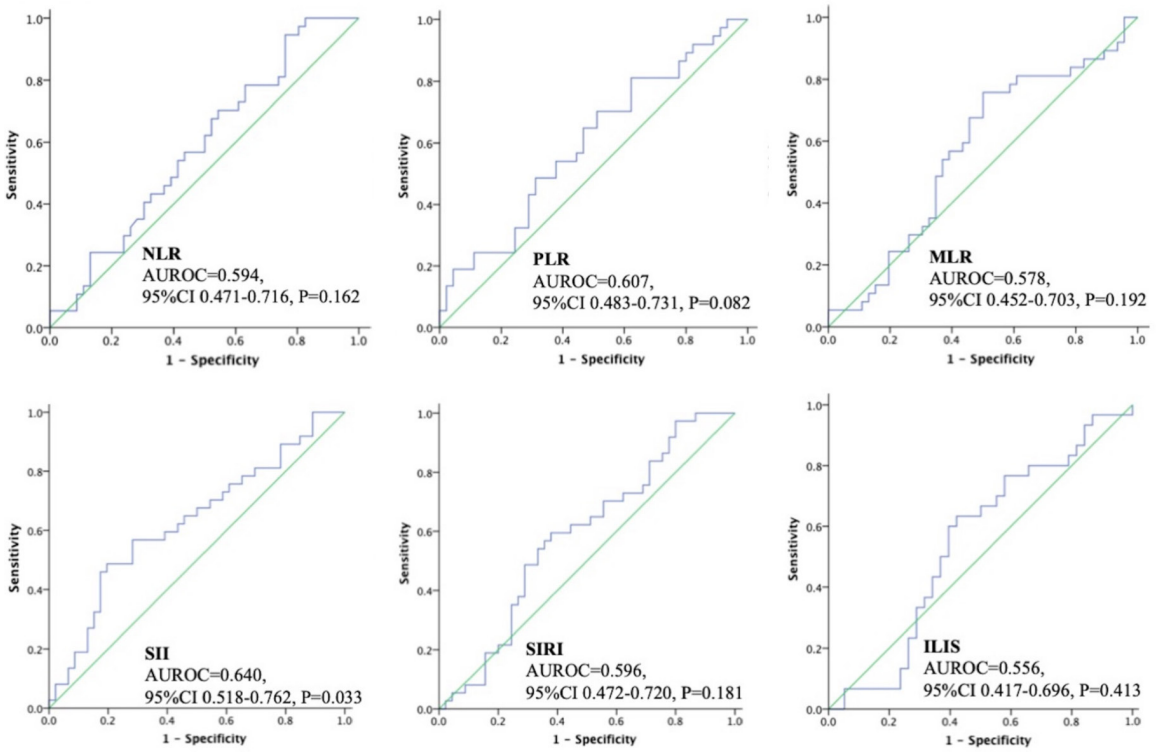


Supplementary Figure 3. ROC curves for progression-free survival (PFS) prediction after regorafenib therapy. Compared with the existing scoring systems or indices (NLR, PLR, MLR, SIRI and ILIS), SII showed the best outperformed discriminatory power.

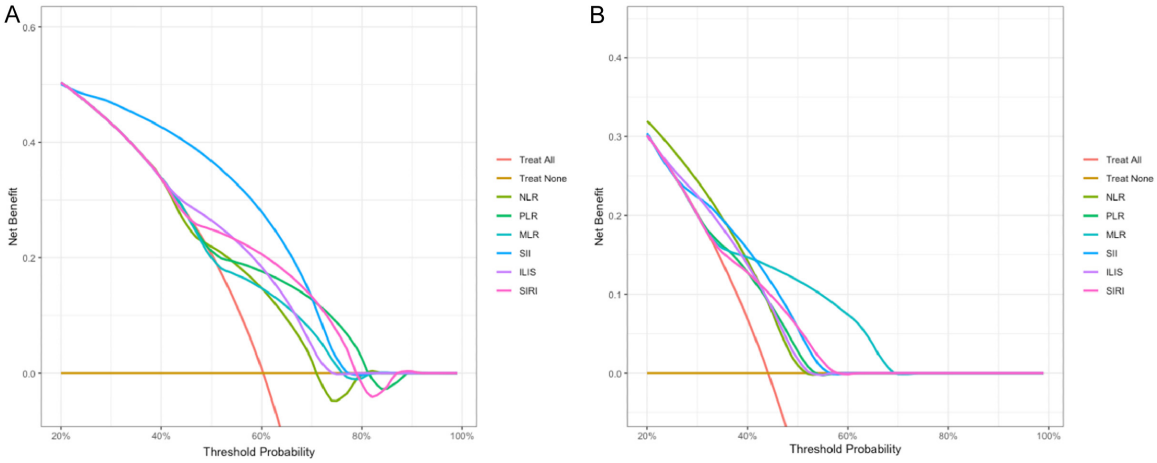
Supplementary Table 6. DeLong's test statistics on clinical comparators for predicting PFS and OS

PFS	NLR	PLR	MLR	SII	SIRI	ILIS
NLR	1	0.386	0.169	0.130	0.171	0.366
PLR	0.386	1	0.815	0.048	0.064	0.837
MLR	0.169	0.815	1	0.038	0.042	0.592
SII	0.130	0.048	0.038	1	0.806	0.049
SIRI	0.171	0.064	0.042	0.806	1	0.062
ILIS	0.366	0.837	0.592	0.049	0.062	1
OS	NLR	PLR	MLR	SII	SIRI	ILIS
NLR	1	0.790	0.227	0.143	0.951	0.686
PLR	0.790	1	0.483	0.496	0.841	0.753
MLR	0.227	0.483	1	0.095	0.207	0.433
SII	0.143	0.496	0.095	1	0.172	0.067
SIRI	0.951	0.841	0.207	0.172	1	0.670
ILIS	0.686	0.753	0.433	0.067	0.670	1

Abbreviations: ILIS, Integrated Liver Inflammatory Score; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PFS, progression free survival; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index.



Supplementary Figure 4. ROC curves for overall survival (OS) prediction after regorafenib therapy. Compared with the existing scoring systems or indices (NLR, PLR, MLR, SIRI and ILIS), SII showed the best outperformed discriminatory power.



Supplementary Figure 5. Decision curves analysis for (A) progression-free survival (PFS) and (B) overall survival (OS) prediction after regorafenib therapy. Compared with the existing scoring systems or indices (NLR, PLR, MLR, SIRI and ILIS).