Risk Factors of Reactive Cutaneous Capillary Endothelial Proliferation in Advanced Non-small Cell Lung Cancer Treated with Camrelizumab

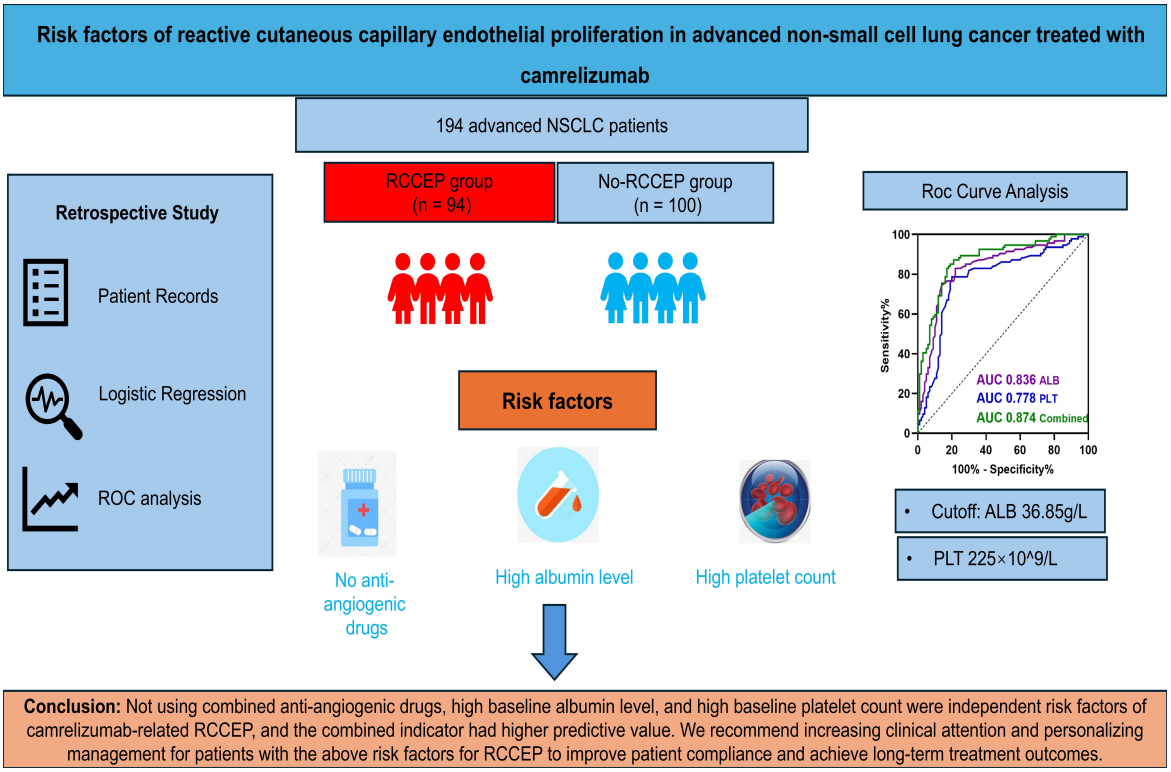
Authors

Liuning Wang, Shuxing Chen, Siyu Sun,Wenyi Li, Congjun Zhang

Correspondence

yfy137907@fy.ahmu.edu.cn (C. Zhang)

Graphical Abstract



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Research Article

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Risk Factors of Reactive Cutaneous Capillary Endothelial Proliferation in Advanced Non-small Cell Lung Cancer Treated with Camrelizumab

Liuning Wang [1†], Shuxing Chen [1†], Siyu Sun [2†], Wenyi Li [1], Congjun Zhang [1*]

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Abstract

Background: Reactive cutaneous capillary endothelial proliferation (RCCEP) is the most common cutaneous immune-related adverse event (irAE) of camrelizumab. The purpose of our research was to explore the risk factors associated with RCCEP and their predictive values.

Methods: We conducted a retrospective investigation examining clinical records of advanced non-small cell lung cancer (NSCLC) patients treated with camrelizumab at our hospital between June 2022 and December 2024. Study participants were grouped based on whether they developed RCCEP. To pinpoint potential risk factors associated with RCCEP, we employed logistic regression analysis, while receiver operating characteristic (ROC) curve analysis helped determine the predictive values of our identified variables.

Results: Among 194 patients, 94 (48.5%) developed RCCEP, of whom 92 cases developed grade 1-2 RCCEP, only 2 cases developed grade 3 RCCEP, with no grade 4-5 cases. Multivariate logistic regression analysis suggested that not using combined anti-angiogenic drugs (OR: 2.962, 95% CI 1.042-8.422, P = 0.042), high baseline albumin level (OR: 1.422, 95% CI 1.264-1.599, P < 0.001), and high baseline platelet count (OR: 1.018, 95% CI 1.010-1.026, P < 0.001) were significantly associated with RCCEP. ROC curve analysis showed that baseline albumin level, baseline platelet count, and their combination predicted RCCEP occurrence in advanced NSCLC patients receiving camrelizumab, with areas under the curve (AUCs) of 0.836 (95% CI 0.777-0.895), 0.778 (95% CI 0.709-0.847), and 0.874 (95% CI 0.823-0.924), respectively. The cutoff values for albumin and platelet were calculated using the maximum Youden index from the ROC curve, which were 36.85 g/L and 225×10^9/L, respectively.

Conclusion: Not using combined anti-angiogenic drugs, high baseline albumin level, and high baseline platelet count were independent risk factors of camrelizumab-related RCCEP, and the combined indicator had higher predictive value. We recommend increasing clinical attention and personalizing management for patients with the above risk factors for RCCEP to improve patient compliance and achieve long-term treatment outcomes.

Keywords: Camrelizumab; advanced non-small cell lung cancer (NSCLC); reactive cutaneous capillary endothelial proliferation (RCCEP); albumin; platelet; anti-angiogenic drugs

Introduction

Lung cancer stands as one of the most prevalent malignant tumors globally, and is a leading cause of cancer-related death. Non-small cell lung cancer (NSCLC) is the main type of lung cancer, and by the time most patients are diagnosed, the disease is already at an advanced stage. As a result, the overall prognosis is not ideal, with a 5-year survival rate of only 10% to 20% [1]. In recent years, immunotherapy, as an emerging treatment strategy, has significantly improved the prognosis of patients with advanced NSCLC, opening a new chapter in lung cancer immunotherapy. The immune checkpoint inhibitors (ICIs) used in tumor immunotherapy are mainly divided into two categories: one is monoclonal antibodies targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4), and the other acts on the programmed cell death protein 1 (PD-1) and its ligand programmed cell death protein ligand 1 (PD-L1) signaling pathway. PD-1 and PD-L1 inhibitors, as new anti-tumor drugs, can block the inhibitory pathway between T lymphocytes and tumor cells or antigen-presenting cells [2], relieve immune suppression, stimulate T cells to attack tumor cells, and strengthen anti-tumor immunity. However, while ICIs activate the patient's immune system to fight cancer, they also enhance the body's immune response, leading to various immune-related adverse events (irAEs). Cancer immunotherapy has different toxic characteristics and management approaches compared to traditional chemotherapy [3-4]. IrAEs are essentially autoimmune in nature and can affect almost any organ system [4].

1 Department of Oncology, The First Affiliated Hospital of Anhui Medical University, Hefei, China

2 Department of Geriatric Pulmonology, The First Affiliated Hospital of Anhui Medical University, Hefei, China

† These authors contributed equally to this work.

* Corresponding Author.

Common irAEs involve the skin, gastrointestinal tract, endocrine organs, liver, and lungs [5]. Severe irAEs may force the discontinuation of ICI treatment, interfering with the patient's cancer treatment process. Therefore, early identification and timely intervention of irAEs are necessary.

Camrelizumab is a high-affinity, humanized monoclonal antibody of the IgG4 kappa subclass that targets PD-1, which is now applied in the treatment of various malignant tumors, such as classical Hodgkin lymphoma, hepatocellular carcinoma, non-small cell lung cancer, small cell lung cancer, melanoma, and esophageal squamous cell carcinoma. It is currently the most widely approved ICI with the most indications in China. However, in a series of clinical studies and practices, it has been found that camrelizumab treatment can lead to a common skin irAE— reactive cutaneous capillary endothelial proliferation (RCCEP) [6-8]. RCCEP has unique clinical manifestations and pathological features. Its occurrence may be due to the disruption of the skin immune microenvironment, leading to an imbalance in the expression of angiogenesis-related factors. RCCEP exhibits five distinct morphological patterns that can be classified as follows: "red-nevus-like", "pearl-like", "mulberry-like", "patch-like" and "tumor-like". It most commonly occurs on the facial and trunk skin, and less frequently on the eyelids, oral mucosa, and nasal mucosa. Previous data from a multicenter phase II trial showed an RCCEP incidence rate of 66.8% [7], while another large-scale pooled analysis covering 10 clinical trials in China further suggested the rate could reach 77.0% [9]. Together, these results indicate that RCCEP has a relatively high incidence rate. However, RCCEP is not unique to camrelizumab. Studies have shown that other ICIs, such as nivolumab or pembrolizumab, can also cause RCCEP, with an incidence rate of about 2.4% [10]. This suggests that while RCCEP may not be specific to camrelizumab, it appears to occur more frequently and present differently with this particular medication [7]. Although RCCEP is usually self-limiting and can be relieved by laser therapy, surgical excision, hemostatic treatment, local steroid treatment, or cryotherapy, for some patients with multiple or widely distributed lesions, local treatments may be limited in effectiveness. This can affect the patient's appearance, impair their quality of life, and reduce patient compliance, leading to delays or interruptions in immunotherapy. Additionally, some tumor patients may have low coagulation function, which could lead to the lesions rupturing and bleeding, increasing the risk of infection, and in severe cases, even life-threatening complications [11]. Given the high incidence rate of RCCEP, identifying patients at high risk of RCCEP before starting treatment with camrelizumab in clinical practice has important clinical value for optimizing the management of camrelizumab therapy. In recent years, the field of international oncology has seen a continuously increasing focus on irAEs. Existing studies suggested that peripheral blood cells, such as eosinophil [12] and lymphocyte [13], and patient clinical characteristics, such as age [14] and sex [15], may have some reference value in predicting irAEs. However, research on predictive factors for specific skin irAEs like RCCEP was still relatively limited, with only a few retrospective studies exploring this to date. A retrospective study in patients with NSCLC, using multivariate logistic regression analysis, found that a baseline peripheral blood eosinophil percentage > 1.75% and not using anti-angiogenic drugs in combination were independent risk factors for developing RCCEP after treatment with camrelizumab [16]. This study was one of the few reports directly exploring predictive factors for the risk of RCCEP, suggesting the potential value of peripheral blood test results in predicting RCCEP. Our study aimed to analyze baseline clinical characteristics and laboratory indicators that may be linked to the occurrence of RCCEP. The findings will help clinicians to early identify populations at high risk for RCCEP, allowing for personalized management.

Subjects and Methods

Study Subjects

This study was a single-center retrospective cohort study. The subjects were patients with advanced NSCLC who received camrelizumab treatment at our hospital from June 2022 to December 2024, with follow-up ending on June 30, 2025. Inclusion criteria: (1) underwent a minimum of two cycles of treatment of camrelizumab; (2) Age ≥ 18 years; (3) Histologically confirmed advanced NSCLC; (4) Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score of 0-3. Exclusion criteria: (1) Previous immunotherapy prior to using camrelizumab; (2) History of autoimmune diseases; (3) Coexisting with other malignant tumors; (4) Severe organ diseases such as heart, brain, and kidney disorders, intolerant to immunotherapy; (5) Death within 24 hours of admission; (6) Had medical records that were incomplete or missing. (7) Patients who could not be evaluated for adverse reactions due to loss to follow-up. This research was carried out in strict accordance with the Declaration of Helsinki and its later revisions.

Clinical Data Collection

We extracted baseline patient data from medical records, capturing information such as age, sex, smoking history, histological type, TNM stage, ECOG-PS score at admission, camrelizumab-containing treatment regimens, line of immunotherapy, along with the grading and initial identification date of RCCEP. Laboratory data obtained within one week before camrelizumab treatment were collected, including neutrophil count (Neu), lymphocyte count (L), eosinophil count (EOS), white blood cell count (WBC), platelet count (PLT), lymphocyte percentage (L%), neutrophil percentage (Neu%), eosinophil percentage (EOS%), lactate dehydrogenase (LDH), albumin level (ALB), C-reactive protein (CRP), and D-dimer (D-D).

Diagnosis and Assessment of RCCEP

The diagnostic and grading criteria for RCCEP were the following [7]:grade 1, nodule(s) with a maximum diameter of ≤ 10 mm, with or without rupture and bleeding; grade 2, nodule(s) with a maximum diameter of > 10 mm, with or without rupture and bleeding; grade 3, generalized nodules throughout the body, potentially complicated by skin infections; grade 4, multiple and generalized nodules accompanied by a life-threatening condition; and grade 5, death.

Statistical Methods

Data analysis was processed using SPSS 27.0 software (New York, USA) and GraphPad Prism (version 10.0, USA). Metric data following a normal distribution were presented as mean ± standard deviation, with independent samples t-tests employed for intergroup comparisons. Metric data not following

a normal distribution were presented as median (M) and interquartile range (Q1, Q3), with non-parametric tests used for intergroup comparisons. Count data were presented as frequency (n) and proportion (%), and compared using the chi-squared test. Univariate and multivariate logistic regression analyses were employed for factor analysis. Factors with P < 0.1 in univariate logistic regression were incorporated into multivariate logistic regression analysis. Receiver operating characteristic (ROC) curves and area under the curve (AUC) were used to evaluate the predictive ability of peripheral blood markers and their combinations for RCCEP. The cut-off values for peripheral blood markers at baseline were set based on the maximum Youden index on the ROC curve. P < 0.05 was considered statistically significant.

Results

Characteristics of the patients

This research enrolled 194 patients with advanced NSCLC who received camrelizumab therapy. Among them, 109 patients (56.2%) were aged ≥ 65 years, 166 patients (85.6%) were male, 122 patients (62.9%) had a smoking history, and 140 patients (72.2%) were in stage IV. There were 44 patients (22.7%) with squamous carcinoma and 150 patients (77.3%) with non-squamous carcinoma. The ECOG-PS score was 0-1 in 180 patients (92.8%). Camrelizumab was used as first-line treatment in 144 patients (74.2%). A total of 158 patients (81.4%) did not receive combined anti-angiogenic therapy, while 36 patients (18.6%) received combined anti-angiogenic therapy. (Table 1). Among 194 patients, 94 cases of RCCEP at different levels were reported, of which 92 cases developed grade 1-2 RCCEP, only 2 cases developed grade 3 RCCEP, with no grade 4-5 cases. No significant differences were found between the RCCEP group and non-RCCEP group regarding age, sex, histological type, smoking history, TNM stage, and ECOG PS score (P ≥ 0.05). However, baseline albumin level, baseline platelet count, and treatment regimen were associated with the development of RCCEP (P < 0.05), as indicated in Table 1. Among patients who received combined anti-angiogenic therapy, 1 received bevacizumab, 15 received anlotinib, 11 received Apatinib and 9 received recombinant human endostatin. (Table 2).

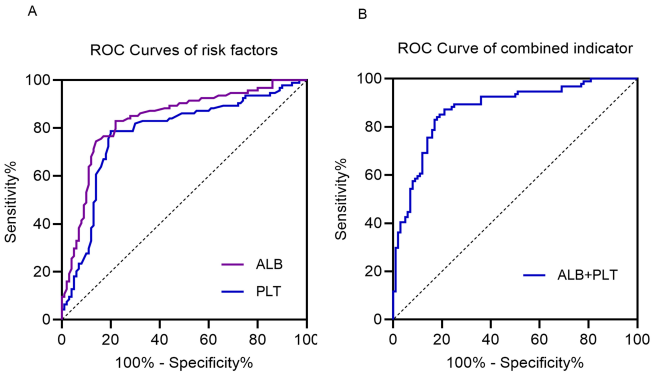
Risk factors for RCCEP

Table 3 presented the results of the univariate logistic regression analysis. Based on these results, we selected variables with P<0.10, including smoking history, treatment regimen, baseline albumin level and baseline platelet count, and incorporated them into the multivariate logistic regression model for further analysis. The findings indicated that not using combined anti-angiogenic drugs (OR: 2.962, 95% CI 1.042-8.422, P = 0.042), high baseline albumin level (OR: 1.422, 95% CI 1.264-1.599, P < 0.001), and high baseline platelet count (OR: 1.018, 95% CI 1.010-1.026, P < 0.001) were independent risk factors for the occurrence of RCCEP.

Predictive Value

(1) The AUC of ALB was 0.836, with an optimal cutoff value of 36.85, sensitivity of 0.830, and specificity of 0.780 (95% CI 0.777-0.895, P < 0.001); (2) The AUC of PLT was 0.778, with an optimal cutoff value of 225, sensitivity of 0.787, and specificity of 0.800 (95% CI 0.709-0.847, P < 0.001); (3) The AUC of the combination of both was 0.874, with sensitivity of 0.872 and specificity of 0.790 (95% CI 0.823-0.924, P < 0.001). Based on the maximum Youden index from the ROC curves, the cutoff values for ALB and PLT were 36.85 g/L and 225×10^9/L, respectively (Table 4). The ROC curves for ALB, PLT, and the combination of both were shown in Figure 1.

Figure 1. The ROC curves of risk factors for RCCEP in advanced NSCLC. Notes: ROC, receiver operating characteristics; RCCEP, reactive cutaneous capillary endothelial proliferation; ALB, albumin level; PLT, low density lipoprotein; NSCLC, non-small cell lung cancer.



Discussion

Lung cancer ranks among the top malignant tumors worldwide in terms of incidence and mortality, seriously threatening public health. The emergence of ICIs has significantly improved the prognosis of patients with advanced NSCLC. Camrelizumab, as the first domestically approved PD-1 inhibitor, is widely used in the treatment of lung cancer and other solid tumors, marking a new chapter in domestic immunotherapy. In recent years, several clinical studies on camrelizumab have revealed that, in addition to the common irAEs associated with ICIs, there is a relatively special irAE known as RCCEP. RCCEP is an irAE that mainly occurs in the skin, characterized by increased capillaries in the dermis and endothelial cell proliferation in capillaries. The exact mechanism remains unclear. Furthermore, more and more studies suggest that RCCEP is associated with the efficacy of immunotherapy. Recently, Lou et al. conducted a pooled analysis of two phase III registration studies on carelizumab in treating advanced esophageal squamous cell carcinoma(ESCC). The results indicated that patients who experienced RCCEP during carelizumab treatment had better objective response rates (ORR), longer median progression-free survival (mPFS), and longer median overall survival (mOS) compared to those who did not experience RCCEP [17]. This result further supports the possibility that the development of RCCEP is linked to better treatment response and survival benefits, suggesting it could serve as a potential biomarker for anti-tumor immunotherapy. This study retrospectively enrolled patients with advanced NSCLC who received camrelizumab treatment at our center from June 2022 to December 2024. It investigated the real-world incidence rate of RCCEP, studied its clinical characteristics and potential predictive factors. The study results showed that 94 patients (48.5%) with advanced NSCLC treated with camrelizumab developed RCCEP. Most cases were grade 1-2. The RCCEP

lesions were mainly distributed on the skin of the head, face, and trunk, and were predominantly red nevus-like (47.9%) and pearl-like (38.3%). Most cases of RCCEP did not require special management. In a small number of patients, symptoms improved significantly after symptomatic treatment. Only 2 patients with grade 3 RCCEP (4.2%) temporarily discontinued camrelizumab treatment to avoid further functional impairment. No life-threatening serious adverse events occurred in any patient. Multivariate logistic regression analysis indicated that not using anti-angiogenic drugs in combination, high baseline albumin level, and high baseline platelet count were independent risk factors for RCCEP occurrence.

Camrelizumab may activate CD4+ T lymphocytes, increase the release of the inflammatory factor interleukin-4 (IL-4), and subsequently induce the differentiation of CD163+ M2 macrophages, which release vascular endothelial growth factor A (VEGF-A) to promote angiogenesis [7]. Additionally, camrelizumab acts on PD-1-expressing cells in the skin and may trigger the release of chemokines, leading to VEGF synthesis [18]. The enhanced immune response induced by camrelizumab may lead to an imbalance in the expression of angiogenesis-related factors, thereby causing RCCEP. Therefore, the activation of the VEGF-A/VEGF receptor-2(VEGFR-2) signaling pathway and increased VEGF-A expression can partially explain the pathogenesis of RCCEP. Anti-angiogenic drugs may block the VEGF/VEGFR signaling pathway, inhibiting the occurrence of RCCEP. Several previous research have consistently demonstrated that combining camrelizumab with anti-angio-

Table 1. Baseline characteristics of patients.

Characteristics	Total (n=194)	Non-RCCEP (n=100)	RCCEP (n=94)	Statistic	P value
Age (years), n (%)					
≥65	109(56.2%)	57(57.0%)	52(55.3%)	0.056	0.814
<65	85(43.8%)	43(43.0%)	42(44.7%)		
Sex, n (%)					
Female	28(14.4%)	16(16.0%)	12(12.8%)	0.410	0.522
Male	166(85.6%)	84(84.0%)	82(87.2%)		
Smoking history, n (%)					
Current or former	122(62.9%)	57(57.0%)	65(69.1%)	3.064	0.080
None	72(37.1%)	43(43.0%)	29(30.9%)		
Histology, n (%)					
Squamous	44(22.7%)	22(22.0%)	22(23.4%)	0.054	0.815
Non-squamous	150(77.3%)	78(78.0%)	72(76.6%)		
Tumor staging, n (%)					
IIIB/IIIC	54(27.8%)	24(24.0%)	30(31.9%)	1.511	0.219
IV	140(72.2%)	76(76.0%)	64(68.1%)		
ECOG PS, n (%)					
<2	180(92.8%)	92(92.0%)	88(93.6%)	0.189	0.664
≥2	14(7.2%)	8(8.0%)	6(6.4%)		
Treatment regimen (Whether to combine with anti-angiogenic drugs), n (%)					
No	158(81.4%)	73(73.0%)	85(90.4%)	9.735	0.002*
Yes	36(18.6%)	27(27.0%)	9(9.6%)		
Treatment line, n (%)					
First-line	144(74.2%)	73(73.0%)	71(75.5%)	0.162	0.687
Second-line and above	50(25. 8%)	27(27.0%)	23(24.5%)		
Peripheral blood biomarkers					
WBC (×10 ^{9} /L)	—	6.71(5.29,8.06)	6.37(5.04,7.71)	1.030	0.303
Neu (×10 ^{9} /L)	—	4.39(3.23,5.86)	4.34(3.19,5.37)	0.578	0.563
L (×10 ^{9} /L)	—	1.44(1.10,1.88)	1.26(1.00,1.62)	1.888	0.059
EOS (×10 ^{9} /L)	—	0.13(0.04,0.26)	0.14(0.07,0.29)	1.133	0.257
PLT (×10 ^{9} /L)	—	197.00(160.75,216.25)	243.50(227.75,267.00)	6.677	<0.001*
L%	—	21.95(16.78,26.90)	20.95(14.85,26.93)	0.604	0.546
Neu% (mean ± SD)	—	66.66±9.92	66.73±9.59	0.051	0.959
EOS%	—	1.80(0.73,3.98)	2.15(1.10,3.73)	0.915	0.360
ALB (mean ± SD, g/L)	—	34.46±3.85	39.32±3.70	8.964	<0.001*
LDH(U/L)	—	205.00(169.25,240.65)	190.40(166.53,235.85)	1.189	0.235
CRP (mg/L)	—	3.55(1.29,11.57)	5.15(1.39,21.79)	0.873	0.383
D-D(μg/mL)	—	0.70(0.53,1.15)	0.62(0.40,1.27)	1.231	0.218

Notes: Student's t-test or Mann-Whitney U test was used for continuous variables; Chi-square test was used for categorical variables. *: P-values < 0.05 represented statistical significant.

genic drugs significantly cuts down on RCCEP occurrences. In a Phase II clinical trial of camrelizumab monotherapy for hepatocellular carcinoma, the incidence of RCCEP was 66.8% [7], while in another trial of camrelizumab combined with apatinib for hepatocellular carcinoma, the RCCEP incidence was only 29.5% [19]. Furthermore, a large-scale pooled analyses encompassing ten clinical trials also indicated that RCCEP occurrence rates were substantially higher among patients receiving camrelizumab alone (77%) or camrelizumab alongside chemotherapy (67.8%) compared to those treated with the combination of camrelizumab and anti-angiogenic drugs (23.6%) [20]. Based on these results, it seems that combining anti-angiogenic drugs may help mitigate the incidence of RCCEP.

Earlier research indicated that elevated serum albumin may increase the risk of immune-related disorders [21-23]. Patients with high serum albumin level and good ECOG scores are more likely to experience irAEs due to better nutritional status and overall condition [24], and this may be associated with a better prognosis [21, 25-26]. It is speculated that good nutritional status may make the immune system more active, and compared to patients with poor nutritional status, these patients are more likely to develop irAEs. No study has yet analyzed the relationship between RCCEP, a specific adverse reaction, and serum albumin level. In this study, multivariate logistic regression analysis found that higher baseline albumin level is an independent risk factor for RCCEP. The level of serum albumin typically serves as an indicator of a patient's nutritional condition and overall immune activation potential, and elevated level may indicate that the immune system is relatively active, potentially leading to multi-organ irAEs, including RCCEP. In addition, serum albumin can also influence the activation of inflammatory cytokines. Studies have shown that when albumin levels increase, prostaglandin

Table 2. The treatment regimen containing camrelizumab.

Variables	Total	Non-RCCEP(n=100)	RCCEP(n=94)
Combination with anti-angiogenic drugs			
Bevacizumab	1	1(100%)	0
Anlotinib	15	13(86.7%)	2(13.3%)
Apatinib	11	8(72.7%)	3(27.3%)
Recombinant human endostatin	9	5(55.6%)	4(44.4%)
Monotherapy or combination with chemotherapy	158	73(46.2%)	85(53.8%)

Table 3. Logistic regression analysis for risk factors of RCCEP.

Variables	Univariate logistic		Multivariate logistic	
	OR(95%CI)	P value	OR(95%CI)	P value
Age	0.934(0.530-1.647)	0.814		
Sex	0.768(0.342-1.724)	0.523		
Smoking history	1.691(0.937-3.051)	0.081*	1.814(0.800-4.113)	0.154
Histology	0.923(0.471-1.808)	0.815		
Stage	0.674(0.358-1.267)	0.220		
ECOG PS	0.784(0.261-2.351)	0.664		
Treatment regimen	3.493(1.544-7.905)	0.003*	2.962(1.042-8.422)	0.042*
Treatment line	0.876(0.460-1.669)	0.687		
Peripheral blood biomarkers				
WBC (×10 ^{9} /L)	0.931(0.828-1.047)	0.232		
Neu (×10 ^{9} /L)	0.941(0.825-1.073)	0.364		
L (×10 ^{9} /L)	0.667(0.386-1.153)	0.147		
EOS (×10 ^{9} /L)	0.935(0.335-2.609)	0.898		
PLT (×10 ^{9} /L)	1.017(1.011-1.024)	<0.001*	1.018(1.010-1.026)	<0.001*
L%	0.986(0.954-1.019)	0.392		
Neu%	1.001(0.972-1.030)	0.959		
EOS%	1.002(0.917-1.096)	0.961		
ALB (g/L)	1.431(1.282-1.598)	<0.001*	1.422(1.264-1.599)	<0.001*
LDH(U/L)	0.997(0.993-1.001)	0.111		
CRP (mg/L)	1.002(0.993-1.011)	0.712		
D-D(μg/mL)	0.877(0.718-1.070)	0.195		

Notes: *: P-values < 0.05 represented statistical significant.

Table 4. The predictive value of ALB, PLT, and their combined indicator for RCCEP.

Factors	AUC	Cut-off value	95%CI	Sensitivity	Specificity	P value
ALB (g/L)	0.836	36.85	0.777-0.895	0.830	0.780	<0.001
PLT (×10 ^{9} /L)	0.778	225	0.709-0.847	0.787	0.800	<0.001
combined indicator	0.874	0.425	0.823-0.924	0.872	0.790	<0.001

E2 levels decrease, which may induce the release of inflammatory cytokines, including tumor necrosis factor-α (TNFα) [27]. TNFα is a major mediator of cancer-related inflammation and has been found to have an indirect pro-angiogenic effect in recent years [28-29]. This may explain the association between elevated baseline albumin level and an increased risk of developing RCCEP. Therefore, the relationship between baseline albumin and RCCEP is worth further investigation.

In addition, the results of the multivariate logistic regression analysis revealed that a high platelet count at baseline independently increased the risk of RCCEP occurrence. Studies conducted in recent years suggest that platelets are key players in thrombosis and hemostasis, and they also contribute to a wide range of other physiological and pathological events, such as immunity, inflammation, tissue remodeling, and angiogenesis [30]. Abnormal activation of these processes may be an important basis for promoting RCCEP. Platelets serve as the main reservoir of VEGF and have been confirmed to have a direct pro-angiogenic effect. VEGF binds specifically to VEGFR2 on the surface of endothelial cells and activates intracellular signaling pathways, which is the key signal driving endothelial cell proliferation, migration, and new vessel formation. At the same time, after VEGF is released, it can also bind to various growth factor receptors, further strengthening the pro-angiogenic effect [30]. In addition to VEGF, platelets can release other types of pro-angiogenic factors, such as epidermal growth factor (EGF), transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), and basic fibroblast growth factor (bFGF) [31]. These factors work together and may provide the conditions for the abnormal blood vessel environment needed for RCCEP to occur. Importantly, there is a complex interaction between platelets and cancer cells. On one hand, cancer cells can activate platelets by releasing platelet-activating mediators such as adenosine diphosphate(ADP) and thromboxane A2(TXA2) or through direct cell contact [32]. On the other hand, activated platelets can further promote tumor cells to express pro-angiogenic factors [33], further driving abnormal angiogenesis. In addition, the role of platelets in immune regulation and inflammation may also promote the occurrence of RCCEP. In the bloodstream, platelets can directly interact with immune cells or activate immune cells by releasing mediators, and they can also affect endothelial cells, amplifying local inflammatory responses [34], which may further induce the occurrence of RCCEP. Further ROC curve analysis suggested that baseline albumin and platelet count at admission had some predictive values for the occurrence of RCCEP in immunotherapy, and their combined predictive value was higher. We also calculated the optimal cutoff values for albumin and platelet using the maximum Youden index from the ROC curve, which were 36.85 g/L and 225 × 10^9 / L, respectively. When the values exceeded these cutoff points, the risk of RCCEP increased. When using camrelizumab treatment, close attention should be paid to blood test indicators such as albumin level and platelet count.

The above study suggested that the choice of treatment regimen, as well as albumin level and platelet count at admission, could serve as important reference indicators for clinicians to predict RCCEP risk. For high-risk patients, health education should be strengthened before medication, focusing on the clinical characteristics and potential clinical significance of RCCEP. This can help patients set reasonable expectations, enhance treatment confidence, and prevent reduced medication adherence due to changes in appearance. During medication treatment, the frequency of skin monitoring should be increased, and relevant adverse reactions should be closely observed, with timely interventions taken. This study, based on baseline peripheral blood biomarkers and treatment regimens, predicted the occurrence of RCCEP, helping provide scientific medication guidance for advanced NSCLC patients receiving camrelizumab and enhancing patient confidence in treatment, ultimately achieving long-term treatment outcomes. At the same time, the results of this study also provided important clues for further exploration of the pathogenesis of RCCEP in the future.

Conclusion

In conclusion, not using combined anti-angiogenic drugs, high baseline albumin level and high baseline platelet count were independent risk factors for the occurrence of RCCEP in advanced NSCLC patients treated with camrelizumab. These factors had certain predictive values for RCCEP, with higher predictive value when combined. However, some limitations existed in this study, including its retrospective design and single-center nature, as well as the relatively small sample size. Future studies could address these issues by using a larger sample, conducting multi-center studies, and considering more potential factors to further validate the conclusions of this study.

Abbreviations

Adenosine diphosphate: ADP; Albumin level: ALB; Area under the curve: AUC; Basic fibroblast growth factor: bFGF; Confidence interval: CI; C-reactive protein: CRP; Cytotoxic T-lymphocyte antigen 4: CTLA-4; D-dimer: D-D; Eastern Cooperative Oncology Group performance status: ECOG PS; Epidermal growth factor: EGF; Eosinophil count: EOS; Eosinophil percentage: EOS%; Esophageal squamous cell carcinoma: ESCC; Immune checkpoint inhibitors: ICIs; Interleukin-4: IL-4; Immune-related adverse events: irAEs; Lymphocyte: L; Lymphocyte percentage: L%; Lactate dehydrogenase: LDH; Median overall survival: mOS; Median progression-free survival: mPFS; Neutrophil: Neu; Neutrophil percentage: Neu%; Non-small cell lung cancer: NSCLC; Objective response rates: ORR; Programmed cell death protein 1: PD-1; Programmed cell death protein ligand 1: PD-L1; Platelet-derived growth factor: PDGF; Platelet count: PLT; Reactive cutaneous capillary endothelial proliferation: RCCEP; Transforming growth factor-β: TGF-β; Tumor necrosis factor-α: TNFα; Thromboxane A2: TXA2; Vascular endothelial growth factor A: VEGF-A; White blood cell: WBC.

Author Contributions

Liuning Wang, Shuxing Chen and Siyu Sun contributed equally to this work. All authors contributed to the research design and conceptualization. Siyu Sun and Wenyi Li were responsible for data collection and analysis, while Liuning Wang, Shuxing Chen, and Congjun Zhang, were involved in writing the article.

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Ethics Approval and Consent to Participate

The study was reviewed and approved by the Medical Ethics Committee of the First Clinical Medical College (First Affiliated Hospital) (PJ2023-08–35). The written informed consent was obtained from patients in accordance with the Declaration of Helsinki.

Competing Interests

The authors declare that they have no existing or potential commercial or financial relationships that could create a conflict of interest at the time of conducting this study.

Data Availability

All data needed to evaluate the conclusions in the paper are present in the paper or the Supplementary Materials. Additional data related to this paper may be requested from the authors.

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