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ORIGINAL RESEARCH

Prediction of Pathologic Response in Unresectable Hepatocellular Carcinoma After Downstaging with Locoregional and Systemic Combination Therapy

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Background: The combination of locoregional and systemic therapy may achieve remarkable tumor response for unresectable hepatocellular carcinoma (HCC).

Objective: We aimed to investigate the correlation between radiologic and pathologic responses following combination therapy, evaluate their prognostic values, and to establish a non-invasive prediction system for pathologic response.

Methods: This single-center retrospective study included 112 consecutive patients with HCC who underwent locoregional and systemic combination therapy followed by liver resection or transplantation. Radiologic response was assessed with Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and modified RECIST (mRECIST). Pathologic necrosis percentage was assessed to determine major pathologic response (MPR, ≥90% tumor necrosis) and pathologic complete response (100% tumor necrosis). Performance of the response criteria in predicting pathologic response was assessed with the area under the receiver operator characteristic curve (AUC).

Results: Among all radiologic and pathologic response criteria, MPR was the only independent predictor of post-resection recurrence-free survival (RFS) (adjusted hazard ratio 0.34, 95% CI 0.16–0.72, p=0.004). In addition, mRECIST showed stronger correlation with pathologic response than RECIST 1.1 (spearman r values: 0.76 vs 0.42, p<0.001). A prediction system for MPR was developed that included a combination of mRECIST response (ie, >70% decrease of viable target lesions) with either >90% decrease in AFP (for AFP-positive group, n=75) or >80% decrease in PIVKA-II (for AFP-negative group, n=37), which yielded a respective AUC of 0.905 and 0.887. Furthermore, the system-defined dual-positive responders showed improved median RFS (not reached) than non-responders (7.1 months for AFP-positive group [p=0.043] and 13.3 months for AFP-negative group [p=0.099]).

Conclusion: mRECIST was more indicative of pathologic response after combination therapy than RECIST 1.1. Integration of mRECIST with AFP or PIVKA-II responses allowed for accurate prediction of MPR and could support decision-making on subsequent curative-intent treatment.

Keywords: hepatocellular carcinoma, chemoembolization therapeutic, systemic therapy, pathologic response, response evaluation criteria in solid tumors

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Introduction

Liver resection and transplantation are recommended as the curative treatment for hepatocellular carcinoma (HCC) that achieve prolonged survival.[1,2] However, over 70% of patients are diagnosed at intermediate- or advanced-stage and ineligible for curative-intent treatment.[3,4] For patients with upfront unresectable HCC, locoregional therapy (LRT), most commonly transarterial chemoembolization (TACE), and systemic therapy, including antiangiogenic targeted therapies and immune checkpoint inhibitors (ICIs), remain the standard of care.[2,5] Although clinical evidence is still insufficient to change guidelines,[6–8] growing studies have reported encouraging results on the combination of LRT and systemic therapy as downstaging treatment with profound, durable and even complete response, converting a subgroup of unresectable HCC into resectable tumors, and providing the opportunity for subsequent curative-intent treatment[9-15.] The individualized decision-making for patients with unresectable HCC requires an accurate evaluation of treatment response, for which radiologic response criteria act as the cornerstone. Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and modified RECIST (mRECIST) are the recommended radiologic response criteria and have been extensively used in clinical practice.[16] However, the different therapeutic mechanisms and response patterns between LRT and systemic therapy pose challenges for current radiologic criteria[17]. To date, the predictive accuracy of these criteria after combination therapy in relation to pathologic response, the most robust surrogate of treatment efficacy,[18] has not been thoroughly investigated.[19,20] A phase 1b clinical trial showed inconsistency between radiologic and pathologic responses,[21] and multiple studies and meta-analyses reported moderate-to-poor correlations between radiologic-based endpoints and patient prognosis.[22–24] Furthermore, conclusive evidence is lacking to show the superiority of one RECIST criteria over another after combination therapy.[2]

Thus, this study aimed to explore the correlation between RECIST-based radiologic responses with pathologic response, and to evaluate their prognostic value in patients with initially unresectable HCC who underwent liver resection or transplantation after downstaging with combination therapy.

Materials and Methods

The protocol of this retrospective study conforms to the 1975 helsinki Declaration and was approved by the institutional review board. Written informed consent was obtained for every procedure from all patients before starting treatments. All patient data were coded to preserve patient privacy.

Study Cohort

From January 2020 to March 2023, consecutive patients with unresectable HCC who underwent combination of TACE and systemic therapy (targeted therapy and/or ICI) followed by liver resection or transplantation were retrospectively screened. Inclusion criteria were: (a) HCC diagnosed based on pathology or composite clinical reference according to the AASLD guideline (for hepatic lesions achieving complete pathologic tumor necrosis);[2] and (b) underwent contrast-enhanced (CE) CT or MRI within 4 weeks before combination therapy and at least one follow-up CE-CT or MRI within 4 weeks before surgery. Exclusion criteria were: (a) previous non-curative-intent treatment; (b) without reports on pathologic necrosis percentage; (c) inconsistent imaging modality used at baseline and before surgery; (d) concomitant with other malignancies that might affect response evaluation; and (e) the interval between TACE and systemic therapy exceeded two months. Noteworthily, patients who underwent liver transplantation were included for the radiologic-pathologic correlation analyses, but were excluded from the prognosis analyses given their anticipated distinct outcomes compared with those who underwent liver resection. Patients lost to follow-up within three months after resection were also excluded from the prognosis analysis.

Patient characteristics at baseline and before surgery were extracted from electronic medical records, including demographic and clinical characteristics, laboratory results and treatment information. Follow-up procedure after liver resection was scheduled at one month, every three months for the first two years, and every six months thereafter, supplemented with telephone interviews annually. Recurrence-free survival (RFS) was defined as time from liver resection to first documented recurrence or death from any cause, whichever occurred first. Overall survival (OS) was

defined as time from liver resection to death from any cause, censoring at the date of the last follow-up if patients were still alive.[16]

Treatments

The decision to perform combination therapy was at the discretion of the institutional multidisciplinary board, and treatment regimens were determined based on guidelines but personalized on the perceived probabilities of success and patient preference.[25,26] Patients were considered unresectable if they were at intermediate or advanced-stage, R0 resection was impossible or had insufficient remnant liver volume after resection. Treatment details are provided in Supplementary materials. Notably, part of the study participants received combination therapy as part of two ongoing clinical trials. All organs were donated voluntarily with written informed consent, and the transplants were conducted in accordance with the Declaration of Istanbul.

Radiologic Response Evaluation

As per institutional standard protocol, CE-CT was performed as the first-line imaging technique for response evaluation due to its wide availability, and MRI was reserved for challenging patients requiring more granular assessment. CT and MRI acquisition protocols are detailed in Supplementary materials and Table S1.

Two abdominal radiologists, with 10 and 7 years of experience in liver imaging and with subspecialty training in tumor response evaluation, independently performed the imaging analysis. The reviewers were informed of the HCC diagnosis and combination therapy but were blinded to the clinical, pathologic and follow-up data. Discrepancies regarding target lesion selection were adjudicated by a third radiologist (with 10 years of liver imaging experience), while discrepancies regarding target lesion measurements were adjudicated by a third reading of the two radiologists one month after the initial assessment to reach a consensus.

According to RECIST 1.1 and mRECIST,[27,28] a maximum of two target lesions per organ and five target lesions in total were selected. For intrahepatic target lesion, the sum of longest diameter (SLD) of target lesions according to RECIST 1.1 and the SLD of viable target lesions (ie, enhancement in the arterial phase) according to mRECIST were measured. Lipiodol deposits of TACE within the tumor on CT was considered as non-viable.[29] Overall response was determined by comprehensively assessing response in target and non-target lesions and the presence of new lesions. Treatment response was categorized as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) based on RECIST 1.1 and mRECIST criteria, respectively. Objective response rate (ORR) was calculated as the percentage of CR plus PR.

Pathologic Assessment

In compliance with the institutional standard protocol, resected tumors or explanted liver were processed for pathologic analysis. Two hepatopathologists who were aware of the clinical and imaging data reviewed all specimens in consensus and reported pathologic response, calculated as the percentage of residual viable tumors in relation to the total tumor area. For those with multiple lesions, the mean percentage of residual viable tumors was calculated. Major pathologic response (MPR) was defined as 10% or less residual viable tumors (ie, ≥90% necrosis), and pathologic complete response (pCR) was defined as no residual viable tumors (ie, 100% necrosis) from completely resected tumors, tumor thrombosis and metastatic lesions.[30] Other recorded pathologic indices included tumor number, size, differentiation, micro and macrovascular invasion and satellite tumors (Supplementary materials).

Statistical Analysis

Continuous variables were reported as mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate, and categorical variables as frequencies and percentages. Response categories based on pathology and each RECIST criterion were compared using chi-squared test or fisher's exact test. Spearman rank correlation was used to evaluate correlations between quantitative radiologic (ie, SLD of target lesions or of viable target lesions), laboratory and pathologic responses (ie, percentage of pathologic necrosis). Univariable and multivariable Logistic and Cox regression analyses were performed to identify independent predictors of pathologic response and post-resection RFS, respectively.

Variables with a univariate p value ≤0.1 or of clinical significance were included in subsequent multivariable analyses. Kaplan–Meier curves with Log rank tests were used for survival analyses.

A non-invasive prediction system for pathologic response with substantial prognostic value was developed by including imaging and HCC-related tumor biomarkers (ie, α-fetoprotein [AFP] and protein induced by vitamin K absence II [PIVKA-II]). The cohort was divided into an AFP-positive (n=75, defined as AFP level >20 ng/mL at baseline or before surgery) and AFP-negative group (n=37, defined as AFP level ≤20 ng/mL both at baseline and before surgery). Of note, the AFP-negative group included one patient with PIVKA- II level ≤40 ng/mL both at baseline and before surgery. Predictive performance was evaluated with the area under the receiver operating characteristic curves (AUC) and compared with the DeLong test, using bootstrap resampling method (with 1000 replicates) to correct for optimism. The optimal cutoff value of candidate predictors was determined by maximizing the Youden index. Furthermore, performance of the prediction system was assessed in prespecified subgroups (Supplementary materials).

Inter-observer agreement was assessed with weighted κ for categorical variables and interclass correlation coefficients for quantitative variables. Missing data were assumed to be missing at random and imputed with multiple imputations with chained equations. Statistical significance was set at 5% level (two-sided). All analyses were performed using R software (version 4.3.1).

Results

Patient Characteristics

A total of 112 patients were included (mean age 54.0 years [SD 11.4]; 100 [89.3%] males) (Figure 1). Up to 108 (96.4%) patients had hepatitis B virus infection. Barcelona Clinic Liver Cancer (BCLC) stage at baseline was B in 32 (28.6%) patients and C in 46 (41.1%) patients (41 with macrovascular invasion and 5 with extrahepatic metastasis). Of note, 34 (30.4%) patients were BCLC-A with a median tumor diameter of 9.8 cm (IQR 6.7–12.2), who received combination therapy due to the insufficient remnant liver volume after primary resection or an R0 resection is impossible. Clinical characteristics are detailed in Table 1.

The median interval between baseline and the last preoperative scan was 4.0 months (IQR 2.9–6.9). All patients received TACE as LRT, including 33 (20.5%) who received multiple sessions. Lenvatinib plus camrelizumab (45.5%) or sintilimab (17.8%) were the predominant systemic regimens applied, and 24 (21.4%) patients received tyrosine kinase inhibitor (TKI) monotherapy (Table S2-3). Subsequently, 104 (92.9%) patients underwent liver resection and eight (7.1%) underwent transplantation.

Tumor Response and Post-Resection RFS

After combination therapy, 49 (43.8%) patients achieved MPR, including 17 (15.2%) with pCR. The distribution among response categories was different between RECIST 1.1 and mRECIST (p<0.001), and the ORR captured by RECIST 1.1 was significantly lower than that by mRECIST (31.3% vs 80.3%, p<0.001; Table S4). The inter-observer agreement on response categories was higher with RECIST 1.1 (weighted κ: 0.64 vs 0.50 for mRECIST; Table S5). The median decrease from baseline was 92.4% (IQR 81.5%-98.1%) for serum levels of AFP and 88.9% (IQR 57.1–98.9%) for PIVKA- II. For patients undergoing resection, 42 (37.5%) experienced recurrence and 14 (12.5%) died during a median follow-up of 12.1 months (IQR 7.3–17.7). The median RFS was 12.5 months (95% confidence interval [CI] 9.1–20.4) and the 12-month RFS rate was 53.0% (95% CI 42.9%-65.4%).

Post-resection RFS was significantly longer in patients with MPR than those without MPR (median RFS: 18.9 months [95% CI 12.5–31.5] vs 9.5 months [95% CI 7.5–16.5]; HR 0.47, 95% CI 0.26–0.87, p=0.016). However, no significant influence on RFS was observed for pCR (HR 0.55, 95% CI 0.20–1.53, p=0.250), CR based on mRECIST (HR 0.83, 95% CI 0.39–1.78, p=0.634), ORR based on RECIST 1.1 (HR 0.97, 95% CI 0.52–1.82, p=0.936) and mRECIST (HR 0.64, 95% CI 0.33–1.23, p=0.180) (Figure 2). Similar results were obtained regarding post-resection OS (Figure S1). In multivariable Cox regression analyses, only MPR (HR 0.35, 95% CI 0.17–0.73, p=0.005), presence of baseline macrovascular invasion (HR 1.87, 95% CI 1.01–3.46, p=0.045) and non-R0 resection (HR 13.6, 95% CI 2.73–67.45, p=0.001) were independently associated with post-resection RFS (Table S6).

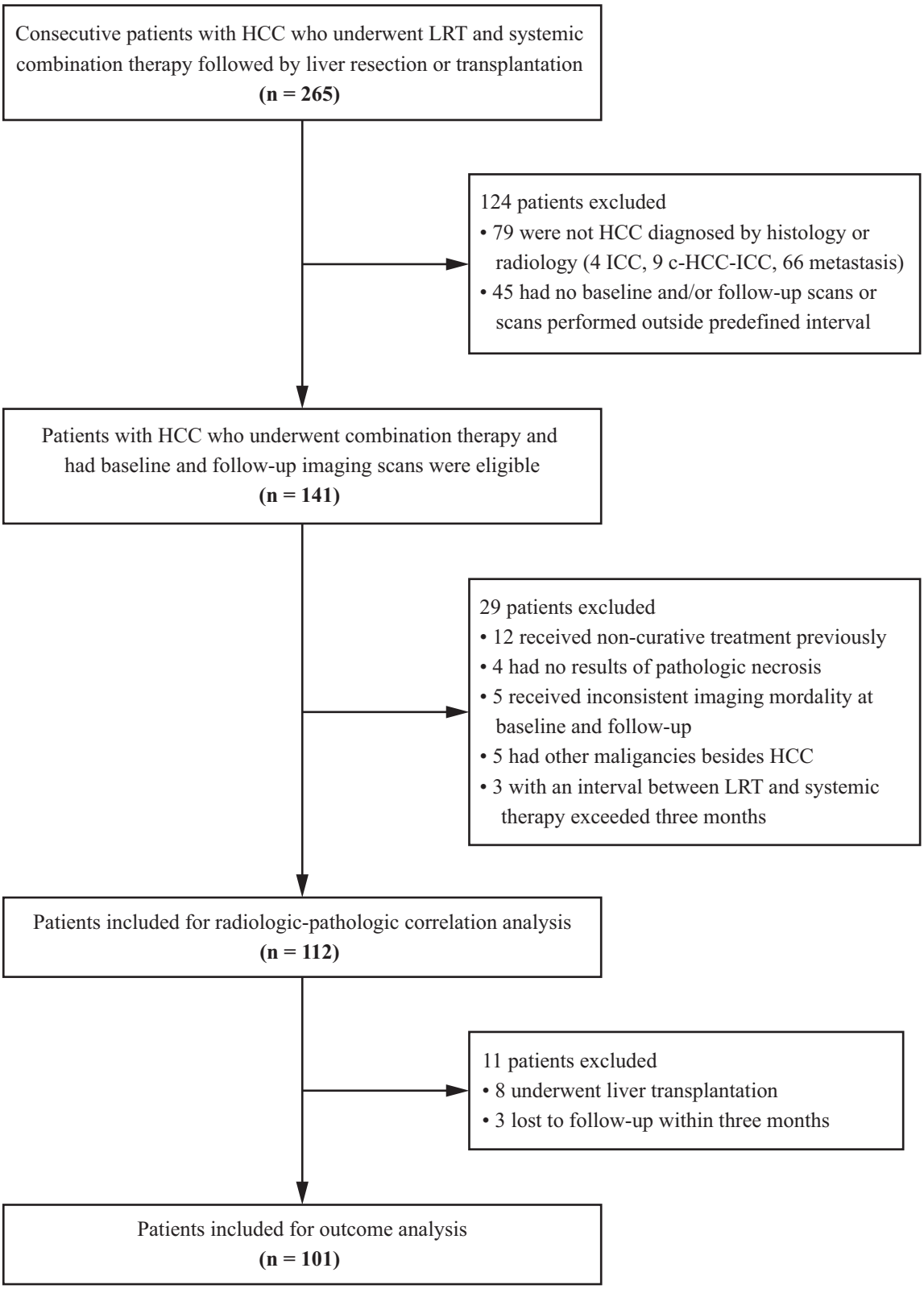

Figure 1 Flowchart of the study cohort. TACE transarterial chemoembolization, HCC hepatocellular carcinoma, ICC intrahepatic cholangiocarcinoma.

Table 1 Patient Demographics and Clinical Characteristics

Variables	Entire Cohort (n=112)	Non-MPR (n=63)	MPR (n=49)	P Value
Sex (Male)	100 (89.3%)	57 (90.5%)	43 (87.8%)	0.878
Median age, years (IQR)	55 (47–62)	54 (48–61)	56 (44–64)	0.496
Etiology (Hepatitis B)				0.998
Hepatitis B	108 (96.4%)	61 (96.8%)	47 (95.9%)	
Others	4 (3.6%)	2 (3.2%)	2 (4.1%)	
Type of combination therapy				0.063
TACE+TKI	24 (21.4%)	18 (28.6%)	6 (12.2%)	
TACE+TKI+ICI	88 (78.6%)	45 (71.4%)	43 (87.8%)	
Median duration of combination therapy, month (IQR)	4.1 (2.9–6.8)	3.9 (2.7–6.9)	4.2 (2.9–6.6)	0.792
Child-Pugh score				0.729
A5	103 (92.0%)	57 (90.5%)	46 (93.9%)	
A6	9 (8.04%)	6 (9.52%)	3 (6.12%)	
BCLC stage				0.735
A	34 (30.4%)	21 (33.3%)	13 (26.5%)	
B	32 (28.6%)	17 (27.0%)	15 (30.6%)	
C	46 (41.1%)	25 (39.7%)	21 (42.9%)	
ALBI score at baseline				0.709
Grade 1	92 (82.1%)	53 (84.1%)	39 (79.6%)	
Grade 2	20 (17.9%)	10 (15.9%)	10 (20.4%)	
ALBI score before surgery				0.737
Grade 1	68 (60.7%)	37 (58.7%)	31 (63.3%)	
Grade 2	40 (35.7%)	23 (36.5%)	17 (34.7%)	
Grade 3	4 (3.57%)	3 (4.76%)	1 (2.04%)	
AFP at baseline (ng/mL)				0.552
≤100	55 (49.1%)	33 (52.4%)	22 (44.9%)	
>100	57 (50.9%)	30 (47.6%)	27 (55.1%)	
AFP before surgery (ng/mL)				0.005
≤100	85 (75.9%)	41 (65.1%)	44 (89.8%)	
>100	27 (24.1%)	22 (34.9%)	5 (10.2%)	
PIVKA- II at baseline (mAU/mL)				0.023
≤100	18 (16.1%)	15 (23.8%)	3 (6.12%)	
>100	94 (83.9%)	48 (76.2%)	46 (93.9%)	

(*Continued*)

Table 1 (Continued).

Variables	Entire Cohort (n=112)	Non-MPR (n=63)	MPR (n=49)	P Value
PIVKA- II before surgery (mAU/mL)				<0.001
≤100	61 (54.5%)	24 (38.1%)	37 (75.5%)	
>100	51 (45.5%)	39 (61.9%)	12 (24.5%)	
Number of tumors				0.119
Single	63 (56.3%)	40 (63.5%)	23 (46.9%)	
Multiple	49 (43.7%)	23 (36.5%)	26 (53.1%)	
Median size of largest lesion at baseline, cm (IQR)	8.0 (4.9–10.7)	7.2 (4.3–10.1)	8.5 (5.8–10.8)	0.099
Median size of largest lesion before surgery, cm (IQR)	6.0 (3.9–9.2)	5.9 (3.9–9.2)	6.2 (4.6–8.6)	0.487
Baseline vascular invasion (Yes)	46 (41.1%)	25 (39.7%)	21 (42.9%)	0.885
Baseline extrahepatic metastasis (Yes)	5 (4.5%)	5 (7.9%)	0 (0.0%)	0.067
Microvascular invasion (Yes)	19 (19.8%)	16 (25.4%)	3 (9.09%)	0.102
Tumor differentiation				0.760
Well/moderately-differentiated	83 (86.5%)	55 (87.3%)	28 (84.8%)	
Poorly-differentiated	13 (13.5%)	8 (12.7%)	5 (15.2%)	

Notes: Data are number (%) unless otherwise stated. MPR major pathologic response, TACE transarterial chemoembolization, TKI tyrosine kinase inhibitor, ICI immune checkpoint inhibitor, ALBI albumin-bilirubin, AFP α-fetoprotein, PIVKA- II protein induced by vitamin K absence II.
Abbreviation: IQR, interquartile range.

Relationship Between Radiologic, Laboratory and Pathologic Response

The correlation between pathologic response with radiologic response and changes in laboratory parameters are detailed in Figure 3. Briefly, the percentage of pathologic necrosis demonstrated a moderate correlation with changes in mRECIST-based SLD of viable target lesions (r=0.76, p<0.001), AFP (r=0.70, p<0.001) and PIVKA- II (r=0.58, p<0.001), while its correlation with changes in RECIST 1.1-based SLD of target lesions and other laboratory parameters was week (r<0.5).

Among patients with MPR, the ORR assessed by mRECIST was significantly higher than that by RECIST 1.1 (93.8% vs 44.9%, p<0.001), including 23 (20.5%) patients categorized as CR by mRECIST and none by RECIST 1.1 (Table 2). Besides, patients with MPR showed greater decrease in serum levels of AFP (median: 98.0% vs 83.5%, p<0.001) and PIVKA- II (median: 98.1% vs 72.7%, p<0.001) than their counterparts (Figure 3).

Prediction System for MPR

A non-invasive prediction system was developed to predict MPR given its substantial prognostic value. The determined cutoffs were: a 70% decrease of SLD of viable target lesions (termed as "mRECIST response") and an 80% decrease of baseline PIVKA- II level (termed as "PIVKA- II response") determined from the entire cohort, and a 90% decrease of baseline AFP level (termed as "AFP response") from the AFP-positive group. Multivariable analyses showed that the above defined mRECIST response (OR 22.68, 95% CI 5.91–118.42, p<0.001) and AFP response (OR 21.36, 95% CI 4.67–142.74, p<0.001) were the only independent predictors of MPR in the AFP-positive group, and that the mRECIST response (OR 14.59, 95% CI 2.50–188.77, p<0.001) and PIVKA- II response (OR 11.24, 95% CI 1.74–119.4, p<0.001) were the only independent predictors in the AFP-negative group (Table 3). Therefore, the prediction system included two dual-biomarker models: the combination of mRECIST and AFP responses for the AFP-positive group, and the

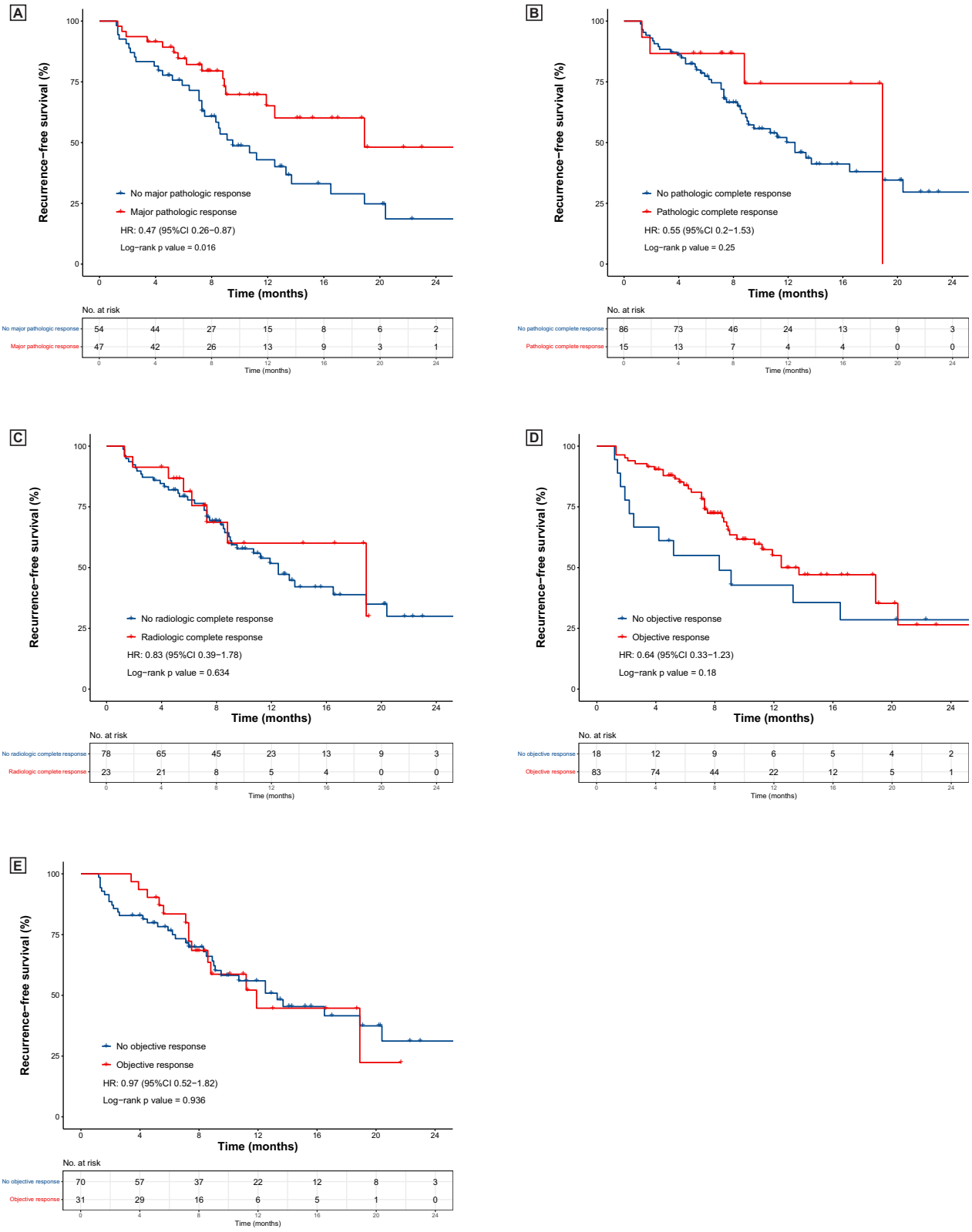

Figure 2 Kaplan-Meier estimates of recurrence-free survival after resection stratified according to (**A**) major pathologic response, (**B**) pathologic complete response, (**C**) radiologic complete response based on mRECIST, and (**D**) objective response based on mRECIST, and (**E**) objective response based on RECIST 1.1. HR hazard ratio.

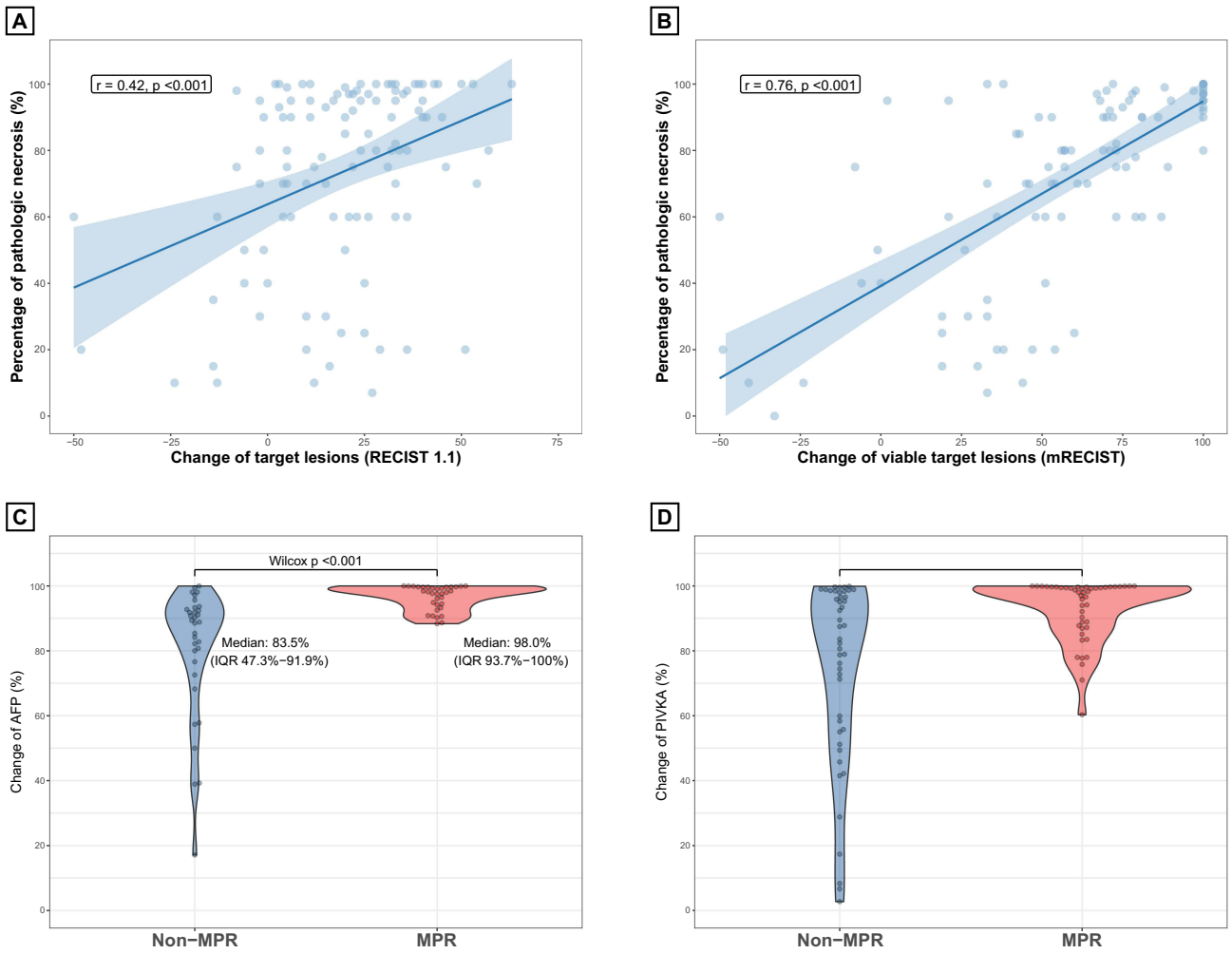

Figure 3 Correlation between radiologic, laboratory and pathologic response following combination therapy. (**A** and **B**) Linear regression analysis comparing pathologic necrosis and quantitative radiologic response according to (**A**) RECIST 1.1 and (**B**) mRECIST. (**C** and **D**) Change in AFP (**C**) and PIVKA- II (**D**) between patients with and without a major pathologic response (MPR).
Abbreviations: AFP α-fetoprotein, PIVKA- II protein induced by vitamin K absence II, ALBI albumin-bilirubin, NLR neutrophil-to-lymphocyte ratio.

combination of mRECIST and PIVKA- II responses for the AFP-negative group, with the same coefficients used in each combination (Figure 4).

Accordingly, both AFP-positive (n=75) and AFP-negative (n=37) groups could be respectively stratified into three response categories according to the number of positive responses. In the AFP-positive group, the MPR rates were 90.0%, 32.0% and 0% in patients achieving both mRECIST and AFP responses (dual-positive responders), either

Table 2 Correlation Between Radiologic and Pathologic Response Categories

Radiologic Criteria	Total n =112	Pathologic Response		p Value
		Non-MPR (n=63)	MPR (n=49)	
RECIST 1.1				
CR	0 (0)	0 (0)	0 (0)	0.004
PR	35 (31.3)	13 (20.6)	22 (44.9)	
SD	67 (59.8)	41 (65.1)	26 (53.1)	
PD	10 (8.9)	9 (14.3)	1 (2.0)	

(*Continued*)

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Table 2 (Continued).

Radiologic Criteria	Total n =112	Pathologic Response		p Value
		Non-MPR (n=63)	MPR (n=49)	
mRECIST				
CR	24 (21.4)	1 (1.6)	23 (46.9)	<0.001
PR	66 (58.9)	43 (68.2)	23 (46.9)	
SD	10 (8.9)	8 (12.7)	2 (4.1)	
PD	12 (10.7)	11 (17.5)	1 (2.1)	

Notes: Data were presented as number (percentage), and p value was calculated using chi-square test or fisher's exact test as appropriate.
Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; MPR, major pathologic response.

Table 3 Univariable and Multivariable Logistic Regression Analyses for Predictors of Major Pathologic Response

	AFP-Positive Group					AFP-Negative Group				
	Univariable Analysis		Multivariable Analysis			Univariable Analysis		Multivariable Analysis		
Variables	OR (95% CI)	P value	β	OR (95% CI)	P value	OR (95% CI)	P value	β	OR (95% CI)	P value
*CR (Yes vs no)	15.06 (4.55–119.6)	<0.001	…	…	…	14.68 (3.24–168.7)	0.009	…	…	…
*ORR (Yes vs no)	4.33 (1.62–16.72)	0.01	…	…	…	2.94 (0.75–24.54)	0.182	…	…	…
mRECIST response (Yes vs no)	19.33 (6.39–67.94)	<0.001	3.12	22.68 (5.91–118.4)	<0.001	17.42 (3.68–110.5)	0.001	2.68	14.59 (2.50–128.8)	0.006
AFP response (Yes vs no)	17.78 (5.23–83.33)	<0.001	3.06	21.36 (4.67–142.7)	<0.001	…	…	…	…	…
PIVKA- II response (Yes vs no)	6.12 (2.06–21.16)	0.002	…	…	…	13.71 (2.82–104.9)	0.003	2.42	11.24 (1.74–119.1)	0.019
Change in ALBI	1.04 (1.01–1.08)	0.034	…	…	…	1.01 (0.96–1.04)	0.855	…	…	…
Change in NLR	0.99 (0.98–1)	0.081	…	…	…	0.99 (0.97–1.01)	0.333	…	…	…
Change in AST/ALT	0.99 (0.98–1)	0.114	…	…	…	0.99 (0.97–1.01)	0.370	…	…	…
†Main tumor size (>10 cm vs ≤10 cm)	1.25 (0.61–2.59)	0.537	…	…	…	1.09 (0.36–3.12)	0.869	…	…	…
†Vascular invasion (Yes vs no)	1.01 (0.40–2.55)	0.415	…	…	…	2.64 (0.57–13.10)	0.215	…	…	…
†BCLC (B/C vs A)	1.11 (0.44–2.81)	0.830	…	…	…	3.37 (0.87–14.51)	0.086	…	…	…

Notes: *CR and ORR were assessed according to mRECIST criteria. †These variables were assessed at baseline.
Abbreviation: CR, complete response; PR, partial response; ALBI, albumin-bilirubin; NLR, neutrophil-to-lymphocyte ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; OR, odds ratio.

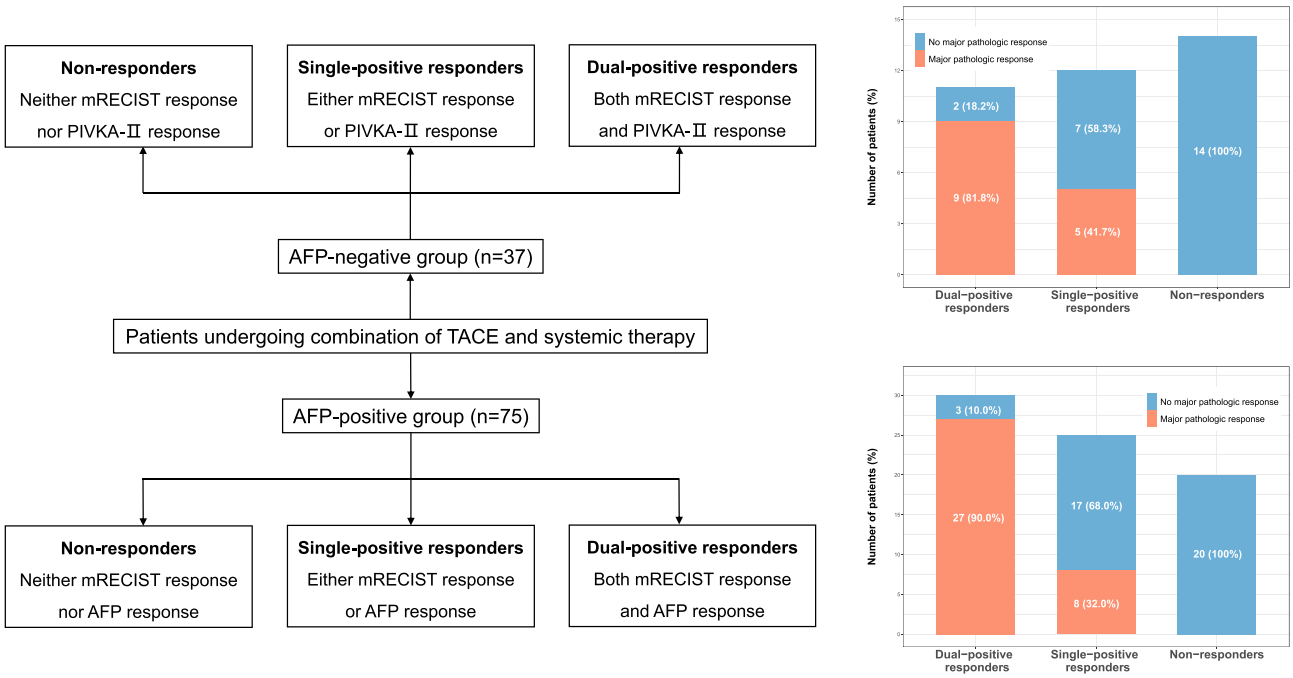

Figure 4 Graphical illustration of the prediction system for major pathologic response. The prediction system included two dual-biomarker models used respectively for the AFP-positive (based on the combination of mRECIST response and AFP-response) and AFP-negative groups (based on the combination of mRECIST response and PIVKA- II response). mRECIST response was defined as a decrease in the sum of longest diameter of viable target lesions >70% from baseline; AFP response was defined as a decrease in AFP >90% from baseline; PIVKA- II response was defined as a decrease in PIVKA- II >80% from baseline.

mRECIST or AFP response (single-positive responders) and non-responders (p<0.001). The corresponding median RFS was not reached (NR), 10.7 months and 7.1 months, with significant difference between dual-positive responders and non-responders (HR 0.41, 95% CI 0.17–0.97, p=0.043) (Figure 5). Similarly, the MPR rates were 81.8%, 41.7% and 0% in the AFP-negative group (p<0.001), and the corresponding median RFS was NR, 18.9 months and 13.3 months (Figure S2, Tables S7-8). The system yielded an AUC of 0.905 (95% CI 0.845–0.966) in the AFP-positive group and 0.887 (95% CI 0.792–0.982) in the AFP-negative group, demonstrating superiority over single criterion (Table 4). Besides, the predictive accuracy remained consistent in internal validation (optimism-corrected AUC: 0.903 [95% CI 0.840–0.965] and 0.887 [95% CI 0.795–0.979]). Moreover, the dual-positive response reduced the percentage of single-positive responders but did not achieve MPR from 21.6% (mRECIST response) and 31.9% (AFP response) to 10.0% in AFP-positive group, and from 26.7% (mRECIST response) and 36.8% (PIVKA- II response) to 18.2% in AFP-negative group (Figure S3). Development and validation of the prediction system is detailed in Supplementary materials.

Subgroup analysis in the AFP-positive group showed that the dual-biomarker model was more predictive of MPR in patients with lower tumor burden (smaller size and fewer number) and without vascular invasion, whereas the types of LRT and systemic therapy did not markedly affect the predictive accuracy (Figure S4). Subgroup analysis was not performed in the AFP-negative group due to the inadequate sample size.

Discussion

LRT plus systemic combination therapy may achieve remarkable tumor response for unresectable HCC and can serve as a selection tool to identify patients with favorable tumor biology that may benefit from subsequent curative-intent surgery. Thus, accurate and timely treatment response evaluation is crucial for individualized decision-making. This radiologic-pathologic correlation study demonstrated that mRECIST had stronger correlation with pathologic response than RECIST 1.1 following combination therapy, and that MPR (instead of pCR) was independently predictive of post-resection RFS. A non-invasive prediction system for MPR was developed based on the combination of mRECIST response with either AFP or PIVKA- II responses, yielding an AUC of 0.905 in the AFP-positive patients and 0.887 in the AFP-negative patients, and showing good prognostic stratification ability.

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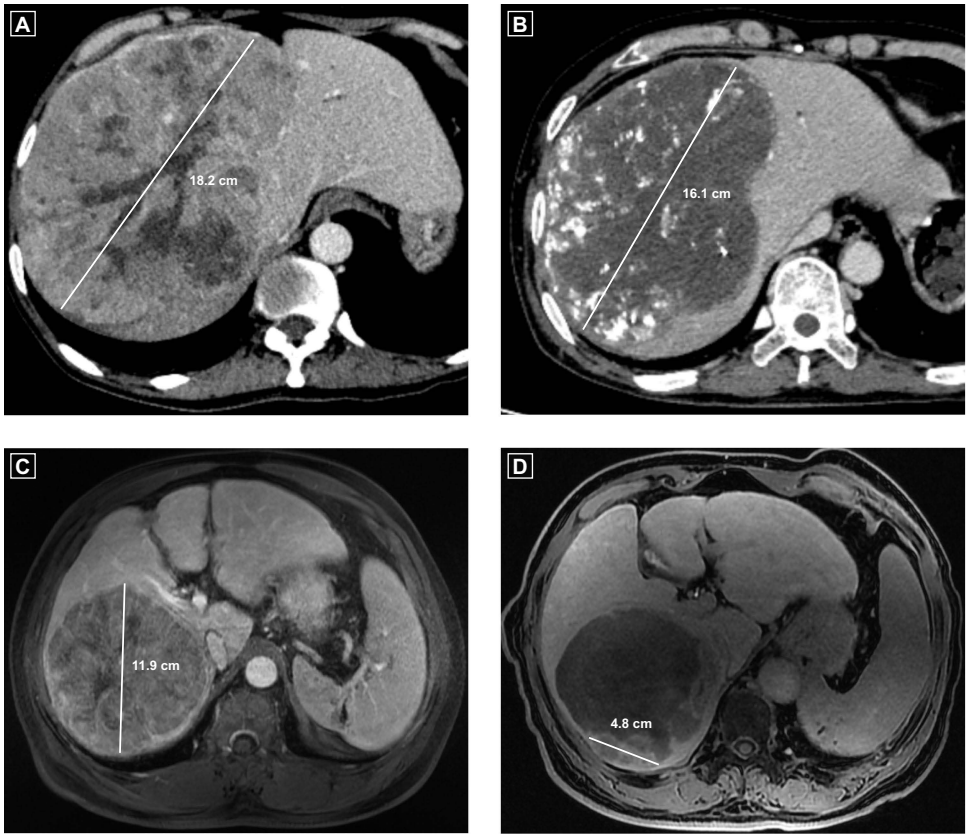

Figure 5 Images in a 59-year-old male (**A** and **B**) and a 68-year-old male (**C** and **D**) with initially unresectable hepatocellular carcinoma before and after combination therapy. For patient 1: (**A**) CE-CT showed a 18.2 cm single HCC, and (**B**) the lesion shrank to 16.1 cm (11.5%, RECIST 1.1: PR) and showed no enhanced portion (100%, mRECIST: CR) after combination therapy, AFP level decreased from 349.1 to 8.2 ng/mL (97.7%). The patient was determined as dual-positive responders, and post-resection pathology found <1% of residual viable tumors. He was still alive and did not develop tumor recurrence at the end of follow-up. For patient 2: (A) MRI found a 11.9cm single HCC, and (**B**) the lesion shrank to 11.1 cm (6.7%, RECIST 1.1: SD), with an enhanced portion of 4.8 cm (59.7%, mRECIST: PR), and AFP level decreased from 585.0 to 65.2 ng/mL (88.9%). The patient was determined as no responders and pathology found 30% of residual viable tumors. The patient experienced tumor recurrence 6.6 months after liver resection.

Multiple studies have reported encouraging results on the efficacy and safety of LRT and systemic combination therapy as a downstaging strategy for initially unresectable HCC.[9,11–15] On one hand, LRT induces tumor cell necrosis and antigen release, which facilitate tumoral antigen presentation and prime antitumor lymphocytes, transforming an immunosuppressive microenvironment into an immunosupportive setting.[31] On the other hand, TKIs inhibit tumor revascularization and ICIs restore immune activity and eradicate subclinical metastasis,[32] which complement the LRT-induced tumor necrosis. These synergistic effects provide the rationale for combination therapy as a promising downstaging or bridge strategy to curative treatment, or as new avenue for prolonged progression-free survival and tumor control revealed by the latest Phase 3 EMERALD-1 trial.[33]

Radiologic-based morphologic changes (ie, the RECIST criteria) remain the current benchmark for response evaluation. However, absence of tumor shrinkage may not rule out treatment activity, and a high ORR may not translate into a proportional survival benefit.[34,35] Similar findings were observed in our study as none of the RECIST-based endpoints were predictive of post-resection RFS. Moreover, specific treatment-related alterations, such as the beam-hardening artifact of lipiodol in TACE and reduced arterial flow after antiangiogenics, may confound radiologic response evaluation.[36,37]

The unsatisfactory prognostic value of radiologic response criteria could be reflected by their relatively weak correlation with pathologic response, a reliable surrogate that strongly reflects treatment efficacy and captures survival benefit.[18] In accordance with reports in other cancers,[38] MPR was suggested as an independent prognostic factor in HCC,[39] which was also observed in our study. This may partially be attributed to the efficacy of subsequent curative-intent surgery after sufficiently decreased tumor burden. Besides, ICIs could achieve clinical benefit by priming antitumor immune response that systemically eradicate microscopic tumor deposits and decrease the risk of recurrence, regardless of whether complete necrosis is achieved by LRT. Given the comparable prognostic value between MPR and

Table 4 Predictive Accuracy of Single Predictors and Their Combinations in Predicting Major Pathologic Response

	AUC	*P* Value	Sensitivity	Specificity	Accuracy
AFP-Positive Group (n=75)					
mRECIST response	0.814 (0.725–0.903)	0.101	0.829 [29/35] (0.704–0.953)	0.800 [32/40] (0.676–0.924)	0.813 (0.809–0.817)
AFP response	0.769 (0.680–0.859)	0.015	0.914 [31/35] (0.822–1)	0.625 [25/40] (0.475–0.775)	0.760 (0.755–0.765)
Dual-biomarker model Non-responders Single-positive Dual-positive	0.905 (0.845–0.966)	ref	1 [35/35] (1–1) 0.229 [8/35] (0.089–0.368) 0.771 [27/35] (0.632–0.911)	0.501 [20/40] (0.345–0.655) 0.575 [23/40] (0.422–0.728) 0.925 [37/40] (0.843–1)	0.853 (0.850–0.857)
AFP-negative group (n=37)					
mRECIST response	0.806 (0.669–0.943)	0.117	0.786 [11/14] (0.571–1)	0.83 [19/23] (0.67–0.98)	0.811 (0.803–0.819)
PIVKA- II response	0.776 (0.641–0.912)	0.039	0.857 [12/14] (0.674–1)	0.69 [15/23] (0.51–0.88)	0.757 (0.747–0.767)
Dual-biomarker model Non-responders Single-positive Dual-positive	0.887 (0.792–0.982)	ref	1 [14/14] (1–1) 0.357 [5/14] (0.106–0.608) 0.643 [9/14] (0.392–0.894)	0.609 [14/23] (0.409–0.809) 0.696 [16/23] (0.508–0.884) 0.913 [20.9] (0.798–1)	0.811 (0.803–0.819)

Notes: 95% confidence intervals are in parentheses, and number of patients are in brackets.

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pCR, and a larger proportion of patients captured by the former (47% vs 15%), MPR may identify additional patients that will benefit from subsequent curative-intent treatment, and thus has greater potential to be applied as a surrogate than pCR. Furthermore, compared with RECIST 1.1, mRECIST showed superiority in prediction of MPR because combination therapy may produce massive tumor necrosis without reducing lesion size.[34] Among laboratory parameters, only AFP and PIVKA- II changes were associated with MPR. These results were consistent with previous findings as only mRECIST and AFP responses were predictive of pCR after systemic therapy.[40]

A prediction system for MPR was developed and yielded high predictive accuracy, which included two dual-biomarker models used respectively for the AFP-positive and AFP-negative groups. For patients classified as having a high probability of MPR (ie, with a dual-positive response), the 12-month RFS rate after resection was comparable to the reported RFS in patients with initially resectable HCC,[41,42] suggesting that this subgroup of patients may benefit the most from subsequent resection. Contrarily, poor response to combination therapy indicates unfavorable tumor biology and is associated with worse prognosis after resection. Thus, the dual-negative response may serve as an exclusion criterion for liver resection, warranting other antitumor treatments. For those with single-positive response, other stratification tools (eg, close-interval follow-up or biopsy) may aid treatment decision-making. Of note, difference on post-resection RFS between response categories in the AFP-negative group was not significant. This could be attributed to the small sample-size and the significantly improved outcomes of this subgroup compared with the AFP-positive group (median RFS 13.7 vs 9.5 months), which attenuated stratification ability of the prediction system.

Our study has some limitations. First, a potential selection bias existed deriving from excluding patients who did not undergo curative-intent treatment (mostly due to disease progression following combination therapy). This bias can be overcome by including drop-out patients, but the pathologic information would be lost. Second, the relatively low inter-observer agreement on mRECIST evaluation (mainly due to heterogeneous or rim enhancement) may challenge its clinical application, and automatically quantitative techniques may help overcome evaluation subjectiveness. Third, various TKIs and ICIs regimens were used that might confound our results. However, this mimics the real-world situation, and the similar results in subgroup analyses confirmed the robustness of our findings. Finally, the single-center design introduced a center effect. However, it minimized variability in procedure approach and scanning protocols. Additionally, this study provides evidence on the prognostic value of MPR after combination therapy, as previous researches scarcely investigated MPR and focused solely on LRT or systemic therapy.[40,43] More importantly, the proposed prediction system may be a step towards more personalized management because it includes two models used respectively for the AFP-positive and AFP-negative patients.

In conclusion, MPR was found as an independent predictor of post-resection RFS after downstaging with the combination of TACE and systemic therapy. Integration of mRECIST, AFP and PIVKA- II responses allow accurate prediction of MPR, thus may help refine patient selection and inform individualized treatment decision-making. This may have particular relevance in the upcoming era of combination therapies.

Abbreviations

HCC, hepatocellular carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors; LRT, locoregional therapy; TACE, transarterial chemoembolization; ICI, immune checkpoint inhibitor; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; RFS, recurrence-free survival; OS, overall survival; AUC, area under the curve.

Data Sharing Statement

The dataset used and analyzed in the present study are available from the corresponding author on reasonable request.

Ethics Approval Statement and Informed Consent

The study protocol was approved by the institutional review board of the West China Hospital, Sichuan University. Informed consent was waived due to the retrospective nature of the current study, and data of the participants have been anonymized.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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