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Predictive Value of Peripheral Blood Markers in Hepatocellular Carcinoma Patients Treated with Anti-PD-1 in Combination with Targeted Therapy

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Abstract

Background: There are currently no recognised biomarkers that identify predictive groups of benefit in patients with hepatocellular carcinoma receiving immune-combined targeted therapy, for which we explored the value of peripheral blood markers as markers of their prognosis. **Methods:** Patients who underwent anti-PD-1 combination targeted therapy for hepatocellular carcinoma from 1 January 2019 to 31 December 2021 at the First Affiliated Hospital of Chongqing Medical University were retrospectively analysed. The data collected were analysed by R software. **Results:** A total of 41 cases were included in our study. The optimal threshold values of peripheral blood markers were obtained by plotting ROC curves and grouping patients. Survival analysis of the grouped patients showed statistically significant differences in survival between the different groups for Platelet-lymphocyte ratio (PLR, P = 0.0022), Monocyte-lymphocyte ratio (MLR, P = 0.042), Fibrinogen-Lymphocyte Ratio (FLR, P = 0.0009), Prognostic nutritional index (PIN, P = 0.0005), and Fibrinogen-albumin ratio (FAR, P = 0.0144). An ANOVA was performed on the basic conditions of the patients between the different groups, except for the statistically significant difference in BCLC stage (P = 0.0128) between the high MLR and low MLR groups, there was no statistically significant difference in age, gender, BCLC stage, and hepatitis status between the groups. COX regression analysis showed that BCLC stage, FAR, FLR and PIN were risk factors associated with the prognosis of patients receiving targeted combination immunotherapy for hepatocellular carcinoma, and FLR was an independent risk factor associated with the prognosis of patients receiving targeted combination immunotherapy for hepatocellular carcinoma. **Conclusions:** We found that peripheral blood markers are promising bio-

markers for predicting the prognosis of patients with hepatocellular carcinoma receiving anti-PD-1 combined with targeted therapy, and this study identified FLR as an independent risk factor for the prognosis of patients having advanced hepatocellular carcinoma treated with anti-PD-1 combined with targeted therapy.

Keywords

Hepatocellular Carcinoma, Immunotherapy, Targeted Therapy, Biomarkers, FLR

1. Introduction

Hepatocellular carcinoma (HCC) accounts for approximately 80% of all liver cancers and is often the leading cause of morbidity and mortality worldwide [1]. Although its incidence is increasing worldwide, targeted therapies and immunotherapy are becoming increasingly important in the treatment of hepatocellular carcinoma, with more and more patients benefiting from them as research into its pathogenesis progresses [2] [3]. In particular, the success of the phase III clinical trial of IMbrave150 has led to the combination of the two being the recommended first-line treatment modality for the systemic treatment of advanced hepatocellular liver cancer because of the higher survival benefit [4] [5]. However, as the treatment spreads, the side effects that occur during treatment and the high treatment costs that patients have to bear as a result of the treatment make it important to identify the benefit groups.

Peripheral blood biomarkers not only have the advantage of being non-invasive, but many studies have also shown their potential as prognostic indicators [6]. Myojin, Kodama [7] found that circulating Interleukin-6 (IL-6) levels were a marker of prognosis for treatment with Atezolizumab (Atezo) plus bevacizumab (Bev). Circulanting Tumor DNA (ctDNA) and Circulating Tumor Cells (CTCs) are both valuable in determining prognosis, but the development of these markers has been limited by their high cost and the need for multi-platform assistance [8].

The inflammatory and nutritional markers, which are easily accessible and can be measured repeatedly, are beginning to receive more attention because they are easier to use in the clinic [9]. Nakano, Kuromatsu [10] suggested that the neutrophil-lymphocyte ratio (NLR) could be used as a prognostic indicator in immunotherapy-based advanced hepatocellular carcinoma. Some studies have suggested that elevated preoperative Fibrinogen-Lymphocyte Ratio (FLR) levels are associated with poor prognosis in patients with hepatocellular carcinoma [11]. Other studies have shown that the platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR), Prognostic nutritional index (PIN), fibrinogen-albumin ratio (FAR) as predictors of the efficacy of immunotherapy or targeted

therapy in malignant tumours [12] [13] [14] [15]. Similar studies in patients with advanced hepatocellular carcinoma treated with immune combination targeted therapy have not been reported, and for this reason our study explored the predictive role of NLR, PLR, MLR, FLR, PIN, and FAR on their prognosis.

2. Methods

2.1. Patient Characteristics

Retrospective analysis of patients who underwent anti-PD-1 combination targeted therapy for advanced hepatocellular carcinoma at the First Affiliated Hospital of Chongqing Medical University from January 1, 2019 to December 31, 2021. Inclusion criteria: 1) Patients with a clinical diagnosis of hepatocellular liver cancer according to the guidelines [16] [17]; 2) Patients with a pathological diagnosis of hepatocellular liver cancer; 3) Patients with hepatocellular liver cancer who had failed first-line or above first-line systemic therapy or progressed or recurred with palliative surgery prior to the initiation of targeted combination immunotherapy; 4) patients with detailed medical history information. Exclusion criteria: 1) Patients with various types of co-infections; 2) Patients with concomitant other malignancies; 3) Women during pregnancy; 4) Patients with concomitant other lymphatic system diseases or malignant haematological diseases; 5) Patients with severe cardiovascular, cerebrovascular, renal and autoimmune diseases; 6) Patients with more missing clinical data and less complete data.

2.2. Clinical Data Collection

General information was collected on patients including gender, age, whether autoimmune disease or other underlying disease was combined, whether hepatitis was combined, child-pugh classification, Barcelona Clinical Liver Cancer (BCLC) stage, and whether pathological tissue biopsy results were available. Test parameters such as neutrophils, lymphocytes, monocytes, platelets, albumin and fibrinogen at the start of treatment and imaging results throughout the follow-up period were also collected. The imaging results during follow-up were assessed according to the response evaluation criteria in solid tumors (RECIST 1.1). Patients were followed up until the date of death or 31 December 2021.

2.3. Calculation of Peripheral Blood Markers

NLR is the ratio of neutrophil to lymphocyte values, PLR is the ratio of platelet to lymphocyte values, MLR is the ratio of monocyte to lymphocyte values, FLR is the ratio of fibrinogen to lymphocyte values, and FAR is the ratio of fibrinogen to albumin values. PIN is serum albumin (g/L) plus 5 times the peripheral lymphocyte count [18].

2.4. Statistical Analysis

Data for categorical variables are expressed as percentages and data for conti-

nuous variables are expressed as mean plus standard deviation (SD). The measurement data were analysed by ANOVA for differences between groups, while the count data were analysed by R*C table chi-square test. The optimal threshold values for NLR, PLR, MLR, FLR, PIN and FAR before PD-1 combination targeted therapy were calculated by subject operating characteristic (ROC) curves. Progression-free survival (PFS) was calculated from the start of drug administration to imaging documentation of disease progression or patient death. The Kaplan-Meier (KM) method was used to estimate survival in each group and survival curves were plotted, and KM curves were compared between groups using log-rank tests. Prognostic correlates were analysed by Cox regression analysis for univariate and multivariate regression. p-values less than 0.05 were considered statistically significant. All the above data were analysed and plotted using R software (version 3.5.3).

3. Results

3.1. Patient Profile

A total of 41 cases were included in this study and the general profile of all patients is shown in Table 1. The total number of male patients was 38 (92.7%) and the total number of female patients was 3 (7.3%). All patients were graded A in the child-pugh classification. The most common chronic liver disease was hepatitis B virus (HBV) infection in 37 cases (90.2%), followed by hepatitis C

Table 1. Baseline patient characteristics.

	All subjects	Stable disease	Partial response	Progression of disease	P value
Number (%)	41 (100)	13 (31.7)	10 (24.4)	18 (43.9)	
Age (y, Mean ± SD)	51 ± 11	53 ± 12	53 ± 8	49 ± 11	0.4514
Gender (%)					0.4504
Male	38 (92.7)	11 (84.6)	10 (100)	17 (94.4)	
Female	3 (7.3)	2 (15.4)	0 (0)	1 (5.6)	
Child-Pugh Class (%)					
A	41 (100)	13 (100)	10 (100)	18 (100)	
Hepatitis (%)					0.3873
Hepatitis B	37 (90.2)	11 (84.6)	9 (90)	17 (94.4)	
Hepatitis C	1 (2.4)	0 (0)	1 (10)	0 (0)	
None	3 (7.3)	2 (15.4)	0 (0)	1 (5.6)	
BCLC Stage (%)					0.051
B	15 (36.6)	6 (46.2)	6 (60)	3 (16.7)	
C	26 (63.4)	7 (53.8)	4 (40.0)	15 (83.3)	

Abbreviation: BCLC, Barcelona Clinical Liver Cancer Staging.

virus (HCV) infection in one case (2.4%) and three patients were not infected with hepatitis virus (7.3%). BCLC stage was grade C in 26 cases (63.4%) and 15 (36.6%) were grade B. According to patient follow-up results there were 13 patients (31.7%) with stable disease, 10 patients (24.4%) with partial response (PR) and 18 patients (43.9%) with progressive disease.

3.2. Optimal Threshold Values for Peripheral Blood Markers Prior to Anti-PD-1 Combination Targeted Therapy

The NLR, PLR, MLR, FLR, PIN and FAR values were calculated from the neutrophil, platelet, lymphocyte and monocyte count values as well as the fibrinogen and albumin values measured before the anti-PD-1 combination targeting therapy. The area under the curve for NLR was 0.6884, and its maximum Jorden index is 0.331 corresponding to a cut-off value of 2.10 (95% CI: 0.5199 - 0.8570). Similarly, the area under the curve for PLR was 0.7705, corresponding to a cut-off value of 72.33 (95% CI: 0.6249 - 0.9162). The area under the curve for MLR was 0.6932, corresponding to a cut-off value of 0.24 (95%CI: 0.5253 - 0.8612). The area of the curve for PIN is 0.7307, corresponding to a cut-off point of 52.18 (95% CI: 0.5711 - 0.8902). The area of the curve for FLR is 0.8019, corresponding to a cut-off point of 1.87 (95% CI: 0.6655 - 0.9384). The area of the curve for FAR is: 0.7246, corresponding to a cut-off value of 0.07 (95% CI: 0.5493 to 0.9000) (Figure 1).

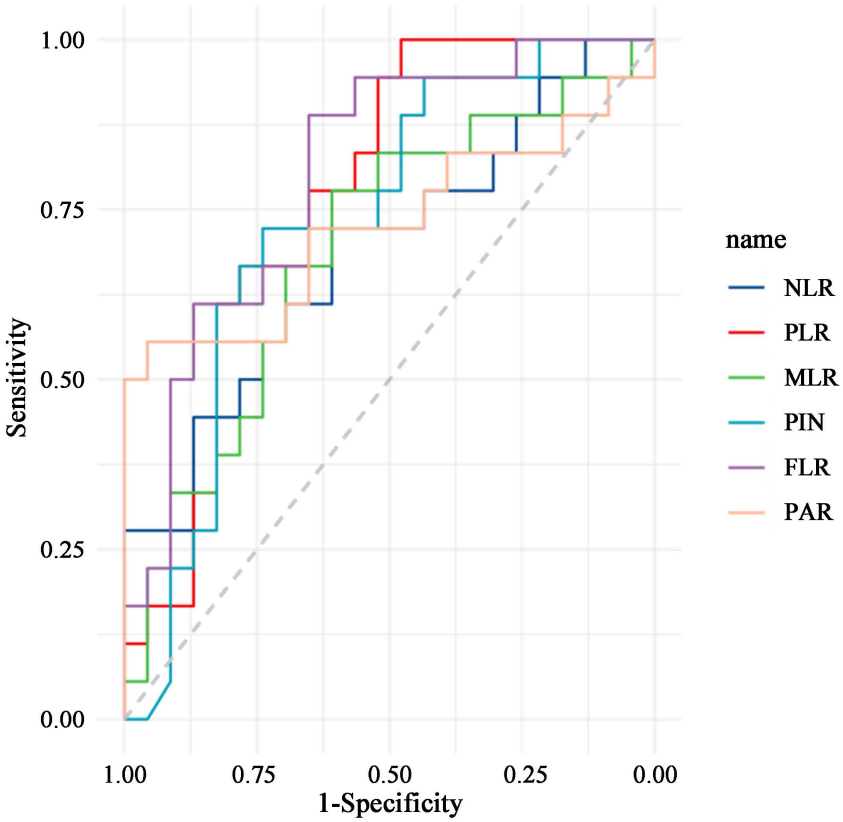

Figure 1. ROC curves for NLR, PLR, MLR, FLR, PIN, FAR.

Patients were divided into the following groups according to the cut-off values NLR ≥ 2.10 (high group), NLR < 2.10 (low group), PLR ≥ 72.33 (high group), PLR < 72.33 (low group), MLR ≥ 0.24 (high group), MLR < 0.24 (low group), PIN ≥ 52.18 (high group), PIN < 52.18 (low group), FLR ≥ 1.87 (high group), FLR < 1.87 (low group), FAR ≥ 0.07 (high group), FAR < 0.07 (low group).

3.3. Response to Treatment and Prognosis

The overall median survival time for the patients was 8 months and survival curves were plotted by the Kaplan-Meier method based on the above groupings (**Figure 2**). There were 23 patients in the high NLR group with a median survival time of 7 months and survival rates of 86.96%, 65.22% and 65.22% at years 1, 3 and 5, with no statistically significant difference compared to the low NLR group (p = 0.0869) (**Figure 2(A)**). There were 30 patients in the high PLR group with a median survival time of 6.5 months and survival rates of 86.67%, 56.67% and 56.67% at years 1, 3 and 5, with a statistically significant difference compared to the low PLR group (P = 0.0022) (**Figure 2(B)**). There were 24 patients in the high MLR group with a median survival time of 7 months and survival rates at years 1, 3 and 5 of 87.50%, 62.50% and 62.50%, a statistically significant difference compared to the low MLR group (P = 0.042) (**Figure 2(C)**). There were 19 patients in the low PIN group with a median survival time of 3 months and survival rates at years 1, 3 and 5 of 78.95%, 45.11% and 45.11%, a statistically significant difference compared to the high PIN group (P = 0.0005) (**Figure 2(D)**). There were 24 patients in the high FLR group with a median survival time of 4.5 months and survival rates at years 1, 3 and 5 of 83.33%, 50.00% and 50.00%, a statistically significant difference compared to the low FLR group (P = 0.0009) (**Figure 2(E)**). The high FAR group had 16 patients with a median survival time of 3 months and survival rates at years 1, 3 and 5 of 75.00%, 43.75% and 43.75%, a statistically significant difference compared to the low FAR group (P = 0.0144) (**Figure 2(F)**).

3.4. Analysis of Factors Associated with Progression-Free Survival in Advanced Liver Cancer

NLR, PLR, MLR, FLR, PIN and FAR were defined as dichotomous variables according to the above classification standards, and clinical information such as peripheral blood markers and gender and age were analysed by COX regression risk factor analysis in relation to the prognosis of patients with hepatocellular carcinoma who received combined treatment (**Table 2**). Based on the results, it was found that BCLC stage (RR = 3.6437 (95% CI: 1.0503, 12.6405), P = 0.0416), FAR (RR = 0.3382 (95% CI: 0.1282, 0.8919), P = 0.0284), FLR (RR = 0.1397 (95% CI: 0.0319, 0.6114), P = 0.009), and PIN (RR = 2.8424 (95% CI: 1.0068, 8.0245), P = 0.0485) were associated risk factors affecting progression-free survival in patients with liver cancer. Further multifactorial analysis revealed that FLR (RR = 0.1939 (95% CI: 0.0422, 0.8909), P = 0.035) was an independent risk factor for

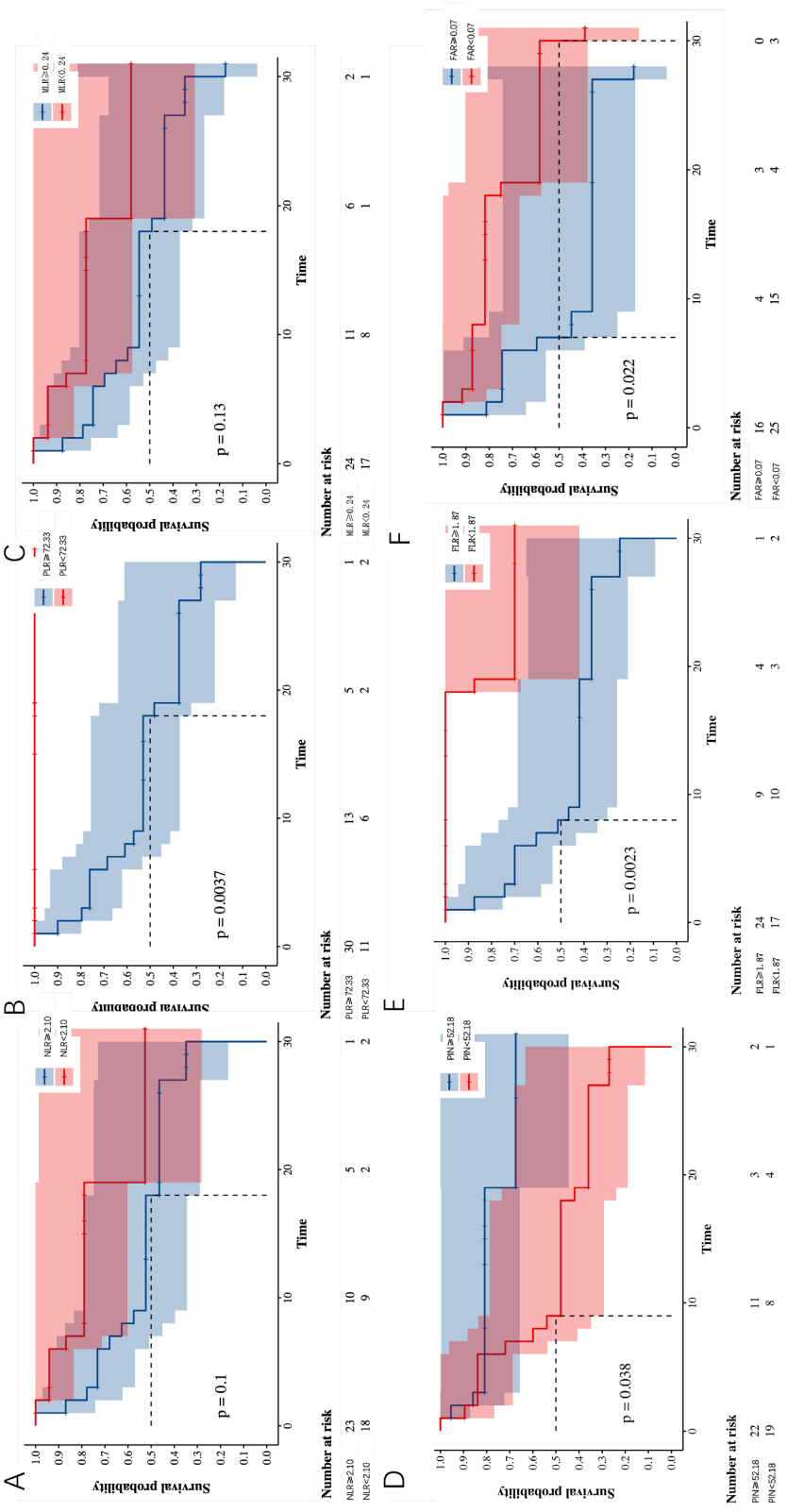

Figure 2. (A) Survival curves for high and low NLR groups; (B) Survival curves for high and low PLR groups; (C) Survival curves for high and low MLR groups; (D) Survival curves for high and low PIN groups; (E) Survival curves for high and low FLR groups; (F) Survival curves for high and low FAR groups.

progression-free survival in patients with hepatocellular carcinoma receiving anti-PD-1 combination targeted therapy (Table 3, Figure 3), and patients with hepatocellular carcinoma with FLR < 1.87 had a reduced risk of death relative to

Table 2. Univariate analysis of PFS in patients with hepatocellular carcinoma receiving combination therapy.

	P	RR (95%CI)
Sex, female	0.5714	1.8081 (0.2325, 14.0621)
Age	0.2496	0.9731 (0.9289, 1.0193)
BCLC stage, BCLC-C	0.0416	3.6437 (1.0503, 12.6405)
NLR, NLR < 2.10	0.1211	0.4398 (0.1557, 1.2424)
PLR, PLR < 72.33	0.9976	2.7207e−9 (0, Infinity)
MLR, MLR < 0.24	0.1467	0.4368 (0.1427, 1.3369)
PIN, PIN < 52.18	0.0485	2.8424 (1.0068, 8.0245)
FLR, FLR < 1.87	0.009	0.1397 (0.0319, 0.6114)
FAR, FAR < 0.07	0.0284	0.3382 (0.1282, 0.8919)

Abbreviations: BCLC, Barcelona Clinical Liver Cancer Staging; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; MLR, monocyte-lymphocyte ratio; PIN, Prognostic nutritional index; FAR, fibrinogen-albumin ratio; FLR, Fibrinogen-Lymphocyte Ratio.

Table 3. Multifactorial analysis of PFS in patients with hepatocellular carcinoma receiving combination therapy.

	P	RR (95%CI)
BCLC stage, BCLC-C	0.0791	3.1412 (0.8755, 11.2702)
PIN, PIN < 52.18	0.4211	1.5634 (0.5263, 4.6439)
FLR, FLR < 1.87	0.035	0.1939 (0.0422, 0.8909)
FAR, FAR < 0.07	0.4418	0.6701 (0.2416, 1.8587)

Abbreviations: BCLC, Barcelona Clinical Liver Cancer Staging; PIN, Prognostic nutritional index; FLR, Fibrinogen-Lymphocyte Ratio; FAR, fibrinogen-albumin ratio.

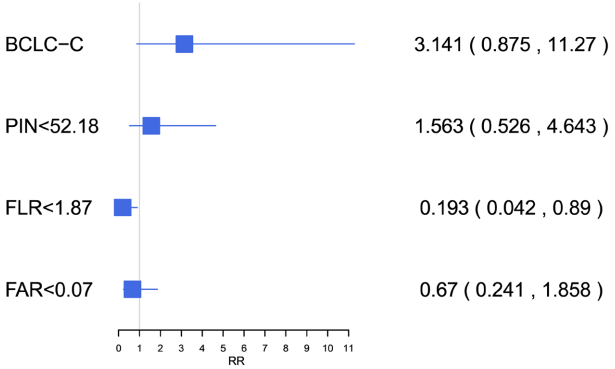

Figure 3.Multifactorial analysis of PFS in patients with hepatocellular carcinoma receiving combination therapy.

those with FLR ≥ 1.87 had an 80.610% lower risk of death.

4. Discussion

A growing number of studies have shown the close relationship between inflammation and tumours, and the development of HCC is similarly associated with chronic inflammation of the liver caused by infections and toxins [19] [20]. Fibrinogen is a glycoprotein produced by the liver that plays an important role in the progression of tumour cell invasion, proliferation and metastasis [21] [22]. Through the thrombin-fibrin (ogen) axis, fibrinogen mediates inflammatory cell activity, while its extravascular deposition exacerbates the inflammatory response [23]. It has been shown that plasma fibrinogen levels are positively correlated with the systemic inflammatory response and that elevated fibrinogen is associated with poor prognosis [24]. Therefore, elevated serum fibrinogen levels may reflect an active tumour microenvironment conducive to tumour progression.

Targeted combination immunotherapy is used to enhance the ability of T cells to attack tumour cells by reversing suppressed dendritic cells and their effector cells with VEGF inhibitors followed by PD-1 inhibitors, thus normalising the tumour microenvironment and allowing activated T cells to effectively attack tumour cells [25] [26]. With the better performance of immune-combined targeted therapy in the application to patients with hepatocellular carcinoma, progress has been made in the systemic treatment of advanced hepatocellular carcinoma, but patient survival rates remain low [27]. Biomarkers that can aid decision-making and guide the treatment of hepatocellular carcinoma are still very limited. The results of the statistical analysis in this study suggested that FLR ($P = 0.035$) was an independent risk factor affecting the prognosis of patients with hepatocellular carcinoma treated with anti-PD-1 combined with targeted therapy, and that patients with hepatocellular carcinoma with FLR < 1.87 had an 80.610% lower risk of death compared to those with FLR ≥ 1.87, with a statistically significant difference in survival curves between the two by grouping patients by FLR ($P = 0.0009$). This suggests that FLR is a new potential biomarker to predict the prognosis of patients with advanced hepatocellular carcinoma treated with anti-PD-1 in combination with targeted therapy. Microsatellite instability (MSI) is an FDA-approved biomarker for anti-pd-1 therapy in some advanced solid tumours, but its low frequency of expression in liver cancer limits its application [28] [29], and similarly the low expression of tumour mutational load (TMB) in liver cancer limits its application as a biomarker [30]. In contrast, FLR is easier to obtain and promote compared to the two aforementioned markers. However, this study also has some limitations. As a retrospective study, the patients were all from a single provider and the majority of patients had hepatitis B-related HCC (90.2%), which may have been subject to selection bias. Also the overall number of patients was small, leading to a possible sampling bias in the trial. Our results can be further validated in the future by

expanding the sample size to include multicenter data and by prospectively designed studies.

5. Conclusion

In conclusion, this study shows that peripheral blood markers are promising markers for predicting the prognosis of patients with hepatocellular carcinoma receiving anti-PD-1 combined with targeted therapy. The FLR was also found to be an independent risk factor for the prognosis of patients with advanced hepatocellular carcinoma receiving anti-PD-1 combination targeted therapy. The FLR has great potential as an easily available, non-invasive and cost-effective biomarker for prognosis prediction in patients with hepatocellular carcinoma, which can be a guide for clinical decision-making.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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