

# Absolute Eosinophil Count May be One of the Most Optimal Peripheral Blood Markers to Identify Risk of Immune-Related Adverse Events in Advanced Malignant Tumors Treated with PD-1/PD-L1 Inhibitors.

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# Abstract

**Background** To investigate the predictive value of serum biomarkers such as AEC, Neutrophil-lymphocyte ratio (NLR) and platelets - lymphocyte ratio (PLR) on immune-related adverse events (irAEs) during the PD-1/PD-L1 inhibitors treatment in advanced malignant tumors. **Methods** We retrospectively analyzed 95 advanced cancer patients treated with PD-1/PD-L1 inhibitor from January 1, 2017 to May 1, 2020 in our cancer center. Then, the associations between irAEs and PD-1/PD-L1 inhibitors response was analyzed and the predictive value of serum biomarkers on irAEs occurrence risk was evaluated. **Results** The incidence of irAEs was 55.8%. There were no statistically significant differences between the irAEs group and the no-irAEs group in Objective response rate (ORR) and Disease control rate (DCR), but the Landmark analysis showed that the irAEs group had better survival after 120 days compared with the no-irAEs group. The incidence of irAEs in the high-AEC and low-NLR groups was greater than that in the low-AEC and high-NLR groups. Univariate logistic analysis results showed that low-NLR, ECOG (0-1) and High-AEC were risk factors for irAEs. However, multivariate logistic analysis not only shows that AEC is an independent factor of irAEs, but also suggests that good ECOG may be more prone to irAEs. **Conclusions** IrAEs may show a survival benefit to a certain extent. Baseline AEC is a strong predictor of irAEs in the treatment of PD-1/PD-L1 inhibitors.

## 1. Introduction

Immune checkpoint inhibitor (ICIs), represented by PD-1/PD-L1, has been widely used in many advanced malignant tumors, with significant and sustained efficacy, and has a strong impact on traditional treatment status such as chemotherapy and targeted therapy(1–5). While focusing on its good curative effect, the concomitant immune-related adverse reactions should not be ignored.

IrAEs is broadly defined as immune-mediated host organ dysfunction caused by abnormal immune system activity following immunotherapy(6). It is most common in the skin, thyroid, and gastrointestinal tract, but any organ or system, including the heart, lungs, liver, and pituitary gland, may be involved (7). IrAEs is usually easy to manage, but about 10% of cases are so severe that ICIs therapy needs to be discontinued or even treated with hormone or immunosuppressive agents (8, 9). In some cases, irAEs can lead to permanent illness, with about 1% of cases potentially fatal (10). It is important to note that irAE can occur at any point in time, including months after withdrawal (11).

Given the above characteristics of irAEs, its diagnosis and prediction are particularly challenging. Peripheral blood markers such as AEC, NLR, PLR have attracted the attention of many scholars due to their non-invasive, rapid, relatively stable and low price characteristics. It has been reported that NLR and PLR can effectively predict irAEs occurrence of PD-1/PD-L1 inhibitors in non-small cell lung cancer (12, 13). Increased NLR was associated with an increased risk of grade 3–4 pulmonary and gastrointestinal irAEs(14). Moreover, eosinophils in peripheral blood were also associated with irAEs(15),and then increased eosinophils at baseline and 1 month were associated with an increased overall irAEs risk of

grade 2 and above(14). Baseline characteristics of high AEC ( $0.125 \times 10^9/L$ ) were associated with an increased risk of immune-associated pneumonia and had better clinical outcomes (16).

At present, the correlation between irAEs and PD-1 /PD-L1 inhibitors treatment response is still controversial. Studies have shown that irAEs is positively correlated with the efficacy of PD-1/PD-L1 inhibitor in NSCLC and melanoma (17–21), but some scholars have suggested that the two are not correlated (22, 23), and even negatively correlated in the study of small cell lung cancer(24). Recently, a study by Professor Rogado involving multiple tumor species showed that irAEs was directly associated with good objective response rates and longer progression-free survival with PD-1/PD-L1 inhibitors(25).

The purpose of this study was to evaluate the correlation between irAEs and the clinical efficacy of PD-1/PD-L1 inhibitors in the treatment of advanced malignant tumors, and to screen predictors of irAEs risk by comparing peripheral blood biomarkers such as baseline AEC and baseline NLR.

## 2. Patients And Methods

### 2.1 Study design and patient population

To collect the malignant tumor patients admitted to the cancer center of Beijing friendship hospital affiliated to capital medical university on January 1, 2017 and May 1, 2020, with relatively complete case data and able to assess the efficacy and record the time of disease progression or treatment failure as well as irAEs. All cases were pathologically confirmed. The follow-up began at the beginning of PD-1 /PD-L1 inhibitor, and ended at disease progression or confirmed death or follow-up as of August 31, 2020. We excluded: Previous medical history or test results indicate the presence of a definite hereditary disease; Patients with autoimmune disease or other serious medical conditions, such as cardiovascular disease (atrioventricular block, atrial fibrillation, congestive heart failure, etc.), kidney disease (hemodialysis), etc; Failure to evaluate or failure to evaluate; No serological test results were recorded before and after treatment, and 95 patients were finally enrolled. PD-1/PD-L1 inhibitors mainly include Nivolumab, Atezolizumab, Sintilimab, Camrelizumab, etc.

Beijing Friendship Hospital's Institutional Review Board (2020-P2-176-01) ratified our study protocol, which we executed in compliance with the postulates of the Declaration of Helsinki.

### 2.2 Data collection

Characteristics and clinical data of all 95 patients treated with PD-1/PD-L1 inhibitors were collected, including age, sex, ECOG PS, tumor type, cancer TNM staging, treatment lines, treatment, clinical efficacy and PFS. Tumor stage was assessed according to the Union for International Cancer Control TNM classification of malignant tumors of 2002.

CT scanning was performed at baseline and after 1 and 2 cycles of PD-1/PD-L1 inhibitor treatment or when the disease progression was considered clinically. Response to anti-PD-1/PD-L1 was determined using the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 criteria. Efficacy was

assessed as Complete response (CR), Partial response (PR), Stable disease (SD) and Progressive disease (PD). CR and PR refers to objective response, CR and PR and SD refers to disease control. Record the progression free survival (PFS), that is, from the beginning of treatment through to the observation of disease progression or death from any cause.

IrAEs were defined as adverse events with a potential immunologic basis that required close monitoring and/or potential intervention with immunosuppressives or hormone replacement [20]. IrAEs were recorded by collecting medical records, changes in serological indicators, and follow-up (including patients and attending physicians). Baseline measurements were defined as the measurements taken within 3 days prior to receiving PD-1/PD-L1 inhibitors treatment. Baseline peripheral blood data included absolute neutrophil count, absolute lymphocyte count, platelet count, and absolute eosinophil count.

## **2.3 Statistical analysis**

All data were statistically analyzed by SPSS25.0. R4.0.2 draw the forest plots. Receiver Operating Characteristic (ROC) curve determines the optimal cutoff value of peripheral blood markers. The Chi-square test was used for 2x2 tables. Survival curves were estimated by Kaplan–Meier analysis, and the log-rank test was utilized to examine the significance of differences. Landmark analysis was adopted in consideration of irAEs's immortal time bias. The correlation between baseline AEC, NLR, PLR and irAEs was evaluated by univariate and multivariate logistic regression analysis. Generally, results with P values of < 0.05 were considered to be statistically significant for all analyses.

## **3. Results**

### **3.1 Patient characteristics**

All 95 patients received PD-1/PD-L1 inhibitors treatment. The characteristics of the patients are summarized in Table 1. The median age was 62 (30–80),and ECOG PS was mostly 1 score (64.2%). First-line and second-line treatment with anti-PD-1/PD-L1 accounted for 65%. The median PFS was 108 days. There were 0 cases of CR, 12 cases of PR, 49 cases of SD and 34 cases of PD.

Table 1  
patient characteristics(n = 95)

<b>Patient characteristics</b>	<b>Patients treated with Anti-PD-1/PD-L1 (n = 95), n (%)</b>
Age at start anti-PD-1/PD-L1 (years)	
Median	62
Rang	30–80
Sex	
Male	66(69.5)
Female	29(30.5)
ECOG	
0	25(26.3)
1	61(64.2)
2	9(9.5)
Tumor types	
Lung cancer(NSCLC:20,small cell lung cancer:5)	25(26.3)
Esophageal carcinoma	17(17.9)
Liver cancer	11(11.6)
Head and neck cancer	8(8.4)
Genital system cancer	6(6.3)
Colorectal cancer	7(7.4)
Gastric carcinoma	7(7.4)
Urogenital carcinoma	4(4.2)
Cutaneous soft tissue carcinoma	3(3.2)
Melanoma	2(2.1)
Gallbladder carcinomas and bile duct carcinomas	2(2.1)
Others	3(3.2)

<b>Patient characteristics</b>	<b>Patients treated with Anti-PD-1/PD-L1 (n = 95), n (%)</b>
TNM clinical classification	
I	29(30.5)
II	58(61.1)
Unknown	7(7.4)
Treatment lines at start anti-PD-1/PD-L1	
First-line therapy	36(37.9)
Second-line therapy	29(30.5)
Third-line therapy and above	30(31.6)
Treatment	
Immunotherapy	38(40)
Immunotherapy + Targeted therapy	22(23.2)
Immunotherapy + Chemotherapy	31(32.6)
Immunotherapy + Chemotherapy + Targeted therapy	4(4.2)
Baseline ACE	0.12 ± 0.017
Mean ± SD	
Baseline PLR	204.899 ± 102.712
Mean ± SD	
Baseline NLR	
Median	3.381
Rang	1.021–40.625
Objective tumor response of anti-PD-1/PD-L1	
Complete response	0(0)
Partial response	12(12.6)
Stable disease	49(51.6)
Progressive disease	34(35.8)
Objective response rate (ORR)	12(12.6)
Disease control rate (DCR)	61(64.2)

<b>Patient characteristics</b>	<b>Patients treated with Anti-PD-1/PD-L1 (n = 95), n (%)</b>
Progression-free survival(days) Median	108
IrAEs	53(55.8)
<b>IrAEs subtype</b>	
<b>Cutaneous</b>	8(15.1)
Rash	2(3.8)
Pruritus	1(1.9)
Vitiligo	
<b>Reactive cutaneous capillary endothelial proliferation</b>	
<b>Endocrine-related events</b>	
Hypothyroidism	5(9.4)
Diabetes	3(5.7)
<b>Hepatotoxicity</b>	
ALT / AST ↑	1(1.9)
<b>Gastrointestinal toxicity</b>	
Diarrhea	11(20.8)
Gastrointestinal bleeding	3(5.7)
Immune associated pneumonia	1(1.9)
<b>Cardiac toxicity</b>	7(12.2)
<b>Hematological toxicity</b>	
Leucopenia	5(9.4)
Thrombocytopenia	4(7.5)
Anemia	4(7.5)
<b>Others</b>	7(12.2)
Creatinine increased	2(3.8)
Peripheral neuropathy	2(3.8)
Shingles	2(3.8)
Thromboembolism	1(1.9)

Patient characteristics	Patients treated with Anti-PD-1/PD-L1 (n = 95), n (%)
Hippocampal inflammation	1(1.9)
Fatigue	1(1.9)
Diastasmus diastase and lipase↑	3(5.7)
Oral mucositis	1(1.9)
	1(1.9)

The incidence of irAEs was 55.8%. Rash, immune associated pneumonia and hepatotoxicity accounted for a large proportion of 8 cases, 7 cases and 11 cases respectively. See Table 1 for more details.

### 3.2 Associations Between irAEs and PD-1/PD-L1 inhibitors respond

ORR of irAEs group and No-irAEs group was 13.2% and 11.9%, while DCR was 60.4% and 69.0%. There was not any statistical difference in ORR and DCR between the two groups (P = 0.763, P = 0.381). See Table 2.

Table 2  
ORR and DCR of irAEs group and No-irAEs group

	irAEs(n = 53)		No-irAEs(n = 42)		P value
	N	%	N	%	
ORR	7	13.2	5	11.9	0.763 <sup>a</sup>
DCR	32	60.4	29	69.0	0.381 <sup>b</sup>

(<sup>a</sup> Continuity Correction, <sup>b</sup> Pearson Chi-Square. Abbreviations: irAEs, immune-related adverse events; ORR, objective response rate ;DCR, disease control rate)

Considering the immortal time bias of irAEs, PFS was studied using landmark analysis (Fig. 1). Taking 120 days as a time point, the survival data was divided into two sections for survival analysis and Kaplan-Meier curve was drawn. 120 days ago, P = 0.951, HR = 0.981. The risk of disease progression in irAEs group was 0.981 times that in No-irAEs group, and there was no statistical difference in PFS between the two groups. After 120 days, P = 0.030, HR = 0.398. IrAEs disease progression risk was 0.398 times higher than that of No-irAEs group, and PFS of irAEs group was better than that of No-irAEs group.

### 3.3 Peripheral Blood Predictive Markers for irAEs

Taking irAEs as the result variable, we drew the ROC curves of NLR, PLR and AEC, and determined that the cutoff value was 8.58, 180.68 and  $0.045 \times 10^9/L$ , respectively. Based on cutoff value grouping, we

compared the incidence of irAEs in each group, and the results showed that the incidence of irAEs in the Low-NLR group and High-NLR group was 59.3% and 22.2%, respectively, with statistically significant differences ( $P = 0.041$ ). In addition, the incidence of irAEs in the High-AEC group (63.0%) was significantly higher than that in the Low-AEC group (31.8%) ( $P = 0.010$ ) (Table 3).

Table 3  
Correlation between the peripheral blood markers and irAE

Blood parameter	Cutoff value	irAEs,n(%)	P value
NLR	8.58		0.041*
Low(n = 86)		51/86	
High(n = 9)		2/9	
PLR	180.68		0.089
Low(n = 50)		32/50	
High(n = 45)		21/45	
AEC	$0.045 \times 10^9/L$		0.010*
Low(n = 22)		7/22	
High(n = 73)		46/73	
(* $P < 0.05$ . Abbreviations: NLR, Neutrophil-lymphocyte ratio; PLR, Platelet-lymphocyte ratio; AEC, absolute eosinophil count.)			

### 3.4 Univariate and Multivariate logistic analysis of Predictive Markers for irAEs

The results of univariate and multivariate logistic analysis are shown in Table 4. In univariate logistic analysis, good ECOG score (0–1), Low-NLR (8.58, cutoff value) and High-AEC ( $0.045 \times 10^9/L$ , cutoff value) were important predictors of irAEs ( $P = 0.0499$ , OR 0.196, 95%CI 0.038–1.000;  $P = 0.0499$ , OR 0.507, 95%CI 0.241–1.065;  $P = 0.012$ , OR 3.651, 95%CI 1.322–10.076). Multivariate logistic analysis was performed for the factors with P value less than 0.2 in univariate analysis and tumor species, and the results showed that High-AEC and good ECOG score were independent factors of irAEs ( $P = 0.014$ , OR 4.114, 95%CI 1.328–12.858;  $P = 0.046$ , OR 0.159, 95%CI 0.026–0.970). In addition, Immunotherapy combined with targeted therapy may be more prone to irAEs than other treatments ( $P = 0.005$ , OR 0.156, 95%CI 0.045–0.544).

Table 4  
Univariate and Multivariate logistic regression analyses for irAEs

	Univariate analyses			Multivariate analyses		
	P value	OR	95%CI	P value	OR	95%CI
Sex	0.330	0.646	0.268–1.555	–	–	–
Age	0.975	1.001	0.957–1.046	–	–	–
ECOG 0–1 2	0.0499*	0.507	0.241–1.065	0.046*	0.159	0.026–0.970
Tumor types	0.795	1.018	0.892–1.161	0.770	–	–
TNM clinical classification	0.508	0.786	0.385–1.605	–	–	–
Treatment lines First-line and Second-line therapy Third-line therapy and above	0.150	1.939	0.787–4.777	0.69	2.908	0.922–9.169
Treatment	0.125	0.780	0.567–1.072	0.044*	–	–
Immunotherapy				Base	–	–
Immunotherapy + Targeted therapy				0.005*	0.156	0.045–0.544
Immunotherapy + Chemotherapy				0.301	0.550	0.178–1.706
Immunotherapy + Chemotherapy + Targeted therapy				0.383	0.363	0.037–3.533
NLR Low( $\leq$ 8.58) High(>8.58)	0.0499*	0.196	0.038–1.000	0.505	0.501	0.066–3.816

(\*P < 0.05. Abbreviations: ECOG, Eastern Cooperative Oncology Group; NLR, Neutrophil-lymphocyte ratio; PLR, Platelet-lymphocyte ratio; AEC, absolute eosinophil count; HR, Odds ratio; CI, confidence interval.)

	Univariate analyses			Multivariate analyses		
PLR	0.091	0.492	0.216– 1.120	0.216	0.537	0.200– 1.440
Low(<180.68)						
High( $\geq$ 180.68)						
AEC	0.012*	3.651	1.322– 10.076	0.014*	4.114	1.328– 12.858
Low( $\leq$ 0.045 $\times$ 10 <sup>9</sup> /L)						
High(>0.045 $\times$ 10 <sup>9</sup> /L)						

(\*P < 0.05. Abbreviations: ECOG, Eastern Cooperative Oncology Group; NLR, Neutrophil-lymphocyte ratio; PLR, Platelet-lymphocyte ratio; AEC, absolute eosinophil count; HR, Odds ratio; CI, confidence interval.)

### 3.5 Forest plot for Multivariate logistic regression analyses for irAEs

In order to more intuitively understand the results of multivariate logistic analysis of irAEs, we drew a forest plot with "irAEs" as the study event (Fig. 2). As shown in the figure, the odds ratio of 95%CI of AEC factors were all greater than 1, which did not intersect with the invalid vertical line and fell to the right of the invalid line. It was considered that the incidence of irAEs in the High-AEC group was higher than that in the low-AEC group and was a risk factor of irAEs. However, the odds ratio of 95%CI of ECOG PS were all less than 1, which did not intersect with the invalid vertical line and fell to the left of the invalid line—so the incidence of irAEs in good ECOG PS (0–1) was greater than that in ECOG PS (2). Similarly, the incidence of irAEs in immunotherapy combined with targeted therapy is relatively low compared with other treatments.

## 4. Discussion

Immune checkpoint inhibitors such as PD-1/PD-L1 inhibitors have become crucial choices for patients with advanced malignant tumors, but the irAEs associated with them may lead to treatment interruption or fatal disease (8–10). Early prediction and correct treatment are particularly critical for irAEs management.

The correlation between irAE and PD-1/PD-L1 inhibitors response in advanced malignant tumors has long been controversial. A recent meta-analysis of 30 included studies showed that irAEs were significantly associated with PFS and OS of PD-1/PD-L1 inhibitors in advanced malignant tumors, especially in endocrine, cutaneous and low-grade irAEs, but objective remission rates were not discussed (26). This study showed no statistical difference in ORR and DCR between irAEs group and No-irAEs group, which was the same as some research results (22, 23), while the correlation between irAEs and PFS was not

directly obtained. In view of the immortal time bias of irAEs and the intersection points in the overall analysis, we used landmark analysis, where the irAEs group showed a survival advantage after PFS 120 days. The reason is related to the initial time of irAEs. Studies have shown that most irAEs appear within 3 months after the beginning of treatment, while serious adverse reactions such as immune associated pneumonia appear within two months(27). Combined with our clinical data, some patients terminate treatment early due to severe adverse reactions such as immune-related myocardial injury and immune-related pneumonia.

Peripheral blood markers such as baseline NLR and PLR showed predictive value not only in the efficacy of PD-1/PD-L1 inhibitors in advanced malignant tumors (28–33), but also in the possibility of predicting the occurrence risk of irAEs(12–14). Moreover, eosinophils in peripheral blood were also associated with irAEs(14–16). This study assessed the predictive value of baseline NLR, PLR and eosinophils to the risk of irAEs, and found that the incidence of irAEs in the baseline Low-NLR group and the baseline High-AEC group was significantly higher than that in the High-NLR group and the Low-AEC group. Previous studies showed that higher baseline NLR predicted poor efficacy of PD-1/PD-L1 inhibitors, which indirectly suggested the possibility of a positive correlation between irAEs and efficacy. Meanwhile, although univariate logistic analysis showed that both baseline Low-NLR and baseline High-AEC were risk factors for irAEs, confound factors such as tumor type, treatments and treatment lines were further included, and multivariate logistic analysis only showed that AEC was an independent influence factor for irAEs. Although studies have shown that baseline PLR can be used as an independent predictor of irAEs in the treatment of advanced non-small cell lung cancer with immune checkpoint inhibitors(12), and our multivariate analysis also found that baseline PLR may be superior to NLR, its predictive value may still be much lower than that of baseline AEC. We speculate that baseline AEC may have higher irAEs occurrence risk prediction value than baseline NLR and PLR. To our knowledge, this is the first comparison of the predictive value of baseline NLR, baseline PLR, and baseline AEC for irAEs.

ECOG PS is intimately related to irAEs, and irAEs is more likely to occur in good ECOG, which is the same as previous research results (20). We balanced the confounding factors such as tumor type, treatments and treatment lines, but good ECOG still showed positive correlation with irAEs, which was an independent predictor of irAEs. In addition, studies have suggested that the treatment lines are also related to irAEs, and second-line treatment and above is more likely to occur irAEs(20), which is different from our results. It is worth noting that we found that the incidence of irAEs in immunotherapy combined with targeted therapy is relatively low, and currently there is no other data to support it, so further large sample size, single tumor species and prospective studies are needed for verification.

Of course, there are a few limitations in this study. On the one hand, we conducted a single-center retrospective study. On the other hand, we underestimated the influence of the use of hormones or immunosuppressants and irAEs classification, etc. Therefore, multi-center, prospective studies are needed to validate our results.

## 5. Conclusion

In summary, baseline AEC and ECOG PS can be used as independent predictors of irAEs occurrence to guide clinical practice, provide early warning and take positive measures for irAEs, thus contributing to the correct management of irAEs.

## **Abbreviations**

ECOG, Eastern Cooperative Oncology Group

NLR, Neutrophil-lymphocyte ratio

PLR, Platelet-lymphocyte ratio

AEC, absolute eosinophil count

HR, Odds ratio

CI, confidence interval

irAEs, immune-related adverse events

ORR, Objective response rate

DCR, Disease control rate

ICIs, Immune checkpoint inhibitor

CR, Complete response

PR, Partial response,

SD, Stable disease

PD, Progressive disease

PFS, progression free survival

ROC, Receiver Operating Characteristic

ECOG, Eastern Cooperative Oncology Group,

PS, Performance status

## **Declarations**

**Ethics approval and consent to participate**

Beijing Friendship Hospital's Institutional Review Board (2020-P2-176-01) ratified our study protocol, which we executed in compliance with the postulates of the Declaration of Helsinki.

### **Consent for publication**

Yes

### **Availability of data and materials**

The datasets during the current study are not publicly available due to privacy but are available from the corresponding author on reasonable request.

### **Competing interests**

The authors declare that they have no competing interests

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### **Authors' contributions**

All authors contributed to the study conception and design. Material preparation, data collection were performed by Yan Ma, Xiao Ma, Jingting Wang, Jing wang, Bangwei Cao. Shanshan Wu provides statistical support. The first draft of the manuscript was written by Yan Ma, and the manuscript was further commented and approved by all authors.

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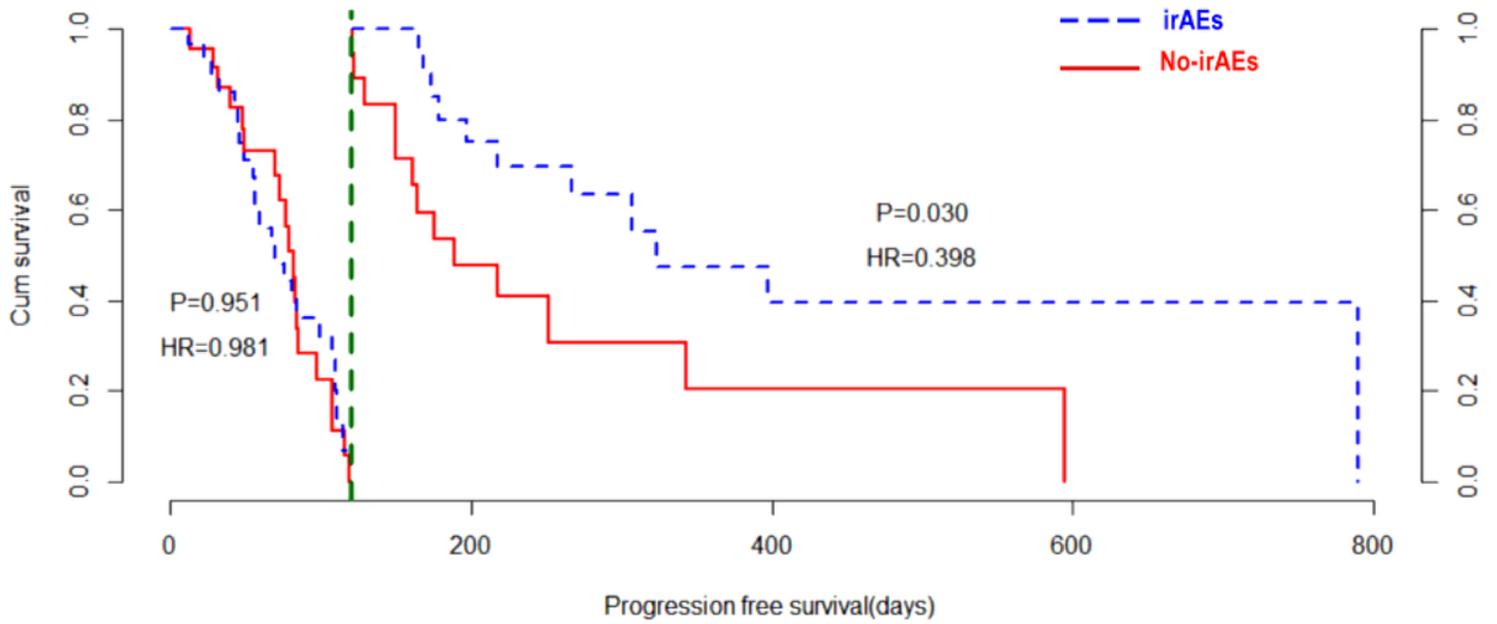
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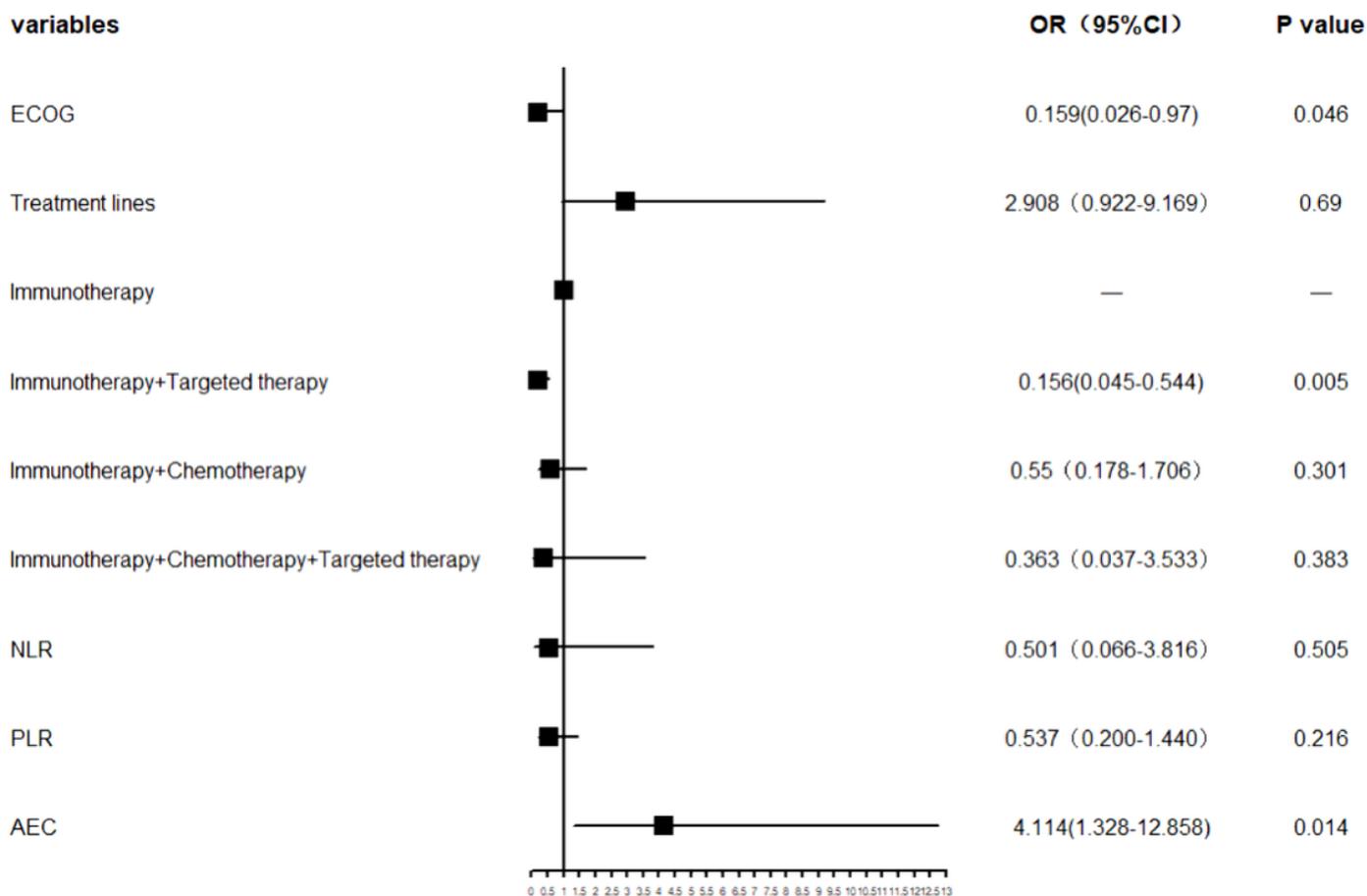
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## Figures



**Figure 1**

Landmark analysis according to the presence of irAEs. Kaplan-Meier curves with the time point (120 days) landmark analysis for progression-free survival. Abbreviations: irAEs, immune-related adverse events; HR, hazard ratio.



**Figure 2**

Forest plot for multivariate logistic regression analyses for irAEs. The vertical line in the middle of the figure is invalid line, that is, OR=1; each horizontal line is the line between the upper and lower limits of 95%CI of the study; the length of its line segment intuitively represents the size of 95%CI; the small square in the center of the horizontal segment is the position of OR value; its size reflects the weight of the study. Abbreviations: ECOG, Eastern Cooperative Oncology Group; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; AEC, absolute eosinophil count; OR, odds ratio; CI, confidence interval.