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Dynamic changes of systemic inflammatory markers and their association with radiologic progression and hepatotoxicity in patients with hepatocellular carcinoma on systemic therapy

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Abstract

Background: *Previous studies reported that inflammatory biomarkers could play a prognostic role in patients with unresectable hepatocellular Carcinoma (HCC) treated with sorafenib therapy, but there are no enough studies on new generations of systemic therapy.* ***Objectives:*** *The aim of this study was to evaluate dynamic changes of systemic inflammatory markers in patients with unresectable HCC on systemic therapy and to investigate their association* with *tumor behavior, drug hepatotoxic side effects and overall survival.* ***Subjects and methods****: This prospective study was carried out on 235 patients with unresectable HCC. Patients were divided into three groups based on type of systemic therapy: sorafenib group, atezolizumab-bevacizumab group, sequential TKI group (patients who received sorafenib then were shifted to regorafenib). CBC was followed up every month and the following ratios neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), monocyte count/lymphocyte count (MLR) and systemic inflammatory response index (SIRI) were calculated and analyzed.* ***Results:*** *A statistically significant increase in median MLR among Atezo-Bev group after 4 months (p=0.007) was observed, while among sorafenib group; MLR values increase significantly at 4, 8, 12 months (p<0.001, 0.05, 0.029 respectively). SIRI decreases after 4 months within sequential TKI group (p=0.006) and after 20 months within sorafenib group (p=0.006). PLR was higher among cases with radiologic progression than those without in sorafenib group (P= 0.006), while within Atezo-Bev group; higher NLR was associated with radiologic progression (P= 0.024). Moreover, NLR was higher in patients who develop hepatotoxic side effects due to sorafenib, atezolizumab-bevacizumab (P= 0.04, 0.012 respectively).* ***Conclusion:*** *Systemic inflammatory response markers may offer prognostic value for an optimized selection of patients with HCC who may benefit more from systemic therapy*

Introduction

Hepatocellular carcinoma (HCC) is the most prevalent type of liver cancer, representing about 90% of cases. It is the third leading cause of cancer-related deaths worldwide, with around 830,000 fatalities in 2020[1]. Treatment options for HCC include surgical resection, liver transplantation, local ablative treatments like radiofrequency ablation (RFA), locoregional therapies such as transarterial chemoembolization (TACE), and systemic therapies like Sorafenib, regorafenib, atezolizumab plus bevacizumab[2]. Sorafenib is an oral multikinase inhibitor approved for treating patients with unresectable HCC. It is considered the standard treatment for patients with advanced HCC in Child-Pugh class A or for those unable to undergo or who have failed locoregional therapies in the intermediate stage of the disease[3]. Additionally, Regorafenib, a new generation of multikinase inhibitors, has FDA approval as a second-line treatment for advanced HCC[4]. Recently, the combination of atezolizumab with bevacizumab (Atezo-Bev) has become the preferred first-line treatment, offering superior survival benefits compared to sorafenib[2]. As measured in peripheral blood samples, NLR (Neutrophil/Lymphocyte Ratio) and PLR (Platelet/Lymphocyte Ratio) were considered as indirect markers of systemic inflammatory response and have been evaluated as predictors of recurrence and survival in various malignancies[5,6]. Several meta-analysis studies suggested that high NLR and PLR are associated with an adverse overall survival (OS) in HCC patients undergoing liver transplantation, hepatectomy[7,8], combination treatment with TACE plus sorafenib[9] and unresectable HCC treated with sorafenib therapy[10,11]. But there are no enough studies on new generations of systemic therapy. So, the aim of this study was to evaluate dynamic changes of systemic inflammatory biomarkers in patients with unresectable HCC on systemic therapy with sorafenib, regorafenib, atezolizumab plus bevacizumab and to investigate their association with tumor behavior, drug hepatotoxic side effects and overall survival.

Patients and Methods

This prospective study was carried out on 235 patients with unresectable HCC (diagnosed by noninvasive criteria according to EASL guidelines 2004[12] on systemic therapy, recruited from both outpatient and inpatient clinics of Tropical Medicine Department, Mansoura University Hospital and followed up for two years. We performed pelviabdominal ultrasound as a screening method for focal hepatic lesions then HCC diagnosis was confirmed by triphasic CT and/or dynamic MRI if needed. Staging and determining appropriate line of treatment was chosen according to BCLC guidelines 2022[2]. Patients

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were divided into three groups based on the type of systemic therapy they received: sorafenib group, atezolizumab-bevacizumab group, and sequential TKI treatment group (patients who initially received sorafenib and were later switched to regorafenib).

Exclusion criteria

Patients with autoimmune diseases, malignancies other than HCC, active infection at the time of blood sampling, severe cardiac disease, severe renal impairment (GFR < 10 ml/min), or acute esophageal or gastric variceal bleeding were excluded from the study.

All patients included in this study underwent a comprehensive evaluation, which included a detailed medical history, thorough clinical examination, and standard laboratory tests such as complete blood count (CBC), liver function tests (including ALT, AST, albumin, and bilirubin), serum creatinine, INR, and tumor markers (such as Alpha fetoprotein). CBC was monitored monthly, and the following ratios were calculated using the formulas: NLR (neutrophil-to-lymphocyte ratio) = neutrophil count/lymphocyte count, PLR (platelet-to-lymphocyte ratio) = platelet count/lymphocyte count, MLR (monocyte-to-lymphocyte ratio) = monocyte count/lymphocyte count, and SIRI (systemic inflammatory response index) = neutrophil count × monocyte count/lymphocyte count. Overall survival (OS) was defined as the time from initiation of systemic therapy to death from any cause or last follow-up.

Follow up of the patients

In addition to monthly complete blood count (CBC) and calculation of NLR, PLR, MLR, and SIRI, we assessed the relationship between these inflammatory markers and radiologic progression, including tumor size increase, portal vein invasion, and extrahepatic metastasis, as well as hepatotoxic side effects such as elevated transaminases, increased bilirubin, ascites, hematemesis, and melena.

Ethical considerations

Every individual who was involved in the study signed a written informed consent form after approval from the Mansoura Faculty of Medicine's Institutional Research Board (IRB) Committee (code number: MS.23.03.2320). The research was conducted in accordance with the basics of the Helsinki declaration.

Statistical analysis

Data were collected and interpreted using SPSS (statistical package for social science) program for statistical analysis (version 25 Inc., Chicago. II). Quantitative variables were reported as mean ± standard deviation or median with interquartile range, while categorical variables were presented as absolute and relative frequencies. The appropriate statistical tests were used to analyze data. Wilcoxon signed rank test was used to detect differences between serial values of systemic inflammatory markers. Mann Whitney U test compared radiologic progression and adverse hepatotoxic side effects in each group. We used chisquare test to analyze categorical variabes. Kaplan-Miere Curve measured overall survival in each group. P value was considered statistically significant when less than 0.05.

Results

Table 1 presents the baseline characteristics of patients in the study, including the type of systemic therapy, age, sex, previous therapy for HCC. **Table 2** shows the comparison of change of systemic inflammatory markers among study groups. There were no statistically significant changes in the NLR median during the follow-up period compared to its baseline in the three groups. Similarly, no statistically significant changes in the median PLR during the follow-up period compared to the baseline value in the three groups, except for a statistically significant increase in median PLR in the sorafenib group at 12 and 16 months of follow-up**.** **Table 2** also, displays the MLR values in the study groups, with a significant increase in MLR values in the sorafenib group at 4, 8, and 12 months, and in the atezolizumab-bevacizumab group after 4 months. The sequential TKI group did not show any significant changes. In addition, a statistically significant decrease in SIRI median after 16 months in the sorafenib group and after 4 months in the sequential group, while the atezolizumab-bevacizumab group did not show any significant changes. **Table 3** illustrates the relationship between radiologic progression and inflammatory response markers among the study groups. In the sorafenib group, a significant association was observed between higher median PLR among cases with radiologic progression compared to those without (p=0.006), while SIRI, NLR, and MLR did not show any significant differences. In the atezolizumab-bevacizumab group, there was a statistically significant higher median NLR among cases with radiologic progression compared to those without, but no significant relationship was found with SIRI, PLR, and MLR. In cases with sequential TKI treatment, there were no significant differences in inflammatory response indices between patients with radiologic progression and those without. **Table 4** shows no significant difference in the frequency of hepatotoxic side effects (hepatitis, ascites, hematemesis, and melena) among the three groups of systemic therapy (p for all >0.05). In **Table 5**, patients who experienced hepatotoxic side effects from sorafenib and atezolizumab-bevacizumab had significantly higher NLR compared to those without such effects. However, there was no statistically significant association between these side effects and SIRI, PLR, and MLR in either group. In the sequential TKI group, there was no significant association between inflammatory response parameters and hepatotoxic adverse effects. In **Figure 1**; Kaplan-Miere curve compared effect of different lines of treatment on overall survival of the three groups which was (67% after 2 years in sorafenib group, 100% after 2 years in sequential TKI group, 100% after 8 months in Atezo-Bev group and **table 6** revealed no association between systemic inflammatory markers and the overall survival in sorafenib group.

Table 1: Baseline Characteristics of patients enrolled in the study.

	Number	Percentage
Type of systemic therapy		
▪ ***Sorafenib***	191	81.3%
▪ ***Atezolizumab plus Bevacizumab***	24	10.2%
▪ ***Sequential TKI therapy***	20	8.5%
Age		

▪ *40-50 years old*	40	17 %
▪ *50-60 years old*	155	66 %
▪ *>60 years old*	40	17%
Sex		
▪ *Male*	184	78.2 %
▪ *female*	51	21.7 %
Previous therapy		
▪ *TACE*	27	11.48 %
▪ *RF*	3	1.27 %
▪ *MWA*	2	0.85 %

Table 2: Comparison of change of systemic inflammatory markers among study groups.

	Sorafenib (N=191)	P value	Atezo-beva (N=24)	P value	Sequential TKI (N=20)	P value
NLR						
▪ *Baseline*	2.0 (0.21-15.85)	-	2.0 (1.02-7.22)		2.38 (0.21-4.29)	
▪ *4 months*	2.0 (0.66-24.55)	0.556	2.24 (1.0-11.37)	0.126	2.04 (0.76-6.91)	0.356
▪ *8 months*	2.0 (0.2-7.72)	0.791	2.18 (1.82-3.23)	0.715	2.43 (1.18-20)	0.163
▪ *12 months*	2.0 (0.2-5.13)	0.442	-	-	2.0 (1.17-3.75)	0.198
▪ *16 months*	2.0 (0.2-5.13)	0.159	-	-	1.89 (0.78-3.75)	0.173
▪ *20 months*	2.0 (0.69-9.81)	0.463	-	-	2.12 (1.18-3.0)	0.686
▪ *24 months*	1.84 (1.5-2.0)	0.138	-	-	2.70 (1.8-3.61)	0.655
PLR						
▪ *Baseline*	0.097 (0.01-1.04)	-	0.101 (0.03-0.28)	-	0.084 (0.02-0.14)	-
▪ *4 months*	0.107 (0.01-1.06)	0.144	0.103 (0.05-0.73)	0.823	0.099 (0.04-0.28)	0.286
▪ *8 months*	0.096 (0.02-0.39)	0.216	0.066 (0.05-0.12)	0.715	0.100 (0.05-0.18)	0.356
▪ *12 months*	0.105 (0.02-0.40)	0.01*	-	-	0.099 (0.03-0.14)	0.609
▪ *16 months*	0.129 (0.03-0.41)	0.001*	-	-	0.095 (0.05-0.21)	0.767
▪ *20 months*	0.109 (0.05-0.23)	0.056	-	-	0.114(0.04-0.23)	0.249
▪ *24 months*	0.053 (0.03-0.27)	0.686	-	-	0.064 (0.06-0.07)	0.180
MLR						
▪ *Baseline*	0.315 (0.03-1.7)	-	0.258 (0.06-0.49)	-	0.345 (0.04-3.85)	-
▪ *4 months*	0.400 (0.03-6.64)	<0.001*	0.385 (0.03-1.69)	0.007*	0.369 (0.19-0.91)	0.795
▪ *8 months*	0.387 (0.04-1.0)	0.05*	0.215 (0.18-1.17)	1.0	0.248 (0.06-0.57)	0.255
▪ *12 months*	0.40 (0.04-0.83)	0.029*	-	-	0.40 (0.09-0.83)	0.778
▪ *16 months*	0.40 (0.04-1.56)	0.098	-	-	0.245 (0.09-0.60)	0.214
▪ *20 months*	0.40 (0.12-1.27)	0.196	-	-	0.295 (0.25-0.90)	0.753
▪ *24 months*	0.333 (0.16-0.40)	0.225	-	-	0.363 (0.25-0.48)	0.655
SIRI						
▪ *Baseline*	2.12 (0.73-419)	-	1.66 (0.129-52.3)	-	2.14 (0.28-15.0)	-
▪ *4 months*	1.78 (0.77-35.6)	0.769	1.27 (0.87-16.6)	0.681	1.22 (0.154-10.5)	0.006*
▪ *8 months*	1.67 (0.837-145.0)	0.221	1.36 (0.4-3.07)	0.273	2.16 (0.76-9.76)	0.210
▪ *12 months*	1.86 (0.57-36.8)	0.226	-	-	2.7(0.1-16.9)	0.530
▪ *16 months*	1.19 (0.238-12.0)	0.001*	-	-	1.22 (0.24-2.4)	0.110
▪ *20 months*	1.16 (0.234-21.6)	0.221	-	-	0.955 (0.57-4.54)	0.075
▪ *24 months*	2.31 (1.06-4.85)	0.225	-	-	4.23 (3.83-4.63)	0.655

NLR: *neutrophil lymphocyte ratio;* ***PLR:*** *platelets lymphocyte ratio;* ***MLR:*** *monocyte to lymphocyte ratio;* ***SIRI:*** *systemic inflammatory index:* ***Used test:*** *Wilcoxon signed rank test;* ****:*** *statistically significant.*

Table 3: The relation between radiologic progression and inflammatory response markers among study groups.

	Sorafenib (191)			Atezo-beva (24)			Sequential TKI (20)		
	-VE radiologic progression (143)	+VE radiologic progression (48)	P value	-VE radiologic progression (17)	+VE radiologic progression (7)	P value	-VE radiologic progression (2)	+VE radiologic progression (18)	P value
NLR	2 (0.66-24.55)	2.17 (0.71-18)	**0.062**	2 (1-8.1)	4.28 (2-11.37)	**0.024***	1.93 (1.86-2)	2.15 (0.76-6.91)	**0.527**
PLR	0.096 (0.01-1.06)	0.126 (0.04-0.57)	**0.006***	0.096 (0.05-0.19)	0.125 (0.06-0.73)	**0.104**	0.068 (0.06-0.07)	0.121 (0.04-0.28)	**0.122**
MLR	0.4 (0.03-6.64)	0.4 (0.06-0.88)	**0.792**	0.37 (0.03-1.5)	0.40 (0.12-1.69)	**0.812**	0.494 (0.4-0.59)	0.348 (0.19-0.91)	**0.325**
SIRI	1012 (151-35836)	1060 (176 -9864)	**0.793**	915 (107-12150)	1220 (296-6709)	**0.251**	1265 (929-1600)	876 (397.13-3938.18)	**0.261**

Used test: *Mann Whitney U test *statistically significant*

Table 4: Comparison of hepatotoxic side effects among sorafenib, atezolizumab-bevacizumab and sequential TKIs groups

	Total	Sorafenib (24)	Atezo-beva (20)	Sequential TKI (191)	P value
Hepatitis (No/ %)	**77 (32.8%)**	**9 (37.5%)**	**7 (35.0%)**	**61 (31.9%)**	**0.840**
Ascites (No / %)	**75 (31.9%)**	**3 (12.5%)**	**9 (45%)**	**63 (33%)**	**0.054**
Hematemesis/ melena (No / %)	**23 (9.8%)**	**0 (0%)**	**2 (10%)**	**21 (11%)**	**0.232**

Used test: *Chi-Square test*

Table 5: The relation between hepatotoxic side effects and inflammatory response markers among sorafenib, atezolizumab-bevacizumab and sequential TKIs groups

	Sorafenib (191)			Atezo-beva (24)			Sequential TKI (20)		
	-VE side effects (101)	+VE side effects (90)	P value	-VE side effects (14)	+VE side effects (10)	P value	-VE side effects (10)	+VE side effects (10)	P value
SIRI	929 (157-5400)	1076 (151-35836)	**0.712**	907 (107-2286)	1233 (296-12150)	**0.082**	1246 (420-3938)	691 (397-1500)	**0.085**
NLR	1.86 (0 .67-18)	2.03 (0.66-24.55)	**0.04***	2 (1-2.5)	3.66 (1.47-11.37)	**0.012***	2 (1.47-6.91)	2.22 (0.76-3.33)	**0.825**
PLR	0.096 (0.01-1.06)	0.115 (0.02-1.02)	**0.177**	0.096 (0.05-0.19)	0.125 (0.06-0.73)	**0.05**	0.117 (0.06-0.28)	0.082 (0.04-0.22)	**0.895**
MLR	0.380 (0.03-1.13)	0.40 (0.04-6.64)	**0.667**	0.385 (0.03-1.14)	0.347 (0.12-1.69)	**0.570**	0.5 (0.19-0.91)	0.33 (0.22-0.51)	**0.102**

Used test: *Mann Whitney U test* ****:*** *statistically significant*

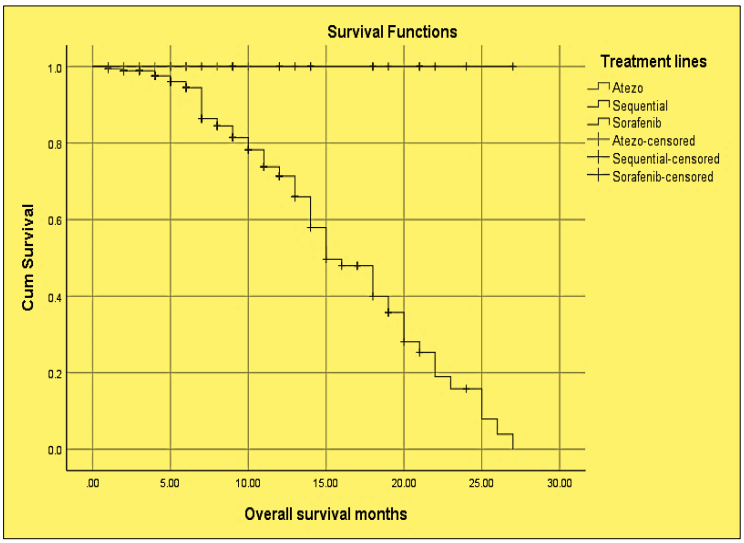

Figure 1: Kaplan-Miere Curve showing effect of different lines of treatment on overall survival of the studied cases

Table 6: The impact of NLR, PLR, MLR and SIRI on the survival of the cases studied on sorafenib based on the optimal cut-off point determined from the ROC curve.

	Median OS	Std. Error	95% Confidence Interval		Log rank χ2
			Lower Bound	*Upper Bound*	
NLR					
▪ ***< cut off (2.44)***	15.000	1.434	12.189	17.811	χ2=2.15 P=0.142
▪ ***> cut off (2.44)***	19.000	4.646	9.894	28.106	
▪ ***Overall***	16.000	1.298	13.456	18.544	
PLR					
▪ ***< cut off (0.097)***	14.0	.810	12.412	15.588	χ2=3.1 P=0.05
▪ ***> cut off (0.097)***	18.0	1.323	15.407	20.593	
▪ ***Overall***	16.0	1.298	13.456	18.544	
MLR					
▪ ***< cut off (0.097)***	15.0	1.301	12.450	17.550	χ2=0.569 P=0.451
▪ ***> cut off (0.097)***	18.0	2.037	14.007	21.993	

▪ ***Overall***	16.0	1.298	13.456	18.544	
SIRI					
▪ ***< cut off (1104.09)***	15.000	.821	13.391	16.609	$\chi 2=3.89$ P=0.05
▪ ***> cut off (1104.09)***	18.000	1.585	14.893	21.107	
▪ ***Overall***	16.000	1.298	13.456	18.544	

Discussion

Inflammation plays a significant role in the development of HCC[11]. Recent studies have highlighted the potential of inflammatory markers like NLR, PLR, MLR, and SIRI as prognostic indicators for cancer[12]. This study aims to evaluate systemic inflammatory response markers in various systemic therapies for HCC. The current study found no statistically significant change in the Neutrophil-to-Lymphocyte Ratio (NLR) throughout the systemic therapy for HCC in all study groups. Consistent with our findings, Zhu et al. observed no significant difference between basal NLR levels in patients with HCC who received Atezo-Bev therapy and their respective values after disease progression[13]. In contrast to these results, Liu et al, suggested that NLR can be a simple and effective biomarker for assessing systemic inflammation in HCC. HCC often develops in the presence of liver injury and inflammation. Elevated neutrophil levels indicate a response to systemic inflammation associated with tumor growth, while lymphocytes play a role in anti-tumor effects and immune function[14]. In our study, we observed no statistically significant change in the median of Platelet-to-Lymphocyte Ratio (PLR) throughout the systemic therapy for HCC in all study groups except, the sorafenib group exhibited a significant increase in PLR median after 12 and 16 months. A cohort study by Wang et al supports our findings, as it demonstrated no statistical difference in PLR values among 64 patients who received anti-PD-1 antibody and 144 patients who received TKIs combined with anti-PD-1 antibody[15]. Also, in line with our results, Zhu et al. reported no significant difference in PLR before and after anti-PD-1 therapy therapy[15]. Our results in sorafenib group cope with the well-known role of platelets in facilitating cancer progression invasion and metastasis[16]. While our results in Atezo-Bev group may be hindered by the short period of follow up. Regarding changes in MLR during follow-up, the present study showed a statistically significant increase in MLR median among the sorafenib group at 4, 8, and 12 months. In the Atezo-Bev group, there was an increase after 4 months. The Sequential TKI group did not show any significant changes. Typically, macrophages are classified into two main groups: classically activated macrophages (M1) and alternatively activated macrophages (M2)[17]. M1 macrophages are pro-inflammatory cells that have potent antimicrobial activities and improve T helper 1 (Th1) cell responses; however, M2 macrophages are immunosuppressive cells supporting T helper 2 (Th2)-associated effector functions[18,19]. Therefore, it is possible that the tumor microenvironment in anti-PD-1-treated HCC patients induces monocytes to differentiate into the M2 macrophage subgroup[20]. As regards changes in SIRI during follow-up, the current study showed a statistically significant decrease in SIRI median after 20 months in the sorafenib group and after 4 months in the sequential TKI group. The Atezo-Bev group did not exhibit any significant changes. The early decrease of SIRI in sequential group was associated with better prognosis and overall survival (survival was 100% after 24 months), on the contrary, a late decrease of SIRI in sorafenib group, was associated with a worse prognosis and short survival (survival was 67% after 24 months) indicating that SIRI change can be used as a prognostic tool in era of systemic therapy. In our study, it was found that in the sorafenib group, a higher PLR was associated with radiologic progression, while SIRI, NLR, and MLR did not show a significant association. In the Atezo-Bev group, a statistically significant higher NLR was observed in cases with radiologic progression compared to those without progression, but this progression was not correlated with SIRI, PLR, or MLR. In the sequential TKI group, no significant impact of inflammatory response indices on radiologic progression was detected. Shindoh et al revealed that NLR at a cut-off of 2.4 was an independent predictor of DFS (disease free survival), although it had poorer accuracy when compared to alpha fetoprotein (AFP) and des-gamma-carboxyprothrombin[21]. Liu et al reported that Lower NLR, MLR, or PLR was associated with earlier BCLC stage, fewer metastatic sites, less frequent extrahepatic metastasis, or better performance status. Furthermore, they found that a decrease in NLR, MLR, or PLR at Cycle 2 of immunotherapy was significantly associated with a higher disease control rate (DCR), favorable survival outcomes (both OS and PFS), and lower PLR was significantly associated with longer PFS[22]. A meta-analysis of 16 studies included 4654 HCC patients showed that high baseline NLR was significantly associated with poor prognosis or recurrence of HCC[23]. Although our results did not show an association of MLR with radiologic progression, Zhu and his team reported that MLR can predict the response to anti-PD-1 therapy. A high MLR is correlated with a shorter time to progression (TTP) in anti-PD-1-treated HCC patients[20]. Our study detected a significant increase in MLR after 4 months in Atezo-Bev group and after 4, 8, 12 months in sorafenib group and this partially agrees with zhu's study[20], but the small sample size in our study may hinder detecting significant association of MLR with radiologic progression. In the present study, we observed a statistically significant higher NLR among cases who developed heaptotoxic side effects from sorafenib or Atezo-Bev. Tada et al. demonstrated that patients with high NLR were more likely to experience adverse effects and discontinue atezolizumab-bevacizumab treatment. Conversely, Wu and colleagues reported no statistically significant difference in the incidence of treatment-related adverse events of any grade between patients with high or low NLR or PLR, but interestingly, patients with low NLR had a greater rate of grade 3 or higher adverse effects[24]. In our study, the overall survival rate was 33% for cases treated with sorafenib, while none of the cases treated with Atezo-Bev or sequential TKI died and this yields a statistically significant difference between overall survival of the three groups. We observed that there was no statistically

significant impact of low or high NLR, MLR, PLR, or SIRI on the median survival time of the sorafenib group. In contrast, a study by Zheng et al on sorafenib reported that a high baseline NLR (>4) was linked to poorer overall survival[25]. Two additional studies have shown that a low SIRI value is associated with improved survival outcomes in patients undergoing treatment with sorafenib for advanced HCC[26,27]. Zhu et al. concluded that SIRI was an independent prognostic factor for patients with HCC undergoing systemic therapy[15]. Furthermore, MLR can predict the response to sorafenib, with a high MLR being associated with shorter overall survival in patients with advanced HCC[28]. Elevated pre-treatment NLR, PLR, and MLR were linked to poorer survival outcomes in HCC patients following hepatic artery interventional therapy. Among them, NLR was an independent prognostic factor for overall survival at 30 days[30]. These discrepancies with our study could be attributed to small sample size and short duration of follow up in our study. Nevertheless, radiologic progression association with systemic inflammatory markers in our study is consistent with these results. Our study has some limitations. Firstly, the sample size of patients was relatively small, which may have made it challenging to identify certain prognostic factors for progression-free survival. Secondly, the follow-up period, particularly for the Atezo-Bev group, may not have been sufficiently long to accurately evaluate overall survival.

Conclusion

The findings of this research may offer useful hints for an optimized selection of patients with HCC who may benefit more from systemic therapy.

Acknowledgements and disclosures

The authors declare no conflict of interests related to this paper.

List of abbreviations

AFP: Alpha Feto Protein
Atezo-Bev: Atezolizumab-Bevacizumab
BCLC: Barcelona Clinic Liver Cancer
DCR: Disease Control Rate
DFS: Disease Free Survival
FDA: Food and Drug Administration
HCC: Hepatocellular Carcinoma
ICI: Immune checkpoint inhibitor
MLR: Monocyte /Lymphocyte Ratio
NLR: Neutrophil /Lymphocyte Ratio
OS: Overall survival
PD-1: Programmed death Protein 1
PFS: Progression Free Survival
PLR: Platelet /Lymphocyte Ratio
RFA: Radiofrequency Ablation
SIRI: systemic inflammatory response index= neutrophil count × monocyte count/lymphocyte count
TACE: Transarterial chemoembolization
TKI: Tyrosine Kinase Inhibitor
TTP: Time to Progression

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