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The association between the serum concentration of CXC subfamily chemokine 13 and post-surgical clinical outcomes in cervical cancer patients

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Abstract. – OBJECTIVE: This study aimed to investigate the relationship between serum levels of CXC subfamily chemokine 13 (CXCL13) and clinical outcomes following radical surgery for cervical cancer.

PATIENTS AND METHODS: A total of 70 cervical cancer patients admitted to our hospital between August 2021 and December 2022 were selected as the study group, while 30 healthy individuals who underwent regular physical examinations during the same period were selected as the control group. The levels of CXCL13 were measured in both groups, and a comparison was made between pre- and post-operative CXCL13 levels in the study group and the control group. Follow-up data on clinical outcomes were collected for the study group, and clinical data were compared between the recurrence/metastasis group and the non-recurrence/metastasis group. Logistic regression analysis was performed to identify factors influencing recurrence and metastasis by incorporating variables showing significant differences. Additionally, Pearson's correlation analysis was used to examine the relationship between CXCL13 and clinical data.

RESULTS: Postoperative levels of CXCL13 in the study group showed a significant decrease compared to preoperative levels, and they were lower than those in the control group ($p<0.05$). Among the 70 patients in the study group, 23 experienced recurrence or metastasis, while 47 did not. Significant differences were observed between the recurrence/metastasis group and the non-recurrence/metastasis group in terms of histological grade, depth of cervical invasion, FIGO stage, parametrial infiltration, lymph node metastasis, and CXCL13 ($p<0.05$). Logistic regression analysis revealed that CXCL13, histological grade, depth of cervical invasion, FIGO stage, parametrial infiltration, and lymph node metastasis were all factors influencing recurrence and metastasis. There was a positive correlation between CXCL13 and histological grade, depth of cervical invasion, FIGO stage, parametrial infiltration, and lymph node metastasis ($p<0.05$).

CONCLUSIONS: The level of CXCL13 is closely associated with the clinical outcome of cervical cancer after radical surgery and can serve as an important indicator for predicting clinical outcomes. Its application in clinical practice is highly recommended.

Key Words:
Radical surgery for cervical cancer, CXC subfamily chemokine 13, Malignant tumors, Human papillomavirus.

Introduction

Cervical cancer, a prevalent gynecological malignancy primarily instigated by human papillomavirus infection, poses significant health risks to women due to its highly invasive nature and proneness to distant metastasis. As reported by Alshowaikh et al[1], the five-year survival rate for patients with advanced cervical cancer stands at approximately 15%.

Radical surgery, currently the most widely adopted treatment for early-stage cervical cancer – particularly for patients at stages Ia1 and Ia2 – aims effectively to excise both tumor tissue and residual cancer cells. However, certain patients may encounter recurrence and metastasis postoperatively, which has a substantial impact on their prognosis[2]. In addition, research by Autorino et al[3] illustrates notable variations in post-surgical clinical outcomes among patients, even with the same stage of cancer, underlining the vital necessity for comprehensive early-stage prognosis.

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In light of these complexities, emerging clinical research[3,4] has identified serum CXC subfamily chemokine 13 (CXCL13) as a novel chemotactic factor. Distributed broadly among peripheral B-cell and T-cell subtypes, CXCL13 has exhibited notable diagnostic value in relation to malignant cell migration in conditions such as renal clear cell carcinoma and osteosarcoma. Furthermore, it appears to have a close connection with occurrences, progression, and invasive tendencies of malignancies.

Despite these findings, the research pool into the role of CXCL13 in relation to cervical cancer remains significantly shallow. Unpacking the relationship between CXCL13 and clinical post-surgical outcomes for cervical cancer patients could facilitate the onset of suitable interventions, thereby potentially augmenting prognoses[5]. To this end, our study investigates the correlation between CXCL13 levels and postoperative outcomes in cervical cancer cases by accessing data from 70 cervical cancer patients received by our institution from August 2021 to December 2022. For a broader context, we included a group of 30 concurrently examined healthy individuals.

Patients and Methods

General Data

We selected 70 patients with cervical cancer admitted to our hospital from August 2021 to December 2022 for the study group. Additionally, we chose 30 healthy individuals who underwent concurrent health examinations during the same period as the control group. The study group had an age range of 42-68 years with an average age of 55.12±3.16 years. Out of these, 25 had an education level of junior high school or below, 28 had a high school education, and 17 had a college education or higher. The body mass index (BMI) of the study group ranged from 22 to 26 kg/m^2, with an average BMI of 24.08±0.63 kg/m^2. The control group had an age range of 40-65 years with an average age of 55.64±2.87 years. Among them, 23 had an education level of junior high school or below, 27 had a high school education, and 20 had a college education or higher. The BMI of the control group ranged from 21 to 26 kg/m^2, with an average BMI of 23.76±0.51 kg/m^2. There were no significant differences in the baseline characteristics between the two groups (p>0.05).

The inclusion criteria for the study were as follows: (1) patients and their relatives were aware of and understood the purpose of the experiment; (2) the study group met the diagnosis criteria for cervical cancer outlined in the "Diagnosis and Treatment Guidelines for Cervical Cancer"[6] and were confirmed through pathological examination; (3) the study group underwent cervical cancer radical surgery at our hospital; (4) all participants had basic language skills in listening, speaking, reading, and writing.

The exclusion criteria were as follows: (1) the study group had contraindications for surgery or anesthesia; (2) other malignant gynecological tumors were present; (3) breastfeeding or pregnant women; (4) participants who received medication or other treatments prior to the experiment; (5) incomplete medical records or withdrawal from the experiment during the course of the study.

Observation Target

Two groups of research subjects were included in the study, and their basic information was collected. This information included age, gender, lesion size, pathological type, histological grade, depth of cervical invasion, FIGO stage, parametrial involvement, and lymph node metastasis. Simultaneously, fasting venous blood samples (3 ml) were obtained in the morning. The samples were then centrifuged at a speed of 3,000 rpm for 10 minutes to separate the serum. The enzyme-linked immunosorbent assay (ELISA) was strictly employed to measure the levels of CXCL13. In the study group, which underwent radical surgery for cervical cancer, CXCL13 levels were measured again 24 hours post-surgery. Follow-up was conducted through phone calls, WeChat, and other means to observe the clinical outcomes of all patients.

The CXCL13 levels before and after surgery in the study group were compared with those in the control group. Clinical outcomes in the study group were also followed up and compared between the recurrence/metastasis group and the non-recurrence/metastasis group. The logistic regression equation was used to analyze the factors influencing recurrence and metastasis by incorporating the items showing differences. Finally, Pearson's correlation analysis was conducted to assess the relationship between CXCL13 and clinical data.

Statistical Analysis

The research data was analyzed using SPSS 25.0 (IBM Corp., Armonk, NY, USA) statistical software. Both the t-test and Chi-square test were utilized for analysis. For metric data, mean ± stan-

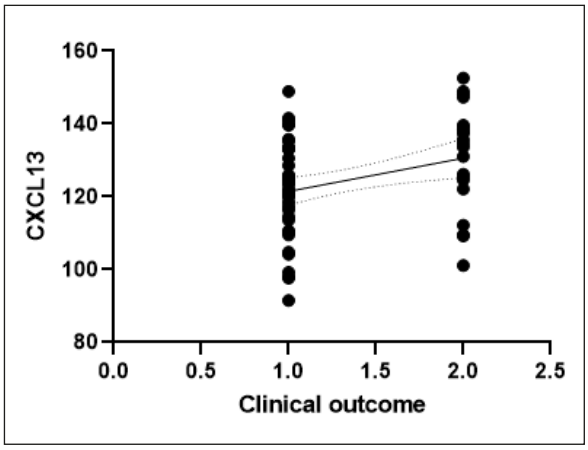

Figure 1. Correlation between CXCL13 and clinical data.

dard deviation was presented, and the *t*-test was used for intergroup comparisons. Count data was expressed as percentages, and the Chi-square test was employed for intergroup comparisons. The significance level was set at $\alpha=0.05$ for all tests. Spearman's correlation analysis was performed to evaluate the correlation between CXCL13 levels and clinical outcomes following radical surgery for cervical cancer. The receiver operating characteristic (ROC) curve was implemented to assess the predictive value of CXCL13 levels in anticipating clinical outcomes after radical surgery. A significance criterion of $p<0.05$ was applied.

Results

Comparison of CXCL13 Levels in Each Group

A comparison of CXCL13 levels among the groups revealed a significant decrease in CXCL13 levels in the study group after surgery (127.54±20.03) compared to pre-surgery levels (182.26±24.95). Additionally, the control group (113.61±15.28) exhibited even lower CXCL13 levels than the study group (182.26±24.95), with a statistically significant difference ($p<0.05$) (Table I).

Clinical Data Analysis of Patients with Different Clinical Outcomes in Study Group

After follow-up, it was observed that among the 70 patients in the study group, 23 experienced recurrence and metastasis, while 47 did not. Within the recurrence and metastasis group, there were significant differences ($p<0.05$) compared to the non-recurrence and non-metastasis group in terms of histological grade (moderate to high, 17 cases), depth of cervical infiltration (≥1/2, 15 cases), FIGO stage (stage II, 19 cases), parametrial infiltration (present, 17 cases), lymph node metastasis (present, 18 cases), and CXCL13 level (134.04±14.19). The non-recurrence and non-metastasis group had the following observations: histological grade (moderate to high, 14 cases), depth of cervical infiltration (≥1/2, 16 cases), FIGO stage (stage II, 14 cases), parametrial infiltration (present, 15 cases), lymph node metastasis (present, 18 cases), and CXCL13 level (123.26±13.19) (Table II).

Correlation between CXCL13 and Clinical Data

Spearman's correlation analysis revealed a positive correlation between CXCL13 and recurrence ($r=0.318$, $p<0.05$, 95% CI: 0.08998-0.5147, $R^2=0.101$), as demonstrated in Table III and Figure 1.

Analysis of Factors Affecting Recurrence and Metastasis

The logistic regression equation revealed that the postoperative CXCL13 coefficient (β) was 0.327, with a standard error (S.E.) of 0.154. The 95% confidence interval (CI) ranged from 0.0821 to 2.2367. The histological grade coefficient was 0.306, with an S.E. of 0.139, and a 95% CI of

Table I. Comparison of CXCL13 levels among groups (pg/ml).

Group	Time	n	CXCL13
Study group	Before surgery	70	182.26±24.95
	After surgery	70	127.54±20.03
Control group		30	113.61±15.28
t (Study group before surgery *vs*. control group)			13.966
p (Study group before surgery *vs*. control group)			<0.001
t (Study group before surgery *vs*. after surgery)			14.309
p (Study group before surgery *vs*. after surgery)			<0.001

CXC subfamily chemokine 13 (CXCL13).

Table II. Analysis of clinical data of patients with different clinical outcomes in the study group.

Clinical data		n	Recurrence and metastasis group (n=23)	Non-recurrence and non-metastasis group (n=47)	χ^2/t	p
Age (years)	<60	33	13	20	1.209	0.271
	≥60	37	10	27		
Lesion size (cm)	≤4	34	11	23	0.008	0.930
	>4	36	12	24		
Pathological type	Adenosquamous carcinoma	14	4	10	0.152	0.927
	Adenocarcinoma	24	8	16		
	Squamous carcinoma	32	11	21		
Histological grade	Low	39	6	33	12.187	0.001
	Moderate to high	31	17	14		
Cervical infiltration depth	<1/2	39	8	31	6.083	0.014
	≥1/2	31	15	16		
FIGO stage	I	37	4	33	17.291	0.001
	II	33	19	14		
Parametrial infiltration	Yes	32	17	15	10.976	0.001
	No	38	6	32		
Lymph node Metastasis	Yes	36	18	18	9.873	0.002
	No	34	5	29		
Postoperative	CXCL13 (pg/ml)	70	134.04±14.19	123.26±13.19	2.769	0.007

CXC subfamily chemokine 13 (CXCL13).

Table III. Correlation between CXCL13 and clinical data.

	CXCL13			
Indicator	r	p	95% CI	R^2
Recurrence	0.518	0.007	0.1899-0.5147	0.101

CXC subfamily chemokine 13 (CXCL13).

0.0517-2.6615. Similarly, the coefficient for cervical infiltration depth was 0.313 (S.E.=0.098, 95% CI=0.1330-1.9768), for FIGO stage was 0.315 (S.E.=0.167, 95% CI=0.0045-3.1353), for parametrial invasion was 0.312 (S.E.=0.132, 95% CI=0.0643-2.5555), and for lymph node metastasis was 0.334 (S.E.=0.126, 95% CI=0.0762-2.4547). Consequently, CXCL13, histological grade, cervical infiltration depth, FIGO stage, parametrial invasion, and lymph node metastasis were all identified as factors influencing recurrence and metastasis (Table IV)

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Predictive Value of CXCL13 Levels for Postoperative Recurrence in Cervical Cancer

The results of the ROC curve analysis demonstrated the predictive value of CXCL13 levels for postoperative recurrence in cervical cancer. The AUC value for CXCL13 levels was 0.890, indicating good discriminative ability. The sensitivity was 0.667, suggesting the ability to correctly identify positive cases, while the specificity was 0.941, indicating the ability to correctly identify negative cases. The Youden index was 0.700, and the optimal cutoff value was determined to be 0.608. The Kappa statistic was 0.28, signifying a substantial agreement. The positive predictive value was 88.3%, and the negative predictive value was 94.8% (Table V and Figure 2).

Discussion

Cervical cancer, one of the most prevalent malignancies in women's reproductive system, primarily arises in the cervix, vagina, and junction of the transformation zone. It ranks as the most common gynecological malignancy in China, posing substantial threats to women's physical

Table IV. Analysis of factors affecting recurrence and metastasis.

Factor	β	S.E.	Df	*p*	95% CI
Postoperative CXCL13	0.327	0.154	1	0.000	0.0821-2.2367
Histological grade	0.306	0.139	1	0.000	0.0517-2.6615
Cervical infiltration depth	0.313	0.098	1	0.000	0.1330-1.9768
FIGO stage	0.315	0.167	1	0.000	0.0045-3.1353
Parametrial invasion	0.312	0.132	1	0.000	0.0643-2.5555
Lymph node metastasis	0.334	0.126	1	0.000	0.0762-2.4547

CXC subfamily chemokine 13 (CXCL13).

Table V. Predictive value of CXCL13 levels for postoperative recurrence in cervical cancer.

Feature	AUC	Sensitivity	Specificity	Youden Index	Cut-off	Kappa	Positive predictive value	Negative predictive value
CXCL13 levels	0.890	0.667	0.941	0.700	0.608	0.28	88.3%	94.8%

CXC subfamily chemokine 13 (CXCL13).

and mental health and overall quality of life[7,8]. The last few years have brought significant advancements in medical technology, which have subsequently refined cervical cancer screening methods, yielding a discernible boost in early detection rates. For early-stage patients, radical surgery remains a primary treatment option, and despite its efficacy in enhancing patients' prognosis, instances of postoperative recurrence and metastasis persist, directly impeding long-term survival rates[9,10]. A study by Gadducci et al[11] showed that the onset, progression, infiltration, and metastasis of malignant tumors are influenced by an array of signaling pathways, transcription factors, and chemokines, underscoring an immediate need for precise prognostic methods to direct subsequent diagnostic and therapeutic strategies.

CXCL13, a key member of the CXC chemokine family, is chiefly synthesized by follicular dendritic cells, macrophages, and secondary lym-

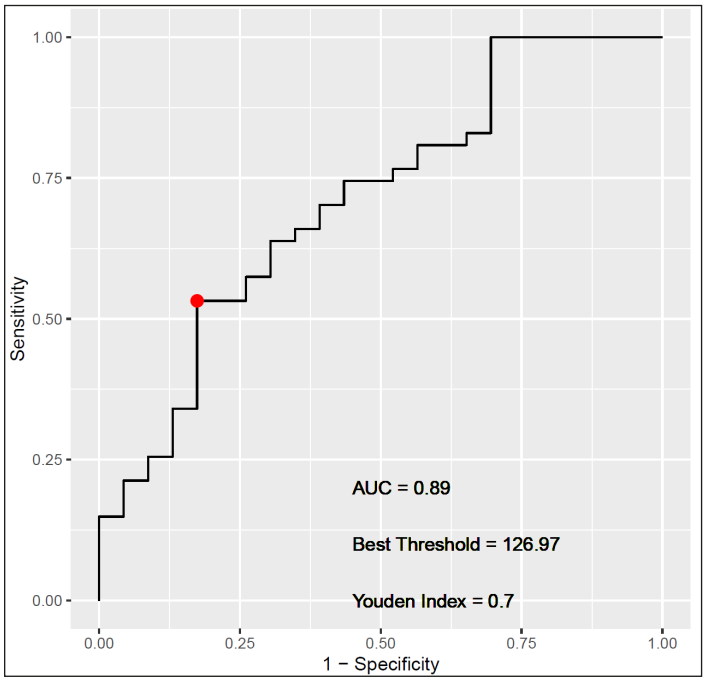

Figure 2. ROC curve for predicting postoperative recurrence in cervical cancer based on CXCL13 levels.

phoid tissues. Its roles extend beyond immunological functions; it also modulates malignant tumor migration and proliferation. Prior research[12,13] has identified elevated levels of CXCL13 in gastric and breast cancer tissues, revealing a strong correlation with postoperative survival rates. Jeong et al[14]'s research linked the overexpression of CXCL13 to increased tactile hypersensitivity in rats afflicted with bone cancer pain, suggesting that the modulation of CXCL13 expression could significantly alleviate pain in these animals. Another investigation[15] discovered that suppressing CXCL13 expression can directly interfere with the CXCL5/extracellular signal-regulated kinase (ERK) signaling pathway, thereby inducing breast cancer cell apoptosis. Despite this compelling evidence of CXCL13's critical role in cancer genesis and evolution, investigations into the association between CXCL13 and cervical cancer are scant, with limited studies suggesting cervical cancer cell migration may be inspired by *CXCL13* gene overexpression. In patients with postmenopausal cervical intraepithelial neoplasia, heightened CXCL13 levels were detected and found[16,17] to correlate with the severity of their lesions.

Currently, research exploring the relationship between CXCL13 and post-radical surgery clinical outcomes in cervical cancer is scarce; thus, our study seeks to fill this void. Our findings show a noticeable decrease in postoperative CXCL13 levels in the study group relative to preoperative levels, with the control group recording even lower levels ($p<0.05$). During follow-up, out of 70 patients, we noted 23 cases of recurrence or metastasis and 47 cases without. Significant differences emerged between the recurrence/metastasis group and non-recurrence/metastasis counterparts concerning histological grade, cervical infiltration depth, FIGO stage, parametrial invasion, lymph node metastasis, and CXCL13 ($p<0.05$). Logistic regression analysis identified CXCL13, histological grade, cervical infiltration depth, FIGO stage, parametrial invasion, and lymph node metastasis as independent predictors of recurrence or metastasis, with a positive correlation found between CXCL13 and these factors ($p<0.05$). This highlights CXCL13's potential utility in disease assessment and prognosis prediction. Its expression significantly influences postoperative clinical outcomes and can serve as a primary prognosis predictor, potentially facilitating early intervention, diminishing recurrence/metastasis rates, and thus optimizing patient outcomes.

Emerging evidence[18,19] unveils chemokines as a multi-transmembrane protein family with considerable implications in cell signaling. Transmitted generally *via* G proteins, their receptors form within multiple subsets of leukocytes originating from bone marrow and are expressed in various cell types, readily activating in response to lipopolysaccharides or cytokines. Under normal conditions, chemokine receptors deliver diverse biological effects, playing pivotal roles in autoimmune diseases, viral infections, and inflammatory responses. Chemokines exert their biological actions by binding to their corresponding receptors, instigating a cascade of signaling pathways responsible for controlling numerous physiological and pathological processes, thereby extensively impacting disease progression[20,21]. Among these, CXCL13 serves as the ligand for CXCR5. Initially proposed to coordinate chemokines and their receptors to instigate inflammatory responses and recruit leukocytes to infection or injury sites, subsequent revelations of their indispensable role in inflammation – a recognized precursor to cancer – prove increasingly interesting. Once CXC chemokines infiltrate the cell nucleus, they can function through diverse mechanisms associated with tumor survival, angiogenesis, proliferation, and even resistance to anti-cancer therapies[22,23]. Our study found that increasing levels of CXCL13 correlated with higher histological grades, deeper cervical infiltration, advanced FIGO staging, and increased incidences of parametrial infiltration and lymph node metastasis, resulting in worsened clinical outcomes for cervical cancer patients. This may be attributed to CXCL13's potential to enhance tumor neovascularization generation and promote tumor cell activation and migration, heightening the risk of recurrence and metastasis[24,25]. In essence, CXCL13 levels are inextricably linked to cervical cancer patients' clinical outcomes following radical surgery, emerging as a crucial predictor of these outcomes, and its further utilization is highly recommended[24,26].

Conclusions

The level of CXCL13 is closely associated with the clinical outcome of cervical cancer after radical surgery and can serve as an important indicator for predicting clinical outcomes. Its application in clinical practice is highly recommended.

Conflict of Interest
The authors declare that they have no conflict of interests.

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Ethics Approval
This study was conducted in accordance with the ethical regulations of the Declaration of Helsinki. The experiments were approved by the Ethics Committee of The Second Affiliated Hospital of Fujian Medical University. The number of the Ethics Committee's acceptance is: 2023373.

Informed Consent
All patients signed the informed consent form.

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Data Availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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