Zheng *et al. Virology Journal* (2025) 22:47
https://doi.org/10.1186/s12985-025-02664-3

Virology Journal

RESEARCH Open Access

Prognostic assessment of cervical cancer based on biomarkers: the interaction of ERRα and immune microenvironment

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Abstract

Background Cervical cancer poses a substantial global health challenge. Estrogen-related receptor alpha (ERRα) is a central regulator of cellular energy metabolism associated with poor cancer prognosis. However, the effect of ERRα expression on cervical cancer prognosis and immune infiltration has not been explored. This study aims to clarify the expression pattern and role of ERRα in cervical cancer.

Methods We analyzed ERRα expression and its clinical prognosis in cervical cancer using multiple databases, including The Cancer Genome Atlas (TCGA) and Tumor Immune Estimation Resource (TIMER). The results were further validated through immunohistochemistry (IHC) on 221 cervical cancer tissue samples. Furthermore, Kaplan-Meier and Cox regression analyses were used to assess the clinical significance of ERRα in cervical cancer patients. All calculations were performed using the R package.

Results ERRα expression was significantly higher in cervical cancer tissues compared to normal tissues. High ERRα expression was associated with poor overall survival (OS), disease-specific survival (DSS), and progression-free survival (PFS). Multivariate Cox regression analysis confirmed ERRα as an independent prognostic factor. Additionally, ERRα expression correlated with various immune cell types and immune checkpoints, indicating its role in the tumor immune microenvironment.

Conclusions ERRα emerges as a promising prognostic biomarker in cervical cancer, influencing immune cell infiltration and potentially guiding personalized therapeutic approaches. Future investigations are warranted to delineate the mechanistic pathways through which ERRα contributes to cervical cancer progression and to assess its viability as a target for innovative immunotherapy strategies.

Keywords Cervical cancer, ERRα, Prognosis, Immune infiltration, Biomarkers

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Introduction

Cervical cancer is the fourth most commonly diagnosed cancer and the fourth leading cause of cancer-related deaths among women. Despite efforts to eliminate the disease with human papillomavirus (HPV) vaccines, it is one of the most common malignancies, often accompanied by life-threatening consequences. According to the latest data from GLOBOCAN, in 2022, there were approximately 661,000 new cases of cervical cancer diagnosed globally, and about 348,000 deaths [1]. Persistent HPV infection is the major factor in the pathogenesis of cervical cancer. Without significant intervention, the global burden of cervical cancer is projected to rise to nearly 700,000 cases and 400,000 deaths by 2030, marking a 21% and 27% increase in cases and deaths, respectively [2].

It has been shown that early detection and timely, effective treatment is important to make improvements in the prognosis of patients with cervical cancer in the last two decades [3]. When cervical cancer is diagnosed at an early stage, the relative 5-year survival rate is 91%. When the cancer has spread to local tissues or lymph nodes, the 5-year relative survival rate drops to 60%. When the cancer has spread to distant organs, the relative 5-year survival rate is 19% [4]. Despite advancements and the use of various treatment modalities, including radiotherapy, chemotherapy, and surgery, clinical outcomes have not significantly improved due to post-surgical recurrence and resistance to treatments. Therefore, it is essential to develop new and effective therapeutic targets and strategies to treat cervical cancer effectively.

Biomarkers play crucial roles in predicting the treatment response, prognosis, and disease progression in cancer, developing new therapies, and elucidating tumorigenesis mechanisms. ERRα, first identified in a screening in 1988, is encoded by the ESRRA gene located on chromosome 11q13 [5]. It is a nuclear receptor with DNA sequence homology to ERα [6]. The role of ERRα in energy balance is well-established, as it regulates a large number of genes encoding enzymes and proteins involved in metabolic processes [7]. Metabolic pathways such as glycolysis, the tricarboxylic acid cycle, gluconeogenesis, and oxidative phosphorylation are the main targets associated with ERRα, as well as various other receptors, transcription factors, and co-regulators [8]. At the same time, ERRα regulates mitochondrial activity, biogenesis, turnover, and lipid metabolism, playing a crucial role in promoting obesity in the body [9–10]. In addition, ERRα also regulates the normal physiological functions and developmental functions of muscles and bones [11–13]. New research findings indicate that ERRα plays a role in many aspects, including immunity, cell growth, development and differentiation, angiogenesis, apoptosis, and autophagy, with its scope continuously expanding [14–16]. In tumor cells, an increasing number of reports have also demonstrated that ERRα expression is closely related to poor cancer prognosis, such as breast cancer and endometrial cancer [17, 18]. Recent studies have identified ERRα as a potential target that can simultaneously suppress tumor metabolism and enhance immunotherapy. Researchers performed a stratified analysis of immune therapy responses in melanoma patients and discovered that ERRα is activated in tumors resistant to immune therapy [19]. The diagnostic and prognostic implications of ERRα expression in cervical cancer remain largely unknown.

In this study, we analyzed a TCGA dataset to identify the clinical characteristics, molecular mechanisms, and biological function of ERRα expression in cervical cancer. Next, we detected the expression of ERRα in different stages of cervical cancer tissue through immunohistochemistry (IHC). Lastly, we utilized the TIMER databases to study the association between ERRα expression and immune infiltration levels, determining the involvement of ERRα in the tumor microenvironment. This study opens a new perspective on the active role of ERRα in cervical cancer and highlights the underlying mechanistic basis by which ERRα affects immune cell-tumor interactions.

Materials and methods

Data sources

Normalized RNA-seq and clinicopathological data were obtained from TCGA-CESC datasets, including 306 cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC) tumor tissue samples and 3 non-paired normal tissues [20]. Further analysis was conducted using the ClusteProfiler and ggplot2 packages in R (version 3.6.3).

Patients and specimens

A total of 221 patients with primary cervical cancer who underwent radical hysterectomy between January 2016 and December 2020 at Fujian Maternity and Child Health Hospital and Zhangzhou Hospital were included in this study. Cervical cancer diagnoses were histologically confirmed, and patients did not have secondary primary tumors. All cervical cancer tissue specimens were formalin-fixed and embedded in paraffin. Inclusion criteria for patients were: (1) clear pathological diagnosis; (2) complete clinical medical records; (3) typical carcinoma in tissue specimens with pathological sections and FFPE; (4) complete follow-up data; (5) no immune system disorders such as acquired immunodeficiency syndrome (AIDS) or autoimmune diseases. Clinical data and prognosis information of corresponding patients, including basic information (age, marriage history, HPV infection, cervical cytology), clinical and pathological information (FIGO

stage, pathological histology type, tumor size, tumor grade, tumor stage, preoperative neoadjuvant chemoradiotherapy, surgical method, surgical margin, lymph node (LN) metastasis, invasion depth, lymphatic vascular space infiltration (Lymph-vascular space invasion, LVSI) and postoperative adjuvant therapy), and prognosis information (OS, DSS, and PFS) were retrospectively collected. This study was approved by the Ethics Review Committee of Fujian Maternity and Child Health Hospital (No.2023KY141) and Zhangzhou Affiliated Hospital of Fujian Medical University (No.2023LWB134), and was conducted in accordance with the Declaration of Helsinki. All participants signed written informed consent.

Immunohistochemical staining (IHC) staining and IHC quantifications

The IHC was performed on tissue microarray (TMA) slides, followed by deparaffinized, rehydrated, blocked with 10% normal goat serum, and incubated with the anti-ERRα (Novus, NBP1-47254; 1:200 dilution) primary antibodies overnight at 4 °C. The slides were then incubated sequentially with a secondary antibody (Vector lab, Burlingame, CA, USA) for 1 h and then with Vectastain Elite ABC reagent (Vector Lab) for 30 min. Moreover, we have included information regarding the use of both positive and negative controls in our IHC staining procedures. The tissue sections were stained with diaminobenzidine (DAB kit; Vector Laboratories) and counterstained with hematoxylin (Sigma-Aldrich). The experimental results were expressed using the H-score. Two independent pathologists evaluated the staining intensity using Image J. We rated the intensity of staining on a scale of 0–3: 0, negative; 1, weak; 2, moderate; 3, strong. Subsequently, we assigned the following proportion scores: X indicates the percentage of the tumor cells that were stained ($0 \leq [X1 + X2 + X3] \leq 100$), where X3 indicates strong staining, X2 moderate staining and X1 weak staining. The H-score was calculated using the formula: $3 \times X1 + 2 \times X2 + 1 \times X3$, resulting in a range of 0-300 [21].

Relationship between ERRα expression level and Tumor Immune Cell Infiltration Level

The Tumor Immune Estimation Resource (TIMER2.0) (https://timer.cistrome.org/) is a database used for the analysis of tumor-infiltrating immune cells and various gene expression levels in different types of cancer [22]. We selected 24 immune cell types and correlated their infiltration levels with ERRα expression using the Spearman correlation test.

Statistics

All statistical analyses were performed using GraphPad Prism 8 or packages implemented in R (version 3.6.3). ERRα expression in unpaired samples was analyzed using the Wilcoxon rank-sum test, while paired samples were analyzed using the Wilcoxon signed-rank test. Prognostic factors were assessed using Cox regression analysis and Kaplan-Meier analysis. Multivariate Cox analysis was employed to compare the impact of ERRα expression on survival and other clinical characteristics. A P-value of < 0.05 was considered statistically significant.

Results

Differential expression analysis of ERRα in pan-cancer

RNA-seq data were downloaded from UCSC XENA (https://xenabrowser.net/datapages/) and uniformly analyzed through the toiling process. Based on an analysis of ERRα expression in TCGA and GTEx normal samples and corresponding tumor samples in TCGA, ERRα expression was significantly high among 11 cancer types, including cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), bladder urothelial carcinoma (BLCA), breast invasive carcinoma (BRCA), cholangiocarcinoma (CHOL), Kidney Chromophobe (KICH), liver hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), prostate adenocarcinoma (PRAD), stomach adenocarcinoma (STAD), and uterine corpus endometrial carcinoma (UCEC). In contrast, 4 cancer types exhibited low ERRα expression, including colon adenocarcinoma (COAD), kidney renal clear cell carcinoma (KIRC), kidney renal papillary cell carcinoma (KIRP), and thyroid carcinoma (THCA) (Fig. 1A). We analyzed ERRα mRNA expression patterns using the GTEx dataset, and found that ERRα mRNA was significantly upregulated in cancer relative to normal tissues (Fig. 1B).

Next, we calculated overall survival (OS), disease-specific survival (DSS) and progress free internal (PFI) to analyze ERRα role in cervix cancer patients. Kaplan-Meier survival curves, based on the TCGA cohort, revealed that high ERRα levels were significantly associated with decreased DSS ($p = 0.010$), PFI ($p = 0.014$) and OS ($p = 0.006$) (Fig. 1C-E).

Verification of ERRα expression in our CESC cohort

To further investigate the differential expression levels of ERRα in cervical lesions, we collected 221 cervical specimens along with clinical information. The average age of the patients was 56.33 ± 9.08 years. Squamous cell carcinoma (SCC) was the major histological type (185/221, 83.70%), while adenocarcinoma (AC) and adeno-squamous cell carcinoma (ASC) (36/221, 16.30%) were less frequent in this study. 175 (79.20%) of the cases were classified as FIGO stage I, while 46 (20.80%) were classified as stage II. Additionally, 15 (6.79%) of the cases were HPV negative and 186 (84.16%) were HPV positive (Table 1).

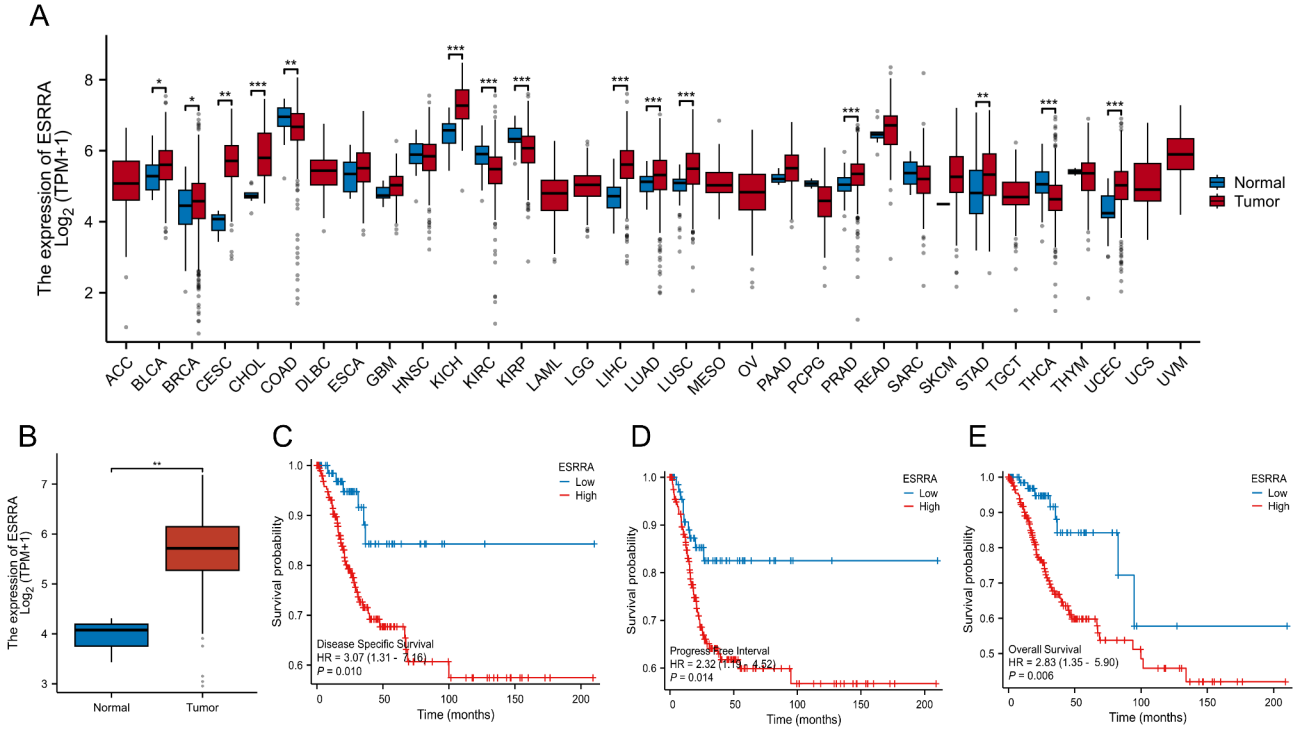

Fig. 1 Differential expression analysis of ERRα in pan-cancer. **(A)** Histogram of ERRα expression in 33 types of unpaired normal and tumor tissues from the TCGA database using Wilcoxon rank-sum test. **(B)** Expression of ERRα gene in normal tissue and tumor tissue. **(C)** Relationship between ERRα expression and disease-specific survival (DSS). **(D)** Relationship between ERRα expression and disease-free interval (DFI). **(E)** Relationship between ERRα expression and overall survival (OS). (∗$P < 0.05$, ∗∗$P < 0.01$, ∗∗∗$P < 0.001$)

To validate the above results, we analyzed ERRα expression levels in the collected specimens using IHC. The ERR H-score for the core region was 52.44 ± 33.91, for the marginal region it was 53.59 ± 37.38, and for the infiltrated region, it was 58.02 ± 37.60. These results indicate slight variations in ERRα expression across different regions of the cervical lesions. When comparing across tissue types, ERRα expression was significantly higher in the tumor core, margin, and infiltration tissues compared to normal tissues ($p < 0.001$) (Fig. 2A). Notably, the H-score analysis of ERRα protein expression in CC tissues revealed significant differences based on clinical parameters (Fig. 2). Specifically, ERRα expression was significantly higher in CC patients with LN metastasis compared to those without LN metastasis in both the tumor core ($p = 0.0013$), margin ($p < 0.001$), and infiltration ($p = 0.0004$). Additionally, a significant difference in ERRα expression was found in the tumor core between patients with and without LVSI ($p = 0.0486$).

ERRα predicts a poor prognosis in CESC

Based on TCGA-CESC data sets, a Kaplan-Meier survival analysis was conducted to investigate ERRα's role in CESC survival. Specifically, OS rates were significantly lower for patients with high H-scores of ERRα in the tumor core (HR = 3.84, $p = 0.019$), margin (HR = 3.76, $p = 0.021$), and infiltration (HR = 3.63, $p = 0.024$) compared to those with low H-scores. Similarly, progression-free survival (PFS) rates were also lower for patients with high H-scores of ERRα in the tumor core (HR = 2.29, $p = 0.068$), margin (HR = 2.76, $p = 0.029$), and infiltration (HR = 2.65, $p = 0.036$) compared to those with low H-scores. These findings suggest that high ERRα expression is associated with worse prognosis in CESC patients (Fig. 3).

The univariate analysis demonstrated that clinical stage (OR = 2.785, 95% CI = 0.953–8.138, $p = 0.038$), ERRα expression in the core (OR = 2.650, 95% CI = 0.479–14.681, $p = 0.019$), margin (OR = 1.094, 95% CI = 0.118–10.178, $p = 0.016$), and infiltration levels (OR = 1.735, 95% CI = 0.228–13.219, $p = 0.020$) affected CESC OS prognosis. Additionally, the univariate analysis showed that ERRα expression in the margin (OR = 1.499, 95% CI = 0.286–7.854, $p = 0.038$) and infiltration levels (OR = 1.840, 95% CI = 0.350–9.662, $p = 0.048$) affected CESC PFS prognosis (Fig. 4). These findings indicate that ERRα expression level was an independent risk factor in CESC patients.

Table 1 Clinical characteristics of the study population

Characteristics	Number of cases (%)
Age (years)	56.33 ± 9.08
BMI (cm^2/kg)	23.46 ± 2.94
FIGO stage*	
I	175(79.20)
II	46(20.80)
Muscle invasive	
No	144(65.20)
Yes	77(34.80)
LVSI	
No	158(71.50)
Yes	63(28.50)
LN metastatic	
No	193(87.30)
Yes	28(12.70)
Pathology	
SCC	185(83.70)
AC/ASC	36(16.30)
HPV status	
Negative	15(6.79%)
Positive	186(84.16%)
Not available	20(9.05%)
ERR H-score (core)	52.44 ± 33.91
ERR H-score (margin)	53.59 ± 37.38
ERR H-score (infiltrated)	58.02 ± 37.60

Continuous variables are presented as mean ± SD (range) and categorical variables as n (%)

Notes: BMI, body mass index; LVSI, lymph-vascular space invasion; LN, lymph node

Association between immune infiltration and ERRα expression in CESC

Tumor-infiltrating immune cells are a crucial component of the complex tumor microenvironment, regulating tumor development and progression. Using TIMER database, we investigated the correlation between ERRα and immune cells infiltrating the tumor microenvironment. The results revealed that ERRα expression was positively associated with central memory T cells (Tcm) ($R = 0.172$, $P = 0.0025$), gamma delta T cells (Tgd) ($R = 0.152$, $P = 0.0079$), and T helper cells ($R = 0.150$, $P = 0.0087$). Conversely, negative correlations were observed with plasmacytoid dendritic cells (pDC) ($R = -0.334$, $P = 2.03e-09$), T follicular helper cells (TFH) ($R = -0.324$, $P = 8.25e-09$), CD56bright natural killer (NK) cells ($R = -0.195$, $P = 0.0006$), NK cells ($R = -0.194$, $P = 0.0007$), eosinophils ($R = -0.153$, $P = 0.0074$), and mast cells ($R = -0.136$, $P = 0.0174$) (Fig. 5A).

Figure 5B illustrates the correlation between ESRRA and various immune checkpoints. Notably, ESRRA showed significant positive correlations with TNFRSF4 ($R = 0.50$, $p < 0.01$), cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4) ($R = 0.50$, $p < 0.01$), and TNFRSF25 ($R = 0.25$, $p < 0.05$). Negative correlations were observed with LGALS9 ($R = -0.50$, $p < 0.01$) and PDCD1LG2 ($R = -0.50$, $p < 0.01$). Scatter plots in Fig. 5C further detail the relationships between ESRRA expression and specific immune checkpoints. ESRRA expression was positively correlated with TNFRSF25 (Spearman $R = 0.243$, $p < 0.001$) and LAG3 (Spearman $R = 0.136$, $p = 0.017$), while negative correlations were observed with CD276 (Spearman $R = -0.140$, $p = 0.014$) and LGALS9 (Spearman $R = -0.145$, $p = 0.011$). These findings suggest that ESRRA expression is intricately linked with immune infiltration and checkpoint expression in cervical cancer, potentially influencing tumor immune microenvironment and patient prognosis.

Discussion

Even though surgery, chemotherapy, radiation therapy, etc. are available today, recurrence and metastasis rates for patients suffering late-stage cervical cancer are up to 40.3% and 31%, respectively [23, 24]. Patients with metastatic cervical cancer continue to have a poor prognosis, with a median survival time ranging from 8 to 13 months. Therefore, it is crucial to identify reliable prognostic biomarkers and molecular mechanisms that can impact cervical cancer prognosis, potentially leading to the discovery of more effective predictive and therapeutic targets.

To our best knowledge, the study was the first one to hypothesize that ERRα might be a novel prognostic biomarker involved in tumor microenvironment in cervical cancer patients. We found that ERRα was not only highly expressed in cervical cancer tumors compared to adjacent normal tissues, but also that high ERRα H-scores in the tumor core, margin, and infiltration regions were associated with poorer OS and DFS in patients with cervical cancer. Additionally, ERRα expression was positively correlated with immune cell infiltration levels, indicating its involvement in the tumor microenvironment.

Recent studies have shown that ERRα plays a key role in the occurrence and development of various types of cancer. High expression of ERRα is associated with poor prognosis in several cancers, including breast cancer, prostate cancer, and ovarian cancer [25, 26]. Research indicates that the overexpression of ERRα is closely related to the aggressiveness and metastatic potential of tumors. In breast cancer, the expression level of ERRα is correlated with the clinical prognosis, and overexpressed ERRα can promote cell proliferation and migration by activating downstream signaling pathways (such as the PI3K/AKT pathway) [27]. Additionally, ERRα influences tumor growth and metastasis by regulating cholesterol metabolism, promoting cell proliferation and migration [28]. ERRα has also been found to be associated with cancer stem cell characteristics, and its inhibition can lead to decreased proliferation and survival of tumor

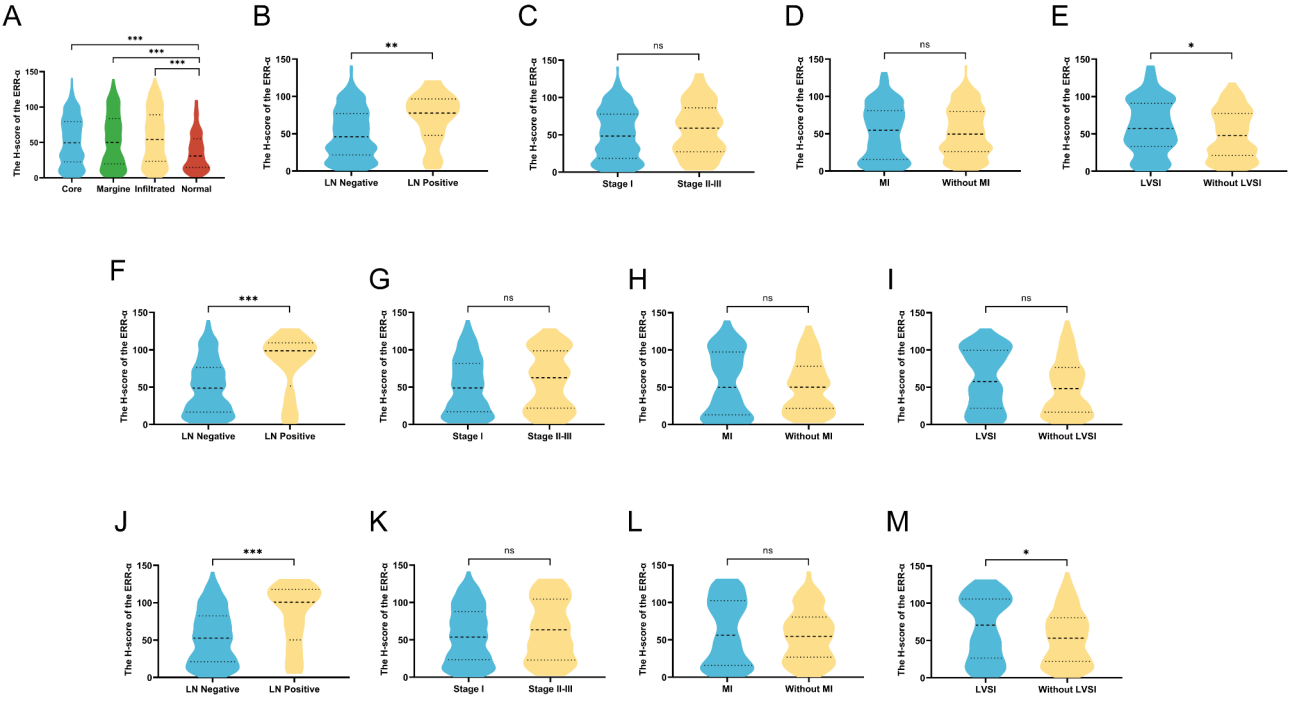

Fig. 2 ERRα protein expression in cervical cancer tissues. (**A**) H-score of ERRα in the tumor core, margin, infiltration and normal tissue of CC patients. (**B**-**E**) H-score of ERRα in the tumor core of CC patients with different groups: with or without LN metastasis, I or II-III stage, with or without MI and with or without LVSI. (**F**-**I**) H-score of ERRα in the tumor margin of CC patients with different groups: with or without LN metastasis, stage I or II-III, and with or without MI and with or without LVSI. (**J**-**M**)) H-score of ERRα in the tumor infiltration of CC patients with different groups: with or without LN metastasis, I or II-III stage, and with or without MI and with or without LVSI. (∗P < 0.05, ∗∗P < 0.01, ∗∗∗P < 0.001,ns: not significant)

cells [29]. In pancreatic cancer, high expression of ERRα is positively correlated with tumor size, metastasis, and TNM staging, promoting cell proliferation and migration through the activation of epithelial-mesenchymal transition (EMT) [30]. The role of ERRα in tumor cells is not limited to metabolic regulation but also involves the development of drug resistance. For example, the expression of ERRα is closely related to chemotherapeutic drug resistance, and studies have found that inhibiting ERRα can increase the sensitivity of osteosarcoma cells to chemotherapeutic drugs, suggesting its potential as a therapeutic target in cancer treatment [31]. Therefore, ERRα is not just a transcription factor but also an important regulatory factor for tumor cell proliferation and survival, making it a potential therapeutic target.

Approximately 99.7% of cervical cancer cases are caused by persistent infections with high-risk HPV [32]. As HPV infection, HPV-infected cells actively instruct the local milieu and create a supportive post-infection microenvironment (PIM), which is becoming recognized as a key factor for viral persistence, propagation, and malignant progression [33]. The PIM is initiated and established via a complex interplay among virus-infected cells, immune cells, and host stroma, as well as their derived components including chemokines, cytokines, extracellular vesicles, and metabolites. Immunotherapy has only relatively recently been recognized as a potential new treatment option for cancer patients suffering from CC [34].

The landscape of immune microenvironment involved in the prognosis of cervical cancer is being studied in depth. A decreased proportion of CD4 + T cells and a reversal of the CD4/CD8 ratio within the cervical cancer microenvironment, indicating depressed antitumor immunity [35]. However, there are limited studies on ERRa and immunoassay. In our immune cell infiltration analysis, ERRα expression was positively associated with Tcm, Tgd, and T helper cells. Conversely, negative correlations were observed with pDC, TFH, NK cells, eosinophils, and mast cells. Harmit et al. reported that ESRRA was a key mediator in the modulation of the immune response [36]. ERRα broadly affected metabolic gene expression and glucose metabolism essential for Teff, and ERRα deficiency reduced activated T-cell numbers in vivo [37]. Our results were in accordance with previous research showing that ESRRA reduced that of NK cells, and cancer-associated fibroblast (CAF) [38]. Activated memory CD4 + T cells, activated mast cells and activated NK cells that performed well in predicting cervical cancer outcomes, with an area under the curve (AUC) of 0.723 and a concordance index (C-index) of 0.739 [39]. Thus, ERRα is a selective transcriptional regulator of immune microenvironment that may provide a metabolic means to modulate tumor microenvironment.

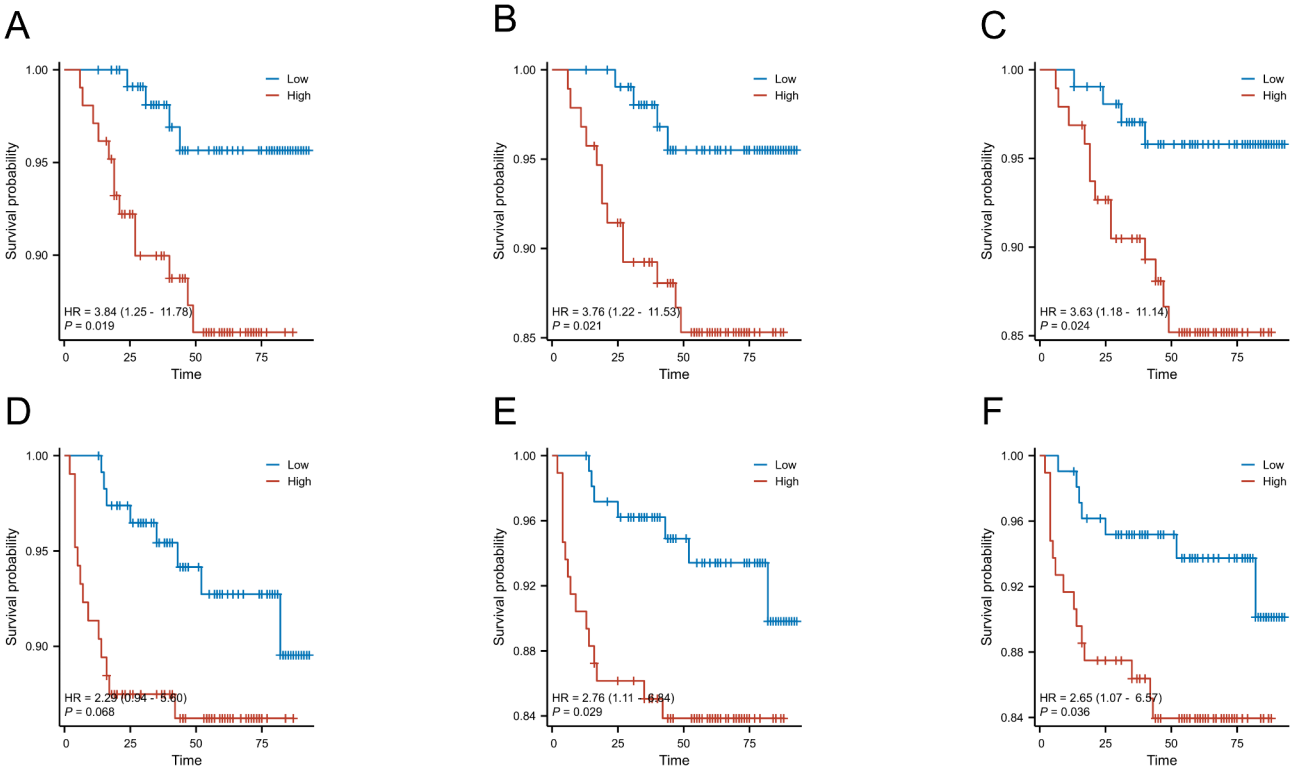

Fig. 3 ERRα overexpression is correlated with poor prognosis in cervical cancer. (**A**–**C**) Survival curves showed OS rates for CC patients with high or low H-score of ERRα in tumor core, margin and infiltration. (**D**–**F**) Survival curves showed PFS rates for CC patients with high or low H-score of ERRα in tumor core, margin and infiltration

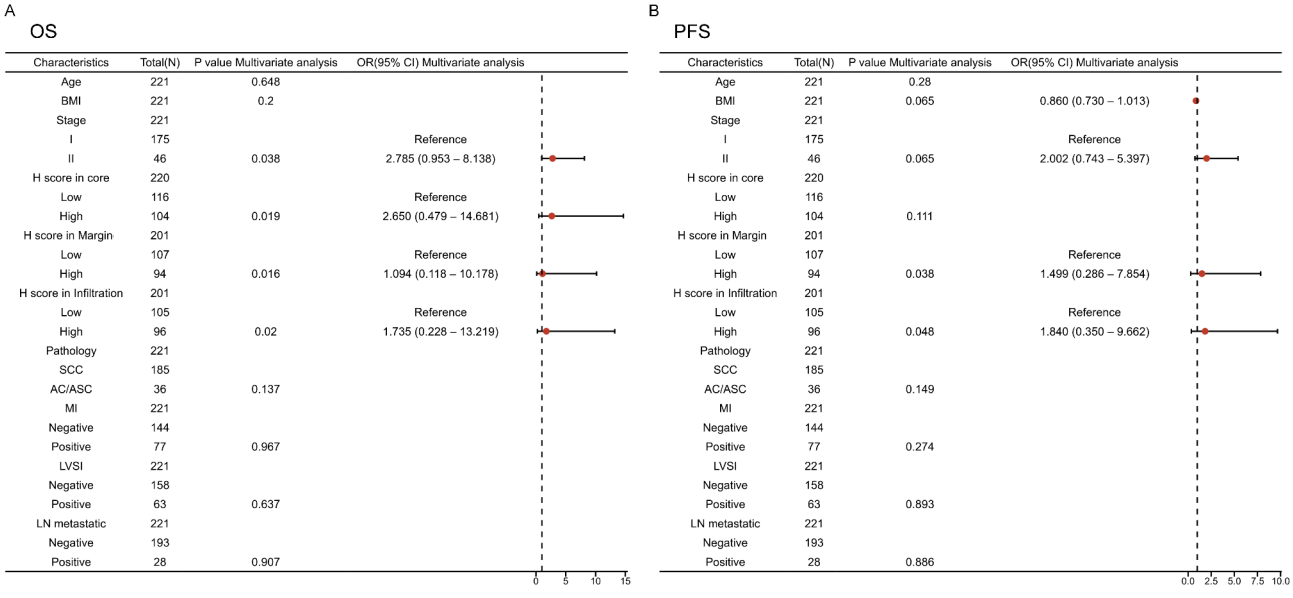

Fig. 4 A forest plot of the correlations between prognostic factors and survival probability, including OS, and PFS. **(A)** Forrest plot of univariate Cox regression analyses between prognostic factors and OS in cervical cancer patients. **(B)** Forrest plot of univariate Cox regression analyses between prognostic factors and PFS in cervical cancer patients. Abbreviations: OR, odds ratio; CI, confidence interval; SCC, squamous cell carcinoma; AC, adenocarcinoma; ASC, adenosquamous carcinoma; MI, myometrial invasion; LN, lymph node; LVSI, lymph vascular space involvement

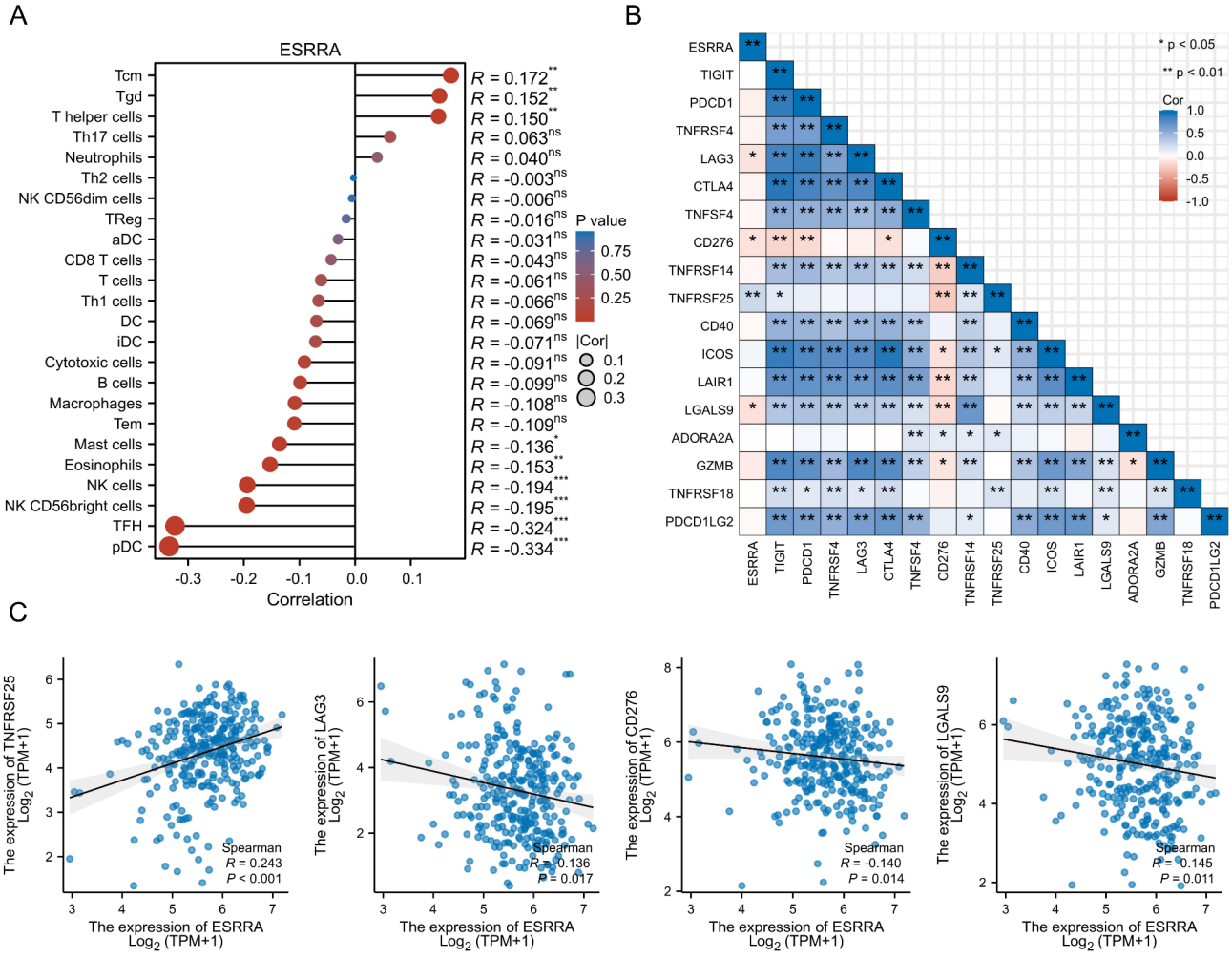

Fig. 5 Immune infiltration analysis in cervical cancer. **(A)** Correlation between ESRRA expression and various immune cell types in cervical cancer. The correlation coefficients (R) are shown along with significance levels The size of the circles represents the strength of the correlation, and the color indicates the *p*-value. **(B)** Heatmap showing the correlation between ESRRA and various immune checkpoints in cervical cancer. The correlation coefficients are represented by color intensity. **(C)** Scatter plots illustrating the correlation between ESRRA expression and the expression of immune checkpoints TNFRSF25, LAG3, CD276, and LGALS9 in cervical cancer. (∗$P < 0.05$, ∗∗$P < 0.01$, ∗∗∗$P < 0.001$, ns: not significant)

Additionally, our study reveals significant correlations between ESRRA expression and various immune checkpoints in cervical cancer. ESRRA was positively correlated with TNFRSF4, CTLA4, and TNFRSF25. The strong correlation of ESRRA with CTLA4, a well-known immune checkpoint, indicates that ESRRA might be involved in modulating T-cell responses, which is critical for anti-tumor immunity. One study showed differences in the expression of CD44, TNFRSF8, LAG3, TNFRSF14, TMIGD2, VTCN1, TNFRSF25, CD80, NRP1, TNFRSF18, CD70, TNFSF9, and LGALS9 in patients with low and high-risk cervical cancer [40]. LGALS9 (also known as Galectin-9) is a β-galactoside binding protein that is the ligand for T cell immunoglobulin mucin-3 (TIM-3). Checkpoint molecule TIM-3 exerts immunosuppressive function by interacting with LGALS9, leading to immune escape during carcinogenesis [41]. LGALS9 was a protective factor affecting the prognosis of patients, and its expression level was negatively associated with prognosis [42]. A negative correlation was observed with LGALS9 (R = -0.50, $p < 0.01$) in our study, suggesting that high ESRRA expression may suppress LGALS9 pathways associated with immune evasion. These findings underscore the complex role of ESRRA in immune regulation within cervical cancer, suggesting its potential as a therapeutic target to enhance immunotherapy efficacy. Further research is needed to validate these associations and explore the underlying mechanisms.

The limitations of this study should be acknowledged. Firstly, the sample size of 221 cervical cancer patients may not adequately represent the broader population, potentially affecting the generalizability of the findings. Additionally, the study lacks extensive clinical validation across diverse cohorts, which could lead to variability

in ESRRA expression and its clinical implications. The absence of basic experiments further restricts our ability to conclusively determine the biological functions of ESRRA in cervical cancer. These factors underscore the need for future research that incorporates larger, multicenter studies and experimental validation to elucidate the precise role of ESRRA in tumor biology and its potential as a therapeutic target. Further research is needed to elucidate the precise mechanisms by which ERRα influences immune cell infiltration and function within the tumor microenvironment.

Conclusions

The above analysis results indicate that ERRα is highly expressed in cervical cancer and can be used as a biomarker for poor prognosis, providing a new target for individualized diagnosis and treatment of cervical cancer.

Abbreviations

CC	Cervical cancer
LN	Lymph node
MI	Muscle invasion
LVSI	Lymph vascular space invasion

Acknowledgements

We would like to thank the participants for their patience and kindness.

Author contributions

MZ: Methodology, Formal analysis, Writing– original draft. WH: Methodology, Investigation, Formal analysis, Writing– original draft. DW and LH: Investigation, Writing– review & editing. YR and QG: Data curation, Investigation; Methodology. YH: Software, Visualization. WL: conceptualization, Formal analysis, Funding acquisition, writing– review & editing. LC: Conceptualization, Resources, Writing– review & editing, Project administration, Funding acquisition.

Funding

The study was supported by grants from the Fujian Provincial Natural Science Foundation of China (grant no. 2022J011036, Leyi Huang), the startup fund for scientific research, Fujian Medical University (grant no. 2021QH1172, Leyi Huang; grant No. 2023QH2047, Wenyu Lin).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Ethical approval for the study was obtained from the Ethics Review Committee of Fujian Maternity and Child Health Hospital (No.2023KY141) and Zhangzhou Affiliated Hospital of Fujian Medical University (No.2023LWB134), China. The procedures followed were in accordance with the ethical standards of the Declaration of Helsinki of the World Medical Association. All women provided informed consent for participation.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 10 December 2024 / Accepted: 12 February 2025
Published online: 24 February 2025

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