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ORIGINAL RESEARCH

# Serum IL-6 Level Predicts the Prognosis and Diagnosis in Cervical Cancer Patients

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**Background:** Interleukin-6 (IL-6) has been reported to be associated with the prognosis of cancers. As for cervical cancer (CC), previous studies investigated the association between IL-6 expression in CC tumor tissue and CC prognosis; however, no studies assessed the effects of serum IL-6 levels on the survival of CC. This study aimed to explore the effects of serum IL-6 levels on prognosis in patients with CC.

**Methods:** In total, 327 patients with CC and 355 controls were recruited from this hospital from May 2015 to May 2016. Serum IL-6 levels were measured before treatment. The Kaplan–Meier method was utilized to estimate survival rates. The overall survival (OS) and disease-free survival (DFS) were evaluated. The univariate and multivariate Cox regression analyses were used to identify risk factors associated with the prognosis of CC.

**Results:** We found that the serum IL-6 level in the CC group was significantly higher than that in the control group. The diagnostic value of serum IL-6 level in detecting CC patients was moderate, and the specificity and sensitivity were 77.46% and 47.09%, respectively. Data suggested that the serum IL-6 level was significantly linked with the smoking status, FIGO stage, tumor size, treatment methods, and HPV infection. The univariate and multivariate analysis indicated that FIGO stage IIB-IIIC, lymph node metastasis, and high serum IL-6 levels were negatively associated with the OS and DFS in patients with CC.

**Conclusion:** Serum IL-6 has a moderate diagnostic ability for detecting CC and may be a potential CC biomarker. High serum IL-6 level is associated with adverse prognosis in patients with CC and could be a prognosis indicator for CC patients.

**Keywords:** interleukin-6, cervical cancer, prognosis, diagnosis

## Introduction

Cervical cancer (CC) is the fourth most frequent female malignancies, which ranks after colorectal cancer, breast cancer, and lung cancer.[1] In addition, CC represents one of the primary causes of cancer-associated mortality worldwide. In 2018, approximately 570,000 cases of CC and 311,000 deaths occurred globally, suggesting the significant global burden of this cancer.[2] The estimated incidence of CC was about 13.1 per 100,000 women worldwide, and it varied widely among countries.[3] Unlike other solid tumors, CC has a proclivity for younger women.[4,5] Several risk factors contributed to development of CC, including family history of CC, human papilloma virus (HPV) infection, age, socioeconomic status, sexual and reproductive history, and smoking.[6] Infection with carcinogenic HPV types (HPV16 and HPV18) is the major cause in triggering the development of CC.[7] The prognosis of CC is still poor, especially for late-stage and relapsed CC, although the use of screening programs and clinical use of a specific vaccine could reduce CC incidence to some extent.

Inflammatory responses are involved in different stages of tumor development, including initiation, malignant conversion, invasion, promotion, and metastasis.[8] Inflammation could promote the development and progression of cancer. Cancer triggers an inflammatory response, which builds up a protumorigenic microenvironment.[9] Inflammation involves recruitment, activation and action of cell of innate and adaptive immunity.[10] The crosstalk of different immune cells belonging to the tumor microenvironment was via cytokine and chemokine production, and these cytokines and chemokines control tumor growth and invasiveness by autocrine and paracrine manners.[8] Different cytokines can either

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promote or inhibit tumor development and progression. Cytokines regulate the inflammatory environment and immune to either promote tumor progression or favor antitumor immunity, which exerts direct effects on cancer cell survival and growth.[8] Among these cytokines, interleukin-6 (IL-6) plays important roles in cancer initiation, metastasis, and development.[11] IL-6, a glycoprotein composed of 184 amino acids and of 26 kDa, is a multifunctional cytokine.[12] IL-6 is involved in the modulation of growth and differentiation and the host immune defense mechanism in various cancers.[11] IL-6 is mainly produced by immune and nonimmune cells including T cell, monocyte, macrophage, and dendritic cell,[13,14] and some cancer cells, for example, CC cells.[15,16] Suradej et al showed that *Kaempferia parviflora* extract inhibits IL-6 production in HeLa cervical cancer cells.[16] IL-6 promotes the growth of CC by vascular endothelial growth factor (VEGF)-dependent angiogenesis via a STAT3 pathway.[17] Wei et al showed that IL-6 had the anti-apoptotic role in human CC, which was mediated by up-regulation of Mcl-1 via a PI3K/Akt pathway.[18] In addition, higher expression of IL-6 was shown in cancerous tissues than in adjacent noncancer tissues in early-stage CC patients.[19]

Previous studies investigated the association between IL-6 expression in CC tumor tissue and CC prognosis[20,21]; however, no studies assessed the effects of serum IL-6 levels on the survival of CC. In this study, we detected the serum levels of IL-6 in 327 CC patients. We aimed to explore the association of serum IL-6 levels with clinicopathological indicators of CC and assess the prognostic effect of serum IL-6 levels in CC patients.

# Patients and Methods

## Subjects

We recruited 327 patients with CC and 355 controls in this hospital from May 2015 to May 2016. Inclusion criteria for CC patients were as follows: 1) patients were older than 18 years; 2) life expectancy was over 3 months; and 3) the diagnosis of CC was according to pathological examination results. Patients with previous diagnosis of cancer, cardiovascular disease, and autoimmune disease, and inflammatory or infectious diseases were excluded from this study. Healthy controls receiving physical examination were included in this study during the same time period. Controls and CC patients were matched for age and body mass index (BMI). Controls were excluded as follows: 1) individuals with malignant tumor; 2.) individuals with infectious disease; and 3) individuals with autoimmune disorder. The 2018 Federation of Gynecologists and Obstetricians (FIGO) stage classification was used to assess tumor staging.[22] Clinicopathological factors for patients with CC were recorded, including age, smoking status, BMI, HPV infection, histology, FIGO stage, tumor size, lymph node metastasis, treatment methods, and differentiation grade. Pretherapeutic serum IL-6 levels were collected and recorded for all individuals. The overall survival (OS) was from the time of CC diagnosis to time of death caused by any accidents, and the disease-free survival (DFS) was from the time of CC diagnosis to disease development or recurrence. We collected the follow-up outcomes by screening medical records or contacting the patients by telephone. The follow-up was conducted once a month after treatment in the first year, and once 2 months in the second and third years, and every 6 months after the third year. The follow-up time ended in September 2021. The follow-up period was from May 2015 to September 2021. The median follow-up time of CC patients were 66 months (interquartile range [IQR], 44–72 months). The adherence rate of post-treatment follow-up was about 87%. Relevant informed consent form was signed by all subjects. This protocol of this research was approved by the ethics committee of the Affiliated Huai'an No. 1 People's Hospital of Nanjing Medical University. This research was in line with the *Helsinki declaration*.

## Measurement of Serum IL-6 Levels

Blood samples were derived from CC patients and controls before treatment. With the method of flow cytometry, cytometric bead array (CBA) analysis was performed by use of the Human Th1/Th2 CBA kit (JIANGXI CELLCENE BIOTECH CO., LTD). All samples were performed according to the manufacturer's suggestion.

## Statistical Analysis

We used the SPSS (version 19.0, Chicago, IL, USA), MedCalc, and GraphPad Prism (version 7.0, La Jolla, CA, USA) software to complete all statistical analyses. The association between serum IL-6 level and clinicopathological indicators

was dissected. The receiver operating characteristic (ROC) curve was utilized to evaluate the diagnostic ability of IL-6 for CC. To explore the role of IL-6 in the survival of CC, the CC patients were divided into low group (IL-6 <5.30 pg/mL) and high group (IL-6 ≥5.30 pg/mL) according to the levels of serum IL-6. The cut-off value of serum IL-6 level was defined as 5.30 pg/mL, which was the upper limit of normal range in our hospital. The Log rank test was used to distinguish the OS and DFS rates between low and high serum levels of IL-6. Univariate and multivariate regression analyses were used to identify risk factors affecting the prognosis of CC. Hazard risk (HR) and relative 95% confidence interval (CI) were calculated. $P < 0.05$ was regarded as significant.

# Results

## Association Between Serum IL-6 Levels and Clinicopathological Variables in CC Patients

Table 1 summarizes the relationship between serum IL-6 levels and clinicopathological parameters in CC patients, including age, smoking, BMI, HPV infection, histology, FIGO stage, tumor size, lymph node metastasis, treatment methods, and differentiation grade. The details of HPV genotyping for CC patients are summarized in Supplemental Table 1. Data suggested that the serum IL-6 level was significantly linked with smoking status, FIGO stage, tumor size,

**Table 1** Demographics and Risk Factors for Cervical Cancer

| Variable | Serum IL-6 Concentrations | | *P* |
|---|---|---|---|
| | High (≥5.30 pg/mL) (n=220) | Low (<5.30 pg/mL) (n=107) | |
| Age, years, n (%) | | | 0.851 |
| <50 | 123 (55.9) | 61 (57.0) | |
| ≥50 | 97 (44.1) | 46 (43.0) | |
| Smoking, n (%) | | | **0.013** |
| Yes | 50 (22.7) | 12 (11.2) | |
| No | 170 (77.3) | 95 (88.8) | |
| BMI, kg/m$^2$ | 20.4 ± 1.68 | 20.29 ± 1.61 | 0.428 |
| HPV infection (+), n (%) | | | **0.027** |
| Yes | 185 (84.1) | 79 (73.8) | |
| No | 35 (15.9) | 28 (26.2) | |
| Histology, n (%) | | | 0.604 |
| Squamous cell carcinoma | 182 (82.7) | 86 (80.4) | |
| Adenocarcinoma/Adenosquamous carcinoma | 38 (17.3) | 21 (19.6) | |
| FIGO stage, n (%) | | | **0.016** |
| I A-II A | 115 (52.3) | 70 (65.4) | |
| II B-III C | 105 (47.7) | 37 (34.6) | |
| Tumor size, cm, n (%) | | | **0.031** |
| <4 | 127 (57.7) | 75 (70.1) | |
| ≥4 | 93 (42.3) | 32 (29.9) | |
| Lymph node metastasis, n (%) | | | 0.071 |
| Yes | 59 (26.8) | 19 (17.8) | |
| No | 161 (73.2) | 88 (82.2) | |
| Differentiation grade, n (%) | | | 0.090 |
| Well/moderately | 167 (75.) | 90 (84.1) | |
| Poorly | 53 (24.1%) | 17 (15.9) | |
| Treatment methods, n (%) | | | **0.015** |
| Surgery | 119 (54.1) | 73 (68.2) | |
| Chemotherapy + radiation therapy | 101 (45.9) | 34 (31.8) | |

**Note**: Bold values are statistically significant ($P < 0.05$).
**Abbreviations**: BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics.

treatment methods, and HPV infection, but not with lymph node metastasis, differentiation grade, histology, BMI, and age.

## Diagnostic Value of Serum IL-6 Levels for CC

We measured the serum levels of IL-6 in CC patients and controls, and found that the serum IL-6 levels in CC patients were remarkedly higher than those in controls. Figure 1 shows the diagnostic value of serum IL-6 in detecting CC patients. The specificity and sensitivity were 77.46% and 47.09% with a cutoff value of 6.9 (Table 2), respectively. The area under the curve was 0.644 (95% CI: 0.607–0.680, $P < 0.001$). In total, the diagnostic ability of serum IL-6 level for CC was moderate.

## Influences of Serum IL-6 Levels on CC Patient's Prognosis

The Kaplan–Meier method was used to evaluate the effect of serum IL-6 levels on OS and DFS rates. Figure 2 shows that the OS rate in the high serum IL-6 level group was markedly lower than that in the low serum IL-6 level group ($P = 0.002$). Similarly, Figure 3 suggests that the DFS rate in the high serum IL-6 level group was also lower than that in the low serum IL-6 level group ($P = 0.001$).

## Influences of Risk Factors on the Prognosis of CC Patients

Finally, univariate and multivariate Cox analyses were used to verify whether the pretreatment serum IL-6 levels and other clinicopathological indicators were independent prognostic factors of CC patients. The univariate analysis showed that FIGO stage IIB-IIIC, lymph node metastasis, poor differentiation grade, and high serum IL-6 levels were negatively associated with the OS in patients with CC; the multivariate analysis suggested that age (≥50 years), adenocarcinoma, FIGO stage IIB-IIIC, lymph node metastasis, and high serum IL-6 levels were risk factors for CC (Table 3). As for the DFS, univariate Cox analyses indicated that FIGO stage IIB-IIIC, lymph node metastasis, tumor size (≥4 cm), poor differentiation grade, and high serum IL-6 levels were associated with adverse prognosis in patients with CC (Table 4). However, the multivariate analysis suggested that FIGO stage IIB-IIIC, lymph node metastasis, and high serum IL-6 levels were negatively associated with the DFS of CC patients (Table 4).

# Discussion

Our study found that serum IL-6 level was associated with the smoking status, FIGO stage, tumor size, treatment methods, and HPV infection. IL-6 could be a moderate diagnostic indicator of CC, with the sensitivity of 47.09% and specificity of 77.46%. In addition, we found that higher serum IL-6 levels were associated with poorer OS and DFS in

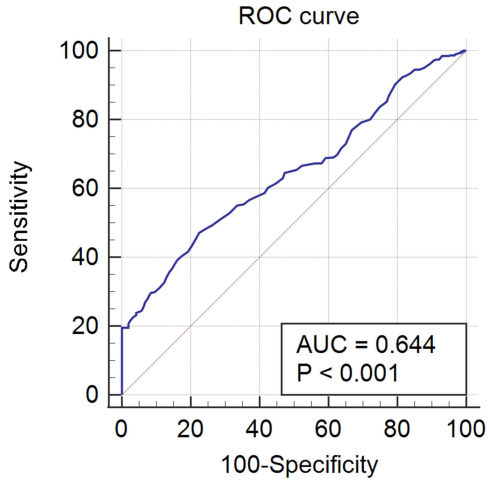


**Figure 1** The receiver operating characteristic curve of IL-6 level for diagnosing cervical cancer.

**Table 2** Receiver Operating Characteristic Curves for Predictive Values of Serum IL-6 level in Cervical Cancer

| Cytokines (pg/mL) | Youden Index J | Associated Criterion | Sensitivity % | Specificity % | AUC (95%) | 95% CI | *P*-value |
|---|---|---|---|---|---|---|---|
| Serum IL-6 | 0.2456 | > 6.9 | 47.09 | 77.46 | 0.644 | 0.607–0.680 | <0.001 |

**Abbreviation**: AUC, area under curve.

patients with CC. Therefore, this study provided evidence that the high serum IL-6 level was related to adverse prognosis in CC and could be a prognosis predictor of CC patients.

Several studies have investigated the prognosis of different types of cancer and IL-6 expression or serum IL-6 levels. Michalaki et al found that serum IL-6 levels in metastatic prostate cancer were significantly higher than those in patients with localised prostate cancer, indicating elevated IL-6 levels were associated with the extent of prostate cancer.[23] As for bladder cancer, Chen et al showed that IL-6 was overexpressed in the bladder cancer specimens than in non-malignant tissues[24] and that IL-6 overexpression was related with an unfavorable prognosis in patients with bladder cancer.[24] Yang et al observed that serum IL-6 levels were decreased in bladder cancer patients with higher myeloid-derived suppressor cell counts, which was associated with a better survival of bladder cancer.[25] Regarding lung cancer, high levels of IL-6 showed worse OS for individuals with non-small cell lung cancer,[26] whose effects of IL-6 on lung cancer survival were also shown in pancreatic cancer[27] and colorectal cancer.[28,29] In addition, higher IL-6 expression was linked with adverse prognosis among gastric cancer patients,[30] which was not in line with the findings observed in breast cancer by Ahmad et al.[31] They showed that high IL-6 expression significantly correlated with improved breast cancer-specific survival and DFS.[31] However, it is of note that IL-6 expression was not an independent prognostic factor after multivariate analysis.[31] To sum up, these results indicated that IL-6 had the potential to be an independent prognostic marker for cancer.

Among gynecological tumors, Scambia et al indicated that IL-6 serum levels correlated with negative prognosis in ovarian cancer.[32–36] However, a study reported that serum IL-6 levels did not correlate with OS, tumor stage, grade of ovarian cancer.[37] Two studies evaluated the association between CC prognosis and IL-6 expression in tumor tissue of CC patients.[20,21] They both showed a better prognosis in CC patients with lower IL-6 expression.[20,21] Actually, it is not convenient to get the prognostic marker from tumor tissue, because it needs to dissect to get the cancer specimen. Thus, for clinicians and CC patients, prognostic markers from peripheral blood are readily available and practical.

In this study, we measured the serum IL-6 level in CC patients, and found that serum IL-6 level was related with the smoking status, FIGO stage, tumor size, treatment methods, and HPV infection. We did not find that serum IL-6 level was associated with lymph node metastasis, which was not in line with the findings from a study by Kotowicz et al.[38] In addition, we found that serum IL-6 level had the moderate diagnostic ability for the occurrence of CC, which provided

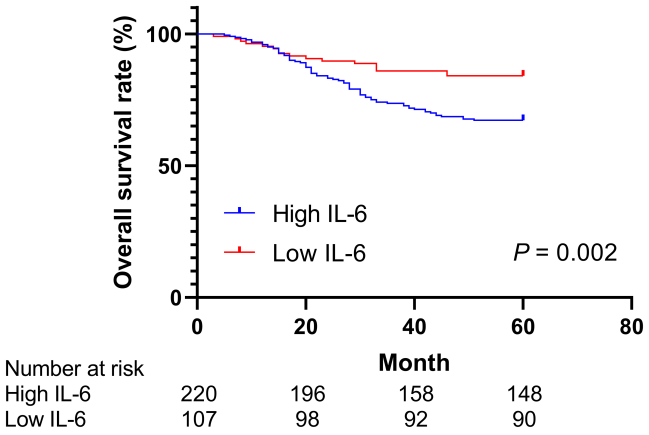


**Figure 2** Comparison of 5-year overall survival rate between high IL-6 group and low IL-6 group (low group <5.30 pg/mL and high group ≥5.30 pg/mL).

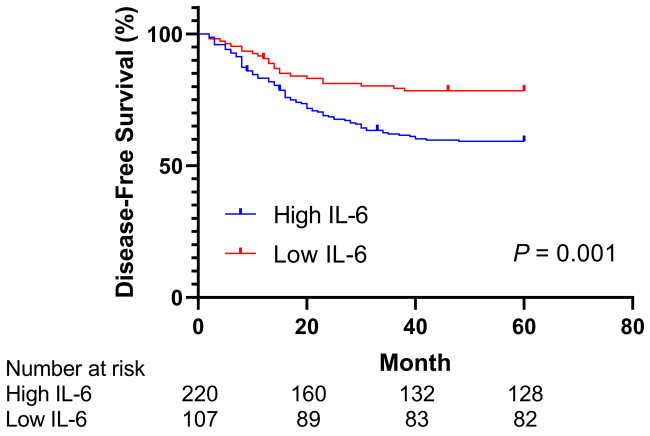


**Figure 3** Comparison of 5-year disease-free survival rate between high IL-6 group and low IL-6 group (low group <5.30 pg/mL and high group ≥5.30 pg/mL).

important supports for detecting potential tumor markers of clinical therapeutic effect for CC patients. Furthermore, this study indicated that the 5-year survival rate of high group (serum IL-6 levels) was obviously lower than the low group, highlighting the role of serum IL-6 exerting a negative impact on CC patients' cumulative survival. Concerning the effect of serum IL-6 levels on the survival of CC, our findings were partly in consistent with other two studies.[20,21] It is of note that this is the first study to observe that high serum IL-6 level was related with an unfavorable prognosis in patients with CC. Further studies in other Asian populations should be conducted to verify these findings of serum IL-6 levels in CC patients. Totally, serum IL-6 level could be a helpful pretherapeutic blood marker to predict the survival of CC patients, which is helpful for evaluating CC prognosis and guiding therapeutic decision.

**Table 3** Univariate and Multivariate Cox Regression Analysis for Overall Survival of Cervical Cancer

| Factors | Overall Survival | | | |
|---|---|---|---|---|
| | Univariate | | Multivariate | |
| | HR(95% CI) | *P*-value | HR(95% CI) | *P*-value |
| Age | | | | |
| ≥50 years vs <50 years | 1.48(0.98–2.25) | 0.064 | **1.55(1.00–2.39)** | **0.048** |
| Smoking | | | | |
| Yes vs no | 1.32(0.81–2.18) | 0.270 | 1.12(0.67–1.87) | 0.674 |
| BMI, kg/m$^2$ | 1.00(0.88–1.14) | 0.984 | 0.92(0.81–1.06) | 0.252 |
| HPV infection | | | | |
| Yes vs no | 1.73(0.94–3.18) | 0.077 | 1.60(0.86–3.00) | 0.139 |
| Histology | | | | |
| Adenocarcinoma/adenosquamous carcinoma vs squamous cell carcinoma | 1.54(0.94–2.51) | 0.085 | **1.73(1.05–2.86)** | **0.032** |
| FIGO stage | | | | |
| II B - III C vs I A - II A | **3.58(2.28–5.64)** | **<0.001** | **2.46(1.31–4.63)** | **0.005** |
| Tumor size | | | | |
| ≥4 cm vs <4 cm | 1.51(0.99–2.28) | 0.054 | 0.88(0.56–1.38) | 0.566 |
| Lymph node metastasis | | | | |
| Yes vs no | **3.55(2.34–5.40)** | **<0.001** | **1.75(1.03–2.98)** | **0.039** |
| Differentiation grade | | | | |
| Poorly vs well/moderately | **2.93(1.91–4.50)** | **<0.001** | 1.35(0.81–2.23) | 0.246 |
| Serum IL-6 levels | | | | |
| High vs low | **2.23(1.31–3.78)** | **0.003** | **1.84(1.07–3.17)** | **0.028** |

**Note**: Bold values are statistically significant ($P < 0.05$).
**Abbreviation**: FIGO, International Federation of Gynecology and Obstetrics.

**Table 4** Univariate and Multivariate Cox Regression Analysis for Disease-Free Survival

| Factors | Disease-Free Survival | | | |
|---|---|---|---|---|
| | Univariate | | Multivariate | |
| | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value |
| Age | | | | |
| ≥ 50 vs < 50 years | 1.18(0.82–1.72) | 0.373 | 1.21(0.82–1.77) | 0.334 |
| Smoking | | | | |
| Yes vs No | 1.54(0.998–2.37) | 0.051 | 1.41(0.90–2.21) | 0.130 |
| BMI, $kg/m^2$ | 1.05(0.94–1.17) | 0.408 | 0.97(0.86–1.10) | 0.644 |
| HPV infection | | | | |
| Yes vs No | 1.63 (0.96–2.77) | 0.070 | 1.52(0.88–2.61) | 0.132 |
| Histology | | | | |
| Adenocarcinoma/adenosquamous carcinoma vs Squamous cell carcinoma | 1.19(0.75–1.90) | 0.467 | 1.32(0.82–2.14) | 0.255 |
| FIGO stage | | | | |
| II B - III C vs I A - II A | **3.83 (2.56–5.74)** | **<0.001** | **2.47(1.42–4.29)** | **0.001** |
| Tumor size | | | | |
| ≥ 4 cm vs < 4cm | **1.50 (1.03–2.17)** | **0.033** | 0.97(0.65–1.44) | 0.884 |
| Lymph node metastasis | | | | |
| Yes vs no | **3.45(2.37–5.03)** | **<0.001** | **1.66(1.04–2.64)** | **0.032** |
| Differentiation grade | | | | |
| Poorly vs Well/Moderately | **3.21(2.19–4.72)** | **<0.001** | 1.51(0.96–2.37) | 0.074 |
| Serum IL-6 levels | | | | |
| High vs low | **2.09(1.32–3.31)** | **0.002** | **1.62(1.02–2.60)** | **0.043** |

**Note**: Bold values are statistically significant ($P < 0.05$).
**Abbreviation**: FIGO, International Federation of Gynecology and Obstetrics.

Due to the important roles in cancer, targeting IL-6 may act as a potential clinical therapy for cancer patients. In recent years, several IL-6 antibodies were developed and assessed in clinical trials,[39–41] such as CNTO 328 (Siltuximab). Trikha et al indicated that IL-6 antibodies were well tolerated, and no serious adverse effects were shown.[40] Furthermore, anti-IL-6 therapy was reported to reduce the incidence of cancer-related symptoms (such as cachexia and anorexia).[40] The inhibition of IL-6 signaling by tocilizumab is therapeutically effective in several diseases.[42,43] Targeting IL-6 receptor using tocilizumab was also effective for the treatment of oral squamous cell carcinoma via inhibiting angiogenesis.[44] Thus, inhibiting the IL-6 or IL-6R or together may benefit for human malignancies in the future.

Several limitations should be considered. First, the sample size of CC patients in this study was moderate. Second, the different treatment strategies may have affected the effect of serum IL-6 levels on the survival of CC patients. Third, the underlying mechanisms of IL-6 affecting the survival of CC were not explored.

In summary, this study finds that high serum IL-6 levels are significantly associated with diagnosis and poor prognosis of CC patients. The pretherapeutic serum IL-6 levels act as a prognostic biomarker for CC patients.

## Disclosure

The authors report no conflicts of interest in this work.

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