Am J Transl Res 2024;16(2):477-486
www.ajtr.org /ISSN:1943-8141/AJTR0154827

Original Article

Effects of neoadjuvant chemotherapy combined with radical laparoscopic surgery with quality nursing care on clinical efficacy and sex hormones in patients with cervical cancer

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Received December 7, 2023; Accepted January 23, 2024; Epub February 15, 2024; Published February 28, 2024

Abstract: Objective: To observe the effects of neoadjuvant chemotherapy combined with radical laparoscopic surgery with quality nursing care on the clinical efficacy and sex hormones of cervical cancer patients. Methods: The clinical data of 107 patients with cervical cancer admitted to Yanan University Affiliated Hospital between January 2017 and January 2020 were retrospectively analyzed in this study. Among them, 50 patients received only laparoscopic radical surgery (surgical group), and the other 57 received neoadjuvant chemotherapy combined with laparoscopic radical surgery (Joint group); patients in both groups received quality nursing care. The baseline and surgical data of the two groups were compared, and the changes in tumor markers and sex hormones before and after treatment were analyzed. Cox regression was used to analyze the independent prognostic factors affecting patients' 2-year survival. Results: The patients in the two groups did not show statistical differences in baseline and surgical data (all $P > 0.05$). After treatment, the levels of squamous cell carcinoma antigen (SCC-Ag), carcinoembryonic antigen (CEA), and serum glycan antigen 125 (CA125) were significantly reduced in both groups. However, the reduction was more pronounced in the joint group than that in the surgical group ($P < 0.0001$). Meanwhile, estrogen (E2) levels decreased more significantly in the Joint group, while follicle-stimulating hormone (FSH) and luteinizing hormone (LH) increased more significantly (all $P < 0.0001$). Multifactorial Cox regression analysis revealed that E2, LH and SCC-Ag were independent prognostic factors affecting 2-year survival (all $P < 0.05$). Conclusion: Neoadjuvant chemotherapy combined with laparoscopic radical surgery is more effective in reducing the levels of tumor markers and significantly affects the levels of sex hormones. E2, LH, and SCC-Ag are the independent prognostic factors for 2-year survival in patients with cervical cancer. This study provides evidence to support the comprehensive treatment of cervical cancer.

Keywords: Cervical cancer, neoadjuvant chemotherapy, radical laparoscopic surgery, survival, prognostic factors

Introduction

The complex interplay between hormonal changes and cervical cancer is a pressing health issue affecting women globally. The menopausal transition and perimenopause, marked by declined ovarian function and reduced estrogen levels, create a vulnerable environment for vaginal microecological imbalances. Such disturbances can lead to atrophic vaginitis and bacterial vaginosis [1]. Hormones are pivotal in maintaining the vaginal microecological balance; any endocrine abnormalities can disrupt this equilibrium, potentially triggering vaginal inflammation, lesions, or even tumors [2].

Cervical cancer, predominantly squamous cell carcinoma, remains a significant threat to women's health. Alarmingly, recent statistics reveal about 493,200 new cases annually, with China accounting for approximately 131,500 [3]. The

https://doi.org/10.62347/NKJK1347

landscape of cervical cancer is evolving. In contrast, squamous cervical cancer incidences have decreased by 41.9% from 1973 to 1996 in the United States, and cervical adenocarcinoma cases have surged by 29.1%, now representing 22.4% of all cervical cancers, up from 10.8%. This upward trend is mirrored in China, with a notable increase in young patients under 35 years old [4]. Treatment modalities like laparoscopic radical cervical cancer surgery, primarily for early-stage cases, aim to excise lesions and lymph nodes. However, these interventions are plagued by high recurrence rates and poor prognoses [5]. Neoadjuvant chemotherapy, administered before surgery or radiotherapy, can potentially shrink tumors, mitigate bodily harm, and enhance surgical outcomes [6, 7]. Yet, the repercussions of these treatments on ovarian function are concerning. The significant drop in estrogen levels after treatment not only triggers menopausal syndromes but also raises risks for coronary heart disease, osteoporosis, and Alzheimer's disease, impacting patients' physical, mental, and social well-being [9-11]. The role of sex hormones, particularly estrogen, in cervical cancer progression is under intense scrutiny. Estrogen, the primary female sex hormone, influences numerous physiological processes, including reproductive function [12]. It's hypothesized that prolonged estrogen exposure might elevate cervical cancer risks by sustaining HPV infection or aiding the progression of HPV-infected cervical cells [13].

This study acknowledges the underappreciated role of sex hormones in cervical cancer progression, emphasizing the need for an in-depth exploration of the impact of estrogen on cervical cells. We hypothesize that treatments like neoadjuvant chemotherapy and laparoscopic surgery might alter sex hormone levels, influencing treatment outcomes. Through this research, we aim to uncover novel personalized treatment approaches for cervical cancer, enhancing patient survival quality and prognosis.

Methodology and information

Ethics statement

The study was conducted with the approval of the Medical Ethics Committee of Yanan University Affiliated Hospital.

Sample acquisition

184 patients with cervical cancer admitted from January 2017 to January 2020 were screened, and their clinical data were collected and retrospectively analyzed in this study.

Inclusion exclusion criteria

Inclusion criteria: (1) Patients with cervical abnormalities (presence of symptoms such as cervical erosion, hypertrophy, ulceration, papillary hyperplasia, and contact bleeding); (2) Patients with squamous carcinoma confirmed by histopathologic examination [8]; (3) Patients who received no radiotherapy or chemotherapy before surgery; (4) Patients with complete clinical and pathological data; (5) Patients with International Federation of Gynecology and Obstetrics (FIGO) stage Ib3-IIa2 cancer [14].

Exclusion criteria: (1) Patients with other concomitant cancers; (2) Patients with a history of oral immunosuppressive drugs; (3) Patients in pregnancy; (4) Patients with comorbidities such as hypertension, diabetes mellitus, or other malignant tumors; or (5) Patients with the presence of severe cardiac, renal, or hepatic insufficiency.

Sample grouping

According to the inclusion and exclusion criteria, 184 patients were screen out, of whom 107 met the requirements. The patients' treatment plans were obtained from their clinical data, and the patients were divided into the joint group (n=57) and the surgical group (n=50) according to the patients' treatment plans.

Access to clinical information

In this study, we collected patients' clinical data, including general data and laboratory indicators from outpatient review records and electronic medical records. The general data encompassed age, body mass index (BMI), duration of the disease, tumor stage, number of lymph node metastases, diameter of the tumor, time of the operation, amount of intraoperative hemorrhage, and time of postoperative drainage. Laboratory parameters included serum glycan antigen 125 (CA125) level, squamous cell carcinoma antigen (SCC-Ag) level, carcinoembryonic antigen (CEA), follicle-stimu-

lating hormone (FSH), luteinizing hormone (LH), and estrogen (E2). CA125 (mI063596, MLBIO Shanghai, China), SCC-Ag (mI058449, MLBIO Shanghai, China), and CEA (mI038471, MLBIO Shanghai, China) were detected by a fully automated chemiluminescence immunoassay analyzer (Snibe, MAGLUMI X3, New Industries, Guangzhou, China), and hormone-related indexes were all measured by a fully automated biochemical analyzer (Beckman Coulter, AU5800), all of which were detected by using the accompanying kits.

Laboratory indicator testing

5 mL of venous blood was collected from patients before and 1 d after surgery, centrifuged at 3000 r/min for 5 min, with a centrifugation radius of 5 cm. The upper layer of serum was extracted, and the levels of CA125, SCC-Ag, and CEA were measured by enzyme-linked immunosorbent assay using an automatic electrochemiluminescence immunoassay analyzer and its accompanying reagent kits. FSH, LH, and E2 were measured by radioimmunoassay and compared between the two groups.

Surgery and nursing program

The surgical group was treated with laparoscopic radical cervical cancer surgery, specifically laparoscopic wide hysterectomy with lymph node dissection. The patient was placed in the cystotomy position, an artificial pneumoperitoneum was established, and the procedure was performed using laparoscopic techniques. Multiple ligaments were first dissected, and the vesicocervical space was separated. The main ligaments, and uterosacral and uterine arteries, were excised and ligated. Lymph node dissection included the common iliac vessels, inguinal lymph nodes, and the obturator lymphatic group. Postoperatively, the vagina was severed, the vaginal stump was sutured, and drains and catheters were placed. The Joint group was combined with neoadjuvant chemotherapy based on the surgical group, referring to the relevant standards in the Standardized Diagnosis and Treatment Guidelines for Cervical Cancer and Precancerous Lesions [4]. Before surgery, patients were first examined for blood routine, X-ray, biochemistry, kidney, liver, etc., to ensure that the indicators were normal and in line with the conditions for chemotherapy, and then neoadjuvant chemotherapy was implemented. Paclitaxel (Yangzijiang Pharmaceutical Group Co., Ltd., State Drug License H20053001, 5 mL:30 mg), 135-175 mg/m^2, was injected intravenously on day 1; carboplatin (Qilu Pharmaceutical Co., Ltd., State Drug License H20020181, 10 mL:50 mg), 400 mg/m^2, was injected intravenously on day 2. After three weeks, the next cycle of chemotherapy was performed, and radical surgery was performed after two cycles of treatment. In addition, patients in both groups received quality nursing care. Before surgical treatment, the patients were provided with knowledge of the disease and surgery and monitored on their emotional changes. All preparations, such as enemas and indwelling urinary catheters, were well prepared. Intraoperatively, nursing staff must ensure a suitable environment in the operating room, prepare surgical equipment, and strictly monitor the patient's vital signs. Critical postoperative care includes observing the patient's vital signs, providing psychosocial support, ensuring drainage and urinary catheterization after surgery, managing the patient's pain, and educating the patient and family about postoperative considerations.

Observation indicators

1. The clinical data of the two groups of patients were compared. 2. The changes of tumor markers before and after treatment were compared between the two groups. 3. The changes in sex hormones before and after treatment were compared between the two groups. 4. The general surgical data of the patients were compared between the two groups. 5. The correlation between sex hormones and tumor markers was analyzed using correlation analysis. 6. Cox regression analysis was adopted to evaluate the prognostic factors affecting the patient's two-year survival.

Statistical analysis

The data collected in this study were analyzed using SPSS 26.0 software and visualized using GraphPad Prism 9 software. Count data were expressed as percentages (%) and compared using the chi-square test. The correlation between sex hormones and tumor markers was analyzed using the Pearson test. K-M survival curves were plotted to analyze the overall survival of patients, which was compared using a Log-rank test. Cox regression was used to ana-

Table 1. Assessment of baseline data of patients in both groups

Index	Surgical group (n=50)	Joint group (n=57)	x^2-value	*P*-value
Age				
≥ 50	28	27	0.794	0.373
< 50	22	30		
BMI				
≥ 25 kg/m^2	18	17	0.461	0.497
< 25 kg/m^2	32	40		
Course of disease				
≥ 2 years	15	18	0.031	0.860
< 2 years	35	39		
Tumor staging				
Phase I	27	35	0.599	0.439
Phase II	23	22		
Lymphatic node metastasis				
Yes	15	20	0.313	0.576
No	35	37		
Tumor diameter				
≥ 4 cm	30	30	0.587	0.444
< 4 cm	20	27		

Note: BMI, body mass index.

Table 2. Comparison of the general data of the two groups of patients

Group	Surgical time (h)	Intraoperative bleeding (mL)	Duration of postoperative drainage (d)
Surgical group (n=50)	3.32±0.86	242.72±96.73	4.36±0.8
Joint group (n=57)	3.49±0.65	241.72±100.68	4.23±0.93
t-value	1.193	0.052	0.782
P-value	0.235	0.958	0.435

lyze the independent prognostic factors for the 2-year survival of patients. P < 0.05 indicated statistical difference.

Results

Evaluation of baseline data

The baseline data of the two groups were evaluated, and the results showed that there were no statistical differences in age, BMI, disease duration, tumor stage, number of lymph node metastases, and tumor diameter between the two groups (all P > 0.05, **Table 1**).

Comparison of general surgical data

The operation time, intraoperative bleeding, and postoperative drainage time were compared between the two groups. It was found that there was no difference in the operation time, intraoperative bleeding, and postoperative drainage time between the two groups (all P > 0.05, **Table 2**).

Changes in tumor markers before and after treatment

Comparison of the changes in SCC-Ag, CEA, and CA125 before and after treatment between the two groups showed that there were no differences in SCC-Ag, CEA, and CA125 levels before treatment between the two groups (all P > 0.05), and the serum levels of SCC-Ag, CEA, and CA125 in both groups were significantly reduced after treatment (all P < 0.0001). However, the decreases in the serum levels of SCC-Ag, CEA, and CA125 of patients in the Joint group after treatment was more prominent than that in the surgical group (all P < 0.0001, **Figure 1**).

Changes in sex hormone indices before and after treatment

The changes in E2, FSH, and LH before and after treatment were compared between the two groups of patients. There were no significant differences in E2, FSH, and LH levels before treatment between the two groups (all P > 0.05). The serum levels of E2 in both groups were significantly decreased after the treatment (P < 0.0001). At the same time, FSH and LH were significantly elevated after the treatment (both P < 0.0001). The decrease in serum E2 level and the increases in serum FSH and LH levels were more significant in the Joint group than those in the surgery group (all P < 0.0001, **Figure 2**).

Correlation analysis of sex hormones and tumor markers

To further determine the correlation between sex hormones and tumor markers, a Pearson correlation test was conducted. The results

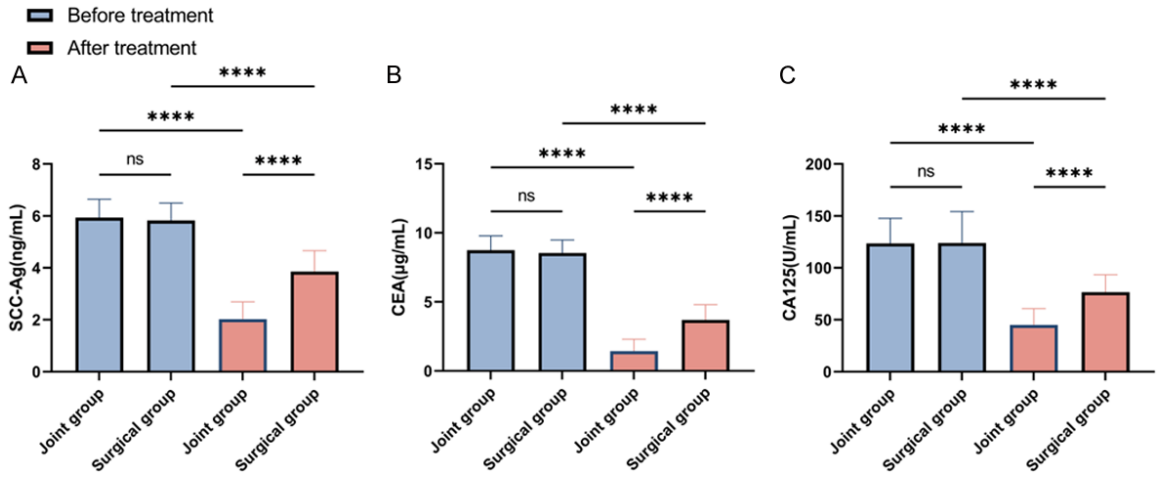

Figure 1. Changes in tumor markers before and after treatment. A. Changes in the expression level of SCC-Ag before and after treatment. B. Changes in the expression level of CEA before and after treatment. C. Changes in the expression level of CA125 before and after treatment. Note: SCC-Ag, squamous cell carcinoma antigen; CEA, carcinoembryonic antigen; CA125, serum glycan antigen 125; ns $P > 0.05$, ****$P < 0.0001$.

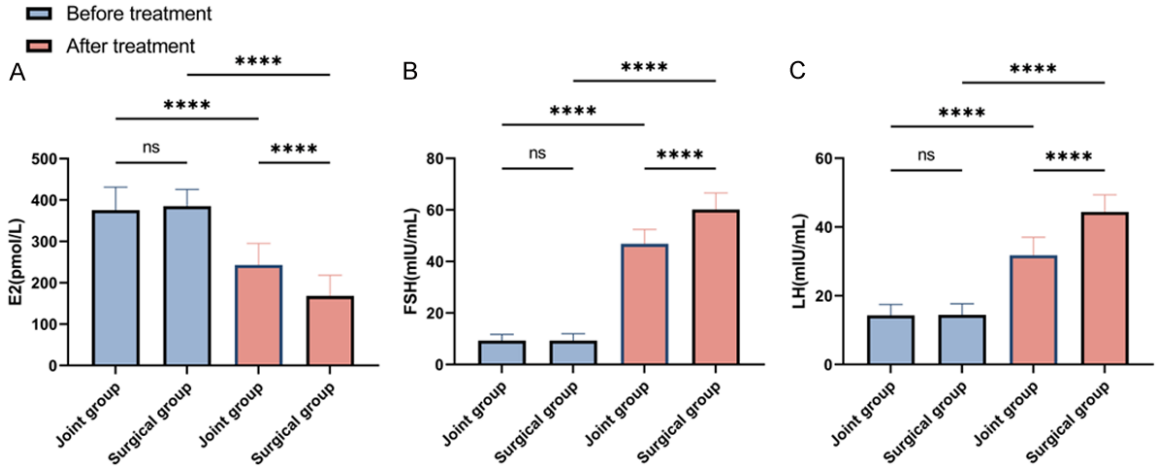

Figure 2. Changes in tumor markers before and after treatment. A. Changes in E2 level before and after treatment. B. Changes in FSH level before and after treatment. C. Changes in LH level before and after treatment. Note: E2, estrogen; FSH, follicle-stimulating hormone; LH, luteinizing hormone; ns $P > 0.05$, ****$P < 0.0001$.

showed that E2 was negatively correlated with tumor markers SCC-Ag, CEA, and CA125 ($P < 0.01$, **Figure 3A**), while FSH and LH were positively associated with SCC-Ag, CEA, and CA125 ($P < 0.001$, **Figure 3B**, **3C**).

Analysis of factors affecting patients' 2-year prognosis

Finally, we analyzed 2-year survival of patients to determine the prognostic factors. 22 of the 107 patients died within two years, giving a survival rate of 79.34%. We then determined the optimal cutoff value for each measure by X-tile software. By univariate Cox analysis, we found that treatment regimen, E2, FSH, LH, and SCC-Ag were prognostic factors affecting patients' 2-year survival (all $P < 0.05$). Subsequently, by multifactorial Cox regression analysis, we found that E2, LH, and SCC-Ag were independent prognostic factors affecting patients' 2-year survival (all $P < 0.05$, **Table 3**; **Figure 4**).

Discussion

Cervical cancer, a notable concern among gynecological malignancies, predominantly arises in specific areas, such as the vaginal

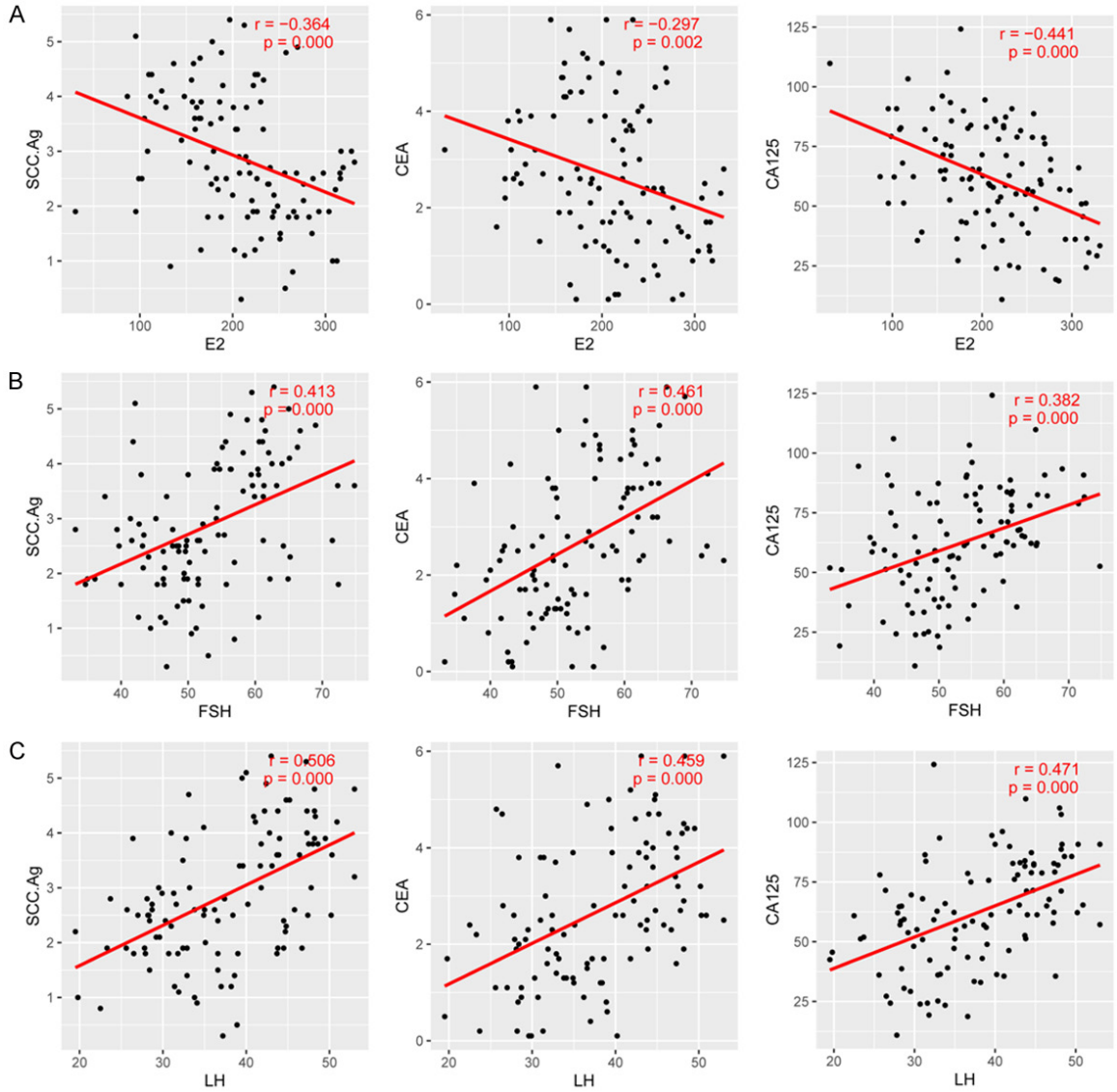

Figure 3. Correlation analysis of sex hormone-related indexes with tumor markers. A. Correlation analysis of E2 with tumor markers SCC-Ag, CEA, and CA125. B. Correlation analysis of FSH with tumor markers SCC-Ag, CEA, and CA125. C. Correlation analysis of LH with tumor markers SCC-Ag, CEA, and CA125. Note: SCC-Ag, squamous cell carcinoma antigen; CEA, carcinoembryonic antigen; CA125, serum glycan antigen 125; E2, estrogen; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

portion of the cervix and the cervical canal. This disease carries a significant mortality rate, with a higher prevalence in less developed regions [4]. The management of cervical cancer typically involves surgical intervention, often complemented by a combination of chemotherapy and radiotherapy. This approach is particularly crucial in advanced stages, where reliance on chemotherapy and radiation therapy intensifies. Recent advancements have introduced more tailored chemotherapy and radiotherapy protocols with varied sequences and a diverse range of drugs as well as different effectiveness [15, 16].

Neoadjuvant chemotherapy has been found to enhance patient outcomes by shrinking tumor lesions, reducing staging, and increasing surgical options [17]. Our study observed that combining neoadjuvant chemotherapy with laparoscopic radical surgery significantly lowered serum levels of SCC-Ag, CEA, CA125, and E2 levels but elevated FSH and LH levels. This can be attributed to the strategic implementation

Table 3. Cox regression analysis of prognostic factors affecting patients' 2-year survival

Factors	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Treatment plan	2.816 (1.148-6.910)	0.024	0.310 (0.062-1.560)	0.155
Age	0.760 (0.328-1.759)	0.521		
BMI	1.520 (0.650-3.557)	0.334		
Course of disease	1.237 (0.519-2.948)	0.632		
Tumor staging	1.365 (0.592-3.148)	0.466		
Lymphatic node metastasis	1.209 (0.507-2.883)	0.668		
Tumor diameter	0.731 (0.317-1.686)	0.463		
Surgical time	1.836 (0.621-5.428)	0.272		
Intraoperative bleeding	0.516 (0.216-1.232)	0.136		
Postoperative drainage time	1.530 (0.453-5.171)	0.494		
E2	4.880 (1.799-13.241)	0.002	3.068 (1.076-8.745)	0.036
FSH	0.404 (0.165-0.991)	0.048	0.565 (0.146-2.189)	0.409
LH	0.190 (0.064-0.562)	0.003	0.199 (0.050-0.794)	0.022
SCC-Ag	0.221 (0.093-0.528)	< 0.001	0.354 (0.139-0.904)	0.030
CEA	0.450 (0.183-1.104)	0.081		
CA125	0.660 (0.285-1.529)	0.333		

Note: BMI, body mass index; SCC-Ag, squamous cell carcinoma antigen; CEA, carcinoembryonic antigen; CA125, serum glycan antigen 125; E2, estrogen; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

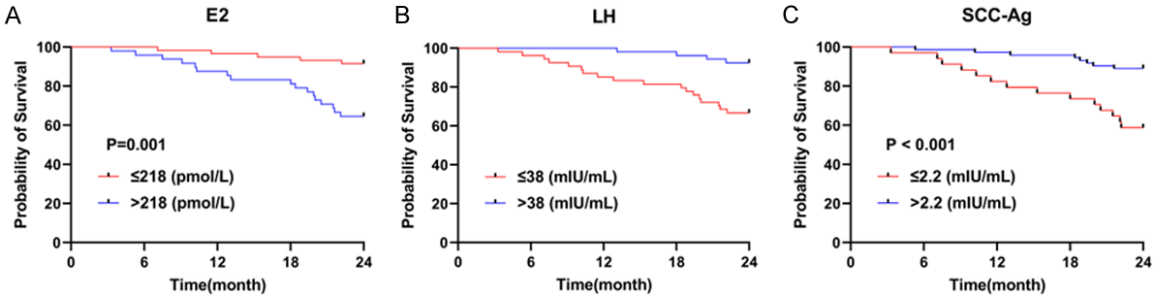

Figure 4. K-M survival curve of patient clustered by different prognostic factors. A. Survival curves of patients in the high and low E2 expression groups. B. Survival curve of patients in the high and low LH expression groups. C. Survival curve of patients in the high and low SCC-Ag expression groups. Note: SCC-Ag, squamous cell carcinoma antigen; E2, estrogen; LH, luteinizing hormone.

of neoadjuvant chemotherapy to decrease tumor volume before surgery, thereby boosting the success rates of subsequent surgical procedures [18]. Paclitaxel and carboplatin, with their direct cytotoxic effects on cancer cells, lead to a substantial reduction in cancer cells before surgery [19]. Consequently, this resulted in a noticeable decrease in SCC-Ag, CEA, and CA125 levels in patients undergoing combined treatment. Additionally, while surgery focuses on the mechanical removal of the tumor, neoadjuvant chemotherapy effectively inhibits and destroys cancer cells at a molecular level [20]. The dual approach of combining these strategies often yields a synergistic effect, leading to enhanced therapeutic results. Moreover, extensive hysterectomy may impact ovarian blood supply, affecting ovarian function. In conjunction with the potential toxicity of chemotherapeutic agents to the ovaries, this could lead to a notable decrease in estradiol and a significant increase in FSH and LH in the combined treatment group. The results of this study are consistent with those reported by Wang et al. [21], providing additional clinical evidence to support the efficacy and advantage of combining neoadjuvant chemotherapy with surgical treatment. It is important to note, however, that

the long-term effects of neoadjuvant chemotherapy on ovarian function need continued monitoring and research to ensure the well-being and long-term health of patients.

The intricate relationship between sex hormones and cervical cancer has emerged as a focal point in medical research. Sex hormones are critical in regulating the female reproductive system, and the cervix, being a vital component of this system, is likely influenced by these hormones in both its normal and abnormal states [10]. First, examining the connection between sex hormones and cervical cancer, initial studies identified the presence of estrogen and progesterone receptors in cervical epithelial cells, suggesting a responsiveness to sex hormones [11]. Furthermore, research indicates that prolonged use of oral contraceptives or hormone replacement therapy might heighten the risk of developing cervical cancer. Second, the onset of cervical cancer can alter the functioning of the ovaries and other endocrine organs, leading to variations in sex hormone levels. Specifically, cervical cancer may interfere with estrogen synthesis and secretion, causing fluctuations in E2 levels [22]. Our study found a negative correlation between E2 and tumor markers, whereas FSH and LH showed a positive correlation. This suggests decreased estrogen synthesis and secretion and increased gonadotropin secretion as the tumor progresses and treatment is administered. Such changes might stem from the tumor's impact on ovarian function or the direct or indirect toxicity of chemotherapy on the ovaries. With reduced E2 levels, the ovaries may try to boost estrogen production by escalating FSH and LH secretion, but this compensatory mechanism could be hampered by ovarian impairment [23]. Additionally, our findings indicate a negative correlation between E2 and SCC-Ag, CEA, and CA125, implying that these tumor markers may increase as estrogen levels decline. This could be linked to estrogen's role in cell proliferation and differentiation, where its reduction might accelerate the growth and invasion of cancer cells [24, 25].

Cervical cancer remains one of the most prevalent malignant tumors affecting women globally. Despite a decline in incidence and mortality rates due to advancements in screening and early diagnostic techniques, the prognosis for advanced and recurrent cases of cervical cancer continues to be challenging [26]. Our current study highlights E2, LH, and SCC-Ag as independent prognostic factors impacting survival, as determined by regression analysis. This finding offers clinicians a valuable tool for assessing the prognosis of cervical cancer patients. However, it is noteworthy that the treatment regimen was not an independent prognostic factor influencing patients' 2-year survival. In a multicenter prospective trial involving patients with FIGO stage IB3 and IIA2 cervical cancer, neoadjuvant chemotherapy was identified as an optional therapy [27]. This study also indicated that deep cervical infiltration significantly affects prognosis in patients receiving neoadjuvant chemotherapy (NACT). Furthermore, research by Zhang et al. [28] adds another perspective on the surgical management of cervical cancer, suggesting that for early-stage cervical adenocarcinoma, laparoscopic radical hysterectomy offers a prognosis comparable to that of conventional open surgery, with an enhanced quality of surgical experience. The role of E2 may be linked to tumor aggressiveness and progression. Changes in LH levels could signify impacts on ovarian function and hormonal imbalances within the body. As a biomarker for squamous cell carcinoma, SCC-Ag provides physicians insights into disease progression and treatment response. Analyzing these studies underscores that cervical cancer treatment necessitates a comprehensive evaluation of various factors [29, 30]. Neoadjuvant chemotherapy, surgical intervention, and subsequent adjuvant therapies hold distinct values for specific patient groups. Therefore, selecting the most suitable treatment strategy is critical and should be tailored to the patient's condition and risk factors.

This study presents significant data and insights into cervical cancer prognosis, yet it is essential to acknowledge its limitations. First, the predominance of participants from less developed regions might limit the generalizability of our findings to other populations or geographic areas. This geographical bias could mean that our results may not fully represent the disease dynamics in more developed or different settings. Second, there are variations in treatment protocols across other regions and hospitals. The treatment approaches used in this study might differ from those employed

elsewhere, potentially influencing the evaluation of treatment efficacy and prognosis. Such disparities in treatment methods can lead to different outcomes, affecting the applicability of our findings in other contexts. Furthermore, our study concentrated on specific indicators, E2, LH, and SCC-Ag, and did not incorporate a broader range of biomarkers or factors that could affect cervical cancer prognosis. This focus might have narrowed our understanding of the comprehensive process of disease. While these biomarkers provide valuable insights, excluding other potentially relevant factors could limit the scope of our conclusions. Future research should aim to broaden the sample size, encompassing varied treatment regimens, and include a wider array of biomarkers. Such comprehensive studies will enable a more holistic and in-depth understanding, potentially enhancing patient survival and quality of life.

In conclusion, this study sheds light on the prognostic factors of cervical cancer, particularly highlighting the roles of E2, LH, and SCC-Ag. The findings underscore the significance of these biomarkers in assessing the prognosis of cervical cancer and offer clinicians valuable insights for formulating more effective treatment strategies, ultimately leading to improved patient outcomes.

Disclosure of conflict of interest

None.

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