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Original Article

Clinicopathological significance of SOX4, β-catenin, and TCF4 expression in esophageal squamous cell carcinoma

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Abstract: Background: Highly expressed SRY-related high mobility group box 4 (SOX4), according to previous reports, forecasts poor prognosis in patients with cancer. WNT/β-catenin pathways are often involved in oncogenesis and cancer development. The current study investigated association levels between SOX4, β-catenin, or T-cell factor 4 (TCF4) and clinical-pathological characteristics of patients with esophageal squamous cell carcinoma (ESCC), examining the roles of these proteins in invasion and metastasis of ESCC. Methods: Proteins of SOX4, β-catenin, and TCF4 were examined by immunohistochemistry (IHC), employing 220 paraffin-embedded ESCC tissue specimens and 60 normal esophageal squamous epithelium tissue samples. Results: Expression levels of SOX4, β-catenin, and TCF4 were upregulated in ESCC patients, compared with controls. High expression levels of SOX4, β-catenin, or TCF4 in ESCC were positively correlated with age, tumor diameter, lymph node metastasis (LNM), depth of invasion, TNM stage, and distant metastasis. Univariate analysis demonstrated that overexpression of SOX4, β-catenin, or TCF4 was positively associated with shorter overall survival (OS) times. Multivariate analysis indicated that independent predictors of prognosis in patients with ESCC included age, distant metastasis, and overexpression of SOX4, β-catenin, and TCF4. Conclusion: Results suggest that SOX4, β-catenin, and TCF4 may play key roles in invasion and metastasis in patients with ESCC. Moreover, SOX4, β-catenin, and TCF4 should be considered potential prognostic markers of ESCC.

Keywords: ESCC, SOX4, β-catenin, TCF4

Background

Esophageal cancer (EC) is one of the most common malignant diseases in the digestive system [1-3]. Esophageal squamous cell carcinoma (ESCC) is the most common type of EC [4]. Although there are many treatments for ESCC, prognosis of patients remains poor [5].

SOX4 gene encoding 47-kDa protein Y-related members of the high mobility of sex-determining region-box family of transcription factors is involved in embryonic development and cellular differentiation [6, 7]. SOX4 has been reported to be associated with various malignancies [8]. It is highly expressed in lung cancer [9], breast cancer [10, 11], prostate cancer, and other malignant tumors [12]. It has been demonstrated that SOX4 promotes SW480 colon cancer cell proliferation by stabilizing β-catenin abnormal activation of Wnt signaling pathways [13]. However, SOX4 has also been reported as a tumor suppressor [14].

β-catenin plays key roles in tumorigenesis and development through its role in E-cadherin-mediated intercellular adhesion and Wnt/wingless pathways [15]. Wnt/β-catenin pathways require Wnt ligands, combined with curly receptors and LRP5/6 coreceptors, to signal through β-catenin nuclear translocation in the cell. The Wnt/β-catenin shaft affects biological events, such as C-myc and cyclin D1 [16, 17]. When β-catenin is translocated into the nucle-

Table 1. Clinicopathological factors

Patient characteristics	Frequency (n)	Percentage (%)
Sex		
Male	153	69.5
Female	67	30.5
Age (years)		
≤60	90	40.9
>60	130	59.1
Position		
Upper	24	11.0
Middle	145	66.2
Lower	50	22.8
Gross		
Medullary	108	49.1
Ulceration	47	21.4
Narrow	16	7.3
Fungating	49	22.3
Diameter (cm)		
≤3.8	108	49.1
>3.8	112	50.9
LNM*		
Negative	96	43.6
Positive	124	56.4
Depth of invasion		
Over serous membrane	127	57.7
Above serous membrane	93	42.3
Tumor grade		
Well	25	11.4
Moderate	107	48.6
Poor	88	40.0
TNM stage		
I	43	19.5
II	43	19.5
III	58	26.5
IV	76	34.5
Distant metastasis		
No	149	67.7
Yes	71	32.3

*means lymph node metastasis.

us or cytoplasm, it can recruit and activate transcription factors downstream of TCF4. Thus, it promotes cell proliferation and tumorigenesis [18].

It has been reported that SOX4 produces important anti-aging effects on progression of esophageal squamous cell carcinoma (ESCC) [19]. WNT/β-catenin pathways are often involved in oncogenesis and cancer development. This observation indicates that the β-catenin/TCF signal is involved in development of ESCC [20]. However, whether SOX4, β-catenin, and TCF4 interact with each other to participate in ESCC requires examination. The current study aimed to examine the hypothesis that SOX4, β-catenin, and TCF4 are associated with ESCC metastasis and prognosis.

Materials and methods

Patients and clinical samples

Paraffin-embedded sections were obtained from 220 ESCC patients and 60 normal esophageal squamous epithelium samples, between January 2011 and November 2012, from the Department of Pathology of the First Affiliated Hospital of Bengbu Medical College. None of the patients had undergone chemotherapy or radiotherapy before surgery. Clinicopathological factors included sex, age (years), tumor position, gross tumor diameter (cm), lymph node metastasis (LNM), depth of invasion, tumor grade, TNM stage, and distant metastasis. The current study was approved by the Human Ethics Committee of Bengbu Medical College. Two experienced clinical pathologists determined the results of pathological diagnosis. Overall survival (OS) times were calculated until the date of death or January 2018 (mean OS: 44.4 months; scope: 1-70 months). Specific parameters are listed in **Table 1**.

Immunohistochemistry (IHC)

According to instructions of the IHC Elivision™ Plus testing equipment (Lab vision, USA), all ESCC tissues and normal tissue buffer controls were fixed in 10% formalin. They were embedded in paraffin, reducing the continuous 4 μm thick parts. All parts were then deparaffinized. Alcohol dehydration in xylene and gradient was conducted, then phosphate (PBS) was used. Endogenous peroxidase activity was hatched with a section of methanol with 3% hydrogen peroxide at room temperature for 10 minutes. It was then heated to a temperature of 95°C in citric acid buffer for antigen retrieval for 30 minutes. All parts of the blocked goat serum, after 20 minutes at room temperature, were washed with PBS. Antibody incubation was conducted overnight at 4°C in a humidity chamber. This included anti-SOX4 (rabbit polyclonal, di-

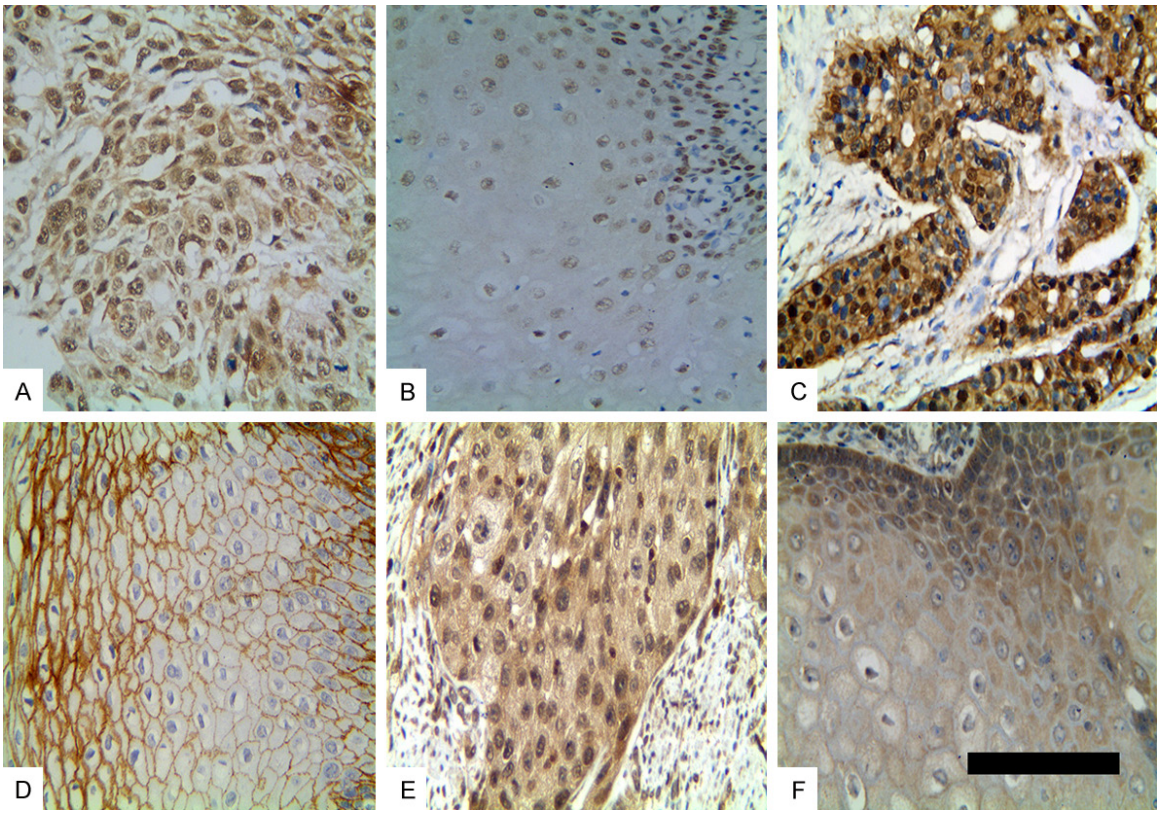

Figure 1. Expression of proteins in ESCC tissues (400× magnification, scale=250 μm). A. Positive SOX4 expression in the nucleus and cytoplasm of cancer cells; B. Positive SOX4 expression mainly localized in the nucleus of normal esophageal squamous epithelial cells; C. Positive β-catenin expression (mutant expression) in the nucleus and cytoplasm of cancer cells; D. β-catenin expression in the membrane of normal esophageal squamous epithelial cells; E. Positive TCF4 expression in the nucleus and cytoplasm of cancer cells; F. Positive TCF4 expression mainly localized in the cytoplasm of normal esophageal squamous epithelial cells.

luted 1: Abcam, ab80261), anti-β-catenin (rabbit monoclonal, dilute 1:100, Abcam ab32572), and ant-TCF4 (rabbit polyclonal, dilute 1:100, Abcam ab185736) antibodies. Slides were added with polymer enhancers (reagents) for 20 minutes at room temperature. After washing with PBS, the slides were treated with goat anti-mouse antibody reagent (B) at room temperature for 30 minutes. After washing with PBS, the slides were placed in freshly prepared diaminobenzidine (DAB) solution. Hematoxylin counterstaining, dehydration, drying, and installation were then performed.

Staining evaluation

Positive staining for SOX4 was present in the nucleus, while TCF4 was present in the nucleus and cytoplasm, in ESCC tissue samples. Ten fields of view were randomly selected from each slide. Protein expression levels of SOX4 and TCF4 were scored based on both the extent and intensity of immunopositivity. Immunopositivity was calculated as degrees, according to the cell staining positive percentage of the score: 1, ≤10%; 2, 11 to 50%; 3, 51 to 75%; and 4, >75%. Intensity levels of positive results were scored as follows: Negative/weak as 1; Moderate as 2; Strong as 3. Final scores were determined by multiplying the intensity of positivity and extent of positivity scores. When scores were ≥3, expression of SOX4 and TCF4 was positive. When scores were <3, expression was negative.

Positive staining for β-catenin was localized in the cytoplasm and/or nucleus in ESCC as ectopic mutant expression. However, expression was mainly localized in the normal esophageal squamous epithelial cell membrane. Staining results were evaluated according to criteria described in the study by Maruyama et al. [21].

Table 2. Association of SOX4, β-catenin, or TCF4 expression with clinicopathological characteristics of ESCC

Variable	SOX4		χ^2	*P*	β-catenin		χ^2	*P*	*TCF4*		χ^2	*P*
	+	-			+	-			+	-		
Sex			0.019	0.348			0.645	0.422			0.150	0.699
Male	111	42			100	53			109	44		
Female	48	19			40	27			46	21		
Age (years)			7.677	0.006			6.987	0.008			6.388	0.011
≤60	56	34			48	42			55	35		
>60	103	27			92	38			100	30		
Position			0.111	0.946			2.271	0.321			0.806	0.668
Upper	18	6			12	12			15	9		
Middle	104	41			95	50			103	42		
Lower	36	14			33	17			36	14		
Gross			1.134	0.987			1.627	0.653			0.466	0.926
Medullary	78	30			71	37			34	15		
Ulceration	34	13			29	18			35	12		
Narrow	11	5			8	8			11	5		
Fungating	36	13			32	17			75	33		
Diameter (cm)			26.399	<0.001			44.249	<0.001			42.639	<0.001
<3.8	61	47			45	63			54	54		
≥3.8	98	14			95	17			101	11		
LNM*			19.708	<0.001			38.336	<0.001			40.521	<0.001
Negative	84	12			83	13			89	7		
Positive	75	59			57	67			66	58		
Depth of invasion			34.314	<0.001			63.930	<0.001			45.392	<0.001
Over serous membrane	111	16			109	18			112	15		
Above serous membrane	48	45			31	62			43	50		
Tumor grade			1.186	0.553			0.084	0.959			0.617	0.734
Well	16	9			16	9			16	9		
Moderate	77	30			69	38			77	30		
Poor	66	22			55	33			62	26		
TNM stage			48.490	<0.001			68.566	<0.001			53.272	<0.001
I	14	26			10	30			13	27		
II	21	14			10	25			18	17		
III	57	17			58	16			58	16		
IV	67	4			62	9			66	5		
Distant metastasis			25.535	<0.001			25.419	<0.001			25.503	<0.001
No	92	57			78	71			89	60		
Yes	67	4			62	9			66	5		

*means lymph node metastasis.

More than 70% of positive stained cell membranes were normal. More than 10% of the cells showed positive expression via cytoplasmic and/or nuclear staining. Negative expression in the cytomembrane and positive expression in the cytoplasm and/or cell nucleus indicated abnormal expression.

Statistical analysis

$P<0.05$ indicates statistical significance. Data are shown as mean ± standard error of the mean. Differences between groups were analyzed by Student's *t*-tests or χ^2 tests. The Kaplan-Meier method was performed to assess

Table 3. Correlation levels between SOX4, β-catenin, and TCF4 in ESCC

Variable	SOX4		*rs*	*P*	TCF4		*rs*	*P*
	+	-			+	-		
β-catenin			0.651	<0.001#	135	20	0.753	<0.001#
+	132	27			5	60		
-	8	53						
TCF4			0.734	<0.001#				
+	145	14						
-	10	51						

#Positive association.

overall survival. All statistical analyses were performed using SPSS version 22.0 software system (IBM Corp., Armonk, NY, USA).

Results

Expression of SOX4, β-catenin, and TCF4 in ESCC and normal esophageal squamous epithelium tissues

Staining for SOX4 was restricted to the nucleus and the cytoplasm (**Figure 1A**, **1B**). SOX4 was positively expressed in 72.3% (159/220) of the ESCC tissue samples and 25.0% (15/60) of the distal normal esophageal squamous epithelium tissue samples. There were significant differences between the ESCC group and distal normal squamous epithelial group of the esophagus (P<0.05). Staining for β-catenin was confined to the nucleus and cytoplasm as ectopic mutant expression (**Figure 1C**, **1D**). β-catenin was positively expressed in 63.6% (140/220) of the ESCC samples and 16.7% (10/60) of distal normal esophageal squamous epithelium tissues. There were significant differences between the ESCC group and distal normal squamous epithelial group of the esophagus (P<0.05). As with SOX4 and β-catenin, TCF4 was positively expressed in the cytoplasm and nucleus (**Figure 1E**, **1F**). TCF4 was positively expressed in 71.4% (157/220) of ESCC samples and 30.0% (18/60) of distal normal esophageal squamous epithelium tissues (P<0.05).

Association between SOX4, β-catenin, and TCF4 expression and clinicopathological factors

Positive expression rates of SOX4, β-catenin, or TCF4 in ESCC were positively correlated with age, tumor diameter (cm), LNM, depth of invasion, TNM stage, and distant metastasis. However, they were not associated with sex, tumor grade, tumor position, or gross morphology (**Table 2**).

Association between SOX4, β-catenin, and TCF4 in ESCC

Association between SOX4 expression and β-catenin expression or TCF4 expression was found to be positive (r=0.651 and r= -0.734, respectively; P<0.001; **Table 3**). Association between β-catenin expression and TCF4 expression was also found to be positive (r=0.753, P<0.001, **Table 3**).

Survival analysis

Univariate analysis showed that OS times were significant and closely related to several clinical-pathological characteristics (**Table 4**), including age (log-rank=53.299, P<0.001), tumor diameter (log-rank=36.130, P<0.001), LNM (log-rank=31.364, P<0.001), depth of invasion (log-rank=35.144, P<0.001), TNM stage (log-rank=118.403, P<0.001), and distant metastasis (log-rank=108.305, P<0.001). In addition, overexpression of SOX4, β-catenin, or TCF4 indicated poor prognosis in terms of OS times (log rank=90.596, 99.464, and 97.068, respectively; P<0.001; **Figure 2A-C**). Univariate analysis also showed that OS times of patients with consistent positive expression of SOX4, β-catenin, and TCF4 were significantly shorter than those of patients with the opposite expression pattern. The positive expression patients showed a poor prognosis (log-rank=123,284; P< 0.001; **Figure 2D**). Multivariate analysis showed SOX4 expression, β-catenin expression, and TCF4 expression, as well as age and distant metastasis, to be independent prognostic factors for OS (P<0.05; **Table 5**).

Discussion

It has been proven that SOX4 plays a very important role in ESCC metastasis. SOX4 serves as an oncogene in various human cancers [19, 22]. SOX4 has been shown to promote proliferation and metastasis of cancer cells by regulating multiple signaling pathways, such as Wnt, Notch1, and p53 pathways [23, 24]. Pre-

Table 4. Results of univariate logistic regression analyses of overall survival (OS) times

Variable	n	Means OS time (months)	*Log-rank*	*P*
Sex			0.001	0.976
Male	153	38.133±1.965		
Female	67	42.612±3.075		
Age (years)			53.299	<0.001
<60	90	52.722±2.179		
≥60	130	27.954±1.805		
Position			2.513	0.285
Upper	24	36.333±4.840		
Middle	145	36.836±2.026		
Lower	50	43.411±1.639		
Gross			3.380	0.337
Medullary	108	36.397±1.634		
Ulceration	47	36.255±3.279		
Narrow	16	39.000±2.304		
Fungating	49	42.837±3.409		
Diameter (cm)			36.130	<0.001
<3.8	108	47.884±2.415		
≥3.8	112	29.009±1.800		
LNM*			31.364	<0.001
Negative	96	28.417±1.853		
Positive	124	45.837±2.278		
Depth of invasion			35.144	<0.001
Over serous membrane	93	49.594±2.546		
Above serous membrane	127	30.102±1.810		
Tumor grade			0.378	0.828
Well	25	38.640±4.747		
Moderate	107	38.860±2.333		
Poor	88	38.314±1.634		
TNM stage			118.403	<0.001
I	43	56.500±3.216		
II	43	48.800±4.012		
III	58	40.838±2.529		
IV	76	19.012±1.339		
Distant metastasis				
No	149	47.315±1.905	108.305	<0.001
Yes	71	19.012±1.339		
SOX4				
Negative	61	65.205±1.895	90.596	<0.001
Positive	159	27.937±1.453		
β-catenin			99.464	<0.001
Negative	80	60.057±2.198		
Positive	140	25.864±1.393		
TCF4			97.068	<0.001
Negative	65	64.514±1.982		
Positive	155	27.284±1.414		

*means lymph node metastasis.

vious studies have shown that it can be inhibit pancreatic cancer [25] and hepatocellular carcinoma metastasis [26] by interfering with SOX4 protein expression. The current study found that expression of SOX4 in ESCC was higher than that in normal esophageal squamous epithelium, according to IHC. Moreover, SOX4 was positively associated with age, tumor diameter, LNM, depth of invasion, TNM stage, and distant metastasis. Results suggest that SOX4 may be a useful biomarker, as it plays a key role in the development of ESCC.

The gene for TCF4 is transcription factor 7-like 2 (TCF7L2), an important member of the TCF family and a Wnt signaling pathway regulator [27]. TCF4 (TCF7L2) has been shown to bind directly to intron 1 of LIN28B and upregulate expression of LIN28B. Thereby, the above process could maintain the dryness of tumor cells, promoting the transformation and metastasis of cancer cells [28]. Abnormally elevated expression of TCF4 has been reported to be involved in the tumorigenesis of hepatocellular carcinomas [29] and colon cancer [30]. Current findings indicate that positive expression of TCF4 in ESCC is positively correlated with invasion, tumor differentiation, LNM, TNM stage, and distant metastasis. Kaplan-Meier survival analysis showed that OS times of patients with TCF4-positive expression were shorter than those with TCF4-negative expression. The current study suggests that positive expression of TCF4 may affect the development, invasion, and metastasis of ESCC. Present results are consistent with previous studies [28, 31].

β-catenin is a key regulator of canonical Wnt pathways and is

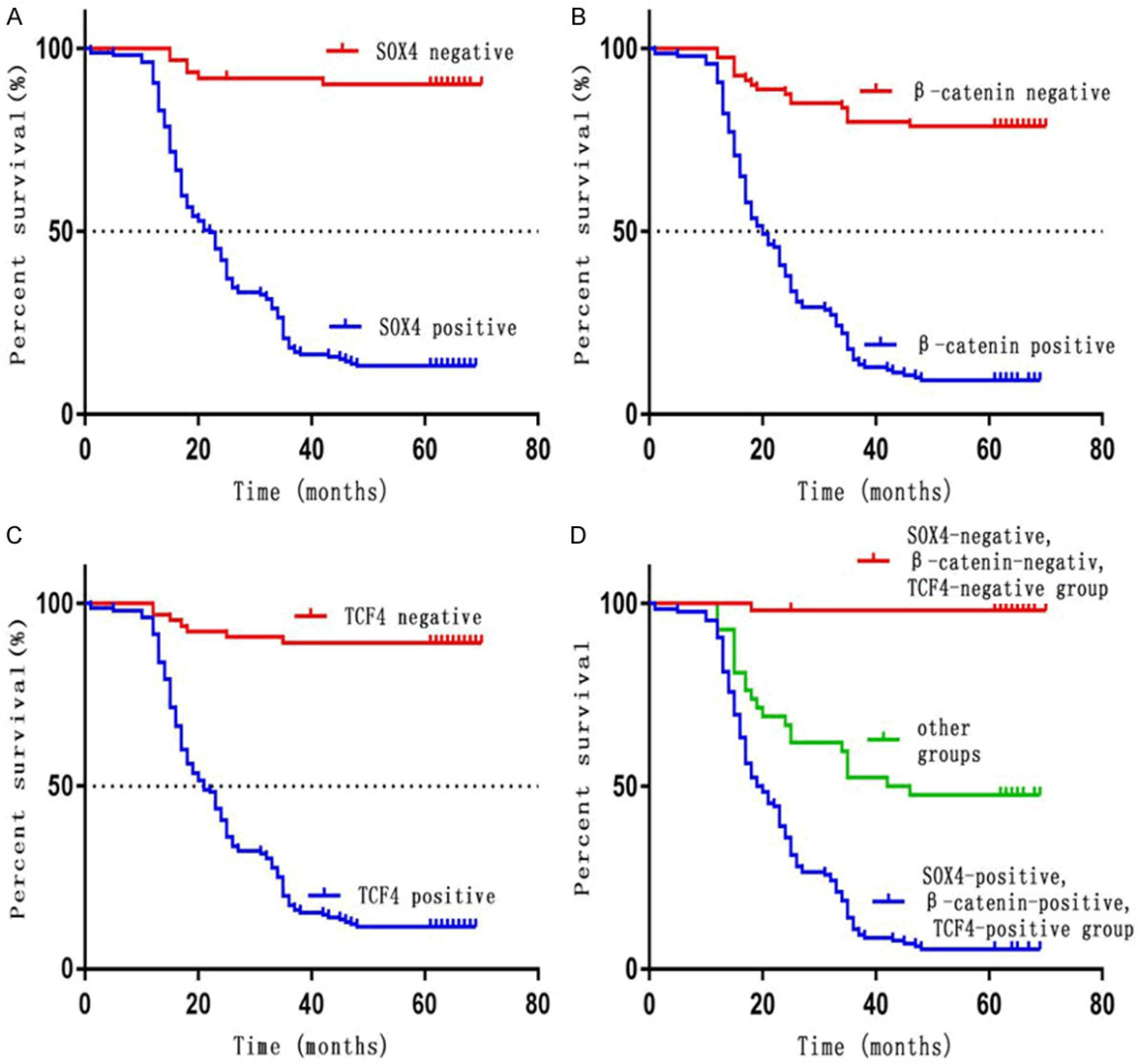

Figure 2. Kaplan-Meier analysis of survival rates of patients with ESCC stratified with respect to expression of SOX4, β-catenin, and (or) TCF4. A. Overall survival of all patients stratified by SOX4 expression (log-rank=90.596, *P*<0.001); B. Overall survival of all patients stratified by β-catenin expression (log-rank=90.596, *P*<0.001); C. Overall survival of all patients stratified by TCF4 expression (log-rank=97.068, *P*<0.001); D. Overall survival of all patients stratified by the combination of SOX4, β-catenin, and TCF4 expression (log-rank=123.284, *P*<0.001). The blue line represents patients with positive expression of SOX4, β-catenin, and TCF4. The red line represents patients with negative expression of SOX4, β-catenin, and TCF4. The green line represents patients with other combinations of positive or negative expression of these proteins. In all analyses, ⊥ in red, blue, or green represents a censored observation.

involved in cell proliferation, survival, migration, and apoptosis [32]. In the current study, β-catenin was abnormally highly expressed in the cytoplasm and cell nucleus of ESCC tissues. Results demonstrated that β-catenin expression in ESCC was positively associated with age, tumor diameter, LNM, depth of invasion, TNM stage, and distant metastasis. In addition, Kaplan-Meier survival analysis indicated that OS rates of ESCC patients with β-catenin-positive specimens had significantly poorer OS, compared to those with β-catenin-negative specimens. Present results suggest that β-catenin could play a key role in ESCC progression and metastasis.

Wnt/β-catenin signaling pathways regulate embryonic development and maintain many cellular functions during tissue homeostasis by regulating somatic stem cells and their niches [33-35]. Wnt-1 has been shown to cause β-catenin to accumulate in the cytoplasm, promoting the activation of β-catenin/TCF-dependent gene transcription in EC [36]. There is growing evi-

Table 5. Results of multivariate logistic regression analyses of overall survival (OS) times

	B	SE	*p*	Exp (B)	95.0% CI for Exp (B)
Sex	0.208	0.199	0.295	1.232	0.834-1.818
Age (years)	0.951	0.194	<0.001	2.589	1.771-3.785
LNM*	0.245	0.324	0.450	1.277	0.676-2.413
Depth of invasion	0.483	0.314	0.123	1.621	0.877-2.998
Tumor grade	-0.255	0.139	0.066	0.775	0.590-1.017
Position	-0.246	0.149	0.099	0.782	0.583-1.048
Gross	0.140	0.071	0.050	1.150	1.000-1.323
Diameter (cm)	0.043	0.339	0.898	1.044	0.538-2.028
Distant metastasis	1.468	0.342	<0.001	4.342	2.220-8.495
TNM stage	-0.399	0.216	0.064	0.671	0.440-1.024
SOX4	-1.786	0.506	<0.001	0.168	0.062-0.452
β-catenin	-1.187	0.349	0.001	0.305	0.154-0.605
TCF4	-1.078	0.517	0.037	0.340	0.123-0.938

*means lymph node metastasis.

dence that this pathway is associated with tumorigenesis and cancer development [37]. The current study showed that high expression of TCF4 was positively correlated with ectopic high expression of β-catenin. This suggests that TCF4 and β-catenin play synergistic roles in ESCC.

SOX4 has been proven to promote tumor cell proliferation by improving Wnt signaling pathways [13, 38, 39]. Makoto Saegusa et al. demonstrated that SOX4 immunoreactivity significantly overlaps nuclear nerves for TCF4 and β-catenine in morula lesions in Em Ca tissues, with significant positive correlation [40]. A TCF4 promoter, indicating that regulation occurs at the transcriptional level, was transfected with SOX4 activation by a -432bp SOX binding element, as evidenced by inhibition of promoter activity following introduction of a four-nucleotide alteration in that site [40]. Present results suggest that SOX4, β-catenin, and TCF4, which are highly expressed, play synergistic roles in promoting invasion and metastasis of ESCC. According to previous studies, as well as present results, it is speculated that SOX4 may induce one of the mechanisms of action of the β-catenin/TCF4 protein complex and that SOX4 may activate Wnt/β-catenin signaling pathways to participate in the development of ESCC.

Conclusion

The present study indicates that SOX4, β-catenin, and TCF4 play key roles in the establishment and maintenance of ESCC differentiation. Therefore, SOX4, β-catenin, and TCF4 should be considered potential markers for prognosis of patients with ESCC.

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Disclosure of conflict of interest

None.

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