Prognostic Significance of TAZ Expression in Resected Non-Small Cell Lung Cancer

Mian Xie, MD, PhD, Li Zhang, MD,† Chao-Sheng He, MD,‡ Jin-Hui Hou, MD,§ Su-Xia Lin, MD, PhD,§ Zhi-Huang Hu, MD,† Fei Xu, MD,† and Hong-Yun Zhao, MD, PhD†*

Introduction: Transcriptional coactivator with PDZ-binding motif (TAZ) is known to bind to a variety of transcription factors to control cell differentiation and organ development. Recently, TAZ has been identified as an oncogene and has an important role in tumorigenicity of non-small cell lung cancer (NSCLC). Therefore, TAZ may present a novel target for the future diagnosis, prognosis, and therapy for lung cancer. We investigated the relationship between TAZ expression and clinicopathological parameters and determined its prognostic significance concerning survival in patients with resected NSCLC.

Methods: TAZ expression was immunohistochemically studied in 181 consecutive patients with NSCLC and 20 cases of normal lung tissue. The association between expression of TAZ and clinicopathological parameters was evaluated. Kaplan-Meier survival analysis and Cox proportional hazards models were used to estimate the effect of TAZ expression on survival.

Results: TAZ expression was observed in 121 of the 181 (66.8%) NSCLC. TAZ had nuclear and cytoplasmic expression. Clinicopathologically, TAZ expression was significantly associated with lung adenocarcinoma ($p = 0.002$), poorer differentiation ($p = 0.001$), p-tumor, node, metastasis stage ($p = 0.001$), lymph node metastasis ($p = 0.032$), intratumoral vascular invasion ($p = 0.004$), pleural invasion ($p = 0.003$), adjuvant chemotherapy ($p = 0.044$), and poorer prognosis ($p = 0.002$). Multivariable analysis confirmed that TAZ expression increased the hazard of death after adjusting for other clinicopathological factors (hazard ratio, 2.56; 95% confidence interval, 1.39–4.66; $p = 0.01$). Overall survival was significantly prolonged in TAZ negative group when compared with TAZ positive group (61.8 versus 47.1 months; $p < 0.0001$), as was disease-free survival (44.3 versus 25.1 months; $p < 0.0001$). Adjuvant chemotherapy prolonged overall survival among resected NSCLC patients with TAZ positive expression ($p = 0.001$).

Conclusions: This study suggests that TAZ expression is a prognostic indicator of poorer survival probability for patients with resected NSCLC.

Key Words: TAZ, Prognosis, Non-small cell lung cancer.

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Primary lung cancer is the leading cause of cancer mortality worldwide. Although surgical resection is the optimal treatment of early-stage, non-small cell lung cancer (NSCLC), 5-year survival rates for surgically resectable NSCLC are still unsatisfactory and range from 19% for stage IIIA to 63% for stage IA.[1] Recurrence that accounts for mortality occurs most commonly in distant extrathoracic regions. Recently, adjuvant cisplatin-based chemotherapy has been recommended to improve survival for NSCLC patients with completely resected stage II and stage IIIA.[2] Although adjuvant chemotherapy shows some improvement of 5-year overall survival (OS), which ranges from 4 to 15%, adjuvant chemotherapy is also associated with serious adverse side effects. Moreover, the benefit of platinum-based adjuvant chemotherapy for stage IB patients has not been established.[3] Therefore, the identification of predictive and/or prognostic markers is important to stratify patients with resected NSCLC and select high-risk patients who should receive aggressive adjuvant chemotherapy.

Transcriptional coactivator with PDZ-binding motif (TAZ), also called WW-domain containing transcription regulator 1 (WWTR1), is a WW-domain-containing transcriptional coactivator that activates many transcriptional factors, which have important roles in the development of various tissue in mammals.[4] TAZ has also been shown to regulate stem cell differentiation and renewal through modulation of the transcription factors PPARγ, Runx2, and Smad.[5] Recently, TAZ has been identified as a component of an emerging Hippo-LATS tumor suppressor pathway that has important roles in regulating cell proliferation, apoptosis, tumor formation, and organ size in both Drosophila and mammals.[6] Significantly, human homologs of Drosophila Hippo and LATS tumor suppressors, *Mst*II and LATS1/2, can suppress tumor cell growth by phosphorylating and inhibiting TAZ and its protein highly paralog Yes-associated protein (YAP).[7] Zhou et al.[8] showed for the first time that TAZ is an oncogene in NSCLC. TAZ was overexpressed in NSCLC cells. To our knowledge, no report has been

*China State Key Laboratory of Respiratory Disease and Guangzhou Institute of Respiratory Disease, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou; †Department of Medical Oncology, Sun Yat-Sen University Cancer Center, Guangzhou; ‡Department of Medicine, Guangdong General Hospital, Guangzhou; and §Department of Pathology, Sun Yat-Sen University Cancer Center, Guangzhou, China.

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Address for correspondence: Mian Xie, MD, PhD, The First Affiliated Hospital of Guangzhou Medical University, 151 Yan Jiang Road, Guangzhou 510120, China. E-mail: xiemiangle76@163.com

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published concerning the relationships between TAZ expression and clinicopathological features and prognosis of lung cancer patients. Therefore, the objectives of this study were (1) to immunohistochemically examine TAZ expression in tumor samples of 181 NSCLC patients, (2) to evaluate the relationships between TAZ expression and the clinicopathological parameters of NSCLC, and (3) to estimate the prognostic impact of TAZ on survival in patients with resected NSCLC patients.

PATIENTS AND METHODS

Patient Selection and Tissue Sample Collection

A total of 181 consecutive NSCLC patients who underwent complete resection (lobectomy and mediastinal lymph node dissection with microscopic examination of margins showing no tumor cells) from January 2003 to March 2005 at the First Affiliated Hospital of Guangzhou Medical University were included in this retrospective cohort study.

Patients who have previous malignant disease, second primary tumor, or those who received preoperative radiotherapy and/or chemotherapy were excluded. Twenty cases of normal lung tissue were included in this study. Three micrometer-thick sections were stained with hematoxylin and eosin. The histological diagnosis was based on the criteria of the World Health Organization/International Association for the Study of Lung Cancer (WHO/IASLC) classification of lung and pleural tumors.[9] Each case was reassigned for tumor, node, metastasis (TNM) classification and pathological stage on the basis of the new IASLC staging system.[10] The following clinical and pathologic parameters were retrospectively reviewed and analyzed for each case: age at surgical resection, gender, smoking habits, histological type, tumor differentiation, pathological TNM (p-TNM) stage, nodal status, intratumoral vascular invasion, pleural invasion, receiving adjuvant chemotherapy, OS, and progression-free survival time (PFS) after surgery. The study was approved by the Ethics Committee of Sun Yat-Sen University cancer center. Informed consent was obtained from all patients for specimen collection.

Immunohistochemical Staining for TAZ

After dewaxing in xylene and rehydrating stepwise in ethanol, sections were subjected to heat-induced antigen retrieval. Endogenous peroxidase activity and nonspecific binding were blocked with 3% H_2O_2 and nonimmune sera, respectively. Sections were then incubated with primary antibodies overnight at 4°C. The primary antibodies were used in this study: rabbit polyclonal TAZ (H-70) antibody (sc-48805, 1:200, Santa Cruz). The following day, primary antibody was detected using the appropriate labeled Streptavidin-Biotin kit (Maixin Biotechnology, Fuzhou, China) according to the manufacturer's instructions. Immunolabeled sections were visualized with 3,3′-diaminobenzidine and counterstained with hematoxylin. Sections were counterstained with hematoxylin, dehydrated, and mounted. Sections were stained in parallel without primary antibody to provide a negative control.

Evaluation of Immunohistochemical Staining

Two investigators (J.H.H. and S.X.L.) separately evaluated all the specimens in a blinded manner. Variant cases were reviewed and discussed until a consensus was obtained. Five areas were selected at random and scored. The percentage of tumor cells with positive staining of TAZ was determined at high magnification (×200). For TAZ, nuclear and cytoplasmic immunostaining in tumor cells was considered to be positive. Tissue was scored (*H* score) based on the total percentage of positive cells and the intensity of the staining (1+, 2+, or 3+), where $H = (\%\ 1+ \times 1) + (\%\ 2+ \times 2) + (\%\ 3+ \times 3)$. The sample was considered negative if $H = 0$ and positive if *H* was more than 0; positive samples were also categorized as weak if $H = 1$ to 50 and strong if *H* was more than 50. A minimum of 100 cells were evaluated in calculating the *H* score.[11]

Cell Lines

The cell lines included seven adenocarcinoma (AD) (A549, NCI-H1975, NCI-H358, PC9, NCI-H3255, NCI-H1838, and HCC827), two squamous cell carcinoma (SCCs) (NCI-H2170 and SK-MES-1), one NSCLC line derived from metastatic lymph node (NCI-H1299), one mucoepidermoid pulmonary carcinoma (NCI-H292), and three normal bronchial epithelial cell lines (HBE-135, HBE-154 and BEAS-2B). PC9, NCI-H1975, A549 cell lines were obtained from Pro. Wu YL (Guangdong Provincial General Hospital, China). BEAS-2B, HBE-135, and HBE-135 cell lines were obtained from Dr. Yang ZF (State Key laboratory of Respiratory Disease, China). NCI-H2170, SK-MES-1, NCI-H292, NCI-H1299, NCI-H358, NCI-3255, NCI-1838, and HCC827 were purchased from the American Type Culture Collection (Manassas, VA). These cell lines were routinely cultured in RPMI-1640 supplemented with 10% fetal calf serum at 37°C in a 5% CO_2 atmosphere.

Western Blot

Total protein was isolated from cells using Cell Extraction Buffer (Biosource, Camarillo, CA) supplemented with protease and phosphatase inhibitors and precleared using centrifugation, followed by measuring protein concentrations using the BCA Protein Assay kit (Pierce, Rockford, IL). Rabbit polyclonal TAZ antibody (sc-48805, Santa Cruz) and β-actin (4967, Cell Signaling Technology) antibodies were used as primary antibodies. Equal protein loading was confirmed with probing for β-actin expression. The blots were washed and incubated with horseradish peroxidase-conjugated goat anti-rabbit antibody (Calbiochem, La Jolla, CA). Proteins were visualized by Amersham enhanced chemiluminescence (GE Healthcare, Palo Alto, CA).

Statistical Analysis

Correlation between immunohistochemical expression and clinicopathological parameters was analyzed by χ^2 test. Survival curves were assessed by the Kaplan-Meier method and compared by the log-rank test. Multivariate survival analysis was performed on all parameters, which were found to be significant on univariate analysis using the Cox regression model. Two-sided $p < 0.05$ was considered statistically

significant. All analyses were performed with the SPSS 16.0 software package.

RESULTS

Patient Characteristics

The baseline characteristics of the patients are shown in Table 1. A total of 117 men and 64 women were included with ages ranging from 30 to 78 years (median, 57 years) of which 113 (62.4%) were former smokers. There were 56 (31.0%) stage I (14 stage IA and 42 stage IB), 63 (34.8%) stage II (23 stage IIA and 40 stage IIB), and 62 (34.2%) stage IIIA diseases, including 114 (63.0%) ADs, 61 (33.7%) SCCs, four (2.2%) large cell carcinomas, and six (1.1%) adenosquamous carcinoma. One hundred twenty-seven patients received three to six cycles of tri-weekly adjuvant chemotherapy, of whom 150 (83.0%) finished four cycles. The adjuvant chemotherapy regimens included docetaxel (19.0%), gemcitabine (21.3%), paclitaxel (36.2%), and vinorelbine (23.5%) combined with cisplatin or carboplatin.

TAZ Expression in NSCLC

First, we examined the expression in 14 lung cell lines by Western blot using a polyclonal antibody raised against TAZ. Specifically, no TAZ expression was observed in three nontumorigenic human bronchial epithelial cell lines, whereas overexpression of TAZ was observed in seven of 11 (63.6%) tumorigenic NSCLC cell lines (Figure 1).

Subsequently, we investigated TAZ expression in 181 cases of NSCLC tissue and 20 cases of normal lung tissue by immunohistochemistry. The TAZ protein was mainly accumulated in the nucleus with a less cytoplasmic presence (Figure 2). TAZ positive expression in tumor cells was observed in 121 of 181 (66.8%) NSCLC (Table 1). They were further divided into 85 of 114 (74.6%) ADs, 36 of 61 (59.0%) SCCs. None of large cell carcinomas expressed

TABLE 1. Relationships between TAZ Expression and Clinicopathological parameters (n = 181)

	TAZ Expression (n, %)				
Characteristics	**Weak Positive (n = 76)**	**Strong Positive (n = 45)**	**Negative (n = 60)**	**Total**	***p***
Age (yr)					
<65	46 (45.5)	23 (22.8)	32 (31.7)	101	0.539
≥65	30 (37.5)	22 (27.5)	28 (35)	80	
Gender					
Male	47 (40.2)	28 (23.9)	42 (25.9)	117	0.568
Female	29 (45.3)	17 (26.6)	18 (28.1)	64	
Smoking history					
Former smoker	51 (45.1)	28 (24.8)	34 (30.1)	113	0.459
Never smoker	5 (36.8)	17 (25.0)	26 (38.2)	68	
Histology					
Adenocarcinoma	55 (48.3)	30 (26.3)	29 (25.4)	114	0.002
Squamous carcinoma	21 (34.4)	15 (24.6)	25 (41.0)	61	
Others	0	0	6 (100)	6	
Tumor differentiation					
Well/moderately	38 (33.6)	22 (19.5)	53 (46.9)	113	0.001
Poorly	38 (55.9)	23 (33.8)	7 (10.3)	68	
p-TNM stage					
StageI	17 (30.4)	7 (12.5)	32 (57.1)	56	0.001
Stage II/III	59 (47.2)	38 (30.4)	28 (22.4)	125	
Nodal status					
N0	22 (37.3)	10 (16.9)	27 (45.8)	59	0.032
N1/N2/N3	54 (44.3)	35 (28.7)	33 (27.0)	122	
Vascular invasion					
Yes	25 (38.5)	25 (38.5)	15 (23.0)	65	0.004
No	51 (44.0)	20 (17.2)	45 (38.8)	116	
Pleural invasion					
Yes	15 (34.9)	19 (44.2)	9 (20.9)	43	0.003
No	61 (44.2)	26 (18.8)	51 (37.0)	138	
Adjuvant chemotherapy					
Yes	59 (46.5)	33 (26.0)	35 (27.5)	127	0.044
No	17 (31.5)	12 (22.2)	25 (46.3)	54	

p-TNM, pathological TNM.

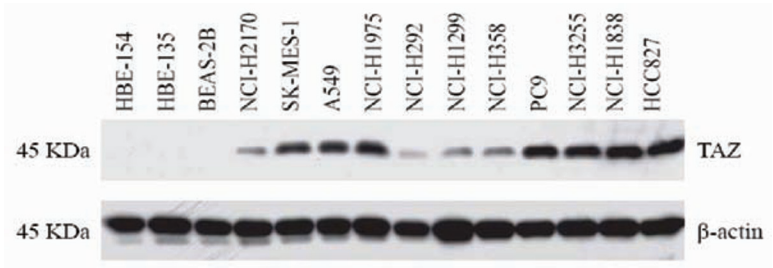

FIGURE 1. Western blot analysis of TAZ expression in normal human bronchial epithelial (HBE) and NSCLC cell lines. Cell lysates extracted from these cell lines were subjected to Western blot using anti-TAZ and anti-β-actin antibodies. The levels of β-actin were used as internal protein loading controls.

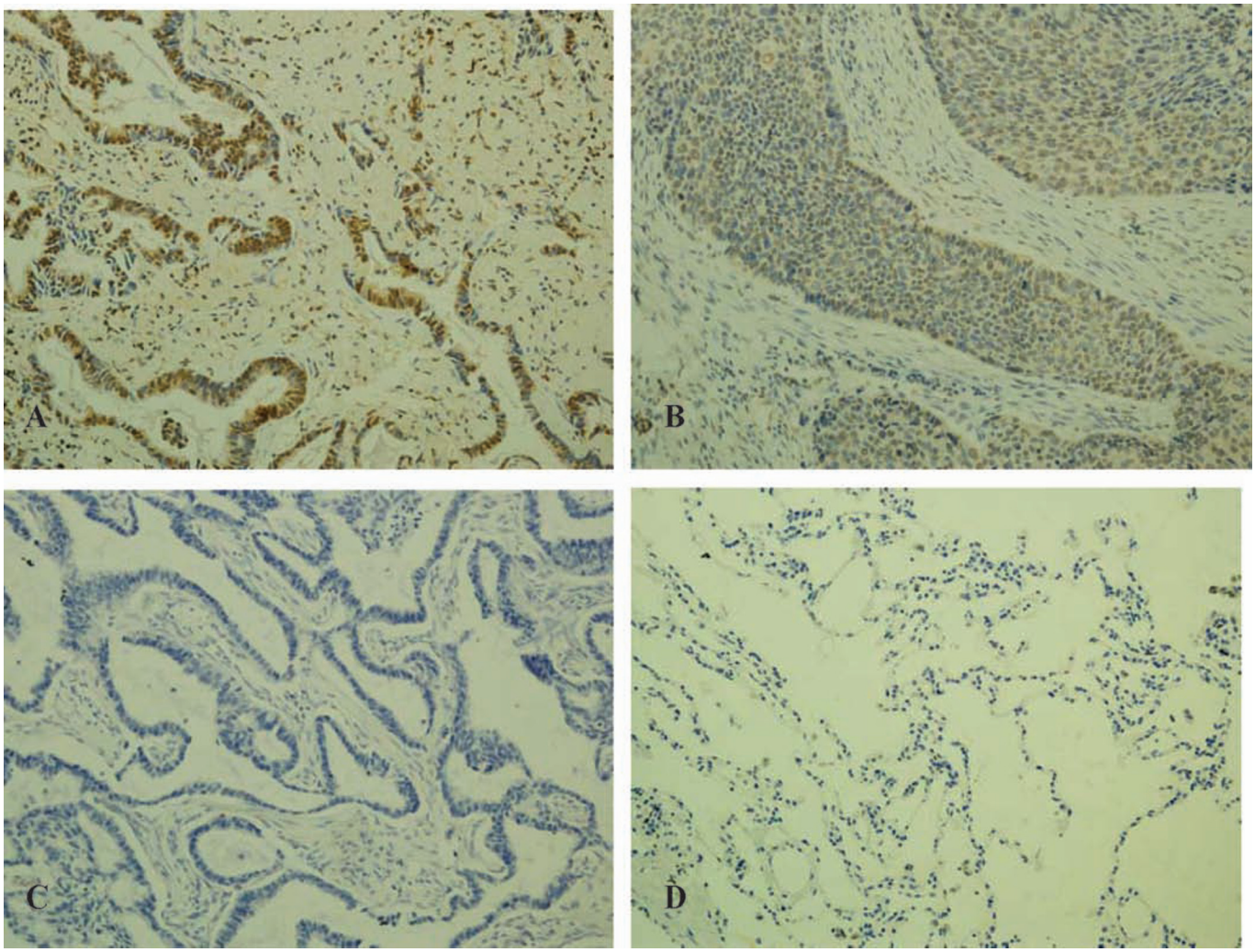

FIGURE 2. Immunohistochemistry staining of TAZ in NSCLC. TAZ positive expression in both nucleus and cytoplasm of lung adenocarcinoma (*A*). TAZ positive expression in lung squamous carcinoma, staining in both cytoplasm and nucleus of tumor cells (*B*). Negative TAZ expression in lung adenocarcinoma (*C*). Negative expression in normal lung tissue (*D*). Original magnification, ×200.

TAZ. TAZ overexpression was not detected in non-neoplastic bronchial or alveolar epithelial cells.

Relationship between TAZ Expression and Clinicopathological Characteristics

The relationships between TAZ expression and clinicopathologic characteristics are summarized in Table 1. TAZ positive expression was more frequently detected in ADs than in SCCs and other histological subtypes ($p = 0.002$). TAZ positive expression was also related to poorer differentiation ($p = 0.001$), p-TNM stage ($p = 0.001$), lymph node metastasis ($p = 0.032$), intratumoral vascular invasion ($p = 0.004$), pleural invasion ($p = 0.003$), and adjuvant chemotherapy ($p = 0.044$);

whereas there was no significant association between TAZ expression and age, gender, smoking history.

Effect of TAZ Expression on Survival with Univariable and Multivariable Analysis

To find practically useful prognostic factors, we performed univariate analysis for TAZ expression and nine clinicopathological factors (Table 2). The clinicopathological factors included age, gender, smoking history, histology, p-TNM stage, adjuvant chemotherapy, tumor differentiation, vascular invasion, and pleural invasion. TAZ positive expression, p-TNM stage, adjuvant chemotherapy, and tumor differentiation were four significant prognostic factors (TAZ positive expression: $p = 0.002$, p-TNM stage: $p < 0.0001$, adjuvant chemotherapy: $p < 0.0001$, tumor differentiation: $p < 0.0001$). The crude hazard ratio (HR) of TAZ positive compared with TAZ negative was 3.26 (95% confidence interval [CI], 2.43–5.51), which indicate that TAZ positive status increased the hazard of lung cancer-related death by three times that of TAZ negative.

We then performed multivariate analysis for these four factors whose presence significantly affected prognosis and for demographic factors, such as age and sex. The results showed that TAZ positive expression, p-TNM stage, and adjuvant chemotherapy were significantly related to prognosis (TAZ positive expression: $p = 0.006$, p-TNM stage: $p = 0.003$, adjuvant chemotherapy: $p = 0.001$). After controlling for the effects of the above clinicopathological factors, the adjusted HR of TAZ positive expression became 2.54 (95% CI, 1.30–4.94; $p = 0.006$) in comparison with TAZ negative expression (Table 3).

We also performed an analysis by using propensity score to adjust the effect of TAZ expression by transforming all other confounding variables (including age, gender, smoking history, histology, p-TNM stage, and adjuvant chemotherapy) into a single estimator and revealed that after the adjustment, the HR of TAZ expression became 2.56 (95% CI, 1.39–4.66; $p = 0.01$). These findings suggested that TAZ positive was an independent and significant predictor of poorer survival.

Kaplan-Meier Estimate of Survival for Resected NSCLC Patients with or without TAZ Expression

All the patients were included in the survival analysis. The overall follow-up durations ranged from 8 to 73 months (median, 62.1 months). Five-year cumulative survival probability was 20.7% for the TAZ positive group and 43.3% for the TAZ negative group. The median OS was 47.1 months for patients with TAZ positive expression, 61.8 months for patients with TAZ negative expression, indicating a significantly poorer rate of OS in the TAZ positive group compared with that in the TAZ-negative group ($p < 0.0001$, Figure 3*A*). In further analyses, TAZ positive expression was significantly associated with shorter OS for stage II/III patients ($p < 0.0001$, Figure 3*C*) and for stage I patients ($p = 0.023$, Figure 3*B*). Five-year survival probability was 12.0% for TAZ positive versus 27.3% for TAZ negative patients with stage II/III, and 48.3% for TAZ positive versus 63.0% for TAZ negative patients with stage I. Similarily, TAZ positive patients had significantly shorter PFS (25.1 months) than TAZ negative patients (44.3 months) in the entire population ($p < 0.0001$) (Figure 4*A*). There were also significant differences of PFS between TAZ positive patients and TAZ negative patients among stage I ($p = 0.017$) and stage II/III ($p < 0.0001$) postoperative patients (Figure 4*B–C*). Median PFS was longer in TAZ weak positive patients (28.6 months) than in patients with TAZ strong positive patients (21.6 months) ($p = 0.044$) (Figure 5*A*). In contrast, there were no significant difference of median OS between those with weak positive (48.1 months) and strong positive expression (44.7 months) ($p = 0.495$) (Figure 5*B*).

TABLE 2. Univariable Analysis for the Effect of TAZ Expression on Overall Survival ($n = 181$)

	Univariable Analysis		
Factors	**HR**	**95% CI**	***p***
TAZ expression			
Positive vs. negative	3.26	2.43–5.51	0.002
Age (yr)			
65 vs. <65	1.23	0.58–1.92	0.081
Gender			
Male vs. female	1.86	0.85–2.88	0.076
Smoking history			
Smoker vs. none smoker	1.92	0.89–3.15	0.062
Histology			
AD vs. non-AD	1.36	0.75–2.27	0.056
p-TNM stage			
Stage II/III vs. stage I	3.83	2.12–6.86	<0.0001
Adjuvant chemotherapy			
No vs. yes	4.12	2.80–7.16	<0.0001
Tumor differentiation			
Poorly vs. well/moderately	3.91	2.23–7.13	<0.0001
Vascular invasion			
Yes vs. no	1.15	0.69–2.83	0.071
Pleural invasion			
Yes vs. no	1.54	0.78–2.46	0.094

AD, adenocarcinoma; p-TNM, pathological TNM; HR, hazard ratio; CI, confidence interval.

TABLE 3. Multivariable Analysis for the Effect of TAZ Expression on Overall Survival ($n = 181$)

	Multivariable Analysis		
Factors	**HR**	**95% CI**	***p***
TAZ expression			
Positive vs. negative	2.54	1.30–4.94	0.006
Age (yr)			
≥65 vs. <65	1.14	0.77–1.96	0.881
Tumor differentiation			
Poorly vs. well/moderately	1.72	0.63–2.15	0.348
p-TNM stage			
Stage II/III vs. stage I	2.83	1.63–4.86	0.003
Adjuvant chemotherapy			
No vs. yes	2.13	1.79–3.90	0.001

HR, hazard ratio; CI, confidence interval; TAZ, transcriptional coactivator with PDZ-binding motif; p-TNM, pathological TNM.

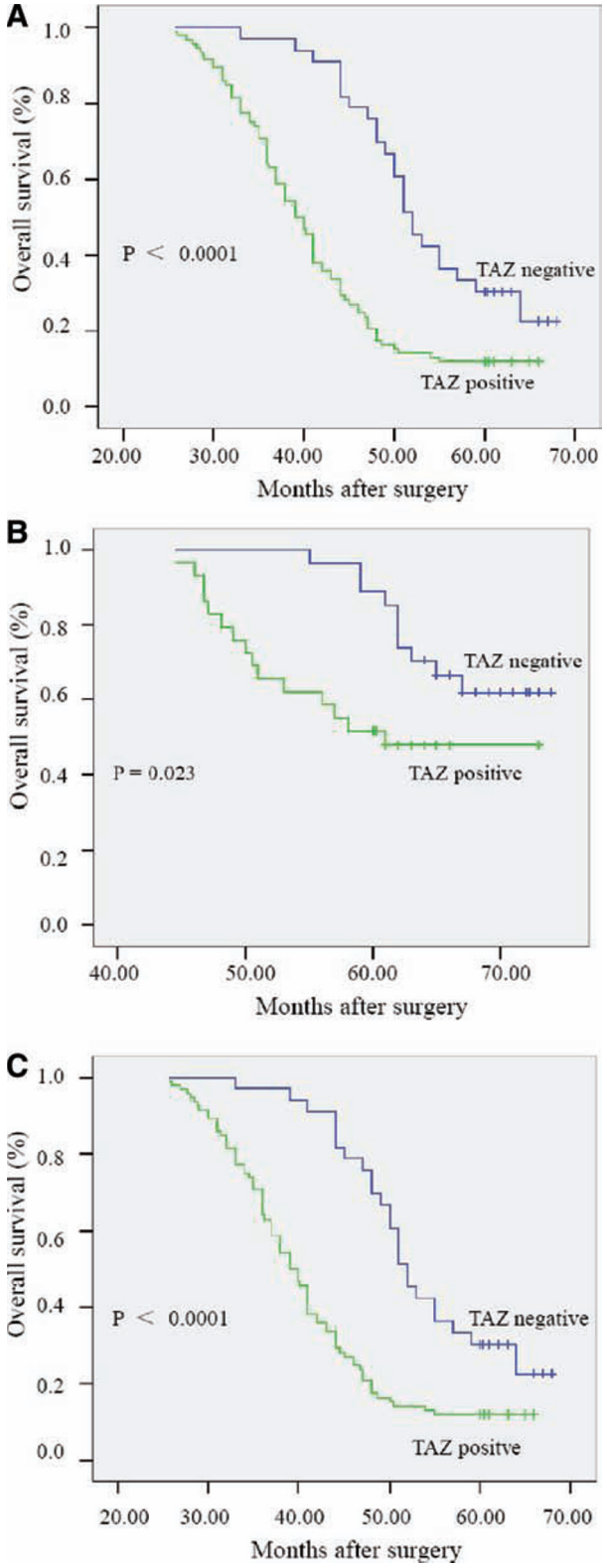

FIGURE 3. Overall survival curves with TAZ expression results in the entire population (*A*), in stage I NSCLC patients (*B*), and in stage II/ III NSCLC patients (*C*).

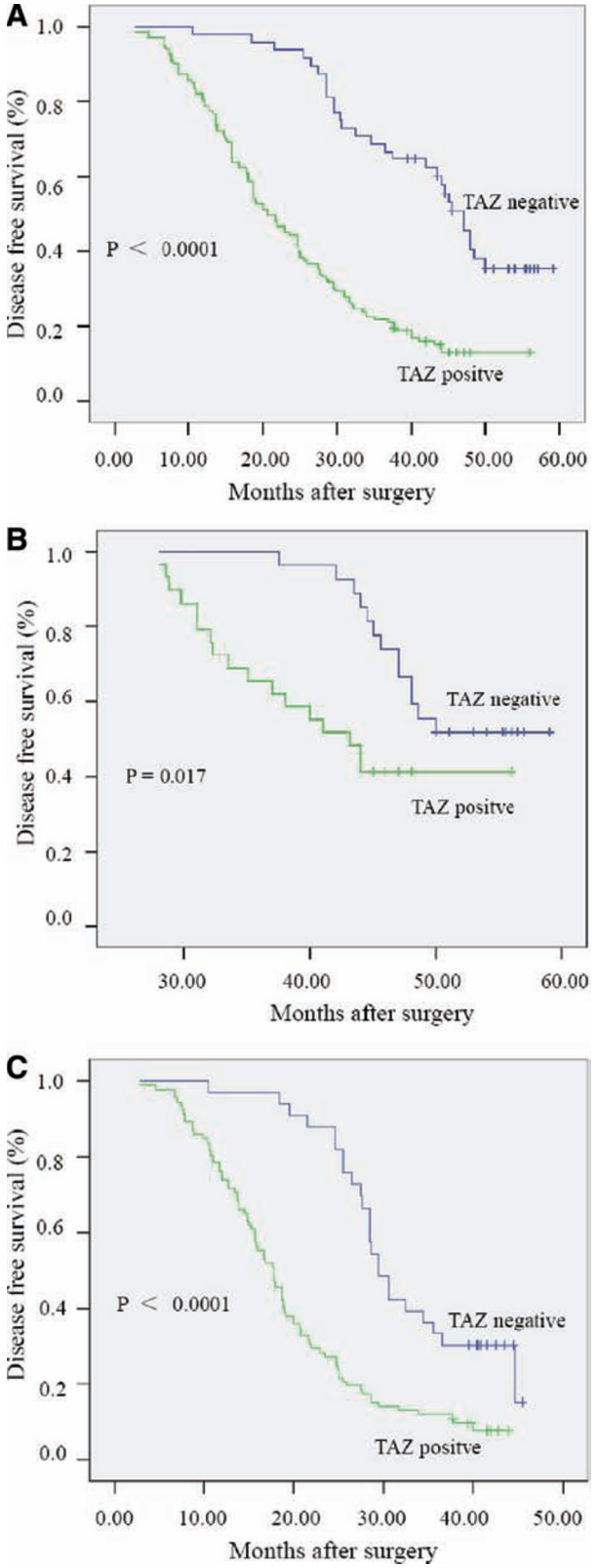

FIGURE 4. Disease-free survival curves with TAZ expression results in the entire population (*A*), in stage I NSCLC patients (*B*), and in stage II/ III NSCLC patients (*C*).

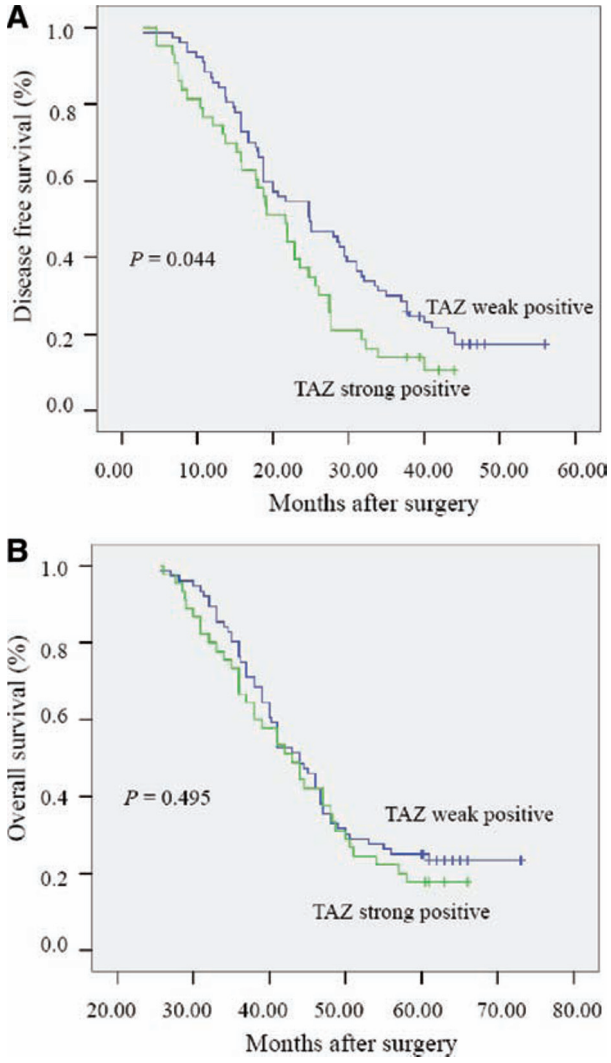

FIGURE 5. Disease-free survival curve (*A*) and overall survival (*B*) among patients with TAZ positive expression.

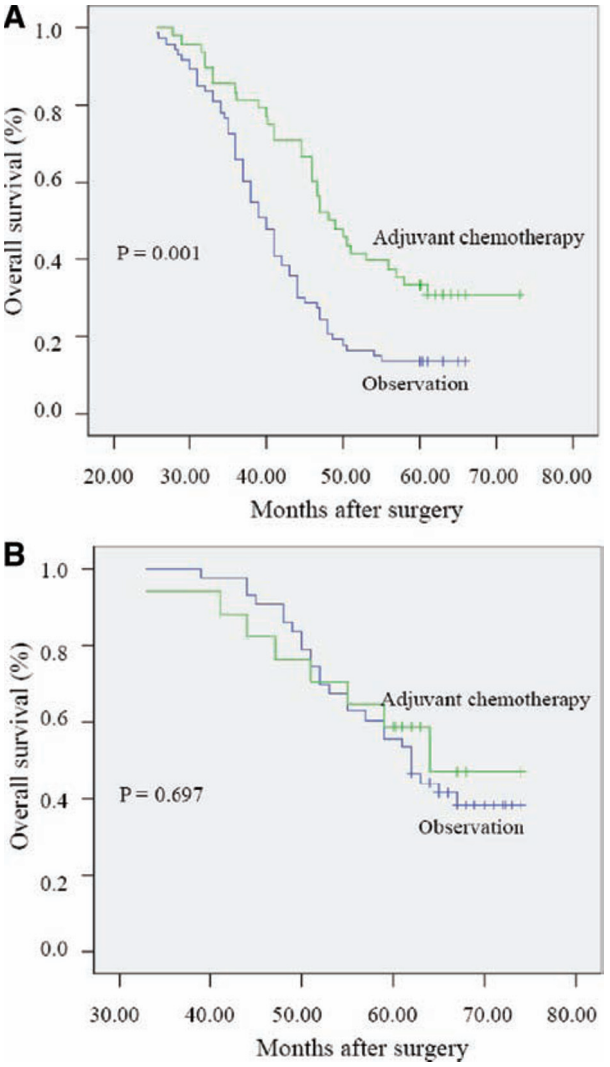

FIGURE 6. Kaplan-Meier estimates of overall survival between adjuvant chemotherapy group and observation group among patients with TAZ positive expression (*A*) or those without TAZ expression (*B*).

Next, we compared OS between adjuvant chemotherapy group and observation group among patients with TAZ positive expression or those without TAZ expression. In NSCLC patients with TAZ positive expression, the median OS in patients with adjuvant chemotherapy was significantly prolonged, at 52.8 months when compared with 42.4 months in the observation group (HR, 0.81; 95% CI, 0.72–0.89; $p = 0.001$) (Figure 6*A*). In patients with TAZ negative expression, the median OS was 61.8 months for those without adjuvant chemotherapy and 61.7 months for those received adjuvant chemotherapy (HR, 0.93; 95% CI, 0.78–1.11; $p = 0.698$) (Figure 6*B*). Subgroup analysis indicated that the survival benefit of receiving adjuvant chemotherapy was only shown in the TAZ positive subgroup.

DISCUSSION

In this study, we demonstrate for the first time that TAZ expression is associated with poorer prognosis and is an independent prognostic factor for survival in patients with resected NSCLC patients. TAZ positive expression was significantly associated with decreased OS and disease-free survival probability among stage II/III and stage I patients, especially stage II/III subgroup ($p < 0.0001$). Although TAZ was detected in both well/moderately and poorly differentiated tumors, its expression incidence was significantly higher in poorly differentiated ones ($p = 0.001$). Moreover, in agreement with previous reports of papillary thyroid carcinoma,[12] our findings revealed that TAZ expression was significantly associated with intratumoral vascular invasion, pleural invasion, and nodal status in NSCLC. These results suggest that TAZ expression may be important for the acquisition of migration and invasion capabilities of tumor cells, which subsequently results in poorer prognosis in patients with resected NSCLC.

Zhou et al.[8] found that TAZ was relatively low in all normal (HBE154 and HBE158) and immortalized HBE cell lines (HBE135, BEAS-2B, and NL20) but was overexpressed

in nine of 11 (81%) tumorigenic NSCLC cell lines examined. However, in our study, TAZ expression was not observed in mature bronchial or alveolar epithelial cells of non-neoplastic peripheral lung tissues but was only detected in tumor cells. de Cristofaro et al.[12] reported that the increase of TAZ expression is a marker of papillary thyroid carcinoma. Particularly, the immunohistochemical staining observed in the cytoplasm suggests that a dislocation of TAZ might be one of the causes of the malignant phenotype. In our study, TAZ was expressed in 66.8% NSCLC, most of which were located in the nuclei and cytoplasm of tumor cells. The location of TAZ staining in NSCLC is similar to that of YAP (a highly paralog of TAZ) in lung cancer.[13]

Although the molecular mechanism governing the function of TAZ is not fully clear, one of the mechanisms for TAZ action is to trigger a loss of epithelial morphology, to promote cell migration and invasion, and to support anchorage-independent growth, all of which are important for cancer initiation, progression, and invasion.[14] TAZ overexpression is not sufficient to enable HBE135 immortalized human bronchial epithelial cells to grow into sizeable colonies in soft agar, nevertheless, it is important for anchorage-independent growth of HBE135 cells. Moreover, A549 lung cancer cells with TAZ knockdown exhibited a significant reduction in anchorage-independent growth on soft agar in vitro and tumor growth in nude mice in vivo. Together, these studies strongly suggest that TAZ is vital for the tumorigenesis of NSCLC cells.[8] Given that YAP and TAZ have independent and overlapping functions, it is possible that both YAP and TAZ may be involved in lung tumorigenesis in vivo.[15]

In our study, NSCLC patients with TAZ positive expression demonstrated a significant survival benefit from adjuvant chemotherapy, whereas those with TAZ negative expression did not. It may be speculated that because patients with TAZ positive expression was related to late stage NSCLC and may benefit more from adjuvant chemotherapy because of the poorer prognosis. de Cristofaro et al.[12] demonstrated that TAZ confered a growth advantage to thyroid cells in vitro and induced epithelia-mesenchymal transition, which was associated with cancer cell invasion and metastasis. ASPP1 (apoptosis-stimulating protein of p53) can inhibit the interaction of YAP/TAZ with LATS1 (large tumor suppressor 1), a kinase that phosphorylates YAP/TAZ and promotes cytoplasmic sequestration and protein degradation.[16] This function of ASPP1 therefore enhances nuclear accumulation of YAP/TAZ and YAP/TAZ-dependent transcriptional regulation. The consequence of YAP/TAZ activation by ASPP1 is to inhibit apoptosis, in part through the down-regulation of Bim expression, leading to resistance to anoikis (a form of programmed cell death, which is induced by anchorage-dependent cells detaching from the surrounding extracellular matrix) and enhanced cell migration. Resistance to anoikis is regarded as a prerequisite for metastasis, therefore, activation of YAP/TAZ may contribute to lung cancer metastasis. In summary, enhanced expression of TAZ induces epithelia-mesenchymal transition and resistance of anoikis, which are the key mechanisms by which tumor cells gain invasive and metastatic ability. This may explain why higher expression of TAZ is associated with poor prognosis of NSCLC and the survival benefit from adjuvant chemotherapy.

Lai et al.[17] reported that elevated levels of TAZ found in human breast cancer cells was responsible for their resistance to Taxol. DNA microarray analysis identified the oncogenes Cyr61 and CTGF as downstream transcriptional targets of TAZ. Short hairpin RNA-mediated knockdown of both Cyr61 and CTGF reversed TAZ-induced Taxol resistance in breast cancer cells. Interaction of TAZ with the TEAD family of transcription factors was essential for TAZ to activate the Cyr61/CTGF promoters and to induce Taxol resistance. Nevertheless, because of the small amount of TAZ positive patients in our study, we could not stratify the data according to the clinical TNM stage and chemotherapy regimens. Thus, large-scale clinical study is needed to clarify whether or not TAZ expression is a prognostic indicator to help select patients who might benefit from receiving adjuvant chemotherapy.

In conclusion, we have provided the first clinical evidence that TAZ is expressed in a subset of NSCLC and its expression is related to clinicopathological factors. We demonstrated that TAZ expression is a prognostic indicator of poor survival among patients with resected NSCLC, although its prognostic significance still requires confirmation with larger patient populations.

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