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Impact of neutrophil-to-lymphocyte ratio on survival outcomes among cirrhotic and non-cirrhotic patients with advanced hepatocellular carcinoma under atezolizumab–bevacizumab combination therapy

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Abstract

Background The efficacy of atezolizumab–bevacizumab in patients with hepatocellular carcinoma (HCC) has not been studied separately in cirrhotic and non-cirrhotic patients. Our aim was to evaluate the efficacy of atezolizumab–bevacizumab in these patients, in relation to baseline values of the neutrophil-to-lymphocyte ratio (NLR).

Methods We divided 57 atezolizumab–bevacizumab-treated HCC patients according to baseline NLR (>3: NLR-H, ≤3: NLR-L) and studied overall survival (OS) and progression-free survival (PFS) in 4 groups: group A, non-cirrhotic/NLR-L; group B, non-cirrhotic/NLR-H; group C, cirrhotic/NLR-L; and group D, cirrhotic/NLR-H.

Results The 4 groups were comparable except for etiology, ALBI grade, macrovascular invasion, Barcelona Clinic Liver Cancer stage and prior therapy. Median OS and PFS were 30, 10, 12 and 5 months, and 14, 4, 8 and 2 months, for groups A, B, C, D, respectively (P<0.001). By Cox regression, cirrhotic/NLR-H patients showed significantly worse OS and PFS. Cirrhotic/NLR-L patients had better OS (12 vs. 5 months, P=0.002) and PFS (8 vs. 2 months, P=0.028) compared to cirrhotic/NLR-H. NLR was significantly correlated with OS (P=0.015). Non-cirrhotic/NLR-L patients had better OS (30 vs. 10 months, P=0.006) and PFS (15 vs. 4 months, P=0.01) compared to non-cirrhotic/NLR-H patients. Prior therapy was significantly correlated with better OS (30 vs. 8 months, P<0.001) and PFS (24 vs. 4 months, P<0.001) in non-cirrhotic patients.

Conclusions Cirrhotic/NLR-H HCC patients presented the worst survival. NLR is an independent risk factor for worse survival in cirrhotic patients. Prior therapy is the only factor significantly correlated with OS and PFS in non-cirrhotic patients.

Keywords Hepatocellular carcinoma, immunotherapy, cirrhosis, neutrophil-to-lymphocyte ratio

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Conflict of Interest: None

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Introduction

Liver cancer is a major clinical entity and has become increasingly frequent during recent decades, being the 6th most common type of cancer and the 4th leading cause of cancer-related mortality globally [1]. The most common type of liver cancer is hepatocellular carcinoma (HCC) [2]. The majority of HCC cases are frequently diagnosed in the intermediate or the advanced stage, where potentially curative interventions are not feasible [3].

In 2007, sorafenib was the first agent to receive approval for the systemic treatment of advanced HCC [4]. Since then, more tyrosine kinase inhibitors (TKIs) have gradually been developed and used for this purpose [5-7]. Recently, the introduction of atezolizumab–bevacizumab in unresectable HCC shifted the balance in the HCC treatment landscape towards new immunological pathways. The IMBRAVE150 study showed a survival benefit in patients with unresectable

HCC compared to sorafenib in first-line systemic treatment, yielding objective response rates up to 20%, accompanied by a great improvement in patients' quality of life [8].

Unfortunately, there are only limited data concerning factors that determine the response to immunotherapy in HCC. In recent years, models have been demonstrated that could predict the response to immunotherapy [9], but more complex parameters need to be assessed in order to predict the survival of immunotherapy-treated HCC patients, taking into consideration the complex molecular profile of HCC [10-12]. Another score that has proved valuable in oncology is the neutrophil-to-lymphocyte ratio (NLR) [13,14]. Low NLR values have been associated with objective response and better survival in patients with solid tumors [15-18], and there is a rationale for using it in HCC, as it is a tumor with a complex microenvironment [19-21]. As a result, NLR has been previously correlated in some HCC cohorts with overall survival and response to atezolizumab–bevacizumab therapy [22-24].

Another important variable in HCC therapeutic management is the combined use of surgery or locoregional therapies with immunotherapy. Recently, the IMBRAVE050 study failed to show better survival rates for high-risk HCC patients who received adjuvant atezolizumab–bevacizumab post-resection, compared to active surveillance [25]. However, the administration of locoregional treatment before the initiation of immunotherapy can reshape the tumor microenvironment, making it less immune-resistant and increasing the chances of demonstrating an objective response with immunotherapy, and probably better survival [26,27].

The majority of HCCs used to arise on a substrate of liver cirrhosis [28]. However, the HCC landscape has changed dramatically over the last years. The increasing and more frequent use of antiviral drugs against hepatitis B and C viruses (HBV and HCV), in addition to the growing prevalence of steatotic liver disease, has led to more HCCs appearing in non-cirrhotic and non-viral patients, something that could definitely have a great impact on survival [29,30].

The aim of our study was to evaluate the efficacy of atezolizumab–bevacizumab combination therapy in patients with locally advanced and/or metastatic HCC not amenable to surgery or locoregional treatment, in relation to the baseline NLR values of histologically proved cirrhotic and non-cirrhotic HCC patients.

Patients and methods

We retrospectively evaluated 57 white European patients with locally advanced and/or metastatic HCC who received first-line systemic treatment with atezolizumab–bevacizumab in our center between January 2021 and December 2023. Patients were evaluated for their baseline characteristics on the first day of atezolizumab–bevacizumab treatment. We gathered demographic, clinical and radiological data, while histological information was obtained from all patients through ultrasound-guided liver biopsy. Recorded parameters included sex, age, body mass index (BMI), HCC etiology, presence of diabetes/varices, α-fetoprotein (AFP), baseline NLR, and liver disease severity scores, including Child–Pugh (CP) grade/score, model for end-stage liver disease (MELD)-Na score [31] and albumin–bilirubin (ALBI) grade [32], as well as tumor data concerning the presence of macrovascular invasion (MVI), extrahepatic disease (EHD), Barcelona Clinic Liver Cancer (BCLC) stage and prior HCC therapy at the start of immunotherapy. The diagnosis of HCC was confirmed in all patients with the combined use of AFP, radiological exams (computed tomography [CT] or magnetic resonance imaging [MRI]) and histology. The presence of varices, CP and MELD-Na scores were not evaluated for non-cirrhotic patients.

HCC etiology was divided into viral and non-viral. Chronic HBV and HCV infections were associated with viral HCC. Patients with chronic HCV infection had received prior treatment with direct-acting antivirals, while patients with chronic hepatitis B were appropriately suppressed with antiviral treatment through long term nucleos(t)ide analogs. All patients who declared alcohol use before initiation of treatment were excluded from the study, as were patients who refused to comply with the protocol. All study participants had undergone an ultrasound-guided liver biopsy that was diagnostic for HCC before the initiation of immunotherapy. The presence of liver cirrhosis was evaluated through histological samples, both in patients treated with liver resection and in those who underwent guided biopsy. Data on morphomolecular HCC characteristics were gathered from all liver biopsies, creating 2 distinct HCC subgroups (proliferative and non-proliferative HCCs), according to the recent morphomolecular classification of HCCs [33].

Patients who had received prior systemic treatments were excluded. Prior treatment was allowed if it involved locoregional treatment (transarterial chemoembolization [TACE] or radiofrequency ablation [RFA]) or liver resection, but not both procedures. Patients had to have undergone liver resection within the past 2 years and experienced relapse in an intermediate or advanced stage before the administration of immunotherapy. Furthermore, patients were allowed to have received a maximum of 2 sessions of locoregional treatment with TACE and/or RFA during the previous 2 years and experienced progressive disease before inclusion in the study. Patients received first-line treatment with 1200 mg of intravenous atezolizumab and intravenous bevacizumab at a dose of 15 mg/kg every 21 days, until unacceptable toxicity or loss of clinical benefit [8]. Generally, patients were on a stable dose of both drugs, but treatment was postponed when a grade 3 treatment-related adverse event was detected, and permanently discontinued in patients who exhibited serious adverse events. All 57 patients had to have received at least 3 consecutive cycles of atezolizumab–bevacizumab and had at least 1 tumor assessment in order to be included in this study. Patients underwent tumor assessment every 2 months with CT or MRI. We used the RECIST 1.1 criteria to assess tumor response [34].

We divided a total of 57 HCC patients into 2 groups according to the presence or absence of cirrhosis. Cirrhotic

patients accounted for 52.7% of patients (N=30), while the rest of the patients were non-cirrhotic (N=27, 47.3%). We then calculated baseline NLR values for all patients on the first day of atezolizumab–bevacizumab infusion, using the absolute count of neutrophil to lymphocytes in peripheral blood, and divided the patients in those with NLR ≤3 (NLR-L groups) and those with NLR >3 (NLR-H groups). As a result, 4 groups were eventually created: group A (non-cirrhotic, NLR-L, N=13); group B (non-cirrhotic, NLR-H, N=14); group C (cirrhotic, NLR-L, N=11); and group D (cirrhotic, NLR-H, N=19). These groups were compared according to their baseline characteristics, overall survival (OS) and progression-free survival (PFS). We then studied the cirrhotic population separately according to their NLR values and prior treatment status, and performed the same analysis in non-cirrhotic patients.

All patients who participated in the current study gave written informed consent before systemic treatment initiation and a written informed consent form was signed by all living patients at the time of study entry. The protocol of our study was in accordance with the Declaration of Helsinki for human trials and was approved by the Ethics Committee and the Scientific Board of the "Agioi Anargyroi" General and Oncology Hospital of Kifisia, Athens, Greece.

Statistical analysis

We used the IBM SPSS Statistics software (IBM Corp. Released 2012. IBM SPSS statistics for Windows, Version 29.0.2.0, Armonk, NY: IBM Corp.) for the statistical analysis of our data. Variables were separated into numerical variables, shown as mean values ± standard deviation (SD), and categorical variables, which are represented as numbers and percentages. When comparing 2 groups of patients, we used the independent samples' *t*-test in order to find significant differences for numerical variables and the chi-square test in order to compare the categorical values of different groups. When 4 groups were compared, we used analysis of variance (1-way ANOVA) to compare groups concerning normally distributed continuous variables, the Kruskal–Wallis H test for non-normally distributed continuous variables, and the chi-square test for categorical variables. We checked normality for continuous variables with the Kolmogorov–Smirnov test. We then did a survival analysis using Kaplan–Meier curves for OS and PFS and compared the median survival of different groups using the log-rank test (Mantel–Cox). If 2 or more groups had statistically significant differences in 1 or more baseline characteristics, we used Cox regression analysis for OS and PFS separately in order to find differences in outcomes between patient groups, adjusting for all covariates in which the groups were not comparable. The Bonferroni correction was used to adjust the significance level for multiple comparisons. Multicollinearity issues were checked while using Cox regression, using values of tolerance and variance inflation factor. Cox regression results are presented using P-values, hazard ratios (HR) and 95% confidence interval (CI) for HR; P-values < 0.05 were considered statistically significant. Lastly, we conducted Cox-regression Kaplan–Meier analysis in order to present survival results at the mean of covariates, in case of comparison between the 2 values of a binary variable.

Results

Of the 57 patients, 45 were males (78.9%). Patients had a mean age of 66.3±11.3 years, a mean BMI of 27.23±4.8 kg/m^2, 19 had diabetes (33.3%), 33 viral etiology (57.9%), 29 were ALBI-I (50.8%), 22 had MVI (38.6%), 23 had EHD (40.4%), while 41 were categorized as BCLC-C (71.9%) and 16 as BCLC-B (28.1%) on study entry. In addition, 22 had AFP levels above 400 ng/mL (38.6%), 27 were categorized as proliferative subgroup HCCs (47.4%), 30 as non-proliferative (52.6%) and 31 had received prior HCC therapy (54.4%). In total, 14 patients (24.6%) underwent resection; only 4 were cirrhotic (28.6%) while the remaining 10 resected patients (71.4%) were non-cirrhotic. All resected patients in our study experienced early relapse, defined as HCC recurrence within 2 years post-resection. Locoregional treatment before immunotherapy onset was recorded in a total of 17 patients (29.8%), of whom 8 (47.1%) were cirrhotic, and 9 (52.9%) non-cirrhotic.

We performed our analysis in 3 steps. First of all, we divided the total of 57 HCC patients into 4 different groups, as described above. We then studied these groups according to their baseline characteristics. Taking into consideration that CP and MELD-Na scores were only used in patients with cirrhosis, and that none of the non-cirrhotic patients had signs of portal hypertension, we did not include CP stage and score, MELD-Na score or the presence of varices as baseline characteristics in this first analysis. On the other hand, we used the ALBI grade—which has already been widely used in patients with HCC and not exclusively in cirrhotic patients—as a baseline characteristic to measure hepatic reserve in all teams. The baseline characteristics of the 4 groups are presented in Table 1: the 4 groups were comparable in terms of all the baseline characteristics except for liver disease etiology (P<0.001), ALBI grade (P=0.014), MVI (P<0.001), BCLC stage at treatment initiation (P=0.014) and prior therapy (P=0.009). More specifically, non-cirrhotic patients tended to have non-viral disease, lower ALBI grade, rarely MVI, frequently BCLC-B stage and had often received prior treatment. Median OS (Fig. 1A) was 30, 10, 12 and 5 months for groups A, B, C and D, respectively and the log-rank test showed a statically significant result (P<0.001). We then performed Cox regression analysis for OS, in order to compare the survival of group D to the other 3 groups, after adjusting for all the baseline parameters for which the 4 groups were not comparable (etiology, ALBI, MVI, BCLC, prior therapy). According to the Bonferroni correction, the adjusted alpha level for statistical significance while comparing group D to groups A, B and C was 0.0167 (0.05/3) and we observed a statistically significant difference in OS when comparing group A to group D (HR 0.1, 95%CI 0.020-0.504; P=0.005), but not when comparing group C to

Table 1 Baseline characteristics of the 4 groups created according to presence/absence of cirrhosis and baseline NLR status

Characteristics	Non-cirrhotic (N=27/57) – 47.3%				Cirrhotic (N=30/57) – 52.7%				P-value
	NLR-L (13/27) *GROUP A*		NLR-H (14/27) *GROUP B*		NLR-L (11/30) *GROUP C*		NLR-H (19/30) *GROUP D*		
	N	%	N	%	N	%	N	%	
Sex									0.681
Female	2	15.4	3	21.4	1	9.1	5	26.3	
Male	11	84.6	11	78.6	10	90.9	14	73.7	
Age (Mean, SD)	69.2	10.6	68.2	13.7	62.9	9.2	64.8	11	0.427
BMI (kg/m^2) (Mean, SD)	28.8	5.6	28	3.75	24.8	3.9	26.9	5.2	0.214
Diabetes									0.596
No	8	61.5	8	57.1	9	81.8	13	68.4	
Yes	5	38.5	6	42.9	2	18.2	6	31.6	
Etiology									<0.001
Viral	1	7.7	2	14.3	9	81.8	12	63.2	
Non-Viral	12	92.3	12	85.7	2	18.2	7	36.8	
ALBI									0.014
1	11	84.6	7	50	6	54.5	5	26.3	
2	2	15.4	7	50	5	45.5	14	73.7	
MVI		100							<0.001
No	13	0	11	78.6	5	45.5	6	31.6	
Yes	0		3	21.4	6	54.5	13	68.4	
EHD									0.866
No	8	61.5	7	50	7	63.6	12	63.2	
Yes	5	38.5	7	50	4	36.7	7	36.8	
BCLC									0.014
Stage B	8	61.5	4	28.6	2	81.8	2	10.5	
Stage C	5	38.5	10	71.4	9	18.2	17	89.5	
AFP								36.8	0.062
<400 ng/mL	10	76.9	10	71.4	8	72.7	7	63.2	
>400 ng/mL	3	23.1	4	28.6	3	27.3	12		
Morphomolecular classification									0.951
Non-proliferative	7	53.8	8	57.1	6	54.5	9	47.4	
Proliferative	6	46.2	6	42.9	5	45.5	10	52.6	
Tumor assessment									0.103
CR	4	30.8	0	0	1	9.1	0	0	
PR	0	0	1	7.1	1	9.1	0	0	
SD	2	15.4	1	7.1	1	9.1	3	15.8	
PD	7	53.8	12	85.8	8	72.3	16	84.2	
Prior therapy									0.009
No	1	7.7	7	50	5	45.5	13	68.4	
Yes	12	92.3	7	50	6	54.5	6	31.6	

NLR-H, high NLR group; NLR-L, low NLR group; SD, standard deviation; BMI, body mass index; ALBI, albumin-bilirubin grade; MVI, macrovascular invasion; EHD, extrahepatic disease; BCLC, Barcelona Clinic Liver Cancer; AFP, α-fetoprotein; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

group D (P=0.032) or group B to D (P=0.055), while the other covariates failed to achieve statistically significant P-values (Supplementary Fig. 1A). Similarly, median PFS (Fig. 1B) differed significantly (P<0.001) between the 4 groups (14, 4, 8 and 2 months for groups A, B, C and D, respectively). Cox regression for PFS, using the Bonferroni correction, showed a statistically significant difference when comparing group A to D (HR 0.140, 95%CI 0.043-0.459; P=0.006), whereas no statistical significance was found when comparing group B to D (P=0.070) and C to D (P=0.054), and no statistically significant P-values were found for the other covariates (Supplementary Fig. 1B).

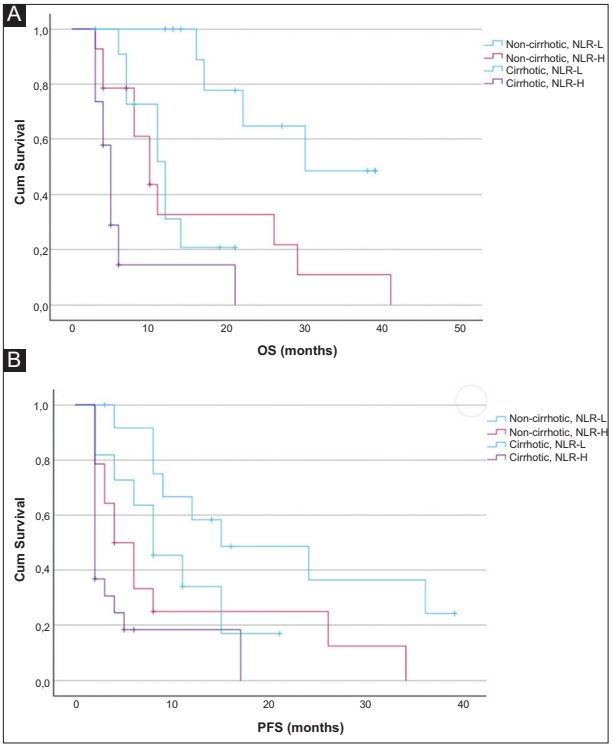

Figure 1 Overall survival (A) and progression-free survival (B) for each of the 4 groups according to cirrhosis presence/absence and baseline NLR status

OS, overall survival; PFS, progression-free survival; NLR-H, high NLR group; NLR-L, low NLR group

We then conducted a Cox regression analysis for all patients, without categorizing them into groups, in order to assess the impact of cirrhosis and NLR separately for OS and PFS. We found that both presence of cirrhosis (HR 3.173, 95%CI 1.083-9.301; P=0.035) and high NLR (HR 3.076, 95%CI 1.337-7.078; P=0.008) were significantly associated with worse OS, independently of other potential confounders. For PFS, only a high NLR emerged as a statistically significant factor associated with worse PFS (HR 2.54, 95%CI 1.188-5.429; P=0.016), independently of all other confounders (Supplementary Fig. 2A,B).

The second analysis included only the cirrhotic HCC patients of our study (N=30). We divided those patients into 2 groups according to their baseline NLR status, and compared NLR-L and NLR-H patients according to their baseline characteristics (Supplementary Table 1). Those 2 groups were comparable for all baseline parameters, except for CP stage (P=0.021) and number (P=0.007). Median OS was significantly higher (P=0.002) in the cirrhotic NLR-L group (12 months) compared to NRL-H cirrhotic patients (5 months), and similarly PFS was significantly higher (8 months) in cirrhotic NLR-L compared to NLR-H patients (2 months, P=0.028; Fig. 2A,B). Cox regression analysis for OS showed that NLR was significantly associated with OS (HR 3.480, 95%CI 1.274-9.508; P=0.015), independently of CP stage and score, while no statistically significant results were achieved with regard to PFS (Supplementary Fig. 3A,B). We then compared cirrhotic patients according to prior therapy status for HCC: the 2 groups were comparable for all the baseline parameters evaluated (Supplementary Table 2) and did not show differences in median OS (P=0.201) or PFS (P=0.792) (Fig. 2C,D).

Finally, we compared the non-cirrhotic HCC patients (N=27) according to their baseline NLR status. The 2 groups were comparable for most of their baseline characteristics (Supplementary Table 3), except for prior therapy (P=0.016). Non-cirrhotic NLR-L patients showed a significantly higher median OS (30 months) compared to NLR-H non-cirrhotic patients (10 months, P=0.006) (Fig. 3A). Cox regression, adjusting for NLR status and prior therapy type, showed that only the latter factor and not NLR was significantly associated with OS (Supplementary Fig. 4A). Regarding PFS, non-cirrhotic NLR-L patients showed significantly higher PFS (15 months) than non-cirrhotic NLR-H patients (4 months, P=0.01, Fig. 3B). Cox regression analysis for PFS, adjusting for NLR and prior therapy type, showed that only prior treatment was significantly associated with PFS (Supplementary Fig. 4B). In our final analysis, we separated our non-cirrhotic patients in 2 groups according to prior HCC therapy status. Supplementary Table 4 shows the baseline characteristics of the 2 groups, which were comparable in terms of most factors, except for BCLC stage on treatment onset (P=0.03) and baseline NLR status (P=0.017). Those 2 groups differed significantly in terms of OS (30 months in patients with prior therapy vs. 8 months in patients without prior therapy, P<0.001) and PFS (24 months vs. 4 months, respectively, P<0.001, Fig. 3C,D). Cox regression analysis showed that only prior therapy, and not NLR or BCLC status, was significantly associated with OS in non-cirrhotic patients, and the same results also applied to PFS (Supplementary Fig. 5A,B). Lastly, we conducted Cox regression Kaplan–Meier analysis in order to present survival results (for both OS and PFS) at the mean of covariates, both for cirrhotic patients (using NLR as grouping variable) and for non-cirrhotic patients (using NLR and prior therapy separately as grouping variables). Results are presented in the supplementary material (Supplementary Fig. 6,7).

Discussion

It is noticeable that the majority of randomized trials, as well as real-world data in the HCC management field, do not separate cirrhotic from non-cirrhotic patients in their analysis of advanced HCC, despite the major impact of liver disease severity on the final clinical outcome [8,35,36]. Furthermore, non-cirrhotic patients in most of these studies are wrongly categorized as CP-A, considering that CP only applies to cirrhotic patients. Therefore, clinical studies of HCC should carefully distinguish between cirrhotics and non-cirrhotics when recruiting HCC patients, as survival outcomes may be affected by the presence of cirrhosis. In this study, we used easily obtained biomarkers, such as pre-treatment NLR, and recorded medical data, such as prior HCC treatment, in order to find possible correlations with survival in cirrhotic/non-cirrhotic patients.

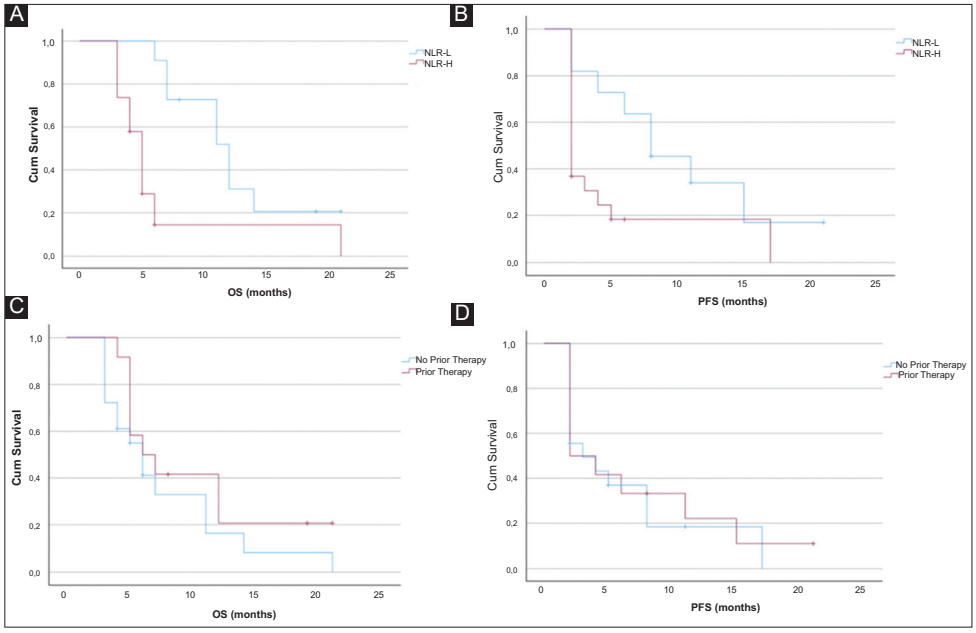

Figure 2 Overall survival (A) and progression-free survival (B) in cirrhotic HCC patients according to baseline NLR status. Overall survival (C) and progression-free survival (D) in cirrhotic HCC patients according to prior therapy status
OS, overall survival; PFS, progression-free survival; NLR-H, high NLR group; NLR-L, low NLR group

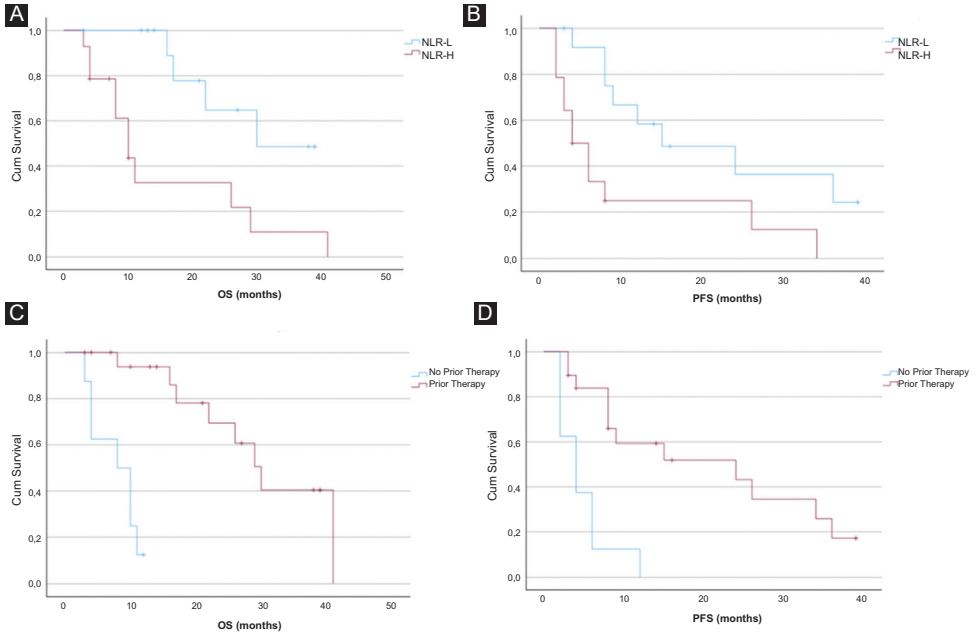

Figure 3 Overall survival (A) and progression-free survival (B) in non-cirrhotic patients according to baseline NLR status. Overall survival (C) and progression-free survival (D) in non-cirrhotic HCC patients according to prior therapy status
OS, overall survival; PFS, progression-free survival; NLR-H, high NLR group; NLR-L, low NLR group

In our study, we evaluated the efficacy of atezolizumab–bevacizumab in terms of OS and PFS, in a mixed population of cirrhotic and non-cirrhotic patients with unresectable HCC, according to baseline NLR. As expected, both OS and PFS were worse in cirrhotic compared to non-cirrhotic patients, and cirrhotic patients with high NLR values exhibited the worst outcomes (median OS 5 months, median PFS 2 months), irrespective of the other baseline parameters that could influence the survival outcome. Cirrhosis and high NLR values have been related to worse survival outcomes in untreated as well as treated HCC patients with all treatment modalities [22,37], including atezolizumab–bevacizumab

therapy [23,24]. Both reports concerning the prognostic impact of NLR in patients treated with atezolizumab–bevacizumab [23,24] referred to fewer than 50 treated patients, without any histological definition of cirrhosis in most of them, while only 5-12.5% of patients were CP-B stage, and the studies had relatively short observation periods. In our study, high NLR values (>3) were an independent predictor of OS but not PFS, among histologically proven cirrhotic patients with HCC (23.3% in CP-B stage) treated with atezolizumab–bevacizumab. Several reports have highlighted the lack of a strong correlation between tumor-based endpoints, such as objective responses, and/or PFS and OS, especially among cirrhotic patients with advanced HCC under systemic treatment [38-40]. It has been suggested that the surrogacy of PFS with OS is variable, and mainly dependent on systemic treatment class (TKIs or immunotherapy-based) and evaluation treatment point [40].

In our study, we found that cirrhosis was a statistically significant factor for worse OS, as anticipated, along with high NLR values, heralding the importance of the separate evaluation of NLR status in cirrhotic and non-cirrhotic patients. As for PFS, in the total population of patients, only high NLR was independently associated with worse PFS; this suggests that NLR could be a very useful tool for predicting tumor response to immunotherapy, independently of cirrhosis and other confounding factors. Median OS was 12 months in cirrhotic patients with low baseline NLR, compared to only 5 months in those with high baseline NLR, a finding that was statistically significant. It is important to note that previous locoregional therapy (n=8) or resection (n=4) did not affect the survival rates of cirrhotic HCC patients (5-12 months for OS and 2-8 months for PFS).

NLR was not found to be an independent predictor of OS and PFS among non-cirrhotic HCC patients treated with atezolizumab–bevacizumab therapy. It is very interesting to note that 10 of the 27 non-cirrhotic HCC patients in our study population had been previously resected, and early disease recurrence was observed within 2 years from the time of resection, whereas locoregional therapy with incomplete response presented in 9 of 27 patients, prior to the initiation of atezolizumab–bevacizumab therapy. In the multivariate analysis, prior therapy, either resection or locoregional, was an independent predictor of long-term OS and PFS, among treated non-cirrhotic HCC patients. A beneficial reshaping of the tumor microenvironment by prior locoregional or surgical therapy has been suggested in many recently published studies, and trials evaluating combinations of these procedures with immunotherapy are already ongoing. Through this observational study, it could be supposed that prior therapy might possibly affect baseline NLR values prior to the start of immunotherapy, shifting the tumor microenvironment balance towards an immune-friendly environment before the initiation of immunotherapy, given that the majority of non-cirrhotic HCC patients (12/13, 92.3%) with a low baseline NLR had been previously treated with surgery or locoregional treatment, compared to only 50% (7/14, P=0.016) of those with high baseline NLR. This finding needs further investigation and evaluation in larger cohorts.

This study had some limitations. The small number of patients in each group could have led to biases, along with the retrospective analysis of the data. However, the grade of statistical significance of our values, in accordance with results from other studies [23,24], might suggest that NLR should be tested in cohorts of large randomized prospective trials to confirm its prognostic value in relation to survival. Another limitation is the small proportion of viral non-cirrhotic patients. This could be possibly explained by the increasing prevalence of steatotic liver disease in Europe, leading to the appearance of HCC in non-cirrhotic livers. On the other hand, this study was conducted in a single HCC referral center, where laboratory examinations were conducted by the same laboratory, and the same HCC specialists cooperated in multidisciplinary patient management, gathering of patient data and presentation of the results.

Summary Box

What is already known:

- Hepatocellular carcinoma (HCC) is the 6th most common cancer and the 4th leading cause of cancer-related deaths globally
- Early-stage diagnosis is rare, with most cases diagnosed at intermediate or advanced stages, limiting treatment options
- Sorafenib was the first FDA-approved systemic treatment for advanced HCC, followed by other tyrosine kinase inhibitors and, more recently, the combination of atezolizumab and bevacizumab, which have shown better survival outcomes and quality of life in patients with unresectable HCC
- The neutrophil-to-lymphocyte ratio (NLR) has been associated with better survival and response to immunotherapy in solid tumors, including HCC

What the new findings are:

- Cirrhotic patients with high baseline NLR values (>3) had significantly worse overall survival (OS) and progression-free survival (PFS), with a median OS of 5 months and PFS of 2 months
- High NLR was found to be an independent predictor of OS, but not PFS, in cirrhotic patients
- Non-cirrhotic patients with low baseline NLR had the best survival outcomes (30 months OS and 15 months PFS), and prior locoregional/surgical therapy (though not NLR) was an independent predictor of better prognosis in non-cirrhotic patients

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Supplementary material

Supplementary Table 1 Baseline characteristics of cirrhotic HCC patients according to baseline NLR status

Characteristics	NLR-L (11/30) – 36.67%		NLR-H (19/30) – 63.33%		P-value
	N	%	N	%	
Sex					0.256
Female	1	9.1	5	26.3	
Male	10	90.9	14	73.7	
Age (mean, SD)	62.91	9.2	64.79	11	0.638
BMI (kg/m^2) (mean, SD)	24.8	3.9	24.9	5.2	0.248
Diabetes					0.424
No	9	81.8	13	68.4	
Yes	2	18.2	6	31.6	
Etiology					0.282
Viral	9	81.8	12	63.2	
Non-viral	2	18.2	7	36.8	
Varices					0.510
No	6	54.5	8	42.1	
Yes	5	45.5	11	57.9	
CP stage					0.021
Stage A	11	100	12	63.2	
Stage B	0	0	7	36.8	
CP Number (mean, SD)	5.09	0.3	6.32	1.3	0.007
MELD-Na (mean, SD)	10.3	2.7	11.2	4.2	0.540
ALBI					0.122
Grade 1	6	54.5	5	26.3	
Grade 2	5	45.5	14	73.7	
MVI					0.447
No	5	45.5	6	31.6	
Yes	6	54.5	13	68.4	
EHD					0.979
No	7	63.6	12	63.7	
Yes	4	36.4	7	36.8	
AFP					0.058
<400	8	72.7	7	36.8	
>400	3	27.3	12	63.7	
Morphomolecular classification					0.705
Non-proliferative	6	54.5	9	47.4	
Proliferative	5	45.5	10	52.6	
BCLC					0.552
B	2	18.2	2	10.5	
Stage C	9	81.8	17	89.5	
Tumor assessment					0.283
CR	1	9.1	0	0	
PR	1	9.1	0	0	
SD	1	9.1	3	15.8	
PD	8	72.7	16	84.2	
Prior therapy					0.216
No	5	45.5	13	68.4	
Yes	6	54.5	6	31.6	
Prior therapy type					0.207
None	5	45.4	13	68.4	
Resection	3	27.3	1	5.3	
Locoregional	3	27.3	5	26.3	

NLR-H, high NLR group; NLR-L, low NLR group; SD, standard deviation; BMI, body mass index; CP, Child-Pugh; MELD, model for end-stage liver disease; ALBI, albumin-bilirubin grade; MVI, macrovascular invasion; EHD, extrahepatic disease; AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

Supplementary Table 2 Baseline characteristics of cirrhotic HCC patients according to prior therapy status

Characteristics	No Prior Therapy (18/30) – 60%		Prior Therapy (12/30) – 40%		P-value
	N	%	N	%	
Sex					0.256
Female	3	16.7	3	25	
Male	15	63.3	9	75	
Age (mean, SD)	64.56	11.6	63.42	8.3	0.772
BMI (kg/m^2) (mean, SD)	25.7	5.2	26.8	4.3	0.543
Diabetes					0.500
No	14	77.8	8	66.7	
Yes	4	22.2	4	33.3	
Etiology					0.745
Viral	13	72.2	8	66.7	
Non-viral	5	27.8	4	33.3	
Varices					0.654
No	9	50	5	41.7	
Yes	9	50	7	58.3	
CP stage					0.860
Stage A	14	77.8	9	75	
Stage B	4	22.2	3	25	
CP Number (mean, SD)	5.72	0.9	6.08	1.6	0.449
MELD-Na (mean, SD)	10.9	3.9	10.7	3.4	0.845
ALBI					0.757
Grade 1	7	38.8	4	33.3	
Grade 2	11	61.2	8	66.7	
MVI					0.757
No	7	38.8	4	33.3	
Yes	11	61.2	8	66.7	
EHD					0.279
No	10	55.5	9	75	
Yes	8	44.5	3	25	
AFP					1.000a
<400	9	50	6	50	
>400	9	50	6	50	
Morphomolecular classification					0.456
Non-proliferative	10	55.5	5	41.7	
Proliferative	8	44.5	7	58.3	
BCLC					0.125
Stage B	1	5.5	3	25	
Stage C	17	94.5	9	75	
Tumor assessment					0.283
CR	0	0	1	8.3	
PR	0	0	1	8.3	
SD	4	22.2	0	0	
PD	14	77.8	10	83.4	
NLR					0.216
NLR-L	5	27.8	6	50	
NLR-H	13	72.2	6	50	

SD, standard deviation; BMI, body mass index; CP, Child-Pugh; MELD, model for end-stage liver disease; ALBI, albumin-bilirubin grade; MVI, macrovascular invasion; EHD, extrahepatic disease; AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NLR-H, high NLR group; NLR-L, low NLR group

Supplementary Table 3 Baseline characteristics of non-cirrhotic HCC patients according to baseline NLR status

Characteristics	NLR-L (13/27) – 48.14%		NLR-H (14/27) – 51.86%		P-value
	N	%	N	%	
Sex					0.686
Female	2	15.4	3	21.4	
Male	11	84.6	11	78.6	
Age (mean, SD)	69.2	10.6	68.2	13.6	0.832
BMI (kg/m^2) (mean, SD)	28.7	5.6	28	3.7	0.701
Diabetes					0.816
No	8	61.5	8	57.1	
Yes	5	38.5	6	42.9	
Etiology					0.586
Viral	1	7.7	2	14.3	
Non-viral	12	92.3	12	85.7	
ALBI					0.057
Grade 1	11	84.6	7	50	
Grade 2	2	15.4	7	50	
MVI					0.077
No	13	100	11	78.6	
Yes	0	0	3	21.4	
EHD					0.547
No	8	61.5	7	50	
Yes	5	38.5	7	50	
AFP					0.745
<400	10	76.9	10	71.4	
>400	3	23.1	4	28.6	
Morphomolecular classification					0.863
Non-proliferative	7	53.8	8	57.1	
Proliferative	6	46.2	6	42.9	
BCLC					0.085
Stage B	8	61.5	4	28.6	
Stage C	5	38.5	10	71.4	
Tumor assessment					0.085
CR	4	30.8	0	0	
PR	0	0	1	7.1	
SD	2	15.4	1	7.1	
PD	7	53.9	12	85.8	
Prior therapy					0.016
No	1	7.7	7	50	
Yes	12	92.3	7	50	

NLR-H, high NLR group; NLR-L, low NLR group; SD, standard deviation; BMI, body mass index; ALBI, albumin-bilirubin grade; MVI, macrovascular invasion; EHD, extrahepatic disease; AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

Supplementary Table 4 Baseline characteristics of non-cirrhotic HCC patients according to prior therapy status

Characteristics	No Prior Therapy (8/27) – 29.6%		Prior Therapy (19/27) – 70.4%		P-value
	N	%	N	%	
Sex					0.099
Female	3	37.5	2	10.53	
Male	5	62.5	17	89.47	
Age (mean, SD)	64.75	16.37	70.37	9.86	0.279
BMI (kg/m^2) (mean, SD)	28.97	3.87	28.17	5.06	0.695
Diabetes					0.824
No	5	62.5	11	57.9	
Yes	3	37.5	8	42.1	
Etiology					0.882
Viral	1	12.5	2	10.53	
Non-viral	7	87.5	17	89.47	
ALBI					0.233
Grade 1	4	50	14	73.7	
Grade 2	4	50	5	26.3	
MVI					0.136
No	6	75	18	94.7	
Yes	2	25	1	5.3	
EHD					0.221
No	3	37.5	12	63.1	
Yes	5	62.5	7	36.9	
AFP					0.373
<400	5	62.5	15	78.9	
>400	3	37.5	4	21.1	
Morphomolecular classification					0.637
Non-proliferative	5	62.5	10	52.6	
Proliferative	3	37.5	9	27.4	
BCLC					0.030
Stage B	1	12.5	11	57.9	
Stage C	7	87.5	8	42.1	
Tumor assessment					0.458
CR	0	0	4	21.1	
PR	0	0	1	5.3	
SD	1	12.5	2	10.6	
PD	7	87.5	12	63.1	
NLR					0.017
NLR-L	1	12.5	12	63.1	
NLR-H	7	87.5	7	36.9	

SD, standard deviation; BMI, body mass index; ALBI, albumin-bilirubin grade; MVI, macrovascular invasion; EHD, extrahepatic disease; AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NLR-H, high NLR group; NLR-L, low NLR group

A

Variables	P-value	HR	95% CI for HR	
			Lower	Upper
Group	0.027			
A vs D	0.005	0.100	0.020	0.504
B vs D	0.055	0.321	0.101	1.022
C vs D	0.032	0.333	0.121	0.911
Prior therapy	0.082	0.475	0.2O5	1.100
BCLC	0.232	1.898	0.664	5.422
MVI	0.871	0.935	0.419	2.090
Etiology	0.834	1.098	0.460	2.623
ALBI	0.052	2.088	0.995	4.384

B

Variables	P-value	HR	95% CI for HR	
			Lower	Upper
Group	0.048			
A vs D	0.006	0.140	0.045	0.600
B vs D	0.070	0.425	0.176	1.229
C vs D	0.054	0.398	0.164	1.169
Prior therapy	0.538	0.780	0.354	1.719
BCLC	0.144	2.019	0.787	5.181
MVI	0.472	0.752	0.347	1.633
Etiology	0.225	1.612	0.746	3.482
ALBI	0.832	1.079	0.535	2.177

Supplementary Figure 1 (A) Cox regression analysis for OS comparing group D (cirrhotic, NLR-H) to the other 3 groups, after adjusting for all baseline parameters in which the 4 groups had statistically significant differences. According to the Bonferroni correction, the adjusted alpha level for statistical significance while comparing group D to groups A, B and C is 0.0167. (B) Cox regression analysis for PFS comparing group D (cirrhotic, NLR-H) to the other 3 groups, after adjusting for all baseline parameters in which the 4 groups had statistically significant differences. According to the Bonferroni correction, the adjusted alpha level for statistical significance while comparing group D to groups A, B and C is 0.0167 group A, non-cirrhotic/NLR-L; group B, non-cirrhotic/NLR-H; group C, cirrhotic/NLR-L; and group D, cirrhotic/NLR-H

BCLC, Barcelona Clinic Liver Cancer; MVI, macrovascular invasion; ALBI, albumin-bilirubin grade; CI, conference interval; HR, hazard ratio

A

Variables	P-value	HR	95% CI for HR	
			Lower	Upper
Prior therapy	0.083	0.476	0.206	1.101
BCLC	0.224	1.908	0.674	5.399
MVI	0.869	0.935	0.418	2.089
Etiology	0.836	1.096	0.460	2.612
ALBI	0.068	2.098	0.987	4.370
NLR	0.008	3.076	1.337	7.078
Cirrhosis	0.035	3.173	1.083	9.301

B

Variables	P-value	HR	95% CI for HR	
			Lower	Upper
Prior therapy	0.552	0.787	0.357	1.734
BCLC	0.143	2.009	0.790	5.109
MVI	0.480	0.756	0.347	1.643
Etiology	0.234	1.586	0.742	3.389
ALBI	0.808	1.091	0.541	2.200
NLR	0.016	2.540	1.188	5.429
Cirrhosis	0.067	2.301	0.945	5.606

Supplementary Figure 2 (A) Cox regression analysis for OS in all patients. (B) Cox regression analysis for PFS in all patients

BCLC, Barcelona Clinic Liver Cancer; MVI, macrovascular invasion; ALBI, albumin-bilirubin grade; NLR, neutrophil-to-lymphocyte ratio; CI, conference interval; HR, hazard ratio

A

Variables	P-value	HR	95% CI for HR	
			Lower	Upper
NLR	0.015	3.480	1.274	9.508
CP stage	0.371	2.774	0.297	25.908
CP score	0.684	0.861	0.419	1.768

B

Variables	P-value	HR	95% CI for HR	
			Lower	Upper
NLR	0.213	1.906	0.690	5.266
CP stage	0.500	1.984	0.271	14.512
CP score	0.927	1.034	0.511	2.089

Supplementary Figure 3 (A) Cox-regression analysis for OS comparing NLR-L and NLR-H cirrhotic HCC patients, after adjusting for all baseline parameters in which the 2 groups had statistically significant differences. (B) Cox-regression analysis for PFS comparing NLR-L and NLR-H cirrhotic HCC patients, after adjusting for all baseline parameters in which the 2 groups had statistically significant differences

NLR, neutrophil-to-lymphocyte ratio; CP, Child-Pugh; CI, confidence interval; HR, hazard ratio

A

Variables	P-value	HR	95% CI for HR	
			Lower	Upper
NLR	0.128	2.729	0.750	9.923
Prior therapy	0.011	0.061	0.007	0.533

B

Variables	P-value	HR	95% CI for HR	
			Lower	Upper
NLR	0.066	2.623	0.939	7.328
Prior therapy	0.006	0.204	0.065	0.639

Supplementary Figure 4 (A) Cox regression analysis for OS in non-cirrhotic NLR-L or NLR-H HCC patients, after adjusting for all baseline parameters in which the 2 groups had statistically significant differences. (B) Cox regression analysis for PFS in non-cirrhotic NLR-L or NLR-H HCC patients, after adjusting for all baseline parameters in which the 2 groups had statistically significant differences

NLR, neutrophil-to-lymphocyte ratio; CI, confidence interval; HR, hazard ratio

A

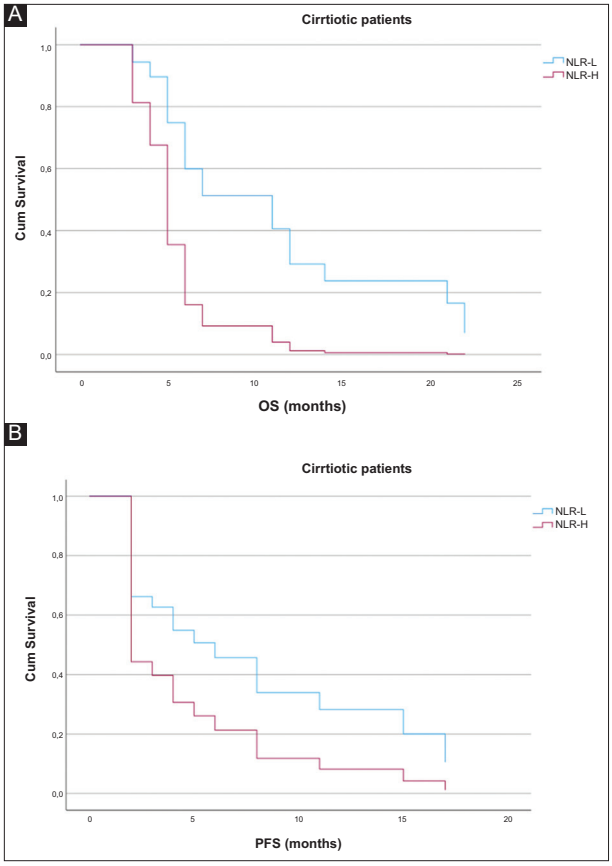
Variables	P-value	HR	95% CI for HR	
			Lower	Upper
NLR	0.145	2.730	0.708	10.525
Prior therapy	0.012	0.061	0.007	0.548
BCLC	0.998	0.998	0.257	3.884

B

Variables	P-value	HR	95% CI for HR	
			Lower	Upper
NLR	0.148	2.225	0.752	6.582
Prior therapy	0.014	0.218	0.065	0.736
BCLC	0.202	1.983	0.693	5.674

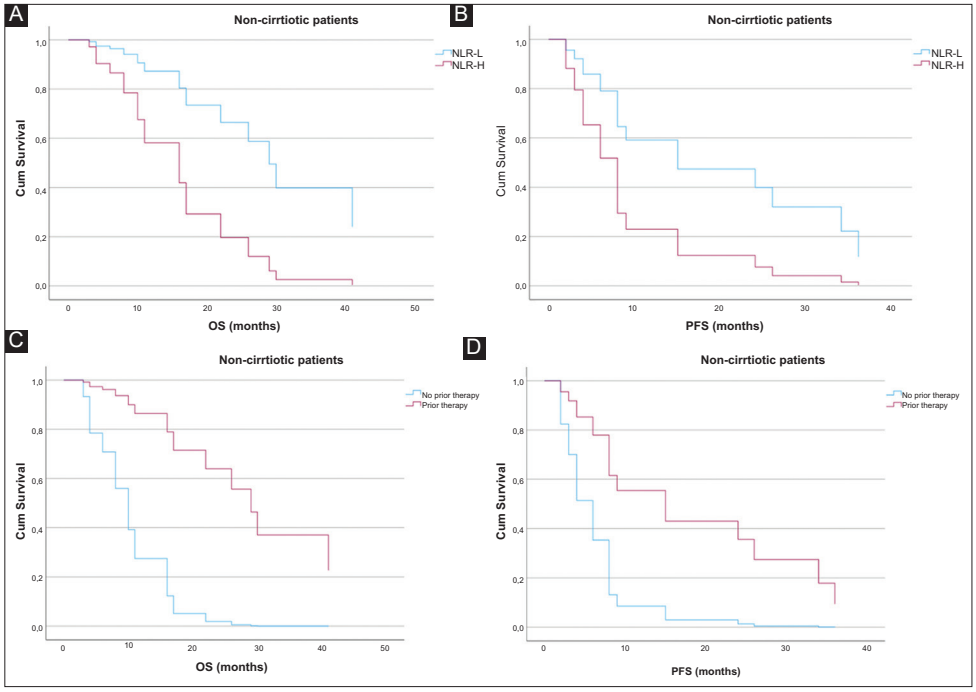
Supplementary Figure 5 (A) Cox regression analysis for OS in non-cirrhotic HCC patients according to prior therapy, after adjusting for all baseline parameters in which the 2 groups had statistically significant differences. (B) Cox regression analysis for PFS in non-cirrhotic HCC patients according to prior therapy, after adjusting for all baseline parameters in which the 2 groups had statistically significant differences

NLR, neutrophil-to-lymphocyte ratio; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; HR, hazard ratio



Supplementary Figure 6 (A) Cox-regression Kaplan–Meier curve for OS of cirrhotic patients at the mean of covariates using NLR (≤ 3 or > 3) as the grouping variable. (B) Cox-regression Kaplan–Meier curve for PFS of cirrhotic patients at the mean of covariates using NLR (≤3 or >3) as the grouping variable

OS, overall survival; PFS, progression-free survival; NLR-H, high NLR group; NLR-L, low NLR group



Supplementary Figure 7 (A) Cox-regression Kaplan–Meier curve for OS of non-cirrhotic patients at the mean of covariates using NLR (≤3 or >3) as the grouping variable. (B) Cox-regression Kaplan–Meier curve for PFS of non-cirrhotic patients at the mean of covariates using NLR (≤3 or >3) as the grouping variable. (C) Cox-regression Kaplan–Meier curve for OS of non-cirrhotic patients at the mean of covariates using prior therapy status as the grouping variable. (D) Cox-regression Kaplan–Meier curve for PFS of non-cirrhotic patients at the mean of covariates using prior therapy status as the grouping variable

OS, overall survival; PFS, progression-free survival; NLR-H, high NLR group; NLR-L, low NLR group