Original Article

Clinicopathological and prognosis significance of RIPK1 in patients with cervical squamous cell carcinoma: a retrospective cohort study

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Background: Cervical cancer is one of the most common types of carcinoma in women and has high morbidity and mortality rates worldwide. Recurrent and metastatic disease remains difficult to treat. Receptor interacting protein kinase 1 (RIPK1) is a key molecule in mediating apoptosis, necroptosis, and inflammatory pathways downstream of death receptors and pattern recognition receptors. This study sought to explore the clinicopathological and prognosis significance of RIPK1 expression in cervical squamous cell carcinoma (CSCC).

Methods: The data of 100 CSCC patients who underwent curative surgery from 2019 to 2020 were retrospectively included in this study. We collected the clinicopathological information of the patients and detected RIPK1 protein expression using immunohistochemistry. The Chi-square test and a 1-way analysis of variance were used to make comparisons between groups stratified by RIPK1 expression. A Pearson linear correlation analysis was used to evaluate the association between RIPK1 expression and the clinicopathological characteristics of the patients. A Cox regression analysis and Kaplan-Meier curves were used to analyze overall survival (OS) and progression-free survival (PFS). A multivariable regression analysis was conducted to identify the risk factors for an impaired prognosis in CSCC.

Results: RIPK1 was found to be overexpressed in the CSCC tissues. RIPK1 expression was significantly associated with age, the preoperative serum squamous cell carcinoma antigen (SCC-Ag) level, lymph node metastasis, invasion depth, International Federation of Gynecology and Obstetrics (FIGO) stage, tumor size, PFS, and OS (P<0.05). The PFS and OS differed significantly among patients with RIPK1 expression (P<0.05). The multivariate analysis showed that RIPK1 was not independent risk factors for PFS and OS in CSCC patients (P>0.05).

Conclusions: The expression of RIPK1 was significantly upregulated in CSCC and was associated with the clinicopathological features of CSCC. RIPK1 might serve as a novel marker that can be used to predict the prognosis of CSCC patients and as a biological target for the treatment of CSCC.

Keywords: Cervical squamous cell carcinoma (CSCC); receptor interacting protein kinase 1 (RIPK1); prognosis; targeted therapy

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Introduction

Cervical cancer is one of the leading gynecologic cancers in women, and thus represents a huge challenge for health workers and researchers worldwide (1). The early screening and pervasive application of the human papillomavirus vaccine have led to a relative decline in the morbidity and mortality of cervical cancer patients. However, the 5-year overall survival (OS) rate of advanced cervical cancer patients remains low (2).

Standardized treatment is the main strategy used to delay the exacerbation of cervical cancer. In the past decade, precision medicine has highlighted the importance of individualized treatment based on gene targets. Cervical squamous cell carcinoma (CSCC) is a major pathologic subtype of cervical cancer (3). The identification of high-precision CSCC molecular markers and an understanding of the mechanisms involved in tumor progression is of great significance to the early diagnosis and precision treatment of CSCC.

Receptor interacting protein kinase 1 (RIPK1) is a regulatory protein of nuclear factor kappa B (NF-κB) signaling (4). It is one of the most important members of the receptor interacting protein (RIP) family. In recent years, RIPK1 kinase has emerged as a promising therapeutic target for the treatment of human neurodegenerative, autoimmune, and inflammatory disease (5). Currently, research suggests that RIPK1 polymorphisms are associated

with the risk of cervical cancer in the Uygur population in China (6). Biologically, RIPK1 plays a significant role in the signal transduction of cell survival, apoptosis, and programmed necrosis through the activation of NF-κB, caspase-8, and reactive oxygen species production (7). Accumulative evidence has revealed the role of RIPK1 in diseases, such as breast cancer, ALS, and liver cancer (8-10). However, evidence on the expression of RIPK1 in CSCC and its relationship with clinicopathological features is limited; thus, in-depth research urgently needs to be conducted on the expression of RIPK1 in CSCC.

In the current study, clinicopathological information on the age, tumor size, vascular metastasis, lymph node metastasis, infiltrating depth, preoperative serum squamous cell carcinoma antigen (SCC-Ag) level, histological grade, and International Federation of Gynecology and Obstetrics (FIGO) stage of the patients with CSCC was collected. The expression of RIPK1 in CSCC was detected, and the association between RIPK1 expression and the aforementioned parameters were examined to identify the potential in the precision treatment of CSCC. We present this article in accordance with the REMARK reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-578/rc).

Methods

Patients

A retrospective cohort study was conducted, and PASS was used to calculate the sample size. A total of 100 CSCC tissue samples were collected from 100 patients who were diagnosed with CSCC and underwent curative surgery at The First Affiliated Hospital of Bengbu Medical College from January 1, 2019 to December 31, 2020. None of the participants received any preoperative chemoradiotherapy, and all of the participants were at the first visit to the hospital. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of The First Affiliated Hospital of Bengbu Medical College (No. 143,2021), and all the patients signed the informed consent form.

Specimen characteristics

The paraffin-embedded sections of the 100 clinical samples were treated with fixation, dehydration, transparency, wax transparency, embedding, sectioning, patching, staining,

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Highlight box

Key findings
- This study found that receptor interacting protein kinase 1 (RIPK1) was highly expressed in cervical cancer tissues. RIPK1 expression was significantly associated with several clinicopathologies. The multivariate analysis showed that RIPK1 was not an independent risk factor for PFS and OS in CSCC (P>0.05).

What is known and what is new?
- A large number of studies have confirmed that RIPK1 is related to the occurrence and development of tumors.
- This study identified high expression of RIPK1 in cervical squamous carcinoma and confirmed its clinicopathology.

What is the implication, and what should change now?
- This study showed that RIPK1 has a specific function in the occurrence and progression of cervical cancer and thus may be a new target for the treatment of cervical cancer. More research needs to be conducted to confirm the cellular level mechanism of RIPK1 activity in cervical cancer.

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transparency, and paraffin embedding. The clinical pathological features of the patients enrolled in the study were obtained from the medical record system of The First Affiliated Hospital of Bengbu Medical College.

Study design

The patients completed telephone follow-up visits from the day of surgery until August 31, 2022. The follow-up period ranged from 20 to 43 months (average: 31 months). Progression-free survival (PFS) was defined as the time from diagnosis to recurrence, death, or last follow-up. OS was defined as the time from diagnosis to death or last follow-up. The surgical-pathological staging and histological grading were performed according to the 2018 FIGO staging standards (11,12). The clinicopathological characteristics included the age at diagnosis, tumor size, vascular metastasis, lymph node metastasis, invasion depth, SCC-Ag level, histological grade, and FIGO stage.

Assay methods

All the operations were conducted according to the manufacturers' instructions. Anti-RIPK1 antibody (A7414, ABclonal Company, Wuhan, China), the DAB Chromogenic Substrate Kit Beijing Zhongshan Jinqiao Co., Ltd., Beijing, China) and the Strepavidin Peroxidase (SP) Detection Kit (Beijing Zhongshan Jinqiao Co., Ltd.) were used in the current study. The expression of RIPK1 in the CSCC tissues and normal tissue was detected by SP immunohistochemical staining. The steps were as follows: paraffin pathological tissue section, dewaxing and hydration, slice washing, blocking endogenous peroxidase antigen repair, adding primary antibody (dilution ratio 1:200) until the tissue was completely covered, adding secondary antibody (dilution ratio 1:1), DAB coloration, hematoxylin counterstaining, dehydration and drying, sealing the slices with neutral gum, and drying.

All the results were interpreted by a professional expert in pathology. RIPK1 staining was observed in the cytoplasm of the CSCC tissue, while the normal tissue was not stained. Five high magnifications (×200) were randomly observed for each CSCC tissue with 100 cells selected for counting. The positive proportion (PP) cell score was calculated according to the proportion of the cytoplasmic coloring and color development comprehensive score. PPs <25%,

25–50%, 50–75%, and 75–100% were defined as PP scores of 1, 2, 3, and 4 points, respectively. Cell staining of yellow, yellow-brown, and dark-brown were defined as cell staining intensity (SI) scores of 1, 2, and 3 points, respectively. The protein expression intensity was quantitated as the PP × SI.

Statistical analysis methods

SPSS20.0 statistical software was used for the data analysis. The Chi-square test and a 1-way analysis of variance were used to make comparisons between groups stratified based on RIPK1 expression. A Pearson linear correlation analysis was used to analyze the correlations between RIPK1 expression and the various clinicopathological indicators. A Cox survival regression analysis and Kaplan-Meier curves combined with a log-rank test were used to analyze the OS and PFS of patients. A multivariate logistic regression analysis was conducted to detect the risk factors for the impaired prognosis of CSCC. A P value <0.05 was considered statistically significant.

Results

Patient pathological characteristics

The patients had a mean age of 51.32±9.72 years (range, 25 to 72 years). Among the 100 patients, 41 patients were classified as FIGO stage I, and 59 patients were classified as FIGO stages II and III. As *Table 1* shows, 79 patients had a histological grade G1/G2, and 21 had a histological grade G3. In addition, 19 (19%) of the patients had vascular metastasis, 30 (30%) had lymph node metastasis, and 75 (75%) had a ≥1/2 muscular layer infiltrating depth.

Expression of RIPK1 in the CSCC and normal samples

Figure 1 shows some representative images of RIPK1 immunostaining in the fresh CSCC tissue samples and normal cervical tissue samples. The immunostaining results showed that the expression of RIPK1 was negative in the normal cervical tissues and positive in the cytoplasm of the CSCC tissues. The immunostaining of the CSCC tissues was further categorized as yellow, yellow-brown, or dark-brown (*Figure 1*). The proportions of samples with low (yellow), moderate (yellow-brown), and high (dark-brown) immunostaining were 15%, 47%, and 38%, respectively. The differences were statistically significant (P<0.05).

Table 1 The clinicopathological features between the groups stratified by RIPK1 expression

Variables	Cases	RIPK1 expression		χ^2	P
		Low	High		
FIGO stage				6.533	0.011*
IA+IB	41	16	25		
II+III	59	14	45		
Histological grade				3.676	0.159
G1/G2	79	24	55		
G3	21	6	15		
Lymph node metastasis				11.111	0.001**
No	70	28	42		
Yes	30	2	28		
Vascular metastasis				0.894	0.344
No	81	26	55		
Yes	19	4	15		
Infiltrating depth				7.683	0.006**
<1/2 muscular layer	25	13	12		
≥1/2 muscular layer	75	17	58		

Analysis of the expression intensity of RIPK1 and the clinical and pathological indicators. *, was significantly correlated at the 0.05 level (bilateral); **, was significantly correlated at the 0.01 level (bilateral). RIPK1, receptor interacting protein kinase 1; FIGO, Federation of Gynecology and Obstetrics.

Association between RIPK1 expression and the clinicopathological features in patients with CSCC

As *Table 2* shows, the PFS and OS differed significantly among the patients with different levels of invasion depth and FIGO stages (P<0.05). Vascular metastasis and the histopathologic grade did not differ significantly between the groups (P>0.05). Lymph node metastasis, the preoperative SCC-Ag level and age were associated with PFS (P<0.05) but were not associated with OS (P>0.05). The Kaplan-Meier analysis showed that the OS and PFS times of the high RIPK1 expression group were significantly lower than those of the low RIPK1 expression group (P<0.05, *Figure 2*). The Pearson linear regression showed that RIPK1 expression was positively correlated with the preoperative SCC-Ag level, tumor size, and age (all P<0.05, *Table 3*).

Multivariate regression analysis of the risk factors for decreased PFS and OS in patients with CSCC

The multivariate regression analysis showed that the preoperative SCC-Ag level, age, vascular metastasis, lymph node metastasis, the invasion depth, the FIGO stage, the histological grade, and RIPK1 expression were not independently associated with PFS and OS in patients with CSCC (P>0.05, *Table 4*).

Discussion

Study found that the expression of RIPK1 was significantly associated with the clinical stage, the histopathologic grade and lymph node metastasis but was not associated with age, tumor size and histopathologic type in breast cancer. The expression of RIPK1 was significantly associated
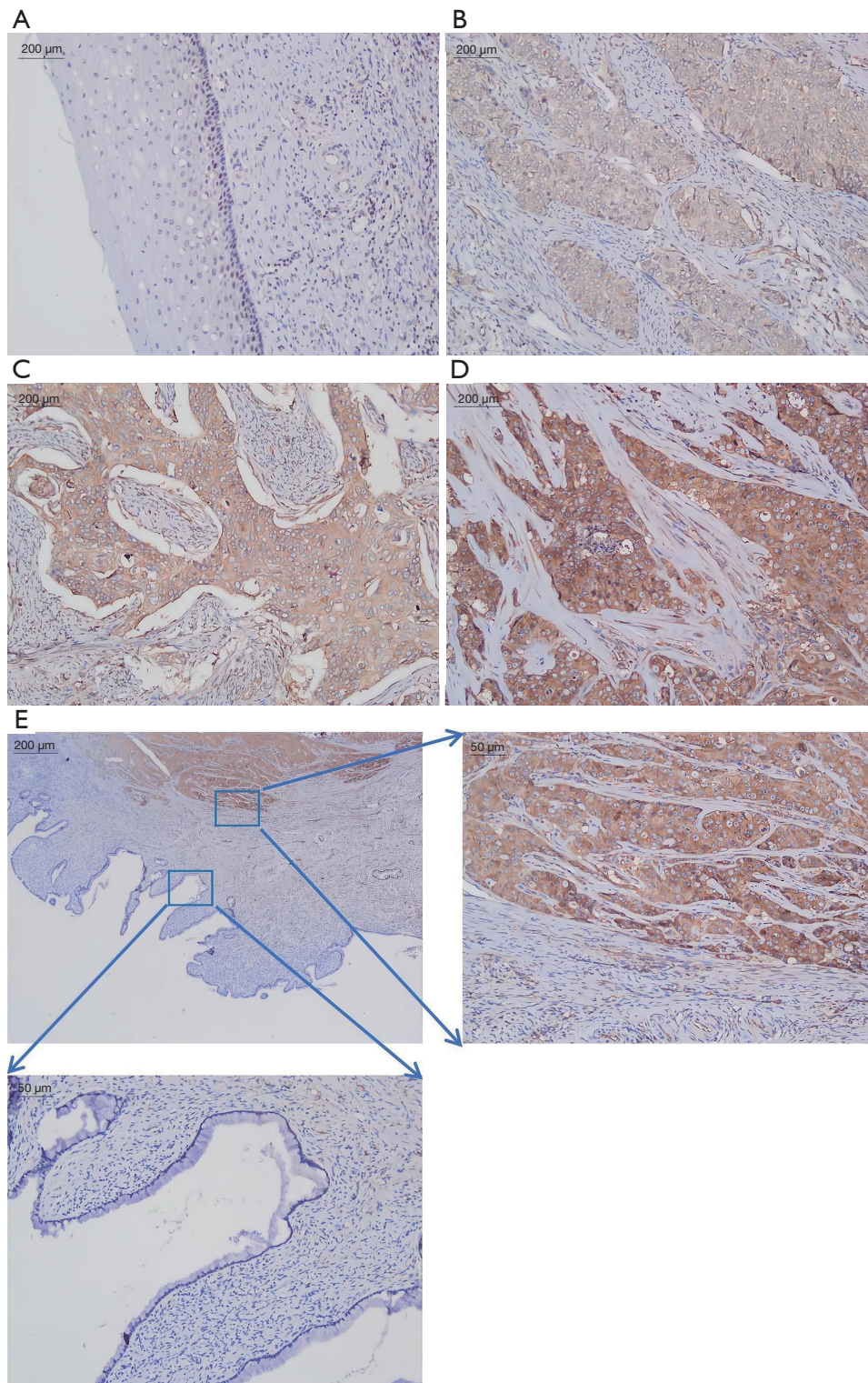
Figure 1 RIPK1 is frequently overexpressed in CSCC patients. Representative images of RIPK1 IHC staining (A) A normal tissue sample; (B) low expression of RIPK1 in a CSCC sample; (C) moderate expression of RIPK1 in a CSCC sample; (D) high expression of RIPK1 in a CSCC sample; (E) detailed views. RIPK1, receptor interacting protein kinase 1; CSCC, cervical squamous cell carcinoma; IHC, immunohistochemistry.

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Table 2 Clinicopathological features and RIPK1 expression and patients' PFS and OS

Variables	Cases	PFS				OS			
		Value	95% CI	χ^2	P	Value	95% CI	χ^2	P
FIGO stage				41.830	0.007**			36.369	0.028*
IA+IB	51	32±5	30–34			32±4	31–34		
II+III	49	30±7	29–32			31±7	29–32		
Histological grade				33.295	0.058			24.869	0.303
G1/G2	79	31±6	29–32			31±6	30–33		
G3	21	30±6	27–33			30±6	28–33		
Lymph node metastasis				40.375	0.001**			31.293	0.090
No	70	31±6	30–33			31±6	30–33		
Yes	30	29±7	29–36			31±7	28–34		
Vascular metastasis				24.610	0.316			23.945	0.350
No	81	30±6	29–31			31±6	29–32		
Yes	19	36±7	29–36			33±7	30–37		
Infiltrating depth				48.966	0.001**			43.930	0.004**
<1/2 muscular layer	25	31±6	29–33			31±6	29–33		
≥1/2 muscular layer	75	31±7	29–32			31±6	30–33		
Age (years)				34.421	0.044*			26.588	0.227
<60	81	31±6	29–32			31±6	30–33		
≥60	19	30±6	27–33			31±6	28–33		
SCC-Ag level (μg/L)				35.984	0.030*			26.651	0.225
<1.95	42	31±7	29–33			31±7	29–33		
≥1.95	58	30±6	29–32			31±6	29–33		
RIPK1 expression				48.903	0.001**			52.091	0.000**
1	6	26±6	20–32			26±6	20–32		
2	13	35±6	31–38			35±6	31–38		
4	11	30±5	27–34			30±5	27–34		
6	32	31±6	29–33			31±6	29–33		
8	5	25±3	21–28			25±3	21–28		
9	23	30±7	28–33			32±6	29–34		
12	10	31±7	26–36			31±7	27–36		

The relationship between RIPK1 expression intensity and clinical pathological indicators and patients' PFS and OS; Value, standard deviation variance. *, was significantly correlated at the 0.05 level (bilateral); **, was significantly correlated at the 0.01 level (bilateral). SCC-Ag, squamous cell carcinoma antigen; RIPK1, receptor interacting protein kinase 1; PFS, progression-free survival; OS, overall survival; FIGO, Federation of Gynecology and Obstetrics.

Survival functions

Survival functions
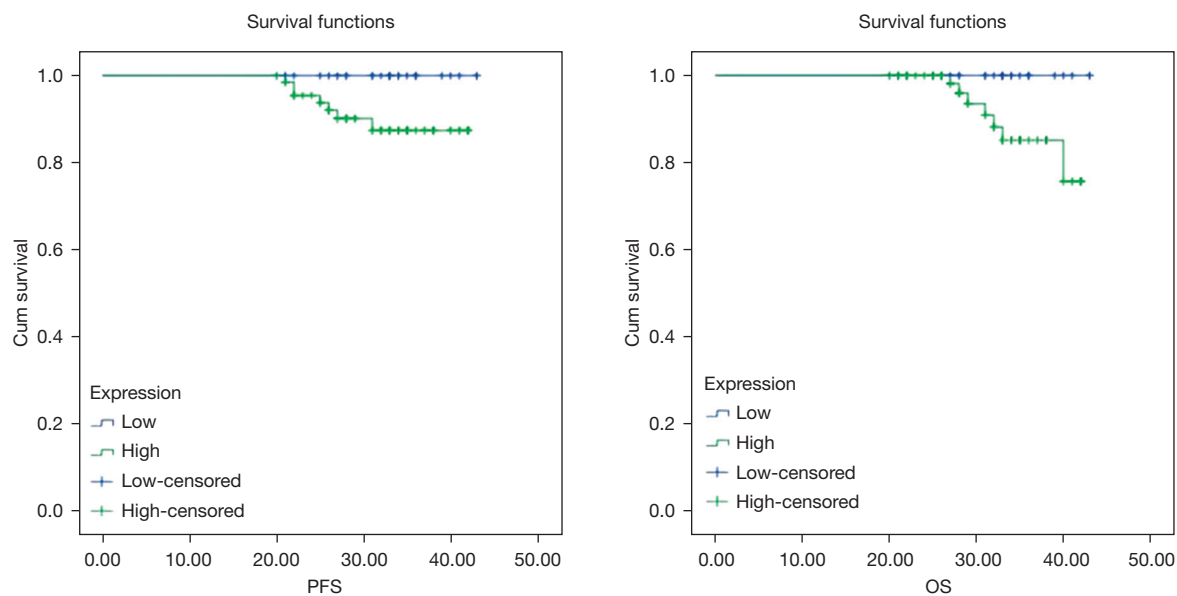
Figure 2 Kaplan-Meier analysis of RIPK1 expression and the PFS and OS survival curves of patients with CSCC. PFS, progression-free survival; OS, overall survival; RIPK1, receptor interacting protein kinase 1; CSCC, cervical squamous cell carcinoma.

Table 3 The association between RIPK1 expression and SCC-Ag level, tumor size, and age

Variables	Pearson correlation	P
SCC-Ag level (μg/L)	0.273	0.006**
Tumor size	0.310	0.002**
Age (years)	0.224	0.025*

Person correlation analysis of the expression intensity of RIPK1 and the clinical indicators. *, was significantly correlated at the 0.05 level (bilateral); **, was significantly correlated at the 0.01 level (bilateral). RIPK1, receptor interacting protein kinase 1; SCC-Ag, squamous cell carcinoma antigen.

with the invasion depth, clinical stage, histopathologic grade, and lymph node metastasis, but was not associated with sex, age and tumor size in esophageal squamous cell cancer. The expression of RIPK1 was significantly associated with the clinical stage, the histopathologic grade, and lymph node metastasis but was not associated with sex and age in colon cancer. In the present study, we assessed the expression of RIPK1 in CSCC tissues and analyzed the association between RIPK1 expression and the clinicopathological features of patients with CSCC. To the

best of our knowledge, this was the first study to examine the expression of RIPK1 in CSCC.

Efforts, including surgery, radiotherapy, chemotherapy, and other treatments, have been made to reduce the mortality of cervical cancer patients; however, cervical cancer is still one of the most commonly diagnosed female cancers. In addition to the reduced survival time of patients, the quality of life of patients with cervical cancer significantly deteriorates. Notably, CSCC is one of the most common types of cervical cancer and has high mortality rates, and the age of onset in patients with CSCC is decreasing worldwide. CSCC are prone to develop tumor metastasis and have a high rate of recurrence. Thus, the present study sought to identify the specific biomarkers for CSCC and thus extend understandings of the pathogenesis of CSCC. Such findings will be of great clinical value.

RIPK1 is a class of serine/threonine protein kinases and is well recognized as a multidomain protein with an N-terminal kinase domain, an intermediate domain, and a C-terminal death domain (13). The RIP family plays an essential role in the inflammation and activation of the pathways involved in cell death (14). RIPK1 contains a death domain through which it can interact with FADD to

Table 4 Multivariate regression analysis of the risk factors of decreased PFS and OS in patients with CSCC

Variables	PFS		OS	
	HR	P	HR	P
FIGO stage	0.092	0.360	0.000	0.131
Histological grade	0.080	0.088	0.000	0.210
Lymph node metastasis	47,919.78	0.822	57.230	0.477
Vascular metastasis	0.108	0.093	0.000	0.190
Infiltrating depth	4.763	0.981	1,264.001	0.783
Age (years)	0.777	0.804	0.067	0.192
SCC-Ag level (μg/L)	1.071	0.9974	27.483	0.093
RIPK1 expression	1.567	0.896	1.396	0.631

Multi-factor Cox analysis. PFS, progression-free survival; OS, overall survival; CSCC, cervical squamous cell carcinoma; HR, hazard ratio; FIGO, Federation of Gynecology and Obstetrics; SCC-Ag, squamous cell carcinoma antigen; RIPK1, receptor interacting protein kinase 1.

recruit caspase 8 and FLIP (and also caspase 10 in humans). Previous study has shown that complexes that contain necrosomes, such as RIPK1 and/or RIPK3, can activate caspase 8 and induce apoptosis (15). However, RIPK1 kinase activity-related cell apoptosis is mediated by the NF-κB essential modulator, which is the regulatory subunit of the inhibitor of the NF-κB kinase (IKK) complex. IKKα and IKKβ have been reported to be other complexes involved (16). We speculated that not only NF-κB-dependent but also NF-κB-independent mechanisms, such as IKKα- or IKKβ-mediated RIPK1 phosphorylation and NF-κB essential modulator-mediated disruption of necrosome formation. However, the physiological circumstances in which RIPK1-dependent apoptosis becomes predominant are poorly understood. The inhibition of RIPK1 kinase activity using improved necrostatin-1 (R-7-Cl-O-Nec-1, Nec-1s) and trials with animal models of RIPK1 kinase-dead mutant mice have shown the efficacy of RIPK1-inhibitors in the treatment of diseases (17-19). However, the mechanism of RIPK1 in CSCC requires further investigation.

In the current study, the immunostaining results showed that the expression of RIPK1 was positive in the CSCC tissues but negative in the normal tissues. Further, the Pearson linear regression analysis revealed a positive correlation between RIPK1 expression and certain clinicopathological features of patients. Additionally, the relationship between RIPK1 expression and PFS and OS was revealed. The Kaplan-Meier survival curve analysis showed that the CSCC patients with high RIPK1 expression levels had worse OS and PFS. The multivariate regression analysis showed that RIPK1 was not an independent prognostic factor for CSCC. These results provide evidence that RIPK1 plays a significant role in the progression of CSCC and might serve as a treatment target for CSCC.

This study had a number of limitations. First, the sample size was small, and the data was collected from a single center. Second, the follow-up time was relatively short. Third, only PFS and OS were considered in examining patient prognosis, and no information on mortality was collected. In the future, clinical research with larger sample sizes and prolonged follow-up periods needs to be conducted to extend understandings of RIPK1 and its association with the progression of CSCC.

Conclusions

In conclusion, our findings demonstrated that an increased expression of RIPK1 in CSCC is closely associated with patients' clinicopathological features and a worse prognosis. The expression of RIPK1 might be involved in the progression of CSCC and might be used to predict the prognosis of CSCC patients. RIPK1 may be a target for the treatment of CSCC.

Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-578/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-578/dss

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-578/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-578/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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of The First Affiliated Hospital of Bengbu Medical College (No. 143,2021), and all the patients signed the informed consent form.

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