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Expression and prognostic value of estrogen-related receptor β alternative splicing isoforms in esophageal squamous cell carcinoma

Kai-Yuan Jiang[1,2†], Jia-Xin Wan[2†], Hong-Yun Li[1†], Wei-Yang Chen[3], Chun-Mei Shen[1], Ke-Xuan Guo[1], Xiang-Yun Zheng[2], Hong-Ying Wen[1,4*] and Dong Tian[2*]

Abstract

Background Estrogen-related receptor β (ERRβ) alternative splicing isoforms, including ERRβsf, ERRβ2, and ERRβΔ10, have been implicated in the pathogenesis of malignant tumors. Nevertheless, their specific impact on esophageal squamous cell carcinoma (ESCC) remains unclear. The study aimed to investigate the expression and prognostic value of ERRβ alternative splicing isoforms in ESCC.

Methods This study prospectively collected ESCC tissues and paired normal tissues of 54 patients with ESCC who underwent esophagectomy without neoadjuvant therapy. The protein expression levels of ERRβ alternative splicing isoforms in ESCC and normal tissues were detected by Western blot. The Kaplan–Meier method with a log-rank test was used to estimate overall survival (OS). The Cox proportional hazards regression analysis was used to evaluate the independent prognostic factors.

Results In ESCC tissues, the ERRβsf/ERRβ ratio was significantly higher ($P=0.017$) compared to paired normal tissues. Based on a cut-off value of 0.24, there were 18 and 36 cases in the high ERRβsf/ERRβ expression group and low ERRβsf/ERRβ expression group, respectively. Patients with high ERRβsf/ERRβ ratios had significantly better OS than those patients with low ERRβsf/ERRβ ratios (77.1% vs 50.8%, $P=0.024$). The multivariate analysis revealed that ERRβsf/ERRβ (hazard ratio [HR] = 0.219, 95% confidence interval [CI] 0.063–0.767, $P=0.018$) and N stage (HR = 7.892, 95% CI 1.328–46.911, $P=0.023$) were independent prognostic factors for ESCC patients.

Conclusions This study is the first to demonstrate the relationship between ERRβ alternative splicing isoforms in ESCC. A high ERRβsf/ERRβ ratio was associated with a better prognosis, indicating that ERRβ alternative splicing isoforms may serve as potential prognostic biomarkers for ESCC.

Keywords Esophageal squamous cell carcinoma, Estrogen-related receptor β, Alternative splicing, Prognosis

†Kai-Yuan Jiang, Jia-Xin Wan and Hong-Yun Li have contributed equally to this work.

*Correspondence:
Hong-Ying Wen
2404738929@qq.com
Dong Tian
22tiandong@wchscu.cn
Full list of author information is available at the end of the article

Introduction

Esophageal cancer (EC) is the 11 th most common cancer and the 7 th leading cause of cancer-associated mortality worldwide, with up to 445,000 new deaths in 2022 [1]. In China, the most common histological type of EC is esophageal squamous cell carcinoma (ESCC), accounting for 85.79% of all EC cases [2]. With the constant progress of new diagnostic techniques and multidisciplinary treatment strategies, there has been a significant improvement in the 5-year survival rate of EC [3–5]. Moreover, various biomarkers have been proven to play a crucial role in malignant tumor diagnosis, treatment, and prognosis prediction, with estrogen-related receptors (ERRs) garnering significant attention in recent years.

ERRs are orphan members of the nuclear receptor superfamily. The ERRs participate in life activities as transcription factors, also leading to the occurrence and development of various malignant tumors [6, 7]. The ERRs subfamily includes three isoforms: ERRα, ERRβ, and ERRγ, encoded by *ESRRA*, *ESRRB*, and *ESRRG*, respectively [8]. ERRβ played pivotal roles in the development of various tumors, such as prostate cancer, breast cancer, ovarian cancer, glioblastoma, and other tumors [9–14]. It induces apoptosis and inhibits proliferation in breast cancer [10] and prostate cancer [15], while promoting cell cycle progression and stimulating proliferation in cervical cancer [16]. However, ERRβ involvement in ESCC is rarely reported.

Alternative splicing is a complex but highly regulated process in human cells, which allows a gene to encode various proteins, the latter known as alternative splicing isoforms [17]. A previous study confirmed that alternative splicing plays a vital role in cancer, which may initiate the malignant occurrence of tumor cells and specifically promote tumor progression [18]. The human ERRβ precursor mRNA consists of 12 exons, which are spliced into three isoforms: ERRβ2 (long form), ERRβΔ10 (10 th exon deleted) and ERRβsf (short form). ERRβ2 mRNA includes 12 exons, and the ERRβ2 protein contains 500 amino acids. ERRβΔ10 comprises exons 3–9, 11, and a portion of 12, which finally encodes the ERRβΔ10 protein containing 508 amino acids. While ERRβsf mRNA contains only exons 3–9, it encodes the ERRβsf protein of 433 amino acids in length [19].

It is worth noting that ERRβ2 and ERRβΔ10 differ in length by only 8 amino acids, making it difficult to distinguish the two splicing isoforms in migrating bands detected by Western blot [19]. To facilitate analysis, this study investigated the relative expression ratios of splice variants ERRβsf and ERRβ2Δ10 within ERRβ, denoted as ERRβsf/ERRβ and ERRβ2Δ10/ERRβ, aiming to explore their expression and prognostic value in ESCC.

Methods

Patients

This study prospectively collected ESCC tissues and paired normal tissues of 54 patients with ESCC who underwent radical esophagectomy between May 2019 and July 2020 at the Affiliated Hospital of North Sichuan Medical College. Normal esophageal tissue was defined as more than 5 cm from the edge of the tumor. The inclusion criteria were as follows: (1) collected specimens included both matched cancerous and normal tissues; (2) patients had not received neoadjuvant therapy (chemotherapy, radiotherapy, or immunotherapy); (3) pathologically confirmed ESCC; and (4) complete clinical data and follow-up information. The pathological tumor staging of ESCC was determined based on the criteria proposed by the 8 th edition American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC). Overall survival (OS) time was defined from the surgery date to death or the date of the last follow-up, and the follow-up period ended in May 2023. This study was approved by the Ethics Committee of the Affiliated Hospital of North Sichuan Medical College, Nanchong (No. 2020ER181-1). Patients were fully informed about the study's purpose, data use, and storage. All patients agreed to use their medical records and tissue samples for research, and the need for patient-informed consent was obtained.

Western blot

The proteins from ESCC and normal esophageal tissues were extracted using RIPA lysis buffer (Solarbio, Beijing, China) containing protease and phosphatase inhibitors (Solarbio, Beijing, China). Protein concentration was qualified by BCA (bicinchoninic acid) Protein Assay Kit (Solarbio, Beijing, China). 6× Loading Buffer was added to the protein sample. The sample was subjected to electrophoresis after boiling for 15 min and then transferred onto polyvinylidene difluoride (PVDF) membranes by semi-dry transfer method. Tris-buffered saline with tween (TBST) solution was used to wash membranes, which were blocked with 5% skimmed milk for 1 h. The primary antibody was incubated overnight at 4 °C. After three 10-min washes with TBST, the secondary antibody was incubated at room temperature for 1 h, and the membrane was also washed with TBST solution. Finally, the color was developed by chemiluminescence and visualized on a Bio-rad gel imager to observe and save the results. Gray values of protein bands were measured using Image J software.

Statistical analysis

Continuous variables are described as the median (interquartile range, IQR), and categorical variables are

described by frequency and percentage. The paired-sample *t*-test was used to compare the protein expression levels of ERRβ alternative splicing isoforms in ESCC tissues and paired normal tissues. Continuous variables were analyzed using the independent-sample *t*-test or Mann–Whitney *U* test, and categorical variables were statistically analyzed using the Chi-square test or Fisher exact test. X-tile software (version 3.6.1, Yale University, New Haven, CT, USA) was used to determine the optimal cut-off value of the ERRβsf/ERRβ ratio that was most significantly associated with OS [20]. Survival curves for OS analysis were estimated using the Kaplan–Meier method with the log-rank test. Univariate and multivariate Cox proportional hazards regression analyses were performed to estimate the factors that contributed to the prognosis of ESCC. Only variables in the univariate analysis at $P < 0.1$ were included in the multivariate analysis. The hazard ratio (HR) and 95% confidence interval (CI) were calculated. All statistical analyses were performed using the SPSS 27.0 software and GraphPad Prism 8.0 software. All statistical tests were two-tailed, and the $P < 0.05$ was considered statistically significant.

Results

Characteristics of patients

A total of 54 patients, comprising 39 men (72.2%) and 15 women (27.8%) with a median age of 67.5 years, were included in this study. Most patients had tumors in the middle thoracic esophagus (72.2%), followed by the lower thoracic esophagus (22.2%). Among all patients, moderately differentiated ESCC accounted for 55.5%, followed by poorly differentiated ESCC at 31.5%. The depth of tumor invasion was predominantly concentrated in the pathological T3 stage, with 36 patients (66.7%), while 18 patients (33.3%) were in pathological T1–2 stages. Most ESCC patients (66.7%) presented with stage III–IV disease, while only 33.3% were in stage I–II. The detailed clinicopathological characteristics of the patients are shown in Table 1.

ERRβ alternative splicing isoform expressions in ESCC and normal tissues

There was no significant difference in the expression levels of ERRβ, ERRβsf, and ERRβ2Δ10 between ESCC tissues and normal tissues (all $P > 0.05$, Supplementary Fig. 1). To further analysis, the expression levels of ERRβsf and ERRβ2Δ10 were performed as ERRβsf/ERRβ and ERRβ2Δ10/ERRβ ratios, respectively. ERRβsf/ERRβ was significantly increased in ESCC tissues compared with paired normal esophageal tissues (mean 0.355 vs 0.290, $P = 0.017$), while ERRβ2Δ10/ERRβ was significantly decreased in ESCC tissues (mean 0.645 vs 0.710, $P = 0.017$, Fig. 1).

Association of ERRβ alternative splicing isoform expressions with clinicopathological characteristics

The optimal cut-off value of prognosis was calculated by X-tile 3.6 software, with cut-off value of 0.24 for ERRβsf/ERRβ. There were 18 patients (33.3%) with a low ERRβsf/ERRβ ratio and 36 patients (66.7%) with a high ERRβsf/ERRβ ratio. No statistically significant differences were found in age, gender, BMI, tumor length, location, G stage, T stage, N stage, and pTNM stage between the groups with low and high ERRβsf/ERRβ ratio (all $P > 0.05$, Table 1).

Cox regression analysis and survival curves

In the univariate analysis, N2-3 stage (HR = 4.323, 95% CI: 0.843–22.185, $P = 0.079$) and ERRβsf/ERRβ (HR = 0.302, 95% CI 0.100–0.910, $P = 0.033$) were associated with OS. There were no statistically significant differences in age, gender, tumor length, G stage, T stage, and pTNM stage (all $P > 0.05$). Variables N2-3 stage and high ERRβsf/ERRβ ratio with $P < 0.1$ in univariate analysis were included in multivariate regression analysis. The multivariate analysis revealed that the N2-3 stage (HR = 7.892, 95%CI 1.328–46.911, $P = 0.023$) and high ERRβsf/ERRβ ratio (HR = 0.219, 95%CI: 0.063–0.767, $P = 0.018$) were independent prognostic factors for ESCC patients (Table 2).

Kaplan–Meier analysis revealed that the OS of patients with high ERRβsf/ERRβ ratio was significantly higher compared to patients with low ERRβsf/ERRβ ratio ($P = 0.024$, Fig. 2A). Meanwhile, the OS rate of patients with high ERRβ2Δ10/ERRβ ratios was significantly lower than that of patients with low ERRβ2Δ10/ERRβ ratios ($P = 0.024$, Fig. 2B).

Discussion

This is the first study to investigate the expression and prognostic value of ERRβ alternative splicing isoforms in ESCC. The main findings are as follows: (1) the ERRβsf/ERRβ ratio was higher in ESCC tissues compared to paired normal tissues; (2) patients with a high ERRβsf/ERRβ ratio showed a better OS; (3) high ERRβsf/ERRβ ratio and N0 stage were favorable independent prognostic factors of ESCC.

The previous study [21] found that *ESRRB* expression in ESCC is downregulated compared with normal tissue in the TCGA dataset. However, there was no significant difference in the expression of ERRβ between ESCC and paired normal tissues in the current study (Supplementary Fig. 1 A). Similarly, there was no significant difference in the expression of ERRβ mRNA between endometrial adenocarcinoma tissues and normal endometrial tissues [22]. In prostate cancer, the expression for

Table 1 Correlations between ERRβsf/ERRβ and clinicopathological characteristics in ESCC patients

Characteristic	All patients, *N* = 54	ERRβsf/ERRβ		*P* value
		Low, *N* = 18	High, *N* = 36	
Age, year (IQR)	67.5 (62.0–72.3)	68.5 (62.0–72.0)	66.5 (62.0–73.0)	0.912[a]
Gender, *n* (%)				0.053[b]
Male	39 (72.2)	16 (88.9)	23 (63.9)	
Female	15 (27.8)	2 (11.1)	13 (36.1)	
BMI (IQR)	21.94 (19.94–24.28)	22.05 (20.51–24.28)	21.50 (19.85–24.56)	0.754[a]
Tumor length, *n* (%)				0.188[b]
≤ 3 cm	24 (44.5)	5 (27.8)	19 (52.8)	
3 cm–5 cm	20 (37.0)	8 (44.4)	12 (33.3)	
≥ 5 cm	10 (18.5)	5 (27.8)	5 (13.9)	
Location, *n* (%)				1.000[b]
Upper	3 (5.6)	1 (5.6)	2 (5.6)	
Middle	39 (72.2)	13 (72.2)	26 (72.2)	
Lower	12 (22.2)	4 (22.2)	8 (22.2)	
G stage, *n* (%)				0.606[b]
G1	17 (31.5)	4 (22.2)	13 (36.1)	
G2	30 (55.5)	11 (61.1)	19 (52.8)	
G3	7 (13.0)	3 (16.7)	4 (11.1)	
T stage, *n* (%)				0.554[b]
T1–2	18 (33.3)	8 (38.1)	10 (30.3)	
T3	36 (66.7)	13 (61.9)	23 (69.7)	
N stage, *n* (%)				0.846[b]
N0	18 (33.3)	10 (32.3)	8 (34.8)	
N1–3	36 (66.7)	21 (67.7)	15 (65.2)	
pTNM stage, *n* (%)				0.695[b]
I–II	18 (33.3)	10 (31.2)	8 (36.4)	
III–IV	36 (66.7)	22 (68.8)	14 (63.6)	

ESCC, esophageal squamous cell carcinoma; y = year; BMI = body mass index; IQR = interquartile range

[a] Mann–Whitney *U* test

[b] Chi-square test

ERRβ was significantly lower in cancerous tissue than in benign tissue [9]. Furthermore, the expression of ERRβ in breast cancer cell lines was decreased compared with normal cell lines [10]. Different ERRβ splicing isoforms may exhibit varying trends, with some showing increased expression and others decreasing during tumor development, resulting in no difference in ERRβ expression between tumor and normal tissues. We used percentages to represent the relative expression of ERRβ splicing isoforms and found that the ERRβsf/ERRβ ratio was significantly higher in tumor tissues compared to normal tissues.

Zhou et al. [19] detected ERRβsf in the stomach, small intestine, and colon tissues, but no ERRβ splicing isoforms were found in the uterus and Ishikawa cells. Bombail et al. [23] employed the reverse transcription-polymerase chain reaction (RT-PCR) to confirm that ERRβsf and ERRβ2 were expressed in normal endometrium, while ERRβΔ10 was not. In addition, the ERRβsf transcripts were detected in prostate cancer cell lines, whereas ERRβ2 and ERRβΔ10 were not observed [15]. Fernandez et al. [24] found the low ERRβsf expression in triple-negative breast cancer. Nevertheless, the current study observed a significantly higher ERRβsf/ERRβ ratio in ESCC tissues, indicating that the expression of ERRβ alternative splicing isoforms varies across different cancer types.

The prognostic role of ERRβ has been reported inconsistently across various cancers. High expression of ERRβ is significantly correlated with improved recurrence-free survival rates in breast cancer [10]. In cervical cancer, the mice in the *ESRRB*-knockout groups showed a longer tumor-free survival [16]. Moreover, there was no significant difference in cancer-specific survival of prostate cancer between the groups with low and high ERRβ expression [9]. However, there are no reports on the

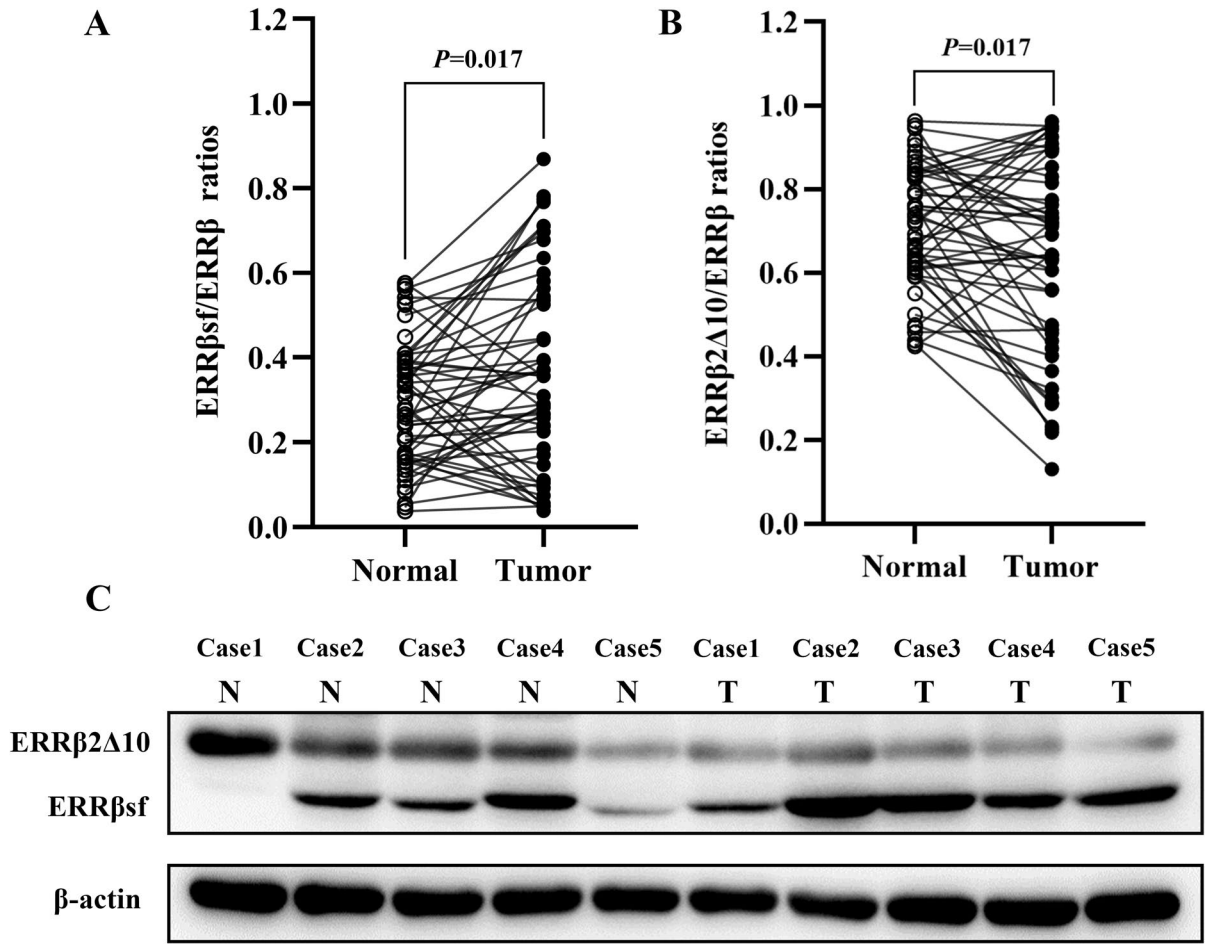

Fig. 1 Expression levels of ERRβsf and ERRβ2Δ10 proteins in ESCC tissues. **A** ERRβsf/ERRβ in ESCC tissues compared with normal tissues was assessed by Western blot in the above tissues. **B** ERRβ2Δ10/ERRβ in ESCC tissues compared with normal tissues. **C** Protein levels of ERRβsf and ERRβ2Δ10 in five representative ESCC tissues (T) and paired normal tissues (N) were analyzed by Western blot. Image J software was used to measure gray values of target bands (ERRβsf, ERRβ2Δ10) and β-actin band (internal reference). The relative expression levels were normalized by calculating the ratio of the gray value of the target protein band to that of the β-actin band for each sample. T: tumor tissues, $n = 54$; N: normal tissues, $n = 54$

relationship between ERRβ alternative splicing isoforms and the prognosis of patients with ESCC. This study firstly demonstrated that a higher ERRβsf/ERRβ ratio was a favorable independent prognostic factor, with patients with higher ERRβsf/ERRβ ratio showing better OS. The expression of ERRβsf may be associated with the biological behavior of tumors or inhibit cell proliferation, which may affect the OS of the patients. An in-depth understanding of the prognostic value of ERRβsf is helpful for the risk stratification of ESCC patients for personalized treatment plans. Targeted drugs against ERRβsf could improve patient prognosis. Meanwhile, dynamic monitoring of changes in the ERRβsf/ERRβ ratio can help assess the efficacy and recurrence risk to adjust the treatment strategy.

Previous study [16] indicated that *ESRRB* is a central link, forming a positive feedback loop with SMAD7 and MYC to inhibit TGF-β signaling, thereby driving cervical cancer cell proliferation and associating ERRβ with poor prognosis. Conversely, ERRβ can inhibit cell proliferation in prostate cancer cells by suppressing the progression of the S phase in the cell cycle and inducing $p21^{WAF1/CIP1}$ expression [15]. However, ERRβ alternative splicing isoforms (ERRβsf and ERRβ2Δ10) may exhibit distinct functions in tumor development and prognosis. ERRβsf could inhibit CDK2/Cyclin E activity by cooperating with p53 in the transactivation of p21, thereby delaying the G1/S transition [25]. ERRβ2 may induce G2/M arrest by promoting CDC25 A destabilization, which in turn reduces CDK1 activity [25, 26]. In addition, Bombail et al. [27] confirmed that the over-expression of ERRβ2 in human endometrium enhanced ERα-dependent ligand-induced activation of an estrogen-response elements (ERE)-luciferase reporter construct, altered the

Table 2 Univariate and multivariate Cox regression analysis for prognostic factors of patients with ESCC

Characteristic	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age (year)						
≤ 70	Ref					
> 70	0.955	0.312–2.927	0.936			
Sex						
Male	Ref					
Female	0.739	0.203–2.688	0.646			
Tumor length (cm)						
≤ 3	Ref					
3–5	1.129	0.364–3.504	0.834			
≥ 5	0.396	0.048–3.287	0.391			
G stage						
G1	Ref					
G2	1.284	0.385–4.289	0.684			
G3	0.803	0.089–7.228	0.845			
T stage						
T1	Ref					
T2	0.145	0.013–1.607	0.115			
T3	0.745	0.162–3.421	0.705			
N stage						
N0	Ref					
N1	1.467	0.447–4.821	0.528	1.181	0.355–3.930	0.768
N2–3	4.323	0.843–22.185	0.079*	7.892	1.328–46.911	0.023**
pTNM stage						
I	Ref					
II	1.522	0.181–13.321	0.689			
III–IV	2.897	0.354–23.697	0.321			
ERRβsf/ERRβ						
Low	Ref			Ref		
High	0.302	0.100–0.910	0.033**	0.219	0.063–0.767	0.018**

Only variables with a $P < 0.1$ in the univariate analysis were included as covariates for the multivariate analysis

ESCC: esophageal squamous cell carcinoma; y: year; HR: hazard ratio; CI: confidence interval; Ref: reference

* $P < 0.1$

** $P < 0.05$

induction of c-myc mRNA and increased cell proliferation, whereas ERRβsf was found to reduce these effects. ERRβsf functions as a transcription factor with activity on multiple DNA response elements, whereas ERRβ2 exhibits minimal transcription factor activity and may partially inhibit ERRβsf-mediated gene transcription [26, 28]. These suggest that ERRβsf and ERRβ2 have opposing effects. Moreover, ERRβsf may play a tumor suppressor role in ESCC by inhibiting the transcriptional activity of nuclear factor-erythroid 2 p45-related factor 2 on antioxidant response element-mediated gene expression [29, 30]. Therefore, these can explain our research findings that ESCC patients with a higher proportion of ERRβsf or a lower proportion of ERRβ2Δ10 expression have a favorable survival outcome. In future studies, we will further regulate the expression levels of ERRβsf, ERRβ2, and ERRβΔ10 using gene knockout and overexpression techniques. Additionally, the roles of ERRβ alternative splicing isoforms will be further investigated in cellular experiments and animal models.

There are several limitations to our study that must be acknowledged. First, this study had a small sample size, with only 54 ESCC patients included. The findings should be investigated in larger cohorts and independently validated with external data. Second, we only detected the protein expression of ERRβ alternative splicing isoforms

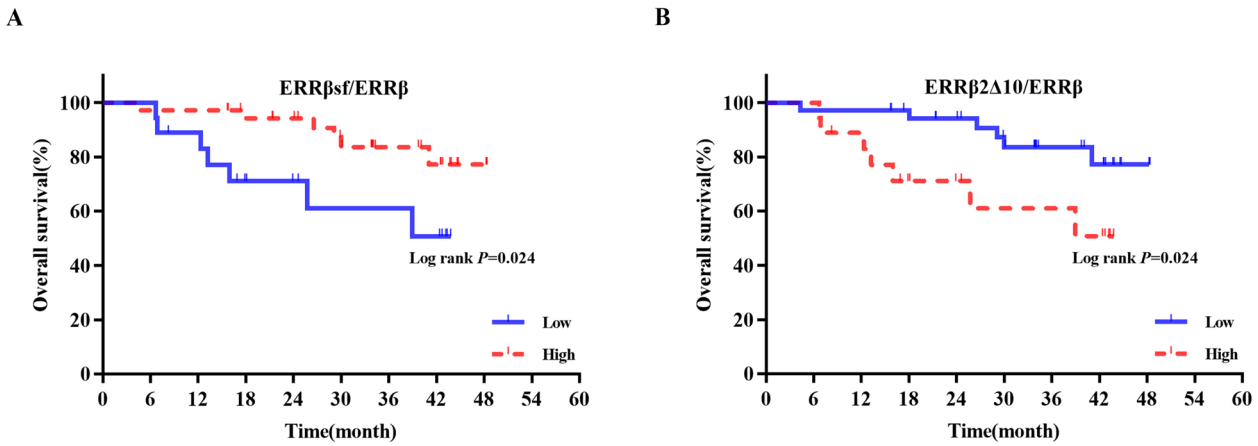

Fig. 2 Kaplan–Meier curves for overall survival of patients with ESCC. **A** The survival curves (OS) of patients with high and low ERRβsf/ERRβ ratios. **B** The survival curves (OS) of patients with high and low ERRβ2Δ10/ERRβ ratios

using Western blotting, which did not allow us to differentiate between ERRβ2 and ERRβΔ10 protein expression. In our next study, we will utilize RT-PCR to differentiate the mRNA expression of ERRβ2, and ERRβΔ10. Third, the specific localization, biological functions, and mechanism of ERRβ alternative splicing isoforms in ESCC cells should be further investigated to verify their prognostic value.

Conclusions

In summary, this study is the first to demonstrate a significant difference in the ratio of ERRβ alternative splicing isoforms in ESCC and normal esophageal tissues, with the ERRβsf/ERRβ ratio being significantly higher in cancer tissues. A higher ERRβsf/ERRβ ratio was associated with improved OS. These findings indicate that ERRβsf is a significant prognostic biomarker for OS in ESCC patients and may provide new strategies for the prevention and treatment.

Abbreviations

ERRβ	Estrogen-related receptor β
EC	Esophageal cancer
ESCC	Esophageal squamous cell carcinoma
ERRs	Estrogen-related receptors
OS	Overall survival
PVDF	Polyvinylidene difluoride
TBST	Tris-buffered saline with tween
HR	Hazard ratio
CI	Confidence interval

Supplementary Information

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Supplementary Material 1.

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Author contributions

Conceptualization, D.T., H.Y.W., K.Y.J., J.X.W. and H.Y.L.; methodology, K.Y.J., J.X.W. and H.Y.L.; formal analysis, J.X.W. and W.Y.C.; data curation, H.Y.L, C.M.S., K.X.G., and X.Y.Z.; writing—original draft preparation, K.Y.J., J.X.W., and H.Y.L.; writing—review and editing, K.Y.J., D.T. and H.Y.W.; supervision, D.T.; project administration, D.T. and H.Y.W.; funding acquisition, H.Y.W. All authors have read and agreed to the published version of the manuscript.

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Availability of data and materials

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

Declarations

Ethical approval and consent to participate

Research procedures were conducted in accordance with the Declaration of Helsinki (2013). This study was approved by the Ethics Committee of the Affiliated Hospital of North Sichuan Medical College, Nanchong (No. 2020ER181-1), and patients were fully informed about the study's purpose, data use and storage. All patients agreed to use their medical records and tissue samples for research, and the need for patient-informed consent was obtained.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Cardiothoracic Intensive Care Unit, Affiliated Hospital of North Sichuan Medical College, No.1, Maoyuan South Road, Shunqing District, Nanchong 637000, China. [2]Department of Thoracic Surgery, West China Hospital, Sichuan University, 37 Guoxue Alley, Chengdu 610041, China. [3]Department of Thoracic Surgery, The First Hospital of China Medical University, Shenyang 110000, China. [4]School of Nurse, North Sichuan Medical College, 234 Fujiang Road, Shunqing District, Nanchong 637000, China.

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