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*Original Article*

# Expression of TAZ, YAP, and β-catenin in cervical squamous cell carcinoma and their clinical significance

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**Abstract:** YAP/TAZ and β-catenin are important effectors in the Hippo and Wnt signaling pathways, respectively, which are involved in the development of human tumors. Using immunohistochemistry, the expression levels of the three proteins were determined in 151 cervical tissue samples (including 28 normal cervical, 31 cervical intraepithelial neoplasia, and 92 cervical squamous cell carcinoma [CSC] tissues), which were excised or biopsied by surgery. The results showed that the three proteins were differently expressed in normal, precancerous, and CSC tissues, and β-catenin expression positively correlated with both YAP and TAZ expression. By analyzing the relationships between YAP, TAZ, and β-catenin expression and the clinicopathologic characteristics of patients with CSC, we found that YAP was related to the depth of invasion > 1/2, the diameter of the tumor > 4 cm, and positive lymph nodes; while TAZ and β-catenin were related to the depth of invasion > 1/2 and positive lymph nodes. Regarding the prognostic factors of patients with CSC, Kaplan-Meier univariate and Cox multivariate regression analysis showed that there were significant correlations between lymph node infiltration; expression of YAP, TAZ, and β-catenin; and patient mortality ($P < 0.05$), all of which were independent factors influencing mortality (OR > 1).

**Keywords:** Cervical carcinoma, TAZ, YAP, β-catenin, immunohistochemistry

## Introduction

Cervical cancer is the second most commonly diagnosed cancer and the third leading cause of cancer death among females in less developed countries [1]. Worldwide, there were an estimated 527,600 new cervical cancer cases and 265,700 cervical cancer-related deaths in one year. The detection of early-stage cervical cancer is associated with excellent survival, but most women in developing countries present with advanced and often untreatable cases and have very poor survival rates. The ratio between cervical cancer incidence and mortality remains very high, largely due to a lack of access to appropriate anti-cancer therapies [2]. Therefore, strengthening the knowledge of the molecular mechanisms underlying the disease and exploring clinical therapies for cervical cancer have been the focal points of current research.

YAP is encoded by the *YAP* gene located on chromosome 11q22 and is a multifunctional intracellular connexin and transcription coactivator in the Hippo signaling pathway. TAZ has been identified as a 14-3-3 binding protein; it is a homologous protein to YAP and very similar in structure and biologic function [3]. Under normal circumstances, YAP/TAZ accumulates in the cytoplasm in a phosphorylated form without any transcription kinase activity, rendering it highly inactive. Under pathological conditions, the Hippo pathway loses its phosphorylation effect on YAP/TAZ, causing it to bind to the corresponding transcription factor TEAD (TEA Domain Transcription factor). As a result, the complex migrates into the nucleus and initiates the transcription of corresponding genes, disturbing the balance between cell proliferation and apoptosis, which can eventually cause tumorigenesis [4]. Worldwide, studies have shown that the newly discovered oncogene YAP/TAZ is involved in the formation and development of human cervical squamous cell carcinoma (CSC), breast cancer, colon cancer, and other tumors [5-7].

β-catenin was initially considered to be an important component involved in intercellular adhesion mediated by cadherin but was later confirmed to be involved in Wnt signaling pathway gene expression. It is widely distributed throughout all kinds of tissues and plays an important regulatory role in cell proliferation, differentiation, and apoptosis. When the Wnt signaling pathway is activated, β-catenin degradation is blocked, causing it to accumulate in the cytoplasm and migrate to the nucleus. Previous studies have shown that the overexpression of β-catenin is associated with the invasion and metastasis of tumors in many malignancies [8].

Recent studies have found that the activation of YAP/TAZ is related to the Wnt pathway, and the activated Hippo pathway can reduce the stability of nuclear β-catenin by phosphorylating YAP/TAZ. Furthermore, when the Wnt signal is activated, β-catenin can degrade the complex and maintain a low level of TAZ [9]. In contrast to other tumor types, there have only been a few studies on the co-expression of YAP/TAZ and β-catenin in CSC. In this study, the expression of YAP, TAZ, and β-catenin in normal cervical, cervical intraepithelial neoplasia (CIN), and CSC tissue was detected by immunohistochemistry. In addition, the relationships between protein expression and the pathologic findingsof CSC and between protein expression and prognoses were further analyzed to provide a clinical basis for the diagnosis and treatment of cervical cancer.

## Materials and methods

### *Tissue specimens*

The study met the approval of the hospital ethics committee, and the informed consent of the patients and their families was provided. A total of 151 cervical tissue specimens from surgically resected or biopsied patients were selected from the First Affiliated Hospital of Bengbu Medical College from January 1, 2013, to December 31, 2014, including 28 normal cervical tissues, 31 CIN tissues, and 92 CSC tissues. None of the 92 CSC cases received any medical treatment, chemotherapy, or radiotherapy before surgery, and the margin tissues were negative. The surgical methods were extensive hysterectomy and/or bilateral adnexectomy plus pelvic lymph node dissection. The patients were 27-70 years old; 45 cases were stage I and 47 cases were stage II according to FIGO staging. In terms of tissue differentiation from high to low (grades I, II, and III), there were 18, 56, and 18 cases for the three levels, respectively; 48 cases had lymph node metastasis, and 44 cases had no lymph node metastasis. All the specimens were fixed by 10% formalin, embedded in paraffin, and sectioned continuously to a thickness of 4 μm.

### *Reagents and methods*

Anti-TAZ mouse monoclonal antibody [CL0371], anti-active YAP1 rabbit monoclonal antibody [EPR19812], and anti-β-catenin rabbit monoclonal antibody [E247]-ChIP Grade were all purchased from Abcam Co., Ltd. The two-step En vision method of immunohistochemistry was used, and the specific procedures were carried out in strict accordance with the kit instructions. Briefly, the sections were dewaxed, hydrated by gradient ethanol, and antigen retrieved with citric acid buffer at successively higher temperatures. Subsequently, the sections were immersed in deionized water with 3% $H_2O_2$ for 10 min to block the activity of endogenous peroxidase and incubated in the primary antibody at 4°C overnight, then the sections were incubated in secondary antibody at 37°C for 15 min. DAB (3,3'-diaminobenzidine) was then added for coloration, with the known positive section as a positive control and using PBS to replace the primary antibody in the negative control.

### *Interpretation of the results*

The results showing expression in the nucleus as fine light yellow to brown-yellow particles were considered evidence of positive YAP and TAZ protein expression. According to the staining intensity (a), the cells were scored as 0 points (no staining), 1 point (light yellow), 2 points (light brown-yellow), or 3 points (dark brown-yellow). Six visual fields were selected to count the percentage of positive cells in the total number of cells (b), according to which the results were scored as 0 points (< 10%), 1 point (10-25%), 2 points (26-50%), 3 points (51-75%), or 4 points (> 75%). The product of the staining intensity (a) and the percentage of positive cells in the total number of cells (b) (a × b) was used to determine the score: negative (-) 0 points, weakly positive (+) 1-4 points, moder-

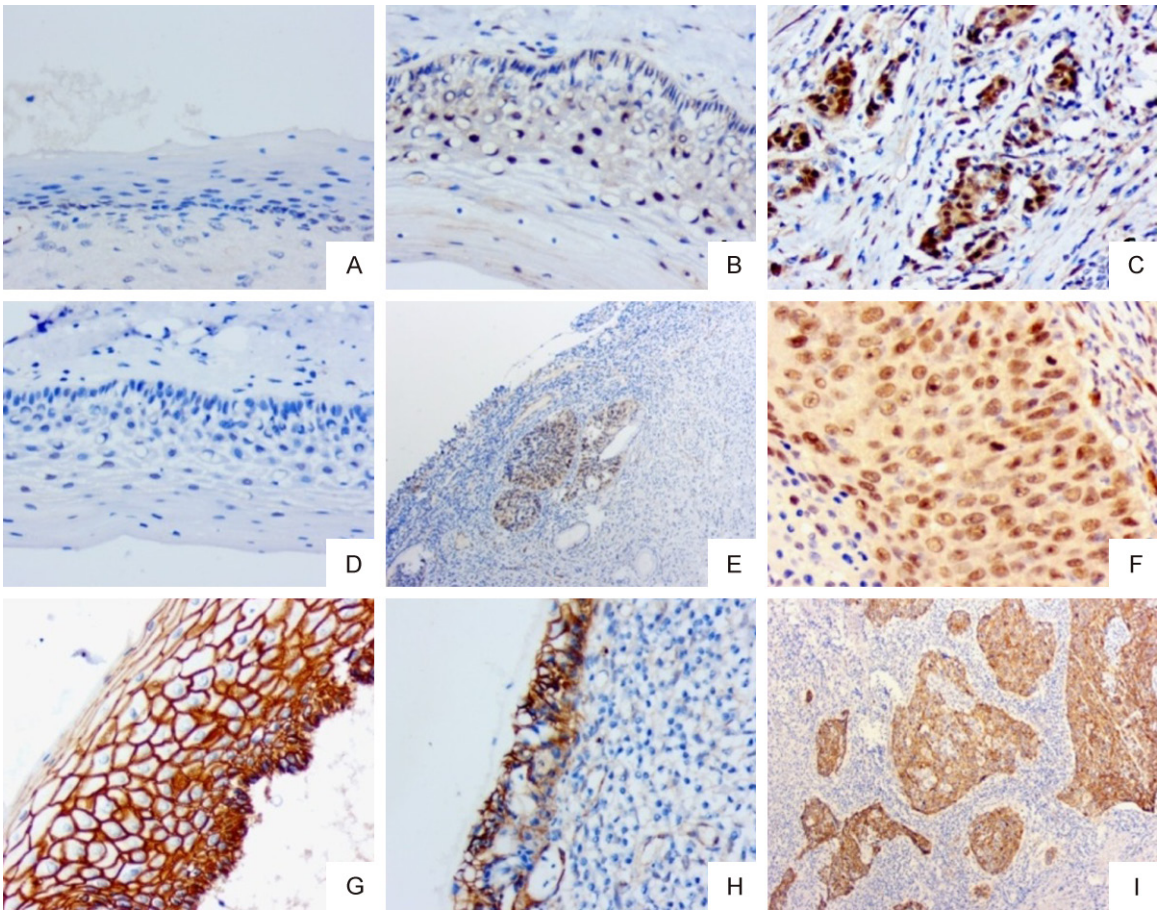


**Figure 1.** Expression of YAP, TAZ, and β-catenin in normal cervical tissue, CIN, and CSC. A-C. Expression of YAP in normal cervical tissue, CIN, and CSC. D-F. Expression of TAZ in normal cervical tissue, CIN, and CSC. G-I. Expression of β-catenin in normal cervical tissue, CIN, and CSC.

ately positive (++) 5-8 points, and strongly positive (+++) 9-12 points. β-catenin was mainly expressed in normal mucosal epithelial cell membranes, and its staining results were judged according to the following criteria: positive expression in the cell membrane of > 70% of cells was normal expression, i.e., negative (-); positive expression in the cell membrane of < 70% of cells was loss of expression (+); and positive expression in the cytoplasm or nucleus of > 10% of cells was ectopic expression (++). The loss of cell membrane, cytoplasmic, or nuclear expression was collectively referred to as abnormal expression (+ to ++). The clinicopathology results were analyzed by two physicians from the pathology department.

*Statistical methods*

The experimental data were processed using SPSS19.0 statistical software. The Chi-square test was used to analyze the frequency of positive correlations, and the relationships between the three proteins and clinicopathologic datawere also analyzed. The correlation analyses were performed using Spearman's test. In addition, a Kaplan-Meier survival curve was used to evaluate the survival analysis, Log-Rank test was used to compare survival rates, and Cox regression analysis was used to analyze prognostic factors. $P < 0.05$ indicated that the difference was statistically significant.

## Results

*Expression of YAP, TAZ, and β-catenin in CSC, CIN, and normal cervical tissue*

YAP (**Figure 1A-C**) and TAZ (**Figure 1D-F**) showed scarce expression in normal cervical tissue, but showed positive expression in the nuclei of CIN and CSC cells. β-catenin was

**Table 1.** Expression of YAP in each group

| Group | Total | YAP | | | | Positive rate (%) | $X^2$ | P |
|---|---|---|---|---|---|---|---|---|
| | | - | + | ++ | +++ | | | |
| CSC | 92 | 21 | 17 | 20 | 34 | 77.2 | 37.087 | 0.000 |
| CIN | 31 | 11 | 9 | 7 | 4 | 64.5 | | |
| Normal | 28 | 22 | 4 | 2 | 0 | 21.4 | | |
| Total | 151 | 54 | 30 | 29 | 38 | 64.2 | | |

**Table 2.** Expression of TAZ in each group

| Group | Total | TAZ | | | | Positive rate (%) | $X^2$ | P |
|---|---|---|---|---|---|---|---|---|
| | | - | + | ++ | +++ | | | |
| CSC | 92 | 22 | 22 | 35 | 13 | 76.1 | 63.037 | 0.000 |
| CIN | 31 | 21 | 7 | 2 | 1 | 32.3 | | |
| Normal | 28 | 26 | 2 | 0 | 0 | 7.1 | | |
| Total | 151 | 69 | 31 | 37 | 14 | 54.3 | | |

**Table 3.** Expression of b-catenin in each group

| Group | Total | β-catenin | | | Positive rate (%) | $X^2$ | P |
|---|---|---|---|---|---|---|---|
| | | - | + | ++ | | | |
| CSC | 92 | 21 | 56 | 15 | 77.17 | 47.185 | 0.000 |
| CIN | 31 | 18 | 10 | 3 | 41.94 | | |
| Normal | 28 | 25 | 3 | 0 | 10.71 | | |
| Total | 151 | 64 | 69 | 18 | 57.62 | | |

**Table 4.** Correlation of the expression of YAP and TAZ with b-catenin

| Index | | β-catenin expression | | Total | r | P |
|---|---|---|---|---|---|---|
| | | - | +/++ | | | |
| YAP expression | - | 13 | 8 | 21 | 0.506 | 0.000 |
| | + to +++ | 8 | 63 | 71 | | |
| TAZ expression | - | 12 | 10 | 22 | 0.424 | 0.000 |
| | + to +++ | 9 | 61 | 70 | | |

expressed in the cell membranes of normal cervical tissue, and it showed no expression in cell membranes but positive expression in the nucleus or cytoplasm of CIN and CSC (**Figure 1G-I**). The positive expression rates of the three proteins in the three tissues were statistically significant (**Tables 1-3**).

*Correlation of YAP and TAZ expression with β-catenin expression in CSC tissues*

Correlation analysis of the expression of YAP and TAZ with that of β-catenin in 92 CSC tissue samples showed that positive expression of YAP and TAZ positively correlated with abnormal expression of β-catenin (r = 0.506, P = 0.000; r = 0.424, P = 0.000; **Table 4**).

*Relationship between expression of YAP, TAZ, and β-catenin and the clinicopathologic characteristics of CSC*

In CSC, YAP expression was not related to lesion size or FIGO stage but showed statistically significant associations with infiltration depth, pathological grade, and the presence or absence of lymph node metastasis (P < 0.05, **Table 5**). TAZ expression was not related to lesion size, FIGO stage, or tissue differentiation in CSC but was significantly associated with infiltration depth and lymph node metastasis (P < 0.05, **Table 6**). Compared with the clinicopathologic characteristics of CSC, the expression of β-catenin showed significant differences according to infiltration depth and with the presence or absence of lymph node infiltration (P < 0.05). The β-catenin expression rate was especially higher in the group with an infiltration depth of > 1/2 and lymph node infiltration. In addition, there were no significant differences in the positive rates of β-catenin expression among the populations with the other characteristics (**Table 7**).

*Related factors affecting the prognosis of CSC patients*

In this group, Kaplan-Meier univariate analysis was performed on the postoperative survival of patients based on the lesion size, infiltration depth, tissue size, and presence or absence of lymph node metastasis, as well as the expression of YAP, TAZ, and β-catenin (**Table 8**). From the results, the overall 5-year survival rate was 78.5%, and the four factors, lymph node infiltration, YAP expression, TAZ expression, and β-catenin protein expression, had significant effects on the survival rate of patients (P < 0.05). Furthermore, the survival rate and survival time of patients with lymph node infiltration were significantly higher than those without lymph node infiltration; the survival rate and survival time of patients with positive expression of YAP, TAZ, and β-catenin were significantly higher than those with negative expression. The other indi-

**Table 5.** Relationship between YAP expression and clinicopathologic features of CSC

| Clinicopathological finding | n | YAP | | Positive rate (%) | $X^2$ | P |
|---|---|---|---|---|---|---|
| | | - | + to +++ | | | |
| Infiltration depth | | | | | 14.646 | 0.000 |
| <1/2 | 37 | 16 | 21 | 56.76 | | |
| >1/2 | 55 | 5 | 50 | 90.91 | | |
| Lymph node infiltration | | | | | 6.075 | 0.014 |
| Negative | 44 | 15 | 29 | 65.91 | | |
| Positive | 48 | 6 | 42 | 87.50 | | |
| Size of lesion | | | | | 2.291 | 0.130 |
| ≥4 | 44 | 7 | 37 | 84.09 | | |
| <4 | 48 | 14 | 34 | 70.83 | | |
| FIGO stage | | | | | 0.738 | 0.390 |
| Stage I | 45 | 12 | 33 | 73.33 | | |
| Stage II | 47 | 9 | 38 | 80.85 | | |
| Pathologic grade | | | | | 6.370 | 0.041 |
| Poor differentiation | 18 | 1 | 17 | 94.44 | | |
| Moderate differentiation | 56 | 13 | 43 | 76.79 | | |
| High differentiation | 18 | 7 | 11 | 61.11 | | |

**Table 6.** Relationships between TAZ expression and clinicopathologic features of CSC

| Clinicopathologic finding | n | TAZ | | Positive rate (%) | $X^2$ | P |
|---|---|---|---|---|---|---|
| | | - | + to +++ | | | |
| Infiltration depth | | | | | | |
| <1/2 | 37 | 15 | 22 | 59.46 | 9.404 | 0.002 |
| >1/2 | 55 | 7 | 48 | 87.27 | | |
| Lymph node infiltration | | | | | 7.185 | 0.007 |
| Negative | 44 | 16 | 28 | 63.64 | | |
| Positive | 48 | 6 | 42 | 87.50 | | |
| Size of lesion | | | | | 1.522 | 0.217 |
| ≥4 | 44 | 8 | 36 | 81.82 | | |
| <4 | 48 | 14 | 34 | 70.83 | | |
| FIGO stage | | | | | 0.014 | 0.907 |
| Stage I | 45 | 11 | 34 | 75.56 | | |
| Stage II | 47 | 11 | 36 | 76.60 | | |
| Pathological grade | | | | | 2.760 | 0.252 |
| Poor differentiation | 18 | 2 | 16 | 88.89 | | |
| Moderate differentiation | 56 | 14 | 42 | 75.00 | | |
| High differentiation | 18 | 6 | 12 | 66.67 | | |

cators had no significant effects on the 5-year survival rate (P > 0.05).

To further test the correlations between the four significant indicators from Kaplan-Meier univariate analysis and the survival rate, and analyze their relationships, Cox multivariate regression analysis was adopted, in which the four observation indicators, lymph node infiltration, YAP expression, TAZ expression, and β-catenin protein expression, were used as independent variables. See **Table 9**.

The results of Cox regression showed that the four indicators, lymph node infiltration, YAP ex-pression, TAZ expression, and β-catenin expression, significantly correlated with patient mortality (P < 0.05), and all of them were independent factors affecting patient mortality (OR > 1). The survival rates were higher for patients with lymph node infiltration, YAP expression, TAZ expression, and β-catenin expression. The conclusions from the Cox multivariate analysis were almost completely consistent with those from the Kaplan-Meier univariate analysis.

*Effects of YAP, TAZ, and β-catenin on the postoperative survival time of CSC*

In this group, curve analysis of the survival time of patients was performed with YAP, TAZ, and β-catenin expression (**Figures 2**-**5**). There was a significant difference in the survival rate between patients with positive YAP expression and those with negative expression (log-rank test: $\chi^2$ = 4.703, P = 0.003), and there was also a significant difference in the survival rate between patients with positive TAZ expression and those with negative expression (log-rank test: $\chi^2$ = 5.264, P = 0.022). There was a significant difference between patients with abnormal expression of β-catenin and those with normal expression (log-rank test: $\chi^2$ = 9.027, P = 0.003).

**Table 7.** Relationships between b-catenin expression and clinicopathologic features of CSC

| Clinicopathologic finding | n | β-catenin | | Positive rate (%) | $X^2$ | P |
|---|---|---|---|---|---|---|
| | | - | + to ++ | | | |
| Infiltration depth | | | | | | |
| <1/2 | 37 | 13 | 24 | 64.86 | 5.323 | 0.021 |
| >1/2 | 55 | 8 | 47 | 85.45 | | |
| Lymph node infiltration | | | | | 6.075 | 0.014 |
| Negative | 44 | 15 | 29 | 65.91 | | |
| Positive | 48 | 6 | 42 | 87.50 | | |
| Size of lesion | | | | | 2.291 | 0.130 |
| ≥4 | 44 | 7 | 37 | 84.09 | | |
| <4 | 48 | 14 | 34 | 70.83 | | |
| FIGO stage | | | | | 0.738 | 0.390 |
| Stage I | 45 | 12 | 33 | 73.33 | | |
| Stage II | 47 | 9 | 38 | 80.85 | | |
| Pathological grade | | | | | 0.661 | 0.719 |
| Poor differentiation | 18 | 3 | 15 | 83.33 | | |
| Moderate differentiation | 56 | 13 | 43 | 76.79 | | |
| High differentiation | 18 | 5 | 13 | 72.22 | | |

**Table 8.** Univariate analysis of the factors affecting disease prognosis

| Clinicopathologic finding | n | 5-year survival rate (%) | P |
|---|---|---|---|
| Overall | 92 | 78.5 | |
| Infiltration depth | | | 0.952 |
| <1/2 | 37 | 77.1 | |
| >1/2 | 55 | 73.2 | |
| Lymph node infiltration | | | 0.029 |
| Negative | 44 | 84.2 | |
| Positive | 48 | 57.3 | |
| Size of lesion | | | 0.385 |
| <4 | 44 | 71.0 | |
| ≥4 | 48 | 78.8 | |
| FIGO stage | | | 0.502 |
| Stage I | 45 | 76.4 | |
| Stage II | 47 | 80.7 | |
| Pathological grade | | | 0.260 |
| Poor differentiation | 18 | 66.1 | |
| Moderate differentiation | 56 | 80.1 | |
| High differentiation | 18 | 75.5 | |
| YAP expression | | | 0.030 |
| - | 21 | 94.4 | |
| + to +++ | 71 | 71.4 | |
| TAZ expression | | | 0.022 |
| - | 22 | 85.7 | |
| + to +++ | 70 | 68.9 | |
| β-catenin | | | 0.003 |
| - | 21 | 92.9 | |
| +/++ | 71 | 64.8 | |

## Discussion

The occurrence and development of tumors is intrinsically linked to the close correlations among complex signaling networks, among which crosstalk between Hippo and Wnt signaling pathways forms an intricate communication network that regulates the activities of the body.

In this study, we found that the positive expression rate of the YAP/TAZ protein in CSC was significantly higher than that in CIN and normal cervical tissues. YAP was closely associated with infiltration depth, tissue size, and lymph node metastasis, and TAZ was closely related to infiltration depth and lymph node metastasis. β-catenin showed abnormal expression in the nucleus and cytoplasm of CIN and CSC, and correlated with the stage, lymph node metastasis, and infiltration depth. This indicates that abnormal expression of YAP, TAZ, and β-catenin plays a role in the formation of CSC, which may serve as a precursor to cell carcinogenesis to effectively participate in the occurrence, invasion, and metastasis of the disease.

Previous studies have found that YAP/TAZ may interfere with the phosphorylation of Dsh by binding to Dsh (frizzled family of transmembrane receptor proteins), thus inhibiting the Wnt signaling pathway [10]. Azzolin provided biochemical, functional, and genetic evidence that YAP and TAZ are integral components of the β-catenin destruction complex that serves as a cytoplasmic sink for YAP/TAZ [11]. Park delineated the “alternative Wnt-YAP/TAZ signal-

**Table 9.** Cox multivariate analysis of the four factors and patient mortality

| Variable | B | SE | Wald | P | HR | 95% CI | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower limit | Upper limit |
| YAP expression | 0.188 | 1.258 | 0.022 | 0.048 | 1.207 | 1.002 | 2.208 |
| TAZ expression | 1.083 | 1.233 | 0.771 | 0.039 | 2.953 | 1.264 | 13.087 |
| β-catenin expression | 2.371 | 1.106 | 4.594 | 0.023 | 10.711 | 1.225 | 93.647 |
| Lymph node infiltration | 1.043 | 0.562 | 3.442 | 0.033 | 2.837 | 1.243 | 8.538 |

B: estimated coefficient; Wald: Chi-Squared; HR: odds ratio, refers to the unit amount increased in the experimental variable; CI: confidence interval.

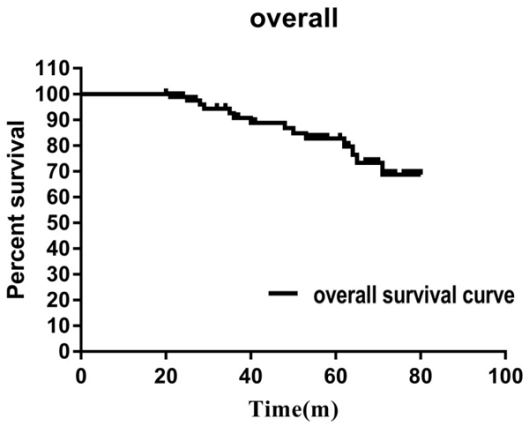


**Figure 2.** The overall survival curve of patients with cervical cancer.

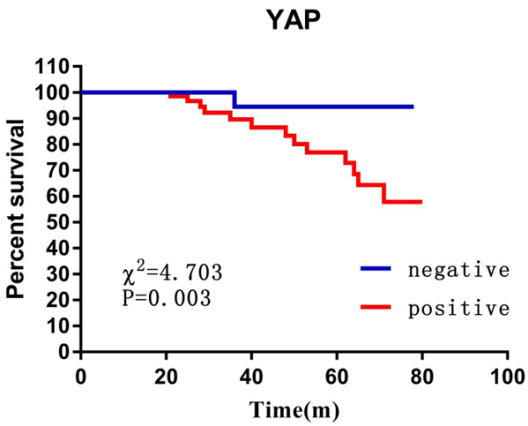


**Figure 3.** Survival curves of patients with CSC with different YAP expression levels.

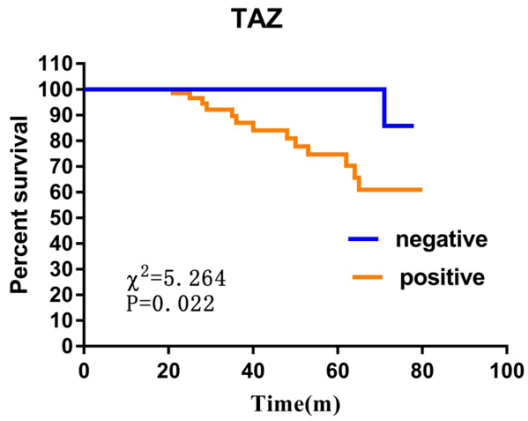


**Figure 4.** Survival curves of patients with CSC with different TAZ expression levels.

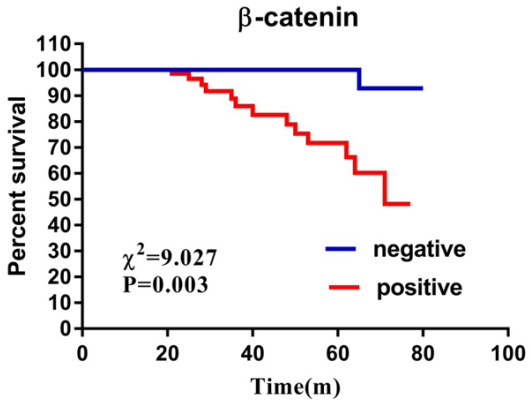


**Figure 5.** Survival curves of patients with CSC with different *β-catenin* expression levels.

ing axis", which consists of Wnt-FZD/RORGα12/13-Rho GTPases-Lats1/2 to promote YAP/TAZ activation and TEAD-mediated transcription. YAP/TAZ mediates the biologic functions of alternative Wnt signaling, including gene expression, osteogenic differentiation, cell migration, and antagonism of Wnt/β-catenin signaling [12]. Consistently, researchers have observed an up-regulation of β-catenin gene expression in the myocardial tissues of mice with high expression of YAP [13]. Konsavage found that YAP can act as a signaling molecule of the Wnt/β-catenin signaling pathway that participates in gene transcription and translation [14], and the abnormal expression of upstream β-catenin enhances the aggregation and migration of YAP to the nucleus. With these

**Table 10.** Comparison of the survival time of patients with different protein expression levels

| Variable | Median survival time | Standard error | 95% CI | |
|---|---|---|---|---|
| | | | Lower limit | Upper limit |
| Overall | 70.150 | 2.265 | 65.712 | 74.589 |
| YAP expression | | | | |
| - | 75.667 | 2.268 | 71.222 | 80.111 |
| + to +++ | 67.080 | 2.915 | 61.367 | 72.793 |
| TAZ expression | | | | |
| - | 77.000 | .926 | 75.185 | 78.815 |
| + to +++ | 66.462 | 3.023 | 60.537 | 72.387 |
| β-catenin | | | | |
| - | 78.929 | 1.032 | 76.905 | 80.952 |
| +/++ | 63.143 | 3.001 | 57.260 | 69.025 |

conclusions, it is suggested that Hippo and Wnt signaling pathways may be inter-regulated.

In this study, the expression levels of both YAP and TAZ positively correlated with β-catenin levels (**Tables 4**-**10**), which further confirms the existence of cross-talk signaling factors between the Hippo and Wnt signaling pathways in CSC. In addition, the abnormal expression of YAP, TAZ, and β-catenin may play a synergistic role in the occurrence, invasion, and metastasis of CSC.

The survival curve shows that the survival rate and time of patients with positive of YAP, TAZ, and β-catenin expression were lower than those with negative expression (**Figures 2**-**4**). Cox multivariate analysis suggested that YAP, TAZ, and β-catenin were all independent factors for poor prognosis in patients with CSC; therefore, we can speculate that the combined detection of YAP, TAZ, and β-catenin may be used as an indicator of CSC prognosis. These findings provide a direction for future research into the molecular diagnosis and targeted therapy of CSC.

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## Disclosure of conflict of interest

None.

## Abbreviations

CSC, Cervical squamous cell carcinoma; CIN, Cervical intraepithelial neoplasia; TAZ, WW domain-containing transcription factor; YAP, yes-associated protein.

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