Dynamic Changes of Peripheral Blood Markers Predict Prognosis of Patients with Advanced Non-Small Cell Lung Cancer Receiving Anti-PD-1/PD-L1 Treatment

Gaoyan Tang
Weifang People's Hospital
Yan Liu
Weifang People's Hospital
Qingyun Zhang
Weifang People's Hospital
Baohong Yang
Weifang People's Hospital
Yanhong Ding (yhding19861018@163.com)
Weifang People's Hospital
Guohua Yu
Weifang People's Hospital

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Abstract

Background Immune checkpoint inhibitors have been routinely used in the treatment of advanced non-small-cell lung cancer (aNSCLC) with significantly improved survival rate. However, the identification of reliable prognositic and predictive biomarkers is lacking. The aim of the study was to investigate the prognostic value of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) and their dynamic changes for aNSCLC.

Methods We retrospectively analyzed 60 patients with aNSCLC who received immunotherapy. The NLR and PLR were assessed at baseline (NLR0 and PLR0) and after 4 cycles of treatment (NLR4c and PLR4c).

Results Of all aNSCLC patients on immunotherapy, 47 (78.3%) cases were in the response group. Whether at baseline or after 4 cycles of treatment, the levels of NLR and PLR in the response group were both significantly lower than those in the non-response group ($p < 0.05$). Patients with a high NLR4c had poor progression-free survival (PFS) and overall survival (OS) independently in multivariate analysis (3.90 vs. 7.50 months, $p = 0.005$; 7.20 vs. 15.90 months, $p = 0.041$, respectively). Patients with high NLR0-highNLR4c were associated with poor PFS and OS ($p = 0.009$, $p = 0.001$ respectively). Results are similar for PLR.

Conclutions NLR after 4 cycles of treatment and dynamic changes of NLR and PLR during immunotherapy might help to predict a more accurate prognosis in aNSCLC patients.

Introduction

Immunotherapy has recently made a breakthrough in patients with advanced non-small cell lung cancer (aNSCLC). Immune checkpoint inhibitors (ICIs) targeting the programmed cell death 1(PD-1)/programmed cell death 1 ligand (PD-L1) axis have revolutionized cancer treatment and provided a new option for the treatment of aNSCLC 2. At present, the anti-PD-1 antibodies nivolumab and pembrolizumab have shown superiority with regards to overall response rates (ORR), overall survival (OS) and progression free survival (PFS) compared to chemotherapy for aNSCLC patients 3-5.However, the effective rate of ICIs alone in the unscreened NSCLC population is usually less than 20% 6, and 9%-29% patients experience rapid progression of the disease after immunotherapy 7. It has been shown that the OS of NSCLC patients who failed to respond to nivolumab is 1.4 months, while the patients who respond to treatment can reach 13.5 months 8. Besides, Immunotherapy is expensive and increases the social economic burden. Therefore, it is important to predict the therapeutic effect of ICIs, screen out patients who can benefit from immunotherapy 9, and maximize the efficacy of immunotherapy for the precise treatment of aNSCLC.

Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) can reflect the inflammatory level of the body 10. Several studies have shown that NLR and PLR are associated with patient prognosis in multiple solid tumors, such as gastric cancer 11, colorectal cancer 12, and NSCLC

13. And some studies have reported that preoperative detection of NLR and PLR levels has some predictive effect on postoperative recurrence in patients with early-stage NSCLC 14,15. However, Reports on the predictive value of NLR, PLR and especially their dynamic changes for the response of immunotherapy in patients with advanced NSCLC are researched rarely. In this study, we retrospectively analyzed the prognostic role of peripheral blood NLR and PLR in 60 patients with aNSCLC in terms of immune efficacy, progression-free survival (PFS) and overall survival (OS). Additionally, we also assessed the dynamics of NLR and PLR during immunotherapy.

Results

Clinical characteristics of patients

A total of 60 patients with aNSCLC treated with immunotherapy were included in this study. Baseline characteristics of patients can be seen in Table 1. Patients' median age was 63 (ranging from 30 to 77 years), with a higher proportion of current/former smokers (71.7%). ECOG was either 0 or 1 for 55 (91.7%) patients, 2 for 5 (8.3%) patients. 18 patients (30.0%) achieved partial response, 29 (48.3%) patients experienced stable disease, and 13 (21.7%) patients had progressive disease.

Table 1 Patients' characteristics at baseline and treatment response

Characteristics	No.of patients (n=60)	Percentage (%)
Gender		
Male	47	78.3
Female	13	21.7
Age (years)		
≤ 65	35	58.3
> 65	25	41.7
Smoking		
Never	17	28.3
Former/current	43	71.7
ECOG		
0-1	55	91.7
2	5	8.3
Actionable mutation		
(−)/undetected	43	71.7
EGFR or ALK/ROS1(+)	17	28.3
Histology		
Adenocarcinoma	39	65.0
Squamous cell carcinoma	21	35.0
No. of metastasis sites		
0	2	3.3
1	22	36.7
2	15	25.0
≥3	21	35.0
Immunotherapy applied in which line		
1	20	33.3
2	14	23.3
≥3	26	43.4
NLR0		

<3	22	36.7
≥3	38	63.3
NLR4c		
<3	38	63.3
≥3	22	36.7
PLR0		
<180	38	63.3
≥180	22	36.7
PLR4c		
<180	45	75.0
≥180	15	25.0
Change in NLR		
LowNLR0-LowNLR4c	16	26.7
LowNLR0-HighNLR4c	6	10.0
HighNLR0-LowNLR4c	22	36.6
HighNLR0-HighNLR4c	16	26.7
Change in PLR		
LowPLR0-LowPLR4c	30	50.0
LowPLR0-HighPLR4c	8	13.3
HighPLR0-LowPLR4c	15	25.0
HighPLR0-HighPLR4c	7	11.7
Best response		
CR	0	0.0
PR	18	30.0
SD	29	48.3
PD	13	21.7

ECOG, Eastern Cooperative Oncology Group; NLR0, neutrophil-to-lymphocyte ratio at baseline; NLR4c, neutrophil-to- lymphocyte ratio after 4 cycles of treatment; PLR0, Platelet-to-lymphocyte ratio at baseline; PLR4c, Platelet-to-lymphocyte ratio after 4 cycles of treatment; CR, Complete response; PR, Partial response; SD, Stable disease; PD, Progressive disease.

Comparison of NLR and PLR between the response and non-response group

Of all aNSCLC patients on immunotherapy, 47 (78.3%) cases were in the response group (18 cases PR, 29 SD). The levels of NLR0 in the response group and the non-response group were 3.9 (2.5, 4.6) and 5.2 (4.1, 5.8), respectively (p = 0.016) and PLR0 in these two groups were 153.8 (96.9, 192.2) and 229.2 (166.5, 270.5), respectively (p = 0.048). Besides, the levels of NLR4c and PLR4c in the response group were both significantly lower than those in the non-response group [NLR4c, 2.5 (1.5, 2.8) vs 6.2 (4.1, 7.0), p < 0.001. PLR4c, 124.2 (66.2, 159.8) vs 250.1 (145.0, 333.9), p = 0.002] respectively (Fig. 1).

NLR, PLR and other factors for PFS

We conducted a univariate analysis of NLR, PLR and other factors, as shown in Table 2. Age, NLR0, NLR4c, PLR0 and PLR4c were associated with PFS (Table 2, Fig.2). But in multivariate analysis, only NLR4c < 3 was significantly associated with longer PFS (hazard ratio [HR]: 0.452, 95% CI: 0.261-0.784, p = 0.005), while PLR0 had marginal significance (p = 0.052).

Table 2 Univariate and Multivariate Analysis for PFS

Variable	Univariate analysis PFS(months)	*p* value	95% CI	Multivariate analysis HR	*p* value	95% CI
Gender		0.134				
Male	7.40	6.864-7.936				
Female	6.90	3.462-10.338				
Age (yrs)		0.047		0.078		
≤ 65	7.40	6.820-7.980				
> 65	6.90	6.778-7.022				
Smoking		0.426				
Never	7.20	6.528-7.872				
Former/current	7.30	6.586-8.014				
ECOG		0.147				
0-1	7.20	6.764-7.636				
2	7.40	0.000-17.915				
Actionable mutation		0.987				
(−)/undetected	7.40	7.017-7.783				
EGFR or ALK/ROS1(+)	6.90	6.303-7.497				
Histology		0.728				
Adenocarcinoma	7.40	6.951-7.849				
Squamous cell carcinoma	6.90	6.222-7.578				
No. of metastasis sites		0.859				
0	7.90					
1	7.10	6.443-7.757				
2	5.00	1.213-8.787				
≥3	7.40	6.733-8.067				
Immunotherapy applied in		0.333				

which line				
1	7.40	6.743-8.057		
2	7.20	5.367-9.033		
≥3	6.90	0.315-6.283		
NLR0		0.079		0.149
<3	7.90	7.649-8.121		
≥3	6.80	6.199-7.401		
NLR4c		0.003	0.261-0.784	0.005
<3	7.50	7.097-7.903	0.452	
≥3	3.90	3.674-4.126	1	
PLR0		0.012		0.052
<180	7.60	7.117-8.083		
≥180	6.40	4.929-7.871		
PLR4c		0.013		0.135
<180	7.40	7.138-7.662		
≥180	5.00	2.633-7.367		

NLR, PLR and other factors for OS

The OS was estimated using the Kaplan-Meier method, and the results were compared across groups using the log-rank test. Patients' age, NLR4c and PLR0 were found to be significantly associated with OS (Table 3, Fig.3). However, in multivariate analysis, age ≤ 65 and NLR4c < 3 were significant prognostic factors for OS (HR: 0.310, 95% CI: 0.168-0.573, p < 0.001, HR: 0.393, 95% CI: 0.170-0.542, p < 0.001, respectively).

Table 3 Univariate and Multivariate Analysis for OS

Variable	Univariate analysis OS(months)	95% CI	Multivariate analysis	
		p value	HR	95% CI *p* value
Gender		0.235		
Male	15.30	14.404-16.196		
Female	13.60	5.967-21.233		
Age (yrs)		<0.001	0.168-0.573	<0.001
≤ 65	15.90	14.393-17.407	0.310	
> 65	12.80	12.310-13.290	1	
Smoking		0.916		
Never	14.30	12.821-15.779		
Former/current	14.90	13.101-16.699		
ECOG		0.140		
0-1	14.90	13.656-16.144		
2	28.40	0.000-74.562		
Actionable mutation		0.978		
(−)/undetected	15.10	12.659-17.541		
EGFR or ALK/ROS1(+)	14.80	13.859-15.741		
Histology		0.919		
Adenocarcinoma	15.10	12.558-17.642		
Squamous cell carcinoma	14.80	13.087-16.513		
No. of metastasis sites		0.985		
0	15.30	-		
1	14.00	11.357-16.643		
2	11.70	1.349-22.051		
≥3	15.10	14.053-16.147		
Immunotherapy applied in which line		0.364		
1	15.60	13.847-17.353		

2	15.70	13.317-18.083		
≥3	13.60	11.976-15.224		
NLR0		0.544		0.363
<3	14.30	11.887-16.713		
≥3	14.90	13.392-16.408		
NLR4c		<0.001	0.170-0.542	<0.001
<3	15.90	14.450-17.350	0.393	
≥3	7.20	6.281-8.119	1	
PLR0		0.034		0.086
<180	15.60	14.996-16.204		
≥180	11.70	6.874-16.526		
PLR4c		0.065		0.521
<180	15.50	14.514-16.486		
≥180	12.60	4.016-21.184		

Relationship of dynamic changes of NLR and PLR with immune efficacy

Statistical analysis showed that 100% (37/37) of patients with low NLR0-low NLR4c and 100% (5/5) of patients with high NLR0-low NLR4c were both in the response group. However, the proportion of patients with high NLR0-high NLR4c and low NLR0-high NLR4C in the non-response group were 61.5% (8/13) and 100% (5/5), respectively (supplementary table S1). After analysis, the immune efficacy of patients with low NLR0-low NLR4c and high NLR0-low NLR4c was significantly better than that of patients with high NLR0-high NLR4c and low NLR0-high NLR4c ($p < 0.001$), and the relationship between PLR dynamic changes and immune efficacy was similar to that of NLR dynamic changes ($p < 0.001$).

Relationship of dynamic changes of NLR and PLR with survival outcomes

We examined the effects of NLR and PLR changes after initial treatments, wherein the PFS and OS were analyzed according to the change in NLR or PLR. Kaplan–Meier analysis revealed that patients with low

NLR0-low NLR4c showed a significantly longer PFS and OS. Compared with a median PFS of 7.90 months for patients with low NLR0-low NLR4c, patients with high NLR0-high NLR4c had the worst PFS (median PFS 3.80 months) (p = 0.009) (Fig.4a). Analyses according to PLR showed similar results (Fig.4b). In addition, patients with high NLR0-high NLR4c had the shortest survival (p = 0.001) and patients with high PLR0 -high PLR4c also had the shortest survival (although p = 0.075) (Fig. 4c and Fig.4d).

Discussion

Immunotherapy has provided substantial benefit in NSCLC with unprecedented results in terms of overall in both first- and second-line therapies. Screen patients who benefit from immunotherapy accurately and thereby achieve more accurate individualized immunotherapy. So it is significant to find biomarkers for predicting the efficacy of immunotherapy.

Immune microenvironment in cancer patients is very complex, and the inflammatory response of the body is important for the occurrence and development of tumors 15. The immune microenvironment in which tumor cells are located infiltrates a large number of inflammatory cells, including neutrophils, lymphocytes, platelets, and natural killer cells. Neutrophils, as the main inflammatory cells, can secrete vascular endothelial growth factor, which promotes the generation of tumor blood vessels. Besides, neutrophils can inhibit activated T lymphocytes, and further weaken the anti-tumor immune response. Many studies have found that neutrophils are closely related to the occurrence and development of tumors in multiple systems of the human body, such as renal cancer, gastric cancer, esophageal cancer, and lung cancer 16-19. Lymphocytes, especially tumor-infiltrating lymphocytes (TILs), play a central role in specific tumor immune responses. TILs are critical in forming the immune environment which is considered to be the "seventh major labeling feature" of tumors 20. As the main exerciser of cellular immunity, lymphocytes play a major anti-tumor immune effect in cancer patients 21. Platelets can produce platelet-derived endothelial growth factor and transforming growth factor-β, which contribute to the growth of tumor cells, and platelets in circulating blood can form polymers with circulating tumor cells (CTCs), allowing CTCs to achieve immune escape and ultimately leading to tumor metastasis 22. Thus, having high NLR and PLR, with a high neutrophil or platelet count and/or low lymphocyte count can contribute to poor prognosis in a variety of cancers.

NLR is considered to be an important indicator of prognosis in many diseases, including the prognosis of chronic obstructive pulmonary disease and silicosis 23-25. Meanwhile, NLR and PLR have also been used as a predictor of malignant tumor prognosis 26-28. Diem et al. found in patients with metastatic NSCLC treated with nivolumab, elevated pretreatment NLR and PLR were associated with shorter OS and PFS as well as reduced response rates, regardless of other prognostic factors 29. Our study found high PLR at baseline was also an independent prognostic factor for PFS and OS in univariate analysis, but NLR at baseline was not significantly associated with prognosis, which was consisted with previous reports 30,31. Besides, we found that both NLR before and after 4 cycles of treatment were related to the efficacy of immunotherapy (p < 0.05), but the relationship between NLR after 4 cycles of treatment and efficacy

was more significant ($p < 0.001$). The relationship between PLR and efficacy was similar to that of NLR. Further, we demonstrated that the NLR after 4 cycles of treatment better reflect the prognosis than the NLR at baseline, however, PLR at baseline seemed to be more closely related to PFS and OS than posttreatment PLR. In our study on multivariable analysis, only NLR after 4 cycles of treatment was strongly associated with survival and could be used as a more accurate predictor for prognosis.

NLR and PLR are conveniently accessible in the clinic, display high reproducibility, and their dynamic changes are easy to observe. Dynamic changes of NLR and PLR are related to the survival of patients with tumors 32-34. In our study, we analyzed the dynamic changes of NLR and PLR during immunotherapy and found patients with low NLR at baseline and low NLR after 4 cycles of treatment (low NLR0-low NLR4c) had the best immune efficacy and NSCLC patients with high NLR0-low NLR4c had similar efficacy to the former. However, patients with high NLR0-high NLR4c had poor immune effect. The immune efficacy of NSCLC patients with low NLR0-low NLR4c was better than that of patients with high NLR0-high NLR4c. The prediction of immune efficacy by dynamic changes of PLR is similar to the dynamic changes of NLR. Therefore, the dynamic changes of NLR and PLR before and after treatment are related to the efficacy of immunotherapy.

In summary, we found that repeated mesaurements of NLR and PLR have greater value in assessing treatment efficacy. We choose at baseline and after 4 cycles of treatment as the time point and found that NLR after 4 cycles of treatment was a more accurate prognostic predictor. Systemic inflammation represented by NLR and PLR predicts the PFS and OS of patients with advanced NSCLC who are receiving immunotherapy. In addition, dynamic changes of NLR and PLR during immunotherapy might be useful to predict post-treatment prognosis in advanced NSCLC and tailor the therapy after.

Our study has several limitations. First, NLR and PLR can reflect the inflammatory changes of immune microenvironment, but the mechanism of their prediction of efficacy and prognosis is still unclear. At present, the most prominent problem in many related clinical studies is that there is no uniform standard for the cut-off values of NLR and PLR, and a large sample of prospective clinical studies are needed for more in-depth exploration in the future. Second, this study is a single-center, small-sample clinical study, which may have influence on the conclusion, so studies with large sample size are still needed to further explore its relationship with the prognosis. Anyway, the detection of NLR and PLR is simple, cheap and has high patient compliance. their changes before and after immunotherapy in patients with advanced small cell lung cancer are related to the therapeutic efficacy, which may be a predictor of disease control and a biomarker to predict the prognosis. It has the value of further exploration and research and is worthy of being widely popularized in clinical practice.

Methods

Ethical approval of study

A retrospective, single-center cohort study was conducted in accordance with the guidelines for good clinical practice (GCP) and the declaration of Helsinki for experiments involving humans. The study was

approved by the ethical committee of Weifang Medical University, Weifang, China (reference number 2020YX034) and all patients had signed the informed consent.

Participants and clinical treatment

Sixty patients with aNSCLC who underwent immunotherapy in the Department of Oncology, Weifang People's Hospital from January 2018 to May 2019 were selected. The inclusion criteria were as follows: age over 18 years; patients with histologically or cytologically diagnosed NSCLC; clinical stage IIIB or IV; The Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score 0-2. Exclusion criteria: patients with acute cardiac disease or chronic underlying diseases, which may interfere with the treatment after evaluation; patients with severe liver and kidney function damage; patients in the terminal stage, who cannot tolerate immunotherapy; patients with autoimmune system diseases. The clinical data of patients were collected and recorded, including age, gender, clinical stage, pathological type, EGFR gene mutation detection, etc. Nivolumab was administered at a dose of 3 mg/kg i.v. every 14 days. Pembrolizumab was administered at a dose of 2 mg/kg i.v. every 21 days. Sintilimab and Tislelizumab were administered at a dose of 200 mg i.v. every 21 days and Camrelizumab was administered at a dose of 200 mg i.v. every 14 days.

Evaluation

Radiological imaging performed before the start of ICIs and during treatment was reviewed. The efficacy was evaluated according to the WHO evaluation criteria for solid tumors 1.1 (RECIST1.1). The evaluation includes complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Patients with CR or PR or SD were defined as clinical response, while patients with PD were defined as non-clinical response.

Hematological parameters

The neutrophils count, lymphocytes count and platelets count at baseline and after 4 cycles of treatment were collected, respectively. The values of NLR and PLR were calculated as follows: NLR = peripheral blood neutrophil count/lymphocyte count, PLR = peripheral blood platelet count/lymphocyte count. The prespecified cutoff values were NLR $\geq$ 3 (high NLR) versus < 3 (low NLR) 13 and PLR $\geq$ 180 (high PLR) versus < 180 (low PLR) 35.

Survival times

PFS was defined as the time from anti-PD-1/PD-L1 antibody initiation to disease progression or death due any cause, and OS was defined as the time from anti-PD-1/PD-L1 antibody initiation to the last follow-up or death, whichever came first.

Statistical analysis

SPSS 26.0 statistical software was used for data analysis. Normally distributed measurement data were expressed as Mean ± SD using t test and measurement data with non-normal distribution were expressed by Md (P25, P75) using two independent sample rank sum test. Enumeration data were expressed as percentages using the chi-square test. In addition, the OS and PFS were assessed and compared using the Kaplan–Meier method and the log-rank test. Multivariate analysis for PFS and OS were performed using the variables that were significant on univariate analysis. $p < 0.05$ was considered statistically significant.

Declarations

Data Availability statement

The data used to support the findings of this study are available from the corresponding author upon request.

Author contributions

GYT and GHY conceived the idea, developed the theory and interpreted the results. GYT drafted the manuscript. YL and QYZ carried out the data collection. BHY conducted the statistical analysis. YHD revised the manuscript. All authors discussed the results and contributed to the final manuscript.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Figures

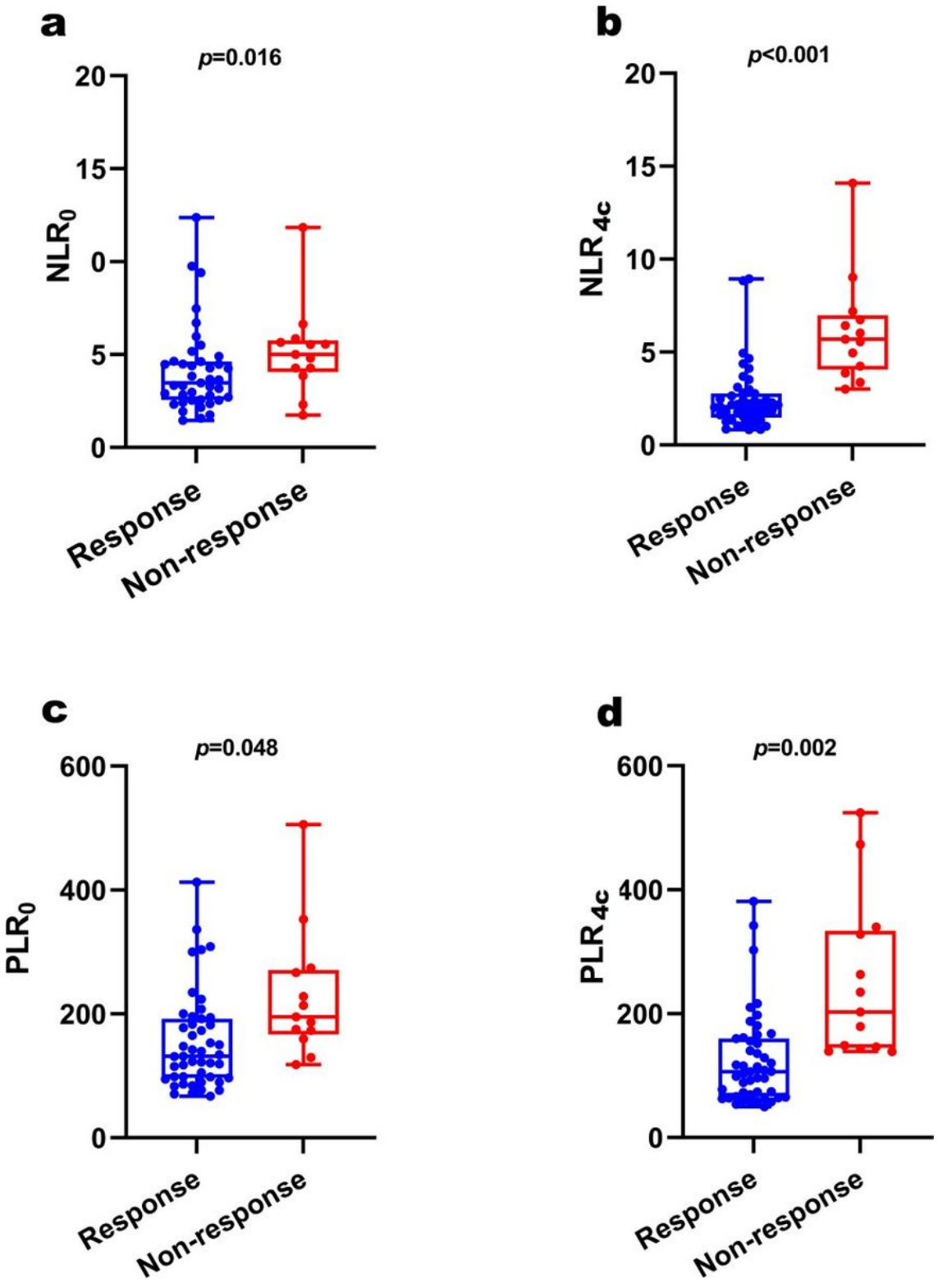

Figure 1

The distribution of NLR and PLR in the response and non-response group. **a** The distribution of NLR0 in two groups. **b** The distribution of NLR4c in two groups. **c** The distribution of PLR0 in two groups. **d** The distribution of PLR4c in two groups

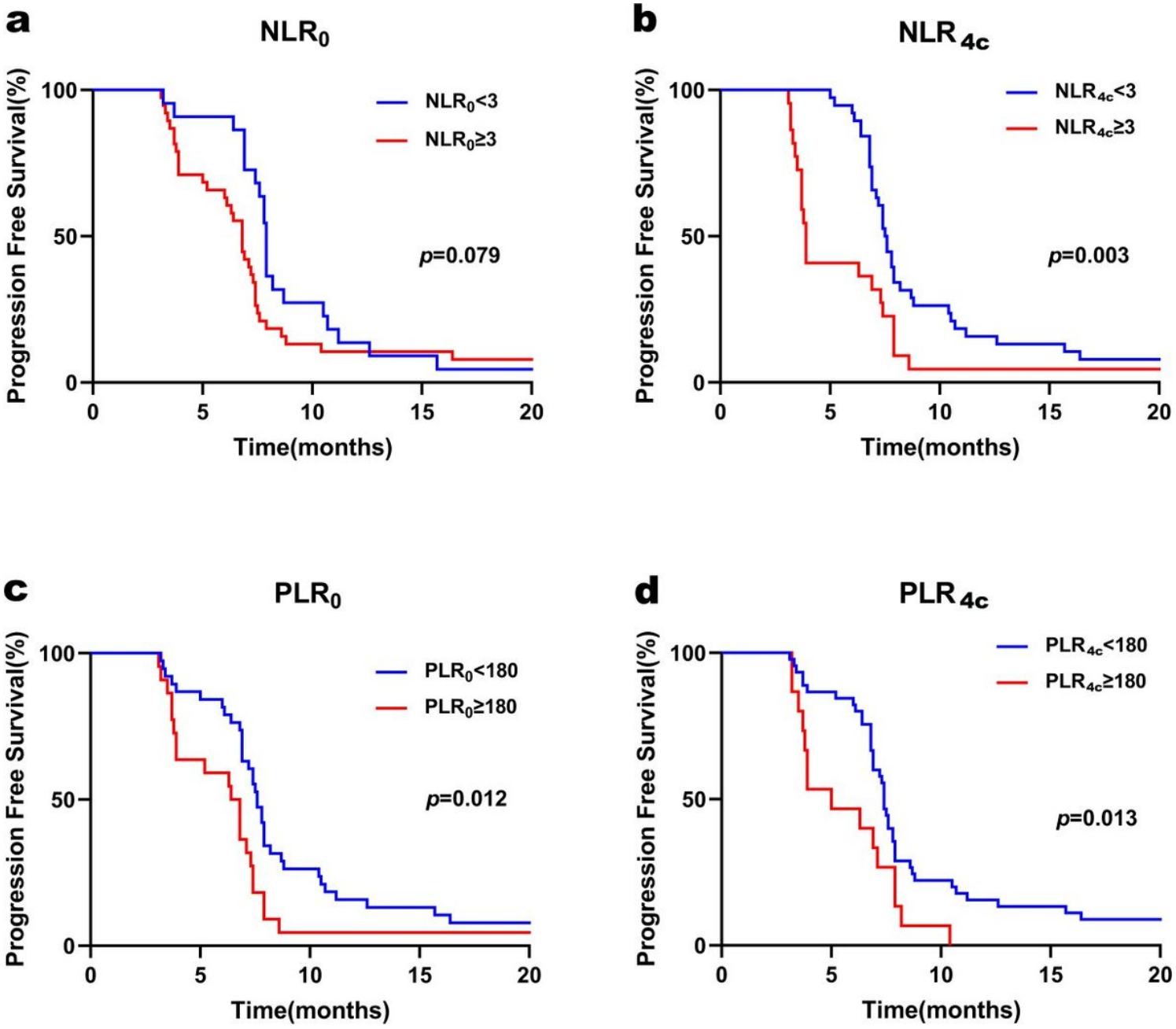

Figure 2

Kaplan-Meier curves for PFS according to NLR0 (**a**), NLR4c (**b**), PLR0 (**c**) and PLR4c (**d**)

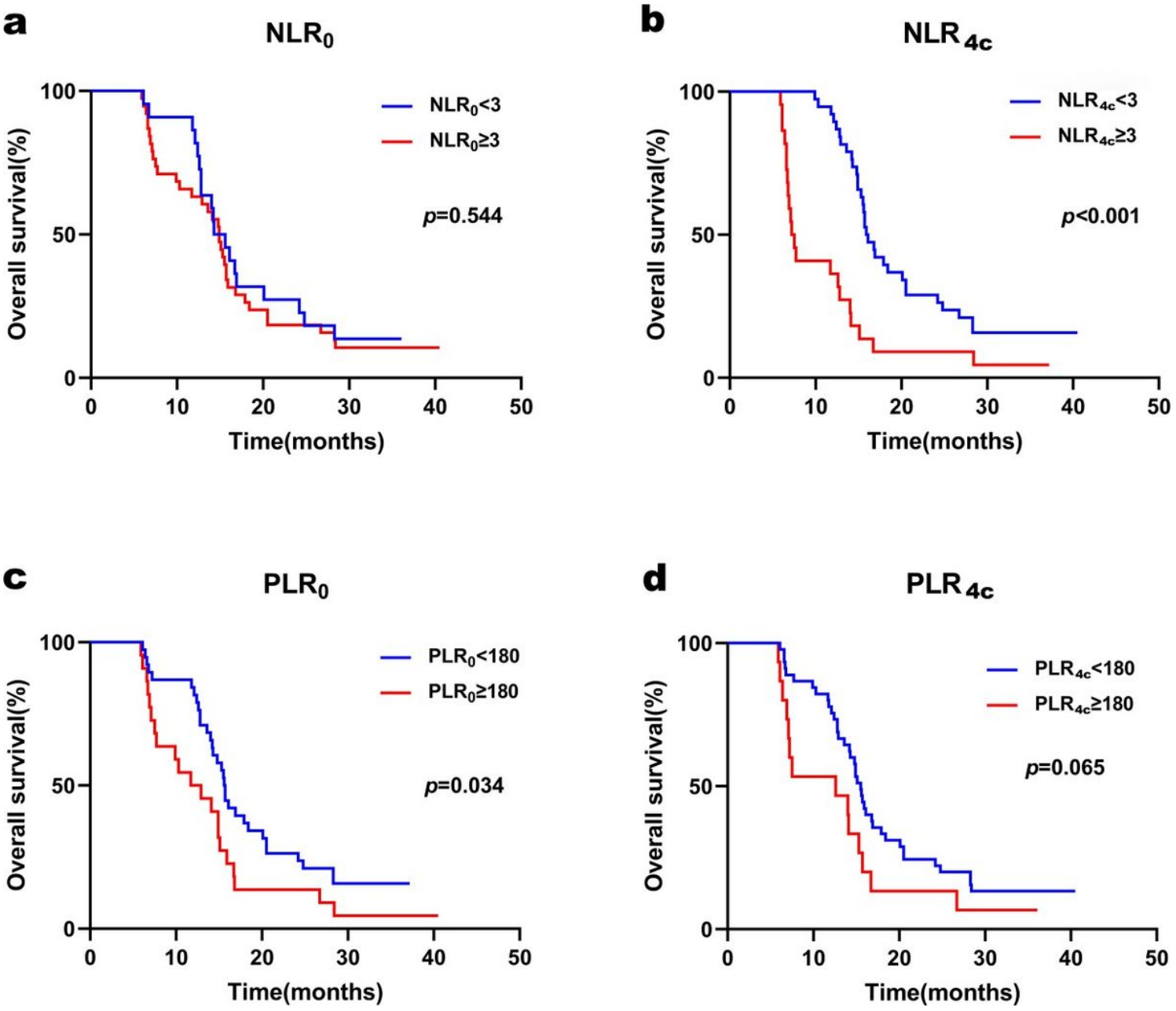

Figure 3

Kaplan-Meier curves for OS according to NLR0 (**a**), NLR4c (**b**), PLR0 (**c**) and PLR4c (**d**)

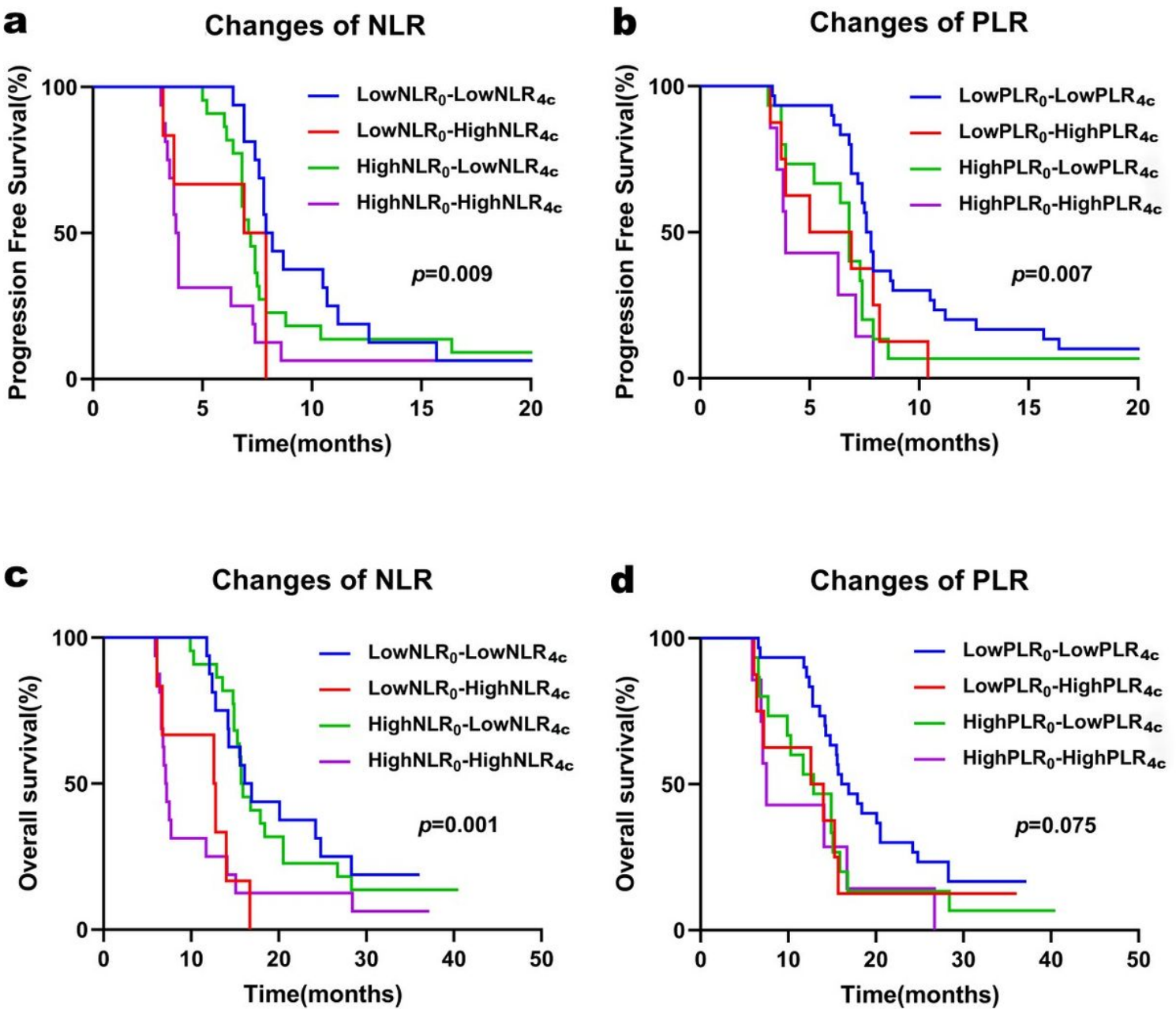

Figure 4

Kaplan-Meier curves for PFS and OS according to dynamic changes of NLR and PLR. **a** Dynamic changes of NLR for PFS. **b** Dynamic changes of PLR for PFS. **c** Dynamic changes of NLR for OS. **d** Dynamic changes of PLR for OS

Supplementary Files

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