Original Article

Association between reactive cutaneous capillary endothelial proliferation and the efficacy of camrelizumab in esophageal cancer: a retrospective cohort study

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Background: Reactive cutaneous capillary endothelial proliferation (RCCEP) is a common immune-related adverse event (irAE) related to camrelizumab. This study sought to investigate the relationship between RCCEP and the treatment efficacy of camrelizumab in esophageal cancer (EC), and to explore the risk factors for RCCEP.

Methods: This retrospective study collected the data of patients with EC who were treated with camrelizumab between November 2019 and November 2023. The patients were divided into RCCEP-negative groups and RCCEP-positive groups based on the occurrence of RCCEP. Subsequently, the Chi-squared test was applied to analyze the differences in objective response rate (ORR) and disease control rate (DCR) between the two groups. The association between progression-free survival (PFS) or overall survival (OS), and RCCEP was analyzed by the log-rank test. The factors associated with RCCEP were analyzed using univariable and multivariable Logistic regression analyses. Data cutoff was on February 2, 2024.

Results: In total, 397 patients were included in this study, of whom 128 (32.24%) suffered from RCCEP. There were no significant differences in the baseline characteristics of the patients in the RCCEP-negative and RCCEP-positive groups. Among the patients with RCCEP, seven had grade 3 RCCEP, and none had grade 4 or 5 RCCEP. Compared with the patients without RCCEP, those with RCCEP had a significantly higher ORR (71.09% *vs.* 43.87%, P<0.001) and DCR (94.53% *vs.* 72.49%, P<0.001). In the multivariate Cox analysis, RCCEP was found to be independently associated with longer PFS (P<0.001) and OS (P<0.001). In the univariate Cox analysis of patients with RCCEP, neither RCCEP time nor grade was associated with prolonged PFS and OS. The multivariable logistic regression analysis revealed that more camrelizumab treatment cycles was significantly associated with a higher risk of RCCEP [odds ratio (OR) =1.24; 95% confidence interval (CI): 1.16–1.31] and camrelizumab combined with antiangiogenic therapy was significantly associated with a lower risk of RCCEP (OR =0.24; 95% CI: 0.07–0.86).

Conclusions: In the EC patients treated with camrelizumab, those with RCCEP had significantly better outcomes in terms of the ORR, DCR, PFS, and OS than those without RCCEP. The emergence of RCCEP may serve as a potential predictor for the therapeutic efficacy of camrelizumab in the treatment of EC. More camrelizumab treatment cycles and not receiving combined anti-angiogenic therapy were independent risk factors for RCCEP.

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Keywords: Camrelizumab; esophageal cancer (EC); reactive cutaneous capillary endothelial proliferation (RCCEP); immune-related adverse events (irAEs)

Submitted Feb 21, 2025. Accepted for publication Apr 22, 2025. Published online Apr 28, 2025.
doi: 10.21037/jtd-2025-366
View this article at: https://dx.doi.org/10.21037/jtd-2025-366

Introduction

Esophageal cancer (EC) is the seventh most common cancer and the sixth leading cause of cancer-related death worldwide (1). Traditional treatments, including chemotherapy and radiotherapy, have limited efficacy, and can cause serious adverse events. The emergence of immune checkpoint inhibitors (ICIs) has fostered renewed optimism in tumor treatment, and ICIs have been widely used to treat tumors such as EC, non-small cell lung cancer (NSCLC), melanoma, and renal cell carcinoma (1,2). ICIs relieve T-cell inhibition, and reactivate their anti-tumor cytolytic function by blocking the inhibitory pathway between T lymphocytes and tumor cells or antigen-presenting cells, thereby enhancing anti-tumor immunity (3). The two major classes of ICIs currently used in cancer immunotherapy are monoclonal antibodies targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4), and the programmed cell death 1 (PD-1)/programmed cell death-ligand 1 (PD-L1) axis. Compared with cytotoxic chemotherapy alone, the combination of chemotherapy with several ICIs, including nivolumab, pembrolizumab, and camrelizumab, has been shown to extend the overall survival (OS) and progression-free survival (PFS) of EC patients (4-6). However, ICIs not only boost the immune system of patients to fight disease but also enhance their body's immune response, resulting in immune-related adverse events (irAEs) (1). Unlike adverse events mediated by traditional cytotoxic drugs, irAEs are associated with an immune-mediated mechanism of action and may impact any other organ systems in the body. The most frequently affected organs include the skin, endocrine system, heart, gastrointestinal (GI) system, lungs, and liver (7,8). Severe irAEs can result in the discontinuation of patients' ICI anti-tumor treatment and can even be life-threatening (9,10). Since irAEs arise from a process of immune activation, this suggests that exhausted immune cells have been reinvigorated and are capable of attacking not only tumor cells but also normal tissues. Theoretically, the occurrence of irAEs may suggest a better response to ICI therapy. However, it remains unclear whether the occurrence of irAEs is associated with improved ICI outcomes in patients.

Camrelizumab, an ICI that targets PD-1, was developed by a Chinese pharmaceutical company. Based on the results of the Esophageal Squamous Cell Carcinoma Immunotherapy Research Trial (ESCORT)-1st trial, on December 8, 2021, camrelizumab was approved by the China National Medical Products Administration as the first-line treatment for patients with unresectable locally advanced/relapsed or metastatic EC in combination with paclitaxel and cisplatin (11). Other clinical studies have shown that camrelizumab combined with chemotherapy can be used as a neoadjuvant therapy for locally advanced EC (12-14). Camrelizumab is a humanized, high-affinity immunoglobulin G4 kappa monoclonal antibody against PD-1. It can activate $CD4^+$ T cells and increase the release of interleukin (IL)-4. IL-4 is an inflammatory

Highlight box

Key findings

- The occurrence of reactive cutaneous capillary endothelial proliferation (RCCEP) is closely associated with the efficacy of camrelizumab in the treatment of esophageal cancer (EC), specifically in terms of the objective response rate, disease control rate, progression-free survival (PFS), and overall survival (OS).

What is known and what is new?

- RCCEP is one of the most common immune-related adverse events (irAEs) of camrelizumab. The occurrence of RCCEP is positively correlated with the prognosis of non-small cell lung cancer and advanced hepatocellular carcinoma.
- In this study, the patients with RCCEP had better outcomes than those with other irAEs. Moreover, RCCEP time and grade had no relationship with extended PFS nor OS.

What is the implication, and what should change now?

- RCCEP was found to be a predictor of camrelizumab efficacy in the treatment of EC; thus, large prospective trials need to be conducted to confirm these findings. In addition, the mechanism of RCCEP was found to be able to predict the efficacy of EC treatments, which also needs to be further explored in future studies.

factor produced by T helper 2 (Th2) cells. IL-4 stimulates the differentiation of $CD163^+$ M2 macrophages, which promotes vascular regeneration by releasing vascular endothelial growth factor (VEGF)-A (15). In addition, camrelizumab acts on cells expressing PD-1 in the skin, which may lead to the synthesis of VEGF through the release of chemokines (16). It is thought that the enhanced immune response induced by camrelizumab may disrupt the dynamic balance between angiogenic and anti-angiogenic factors, leading to reactive cutaneous capillary endothelial proliferation (RCCEP). So far, the exact mechanisms of RCCEP remain unknown. RCCEP was the most frequently observed immune-related adverse reaction associated with camrelizumab treatment (11), and originally thought to be an irAE specific to camrelizumab. However, recent observations have indicated that RCCEP also occurs in patients with metastatic melanoma who are treated with nivolumab or pembrolizumab, although the incidence rate is relatively low at 2.4% (17). Previous studies have reported a positive correlation between RCCEP occurrence and prognosis in patients with NSCLC or advanced hepatocellular carcinoma (HCC) treated with carrilizumab (9,18). However, it remains unclear whether RCCEP occurrence can predict the efficacy of camrelizumab in treating patients with EC.

The strict eligibility criteria of randomized controlled trials may limit their generalizability to daily clinical practice and cannot fully capture the complexities of real-world treatment scenarios, we decided to conduct a real-world study. This study was conducted to investigate the association between RCCEP and the outcomes of camrelizumab-treated EC patients and to identify any related factors. Additionally, this study sought to clarify the risk factors for RCCEP to identify patients at high risk of RCCEP and to provide a foundation for future research on its mechanism of occurrence. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-2025-366/rc).

Methods

Study design and patients

This was a single-center retrospective cohort study of EC patients who were treated with camrelizumab at The Fourth Hospital of Hebei Medical University between November 2019 and November 2023. The last follow-up date was on February 2, 2024. To be eligible for inclusion in the study, the patients had to meet the following inclusion criteria: (I) had histologically confirmed EC; (II) had received at least one cycle of camrelizumab monotherapy or combined standard therapy (chemoradiotherapy or targeted therapy); (III) aged ≥18 years; (IV) had an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0–3; (V) had measurable lesions according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1); and (VI) had complete imaging data obtained before and after treatment. Patients were excluded from the study if they met any of the following exclusion criteria: (I) had previously received an immunotherapy treatment before the administration of camrelizumab; (II) had a history of autoimmune disease; (III) had a history of malignant tumors or other malignant tumors; (IV) had received neoadjuvant therapy with camrelizumab and had undergone surgical resection of EC after treatment; (V) had uncontrolled organic disease or infection, such as decompensated heart failure, lung failure, or kidney failure; and/or (VI) had incomplete or missing medical records. This study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Ethical Research Committee of The Fourth Hospital of Hebei Medical University (approval No. 2022KS014). Due to the retrospective nature of the study, the requirement of informed consent was waived.

Data collection and outcomes

Before initiating camrelizumab treatment, the medical records and the following patient characteristics were reviewed: patient age, sex, laboratory data, ECOG PS score, family history of cancer, stage, histology, metastatic status, history of alcohol consumption, history of smoking, lactate dehydrogenase (LDH) level, number of camrelizumab treatment cycles completed, combination treatment regimen (chemoradiotherapy, or targeted therapy), immunotherapy line, the start and end dates of camrelizumab treatment, the date of clinical or radiological disease progression based on RECIST 1.1 criteria, the date of death, the last known follow-up date (if the date of death was not recorded), as well as the grade and onset date of irAEs. Data regarding irAEs and laboratory examination values were collected from clinical notes, including hospital records. All irAEs were graded by senior physicians based on the Common Terminology Criteria for Adverse Events version 5.0. The grading criteria for RCCEP were defined as follows: 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. We defined the timing of RCCEP as the interval from the first camrelizumab dose to the occurrence of RCCEP. OS was calculated as the time from the first camrelizumab dose to death due to any causes. PFS was calculated as the time from the first camrelizumab dose to disease progression (clinical and/or radiographic) or death from any causes. The RECIST 1.1 was used to assess the treatment response. The objective response rate (ORR) was defined as the percentage of patients who achieved a complete response (CR) or partial response (PR) to immunotherapy. The disease control rate (DCR) was defined as the percentage of patients who had CR, PR, or stable disease (SD).

Prognostic nutritional index (PNI) was calculated by the formula 10 × albumin (g/dL) + 0.005 × lymphocyte count (/μL) (19). Body mass index (BMI) was defined as the weight before treatment divided by the square of the height; that is: BMI = weight (kg)/height (m^2). In accordance with previous research results (20-23), the truncation value of albumin, BMI, PNI, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) were set at 36.8 g/L, 18.5 kg/m^2, 45.7, 5, and 152, respectively.

The patients were divided into an RCCEP-positive group (with RCCEP or RCCEP+) and an RCCEP-negative group (without RCCEP or RCCEP–) based on the occurrence of RCCEP. Additionally, based on the occurrence of both RCCEP and irAEs, patients were categorized into a group that was RCCEP positive (with RCCEP or RCCEP+), a group that was irAE positive but RCCEP negative (with irAEs but without RCCEP or irAEs+, RCCEP–), and a group that was irAE negative (without irAEs or irAEs–). Differences in efficacy were analyzed according to the occurrence of RCCPE and irAEs.

Statistical analysis

The categorical data were described as the number (percentage), and the quantitative data were described as the median (range). The Chi-squared test was used to analyze the categorical data, and the Student's *t*-test was used to analyze the quantitative data. The survival data were evaluated by both Kaplan-Meier analysis and the log-rank test. Univariate and multivariate Cox regression analyses were conducted to identify potential predictive factors for PFS and OS. Variables with P value ≤0.10 in univariate analyses were included in the multivariate model, statistical significance was defined as P<0.05. The predictive factors of RCCEP were analyzed by logistic regression analyses. A two-tailed P value <0.05 was considered statistically significant. For the patients with RCCEP, as the timing of RCCEP onset varied widely, we incorporated RCCEP latency as a time-dependent covariate in the regression models. To identify a specific cut-off time when RCCEP development was most likely to influence outcomes, RCCEP latency was transformed from a continuous covariate to an ordinal variable with 1-month intervals in a time-dependent Cox regression model. To ensure that early death in patients with RCCEP did not interfere in determining the relationship between RCCEP timing and efficacy, we conducted a 6-month landmark analysis of the patients who developed RCCEP within 6 months after receiving camrelizumab treatment but who remained alive after this landmark time point. We used SPSS 26.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 8.0 (GraphPad Software, La Jolla, CA, USA) for the statistical analyses and data visualization.

Results

Patient characteristics

In total, 397 patients were included in the study. The patients had a median age of 66 (range, 27–87) years, and the majority were male (n=291, 73.30%). Their demographics and clinical backgrounds are detailed in *Table 1*. There were no significant differences in the baseline characteristics between the patients with and without RCCEP (*Table 1*).

Treatment patterns

Of the 397 patients, 297 (74.81%) received camrelizumab in the 1st line, 94 (23.68%) in the 2nd line, and 6 patients (1.51%) in the third line and above. Of the patients, 52 received immunotherapy alone, 320 received immunotherapy combined with chemotherapy, and 25 received immunotherapy combined with anti-angiogenic therapy. The median cycle was 3 (range, 1–38) times, and the median duration of camrelizumab treatment was 106 (range, 21–1,137) days. The specific treatment patterns are shown in *Table 2*. Of the patients treated with camrelizumab, 71 received one cycle of camrelizumab, 69 received two cycles, and 59 received

Table 1 Baseline characteristics of patients

Characteristics	All patients	RCCEP– group	RCCEP+ group	P value
Total	397 (100.00)	269 (67.76)	128 (32.24)	–
Age (years)	66 [27–87]	66 [27–87]	66 [42–84]	0.18
Sex				0.16
Female	106 (26.70)	66 (16.62)	40 (10.08)	
Male	291 (73.30)	203 (51.13)	88 (22.17)	
ECOG PS				0.55
<2	371 (93.45)	250 (62.97)	121 (30.48)	
≥2	26 (6.55)	19 (4.79)	7 (1.76)	
Family history of cancer				0.16
No	285 (71.79)	199 (50.13)	86 (21.66)	
Yes	112 (28.21)	70 (17.63)	42 (10.58)	
Histology				0.76
Squamous cell carcinoma	385 (96.98)	260 (65.49)	125 (31.49)	
Other	12 (3.02)	9 (2.27)	3 (0.76)	
Metastasis				0.67
No	211 (53.15)	141 (35.52)	70 (17.63)	
Yes	186 (46.85)	128 (32.24)	58 (14.61)	
Drinking history				0.92
No	200 (50.38)	136 (34.26)	64 (16.12)	
Yes	197 (49.62)	133 (33.50)	64 (16.12)	
Smoking history				0.07
No	188 (47.36)	119 (29.97)	69 (17.38)	
Yes	209 (52.64)	150 (37.78)	59 (14.86)	
LDH level				0.11
≤ ULN	380 (95.72)	254 (63.98)	126 (31.74)	
> ULN	17 (4.28)	15 (3.78)	2 (0.50)	
Stage				0.46
I	9 (2.27)	5 (1.26)	4 (1.01)	
II	75 (18.89)	49 (12.34)	26 (6.55)	
III	162 (40.81)	106 (26.70)	56 (14.11)	
IV	151 (38.04)	109 (27.46)	42 (10.58)	
Primary EC				0.09
Upper thoracic	105 (26.45)	68 (17.13)	37 (9.32)	
Middle thoracic	197 (49.62)	128 (32.24)	69 (17.38)	
Lower thoracic	95 (23.93)	73 (18.39)	22 (5.54)	

Data are presented as n (%) or median [range]. EC, esophageal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; RCCEP, reactive cutaneous capillary endothelial proliferation; ULN, upper limit of normal.

Table 2 Treatment patterns of camrelizumab

Variables	Data (n=397)
Treatment line, n (%)	
1	297 (74.81)
2	94 (23.68)
≥3	6 (1.51)
Systemic treatment, n (%)	
Camrelizumab alone	52 (13.10)
Camrelizumab plus chemotherapy	320 (80.60)
Albumin-bound paclitaxel plus platinum	179 (45.09)
Paclitaxel plus platinum	43 (10.83)
Albumin-bound paclitaxel	19 (4.79)
Docetaxel plus platinum	19 (4.79)
Paclitaxel	12 (3.02)
S-1 (tegafur-gimeracil-oteracil potassium)	9 (2.27)
Fluorouracil plus platinum plus folinic acid calcium salt hydrate	8 (2.02)
Capecitabine	6 (1.51)
Platinum	5 (1.26)
Capecitabine plus platinum	4 (1.01)
Etoposide plus platinum	4 (1.01)
Fluorouracil plus platinum	3 (0.76)
Irinotecan	2 (0.50)
S-1 plus platinum	2 (0.50)
Irinotecan plus capecitabine	1 (0.25)
Fluorouracil plus irinotecan plus folinic acid calcium salt hydrate	1 (0.25)
Albumin-bound paclitaxel plus S-1	1 (0.25)
Fluorouracil	1 (0.25)
Fluorouracil plus folinic acid calcium salt hydrate	1 (0.25)
Camrelizumab plus chemotherapy and antiangiogenic therapy	10 (2.52)
Docetaxel plus platinum plus apatinib	3 (0.76)
Paclitaxel plus platinum plus apatinib	2 (0.50)
Albumin-bound paclitaxel plus apatinib	2 (0.50)
Etoposide plus platinum plus apatinib	1 (0.25)
Fluorouracil plus platinum plus folinic acid calcium salt hydrate plus apatinib	1 (0.25)
Irinotecan plus S-1 plus apatinib	1 (0.25)
Camrelizumab plus antiangiogenic therapy	15 (3.78)
Apatinib	8 (2.02)

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Data
Anlotinib	5 (1.26)
Bevacizumab	1 (0.25)
Recombinant human endostatin	1 (0.25)
Combination of radiotherapy, n (%)	
No	197 (49.62)
Yes	200 (50.38)
Cycle of camrelizumab (times), median [range]	3 [1–38]
Duration of camrelizumab (days), median [range]	106 [21–1,137]

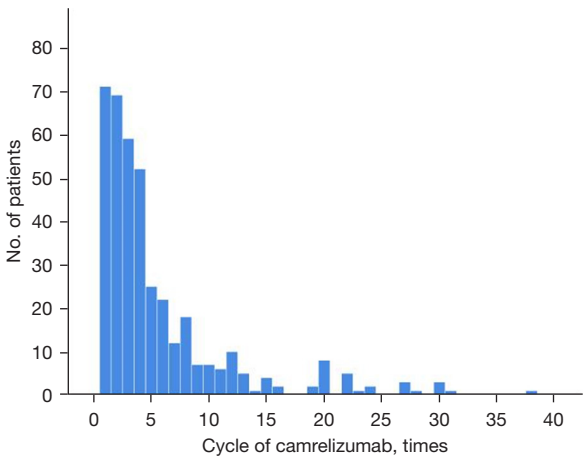

Figure 1 Number of patients by treatment cycles.

three cycles. The number of patients by treatment cycles are shown in *Figure 1*.

Incidence of irAEs

In total, 192 (48.36%) patients experienced irAEs. Of these patients, 28 (7.05%) experienced grade 3 or higher irAEs, but no grade 5 irAEs were observed. In total, 152 (35.32%) and 40 (8.49%) patients had a single irAE and multiple irAEs, respectively. In total, 128 (32.24%) patients suffered from RCCEP. Of the patients with RCCEP, seven (1.76%) had grade 3 RCCEP, but no patient had grade 4 or 5 RCCEP. Among the patients who experienced irAEs, 25 (6.30%) were treated with glucocorticoids for serious events, and 23 (5.80%) required hormonal replacement therapy for endocrine-related issues; however, no deaths due to irAEs occurred. For further details about the irAEs, see *Table 3*.

We also analyzed the incidence of irAEs associated with camrelizumab by cycle. We found that 82.81% (106/128) of RCCEP events occurred within 3 months of the first administration of camrelizumab, and the highest incidence of RCCEP was observed at 2–3 months (*Figure 2A*). A total of 242 irAEs occurred in 191 patients, 78.53% (150/191) of RCCEP events occurred within 3 months after the first administration of camrelizumab, and the highest incidence of irAEs was observed at 1–2 months (*Figure 2B*). The median follow-up time was 18.23 (range, 0.23–50.87) months.

Univariate and multivariate Cox analyses of PFS and OS

The univariate Cox analysis revealed that the >3 treatment cycles, the presence of irAEs or RCCEP, a BMI ≥18.5 kg/m^2, albumin >36.8 g/L, and a PNI ≥45.7 were significantly associated with longer PFS. An ECOG PS score ≥2, LDH > upper limit normal (ULN), the ≥ 2nd line therapy, a NLR >5, and a PLR >152 were associated with shorter PFS. The variables with a P value ≤0.10 in the univariate Cox analysis were included in the multivariate Cox analysis. The multivariate analysis showed that the presence of RCCEP and albumin >36.8 g/L were independent factors associated with longer PFS. The ≥ 2nd line therapy and a NLR >5 were independent factors associated with shorter PFS (*Table 4*).

The univariate Cox analysis indicated that the >3 treatment cycles, the presence of irAEs or RCCEP, a BMI ≥18.5 kg/m^2, albumin >36.8 g/L, and a PNI ≥45.7 were significantly associated with longer OS. An ECOG PS score ≥2, LDH > ULN, the ≥ 2nd line therapy, a NLR >5, and a PLR >152 were associated with shorter OS. The variables

Table 3 irTAEs according to CTCAE-V 5.0

Category	Total	Grade 1	Grade 2	Grade 3	Grade 4
Any	242 (60.96)	128 (32.24)	86 (21.66)	25 (6.30)	3 (0.76)
RCCEP	128 (32.24)	85 (21.41)	36 (9.07)	7 (1.76)	0 (0.00)
irTAEs	46 (11.59)	22 (5.54)	21 (5.29)	3 (0.76)	0 (0.00)
Skin rash/itch	17 (4.28)	8 (2.02)	5 (1.26)	3 (0.76)	1 (0.25)
Pneumonitis	13 (3.27)	1 (0.25)	8 (2.02)	4 (1.01)	0 (0.00)
Cardiovascular toxicities	7 (1.76)	1 (0.25)	5 (1.26)	1 (0.25)	0 (0.00)
Diarrhea/colitis	5 (1.26)	2 (0.50)	1 (0.25)	2 (0.50)	0 (0.00)
Infusion-related reactions	5 (1.26)	1 (0.25)	3 (0.76)	1 (0.25)	0 (0.00)
Elevated transaminase	4 (1.01)	0 (0.00)	2 (0.50)	1 (0.25)	1 (0.25)
Nephritis	4 (1.01)	1 (0.25)	1 (0.25)	1 (0.25)	1 (0.25)
Arthritis	4 (1.01)	3 (0.76)	1 (0.25)	0 (0.00)	0 (0.00)
Hyperglycemia	3 (0.76)	2 (0.50)	1 (0.25)	0 (0.00)	0 (0.00)
Myositis	3 (0.76)	1 (0.25)	1 (0.25)	1 (0.25)	0 (0.00)
Adrenal hypofunction	2 (0.50)	1 (0.25)	0 (0.00)	1 (0.25)	0 (0.00)
Neurovirulence	1 (0.25)	0 (0.00)	1 (0.25)	0 (0.00)	0 (0.00)

Data are presented as n (%). CTCAE-V 5.0, Common Terminology Criteria for Adverse Events Version 5.0; irTAEs, immune-related thyroid adverse events; RCCEP, reactive cutaneous capillary endothelial proliferation.

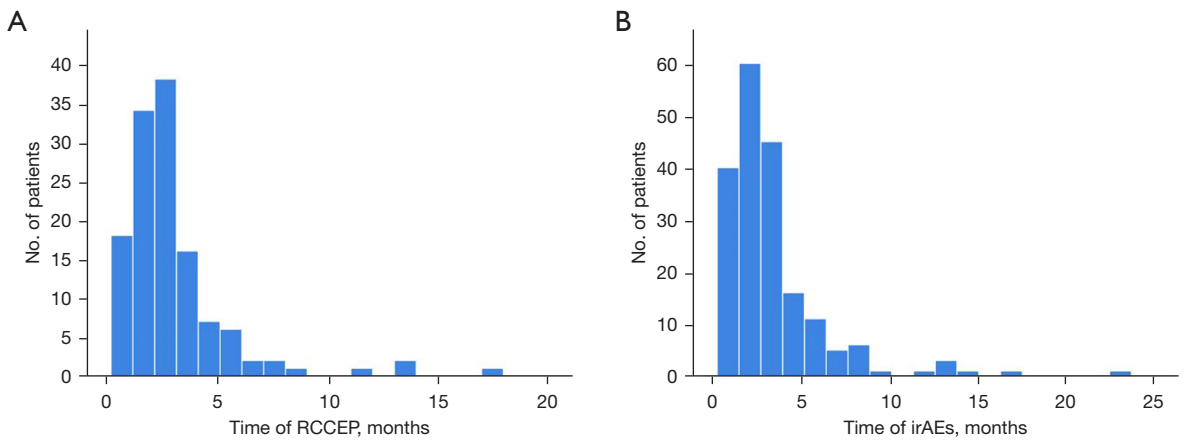

Figure 2 Number of patients with (A) RCCEP and (B) irAEs by onset time. irAEs, immune-related adverse events; RCCEP, reactive cutaneous capillary endothelial proliferation.

with a P value ≤0.10 in the univariate Cox analysis were included in the multivariate Cox analysis. The multivariate analysis revealed that the presence of irAEs or RCCEP and albumin >36.8 g/L were independent factors for longer OS. An ECOG PS score ≥2, the ≥ 2nd line therapy, and a NLR >5 were independent factors associated with shorter OS (*Table 5*).

Age, sex, a family history of cancer, histology, metastasis, a history of alcohol consumption, a history of smoking, treatment type, radiation, and immune-related thyroid adverse events (irTAEs) were not found to be associated with PFS nor OS (*Tables 4,5*).

Table 4 Univariable and multivariate Cox regression analyses of PFS

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years) (*vs*. <65)				
≥65	0.97 (0.74–1.28)	0.86		
Sex (*vs*. female)				
Male	1.18 (0.86–1.62)	0.30		
ECOG PS (*vs*. <2)				
≥2	2.81 (1.78–4.43)	<0.001*		
Family history of cancer (*vs*. no)				
Yes	1.03 (0.76–1.39)	0.87		
Histology (*vs*. squamous cell carcinoma)				
Other	1.25 (0.59–2.67)	0.56		
Metastasis (*vs*. no)				
Yes	1.28 (0.98–1.68)	0.08		
Drinking history (*vs*. no)				
Yes	0.98 (0.75–1.29)	0.88		
Smoking history (*vs*. no)				
Yes	1.03 (0.78–1.35)	0.85		
LDH level (*vs*. ≤ ULN)				
> ULN	2.43 (1.39–4.28)	0.02*		
Cycles (*vs*. ≤3)				
>3	0.48 (0.36–0.63)	<0.001*		
Treatment type (*vs*. monotherapy)				
Combined therapy	0.74 (0.51–1.07)	0.11		
Radiation (*vs*. no)				
Yes	1.15 (0.88–1.52)	0.31		
Line of therapy (*vs*. 1st)				
≥ 2nd	1.65 (1.23–2.22)	0.001*	1.47 (1.06–2.03)	0.02*
irAEs (*vs*. irAEs–)				
irAEs+	0.25 (0.18–0.34)	<0.001*		
RCCEP (*vs*. RCCEP–)				
RCCEP+	0.10 (0.06–0.16)	<0.001*	0.14 (0.08–0.25)	<0.001*
BMI (kg/m^2) (*vs*. <18.5)				
≥18.5	0.61 (0.42–0.88)	0.01*		
Albumin (g/L) (*vs*. ≤36.8)				
>36.8	0.39 (0.28–0.55)	<0.001*	0.64 (0.43–0.95)	0.03*

Table 4 (*continued*)

Table 4 (*continued*)

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
PNI (*vs*. <45.7)				
≥45.7	0.70 (0.53–0.93)	0.01*		
NLR (*vs*. ≤5)				
>5	1.76 (1.31–2.37)	<0.001*	1.54 (1.09–2.17)	0.02*
PLR (*vs*. ≤152)				
>152	1.97 (1.44–2.70)	<0.001*		

*, represents P<0.05. BMI, body mass index; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; irAEs, immune-related adverse events; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PFS, progression-free survival; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; RCCEP, reactive cutaneous capillary endothelial proliferation; ULN, upper limit of normal.

Table 5 Univariable and multivariate Cox regression analyses of OS

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years) (*vs*. <65)				
≥65	1.03 (0.79–1.36)	0.82		
Sex (*vs*. female)				
Male	1.18 (0.86–1.61)	0.31		
ECOG PS (*vs*. <2)				
≥2	3.29 (2.08–5.20)	<0.001*	1.92 (1.15–3.23)	0.01*
Family history of cancer (*vs*. no)				
Yes	0.97 (0.72–1.31)	0.84		
Histology (*vs*. squamous cell carcinoma)				
Other	0.99 (0.47–2.12)	0.99		
Metastasis (*vs*. no)				
Yes	1.21 (0.92–1.59)	0.17		
Drinking history (*vs*. no)				
Yes	0.98 (0.75–1.29)	0.88		
Smoking history (*vs*. no)				
Yes	1.03 (0.78–1.35)	0.85		
LDH level (*vs*. ≤ ULN)				
> ULN	1.95 (1.11–3.4)	0.02		
Cycles (*vs*. ≤3)				
>3	0.44 (0.33–0.59)	<0.001*		

Table 5 (*continued*)

Table 5 (*continued*)

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Treatment type (*vs*. monotherapy)				
Combined therapy	0.74 (0.51–1.07)	0.11		
Radiation (*vs*. no)				
Yes	1.12 (0.85–1.48)	0.41		
Line of therapy (*vs*. 1st)				
≥ 2nd	1.51 (1.13–2.03)	<0.01*	1.41 (1.02–1.94)	0.04*
irAEs (*vs*. irAEs–)				
irAEs+	0.23 (0.17–0.31)	<0.001*	0.67 (0.46–0.97)	<0.03*
RCCEP (*vs*. RCCEP–)				
RCCEP+	0.09 (0.06–0.16)	<0.001*	0.14 (0.08–0.26)	<0.001*
BMI (kg/m^2) (*vs*. <18.5)				
≥18.5	0.59 (0.41–0.85)	0.004		
Albumin (g/L) (*vs*. ≤36.8)				
>36.8	0.36 (0.25–0.51)	<0.001	0.59 (0.40–0.88)	<0.01*
PNI (*vs*. <45.7)				
≥45.7	0.70 (0.53–0.93)	0.01		
NLR (*vs*. ≤5)				
>5	1.72 (1.28–2.31)	<0.001	1.55 (1.10–2.19)	<0.01*
PLR (*vs*. ≤152)				
>152	2.02 (1.47–2.77)	<0.001		

*, represents P<0.05. BMI, body mass index; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; irAEs, immune-related adverse events; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; RCCEP, reactive cutaneous capillary endothelial proliferation; ULN, upper limit of normal.

Association between RCCEP and the efficacy of camrelizumab

Compared to those without RCCEP, the patients with RCCEP had a higher ORR (71.09% *vs.* 43.87%, P<0.001) and DCR (94.53% *vs.* 72.49%, P<0.001) (*Table 6*). The 397 patients who received camrelizumab treatment had a median PFS of 16.5 months [95% confidence interval (CI): 12.3–20.6] (*Figure 3A*), and a median OS of 23.1 months (95% CI: 18.8–27.4) (*Figure 3B*). The patients in the RCCEP-positive group had a higher median PFS than those in the RCCEP-negative group [not reached *vs.* 9.8 months; hazard ratio (HR) =0.10; 95% CI: 0.06–0.16; P<0.001] (*Figure 3C*). Moreover, the patients in the RCCEP-positive group had a higher median OS than those in the RCCEP-negative group (not reached *vs.* 14.5 months; HR =0.09; 95% CI: 0.06–0.16; P<0.001) (*Figure 3D*). The patients in the RCCEP-positive group had a higher median PFS than those in the irAE-positive, RCCEP-negative group (not reached *vs.* 13.2 months, P<0.001); the patients in the RCCEP-positive group had a higher median PFS than those in the irAE negative group (not reached *vs.* 8.6 months, P<0.001); the patients in the irAE-positive, RCCEP-negative group had a higher median PFS than those in the irAE negative group (13.2 *vs.* 8.6 months, P=0.01) (*Figure 3E*). The patients in the RCCEP-positive group had a higher median OS than those in the irAE-positive, RCCEP-negative group (not reached *vs.* 20.4 months, P<0.001); the patients in the

Table 6 Best overall response during camrelizumab according to RECIST 1.1

Variables	All patients	RCCEP– group	RCCEP+ group	P value
Total, n	397	269	128	–
CR, n	49	11	38	–
PR, n	160	107	53	–
SD, n	107	77	30	–
PD, n	81	74	7	–
ORR (%)	52.64	43.87	71.09	<0.001
DCR (%)	79.60	72.49	94.53	<0.001

CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; RCCEP, reactive cutaneous capillary endothelial proliferation; RECIST 1.1, Response Evaluation Criteria in Solid Tumor version 1.1; SD, stable disease.

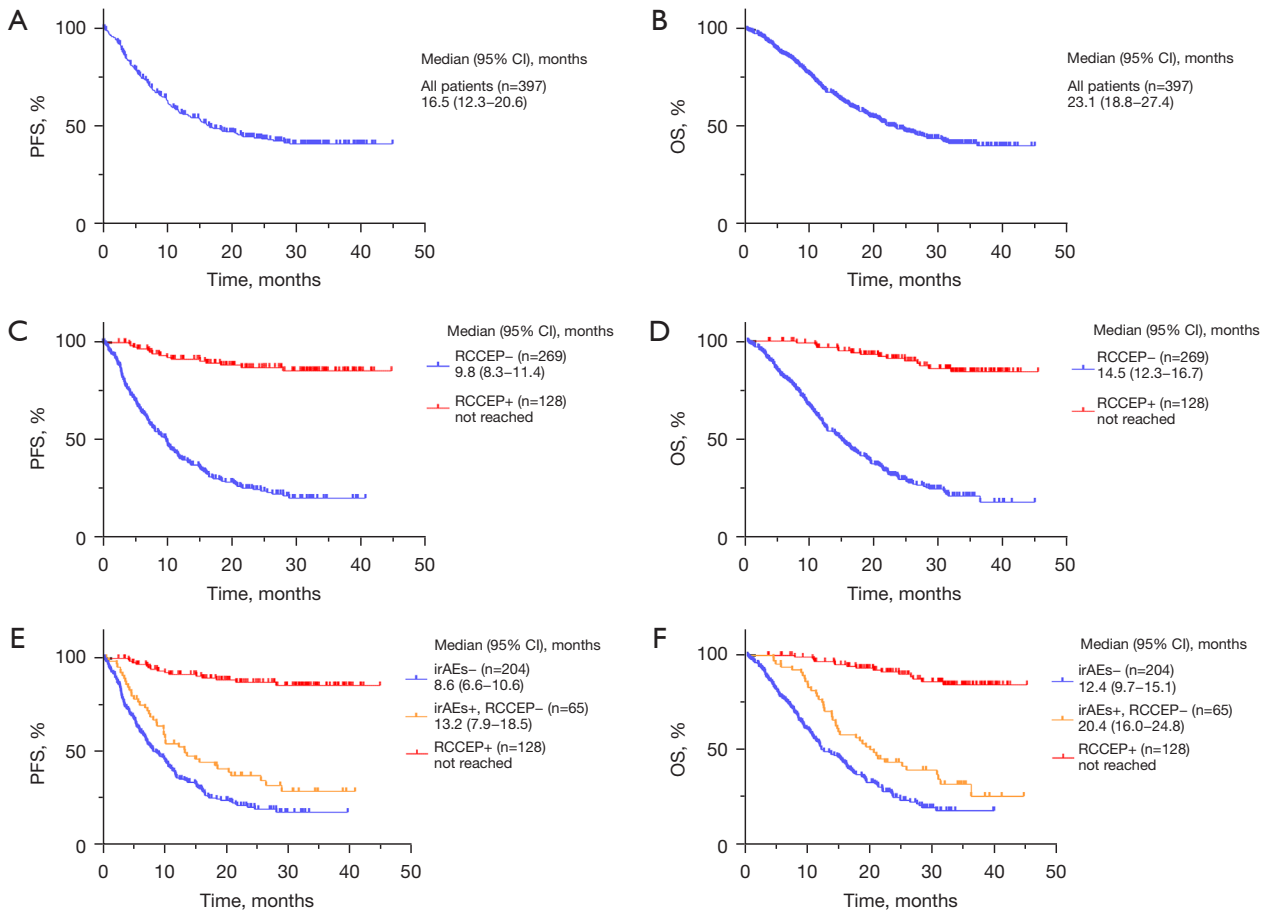

Figure 3 PFS and OS after the camrelizumab treatment using the Kaplan-Meier method. Kaplan-Meier curves for the (A) PFS and (B) OS of all patients; the (C) PFS and (D) OS of patients with or without RCCEP; the (E) PFS and (F) OS of patients without irAEs, with irAEs but without RCCEP, and with RCCEP. CI, confidence interval; irAEs, immune-related adverse events; OS, overall survival; PFS, progression-free survival; RCCEP, reactive cutaneous capillary endothelial proliferation.

Table 7 Cox regression model of OS and PFS of patients who developed RCCEP with RCCEP latency and the grade of RCCEP as ordinal variables

Variables	PFS		OS	
	HR (95% CI)	P value	HR (95% CI)	P value
Time to RCCEP				
≤1 month	Reference		Reference	
>1 and ≤2 months	0.43 (0.06–3.06)	0.40	0.37 (0.05–2.65)	0.32
>2 and ≤3 months	0.82 (0.15–4.46)	0.82	0.69 (0.13–3.78)	0.67
>3 and ≤5 months	1.39 (0.27–7.19)	0.69	1.21 (0.23–6.27)	0.82
>5 months	1.14 (0.16–8.10)	0.90	0.95 (0.13–6.74)	0.96
Grade of RCCEP				
1	Reference		Reference	
2	0.99 (0.30–3.21)	0.98	0.91 (0.28–2.95)	0.87
3	2.69 (0.58–12.48)	0.21	2.46 (0.53–11.40)	0.25

CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RCCEP, reactive cutaneous capillary endothelial proliferation.

RCCEP-positive group had a higher median OS than those in the irAE-negative group (not reached *vs.* 12.4 months, P<0.001); the patients in the irAE-positive, RCCEP-negative group had a higher median OS than those in the irAE negative group (20.4 *vs.* 12.4 months, P=0.01) (*Figure 3F*).

In the time-dependent Cox regression model of patients who developed RCCEP and that included RCCEP latency as an ordinal variable, there was no difference in the PFS or OS between the patients who developed RCCEP 2–5 months and >5 months after the initiation of camrelizumab treatment compared to those who developed RCCEP within the first month of treatment (*Table 7*).

In the Cox regression model that included RCCEP grade as a sequential variable, there was no difference in the PFS or OS between the patients who developed grade 2 and 3 RCCEP after camrelizumab treatment compared to those who developed grade 1 RCCEP (*Table 7*).

Modified 6-month landmark analysis of patients who developed RCCEP

A modified 6-month landmark survival analysis was conducted for patients with RCCEP, aiming to explore whether the survival difference between early-onset and late-onset RCCEP patients was entirely attributed to the early death of early-onset patients. In this analysis, patients who died within 6 months or developed RCCEP after 6 months were excluded. The reduced sample size of this analysis might have introduced an additional source of bias; however, it helped to alleviate the influence of immortal time bias. No significant association between RCCEP time and PFS or OS (*Table 8*) was found in the univariate Cox regression analyses.

Prognostic factors predicting RCCEP

The risk factors of RCCEP were determined through logistic regression analysis. The variables with a P value ≤0.10 in the univariate logistic analysis (i.e., smoking history, LDH level, treatment cycles, albumin, the PLR, and the neutrophil count) were included in the multivariate logistic regression analysis, which showed that more camrelizumab treatment cycles were independently associated with a higher risk of RCCEP [odds ratio (OR) =1.24; 95% CI: 1.16–1.31; P<0.001], and camrelizumab combined with an anti-angiogenic agent was independently associated with a lower risk of RCCEP (OR =0.24; 95% CI: 0.07–0.86; P=0.03) (*Table 9*).

Discussion

In this retrospective study, 32.24% of the EC patients treated with camrelizumab developed RCCEP, but the symptoms of RCCEP were mild in most patients. The incidence rate of irTAEs was 11.59%, while that of other irAEs was <5%. A positive correlation was found between

Table 8 Cox regression model of OS and PFS of patients who developed RCCEP with RCCEP latency as an ordinal variable in the 6-month landmark analyses

Variables	PFS		OS	
	HR (95% CI)	P value	HR (95% CI)	P value
Time to RCCEP				
≤1 month	Reference		Reference	
>1 and ≤2 months	0.42 (0.06–3.01)	0.39	0.38 (0.05–2.68)	0.33
>2 and ≤3 months	0.80 (0.15–4.37)	0.80	0.70 (0.13–3.82)	0.68
>3 and ≤5 months	1.36 (0.26–7.04)	0.71	1.23 (0.24–6.38)	0.80
>5 and ≤6 months	1.81 (0.16–19.98)	0.63	1.37 (0.12–15.15)	0.80

CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RCCEP, reactive cutaneous capillary endothelial proliferation.

Table 9 Logistic regression analysis for the associated factors of RCCEP

Variables	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.01 (0.98–1.03)	0.65		
Gender (*vs*. female)				
Male	0.72 (0.45–1.14)	0.16		
ECOG PS (*vs*. <2)				
≥2	0.76 (0.31–1.86)	0.55		
Family history of cancer (*vs*. ≤no)				
Yes	1.39 (0.88–2.20)	0.16		
Histology (*vs*. squamous cell carcinoma)				
Other	0.69 (0.18–2.61)	0.59		
Metastasis (*vs*. no)				
Yes	0.91 (0.60–1.40)	0.67		
Drinking history (*vs*. no)				
Yes	1.02 (0.67–1.56)	0.92		
Smoking history (*vs*. no)				
Yes	0.68 (0.45–1.04)	0.07		
LDH level (*vs*. ≤ ULN)				
> ULN	0.27 (0.06–1.19)	0.08		
Cycles (*vs*. ≤3)				
>3	1.23 (1.16–1.30)	<0.001*	1.24 (1.16–1.31)	<0.001*
Antiangiogenic therapy (*vs*. no)				
Yes	0.27 (0.08–0.92)	0.04*	0.24 (0.07–0.86)	0.03*
Radiation (*vs*. no)				
Yes	1.12 (0.74–1.71)	0.59		

Table 9 (*continued*)

Table 9 (*continued*)

Variables	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Line of therapy (*vs*. 1st)				
≥ 2nd	0.67 (0.41–1.12)	0.12		
BMI (kg/m^2) (*vs*. <18.5)				
≥18.5	1.30 (0.68–2.50)	0.43		
Albumin (g/L) (*vs*. ≤36.8)				
>36.8	3.38 (1.48–7.73)	0.004		
PNI (*vs*. <45.7)				
≥45.7	1.40 (0.90–2.17)	0.14		
NLR (*vs*. ≤5)				
>5	0.76 (0.46–1.26)	0.29		
PLR (*vs*. ≤152)				
>152	0.58 (0.38–0.90)	0.02*		
Neutrophil (×10^9/L)	0.87 (0.78–0.97)	0.02*		

*, represents P<0.05. BMI, body mass index; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; RCCEP, reactive cutaneous capillary endothelial proliferation; ULN, upper limit of normal.

the occurrence of irAEs and the efficacy of camrelizumab in the treatment of EC, and the treatment efficacy of the RCCEP patients was better than that of the irAE patients without RCCEP. In patients with RCCEP, there were no significant differences in OS and PFS among individuals classified according to the timing or grading of RCCEP occurrence. More camrelizumab treatment cycles and not receiving combined anti-angiogenic therapy were independent risk factors for RCCEP.

In this study, the incidence rate of RCCEP was 32.24%, which was lower than that of 79.9% reported in the ESCORT-1st study (6). A previous study reported that the occurrence rate of RCCEP after two cycles of standard chemotherapy combined with camrelizumab was 21.1% (14). In the NIC-ESCC2019 study, the occurrence rate of RCCEP after two cycles of neoadjuvant therapy was only 9% (13). In a retrospective study on camrelizumab treatment for NSCLC, for the patients having received at least two cycles of camrelizumab combined therapy, the incidence rate of RCCEP was only 30% (9). Therefore, the number of treatment cycles of camrelizumab was associated with the incidence of RCCEP. A large-scale pooled analysis of 10 studies in China found that the incidence rate of RCCEP was higher in patients using camrelizumab alone (77%) than in patients using combined chemotherapy (67.8%), and both these incidence rates were higher than the incidence rate of patients using combined anti-angiogenic drugs (23.6%) (24). In a study of nasopharyngeal cancer, the incidence of RCCEP with camrelizumab monotherapy was 88% (82/93), whereas the incidence of RCCEP with camrelizumab in combination with gemcitabine/cisplatin was reduced to 22% (5/23) (25). Therefore, the types of drugs used in combination therapy with camrelizumab were associated with the incidence of RCCEP. In the present study, most patients received one or two cycles of camrelizumab treatment, accounting for 17.88% and 17.38%, respectively. However, the patients who received three treatment cycles had the highest incidence rate of RCCEP [31 patients (7.81%)]. After excluding patients who received less than three cycles of therapy and those who received anti-angiogenic therapy, the incidence rate of RCCEP increased to 48.71% (113/232). Unlike standard treatment with only paclitaxel, albumin-bound paclitaxel, or docetaxel combined with platinum-based drugs, camrelizumab was combined with multiple chemotherapy agents in this study, and some patients received underlying disease treatment during anti-tumor therapy. Additionally, various factors such as patients'

economic status, transportation barriers, and adverse drug reactions may affect the continuity of camrelizumab treatment in real-world studies, which can also affect the incidence rate of RCCEP. Further, limitations in real-world research, such as incomplete electronic medical records, a failure to report some minor lesions by patients, and patient recall bias, can also influence the statistical analysis of the RCCEP incidence rate. Therefore, while the occurrence rate of RCCEP in this study was low, it holds greater clinical reference value, as the results were based on real-world statistics.

The patients with RCCEP had a higher ORR and DCR than those without RCCEP. The survival analysis showed that the RCCEP-positive group had significantly longer OS and PFS than the RCCEP-negative group. Moreover, the OS and PFS of the RCCEP-positive group was significantly longer than the OS and PFS of the RCCEP-negative, irAE-positive group, and the irAE-negative group; the OS and PFS of the RCCEP-negative, irAE-positive group was significantly longer than the OS and PFS of the irAE-negative group. The Cox analysis also indicated that RCCEP was an independent risk factor for both OS and PFS, while irAEs were independent risk factors for OS but not PFS. Therefore, we speculate that RCCEP, a dermatological abnormality, may be associated with longer OS and PFS.

The treatment efficacy of patients with irAEs who did not experience RCCEP was lower than that of those with RCCEP, but they still had better outcomes than the patients without irAEs. However, the relationship between the irAEs other than RCCEP and treatment efficacy could not be individually evaluated due to the small sample size of the study and the low incidence rates. Therefore, we need to collect more samples collected for statistical analysis in the future.

Further, our study found no relationship between RCCEP time and OS or PFS, which is consistent with the results that we obtained in the modified 6-month landmark analysis. However, we only analyzed the RCCEP time on a monthly basis for the first 6 months; thus, it remains unclear whether there is an inflection point between RCCEP time and efficacy after 6 months. Therefore, we need to observe with a larger sample size over a longer period.

Additionally, we found no relationship between RCCEP grade and OS or PFS. However, a systematic review and meta-analysis has shown that low-grade irAEs have a significant predictive effect on treatment efficacy, but this is not the case for severe-grade irAEs (3). There could be two potential explanations for this finding. First, effective ICIs need to be discontinued temporarily or even permanently when severe irAEs occur; however, as most RCCEP lesions are grade 1 or grade 2, camrelizumab does not need to be discontinued (24,26). Conversely, while treatment does need to be suspended for grade 3 RCCEP, when the RCCEP is reduced to grade 1, camrelizumab treatment can be resumed (26). Cases of grade 4 or 5 RCCEP have not been reported (27,28); therefore, it is likely that patients with RCCEP will not experience the reduction in efficacy associated with the discontinuation of camrelizumab. Second, systemic immunosuppressive therapy is required for severe irAEs, which may counteract the effects of ICIs. Glucocorticoids extensively alter cytokine signaling and inhibit the IL-2 and interferon (INF)-γ pathways (29-31) that are reactivated during ICI treatment to create an inflammatory tumor microenvironment, and exposure to large amounts of immunosuppressive agents during high-grade irAEs may alter the anti-tumor effect. However, most cases of RCCEP do not require special treatment, as the majority of lesions spontaneously resolve within 1 to 2 months of the discontinuation of camrelizumab, and the remaining cases can be managed with symptomatic treatments, such as laser therapy, minor excision, hemostasis procedures, local corticosteroid administration, systemic antibiotics usage, and cryotherapy (18). RCCEP is not sensitive to glucocorticoids, and the treatment of RCCEP does not require immunosuppressive reagents, which may be another key reason why the grade of RCCEP was not found to be related to OS or PFS.

The predictive role of RCCEP in the efficacy of EC treatment is consistent with findings for NSCLC and HCC. However, opinions differ as to whether irAEs can serve as predictors for the effectiveness of ICIs in tumor therapy. A significant association between increased survival after ICI treatment and irAEs has been reported for both GI cancer (32) and NSCLC (33). However, it is not yet known whether the occurrence of irAEs is correlated with a superior response and improved survival outcomes in patients with melanoma (34,35). Moreover, studies have shown that the irAEs induced by PD-1 inhibitors are predictive of a better clinical response in patients with cancer, but the association between irAEs and survival in patients undergoing anti-CTLA-4 therapy remains controversial (36-41). According to another study, the type of irAE may also be predictive of ICI efficacy in tumor treatment. Significant survival benefits were observed in patients with endocrine and skin abnormalities, whereas

no comparable survival advantages were noted in patients with GI, pulmonary, hepatobiliary, or musculoskeletal abnormalities (3). In studies investigating the relationship between the number of irAEs and treatment efficacy, some have found that a higher number indicates better efficacy (33,42), while others have reached the opposite conclusion (1). Regarding severity grading, some studies reported a correlation between higher grades and good efficacy (43,44), while others have not found evidence of any such correlation (3). In terms of timing, there is research suggesting that patients with late onset irAEs (i.e., irAE onset >3 months) have better outcomes than those with early onset irAEs (i.e., irAE onset ≤3 months) (45). However, there are limited studies on the timing of irAE occurrence, and no conclusive results have been obtained. Such conflicting findings currently prevent us from drawing definitive and unified conclusions. Therefore, we speculate that the predictive role of the site, frequency, severity, and timing of irAE occurrence on treatment efficacy may vary in different tumors treated with different ICIs. In the future, we should consider conducting prospective trials to further explore the relationship between irAEs and the efficacy of cancer treatments.

In this study, more camrelizumab treatment cycles and not receiving combined anti-angiogenic therapy were significantly associated with RCCEP occurrence. The precise mechanism underlying the induction of RCCEP by camrelizumab remains elusive. We hypothesize that camrelizumab disrupts the dynamic balance between angiogenic factors and anti-angiogenic factors (46), resulting in an increased risk of RCCEP. As the treatment regimen with camrelizumab progresses, this disruptive effect persists and intensifies, consequently augmenting the likelihood of RCCEP occurrence. Studies have shown that the incidence of RCCEP was significantly reduced when camrelizumab was combined with anti-angiogenic drugs (9,24,47), which is consistent with the results of this study. It has been suggested that anti-angiogenic drugs may block angiogenesis by targeting the VEGF/VEGF receptor (VEGFR) signaling pathway, thereby further preventing the occurrence of RCCEP (9). To date, no consensus has been reached as to whether the application of anti-angiogenic drugs solely prolongs the onset time of RCCEP or prevents its occurrence (24). This study found that patients with RCCEP had better treatment outcomes than those without RCCEP. However, currently, it is unclear whether there are differences in treatment efficacy between patients who experienced RCCEP after the application of anti-angiogenic drugs and those who did not experience RCCEP, as well as those who should have experienced RCCEP but did not due to the use of anti-angiogenic drugs. Thus, further research with larger sample sizes is needed to be conducted in the future.

There are several limitations in this study that should be addressed. First, as it employed a single-center, retrospective design, bias related to the selection of patients is inevitable, and potential confounding factors could have been left unaccounted for. Second, while our study examined a large volume of data, the sample size and follow-up time for specific indicators were not particularly robust. Third, methodology limitations include potential underreporting of adverse events, and lack of mechanistic exploration into the RCCEP-efficacy relationship. Given these limitations, the findings should be interpreted carefully. Multicenter prospective studies are warranted to validate the association between RCCEP and camrelizumab, and to further analyze the impact of treatment heterogeneity in combination therapies (chemotherapy/anti-angiogenics) on the outcomes. Currently, the underlying mechanism or relationship between RCCEP and therapeutic efficacy remains unclear, necessitating additional studies for in-depth investigation.

Conclusions

In EC patients treated with camrelizumab, those with RCCEP experienced significantly better outcomes in terms of the ORR, DCR, PFS, and OS than those without RCCEP. The patients who developed irAEs other than RCCEP did less well than the RCCEP-positive patients, but better than the patients without irAEs, and no correlation was found between the duration and severity of RCCEP and prolonged PFS or OS. More camrelizumab treatment cycles and not receiving combined anti-angiogenic therapy were independent risk factors for RCCEP. These findings may provide a basis for clarifying the mechanism underlying RCCEP.

Acknowledgments

None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.

amegroups.com/article/view/10.21037/jtd-2025-366/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-2025-366/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-2025-366/prf

Funding: This study was funded by the Zhongguancun Precision Medicine Foundation (No. 3202425202203012) and the Natural Science Foundation of Hebei Province (No. H2022206538).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-2025-366/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. Ethical approval for the current research was granted by the Research Ethics Committee of The Fourth Hospital of Hebei Medical University (approval No. 2022KS014). The requirement of individual consent for this retrospective analysis was waived.

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(English Language Editor: L. Huleatt)

Cite this article as: Qiu Y, Su G, Zhang L, Fan H, Zhao H, Wang C, Liu L, Chen B, Li X, Li S. Association between reactive cutaneous capillary endothelial proliferation and the efficacy of camrelizumab in esophageal cancer: a retrospective cohort study. J Thorac Dis 2025;17(4):2453-2472. doi: 10.21037/jtd-2025-366