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ORIGINAL RESEARCH

The Prognostic Value of Baseline Clinical and Radiologic Imaging Features in Patients with Unresectable Hepatocellular Carcinoma Treated with Atezolizumab Plus Bevacizumab

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Purpose: To identify prognostic clinical and radiologic features in patients with unresectable hepatocellular carcinoma (HCC) treated with atezolizumab plus bevacizumab.

Patients and Methods: Clinical and imaging records of patients with unresectable HCC were retrospectively reviewed, and baseline features were recorded. Patients' records and imaging studies were used to determine the patients' overall survival (OS) and progression-free survival (PFS). Univariate and multivariate analyses were performed to determine prognostic features. Subanalyses of treatment-naïve patients (who never received local or systemic therapy) and previously treated patients were also performed.

Results: Fifty-five patients were included in the final analysis, 23 (41.8%) of whom were treatment naïve. The median PFS and OS for the entire cohort were 3.0 months and 7.9 months. The 3-, 6- and 12-month OS rates were 85.5%, 79.8% and 45.7%, respectively. The 3-, 6- and 12-month PFS rates were 50.1%, 41.2% and 20.1%, respectively. On multivariate analysis, independent prognostic features for poor PFS of the entire cohort were pleural effusions ($p = 0.047$, HR: 6.3; CI: 1.03–38.90) and hepatic vein tumor thrombus ($p = 0.005$; HR: 23.37; CI: 2.63–207.67); independent prognostic features for poor OS were ascites ($p = 0.008$; HR: 37.37; CI: 2.53–467.64), pleural effusion ($p = 0.003$; HR: 110.17; CI: 5.00–2426.54), and low (<40HU) pre-contrast attenuation on CT images ($p = 0.007$; HR: 0.09; CI: 0.02–0.53). On subanalysis of treatment-naïve patients, the median OS and PFS were 7.4 months and 2.8 months, respectively. The 3-, 6- and 12-month PFS rates were 43.5%, 38.6% and 24.8%, respectively. Pleural effusion was the only independent poor prognostic feature ($p = 0.036$; HR: 206.34; CI: 1.41–30,167.58).

Conclusion: Independent prognostic features for survival outcomes include the presence of ascites, pleural effusions, hepatic vein tumor thrombus, and HCC with low attenuation (<40 HU) on unenhanced CT images. Although several biochemical variables were significant on univariate analysis, none were independent predictors of OS or PFS.

Keywords: radiographic, radiology, RECIST, survival, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio

Introduction

Treatment options for hepatocellular carcinoma (HCC) vary according to disease stage, performance status, and liver function.[1] Systemic therapy is recommended for unresectable HCC patients with adequate liver function who are not candidates for locoregional therapy. The IMbrave150 trial was published in 2020 and it changed the landscape of systemic therapy for HCC by showing better overall survival and progression-free survival in patients receiving the combination of atezolizumab plus bevacizumab compared to sorafenib monotherapy.[2] Soon after publishing the results of this trial, the American Society of

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Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) updated their guidelines recommending atezolizumab-bevacizumab as the first line of systemic therapy for unresectable HCC.[3,4]

Despite the promising data of the IMbrave150 trial, response to treatment was heterogeneous with complete response being achieved in 10% and disease control rate (complete response, partial response and stable disease) achieved only in 74% of patients receiving atezolizumab-bevacizumab.[2]

The primary objective of the current study is to determine the prognostic value of baseline imaging features and clinical/laboratory parameters in patients with unresectable HCC receiving atezolizumab-bevacizumab. The secondary objective is to evaluate the response rate according to RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) and mRECIST (modified Response Evaluation Criteria in Solid Tumors) criteria.

Methods

After institutional review board approval, patients with unresectable HCC who received the combination of atezolizumab plus bevacizumab between June 2018 and February 2022 were identified from clinical records. Patients who received locoregional therapy (eg, percutaneous ablation, transcatheter radio/chemoembolization, external beam radiotherapy) or who underwent surgery after initiation of atezolizumab-bevacizumab were excluded from the analysis. Both treatment naïve patients and patients who had received prior therapy (eg, surgery, percutaneous interventions, radiotherapy and systemic therapy) were included in this study. Patients who received locoregional therapy (radiotherapy) for extrahepatic metastases after initiation of atezolizumab-bevacizumab were also included in the analysis, but these lesions were not selected as target lesions for radiologic response assessment.

Prospectively maintained medical and imaging records were reviewed to determine the progression-free survival and overall survival. Patients' records were retrospectively reviewed to collect demographic, biochemical/laboratory, clinical and radiologic (computerized tomography (CT) and magnetic resonance imaging (MRI)) data at baseline (ie, prior to initiation of atezolizumab-bevacizumab). Progression-free survival was defined as death from any cause, radiologic progression (as defined by RECIST 1.1 and mRECIST criteria),[5,6] occurrence of severe treatment-related adverse effects necessitating cessation of atezolizumab-bevacizumab (eg, immunotherapy related adverse events, bowel perforation, gastrointestinal hemorrhage) or clinical deterioration requiring cessation of systemic therapy which ever occurred first. Overall survival was defined as the duration between the initiation of atezolizumab-bevacizumab and death from any cause. The best overall radiologic response (as defined by RECIST 1.1 and mRECIST criteria)[5,6] was also recorded.

Most recent imaging studies (CT or MRI) prior to initiation of systemic therapy with atezolizumab-bevacizumab were reviewed by a fellowship trained abdominal radiologist. Radiologic features related to cirrhotic liver morphology, portal hypertension, presence/absence of nodal spread or distant metastases were recorded. In addition, data regarding the size, number of disease foci, presence of tumor-in-vein, and extrahepatic extension were recorded. Enhancement characteristics on CT were investigated. Pre-contrast, arterial phase, portal phase and delayed phase attenuation were recorded by placing region of interest (ROI) on the viable enhancing portions of the tumor.

Categorical variables were expressed as number (percentage). Continuous variables were expressed as median (min-max; interquartile range). Univariate analysis was performed using the Kaplan–Meier method to determine features having a statistically significant ($p < 0.05$) association with overall survival and progression-free survival. Subsequently, multivariate cox regression analysis was conducted to determine the hazard ratio (HR) and 95% confidence intervals (CI) for these variables. Univariate and multivariate analyses were conducted for the entire cohort, and sub-analyses were performed for treatment naïve and previously treated patients. A p-value of <0.05 was considered statistically significant in this study.

Results

A total of 76 HCC patients who received atezolizumab-bevacizumab were identified. Twenty-one patients were excluded from the analysis because they received surgical or percutaneous interventions to intrahepatic disease foci after initiation of systemic therapy. Fifty-five patients were included in the final analysis, 23 (41.8%) of whom were treatment naïve patients. Forty-two patients (57.5%) had baseline CT scans and 13 had baseline MRI. Descriptive statistics of patients' baseline features are outlined in Tables 1 and S1 in the supplementary materials.

Table 1 Baseline Descriptive Clinical, Biochemical and Radiologic Statistics

Characteristics	Entire Cohort (n = 55)	Treatment Naïve Patients (n = 23)	Patients Who Received Prior Treatment (n = 32)
Age - median year - median (min-max; IQR)	66.0 (36–80; 12)	65 (36–80; 10)	68.0 (52–80; 14)
≤65	24 (43.6)	12 (52.2)	12 (37.5)
>65	31 (56.4)	11 (47.8)	20 (62.5)
Gender - n (%)			
Female	10 (18.2)	7 (30.4)	3 (87.5)
Male	45 (81.8)	16 (69.6)	4 (12.5)
Largest intrahepatic tumor diameter, median cm (min-max; IQR)	6.9 (1.4–17.5; 7.5)	9.2 (2.8–17.5; 7.2)	4.3 (1.4–16.1; 7.5)
≤7 cm	28 (52.8)	8 (34.8)	20 (66.7)
>7 cm	25 (47.2)	15 (65.2)	10 (33.3)
Number of intra-hepatic disease foci - n (%)			
0–3	9 (16.4)	1 (34.8)	8 (25.0)
≥4	46 (83.6)	22 (95.7)	24 (75.0)
Portal vein tumor thrombus - n (%)			
None	34 (61.8)	12 (52.2)	22 (68.8)
Small (<2cm)	6 (10.9)	3 (13.0)	3 (9.4)
>2cm without main portal vein involvement	10 (18.2)	4 (17.4)	6 (18.8)
>2cm with main portal vein involvement	5 (9.1)	4 (17.4)	1 (3.1)
Hepatic vein tumor thrombus - n (%)			
None	49 (89.1)	19 (82.6)	30 (93.8)
Small (<2cm)	4 (7.3)	2 (8.7)	2 (6.3)
>2cm without inferior vena cava involvement	1 (1.8)	1 (4.3)	0 (0.0)
>2cm with inferior vena cava involvement	1 (1.8)	1 (4.3)	0 (0.0)
Metastases (nodal and non-nodal) - n (%)			
Absent	37 (67.3)	17 (73.9)	20 (62.5)
Present	18 (32.7)	6 (26.1)	12 (37.5)
AFP, median ng/dL (min-max; IQR)	349 (2.7–201,700; 5695)	954 (3.2–169,990; 11,385)	27.5 (2.7–201,700; 1327)
≤400 ng/dL	28 (50.9)	7 (30.4)	21 (65.6)
>400 ng/dL	27 (49.1)	16 (69.6)	11 (34.4)
INR, median (min-max; IQR)	1.1 (0.9–1.96; 0.2)	1.18 (0.99–1.96; 0.29)	1.1 (0.9–1.7; 0.2)
≤1.5	53 (96.4)	22 (95.7)	31 (96.9)
>1.5	2 (3.6)	1 (4.3)	1 (3.1)
Albumin, median g/dL (min-max; IQR)	3.6 (2.6–3.8; 0.7)	3.6 (2.8–4.7; 0.7)	3.6 (2.6–4.7; 0.6)
<3.5 g/dL	27 (49.1)	11 (47.8)	16 (50.0)
>3.5 g/dL	28 (50.9)	12 (52.2)	16 (50.0)

(*Continued*)

Table 1 (Continued).

Characteristics	Entire Cohort (n = 55)	Treatment Naïve Patients (n = 23)	Patients Who Received Prior Treatment (n = 32)
Total bilirubin, median mg/dL (min-max; IQR)	0.8 (0.3–3.8; 0.6)	0.8 (0.3–1.9; 0.6)	0.9 (0.3–3.8; 0.8)
<2.0 mg/dL	51 (92.7)	23 (100.0)	28 (87.5)
>2.0 mg/dL	4 (7.3)	0 (0.0)	4 (12.5)
Child-Pugh score - n (%)			
A5	21 (38.2)	10 (43.5)	11 (34.4)
A6	9 (16.4)	4 (17.4)	5 (15.6)
B7	15 (27.3)	5 (21.7)	10 (31.3)
B8	9 (16.4)	3 (13.0)	6 (18.8)
B9	1 (1.8)	1 (4.3)	0 (0.0)
MELD score, median (min-max; IQR)	9 (6–21; 3)	9 (6–21; 2)	9 (6–15; 3)
≤9	36 (65.5)	17 (73.9)	19 (59.4)
>9	19 (34.5)	6 (26.1)	13 (40.6)

Note: More detailed data can be found in the supplementary material.
Abbreviations: INR, international normalized ratio; IQR, interquartile range; MELD, model for end-stage liver disease.

The median follow-up period for the study cohort was 7.9 months (1.0–46.6; 10.0). Forty-five (81.8%) of all patients had disease progression during the follow-up period. The median progression-free survival was 3.0 months (0.3–26.9; 6.1). Thirty-three patients (60%) of the entire cohort died during the follow-up period and the median overall survival was 7.9 months (1.0–46.6; 10.0). The 3-, 6- and 12-month overall survival rates were 85.5%, 79.8% and 45.7%, respectively. The 3-, 6- and 12-month progression-free survival rates were 50.1%, 41.2% and 20.1%, respectively (Tables 2 and S2 in the supplementary materials).

Disease control rate (complete response, partial response and stable disease as determined on RECIST 1.1 and mRECIST criteria) on follow-up imaging was 49.1%. Twenty-one patients (38.2%) had no radiologic evidence of disease control despite systemic therapy. Response assessment to atezolizumab-bevacizumab is outlined in Table 2.

Progression-Free Survival of the Entire Cohort

Univariate analysis of progression-free survival showed a significantly better progression-free survival with absence of ascites (p = 0.005), absence of pleural effusion (p = 0.022), tumors with well-demarcated margins (p = 0.017), tumors with pre-contrast attenuation >40 HU (p = 0.037), tumors having arterial phase attenuation >100 HU (p = 0.012), tumors with no or small (<2cm) tumor-in-vein involving the portal vein (p = 0.044), tumors with no hepatic vein tumor thrombus (p = 0.001), absence of cavernous transformation (p = 0.001), splenic volume <450cm^3 (p = 0.014), absence of heterogeneous extra-abdominal lymph nodes (p = 0.016), tumor signal drop of <10% on opposed phase MRI (p = 0.047), serum albumin levels >3.5 mg/dL (p = 0.002), neutrophil-to-lymphocyte ratio of <3.0 (p = 0.042), platelet-to-lymphocyte ratio <230 (p = 0.033), and albumin-bilirubin (ALBI) grade 1 (p = 0.010).

Multivariate analysis including variables that were statistically significant on univariate analysis was conducted. Tumor signal drop ratio on out-of-phase imaging could not be included in multivariate analysis because of the small proportion of patients with baseline MRI (n = 13). Serum albumin level was not included in multivariate analysis model because it is used for calculation of ALBI score. Independent prognostic factors for progression-free survival of the entire cohort were the presence of pleural effusion (p = 0.047, HR: 6.3; CI: 1.03–38.90) and tumor-in-vein involving the hepatic veins (p = 0.005; HR: 23.37; CI: 2.63–207.67). Outcomes of univariate and multivariate analyses for progression-free survival of the entire cohort are outlined in Tables 3 and S3 in the supplementary materials.

Table 2 Response Assessment to Atezolizumab-Bevacizumab

Characteristics	Entire Cohort (n = 55)	Treatment Naïve Patients (n = 23)	Patients Who Received Prior Treatment (n = 32)
Follow-up duration, median months (min-max; IQR)	7.9 (1.0–46.6; 10.0)	7.4 (1.0–26.9; 7.3)	9.2 (1.6–46.6; 9.4)
Progression - n (%)			
Absent	10 (18.2)	5 (21.7)	5 (15.6)
Present	45 (81.8)	18 (78.3)	27 (84.4)
Cause of progression - n (%)			
Toxicity/lack of tolerance	9 (16.4)	6 (26.1)	3 (9.4)
Radiologic progression	31 (56.4)	11 (47.8)	20 (62.5)
Death	5 (9.1)	1 (4.3)	4 (12.5)
No progression	10 (18.2)	5 (21.7)	5 (15.6)
Progression free survival, median months (min-max; IQR)	3.0 (0.3–26.9; 6.1)	2.8 (0.3–26.9; 6.1)	3.9 (0.6–16.0; 6.1)
3-month progression-free survival (%)	50.1	43.5	56.3
6-month progression-free survival (%)	41.2	38.6	43.3
12-month progression-free survival (%)	20.1	24.8	17.3
Overall survival, median months (min-max; IQR)	7.9 (1.0–46.6; 10.0)	7.4 (1.0–26.9; 7.3)	9.2 (1.6–46.6; 9.4)
3-month overall survival (%)	85.5	83	93.8
6-month overall survival (%)	79.8	64.7	90.6
12-month overall survival (%)	45.7	33.6	53.9
Best overall response RECIST 1.1 - n (%)			
Progressive disease	21 (38.2)	8 (34.8)	13 (40.6)
Stable disease	12 (21.8)	4 (17.4)	8 (25.0)
Partial response	15 (27.3)	7 (30.4)	8 (25.0)
Complete response	0 (0.0)	0 (0.0)	0 (0.0)
Could not be evaluated	7 (12.7)	4 (17.4)	3 (9.4)
Best overall response mRECIST - n (%)			
Progressive disease	21 (38.2)	8 (34.8)	13 (40.6)
Stable disease	12 (21.8)	4 (17.4)	8 (25.0)
Partial response	13 (23.6)	6 (26.1)	7 (21.9)
Complete response	2 (3.6)	1 (4.3)	1 (3.1)
Could not be evaluated	7 (12.7)	4 (17.4)	3 (9.4)

Note: More detailed data can be found in the supplementary material.
Abbreviations: IQR, interquartile range; RECIST, response evaluation criteria in solid tumors; mRECIST, modified response evaluation criteria in solid tumors.

Overall Survival of the Entire Cohort

Univariate analysis of overall survival showed a significantly better overall survival with absence of ascites (p = <0.001), absence of pleural effusion (p = 0.015), largest intrahepatic tumor <7cm in size (p = 0.016), <4 foci of intrahepatic disease (p = 0.042), well-demarcated tumors (p = <0.001), presence of enhancing capsule on delayed images (p = 0.032), tumor pre-contrast attenuation of >40 HU (p = 0.046), no or small (<2cm) tumor-in-vein involving the portal veins (p = 0.012), absence of tumor-in-vein involving the hepatic veins (p = 0.003), absence of cavernous transformation (p = <0.001), absence of biliary dilatation or biliary stent (p = 0.021), splenic volume <450cm^3 (p = 0.002), absence of recanalized umbilical vein (p = 0.005), short axis of the largest locoregional lymph node <1.0 cm (p = 0.039), serum albumin level >3.5 mg/dL (p = <0.001), serum direct bilirubin <0.8 mg/dL (p = 0.001), serum hemoglobin >12.0 g/dL (p = 0.011), MELD score of ≤9 (p = 0.045), and ALBI score ≤-2.6 (p = <0.001).

Multivariate analysis including variables that were statistically significant on univariate analysis was conducted. Serum albumin level and bilirubin levels were not included in multivariate analysis because they are used for calculation of ALBI score. Independent prognostic factors for poor overall survival of the entire cohort were the presence of small volume ascites

Table 3 Univariate and Multivariate Analyses for Progression Free Survival of the Entire Cohort

Characteristics	Progression-Free Survival of the Entire Cohort (n = 55)				
	Univariate Analysis			Multivariate Analysis	
	Censored, n (%)	Median (95% CI), Months	p-value	HR (95% CI)	p-value
Ascites					
None	7 (18.9)	6.3 (1.2–11.4)	**0.005**	1.34 (0.36–5.05)	0.663
Mild	3 (16.7)	2 (0.3–3.7)			
Pleural effusion					
None	10 (20.0)	3.2 (0.0–6.7)	**0.022**	6.3 (1.03–38.90)	**0.047**
Mild	0 (0.0)	0.9 (0.3–1.5)			
Tumor margin					
Well-demarcated	6 (27.3)	4.6 (0.0–17.9)	**0.017**	0.96 (0.25–3.61)	0.946
Irregular/infiltrative	4 (12.9)	2.8 (2.5–3.1)			
Tumor pre-contrast density					
<40	1 (5.9)	2.8 (2.3–3.3)	**0.037**	0.55 (0.19–1.62)	0.279
≥40	5 (29.4)	4.9 (0.0–14.5)			
Tumor arterial phase density					
≤100	1 (5.3)	2.7 (2.1–3.3)	**0.012**	0.51 (0.13–1.92)	0.317
>100	5 (33.3)	7.2 (0.0–17.6)			
Portal vein tumor thrombus					
None or <2cm	7 (17.5)	4.9 (0.4–9.4)	**0.044**	0.12 (0.05–1.39)	0.117
> 2cm with or without main portal vein involvement	3 (20.0)	1.6 (0.4–2.8)			
Hepatic vein tumor thrombus					
Absent	10 (20.4)	4.9 (1.4–8.4)	**<0.001**	23.37 (2.63–207.67)	**0.005**
Present	6 (0.0)	0.7 (0.1–1.3)			
Cavernous transformation					
Absent	10 (20.4)	4.9 (0.7–9.1)	**0.001**	1.36 (0.16–11.72)	0.779
Present	0 (0.0)	0.8 (0.0–1.9)			
Spleen volume					
<450 cm^3	7 (28.0)	7.7 (0.4–15.0)	**0.014**	4.12 (0.97–17.56)	0.056
>450 cm^3	3 (10.0)	2.8 (2.4–3.2)			
Heterogeneous extra-abdominal lymph node					
Absent	10 (20.0)	4.5 (0.9–8.1)	**0.016**	0.84 (0.12–5.79)	0.859
Present	0 (0.0)	2.0 (0.7–3.3)			
Tumor in/out of phase drop ratio					
≤10%	3 (37.5)	15.4 (1.2–29.6)	**0.047**		
>10%	0 (0.0)	0.8 (0.0–3.0)			
Albumin					
<3.5 g/dL	3 (11.1)	2.8 (2.1–3.5)	**0.002**		
>3.5 g/dL	7 (25.0)	6.5 (0.1–12.9)			
Neutrophil to lymphocyte ratio					
≤3	4 (19.0)	7.3 (3.6–10.9)	**0.042**	1.28 (0.32–5.20)	0.726
>3	6 (17.6)	2.8 (2.3–3.3)			
Platelet to lymphocyte ratio					
<230	7 (19.4)	6.3 (3.2–9.4)	**0.033**	2.40 (0.40–14.34)	0.337
≥230	3 (15.8)	2.4 (2.0–2.8)			
ALBI score					
≤-2.6 (grade 1)	5 (29.4)	8.6 (0.0–19.5)	**0.010**	0.47 (0.09–2.42)	0.363
> −2.6 (grade 2 and 3)	5 (13.2)	2.8 (2.3–3.3)			

Notes: Note that only parameters that reached statistical significance on univariate analysis (p<0.05, indicated in bold) are listed above; analyses of other variables are detailed in the supplementary material.

Abbreviation: ALBI score, Albumin-Bilirubin score.

(p = 0.008; HR: 37.37; CI: 2.53–467.64), presence of pleural effusions (p = 0.003; HR: 110.17; CI: 5.00–2426.54), and tumor pre-contrast attenuation of >40 HU (p = 0.007; HR: 0.09; CI: 0.02–0.53). Outcomes of univariate and multivariate analyses for overall survival of the entire cohort are detailed in Tables 4 and S4 in the supplementary materials.

Table 4 Univariate and Multivariate Analyses of Overall Survival for the Entire Cohort

Characteristics	Overall Survival of the Entire Cohort (n = 55)				
	Univariate Analysis			Multivariate Analysis	
	Censored, n (%)	Median (95% CI), Months	p-value	HR (95% CI)	p-value
Ascites					
None	17 (45.9)	12.8 (7.1–18.5)	**<0.001**	34.37 (2.53–467.64)	**0.008**
Mild	5 (27.8)	7.3 (1.2–13.4)			
Pleural effusion					
None	21 (42.0)	12.3 (8.6–16.0)	**0.015**	110.17 (5.00–2426.54)	**0.003**
Mild	1 (20.0)	7.7 (2.1–13.3)			
Largest intrahepatic tumor diameter					
≤7 cm	15 (53.6)	15.5 (12.6–18.4)	**0.016**	0.34 (0.01–11.05)	0.542
>7 cm	5 (20.0)	8.9 (7.3–10.5)			
Number of intra-hepatic disease foci					
0–3	8 (88.9)	N/A	**0.042**	N/A	0.979
≥4	14 (30.4)	9.4 (6.7–12.1)			
Tumor margin					
Well-demarcated	12 (54.5)	19.2 (14.7–23.7)	**<0.001**	6.11 (0.13–282.3)	0.355
Irregular/infiltrative	8 (25.8)	7.9 (6.9–8.9)			
Enhancing capsule					
Absent	14 (36.8)	9.0 (7.4–10.6)	**0.032**	0.34 (0.01–11.01)	0.542
Present	6 (40.0)	18.7 (12.6–24.8)			
Tumor pre-contrast density					
<40	5 (29.4)	8.9 (6.3–11.5)	**0.046**	0.09 (0.02–0.53)	**0.007**
≥40	7 (41.2)	11.3 (0.0–24.1)			
Portal vein tumor thrombus					
None or <2cm	16 (40.0)	12.8 (7.4–18.2)	**0.012**	1.52 (0.14–16.07)	0.727
> 2cm with or without main portal vein involvement	6 (40.0)	7.9 (1.9–14.0)			
Hepatic vein tumor thrombus					
Absent	20 (40.8)	11.3 (7.6–15.0)	**0.003**	7.48 (0.30–188.2)	0.222
Present	2 (33.3)	2.8 (0.8–4.8)			
Cavernous transformation					
Absent	21 (42.9)	11.3 (7.6–15.0)	**<0.001**	0.30 (0.01–11.36)	0.515
Present	1 (16.7)	1.4 (0.0–3.2)			
Biliary dilatation or biliary stent					
Absent	17 (42.5)	12.8 (7.8–17.8)	**0.021**	2.60 (0.22–31.34)	0.452
Present	5 (33.3)	6.3 (0.0–13.1)			
Spleen volume, cm^3					
<450 cm^3	14 (56.0)	18.7 (9.1–28.3)	**0.002**	6.91 (0.68–69.79)	0.101
>450 cm^3	8 (26.7)	7.7 (7.0–8.4)			
Recanalization of umbilical vein					
Absent	14 (51.9)	14.8 (8.0–21.6)	**0.005**	4.44 (0.71–27.97)	0.112
Present	8 (28.6)	7.9 (5.3–10.5)			
Short axis of largest locoregional lymph node					
<1.0 cm	15 (45.5)	12.3 (6.9–17.7)	**0.039**	0.49 (0.05–4.42)	0.521
>1.0 cm	7 (31.8)	7.7 (5.5–9.9)			
Albumin					
<3.5 g/dL	6 (22.2)	7.7 (5.8–9.6)	**<0.001**		
>3.5 g/dL	16 (57.1)	18.7 (14.6–22.8)			
Direct bilirubin					
<0.8 mg/dL	20 (40.8)	11.3 (7.7–14.9)	**0.001**	5.69 (0.09–362.51)	0.412
>0.8 mg/dL	2 (33.3)	1.6 (0.0–4.5)			
Hemoglobin					
<12.0 g/dL	7 (35.0)	7.9 (7.6–8.2)	**0.011**	5.04 (0.40–63.19)	0.21
>12.0 g/dL	15 (42.9)	14.8 (6.4–23.2)			

(*Continued*)

Table 4 (Continued).

Characteristics	Overall Survival of the Entire Cohort (n = 55)				
	Univariate Analysis			Multivariate Analysis	
	Censored, n (%)	Median (95% CI), Months	p-value	HR (95% CI)	p-value
MELD score					
≤9	15 (41.7)	12.8 (3.2–22.4)	**0.045**		
>9	7 (36.8)	8.9 (5.8–12.0)			
ALBI score					
≤-2.6 (grade 1)	11 (64.7)	19.2 (18.1–20.3)	**<0.001**	1.23 (0.05–29.47)	0.898
> −2.6 (grade 2 and 3)	11 (28.9)	7.9 (6.4–9.4)			

Notes: Note that only parameters that reached statistical significance on univariate analysis (p<0.05, indicated in bold) are listed above; analyses of other variables are detailed in the supplementary material.
Abbreviations: ALBI score, Albumin-Bilirubin score; MELD, model for end-stage liver disease.

Overall Survival and Progression-Free Survival for Treatment Naïve Patients and for Patients Who Received Prior Therapy

The entire cohort was dichotomized into treatment naïve patients and patients who received prior therapy. Univariate and multivariate analyses were repeated for both groups, and their outcomes are detailed in Tables 5–8 and Tables S5-8 in the supplementary materials.

No independent factors were identified on multivariate analysis of progression-free survival for treatment naïve patients. The presence of pleural effusions was the only independent factor for overall survival in treatment naïve patients (p = 0.036; HR: 206.34; CI: 1.41–30,167.58) (Tables 5 and 6).

In patients who had received prior therapy, multivariate analysis yielded two independent factors for progression-free survival: tumor pre-contrast attenuation >40 HU (p = 0.027; HR: 0.22; CI 0.06–0.84) and presence of hepatic vein tumor thrombus (p = 0.027; HR: 24.87; CI: 1.44–430.07). Multivariate analysis of overall survival in previously treated patients identified two independent variables, the presence of ascites (p = 0.007; HR: 58.83; CI: 2.98–1163.13) and tumor pre-contrast attenuation >40 HU (p = 0.030; HR: 0.09; CI 0.01–0.80) (Tables 7 and 8).

Discussion

The current study identified prognostic biomarkers and evaluated the response rates of patients with unresectable hepatocellular carcinoma receiving atezolizumab plus bevacizumab.

Our study showed that atezolizumab-bevacizumab therapy could achieve disease control in 49% of patients with unresectable HCC. However, most patients eventually had disease progression and only 18% did not have disease progression during the entire follow-up period. In addition, the present study identified a few independent predictors for progression-free survival and overall survival. The presence of pleural effusion and tumor-in-vein involving the hepatic veins were independent predictors of worse progression-free survival. Independent variables predictive of worse overall survival are the presence of ascites, pleural effusion, and tumor attenuation <40 HU on pre-contrast CT images. Although several biochemical variables were significant on univariate analysis, none were independent predictors of overall or progression-free survival.

A few studies evaluated the prognostic value of non-radiological parameters in patients with unresectable HCC receiving atezolizumab-bevacizumab. Wang et al identified four independent factors for progression-free survival: platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, serum alpha-fetoprotein (AFP) level, and prior hepatectomy.[7] Our study used similar cutoff values for platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, and serum AFP levels to those used by by Wang et al, but several additional variables were also included in our analysis. Similar to the results of Wang et al, platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio were significantly associated with progression-free survival on univariate analyses; but on the contrary, these two variables were not

Table 5 Univariate and Multivariate Analyses of Progression Free Survival for Treatment Naïve Patients (n = 23)

Characteristics	Progression-Free Survival for Treatment Naïve Patients (n = 23)				
	Univariate Analysis			Multivariate Analysis	
	Censored, n (%)	Median (95% CI), Months	p-value	HR (95% CI)	p-value
Pleural effusion					
None	5 (23.8)	2.8 (0.0–6.0)	**0.048**	0.00 (0->1000)	0.947
Mild	0 (0.0)	0.3 (N/A)			
Tumor margin					
Well-demarcated	3 (33.3)	12.0 (0.0–28.1)	**0.028**	4.08 (0.06–263.30)	0.508
Irregular/infiltrative	2 (14.3)	2.4 (0.0–4.8)			
Tumor arterial phase density					
≤100 HU	0 (0.0)	2.3 (0.8–3.8)	**0.022**	0.00 (0->1000)	0.931
>100 HU	3 (37.5)	4.9 (0.0–18.0)			
Hepatic vein tumor thrombus					
Absent	5 (26.3)	4.9 (0.4–9.4)	**0.001**	8119.5 (0->1000)	0.929
Present	0 (0.0)	0.7 (0.0–1.7)			
Cavernous transformation					
Absent	5 (27.8)	4.9 (0.0–12.9)	**0.002**	0.38 (0.01–26.11)	0.651
Present	0 (0.0)	0.8 (0.6–1.0)			
Spleen volume, cm^3					
<450 cm^3	4 (30.8)	12.0 (0.0–25.9)	**0.042**	1466.5 (0->1000)	0.943
>450 cm^3	1 (10.0)	2.3 (0.1–4.5)			
Short axis of largest locoregional lymph node					
<1.0 cm	4 (30.8)	7.3 (0.0–14.9)	**0.045**	3.69 (0.14–99.1)	0.437
>1.0 cm	1 (10.0)	1.6 (0.1–3.2)			
INR					
≤1.5	5 (22.7)	2.8 (0.0–5.6)	**0.049**		
>1.5	0 (0.0)	0.7 (N/A)			
Albumin					
<3.5 g/dL	1 (9.1)	1.6 (0.0–3.8)	**0.010**		
>3.5 g/dL	4 (33.3)	12.0 (0.0–32.4)			
Direct bilirubin					
<0.8 mg/dL	5 (23.8)	2.8 (0.0–6.0)	**0.010**		
>0.8 mg/dL	0 (0.0)	0.7 (N/A)			
Platelet to lymphocyte ratio					
<230	4 (26.7)	7.3 (0.0–15.1)	**0.050**	0.00 (0->1000)	0.942
≥230	1 (12.5)	1.6 (0.1–3.1)			
MELD score					
≤9	5 (29.4)	7.3 (0.0–15.0)	**0.008**	0.00 (0->1000)	0.950
>9	0 (0.0)	0.7 (0.0–2.0)			
ALBI score					
≤-2.6 (grade 1)	3 (33.3)	12.0 (0.0–27.6)	**0.010**		
> −2.6 (grade 2 and 3)	2 (14.3)	1.6 (0.0–3.4)			

Notes: Note that only parameters that reached statistical significance on univariate analysis (p<0.05, indicated in bold) are listed above; analyses of other variables are detailed in the supplementary material.

Abbreviations: ALBI score, Albumin-Bilirubin score; INR, international normalized ratio; MELD, model for end-stage liver disease.

independent predictors of survival at multivariate analysis. Serum AFP level was not associated with progression-free survival.

To our knowledge, the current study is the first to evaluate the prognostic value of radiologic features in HCC patients who received atezolizumab-bevacizumab. Hence, the authors evaluated imaging features which have been associated with worse survival in HCC patients receiving other forms of treatment such as tumor size, number of tumor foci, tumor capsule, tumor margin, transient hepatic attenuation/intensity differences (THID/THAD), vascular invasion, bile duct invasion, spleen size, metastases, ascites, and pleural effusion in addition to other clinical and radiologic variables.[8–11]

Table 6 Univariate and Multivariate Analyses of Overall Survival for Treatment Naïve Patients (n = 23)

Characteristics	Overall Survival for Treatment Naïve Patients (n = 23)				
	Univariate Analysis			Multivariate Analysis	
	Censored, n (%)	Median (95% CI), Months	p-value	HR (95% CI)	p-value
Ascite					
None	5 (35.7)	10.0 (7.1–12.9)	**0.029**	3.78 (0.2–69.69)	0.372
Mild	3 (33.3)	3.3 (0.0–7.9)			
Pleural effusion					
None	8 (38.1)	9.0 (7.1–10.9)	**0.021**	206.34 (1.41–30,167.58)	**0.036**
Mild	0 (0.0)	1.0 (N/A)			
Tumor margin					
Well-demarcated	5 (55.6)	19.2 (18.2–20.2)	**0.005**	9.18 (0.21–393.27)	0.248
Irregular/infiltrative	3 (21.4)	7.7 (0.0–19.0)			
Extracapsular extension					
Absent	5 (27.8)	7.9 (2.8–13.0)	**0.017**	0.43 (0.03–5.52)	0.517
Present	3 (60.0)	N/A			
Cavernous transformation					
Absent	7 (38.9)	9.0 (6.6–11.4)	**0.013**	8.62 (0.51–145.12)	0.135
Present	1 (20.0)	1.4 (1.0–1.8)			
Spleen volume, cm^3					
<450 cm^3	7 (53.8)	18.7 (7.1–30.3)	**0.001**	0.15 (0.01–1.97)	0.150
>450 cm^3	1 (10.0)	3.3 (2.4–4.2)			
Recanalization of umbilical vein					
Absent	5 (50.0)	10.0 (7.5–12.5)	**0.028**	0 (0->10,000)	0.913
Present	3 (23.1)	3.4 (2.9–4.5)			
Periesophageal varices					
Absent	6 (54.5)	10.0 (0.0–22.2)	**0.008**	202,203.26 (0->10,000)	0.905
Present	2 (16.7)	3.3 (2.3–4.3)			
INR					
≤1.5	8 (36.4)	8.2 (6.3–10.1)	**0.002**	15.74 (0.04–6864.24)	0.374
>1.5	0 (0.0)	1.2 (N/A)			
Albumin					
<3.5 g/dL	2 (18.2)	2.7 (0.0–9.0)	**0.003**		
>3.5 g/dL	6 (50.0)	18.7 (0.0–41.3)			
Direct bilirubin					
<0.8 mg/dL	8 (38.1)	9.0 (7.0–10.9)	**0.001**		
>0.8 mg/dL	0 (0.0)	1.2 (N/A)			
Neutrophil to lymphocyte ratio					
≤3	4 (30.8)	10.0 (7.1–12.9)	**0.038**	7.21 (0.3–172.93)	0.223
>3	4 (40.0)	3.3 (0.6–6.0)			
ALBI score					
≤-2.6 (grade 1)	5 (55.6)	19.2 (8.1–30.3)	**0.001**	8.79 (0.36–213.3)	0.182
> −2.6 (grade 2 and 3)	3 (21.4)	3.3 (2.2–4.4)			

Notes: Note that only parameters that reached statistical significance on univariate analysis ($p<0.05$, indicated in bold) are listed above; analyses of other variables are detailed in the supplementary material.

Abbreviations: ALBI score, Albumin-Bilirubin score; INR, international normalized ratio.

Ascites is a sign indicating decompensated liver disease, and it is associated with worse survival outcomes.[8,12] Pleural effusion is another predictor of worse long-term survival in cirrhotic patients and in HCC patients, and it may develop secondary to anatomic defects in the diaphragm or due to coexisting cardiac disease.[8,13] None of the patients included in our study had moderate or large volume ascites or pleural effusion. Despite this, small volume ascites/pleural effusion were independent factors predictive of overall and/or progression-free survival. However, other laboratory and imaging

Table 7 Univariate and Multivariate Analyses of Progression Free Survival for Patients Who Received Prior Therapy (n = 32)

Characteristics	Progression-Free Survival for Patients Who Received Prior Therapy (n = 32)				
	Univariate Analysis			Multivariate Analysis	
	Censored, n (%)	Median (95% CI), Months	p-value	HR (95% CI)	p-value
Ascites					
None	4 (17.4)	6.5 (0.7–12.4)	**0.035**	2.84 (0.67–11.99)	0.156
Mild	1 (11.1)	3.0 (1.2–4.8)			
Tumor pre-contrast density					
<40 HU	0 (0.0)	2.8 (1.4–4.2)	**0.026**	0.22 (0.06–0.84)	**0.027**
≥40 HU	3 (33.3)	11.3 (0.0–27.7)			
Hepatic vein tumor thrombus					
Absent	5 (16.7)	4.5 (0.5–8.5)	**<0.001**	24.87 (1.44–430.07)	**0.027**
Present	0 (0.0)	0.6 (N/A)			
Heterogeneous extra-abdominal lymph node					
Absent	5 (17.2)	6.0 (1.0–11.0)	**<0.001**	12.26 (0.89–169.46)	0.061
Present	3 (0.0)	1.4 (0.1–2.7)			
Tumor in/out of phase drop ratio					
≤10%	1 (33.3)	15.4 (N/A)	**0.039**		
>10%	0 (0.0)	1.4 (N/A)			

Notes: Note that only parameters that reached statistical significance on univariate analysis ($p<0.05$, indicated in bold) are listed above; analyses of other variables are detailed in the supplementary material.

features suggestive of portal hypertension and decompensated liver disease (eg, ALBI score, MELD score, splenomegaly) were significantly associated with worse survival on univariate analysis. Only ascites and pleural effusion were independent prognostic factors on multivariate analysis, which emphasizes the importance of these features.

Tumor-in-vein involving the portal vein is a negative prognostic feature, and it is associated with higher tumor grade, more numerous disease foci, higher serum AFP levels, compromised liver function and worse performance status.[14] Greater tumor-in-vein extension through the portal system is associated with worse survival outcomes.[15,16] In our study, patients with small portal vein involvement (<2cm regardless of involvement of the main portal vein) were grouped together with patients without radiologic evidence of tumor-in-vein; this group was compared with patients having tumor in-vein >2cm in longest diameter. Although patients with larger extent of tumor-in-vein had significantly worse overall and progression-free survival on univariate analysis, portal vein tumor thrombus was not an independent prognostic factor on multivariate analysis. Cavernous transformation develops secondary to occlusion of the portal vein by bland or tumor thrombi. The authors evaluated the impact of cavernous transformation on survival outcomes. All patients with cavernous transformation in the current study had large volume tumor-in-vein involving the portal system, and they were associated with significantly worse survival outcomes on univariate analyses. However, cavernous transformation was not an independent prognostic feature on multivariate analyses.

Hepatic vein tumor thrombus is a negative prognostic feature for HCC.[17,18] In the current study, hepatic vein tumor thrombi were identified in 10.9% of patients, whereas 38.2% of patients had portal vein tumor thrombus. Hepatic vein tumor thrombus was an independent prognostic factor associated with significantly worse progression-free survival rates. In a large cohort of HCC patients with hepatic vein tumor thrombus who underwent surgical resection, Kokudo et al reported similar outcomes where portal vein tumor thrombus was not an independent prognostic factor.[17] Thus, the results of the current study re-emphasize Kokudo's outcomes and highlight the importance of hepatic vein tumor thrombus as a negative prognostic factor as opposed to portal vein tumor thrombus.

Bland thrombi involving the portal system or hepatic veins were not significantly associated with survival outcomes.

Attenuation of HCC on pre-contrast CT images has been associated with tumor differentiation, with 75% of poorly differentiated lesions demonstrating lower attenuation compared to the liver parenchyma and 2/3 of hyperattenuating lesions being well differentiated.[19] In the current study, low attenuation (<40 HU) of HCC on unenhanced CT images was significantly associated with worse overall survival and it was an independent prognostic factor at multivariate analysis,

Table 8 Univariate and Multivariate Analyses of Overall Survival for Patients Who Received Prior Therapy (n = 32)

Characteristics	Overall Survival for Patients Who Received Prior Therapy (n = 32)				
	Univariate Analysis			Multivariate Analysis	
	Censored, n (%)	Median (95% CI), Months	p-value	HR (95% CI)	p-value
Ascites					
None	12 (52.2)	12.8 (7.0–18.6)	**0.014**	58.83 (2.98–1163.13)	**0.007**
Mild	2 (22.2)	7.3 (5.4–9.2)			
Largest intrahepatic tumor diameter					
≤7 cm	11 (55.0)	15.5 (13.0–18.0)	**0.028**	3.82 (0.47–31.06)	0.210
>7 cm	1 (10.0)	8.9 (4.4–13.4)			
Tumor margin					
Well-demarcated	7 (53.8)	16.5 (5.2–27.8)	**0.006**	0.60 (0.07–5.25)	0.646
Irregular/infiltrative	5 (29.4)	9.4 (5.7–12.9)			
Extracapsular extension					
Absent	11 (52.4)	14.8 (6.4–23.2)	**0.046**	0.11 (0.00–3.82)	0.221
Present	1 (11.1)	11.3 (6.5–16.1)			
Tumor pre-contrast density					
<40 HU	2 (16.7)	8.9 (5.2–12.6)	**0.012**	0.09 (0.01–0.80)	**0.030**
≥40 HU	5 (55.6)	27.0 (N/A)			
Portal vein tumor thrombus					
None or <2cm	11 (44.0)	14.8 (10.5–19.1)	**0.060**	1.29 (0.08–21.70)	0.860
> 2cm with or without main portal vein involvement	3 (42.9)	8.9 (3.4–14.4)			
Hepatic vein tumor thrombus					
Absent	13 (43.3)	12.8 (7.8–17.8)	**0.031**	2.5 (0.02–281.26)	0.703
Present	1 (50.0)	2.8 (N/A)			
Cavernous transformation					
Absent	14 (45.2)	12.8 (7.9–17.7)	**0.003**	0.73 (0.01–65.58)	0.890
Present	0 (0.0)	3.1 (N/A)			
Albumin					
<3.5 g/dL	4 (25.0)	7.7 (6.0–9.4)	**<0.001**		
>3.5 g/dL	10 (62.5)	27.0 (11.4–42.6)			
Direct bilirubin					
<0.8 mg/dL	12 (42.9)	12.8 (7.9–17.7)	**0.008**		
>0.8 mg/dL	2 (50.0)	12.3 (9.0–15.5)			
Hemoglobin					
<12.0 g/dL	4 (30.8)	8.9 (7.3–10.5)	**0.005**	0.32 (0.01–8.83)	0.498
>12.0 g/dL	10 (52.6)	16.5 (6.9–26.1)			
ALBI score					
≤-2.6 (grade 1)	6 (75.0)	N/A	**0.008**	6.00 (0.3–118.48)	0.239
> −2.6 (grade 2 and 3)	8 (33.3)	9.4 (6.1–12.7)			

Notes: Note that only parameters that reached statistical significance on univariate analysis (p<0.05, indicated in bold) are listed above; analyses of other variables are detailed in the supplementary material.
Abbreviation: ALBI score, albumin-bilirubin score.

particularly in patients who had received prior therapy. Low attenuation of HCC may occur secondary to intracellular fat which, on MRI, can show drop of signal on opposed-phase imaging. Interestingly, among 12 patients with baseline MRI, patients with >10% drop in signal on opposed-phase imaging had significantly worse progression-free survival. However, due to the small number of cases, these patients could not be included in multivariate analysis. On the contrary to our outcomes, a study by Koulakian et al failed to identify a statistically significant association between tumor pre-contrast attenuation and survival outcomes in patients who received sorafenib.[20] To our knowledge, no prior studies reported such an association; hence, these results should be verified in future studies.

Portal vein tumor thrombi are typically classified using the Japanese VP system and Cheng's classification systems.[21,22] However, these systems include categories for second order portal branch involvement and microscopic portal vein tumor thrombi which may not be identifiable on current cross-sectional imaging and may require evaluation

of the surgical specimen for accurate classification. These two systems do not take into consideration the size of the tumor thrombus and only consider its anatomic location. Hence, a central HCC (eg, in the caudate lobe) directly invading the main portal vein and a peripheral tumor with a tumor thrombus extending for several centimeters through portal system down to the main portal vein are both classified similarly. From a surgical point of view, both cases have a major impact on any potential surgical approach. During data collection, the authors recognized that several patients with central HCC with a small tumor-in-vein directly invading the main portal vein and/or its main branches had better prognosis compared to patients with larger tumor thrombi extending from peripheral branches down to the main portal veins. Therefore, the authors classified portal vein thrombi by taking into consideration both their size and location as follows: 1) no identifiable tumor thrombi, 2) tumor thrombi <2cm regardless of their location, 3) tumor thrombi >2cm without invasion of the main portal vein, 4) tumor thrombi >2cm with involvement of the main portal vein. Due to the small number of patients, the former two categories were grouped together and compared with the latter two categories. Patients with small/absent tumor thrombi had significantly better progression-free survival on univariate analysis (4.9 months vs 1.6 months; $p = 0.044$), but this was not statistically significant on multivariate analysis (HR: 0.12; 95% CI: 0.05–1.39, $p = 0.117$).

Cavernous transformation is a feature closely associated with occlusive (tumor or bland) thrombi involving the main portal vein. This condition develops when small venous structures in the gastrohepatic ligament are recruited to "bypass" occluded segments of the portal vein and in order to drain blood from the mesenteric/splenic veins to the liver. Cavernous transformation is identifiable on cross-sectional imaging. In the current study, cavernous transformation was associated with significantly worse progression-free survival on univariate analysis (4.9 months vs 0.8 months, $p = 0.001$). These patients universally had ascites, likely related to portal hypertension, which may explain why this feature was not an independent predictor of survival on multivariate analysis (HR: 1.36; 95% CI: 0.16–11.72, $p = 0.779$).

The IMbrave 150 trial reported a median progression-free survival of 6.8 months and a 12-month overall survival rate of 67.2% as opposed to 3.0 months and 45.7%, respectively, in the current study.[2] This difference in survival outcomes is likely related to differences in study cohort. The IMbrave 150 trial only included patients with Child-Pugh score A (72% had A5 and 28% had A6);[2] whereas the current study included patients with higher Child-Pugh scores (45.5% of patients had Child-Pugh score B).

In the current study, patients with prior therapy had better survival outcomes compared to treatment naïve patients (overall survival and progression-free survival were 9.2 months and 3.9 months vs 7.4 months and 2.8 months, respectively). This was an unexpected finding and the authors speculate that this may be secondary to selection bias related to potentially less aggressive tumor biology in previously treated patients, particularly since they had a longer interval between diagnosis to initiation of atezolizumab plus bevacizumab therapy (23.0 months vs 1.3 months).

The limitations of the current study include the small population size, single-institution and retrospective study design. In addition, the group of previously treated patients consisted of a heterogeneous group of patients who had received a variety of surgical interventions, percutaneous ablation procedures, chemo/radioembolization and/or different lines of systemic therapy (including investigational drugs). Therefore, investigators should be cautious when interpreting the outcomes of this group of patients. In addition, most patients received different types of local and/or systemic therapy regimens after disease progression, which limits the ability to confidently identify predictors of overall survival.

Conclusion

Independent prognostic features predictive of worse survival outcomes in patients with unresectable HCC patients receiving atezolizumab plus bevacizumab combination include ascites, pleural effusion, hepatic vein tumor thrombus and lesions with low pre-contrast attenuation on CT images. None of the laboratory parameters included in the current study was an independent prognostic factor on multivariate analysis.

Abbreviations

AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; ASCO, American Society of Clinical Oncology; CI, confidence intervals; CT, computerized tomography; ESMO, European Society for Medical Oncology; HCC, hepatocellular

carcinoma; HR, hazard ratio; HU, Hounsfield unit; mRECIST, modified response evaluation criteria in solid tumors; MRI, magnetic resonance imaging; RECIST, response evaluation criteria in solid tumors; ROI, region of interest; THAD, transient hepatic attenuation differences; THID, transient hepatic intensity differences.

Data Sharing Statement

The study data may be provided by contacting the corresponding author.

Ethics Approval and Informed Consent

Institutional Review Board (IRB) of the University of Texas MD Anderson Cancer Center approved the study and patient consent was waived for this retrospective study, in compliance with the Helsinki Declaration.

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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