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Posttreatment squamous cell carcinoma antigen predicts treatment failure in patients with cervical squamous cell carcinoma treated with concurrent chemoradiotherapy

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HIGHLIGHTS

- Posttreatment SCC Ag could predict tumor relapse after CCRT for patients with cervical cancer.
- The 3-year DFS of patients with posttreatment SCC Ag ≥ 1.8 ng/mL was just 31.9%.
- Consolidation therapy or extensive follow-up should be considered for these patients.

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ABSTRACT

Objective: To analyze the association between posttreatment squamous cell carcinoma antigen (SCC Ag) and treatment failure in patients with cervical SCC treated with concurrent chemoradiotherapy (CCRT).

Methods: We reviewed patients with cervical SCC who were treated with definitive radiotherapy or CCRT between June 2012 and May 2015 at our institute. A receiver operating characteristic (ROC) curve was used to analyze the cutoff value of posttreatment SCC Ag in predicting treatment failure. Log-rank tests and Cox proportional hazards models were used to identify whether posttreatment SCC Ag was significant in predicting disease-free survival (DFS).

Results: A total of 559 patients were included in this study. With the ROC curve, the optimal cutoff posttreatment SCC Ag level was 1.8 ng/mL (sensitivity 27.1%, specificity 96.6%). A posttreatment SCC Ag level ≥ 1.8 ng/mL was observed in 47 patients. The multivariate analysis showed that posttreatment SCC Ag (hazard ratio 5.10; 95% confidence interval, 3.31–7.88; $p < 0.001$) was an independent prognostic factor of DFS. The 3-year overall survival (OS), DFS, local control, and distant control rates of patients with posttreatment SCC Ag < 1.8 ng/mL and ≥1.8 ng/mL were 90.7% and 46.4% ($p < 0.001$), 84.8% and 31.9% ($p < 0.001$), 81.4% and 69.5% ($p < 0.001$), and 90.4% and 54.1% ($p < 0.001$), respectively.

Conclusion: Patients with posttreatment SCC Ag ≥ 1.8 ng/mL suffer due to a high rate of treatment failure and poor survival.

1. Introduction

At present, the standard treatment approach for patients with locally advanced cervical cancer is concurrent chemoradiotherapy (CCRT). For patients with R0 resection, a complete response (CR) is achieved immediately after surgery. In contrast to surgery, tumor regression may take several months after definitive radiotherapy for patients with cervical cancer. For patients with residual disease after radiotherapy, an additional radiation dose or salvage surgery (in time) is beneficial. However, it is difficult to accurately define a CR for

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patients with cervical cancer after radiotherapy with a gynecologic examination, magnetic resonance imaging (MRI) or even a biopsy in clinical practice. It was reported that 60% of patients with a residual tumor on MRI 3 months after CCRT showed spontaneous regression of the residual tumor during follow-up [1]. On the other hand, some patients experienced tumor relapse after a CR. If we can accurately find patients with a high risk of tumor relapse and give them more aggressive treatment, such as consolidation chemotherapy [2,3] or additional brachytherapy, we have opportunity to further improve the survival of patients with cervical cancer.

SCC accounts for >70% of all cervical cancers [4]. Squamous cell carcinoma antigen (SCC Ag) is widely used in cervical SCC. Elevated pretreatment SCC Ag is associated with an advanced International Federation of Gynecology and Obstetrics (FIGO) stage, a larger tumor size, extensive lymph node metastases, and worse survival [5–8]. SCC Ag is also used in the follow-up of patients to detect disease recurrence [9,10]. After CCRT, elevated SCC Ag decreases to normal for most patients. However, for a small number of patients, SCC Ag fails to normalize after treatment. It was reported that the failure of SCC Ag to normalize after CCRT was associated with cancer recurrence or poor survival for patients with cervical cancer treated with CCRT [11–13]. High posttreatment SCC Ag is a potential risk factor for treatment failure, including a non-CR and tumor relapse after CR.

At present, studies on the association between posttreatment SCC Ag and survival in cervical cancer are limited [11,12]. In the present study, we reviewed patients with SCC of the cervix and analyzed the association between posttreatment SCC Ag and treatment failure or survival.

2. Methods

2.1. Patients

After obtaining the Institutional Review Board approval of Peking Union Medical College Hospital (protocol number B252), we reviewed patients with cervical cancer and treated them with definitive radiotherapy or CCRT between June 2012 and May 2015 at our institute. The inclusion criteria were as follows: histology confirmed SCC, FIGO stage IB-IVA, no evidence of distant metastases, and treated with definitive radiotherapy or CCRT. Because the aim of this study was to evaluate the significance of SCC Ag, patients without pretreatment or posttreatment SCC Ag were excluded.

Pretreatment evaluations included a medical history, a gynecological pelvic examination, a blood cell count, liver and kidney function tests, SCC Ag levels, chest and abdomen computed tomography (CT), and pelvic MRI. A portion of the patients received positron emission tomography/CT (PET/CT).

2.2. Treatment

As described previously [14,15], all patients were scheduled to receive intensity-modulated radiation therapy (IMRT) and intracavitary brachytherapy (ICBT). IMRT was delivered with fix-field IMRT, volumetric-modulated arc therapy, or helical tomotherapy. A dose of 50.4 Gy in 28 fractions was delivered to the pelvis, and 59–61 Gy was prescribed to the metastatic lymph nodes (MLNs). Daily megavoltage CT or weekly cone beam CT was used for image guidance. ICBT was delivered with an Ir192 resource, with 30–36 Gy in five to six fractions to point A. Weekly cisplatin was the first-line regimen of concurrent chemotherapy.

2.3. Follow-up

A gynecological pelvic examination, SCC Ag, and pelvic MRI were performed 1 month after treatment. Then, patients had follow-up examinations approximately every 3 months in the first 2 years, every 6 months in 3 to 5 years, and then once per year.

2.4. Statistics

Serum SCC Ag levels were measured using a chemiluminescent microparticle with Architect i2000SR (IMX; Abbott Diagnostics, Chicago, IL, USA). A cutoff level of 1.5 ng/mL is recommended by the manufacturer. The measurable magnitude of the SCC Ag level ranged from 0 to 70 ng/mL in the hospital. The pretreatment SCC Ag level was determined at the time of diagnosis of cervical cancer. In the present study, the posttreatment SCC Ag level was measured 20 to 60 days after the completion of radiotherapy. Clinical stage was determined according to the 2009 FIGO staging system [16]. As described previously, lymph nodes confirmed by PET/CT or those with a short diameter larger than 1 cm on CT were defined as MLNs [17].

Receiver operating characteristic (ROC) curve analysis was performed to analyze the cutoff values of pretreatment and posttreatment SCC Ag levels in predicting treatment failure. The optimal cutoff values were determined by maximizing the sum of the sensitivity and specificity. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated.

Overall survival (OS), disease-free survival (DFS), local control, and distant control were estimated with the Kaplan-Meier method. The log-rank test and the Cox proportional hazards model were used to identify significant predictors of DFS. All p values were two-sided, and $p < 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS (version 23.0, IBM Corp., Armonk, NY, USA).

3. Results

As shown in Fig. 1, 559 of the 758 patients met the inclusion criteria and were included in this study. The detailed characteristics of the patients are shown in Table 1. The median pretreatment and posttreatment SCC Ag levels were 4.7 ng/mL and 0.8 ng/mL, respectively.

The median follow-up period was 39.9 months (range, 3.0–65.2 months). A total of 118 patients (21.1%) experienced treatment failure, including 42 patients with pelvic failure, 58 patients with distant failure, and 18 patients with concurrent pelvic

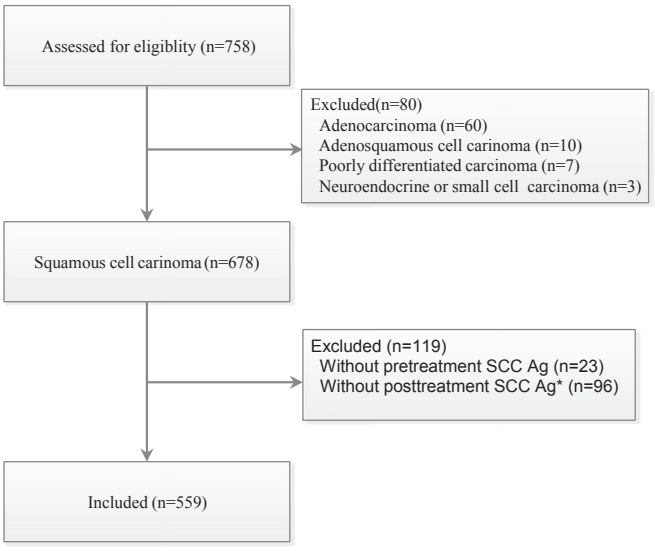

Fig. 1. Follow-up chart for included patients.
*The posttreatment squamous cell carcinoma antigen (SCC Ag) level refers to SCC Ag measured 20 to 60 days after the completion of radiotherapy.

Table 1
The characteristics of patients with cervical cancer treated with concurrent chemoradiotherapy.

Characteristics	No. (N = 559)	Percentage
Pretreatment SCC Ag (ng/mL)		
Median	4.7 (range, 0–70)	
<8.6 ng/mL	344	61.5
≥8.6 ng/mL	215	38.5
Posttreatment SCC Ag (ng/mL)		
Median	0.8 (range, 0–70)	
<1.8 ng/mL	512	91.6
≥1.8 ng/mL	47	8.4
Age (years old)		
Median	51 (range, 26–88)	
<65	500	89.4
≥65	59	10.6
FIGO stage		
IB	66	11.8
IIA	47	8.4
IIB	338	60.5
IIIA	17	3.0
IIIB	88	15.7
IVA	3	0.5
Primary tumor size		
<4 cm	216	38.6
≥4 cm	343	61.4
Regional MLNs*		
Yes	176	31.5
No	383	68.5
Para-aortic MLNs		
Positive	24	4.3
Negative	535	95.7
Pelvic MLNs		
Positive	174	31.1
Negative	385	68.9
Concurrent chemotherapy		
Positive	49	8.8
Negative	510	91.2

Abbreviations: FIGO = International Federation of Gynecology and Obstetrics; MLNs = metastatic lymph nodes; SCC Ag = squamous cell carcinoma antigen.
* Regional MLNs include para-aortic and pelvic MLNs.

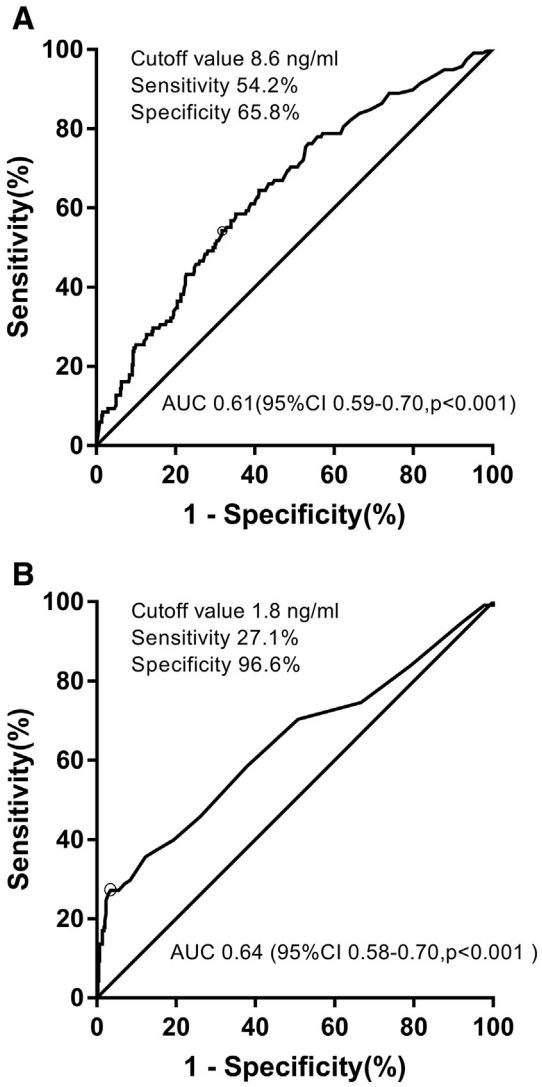

Fig. 2. Receiver operating characteristic (ROC) curve for pretreatment (A) and posttreatment (B) squamous cell carcinoma antigen in predicting treatment failure.
Abbreviations: AUC = area under the curve.

and distant failure. The total pelvic failure and distant failure rates were 10.7% and 13.6%, respectively. The 3-year OS, DFS, local control, and distant control rates were 87.2%, 80.3%, 89.5%, and 87.5%, respectively.

After treatment failure, radiotherapy, systemic therapy, surgery and no treatment were performed in 59 patients (50.0%), 56 patients (47.5%), 5 patients (4.2%) and 42 patients (35.6%), respectively. After treatment failure, the median follow-up period was 10.3 months (range, 1.0–55.9 months). And the median OS after treatment failure was 12.8 months (95% confidence interval [95% CI] 10.1–15.5 months). For patients who received treatment (76 patients) and did not receive treatment (42 patients) after treatment failure, the median OS after treatment failure was 17.9 months (95% CI 10.9–24.9 months) and 9.4 months (95% CI 8.0–10.8 months), respectively, and the 1-year OS rates after treatment failure were 66.4% and 28.3%, respectively ($p < 0.001$). For patients treated with radiotherapy and systemic therapy, the 1-year OS rates after treatment failure were 72.0% and 76.5% ($p = 0.930$), respectively.

ROC curve analysis was used to obtain the optimal cutoff points of pretreatment and posttreatment SCC Ag levels in predicting treatment failure (Fig. 2). Both pretreatment and posttreatment SCC Ag levels were significant in predicting treatment failure. The area under the curve was 0.61 (95% CI 0.59–0.70) for pretreatment SCC Ag ($p < 0.001$) and 0.64 (0.58–0.70) for posttreatment SCC Ag ($p < 0.001$). The optimal cutoff value of the pretreatment SCC Ag level was 8.6 ng/mL (sensitivity 54.2%, specificity 65.8%, PPV 29.7%, NPV 84.3%). The cutoff value of the posttreatment SCC Ag level was 1.8 ng/mL (sensitivity 27.1%, specificity 96.6%, PPV 68.1%, NPV 78.9%). Pretreatment SCC Ag levels ≥8.6 ng/mL and posttreatment SCC Ag levels ≥1.8 ng/mL were observed in 215 and 47 patients, respectively.

The univariate analysis showed that pretreatment SCC Ag, posttreatment SCC Ag, FIGO stage, primary tumor size, paraaortic MLNs, and pelvic MLNs were significant factors predicting DFS (Table 2). After the multivariate analysis, posttreatment SCC Ag (hazard ratio [HR] 5.10; 95% CI, 3.31–7.88; $p < 0.001$) remained significant in predicting DFS. Pretreatment SCC Ag was not an independent predictive factor of DFS (HR 1.26; 95% CI, 0.76–1.86; $p = 0.238$) (Table 2).

The 3-year OS, DFS, local control, and distant control rates for patients with posttreatment SCC Ag < 1.8 ng/mL and ≥1.8 ng/mL were 90.7% and 46.4% ($p < 0.001$), 84.8% and 31.9% ($p < 0.001$), 81.4% and 69.5% ($p < 0.001$), and 90.4% and 54.1% ($p < 0.001$), respectively (Fig. 3).

For the 47 patients with posttreatment SCC Ag ≥ 1.8 ng/mL, the median follow-up period was 19.2 months (range, 3–64.9 months). The median DFS period was 6.7 months (95% CI, 4.0–9.3 months). The 6-, 12-, and 18-month DFS rates were 53.2%, 40.4%, and 31.9%, respectively. Of these patients, 32 (68.0%) experienced treatment failure during follow-up, including 12 patients with local failure, 18

Table 2
Univariate and multivariate analyses for disease free survival in patients with cervical cancer treated with concurrent chemoradiotherapy.

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (years old)				
<65	1	0.759		
≥65	1.09 (0.62–1.95)			
Pretreatment SCC Ag				
<8.6 ng/mL	1	<0.001	1	
≥8.6 ng/mL	2.34 (1.63–3.37)		1.26 (0.76–1.86)	0.238
Posttreatment SCC Ag				
<1.8 ng/mL	1	<0.001	1	
≥1.8 ng/mL	7.21 (4.79–10.87)		5.10 (3.31–7.88)	<0.001
FIGO stage				
IB	1		1	
IIA and IIB	1.65 (0.80–3.42)	0.177	1.11 (0.53–2.32)	0.787
IIIA–IVA	3.10 (1.44–6.68)	0.004	1.40 (0.63–3.11)	0.405
Primary tumor size				
<4 cm	1	<0.001	1	
≥4 cm	2.50 (1.62–3.85)		1.62 (1.02–2.56)	0.040
Para-aortic MLNs				
Positive	4.15 (2.37–7.27)	<0.001	1.64 (0.90–2.99)	0.104
Negative	1		1	
Pelvic MLNs				
Positive	3.31 (2.31–4.75)	<0.001	2.39 (1.61–3.54)	<0.001
Negative	1		1	
Concurrent chemotherapy				
Yes	1	0.332		
No	1.33 (0.75–2.37)			

Abbreviations: CI = confidence interval; FIGO = International Federation of Gynecology and Obstetrics; HR = hazard ratio; MLNs = metastatic lymph nodes; SCC Ag = squamous cell carcinoma antigen.

patients with distant failure, and 2 patients with concurrent local failure and distant failure. Of the 32 patients who experienced treatment failure, treatment failure occurred 6 months after treatment in 27 patients (84.4%) and 12 months after treatment in 31 patients (96.9%). The most common site of local failure was the cervix (10 patients), and the most common site of distant metastasis was the lung (9 patients).

4. Discussion

The history of studies on SCC Ag in cervical cancer dates back to the 1880s [18–20]. As a prognostic biomarker in cervical cancer, SCC Ag has been discussed extensively in the literature [12,21–24]. However, most studies have focused on pretreatment SCC Ag. Studies on posttreatment SCC Ag in patients with cervical cancer are limited at present [11–13]. Kawaguchi et al. analyzed 116 patients with cervical SCC treated with CCRT. The pretreatment SCC Ag level was >1.5 ng/mL for all patients. The multivariate analysis showed that posttreatment SCC Ag was an independent prognostic factor of OS ($p = 0.001$). The optimal cutoff of SCC Ag was 1.15 ng/mL (sensitivity 80.0%, specificity 74.0%) [11]. Ryu et al. reviewed 783 cervical SCC patients treated with CCRT or surgery and found that posttreatment SCC Ag > 0.9 ng/mL was significantly associated with poor DFS ($p = 0.003$) [12]. Olsen et al. reported that the failure of SCC Ag to normalize after CCRT was associated with an incomplete metabolic response of PET/CT and decreased progression-free survival [13]. Similar to previous studies, the present study showed that posttreatment SCC Ag was associated with poor survival.

In the present study, the 3-year DFS of patients with posttreatment SCC Ag ≥ 1.8 ng/mL was only 31.9%. Patients with elevated posttreatment SCC Ag suffered from a high risk of treatment failure. At present, there is no definite evidence that cervical cancer patients with a high risk of treatment failure could benefit from consolidation therapy. Duenas-Gonzalez et al. reported that CCRT followed by adjuvant gemcitabine/cisplatin chemotherapy could improve progression-free survival compared with CCRT alone [2]. There is an ongoing phase III trial comparing CCRT alone and CCRT followed by adjuvant chemotherapy (paclitaxel and carboplatin), the OUTBACK trial (NCT01414608). More clinical trials are needed to investigate whether consolidation therapy could improve the survival of cervical cancer patients with a high risk of treatment failure. And unnormalized posttreatment SCC Ag can be used as a potential inclusive criterion in clinical trials in the future.

In the present study, 14 patients (29.8%) with posttreatment SCC Ag ≥ 1.8 ng/mL experienced local failure. The most common site of local failure was the cervix (10 patients). Treatment failure occurred

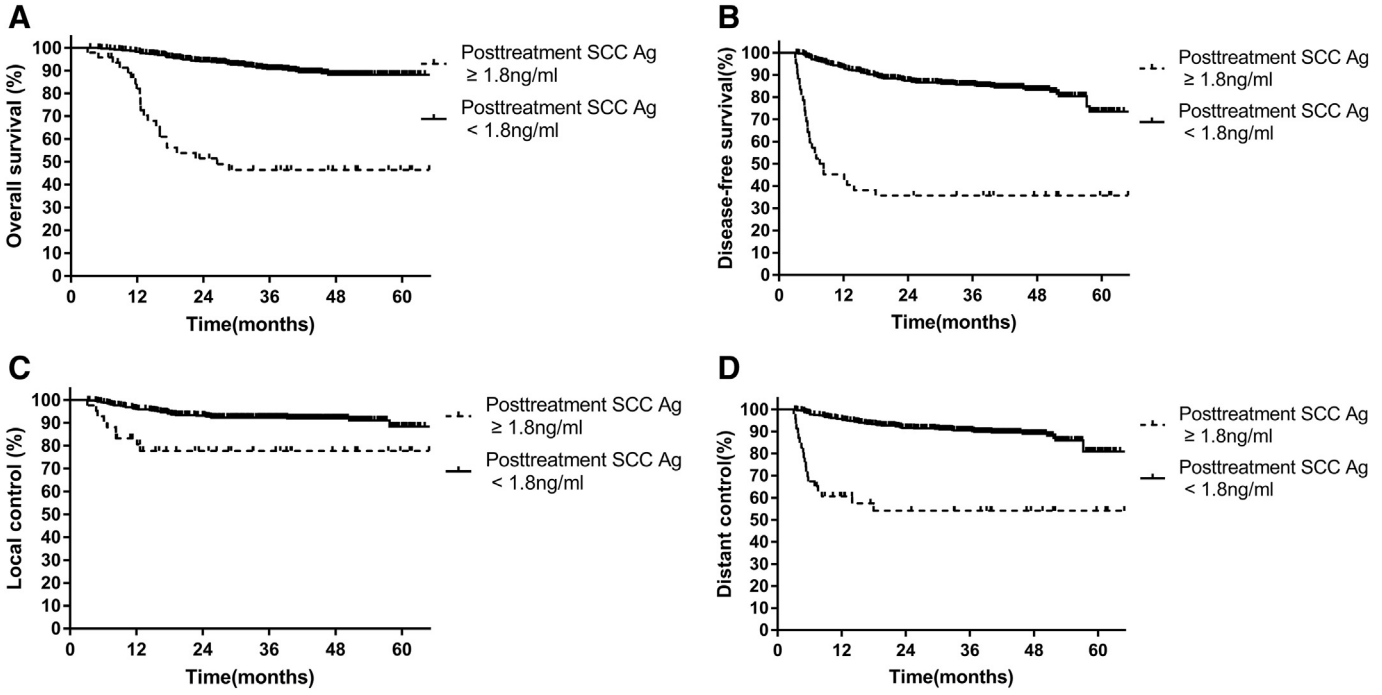

Fig. 3. Overall survival (A), disease-free survival (B), local control (C), and distant control (D) curves of cervical cancer patients with squamous cell carcinoma antigen ≥1.8 and <1.8 ng/mL.

6 months after treatment in 84.4% of patients. Therefore, we need studies to analyze whether pelvic MRI or biopsy in addition to a gynecological pelvic examination is beneficial for cervical cancer patients with unnormalized posttreatment SCC Ag.

This study had some limitations. First, this was a retrospective study, and 129 patients were excluded due to a lack of pretreatment or posttreatment SCC Ag data. This may lead to selection bias. Second, the follow-up period was 39.9 months, which is not long enough. As a result, we chose treatment failure and DFS, but not OS, as the main endpoint when we analyzed the significance of posttreatment SCC Ag.

5. Conclusion

Posttreatment SCC Ag could predict treatment failure and survival for patients with cervical cancer treated with CCRT. Patients with posttreatment SCC Ag $\geq$ 1.8 ng/mL suffer from a high risk of treatment failure.

Author contributions

Conceptualization: Jie Qiu, Ke Hu and Weiping Wang.
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Funding acquisition: Fuquan Zhang.
Methodology: Zhikai Liu, Jie Shen, Shuai Sun and Jiangxuan Fu.
Project administration: Junfang Yan and Qingyu Meng.
Supervision: Zheng Miao and Dunhuang Wang.
Writing - original draft: Weiping Wang.
Writing - review & editing: Jie Qiu and Ke Hu.

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Declaration of competing interest

The authors have no potential conflicts of interest to report.

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