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Etiology of Hepatocellular Carcinoma May Influence the Pattern of Progression under Atezolizumab-Bevacizumab

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Abstract
Background: Preclinical models have shown that metabolic dysfunction-associated steatotic liver disease (MASLD)-related hepatocellular carcinoma (HCC) may exhibit reduced responsiveness to immunotherapy, especially for intrahepatic lesions due to liver tumor microenvironment. Radiological pattern of progression has been validated in clinical studies as a useful tool for predicting outcomes in HCC undergoing systemic treatments. ***Aims:*** The aim of this study was to determine whether MASLD influences the pattern of progression in patients treated with atezolizumab-bevacizumab. ***Methods:*** This multicenter, prospective study included patients with unresectable HCC receiving atezolizumab-bevacizumab. Progression patterns were defined as previously proposed. Patients were categorized as either MASLD or controls based on a recent multisocietal Delphi consensus statement. Multivariable models analyzed the risk of specific progression patterns and their impacts on post-progression survival (PPS) and overall survival (OS). A historical cohort treated with sorafenib was also analyzed to determine whether observed patterns were specific for atezolizumab-bevacizumab. ***Results:*** Four-hundred twenty patients were included (MASLD: n = 88, 21.0%). Time to progression (TTP) was shorter in MASLD compared to controls, due to an increased risk of intrahepatic growth (IHG – hazard ratio [HR] 1.739, 95% confidence interval [CI] 1.206–2.507, p = 0.003]). Neither etiology nor IHG predicted a different PPS. No differences between etiologies were found in OS. Etiology did not influence the pattern of progression under sorafenib in the historical cohort. ***Conclusion:*** IHG was more frequently associated with MASLD-HCC compared to controls, confirming preclinical data and suggesting biological differences between tumors, with potential implications for future research. MASLD should not be seen as a contraindication to immunotherapy.

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Introduction

The therapeutic landscape of hepatocellular carcinoma (HCC) has been transformed with the introduction of immune checkpoint inhibitors (ICIs). Currently, the combinations of atezolizumab plus bevacizumab and durvalumab plus tremelimumab represent the standard of care, following the demonstrated superiority of these regimens over sorafenib [1–4].

ICIs are recommended as the first-line treatment regardless of the etiology of the underlying liver disease. Nonetheless, their effectiveness in the context of metabolic dysfunction-associated steatotic liver disease (MASLD) has sparked debate since their inception in clinical practice. Pfister et al. [5] suggested that the efficacy of ICIs might be compromised when used as monotherapy in a murine model. This hypothesis was corroborated by a subsequent preclinical study, which also indicated the necessity for additional interventions to potentiate the effects of immunotherapy in metabolic dysfunction-associated steatohepatitis (MASH) [6]. Moreover, Geh et al. [7] examined the efficacy of the anti-PD-L1 and anti-VEGF antibody combination in mice, noting that only intrahepatic tumors showed a diminished response, whereas subcutaneous tumors responded favorably. These findings suggested a key role for the hepatic microenvironment of MASH in influencing and regulating the response to ICIs [7].

Despite preclinical evidence, an impaired efficacy of immunotherapy has not been confirmed in clinical practice [8]. However, it has been noted that responses to ICIs can vary between different disease sites, with liver lesions being less likely to achieve an objective response compared to extrahepatic lesions [9]. Still, other reports contradicted this finding, leading to further uncertainty on this topic [10].

To validate both preclinical and clinical hypotheses that liver lesions are less responsive than extrahepatic ones, a rigorous methodology employing prospective data and validated tools is essential. Furthermore, treatment decisions in clinical settings are often guided by progression rather than objective response. Radiological progression patterns are established predictors of both post-progression survival (PPS) and overall survival (OS) in liver cancer, offering a valuable metric to assess the response of both intrahepatic and extrahepatic tumors. The prognostic abilities of patterns of progression have been demonstrated in patients receiving sorafenib [11], tivantinib [12], ramucirumab [13], and immunotherapy [14, 15]. An unfavorable pattern of progression may influence PPS also in patients with intrahepatic cholangiocarcinoma [16].

Analysis of these progression patterns could elucidate potential differences in the efficacy of atezolizumab-bevacizumab treatment on intrahepatic versus extrahepatic lesions depending on HCC etiology. In hypothetical

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scenarios where liver lesions are more prone to progression under immunotherapy due to local microenvironmental factors, metrics such as the time to intrahepatic growth (IHG), emergence of new intrahepatic lesions, or new vascular invasion (nVI) might be adversely affected. Conversely, HCC progression due to extrahepatic growth (EHG) or new extrahepatic lesions (NEHLs) is likely unaffected by the etiology. Therefore, the primary objective of this study was to determine whether patients with MASLD exhibit distinct radiological progression patterns under atezolizumab-bevacizumab and to evaluate the impact of these progression patterns on PPS and OS.

Methods

Study Population

The ARTE (Atezolizumab-bevacizumab Real-life Experience for Treatment of Hepatocellular Carcinoma) database compiles prospectively and collects data from patients treated with the atezolizumab-bevacizumab combination as a frontline systemic therapy. These patients are monitored following routine clinical practice guidelines. Data entries are made biannually using the REDCap platform [17] and are subject to internal consistency checks at the data management center located at IRCCS Azienda Ospedaliero-Universitaria di Bologna. The most recent update to the database was completed in November 2024.

Atezolizumab-Bevacizumab Prescription

All patients received atezolizumab at a dose of 1,200 mg combined with bevacizumab at 15 mg/kg IV every 3 weeks [1]. At the initiation of treatment, the following data were collected: time elapsed since the initial diagnosis of HCC, history of prior treatments for HCC, etiologies of the underlying liver disease, presence or absence of liver cirrhosis, and any comorbidities. Key parameters indicating residual liver function, including the Child-Pugh and ALBI scores, were also documented. Additionally, tumor staging was classified according to the Barcelona Clinic Liver Cancer (BCLC) recommendations [4]. Baseline levels of alpha-fetoprotein (AFP) were recorded for all patients.

Definition of MASLD

MASLD was defined in accordance with the recent multisociety Delphi consensus statement for the classification of steatotic liver diseases [18]. The criteria for MASLD included the presence of hepatic steatosis and at least one metabolic risk factor, excluding other chronic liver diseases. Patients meeting the criteria for MASLD, but with concurrent causes of chronic liver diseases, were categorized as "mixed steatotic liver disease" or "metabolic dysfunction and alcohol-related liver disease (MetALD)," depending on the co-etiology [18], and were excluded from the MASLD group.

Follow-Up

In routine clinical practice, biochemistry was reassessed every 3 weeks. The initial imaging follow-up was scheduled between 9 and 12 weeks after the first administration of atezolizumab-bevacizumab, with subsequent imaging approximately every 12 weeks. The preferred imaging method was computed tomography of the thorax, abdomen, and pelvis with iodinated contrast medium. For patients with contraindications to iodinated contrast, magnetic resonance imaging of the abdomen paired with high-resolution computed tomography of the chest was conducted. Radiological response evaluation was performed by local radiologists, blinded to clinical data, using the Response Evaluation Criteria In Solid Tumors (RECIST) v1.1. Radiologists were blinded to clinical data of the patients, including etiologies.

Patterns of Radiological Progression

Progression patterns of HCC were recorded at the time of the first radiological progression and classified as proposed by Reig et al. [11] into 5 nonexclusive categories: 20% increase in tumor size against a known baseline lesion (IHG or EHG), new intrahepatic or NEHL, and new vascular invasion (nVI). We also assessed the impact of progression patterns on OS and PPS in patients with radiological progression (Fig. 1).

Viral vs. Nonviral Disease

To facilitate comparison with previous studies on the influence of liver disease etiology on the response to immunotherapy in HCC, we conducted an additional analysis, dichotomizing patients into viral vs. nonviral disease categories. Patients testing positive for HBsAg and/or antihepatitis C virus antibodies were classified as having viral disease.

Historical Sorafenib Controls

To determine whether our observations regarding the patterns of progression were specific to AB or related to the etiology itself, we conducted a separate analysis within a multicenter cohort of patients treated with sorafenib. These data were sourced from the ARPES database, which

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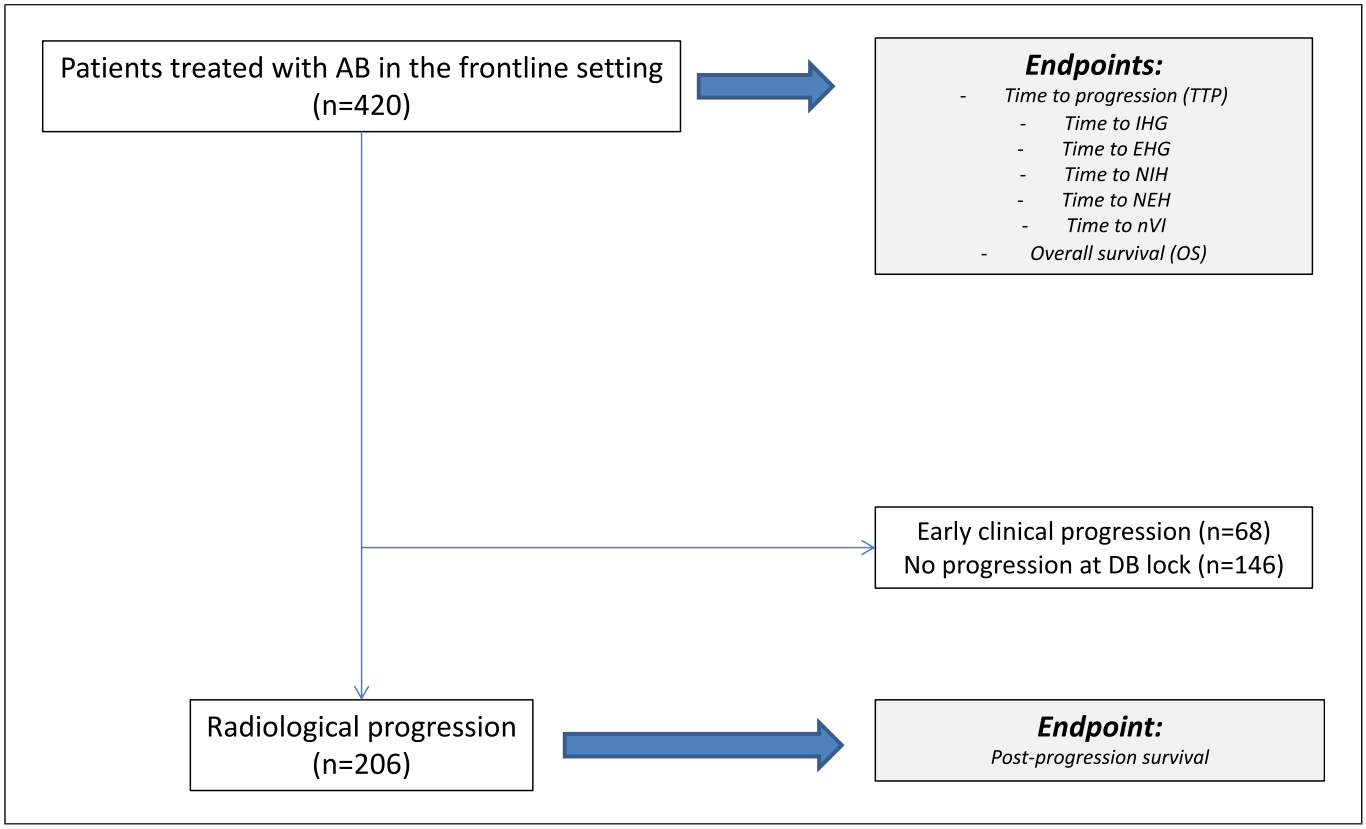

Fig. 1. Patients flowchart and study endpoints.

includes records of patients who received sorafenib as a frontline systemic treatment in six Italian centers from 2008 to 2019. The ARPES cohort was specifically analyzed to assess the risk associated with each progression pattern based on the etiology of the underlying liver disease. Given that the ARPES database also provides details on cardiometabolic risk factors, a reclassification of nonalcoholic fatty liver disease into MASLD was undertaken.

Statistical Analysis

Continuous variables were described using the median and interquartile range, while categorical variables were expressed in absolute and relative frequencies. Time to progression (TTP) was defined as the period from the first treatment dose to either evidence of tumor progression or the last follow-up. PPS was measured from the first instance of radiological progression until death. OS was defined from the initial treatment dose to death. Censoring was applied for the following conditions: (i) patients who received a locoregional treatment after the start of AB due to HCC progression had their progression recorded, but OS was censored at the time of the procedure; (ii) patients who received a surgical or locoregional treatment following a response to AB (for instance to complete a downstaging in anticipation of curative resection or liver transplantation) had both TTP and OS censored at the time of the treatment.

Survival analyses were conducted using the Kaplan-Meier method, with the log-rank test for comparing survival outcomes. Cox regression was employed to assess the independent prognostic value of each factor. Statistical analyses and graphs were generated using SPSS version 24.0 or RStudio 2023.12.1.

Ethics

This study adhered to the ethical guidelines of the Declaration of Helsinki. The ARTE database data collection was approved by the Independent Ethic Committee of the IRCCS Azienda Ospedaliero-Universitaria di Bologna (Protocol 811.2022.Oss.AOUBo), which served as the coordinating center. All other centers received approval from their respective local ethics committees.

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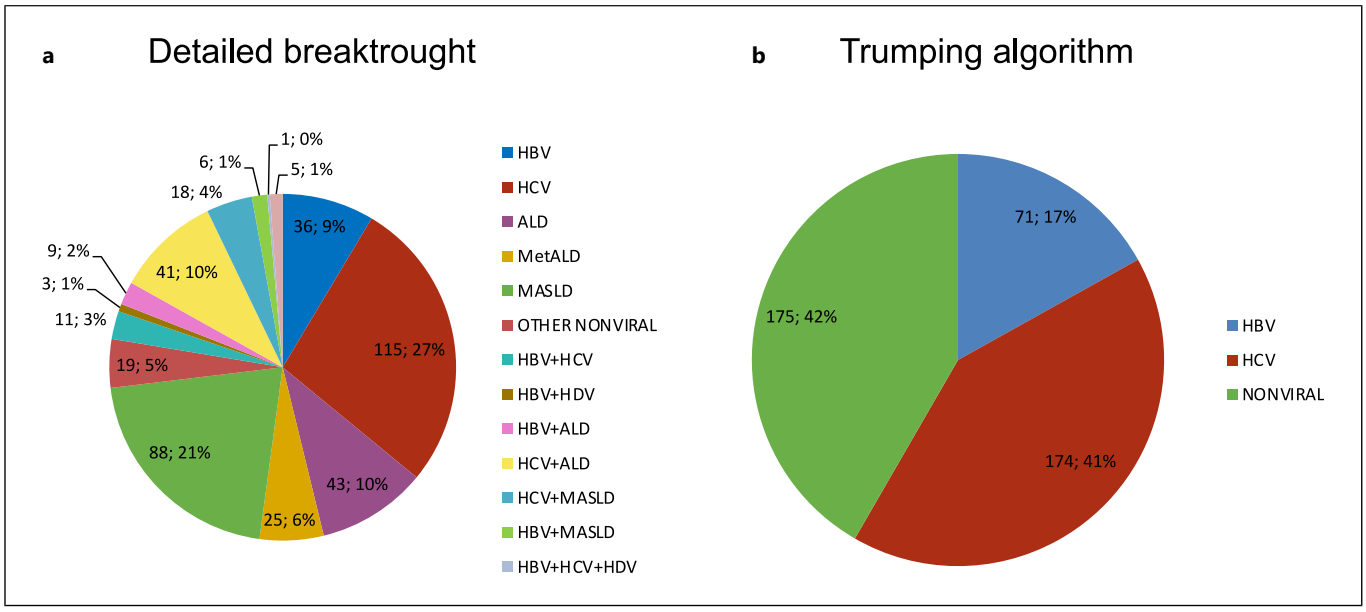

Fig. 2. Detailed report (**a**) of the etiologies of the underlying liver disease in the whole study population (n = 420) paired with a classification according to the classical trumping algorithm used in clinical studies (**b**). According to the trumping algorithm, all patients with positive serology for hepatitis B virus (HBV) are classified as HBV regardless of other concurring etiologies. HBV-negative patients with positive serology for hepatitis C virus (HCV) are classified as HCV regardless of other concurring etiologies. All remaining patients are classified as nonviral.

Results

At the time of database lock (November 2024), the ARTE database comprised 420 patients with a median follow-up of 19.2 months.

Study Population

The majority of the patients had underlying liver cirrhosis (n = 354, 84.1%) and a history of previous treatments for HCC (n = 251, 61.7%). Among these, 88 (21.0%) were classified as MASLD (Fig. 2). Compared to patients with other etiologies, those with MASLD had a lower prevalence of previous treatments for HCC, though no other significant differences were observed between the groups (Table 1).

Follow-Up

By the time of database lock, 296 patients had permanently discontinued AB for reasons including tumor progression (n = 205), adverse events (n = 35), liver failure without HCC progression (n = 26), deterioration of clinical conditions from nonliver-related issues (n = 14), or other causes (n = 16). During the treatment period, 59 (14.0%) patients underwent at least one surgical or locoregional treatment.

The best treatment responses were objective response in 113 (26.8%) patients, stable disease in 166 (39.4%) patients, and progressive disease in 142 (33.7%) patients. The disease control rate did not differ significantly between study groups (60.2% vs. 71.4% in MASLD versus controls, p = 0.052), while the objective response rate was significantly lower in MASLD patients compared to controls (15.9% vs. 30.1%, p = 0.008). In the whole study population, the median TTP and OS were 10.5 (95% CI: 8.7–12.4) and 18.5 months (95% CI: 16.1–21.0), respectively.

Outcome Correlates

Univariable analysis identified potential predictors of TTP including ECOG-PS >0, NLR >3, AFP >400 ng/mL, maximum tumor diameter >6 cm, macrovascular invasion, extrahepatic spread, and MASLD etiology. Multivariable Cox regression narrowed these predictors to ECOG-PS >0, AFP >400 ng/mL, ALBI grade >1, extrahepatic spread, and MASLD etiology (Table 2). The TTP stratified according to etiology was 7.7 (5.0–10.6) and 11.8 (9.7–14.0) months in MASLD and controls, respectively (Fig. 3).

The risk of progression due to IHG was significantly increased in the MASLD group in both univariable and multivariable analyses (Table 3). However, the risks associated with NIHL, EHG, NEHL, and nVI did not

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Table 1. Characteristics of the study population

VARIABLES	Whole cohort (n = 420)	MASLD (n = 88)	Controls (n = 332)	*p* value
Age >75 years	136 (32.3)	35 (39.8)	101 (30.4)	0.098
Male sex	332 (79.0)	71 (80.7)	268 (79.1)	0.993
Cirrhosis	354 (84.1)	69 (78.4)	285 (85.6)	0.102
Previous treatments	259 (61.7)	41 (47.1)	218 (65.5)	0.002
ECOG-PS >0	132 (31.4)	27 (30.6)	105 (31.6)	0.845
Child-Pugh B[a]	38 (9.3)	10 (11.7)	28 (8.7)	0.405
ALBI grade >1[a]	218 (53.7)	40 (47.1)	178 (55.1)	0.222
NLR >3[b]	178 (44.4)	45 (53.6)	133 (42.0)	0.064
AFP >400 ng/mL	112 (27.3)	21 (24.4)	91 (28.8)	0.507
Number of liver nodules ≥7	175 (41.8)	32 (36.8)	143 (43.1)	0.290
Largest liver nodule >6 cm	169 (40.3)	40 (46.0)	129 (38.9)	0.269
Macrovascular invasion	135 (32.2)	24 (27.6)	111 (33.4)	0.367
Extrahepatic spread	169 (40.2)	32 (36.4)	137 (41.3)	0.464

MASLD, metabolic dysfunction-associated steatotic liver disease; ECOG-PS, Eastern Cooperative Group – Performance Status; ALBI, albumin-bilirubin; NLR, neutrophils-to-lymphocytes ratio; AFP, alpha-fetoprotein. [a]Albumin serum levels missing in 14 (3.3%) patients. [b]NLR missing in 19 (4.5%) patients.

Table 2. Univariable and multivariable Cox regression to TTP in the whole cohort population (*n* = 420)

Univariable				Variable	Multivariable			
HR	95% CI		*p* value		HR	95% CI		*p* value
1.030	0.803	1.320	0.818	Age >75 years				
0.859	0.636	1.161	0.316	Male sex				
1.460	1.108	1.924	0.007	MASLD etiology	1.732	1.274	2.355	<0.001
0.841	0.628	1.126	0.252	Cirrhosis				
0.867	0.680	1.106	0.251	Previous treatments				
1.459	1.144	1.862	0.002	ECOG-PS >0	1.437	1.094	1.886	0.009
1.314	1.032	1.672	0.027	ALBI grade >1	1.318	1.009	1.722	0.043
1.293	1.006	1.663	0.045	NLR >3	1.231	0.949	1.597	0.117
1.675	1.295	2.168	<0.001	AFP >400 ng/mL	1.618	1.219	2.148	0.001
1.228	0.967	1.559	0.092	Number of liver nodules ≥7	1.237	0.950	1.612	0.115
1.141	0.898	1.451	0.280	Largest liver nodule >6 cm				
1.310	1.021	1.680	0.034	Macrovascular invasion	1.094	0.827	1.446	0.531
1.336	1.053	1.695	0.017	Extrahepatic spread	1.336	1.028	1.736	0.030

HR, hazard ratio; CI, confidence intervals; MASLD, metabolic dysfunction-associated steatotic liver disease; ECOG-PS, Eastern Cooperative Group – Performance Status; ALBI, albumin-bilirubin; NLR, neutrophils-to-lymphocytes ratio; AFP, alpha-fetoprotein.

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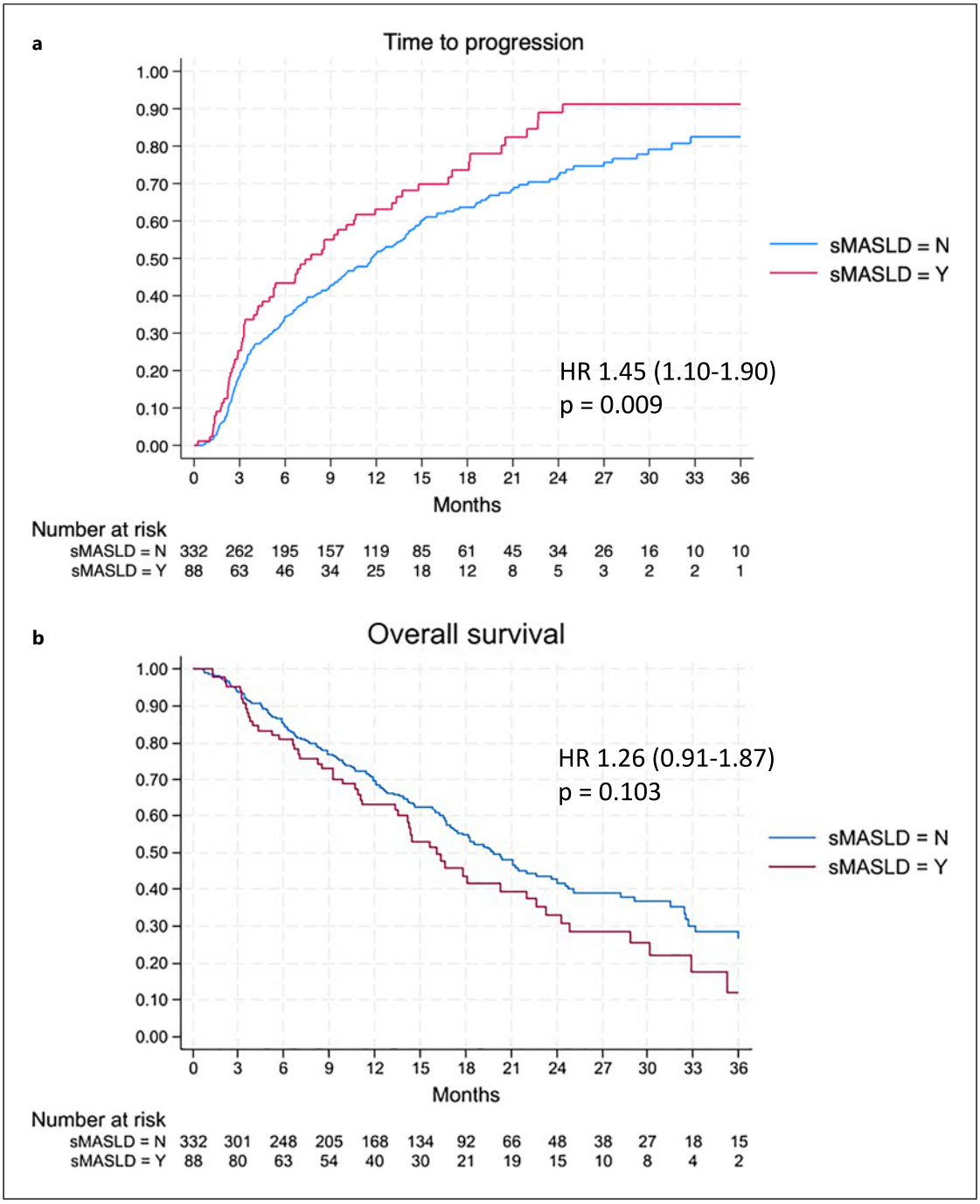

Fig. 3. a, **b** TTP and OS in the whole study cohort ($n = 420$), stratified according to the diagnosis of single-etiology metabolic dysfunction-associated steatotic liver disease (sMASLD).

significantly differ across etiology groups (Fig. 4). Considering the lower prevalence of previous treatments in the MASLD compared to the control group and the possible influence of such treatments on the local pattern of progression, a stratification analysis was performed. This analysis showed no significant interaction of previous treatments with the outcome ($p = 0.826$) and confirmed the trend of a shorter time to IHG in the MASLD group both in patients with and without a history of previous treatments. MVI did not influence

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Table 3. Univariable and multivariable Cox regression to the risk of progression due to IHG in the whole cohort population (n = 420)

Univariable				Variable	Multivariable			
HR	95% CI		p value		HR	95% CI		p value
0.863	0.617	1.208	0.392	Age >75 years				
1.006	0.675	1.500	0.977	Male sex				
1.739	1.206	2.507	0.003	MASLD etiology	1.655	1.119	2.446	0.012
0.663	0.453	0.981	0.045	Cirrhosis	0.717	0.482	1.065	0.149
0.823	0.589	1.151	0.255	Previous treatments				
1.323	0.940	1.863	0.109	ECOG-PS >0				
0.903	0.647	1.260	0.547	ALBI grade >1				
1.281	0.898	1.828	0.172	NLR >3				
1.642	1.155	2.334	0.006	AFP >400 ng/mL	1.589	1.104	2.286	0.013
1.421	1.022	1.976	0.037	Number of liver nodules ≥7	1.562	1.114	2.192	0.010
1.316	0.946	1.831	0.103	Largest liver nodule >6 cm				
1.216	0.857	1.723	0.273	Macrovascular invasion				
1.194	0.857	1.663	0.295	Extrahepatic spread				

HR, hazard ratio; CI, confidence intervals; MASLD, metabolic dysfunction-associated steatotic liver disease; ECOG-PS, Eastern Cooperative Group – Performance Status; ALBI, albumin-bilirubin; NLR, neutrophils-to-lymphocytes ratio; AFP, alpha-fetoprotein.

progression due to IHG neither in the MASLD (p = 0.968) and in the control groups (p = 0.129).

MASLD etiology did not predict OS, whereas ALBI grade >1, ECOG-PS >0, NLR >3, and AFP >400 ng/mL were independently correlated with OS in the multivariable analysis (online suppl. Table 1; for all online suppl. material, see https://doi.org/10.1159/000545494).

Subgroup Analyses

- Stratification for metabolic syndrome in patients without pure MASLD

To clarify the role of metabolic dysfunction, we performed a stratified analysis based on metabolic syndrome in patients without pure MASLD (n = 322). We found no differences in terms of OS (HR 0.821 [0.540–1.247, p = 0.355]), TTP (HR 0.850 [0.592–1.219, p = 0.377]), and risk of progression due to IHG (HR 1.177 [0.714–1.941, p = 0.523]) (online suppl. Fig. 1).

- Subanalysis of MASLD vs. alcoholic liver disease (ALD)

To clarify the role of steatosis, we performed a comparison of the outcomes of patients with pure MASLD vs. patients with pure ALD (n = 43). We confirmed a shorter TTP (HR 1.662 [1.055–2.620, p = 0.028]) and an increased risk of IHG (HR 1.957 [1.043–3.671, p = 0.036]) in the MASLD group. Also, we found a trend toward a reduced OS in the MASLD compared to the ALD group (HR 1.652 [0.951–2.870, p = 0.075]) (online suppl. Fig. 2).

Post-Progression Survival

Among the 206 patients with radiological progression, the median PPS was 7.2 months (95% CI: 4.8–9.2). Of these, 126 patients remained compensated and 118 received second-line agents. The most common second-line treatment was sorafenib (online suppl. Table 2). PPS did not significantly differ between MASLD patients and controls (6.6 vs. 7.3 months, p = 0.594). Being compensated was the main determinant of PPS in the multivariable analysis (Table 4). Only the NEHL/nVI progression pattern was associated with a shorter PPS. Online supplementary Figure 3 reports OS and PPS stratified according to the BCLC-p classification.

Viral vs. Nonviral Disease

A total of 245 (58.3%) patients had viral HCC, while the remaining cases were classified as nonviral HCC. There were no differences in TTP, pattern of progression, and OS between the viral and nonviral HCC groups (online suppl. Figs. 4, 5).

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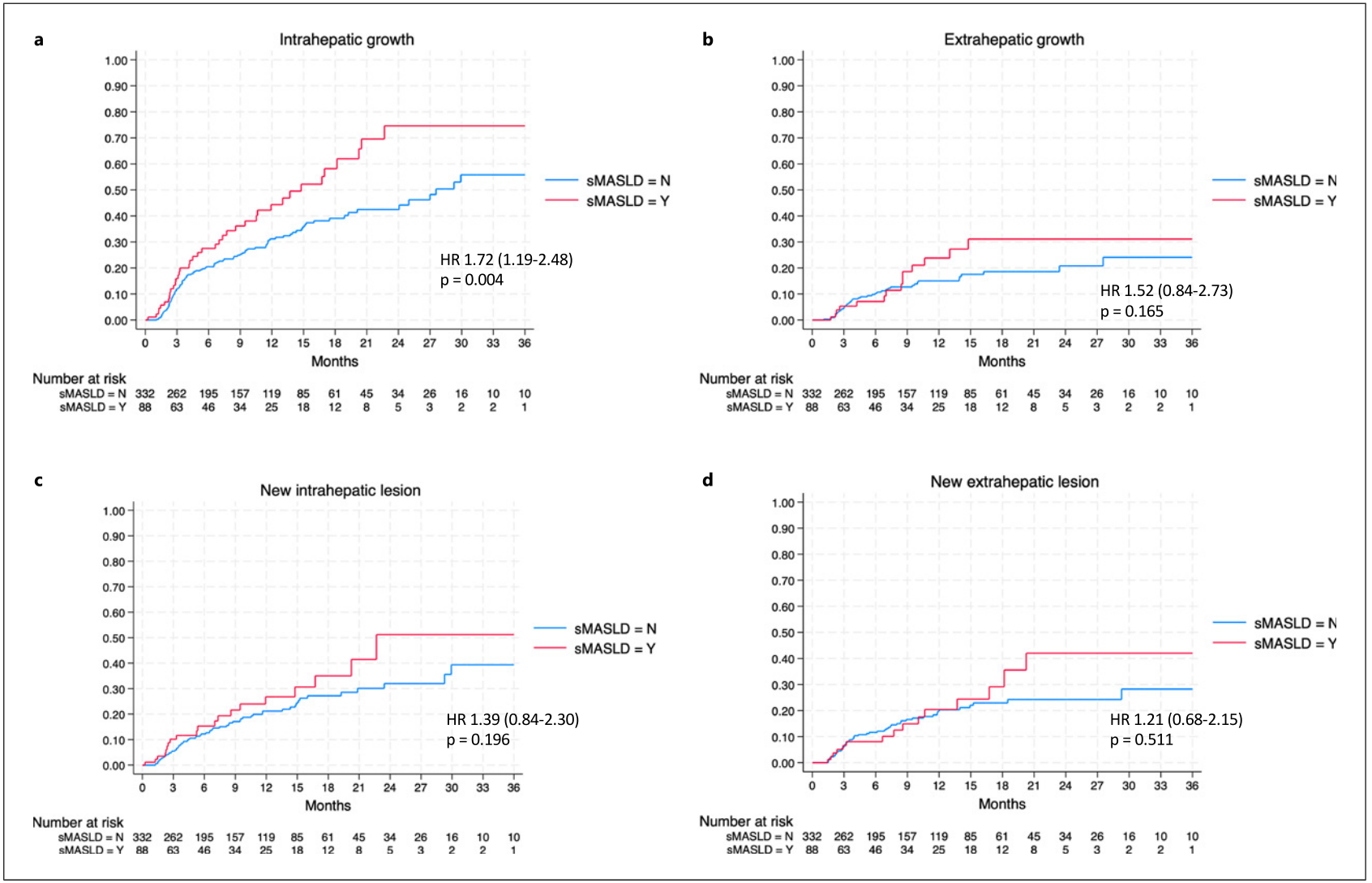

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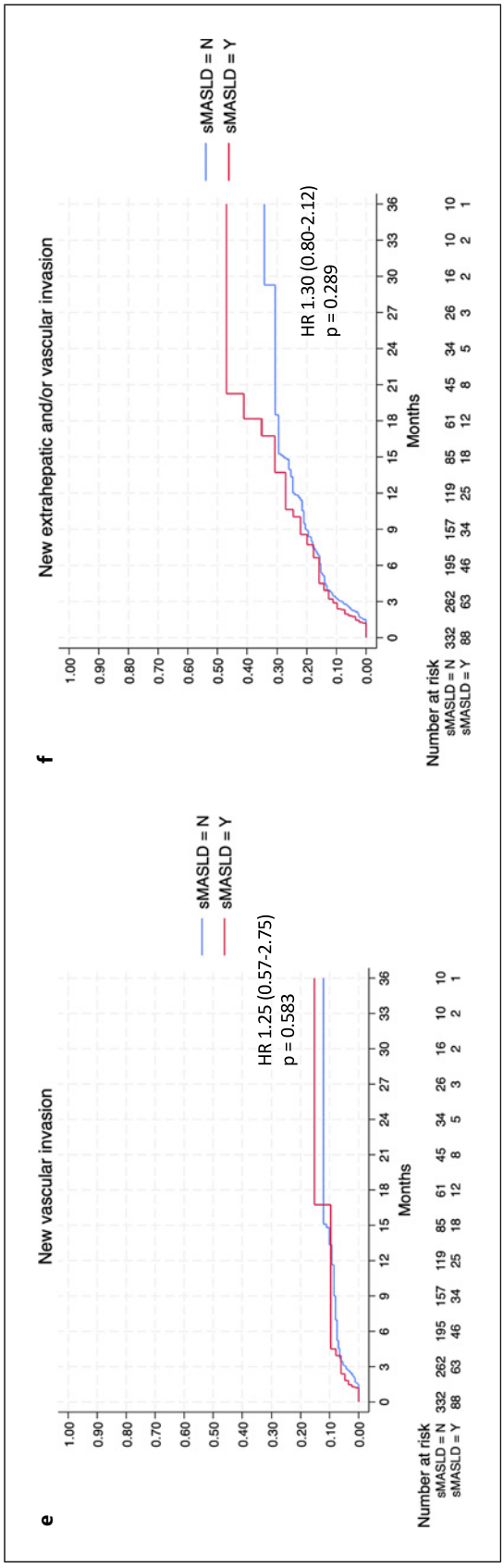

Fig. 4. a–f Pattern of progression under atezolizumab-bevacizumab of patients with single-etiology metabolic dysfunction-associated steatotic liver disease (sMASLD) and controls in the whole study population (n = 420).

Historical Sorafenib Controls

Among the 571 patients included in the ARPES dataset, 63 (11.1%) were classified MASLD. The concordance between the nonalcoholic fatty liver disease and MASLD classifications was 99.1%. During the follow-up, 424 (74.5%) patients had a radiological progression. TTP and progression patterns did not differ between MASLD patients and controls (online suppl. Fig. 6).

Discussion

The role of MASLD in HCC has sparked considerable debate over the past 2 years. While some studies have suggested that MASLD may diminish responsiveness to ICIs, potentially affecting OS [19], others did not find significant etiology-related differences in treatment outcomes [8].

In our study, MASLD patients exhibited a shorter TTP compared to other etiologies, primarily due to an increased risk of IHG progression pattern. The impact on OS, however, was mitigated by the absence of correlation between IHG and PPS. This finding aligns with earlier evidence from studies using sorafenib and AB, which noted a relatively weaker impact of IHG.

Our results fit well with preclinical evidence, suggesting a possible reduced efficacy of ICIs on intrahepatic lesions in the setting of MASLD, when efficacy is measured using surrogate endpoints. Pfister et al. [5] reported that anti-PD1 or anti-PD-L1 immunotherapy was less effective in regressing intrahepatic HCC nodules in an MASLD-related mouse model. Additionally, increased hepatic CD8+ PD1+ T cells and tumor necrosis factor-positive (TNF+) T cells were observed in MASLD-related HCC. Geh et al. [7] analyzed mice treated with the combination of anti-PD-L1 plus anti-VEGF antibodies and noted that subcutaneous tumors showed favorable responses compared to intrahepatic tumors that responded poorly, highlighting the significant influence of the hepatic microenvironment of MASH on ICI responsiveness. Therefore, there is rationale for modulating the liver microenvironment. Leslie et al. [6] demonstrated that the inhibition of CXCR2 was able to overcome the resistance to anti-PD1 therapies in NASH-HCC mice, promoting a switch from a protumor to antitumor progenitor-like neutrophil phenotype. Protumor neutrophil phenotype in MASLD can also be favored by cytokines (such as transforming-growth factor β) and by other myeloid-derived suppressor cells [20]. Intriguingly, the modulation of both transforming-growth factor β (NCT05822752, NCT06109272) and myeloid-derived

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Table 4. Multivariate Cox analysis of PPS in patients with radiological tumor progression under atezolizumab-bevacizumab

	HR	95% CI		*p* value
Clinical and tumor status at the progression				
BCLCp-B patients (reference compensated)	Reference			<0.001
BCLCp-B patients decompensated	6.048	2.596	14.093	<0.001
BCLCp-C patients compensated	1.557	0.784	3.091	0.206
BCLCp-C patients decompensated	6.891	3.297	14.402	<0.001
Pattern of progression				
IHG (yes/no)	1.375	0.921	2.052	0.119
New intrahepatic lesion (yes/no)	0.913	0.603	1.384	0.669
EHG (yes/no)	1.175	0.801	1.706	0.395
NEHL and/or nVI (yes/no)	1.779	1.194	2.650	0.005

BCLCp-B, patients with radiological progression but still within BCLC-B stage, being Child-Pugh ≤7 without ascites or encephalopathy; BCLCp-C, patients with radiological progression corresponding to BCLC-C including those who were already BCLC-C already at baseline, and being Child-Pugh ≤7 without ascites or encephalopathy.

suppressor cells (NCT05220722) is being investigated as possible strategies in combination with immunotherapy for HCC [21].

Our study confirmed recent data suggesting no significant differences in the outcome of patients treated with AB when stratified according to viral vs nonviral etiologies [22–24]. Indeed, the subclassification of nonviral disease poses undoubted challenges in clinical practice. The challenges of subclassifying nonviral diseases – such as accurately quantifying alcohol intake and confirming liver steatosis through imaging – are significant, yet understanding these biological aspects could help understand enhance biological aspects of hepatocarcinogenesis and prediction of treatment response. Therefore, we advocate for etiology-based stratification in future HCC clinical trials.

Most observational real-life studies also focus on the viral versus nonviral etiology distinction, providing limited comparability with our findings. Recent studies by Rossari et al. [23] and Copil et al. [24] found no differences in OS between MASLD patients and other etiologies. In both studies, a trend toward a shorter TTP (in Rossari paper [23]) or PFS (in Copil paper [24]) was found for MASLD patients. In the former case, MASLD had the numerically lowest TTP, but the pairwise comparisons with other etiologies found no significant differences. However, the authors did not report the dichotomous comparison between MASLD and non-MASLD groups, so no comparison can be made with our results. In the latter case, the French collaborative group reported a notably lower prevalence of MASLD compared to our study (13% vs. 23%). While our prevalence is consistent with a recent large observational study on single-etiology metabolic dysfunction-associated steatotic liver disease-related HCC in Italy [25] and other clinical studies about AB [23], this difference underscores the challenges in subclassifying nonviral patients. Espinoza et al. [26] recently published a post hoc analysis of the IMbrave-150 trial after a manual readjudication of nonviral patients to nonalcoholic steatohepatitis. The authors reported no differences in PFS and OS according to etiologies. However, it has been pointed out that these data are difficult to interpret and discuss because readjudication of most nonalcohol cases to a nonalcoholic steatohepatitis etiology did not match the data originally reported by the IMbrave 150 investigators [27].

Our results also validate previous findings, supporting the pattern of radiological progression as a prognosticator of PPS. It is important to note that, in Italy, sorafenib is the only approved second-line treatment according to current labeling. Consequently, differences in PPS observed between our study and other reports might be attributable to the use of various second-line treatment options, especially as observational studies seem to suggest a superiority of lenvatinib compared to sorafenib

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in this setting [28, 29]. Our study has inherent limitations typical of real-world observational studies, such as assessments by local radiologists (without a centralized imaging review) and a less stringent imaging follow-up protocol compared to randomized clinical trials. However, these limitations likely had minimal impact on our main findings, as all local radiologists were blinded to clinical data and a possible delayed diagnosis of progression should have affected the study groups similarly. The heterogeneous composition of the non-MASLD group presents an additional limitation. Theoretically, it would be ideal to perform multiple comparisons between MASLD and each other etiology, whether considered individually or as a mixed category. However, such comparisons would require studies with extremely large populations to be reliable, given the numerous possible combinations of etiologies and the necessity to account for additional prognosticators in multivariable models. Concerns might arise about the potential misclassification of nonviral cases affecting our results. Yet, the number of patients identified as having "other nonviral causes" is very low. Furthermore, while the estimation of alcohol consumption was not systematically conducted using structured questionnaires for alcohol abuse, the prevalence of ALD and MASLD aligns with prior studies. A significant and systematic underestimation or overestimation of alcohol consumption would be necessary to challenge the association of MASLD with TTP and the IHG pattern of progression.

In conclusion, we found an increased risk of intrahepatic progression among patients treated with AB, when affected by MASLD, compared with controls. On the contrary, the classical distinction between viral and nonviral etiologies was not able to capture different outcomes. The effects on OS were not significant, probably due to the lack of repercussions on PPS. In any case, the interpretation of OS in MASLD patients offers peculiar changes due to subtle factors, such as the cardiovascular and noncardiovascular comorbidities and the potential effect of continued liver insult consequent to persistent metabolic dysfunction [30] (differently from patients with treated viral infection or abstinent from alcohol). In this complex setting, the relatively low absolute number of MASLD patients in this study might prevent strong conclusions about OS. Therefore, we feel that such conclusions should rely exclusively on RCTs with preplanned stratification for etiology. Our results do not support avoiding immunotherapy for MASLD-HCC patients. Rather, they encourage the design of precise testing in future RCTs and (paired with the preclinical supporting evidence) point toward a relevant role of MASLD intrahepatic microenvironment in determining the response of liver lesions to different systemic treatments. Future real-life studies of durvalumab-tremelimumab are expected to yield additional insights into the relationship between etiology and patterns of progression, further elucidating this complex and intriguing topic.

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Statement of Ethics

This study protocol was reviewed and approved by the Independent Ethic Committee of the IRCCS Azienda Ospedaliero-Universitaria di Bologna (Protocol Approval No. 811.2022.Oss.AOUBo), which served as the coordinating center. All other centers received approval from their respective local ethics committees. Written informed consent for treatment and participation in this study was obtained from all participants.

Conflict of Interest Statement

Fabio Piscaglia has served on advisory boards for AstraZeneca, EISAI, Exact Sciences, MSD, Roche, and Siemens Healthineers; Speeches at symposia for AstraZeneca, Bayer, Bracco, ESAOTE, EISAI, GE, IPSEN, MSD, Roche, and Samsung; and is a consultant for Bracco and Nerviano. Massimo Iavarone received honoraria/consultation fees for speaker consultancy, or advisory roles from Bayer, IPSEN, Eisai, Roche, MSD, AstraZeneca, Gilead, and Roche Diagnostics; travel grants from AstraZeneca and Roche. Tiziana Pressiani received/reports consulting fees from Bayer, Ipsen, and AstraZeneca; institutional research funding from Roche, Bayer, and AstraZeneca; support for congress attendance from Roche. Sara Lonardi reports research funding from Amgen, Astellas,

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Author Contributions

Study concept and design: B.S., F.P., and F.T. Analysis and interpretation of data, and drafting of the manuscript: B.S. and F.T. Statistical analyses: F.T. and B.S. Supervision: F.T. and F.P. B.S., F.P., F.M., M.I., C.V., G.C., A.P., T.P., A.D., B.St., L.S., P.F., G.S.-B., S.L., C.S., L.I., S.L., I.G., C.C., M.B., G.M., C.Ce., G.B., A.A., B.D., F.Po., L.L., R.C., M.Bo., A.G., L.R., and F.T.: data acquisition and critical revision of the manuscript. All authors approved the final version of the manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author upon reasonable request.

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