Peroxiredoxin 2 as a potential prognostic biomarker associated with angiogenesis in cervical squamous cell cancer

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Abstract. Peroxiredoxins (Prxs) are a ubiquitously expressed family of antioxidant enzymes that either facilitate or inhibit tumorigenesis, depending on the cancer type and Prx isoform. Prx2 is a typical Prx that has a dual role in tumorigenesis and tumor progression. However, the expression of Prx2 and its precise role in cervical cancer remains to be elucidated. Therefore, the present study aimed to investigate the expression of Prx2 and its association with the progression and prognosis of cervical squamous cell cancer (CSCC). In the present study, the clinicopathological data of 105 patients diagnosed with CSCC were collected from the medical record system at Jingzhou Central Hospital, Tongji Medical College of Huazhong University of Science and Technology (Jingzhou, China). Prx2 protein was also detected in 105 CSCC tissues and 40 adjacent peri-tumoral tissues by immunohistochemical staining. The relationships between Prx2 expression and clinicopathological features, vascular endothelial growth factor A (VEGF-A) expression and micro-vessel density (MVD) in CSCC were then analyzed. Progression-free survival (PFS) was also assessed using both univariate and multivariate analyses. The results of the present study demonstrated that the expression of Prx2 was upregulated in CSCC tissues compared with the adjacent peri-tumoral tissues (P<0.001). In addition, higher Prx2 expression was associated with greater depth of stromal invasion (P=0.023) and positive lymph vascular space invasion (P=0.044), while the Prx2 expression level was not associated with age, tumor size, histological grade, lymph node (LN) metastasis or International Federation of Gynecology and Obstetrics (FIGO) stage (all P>0.05). Furthermore, increased Prx2 expression was associated with high MVD (P=0.016), while expression of VEGF-A was not associated with Prx2 expression (P>0.05). Kaplan-Meier analysis showed that patients with high Prx2 expression (log-rank test, P=0.039), high MVD (log-rank test, P=0.015), a higher FIGO stage (log-rank test, P=0.021) and LN metastasis (log-rank test, P=0.022) had a shorter PFS time than patients with low Prx2 expression, low MVD, a lower FIGO stage and without LN metastasis, respectively. Cox proportional hazard regression analysis revealed that expression of Prx2 [hazard ratio (HR), 2.551; 95% confidence interval (CI), 1.056-6.162; P=0.037], MVD (HR, 2.436; CI, 1.034-5.735; P=0.042) and FIGO stage (HR, 1.543; CI, 1.027-2.319; P=0.037) were independent factors for PFS time. In conclusion, the results of the present study suggested that Prx2 could act as a potential biomarker for predicting CSCC progression and prognosis and could be a novel target for antiangiogenic therapy of CSCC.

Introduction

Cervical cancer (CC) is the fourth most widespread malignancy and the fourth leading cause of cancer-related death among women worldwide (1). Despite several advances in the screening, prevention and treatment of cancer, more than half a million women are diagnosed with CC every year, resulting in >300,000 deaths globally (2,3). Cervical squamous cell cancer (CSCC) is the most common pathological type of CC, accounting for ~70% of CC cases. Most CSCC cases are diagnosed in an advanced stage, with a high incidence of metastasis, resulting in unfavorable outcomes (4). Therefore, a number of studies have been conducted to discover biological indicators related to the progression and prognosis of CC to provide new potential therapeutic targets in recent years (5,6). Antiangiogenic therapy has emerged as a therapeutic target in CC, but identification of the mechanisms affecting neovascularization in CC are still needed.

Angiogenesis, which refers to the formation of vessels from a preexisting vascular network, is the most common form of tumor blood vessels and plays an essential role in tumor growth and metastasis (7). Vascular endothelial growth factor

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(VEGF)-A is a critical pro-angiogenic factor that modulates angiogenesis by binding and interacting with VEGF receptors (VEGFRs). Upregulation of VEGF-A in tumor tissues is closely related to the occurrence, development and progression of solid tumors (8). Micro-vessel density (MVD) has become the morphological gold standard to assess the neo-vasculature in human tumors and is significantly associated with metastasis and prognosis in several tumor types, such as renal cell carcinoma and ovarian cancer (9,10). Studies have demonstrated that increased VEGF expression and MVD are significantly correlated with poor prognosis in CC (11,12). However, the mechanisms affecting VEGF expression and MVD have not been well elucidated.

Reactive oxygen species (ROS), including hydrogen peroxide (H_2O_2), are well-known as harmful substances of normal cellular metabolism by inducing intracellular oxidative stress. Antioxidant enzymes play a crucial role in regulating intracellular redox homeostasis, protecting cells from oxidative stress by reducing the intracellular accumulation of ROS. Notably, the peroxiredoxins (Prxs) are a ubiquitous family of antioxidant enzymes highly involved in various physiological functions, including cell growth, differentiation and apoptosis (13). It has been indicated that Prxs are engaged in either inhibiting or promoting cancer, depending on the cancer type and the Prx isoform (14). Prx2 is a typical Prx and plays a dual role as both a tumor suppressor and promoter. Certain reports have indicated that the expression of Prx2 protein is increased in the development of CC (15,16). However, to the best of our knowledge, no study has evaluated the potential of Prx2 in the prognosis of CSCC.

Kang *et al* (17) showed that Prx2 protects VEGFR-2 against H_2O_2-mediated oxidative inactivation in vascular endothelial cells. The absence of Prx2 increased cellular H_2O_2 levels and VEGFR-2 was inactive in response to VEGF stimulation. It was then further demonstrated that Prx2 deficiency suppressed tumor angiogenesis *in vivo*. These results indicated that Prx2 is an essential antioxidant enzyme that preserves VEGF signaling by protecting VEGFR2 against oxidative inactivation, thus promoting tumor angiogenesis. However, to the best of our knowledge, whether Prx2 expression is associated with angiogenesis in CC is currently unknown.

Hence, the present study aimed to investigate Prx2 expression in relation to the progression and prognosis of CSCC and its association with angiogenesis. Prx2 expression was detected by immunohistochemistry (IHC) staining. Then, the association of Prx2 expression with clinicopathological features, VEGF-A expression and MVD of CSCC was analyzed. Furthermore, Kaplan-Meier and Cox proportional hazard regression analyses were performed to explore the prognostic factors influencing patient survival.

Materials and methods

Patients. The records of 105 patients with CSCC treated at the Jingzhou Central Hospital, Tongji Medical College of Huazhong University of Science and Technology (Jingzhou, China) between January, 2015 and August, 2020 were retrospectively reviewed. The inclusion criteria included: i) Patients with a first diagnosis of cervical squamous cell carcinoma; and ii) patients that did not receive chemotherapy, radiotherapy, immunotherapy or hormonal therapy before surgery. The exclusion criteria included: i) Patients with recurrent CC; ii) patients that received chemotherapy, radiotherapy, immunotherapy, or hormonal therapy before surgery; and iii) patients with CSCC combined with other diseases, such as malignant tumors, systemic immune diseases, infectious diseases, organ failure diseases and cancer complications. A total of 40 adjacent peri-tumoral tissues were selected and included as the control group.

Follow-up. The follow-up duration was defined as the time from the diagnosis of CSCC until disease progression or death or the cut-off date of December, 2022. The progression-free survival (PFS) time was the interval from the surgery date to the first documentation of disease progression or death. The median follow-up time of the patients was 34.5 months (range, 4.3-90 months). Patients lost to follow-up were excluded from the present study.

IHC. Neutral formaldehyde solution (4%) fixed (at room temperature for 12-24 h) and paraffin-embedded CSCC tumor tissue and adjacent non-neoplastic tissue blocks were cut into 4-μm-thick sections, dried, deparaffinized and dehydrated in a graded ethanol series. The antigen was retrieved by a high-pressure method using alkaline pH (pH 8.0) for 1 min, and then washed by phosphate buffered saline (PBS) 3 times. Then, the tissue sections were treated with 1% hydrogen peroxide for 10 min to block endogenous tissue peroxidase activity and non-specific protein binding. The slides were incubated with rabbit polyclonal anti-human Prx2 antibody (Proteintech Group, Inc.; cat. no. 10545-2-AP; 1:500), rabbit polyclonal anti-human VEGF-A antibody (ImmunoWay Biotechnology Company; cat. no. YT5108; 1:100) and mouse monoclonal anti-human CD34 antibody (Dako; Agilent Technologies, Inc.; clone no. QBEnd 10; cat. no. IR632; ready-to-use) overnight at 4˚C, followed by incubation at room temperature for 30 min with the Ultra-Sensitive S-P Kit (containing the secondary antibodies; Fuzhou Maixin Biotech Co., Ltd.; cat. no. KIT-9710). The slides were washed with PBS before color development using a 3,3'-diaminobenzidine substrate kit for 3-10 min and were then counterstained with hematoxylin at room temperature for 1-2 min, before visualization with a light microscope.

Evaluation of IHC. The immunoreactivity of Prx2 and VEGF-A was examined by two senior pathologists blinded to the clinicopathological data. The staining was evaluated semi-quantitatively based on the staining intensity and percentage of positive cells. The intensity of the stained cells was graded into four levels as follows: 0 (no staining), 1 (weak staining: light yellow), 2 (moderate staining: yellow-brown) and 3 (intense staining: brown). The percentage of positive cells was graded into five levels as follows: 0 (≤5% of cells), 1 (6-25% of cells), 2 (26-50% of cells), 3 (51-75% of cells) and 4 (>75% of cells). The immunoreaction score of each marker was calculated by multiplying the intensity and percentage of positive cells. Scores ≤3 were defined as low expression and scores >3 were described as high expression.

MVD was evaluated by detecting $CD34^+$ cells, including the single endothelial cell or endothelial cell cluster separated from the adjacent micro-vessels or other connective tissue elements.

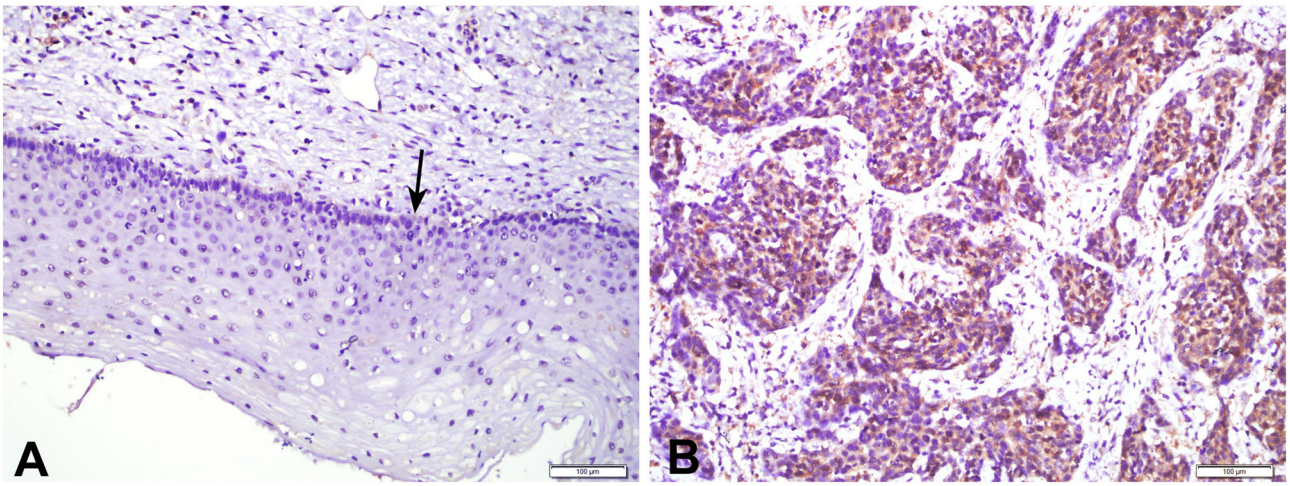

Figure 1. Immunohistochemical staining of Prx2 in normal cervical squamous tissues and CSCC tissues (magnification, x200). (A) Weak positive staining of Prx2 in the basal layer cells of normal cervical tissues (indicated with an arrow). (B) Positive staining of Prx2 protein was mainly observed in the cytoplasm of CSCC tumor cells. CSCC, cervical squamous cell cancer; Prx2, peroxiredoxin 2.

The entire section was initially scanned at a low magnification (x40-100) to identify the highest density of $CD34^+$ cells within the tumor samples, and necrotic and ulcerated areas were avoided. Within these areas, micro-vessels were manually counted in a x200 magnified field in five of the most vascularized regions, and the average value was taken as the MVD count for each sample.

Statistical analysis. Statistical analysis was performed using SPSS 21.0 software (IBM Corp.). Continuous variables are presented as the mean ± standard deviation, and non-normally distributed variables are presented as the median (P25-P75). The differences in Prx2 expression between cervical cancerous and normal tissues were analyzed by Unpaired Student's t-test. The association between Prx2 expression with the clinicopathological features, VEGF-A expression and the MVD of CSCC were compared by χ^2 test. The Kaplan-Meier method and the log-rank test was used to analyze patient survival, and the Cox proportional hazard regression model was used to identify the prognostic factors that influenced patient survival. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patients. The median age of the patients at surgery was 50 years (range, 33-67 years), and the tumor diameter was >4 cm in 72 cases and ≤4 cm in 33 cases. The histological grade was well-differentiated (G1) in 30 cases, moderately differentiated (G2) in 49 cases and lowly differentiated (G3) in 26 cases [as determined using the 2020 World Health Organization Classification of Female Genital Tumors (18)]. The depth of stromal invasion was superficial 1/3 in 38 cases, middle 1/3 in 55 cases and deep 1/3 in 12 cases. There were 79 cases without LN metastasis and 26 cases with LN metastasis. The International Federation of Gynecology and Obstetrics (FIGO) stage was stage I in 62 cases, stage II in 17 cases and stage III in 26 cases, according to 2018 FIGO cervical cancer staging (19). A total of 55 cases exhibited lymph vascular space invasion (LVSI) and 50 cases were without LVSI.

Expression of Prx2 in CSCC and normal cervical squamous tissues. The expression levels of Prx2 in 105 CSCC tissues and 40 adjacent peri-tumoral tissues were analyzed by IHC. Positive staining of the Prx2 protein was mainly observed in the cytoplasm of both CSCC tumor cells and the basal layer cells of normal tissues (Fig. 1). The expression of Prx2 in CSCC tissues was significantly higher than that in adjacent peri-tumoral tissues ($P<0.001$; Table I).

Association of Prx2 expression with clinicopathological features and angiogenesis in CSCC. Based on Prx2 immunoreactivity, 69.5% (73/105) of CSCC tissue samples exhibited high Prx2 expression and 30.5% (32/105) exhibited low Prx2 expression. The association of Prx2 expression with the patient clinicopathological features of CSCC is shown in Table II. It was found that high Prx2 expression was associated with a higher depth of stromal invasion ($P=0.023$) and occurrence of LVSI ($P=0.044$). By contrast, Prx2 expression was not associated with age, tumor size, histological grade, LN metastasis or FIGO stage (all $P>0.05$).

Expression of Prx2 (Fig. 2A and D) and VEGF-A (Fig. 2B and E), and MVD (Fig 2C and F) were analyzed in the 105 CSCC tissue samples. Positive staining of VEGF-A was mainly found in the cytoplasm of tumor cells. Increased Prx2 expression was associated with high MVD ($P=0.016$), while VEGF-A expression was not associated with Prx2 expression ($P>0.05$) (Table II).

Survival analysis. The median follow-up time of the selected patients was 34.5 months (range, 4.3-90 months). Kaplan-Meier plus log-rank and Cox proportional hazard regression model analyses were used to evaluate the risk factors of PFS of patients with CSCC. Kaplan-Meier analysis showed that patients with high Prx2 expression (log-rank test, $P=0.039$; Fig. 3A), high MVD (log-rank test, $P=0.015$; Fig. 3B), a higher FIGO stage (log-rank test, $P=0.021$; Fig. 3C) and LN metastasis (log-rank test, $P=0.022$; Fig. 3D) had a shorter PFS time than patients with low Prx2 expression, low MVD, a lower FIGO stage and without LN

Table I. Expression of Prx2 in cervical cancer tissues and adjacent normal tissues.

Tissue type	No.	Prx2 expression, median (P25-P75)	P-value
Adjacent normal tissue	40	2.00 (2.00-3.00)	<0.001[a]
Cervical cancer tissue	105	8.00 (4.00-9.00)	

[a]P<0.05, unpaired Student's t-test. Prx2, peroxiredoxin 2.

Table II. Association of Prx2 expression with clinicopathological features, VEGF-A expression and MVD in cervical squamous cell cancer.

		Prx2 expression		
Feature	No. of patients (n=105)	Low (n=32)	High (n=73)	P-value
Age, n				
<50 years	50	12	38	0.171
≥50 years	55	20	35	
Mean tumor size, cm ± SD	-	4.138±1.148	4.056±1.262	0.756
Histological grade, n				
G1	30	14	16	0.566
G2	49	7	42	
G3	26	11	15	
Depth of stromal invasion, n				
Superficial 1/3	38	16	22	0.022[a]
Middle 1/3	55	15	40	
Deep 1/3	12	1	11	
LN metastasis, n				
No	79	24	55	0.970
Yes	26	8	18	
FIGO stage, n				
I	62	15	47	0.076
II	17	9	8	
III	26	8	18	
LVSI, n				
No	50	20	30	0.043[a]
Yes	55	12	43	
VEGF-A expression, n				
Low	38	15	23	0.133
High	67	17	50	
MVD, n				
Low	32	15	17	0.015[a]
High	73	17	56	

[a]P<0.05, χ^2 test. FIGO, International Federation of Gynecology and Obstetrics; LN: Lymph node; LVSI, lymph vascular space invasion; MVD, micro-vessel density; Prx2, peroxiredoxin 2; VEGF-A, vascular endothelial growth factor A.

metastasis, respectively. Cox proportional hazard regression analysis revealed that expression of Prx2 [hazard ratio (HR), 2.551; 95% confidence interval (CI), 1.056-6.162; P=0.037], MVD (HR, 2.436; CI, 1.034-5.735; P=0.042) and FIGO stage (HR, 1.543; CI, 1.027-2.319; P=0.037) were identified as independent factors for PFS (Table III).

Discussion

The Prxs are a class of antioxidant enzymes known to either facilitate or inhibit tumorigenesis depending on the cancer type and Prx isoform (13,14). Thus far, six Prx isoforms have been revealed in mammals and are categorized according to

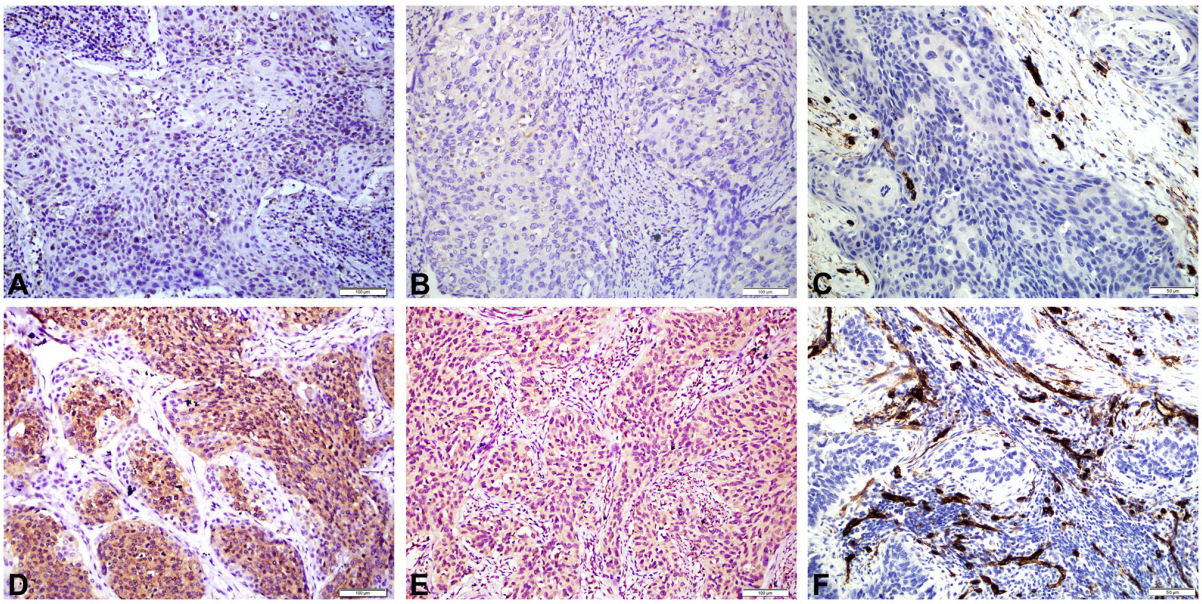

Figure 2. Immunohistochemical staining of Prx2, VEGF-A and MVD in CSCC tissues (magnification, x200). (A) Low expression of (A) Prx2, (B) VEGF-A and (C) MVD (CD34). High expression of (D) Prx2, (E) VEGF-A and (F) MVD (CD34). CSCC, cervical squamous cell cancer; MVD, micro-vessel density; Prx2, peroxiredoxin 2; VEGF-A, vascular endothelial growth factor A.

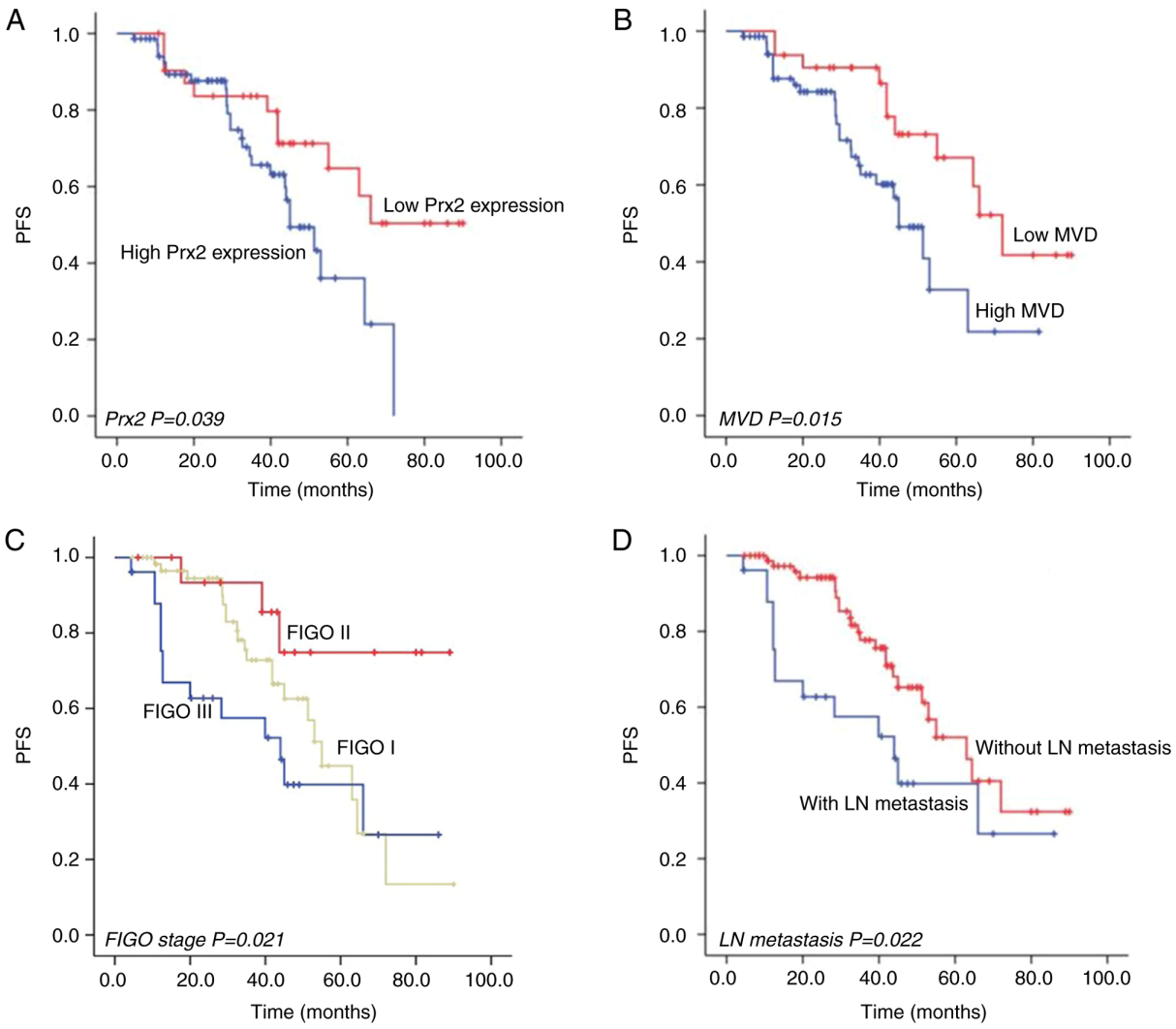

Figure 3. Kaplan-Meier analysis. Kaplan-Meier analysis of (A) Prx2 expression, (B) MVD, (C) FIGO stage and (D) LN metastasis. (+) Data censored. FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node; MVD, micro-vessel density; PFS, progression-free survival; Prx2, peroxiredoxin 2.

Table III. Univariate and multivariate analysis of predictive factors for progression-free survival in patients with cervical squamous cell cancer.

			Multivariate analysis	
Factor	No. of patients (n=105)	Univariate analysis P-value	HR (95% CI)	P-value
Age, years				
<50	50	0.108	0.785 (0.353-1.744)	0.552
≥50	55			
Tumor size, cm				
≤4	33	0.091		
>4	72			
Histological grade				
G1	30	0.414	1.202 (0.700-2.062)	0.504
G2	49			
G3	26			
Depth of stromal invasion				
Superficial 1/3	38	0.368	1.029 (0.577-1.833)	0.924
Middle 1/3	55			
Deep 1/3	12			
LVSI				
No	50	0.799	0.856 (0.408-1.797)	0.681
Yes	55			
LN metastasis				
No	79	0.022[a]		
Yes	26			
FIGO stage				
I	62	0.021[a]	1.543 (1.027-2.319)	0.037[b]
II	17			
III	26			
Prx2 expression				
Low	32	0.039[a]	2.551 (1.056-6.162)	0.037[b]
High	73			
VEGF-A expression				
Low	38	0.789	0.765 (0.384-1.526)	0.448
High	67			
MVD				
Low	32	0.015[a]	2.436 (1.034-5.735)	0.042[b]
High	73			

[a]P<0.05, log-rank test; [b]P<0.05, Cox proportional hazard regression. CI, confidence interval; HR, hazard ratio; FIGO, International Federation of Gynecology and Obstetrics; LN: Lymph node; LVSI, lymph vascular space invasion; MVD, micro-vessel density; Prx2, peroxiredoxin 2; VEGF-A, vascular endothelial growth factor A.

the number and position of the conserved Cys residue and the type of disulfide bond formed during the catalytic cycle. These include typical 2-Cys Prx (Prx 1-4), atypical 2-Cys Prx (Prx 5) and 1-Cys Prx (Prx 6) (13). Numerous studies have demonstrated that these Prx isoforms are closely related to cancer development, and the expression of the Prx family member is altered in different types of cancer (20,21).

Prx2 is a typical Prx and plays a dual role in tumorigenesis, depending on the tumor type. Decreasing expression of Prx2 resulted in metastasis of melanoma cells to the lungs or other organs, suggesting a tumor suppressor role of Prx2 in melanoma (22). Conversely, in other studies, Prx2 was shown to be increased in various types of human cancer, including gastric and colorectal cancer (23,24). This suggested that Prx2 may be a tumor promoter and could be a potential target for treatment in these tumor types. Kim *et al* (15) evaluated the expression patterns of the Prx family and found that the Prx2 protein was upregulated in the development of CC. In another study,

Zhu *et al* (16) revealed that the Prx2 protein was also frequently upregulated in CSCC. In parallel with these studies, the Prx2 protein was also found to be upregulated in CSCC in the present study. The results of the present study further demonstrated that upregulation of Prx2 was associated with a greater depth of stromal invasion and LVSI of CSCC, indicating that Prx2 might play a role in the progression and invasion of CSCC. However, the mechanisms through which Prx2 participates in the progression and invasion of CSCC and its correlation with the prognosis of CSCC require further investigation.

VEGF-A, typically referred to as VEGF, is the primary mediator of tumor angiogenesis in the VEGF family in the vast majority of solid tumors. The receptors, VEGFR-1 and VEGFR-2, bind VEGF-A in vascular endothelial cells. Among these two receptors, VEGFR-2 is predominant in stimulating angiogenic signaling pathways by reacting with ROS (25,26). Kang *et al* (17) explored the endogenous antioxidant enzymes that modulate VEGFR-2 function and found that Prx2 was a specific antioxidant enzyme protecting VEGFR-2 against H_2O_2-mediated oxidative inactivation in vascular endothelial cells. The absence of Prx2 increased cellular H_2O_2 levels and VEGFR-2 became inactive in response to VEGF stimulation. It was further demonstrated that Prx2 deficiency suppressed tumor angiogenesis *in vivo*. Zhang *et al* (27) also demonstrated that Prx2 is involved in vasculogenic mimicry formation by targeting VEGFR2 activation in colorectal cancer. These results indicated that Prx2 is an essential antioxidant enzyme that preserves VEGF signaling by protecting VEGFR2 against oxidative inactivation, thus promoting tumor angiogenesis. However, whether Prx2 expression is correlated with angiogenesis in CSCC remains unknown.

MVD is the morphological gold standard to assess the neo-vasculature in human tumors and is significantly associated with metastasis and prognosis in several tumor types (9,10). CD34 is a sensitive and commonly used vascular endothelial marker, which is more resistant to formalin fixation and stains deeper in neoplastic endothelium than normal endothelium (28). In the present study, the Prx2 expression level was compared with VEGF-A expression and MVD, and the results showed that increased Prx2 expression was associated with high MVD, but not with VEGF-A expression. These results indicated that increased Prx2 expression may regulate tumor angiogenesis in CSCC, but not regulate VEGF-A expression.

Risk factors that affect the prognosis of patients with CSCC were further analyzed in the present study. Kaplan-Meier analysis revealed that patients with high Prx2 expression, high MVD, a higher FIGO stage and LN metastasis had a shorter PFS time compared with patients with low Prx2 expression, low MVD, a lower FIGO stage and without LN metastasis, respectively. Furthermore, the Cox proportional hazard regression analysis demonstrated that Prx2 expression, MVD and LN metastasis were independent factors for PFS among the aforementioned variables. However, the mechanisms by which Prx2 influences tumor angiogenesis in CSCC require further investigation. In addition, due to the limited number of patients included in the present study, a more extensive study is needed, particularly one that includes a prolonged follow-up time to analyze overall survival.

In conclusion, the present study revealed that Prx2 was upregulated in CSCC. Increased expression of Prx2 was associated with the depth of stromal invasion, LVSI and MVD in CSCC, which may be related to poor prognosis. Therefore, Prx2 may be a potential biomarker for predicting CSCC prognosis and a novel target for antiangiogenic therapy in CSCC; however, further studies are required to elucidate the mechanisms of Prx2.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

KZ and MH contributed to the concept and design of the study and were major contributors to writing the manuscript. RY contributed to data acquisition, analysis and interpretation. TZ, JL and MH provided technical support and performed the histological examination. All authors read and approved the final version of the manuscript. KZ and MH confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was approved by The Medical Ethics Committee of Jingzhou Central Hospital, Tongji Medical College of Huazhong University of Science and Technology (Jingzhou, China; approval no. 2020123001). Written informed consent was obtained from each patient regarding the use of tissues for *ex vivo* experiments.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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