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Original Article

C-reactive protein to albumin ratio as prognostic markers in patients with advanced non-small cell lung cancers treated with tyrosine kinase inhibitors

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Abstract: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) have demonstrated a dramatic response rate and prolonged progression free survival (PFS) in patients harboring an activating EGFR mutation, but reliable prognostic markers are lacking. High C-reactive protein to albumin ratio (CAR) is a marker of host systemic inflammation and associated with poor outcome in various carcinomas, but has not been analyzed in advanced NSCLC patients treated with EGFR-TKI. We retrospectively analyzed 392 advanced NSCLC patients with activating EGFR mutations to examine the predictive value of CAR in the era of targeted therapy. The optimal cutoff level of CAR was set at 0.146 according to the receive operating characteristic (ROC) analysis. Survival analysis was determined using the Kaplan-Meier analysis and prognostic factors were determined using a Cox proportional hazards model. We found that high CAR (≥0.146) was associated with poorer PFS and lower objective response rate. Subgroup analysis of both gefitinib and erlotinib showed that CAR was significantly associated with PFS. Multivariate analysis showed that pretreatment CAR was an independent predictive marker for PFS (HR: 1.48, 95% CI: 0.96-1.33). The findings of the present study demonstrated that advanced NSCLC patients with activating EGFR mutations who have pretreatment CAR values higher than 0.146 should be considered to have a high risk of early EGFR-TKI treatment failure.

Keywords: C-reactive protein, albumin, non-small-cell lung carcinoma, epidermal growth factor receptor, tyrosine kinase inhibitors, progression-free survival

Introduction

Lung cancer remains the one of the leading causes of cancer-related death worldwide [1]. In particular, advanced non-small-cell lung cancer (NSCLC) continues to be a challenging disease with poor outcomes [2]. Recently, the identification of activating mutations in epidermal growth factor receptor (EGFR), mostly seen in exon 19 (deletion) or in exon 21 (L858R point mutation), together with an increased sensitivity to EGFR tyrosine kinase inhibitors (TKI), has been the first and most important step toward molecular-guided precision therapy of lung cancer [3]. Multiple randomized controlled trials have demonstrated improvement in progression-free survival (PFS) when comparing EGFR-TKI against chemotherapy in this genetically distinct subset of NSCLC [4-7]. After the start of the treatment, the presence in the tumor of a mutation of the EGFR gene is a strong predictor of response to EGFR TKI therapy [8]. Unfortunately, some patients with activating EGFR mutations still respond poorly to EGFR-TKI therapy, and early identification of them is difficult because the mechanism of resistance remains unclear. The most frequently reported mechanism of acquired resistance is the EGFR T790M point mutation within exon 20 [9, 10] and such patients are suitable candidates for second or third-generation EGFR-TKI [11]. Small cell histologic transformation has also been implicated in the development of acquired resistance [12]. Once resistance occurs, either conventional cytotoxic chemotherapy or other small molecular inhibitors should be considered [13]. To this

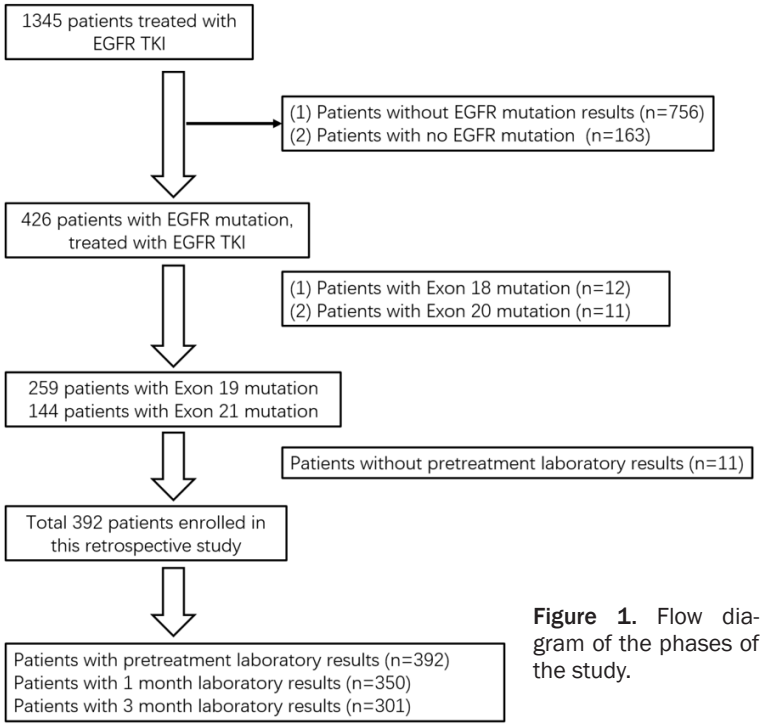

Figure 1. Flow diagram of the phases of the study.

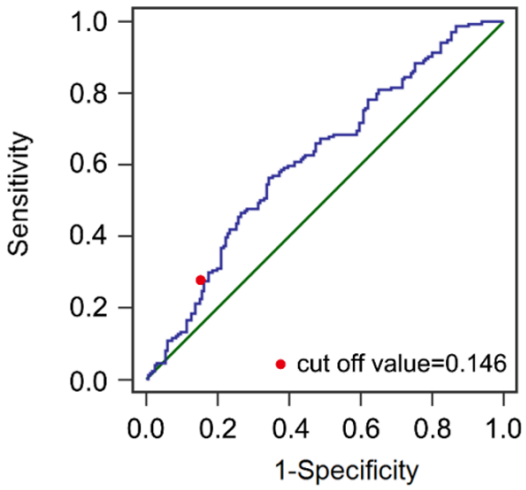

Figure 2. Cutoff value of C-reactive protein to albumin ratio (CAR) assessed by ROC curve. The sensitivity and specificity was 56.32 and 65.66, respectively.

end, it is essential to predict the failure before treatment and plan for timely alternative therapies.

Recently, inflammation-based scoring systems, such as Glasgow prognostic score and neutrophil to lymphocyte ratio, have been treated as useful prognostic predictors for cancer specific survival [14, 15]. In addition, C-reactive protein to albumin ratio (CAR), is considered as an indicator of systemic inflammatory response, has been reported to predict prognosis in gastric cancer [16], pancreatic cancer [17], colorectal cancer [18], esophageal cancer [19], and lung cancer [20]. Nevertheless, the prognostic value of the CAR in NSCLC patients with EGFR-TKI treatment has not been reported. Therefore, this study aims to investigate the predictive significance of CAR for PFS, so that to develop a strategy for risk stratification of initial EGFR-TKI treatment in NSCLC patients with EGFR mutations.

Materials and methods

Patients

We retrospectively analyzed clinical data of 1345 consecutive patients with cytologically or histologically confirmed locally advanced (IIIB) or metastatic-stage (IV) disease, who were treated with EGFR TKI treatment including gefitinib and erlotinib in West China Hospital, from January 2008 to December 2016. Among these, 403 subjects were confirmed with activating EGFR mutations, either an exon 19 microdeletion or exon 21 point mutation. Patients who had a concomitant infection including human immunodeficiency virus or hepatitis, concomitant radiotherapy or simultaneously treated with any other agents, such as cytotoxic agents or investigational drugs were excluded. Finally, after excluding another 11 patients without pretreatment laboratory results, a total of 392 patients were enrolled into the study (**Figure 1**). The study was conducted according to the declaration of Helsinki and was approved by the Research Ethics Committee of the West China Hospital.

Data extraction

Baseline characteristic of each subject, including age, gender, smoking status, tumor pathology, treatment history, Eastern Cooperative Oncology Group (ECOG) performance scores

Table 1. Baseline characteristics of the study subjects, divided into two groups according to the value of C-reactive protein to albumin ratio (CAR)

Clinical Characteristics	Total (n=392)	CAR<0.146 (n=209)	CAR≥0.146 (n=183)	*P* value*
Age				0.037
<60	175	104	71	
≥60	227	105	112	
Gender				0.156
Male	155	90	65	
Female	237	119	118	
Smoking				0.001
Yes	269	160	109	
No	123	49	74	
Pathology				0.402
Adenocarcinoma	258	141	117	
Squamous cell carcinoma	118	62	56	
Others	16	6	10	
Pathological TNM stage				0.022
III	113	71	42	
IV	279	138	141	
EGFR MT				0.082
Exon 19	227	130	97	
Exon 21	165	79	86	
TKI type				0.779
Gefitinib	344	182	162	
Erlotinib	48	27	21	
TKI as				0.127
1st line	231	132	99	
2nd line	147	72	75	
≥3rd line	14	5	9	
ECOG PS				0.004
0-1	320	182	138	
2-4	72	27	45	
CEA (ng/ml)				0.262
<5	154	88	66	
≥5	238	121	117	
Hemoglobin (g/L)				0.305
<120	194	109	85	
≥120	198	100	98	
Calcium (mmol/L)				0.148
<2.5	129	76	53	
≥2.5	263	133	130	

Note: CAR=C-reactive protein to albumin ratio; EGFR MT=epidermal growth factor receptor mutation; ECOG PS=The Eastern Cooperative Oncology Group performance scores; CEA=carcinoembryonic antigen. *Chi-squared test by 2-sided Pearson exact test.

(PS), laboratory results, and imaging data, were collected from patients' medical records. The baseline CRP and albumin level were measured prior to the start of EGFR TKI treatment within 1 week. CAR was calculated by dividing the serum CRP level by the serum albumin level [21]. For analysis of the distribution of CAR during the treatment, the level of CRP and albumin at 1 month and 3 months after the start of treatment were also measured. EGFR mutation analysis was determined using direct DNA sequencing or quantitative polymerase chain reaction (PCR) [22, 23]. PFS was defined from the time initial chemotherapy started to the first progression or death from any cause without progression. Patients received dynamic computed tomography (CT) scan every 2 cycles of chemotherapy or every 6 weeks. The response of treatment was evaluated by a systematical radiologic review committee according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [24].

Statistical analysis

All data were analyzed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). Descriptive characteristics of patients were recorded, categorical variables were presented as numbers and percentages, and continuous variables were allocated in groups according to the optimal cut-off value using receiver operating characteristics (ROC) analysis [25]. The area under the curve (AUC) was 0.617 (95% CI, 0.563-0.669) for the CAR (**Figure 2**), as for the PFS in the enrolled patients. The score closest to the point with both maximum sensitivity (56.3%) and specific-

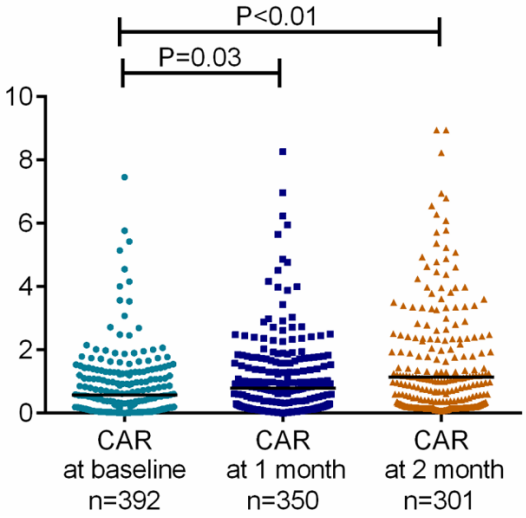

Figure 3. Distribution of C-reactive protein to albumin ratio (CAR) during the treatment with Tyrosine Kinase Inhibitors.

ity (65.7%) was selected as the cut-off value of CAR (0.146). The groups were compared using the chi-square analysis. Statistical significance of the differences in Kaplan-Meier estimates was assessed using the log-rank test. Cox proportional hazards model was used to evaluate the effect of all potential prognostic factors on the survival measures. A *P*-value of <0.05 was considered statistically significant.

Results

Patient characteristics

The baseline characteristics of the 392 patients enrolled in the study are listed in **Table 1**. All patients were divided into groups according to the value of pretreatment CAR and 209 patients owned lower CAR values (<0.146), while the remaining had higher CAR values (≥0.146) in our cohort. As shown that, an elevated CAR was significantly associated with age (P=0.037) and smoking history (P=0.001). In addition, Patients with high CAR had advanced TNM stage (P=0.022), and higher ECOG PS (P=0.004), as compared to those with low CAR values. However, there were no significant differences between the two CAR groups in terms of sex, clinical pathology, EGFR MT, TKI type, the levels of CEA, hemoglobin, or calcium. Subsequently, the distribution of CAR values during EGFR TKI treatment were compared. As illustrated in **Figure 3**, the median CAR value was 0.180 (range 0.004-7.462) before treatment. The median CAR value was 0.260 (range 0.005-8.262) at 1 month and 0.339 (range 0.026-8.947) at 3 months, respectively, showing significant increasing trend when compared to pretreatment values.

Predictive value of CAR for PFS

To reveal the prognostic significance of CAR in subjects with the treatment of EGFR TKI, the relationship between CAR and PFS is presented as Kaplan-Meier curves in **Figure 4**. The median PFS was 15.45 months (95% CI: 11.62-17.07) for patients with pretreatment CAR< 0.146 and 10.38 months (95% CI: 6.18-12.45) for CAR≥0.146 (**Figure 4A**). We also conducted analyses using CAR values at 1 or 3 months for patients with PFS longer than 1 or 3 months. Patients with CAR<0.146 and those with CAR≥0.146 had PFS of 14.36 months (95% CI: 10.39-15.69) and 10.61 months (95% CI: 8.53-12.04), respectively, when analyzing CAR values at 1 month after the treatment (**Figure 4B**). while using the CAR values at 3 months for analysis, the median PFS was 15.65 months (95% CI: 10.97-21.53) and 13.53 months (95% CI: 11.50-15.64) for CAR<0.146 group and CAR≥0.146 group, respectively. In addition, the results of subgroup analyses according to TKI type showed that in subjects received gefitinib treatment, those who had high CAR had lower PFS than patients with low CAR (14.67 vs 13.15 months, P=0.002; **Figure 5A**). Similar trend was observed in subjects with erlotinib treatment (13.36 vs 7.18 months, P=0.024; **Figure 5B**).

In univariate analysis, PFS was found significantly associated with variables of age (HR: 0.99, 95% CI: 0.96-1.00, P<0.001), TNM stage (HR:2.16, 95% CI: 0.61-5.58, P<0.001), ECOG PS (HR: 2.07, 95% CI: 0.11-0.35, P<0.001), calcium (HR: 0.88, 95% CI: 0.50-0.96, P=0.035), CAR at baseline (HR: 1.95, 95% CI: 1.05-2.50, P<0.001) and at 1 month (HR: 1.54, 95% CI: 0.99-1.90, P<0.001). However, CAR at 3 months was not correlated with PFS in patients receiving EGFR TKI treatment (P=0.102). After adjusting confounders, multivariate analysis showed the similar results with those of univariate analysis. CAR at baseline 1.48 (0.96-1.33) and 1 months 1.21 (1.03-1.59) were indepen-

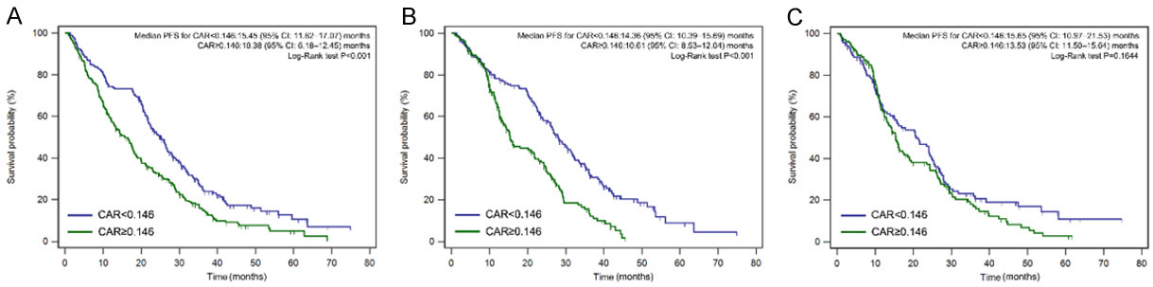

Figure 4. Kaplan-Meier curve of progression free survival: (A) Plotted by binary distribution using cutoff CAR value of 0.146 at Pretreatment; (B) Plotted by binary distribution using cutoff CAR value of 0.146 at 1 month; (C) Plotted by binary distribution using cutoff CAR value of 0.146 at 3 months.

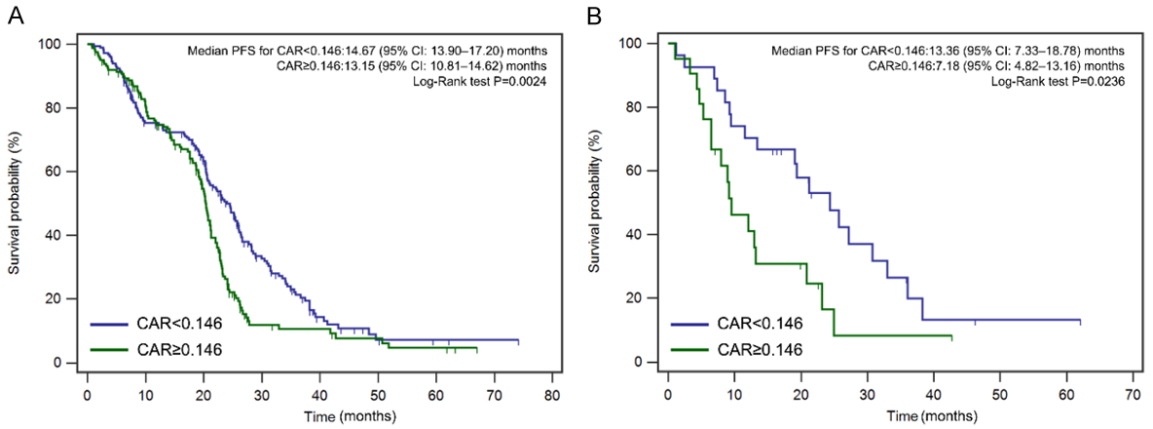

Figure 5. Differences in the prognostic significance of CAR according to TKI type. A. Comparison of PFS on patients who received gefitinib treatment with high CAR vs low CAR; B. Comparison of PFS on patients who received erlotinib treatment with high CAR vs low CAR.

Table 2. Effects of various variables on progression free survival in univariate and multivariate analyses

Variable	Univariable		Multivariable	
	HR (95% CI)	*P*-value	aHR (95% CI)	*P*-value
Age	0.99 (0.96-1.00)	<0.001	0.99 (0.97-1.00)	<0.001
Gender	1.06 (0.65-4.67)	0.253		
Smoking	1.02 (0.74-2.33)	0.350		
TNM stage	2.16 (0.61-5.58)	<0.001	1.77 (0.80-3.65)	<0.001
TKI type	0.84 (0.59-0.98)	0.452		
ECOG PS	2.07 (0.11-0.35)	<0.001	1.42 (0.75-1.91)	<0.001
CEA (ng/ml)	1.18 (0.99-4.58)	0.294		
Hemoglobin (g/L)	0.71 (0.19-0.82)	0.412		
Calcium (mmol/L)	0.88 (0.50-0.96)	0.035	0.87 (0.52-0.91)	0.039
CAR at baseline	1.95 (1.05-2.50)	<0.001	1.48 (0.96-1.33)	<0.001
CAR at 1 month	1.54 (0.99-1.90)	<0.001	1.21 (1.03-1.59)	0.002
CAR at 3 months	1.13 (0.90-7.86)	0.102		

Note: HR=hazard ratio; aHR=adjust hazard ratio; ECOG PS=The Eastern Cooperative Oncology Group performance scores; CEA=carcinoembryonic antigen; CAR=C-reactive protein to albumin ratio.

dent predictive factors for PFS (**Table 2**). Subgroup analysis was then performed by dividing the patients into 4 groups by CAR value at baseline and 1 month. The results suggested that compared to patients with CAR<0.146 both at baseline and 1 month, patients with CAR≥0.146 at baseline showed increased HR regardless of CAR level at 1 month. Similar phenomenon was observed when using CAR value at pretreatment and 3 months for analysis (**Table 3**).

Table 3. Cox-proportional hazard ratio of progression free survival by changes of C-reactive protein to albumin ratio (CAR)

CAR≥0.146 at baseline	CAR≥0.146 at 1 month	n (350)	HR* (95% CI, P)
-	-	296	Control
+	-	37	1.45 (1.11-2.37, P=0.001)
-	+	5	1.14 (0.82-1.89, P=0.245)
+	+	12	1.28 (1.04-2.02, P=0.012)
CAR≥0.146 at baseline	CAR≥0.146 at 3 month	n (301)	HR# (95% CI, P)
-	-	232	Control
+	-	36	1.50 (1.20-3.01, P<0.001)
-	+	19	0.94 (0.75-1.67, P=0.172)
+	+	14	1.41 (1.16-2.92, P=0.009)

Note: HR, hazard ratio; *HR was calculated by compared to subjects CAR level<0.146 both at baseline and 1 month; #HR was calculated by compared to subjects CAR level<0.146 both at baseline and 3 months.

Table 4. Tumor responses according to the pretreatment value of C-reactive protein to albumin ratio (CAR)

Response	Total (n=176)	CAR<0.146 (n=82)	CAR≥0.146 (n=94)	*P* value
Complete response	3 (1.7%)	3 (3.7%)	0 (0%)	0.016
Partial response	105 (59.7%)	56 (68.3%)	49 (52.1%)	
Stable disease	46 (26.1%)	17 (20.7%)	29 (30.9%)	
Progressive disease	22 (12.5%)	6 (7.3%)	16 (17.0%)	
Objective response rate	108 (61.4%)	59 (72.0%)	49 (52.1%)	

Note: Tumor response means Objective response rate included complete response and partial response. *P* value was obtained using Chi-squared test by 2-sided Fisher exact test.

Tumor response according to CAR

The tumor response data were collected among 176 patients. The percentage of partial response patients were lower in the CAR≥0.146 group compared with those in the CAR<0.146 group (52.1% vs 68.3%). The objective response rate was 52.1% and 72.0%, respectively in the CAR≥0.146 group and CAR<0.146 group (**Table 4**).

Discussion

To the best of our knowledge, this was the first study to identify the prognostic value of CAR on PFS in advanced NSCLC with activating mutations of the EGFR genes. CAR is a simple index that calculated by routine biochemical examinations. High CAR was reported to be correlated with poor outcomes in patients with acute medical admissions and sepsis [26, 27]. The presence of systemic inflammation, as indicated by a high CRP level and a low albumin level, has been repeatedly demonstrated to play an important role in cancer initiation, progression and prognosis [20, 21, 28]. However, the link between CAR and PFS in NSCLC patients with EGFR-TKI treatment is still undefined and its role as a predictive marker in this area needs to be elucidated.

In our single-center retrospective study of 392 patients with activating EGFR mutations, advanced stage III and IV NSCLC who underwent EGFR-TKI therapy, we evaluated whether CAR could predict which patients would have a response to target therapy and thus longer PFS. We showed that high CAR is associated initial resistance to EGFR-TKI therapy and it is reasonable to conclude that high CAR may reflect the immune responses and systemic inflammation that could alter the treatment response in patients with cancer [29]. Systemic inflammation consists of circulating cytokines, small inflammatory proteins, circulating immune cells, and acute-phase proteins, which produce the clinical symptoms that frequently mark the presence and progression of cancer [30]. Both C-reactive protein (CRP) and albumin are synthesized in the liver and secreted into the circulation. Together with the enzyme lactate dehydrogenase, they are accepted markers of systemic inflammation [31]. So far, limited data are available in literatures regarding the effects of systemic pretreatment inflammation on the prognosis of NSCLC patients. Studies have suggested that the values of preoperative CRP hold important prognostic information on short or long-term mortality in operable lung cancer [32, 33]. Similar prognostic value of CRP was then observed in advanced NSCLC patients receiving palliative chemotherapy, and provide additional information to

established prognostic factors such as stage of disease and performance status [34-36]. A recent study identified its role in patients treated with erlotinib and found serum high level of CRP was independently associated with PFS and also with OS [37]. On the other hand, the study by Miura et al revealed that low preoperative serum albumin level was useful indicator of poor outcome in NSCLC patients with surgical resection [38]. Low albumin in cancer patients has always considered as a reflection of malnutrition, which could impair anatomic barriers, immunity, and other defense mechanisms [39]. Base on above analysis, we hypothesized that CAR, could both reflect body systemic inflammation and immune status, was sufficient to predictive outcome of EGFR-TKI therapy in advanced NSCLC patients. Up to now, although numerous studies have determined the role of pretreatment CAR in predicting prognosis in different cancers including NSCLC [40], we firstly showed that pretreatment CAR was predictive of the duration of response to EGFR TKI. Subgroup analysis also validated the predictive ability of CAR in NSCLC patients treated with gefitinib or erlotinib. This was supported by the findings that gefitinib and erlotinib, both as first-generation EGFR-TKIs, have equivalent therapeutic efficacy in NSCLC patients harboring EGFR mutation [41]. However, the predictive property was gradually decreased when using CAR at 1 month after therapy and even disappeared when using CAR at 3 months. Above results suggested that the mechanism of the high CAR during target therapy should be affected by various ways, which should be further explored.

There were several limitations in this study. Firstly, it was a retrospective study from a single institution with relative small sample size. Although no missing data concerning laboratory results and survival data were observed, the selective or information bias of the study cannot be avoided. Prospective studies with large samples are needed to confirm our conclusions before its usage in the clinical settings. Moreover, there was no consistent cutoff value for CAR so far, the cut-off value of CAR in this study is likely biased due to its calculation by ROC analysis. However, the value was similar with other published studies [25, 42, 43] and more studies were needed to set a uniform cutoff value.

Collectively, our findings demonstrated that high pretreatment CAR might be an unfavorable prognostic factor for NSCLC patients with EGFR mutations and those have high pretreatment CAR (≥0.146) are more likely to have a low response rate to EGFR-TKIs.

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Disclosure of conflict of interest

None.

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