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ORIGINAL ARTICLE

Loss of phosphatase and tensin homolog expression correlates with clinicopathological features of non-small cell lung cancer patients and its impact on survival: A systematic review and meta-analysis

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Meta-analysis; non-small cell lung cancer; phosphatase and tensin homolog; prognosis.

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Abstract

Background: Phosphatase and tensin homolog (*PTEN*), regarded as a tumor suppressor gene, may act as a prognostic biomarker in human cancers.

Methods: All eligible studies from MEDLINE, Embase, CENTRAL, and the Chinese BioMedical Literature Database to October 2016 were incorporated. Two reviewers independently screened the literature according to inclusion and exclusion criteria, extracted the data, assessed the methodological quality of the included studies, and conducted meta-analysis.

Results: A total of 2486 patients from 19 studies were included. PTEN expression was significantly correlated with gender, smoking history, histology (adenocarcinoma [ADC] vs. squamous cell carcinoma), tumor node metastasis stage (I–II vs. III–IV), N status (N0 vs. N1–N3), and distant metastasis (M0 vs. M1). Loss of PTEN expression was associated with poorer overall survival, but had no significant association with disease-free survival. Subgroup analysis showed that negative PTEN expression was associated with a poorer outcome in Asian and ADC patients, but not in Western or squamous cell carcinoma patients.

Conclusion: Loss of PTEN might play an unfavorable prognostic role for overall survival of non-small cell lung cancer patients, especially Asian or ADC patients.

Introduction

Lung cancer is the main cause of cancer-related death around the world, with about 1.4 million deaths worldwide each year. Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancer cases.[1] Although some advances have been achieved in treatments, lung cancer has an extremely poor prognosis, with a five-year overall survival (OS) of 16% in the United States and less than 10% in the United Kingdom.[2] Alone or in combination, the prognostic factors are variable measured indicators of individual patients, which may explain part of the population heterogeneity and provide information on clinical outcomes at the time of diagnosis. The tumor node metastasis (TNM) stage is thought to have an effect on survival in NSCLC patients; however, problems such as similar prognoses for patients with different tumor stages and varied prognoses for patients with the same tumor stage have been indicated. Recent research has revealed that some biological markers may have an impact on survival in NSCLC patients.[3–5]

Phosphatase and tensin homolog (*PTEN*), also known as mutated in multiple advanced cancer 1 (MMAC1) or TGF-βregulated and epithelial cell-enriched phosphatase 1 (TEP1), is a 47 kDa dual specific protein-phospholipid phosphatase, which was first identified as a tumor suppressor gene located at chromosome 10q23.3 by three separate groups of investigators in 1997.[6–8] *PTEN* is an important negative regulator of the protein kinase B/phosphatidylinositol 3-kinase (PI3K) pathway, which is one of the most important pathways for cell growth, proliferation, and survival, by dephosphorylating phosphatidylinositol 3,4,5-triphosphate (PIP3) at its D3 position.[9–12] It has also been suggested that *PTEN* regulates focal adhesion structure and

cell invasion and migration by controlling focal adhesion kinase (FAK) activity.[13,14] In addition, *PTEN* can restrict cellular differentiation by decreasing the activation of mitogen-activated protein kinase (MAPK).[15,16] *PTEN* may also inhibit angiogenesis by downregulating both hypoxia-inducible factor-1 alpha (HIF-1 alpha) and vascular endothelial growth factor (VEGF) in tumor cells.[17,18] Recently, many studies have indicated that *PTEN* is related to survival in patients with malignant tumors, including esophageal squamous cell carcinoma,[19] acute myeloid leukemia,[20] and breast,[21] prostate,[22] and gastric cancers.[23] However, the results relating to the prognostic role of PTEN expression in NSCLC are inconsistent among clinical studies; therefore, a systematic review and meta-analysis based on the published literature is necessary to provide further insights into this conflicting issue.

The aim of our study was to identify the prognostic value of PTEN expression in NSCLC patients. We also investigated the correlation between PTEN expression and clinicopathological characteristics.

Methods

This systematic review and meta-analysis was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement protocol.[24]

Search strategy

We searched MEDLINE (via PubMed), Embase (via OVID), CENTRAL (via the Cochrane Library), and the Chinese BioMedical Literature Database (CBM) to October 2016 to identify studies relevant to this review. Our search strategy included the following subject headings and/or keywords variably combined by "lung neoplasm," "PTEN," and "prognosis." The detailed PubMed search strategy is shown in Figure 1. In addition, reference lists of the articles initially detected were searched manually to identify additional relevant reports. The eligibility of references retrieved by the search was assessed independently by two of the authors, and the review authors resolved differences of opinion by discussion or by appeal to a third review author when necessary. The full text of the remaining articles, including the references, was examined to determine whether the articles contained relevant information.

Inclusion and exclusion criteria

Studies were considered eligible if they met all of the following inclusion criteria: (i) the study population consisted of primary NSCLC patients; (ii) PTEN expression was evaluated in primary lung carcinoma tissues by immunohistochemistry (IHC), reverse-transcriptase (RT)-PCR, or fluorescence in situ hybridization (FISH); and (iii) the association between PTEN expression and OS and disease-free survival (DFS) were measured and/or the associations of PTEN expression and clinical characteristics was reported. Studies were excluded based on any of the following criteria: (i) reviews, letters, laboratory research, and animal experiments were excluded; (ii) the language was not English or Chinese; or (iii) the study lacked critical data for hazard ratio (HR) analysis.

Search strategy of PubMed

#1	lung carcinoma* [Title/Abstract]
#2	lung cancer* [Title/Abstract]
#3	lung tumo* [Title/Abstract]
#4	lung neoplasm* [Title/Abstract]
#5	lung neoplasms [MeSH Terms]
#6	#1 or #2 or #3 or #4 or #5
#7	PTEN [Title/Abstract]
#8	phosphatase and tensin homolog [Title/Abstract]
#9	#7 or #8
#10	prognosis [MeSH Terms]
#11	prognos* [Title/Abstract]
#12	outcome [Title/Abstract]
#13	#10 or #11 or #12
#14	#6 and #9 and #13

Figure 1 PubMed search strategy. PTEN, phosphatase and tensin homolog.

Quality assessment

Quality assessment of individual studies was performed independently by two of the authors, using the Newcastle–Ottawa Scale (NOS) for cohort studies. The scale allocates stars (maximum of 9) for quality of selection, comparability, and outcome of study participants.[25] NOS scores of >6 were defined as high-quality studies. Any discrepancies were addressed by joint reevaluation of the original article.

Data extraction

Data were extracted from the selected studies independently by two of the authors, using a predefined standardized form and disagreements were resolved by discussion between two review authors or by appealing to a third review author. The original data included PTEN expression, Kaplan–Meier (K–M) survival curves, or HR and 95% confidence interval (CI) of survival outcomes. Multivariate Cox hazard regression analysis data was our priority, but if not obtained, univariate Cox hazard regression analysis or K–M survival curves with log-rank *P* value of survival outcomes were used instead. Because HRs were not available in all of the included studies, we calculated

the HR with 95% CI using survival rates, enrolled samples, and corresponding *P* values from log-rank test in accordance with the described instructions. The relevant formulas are as follows:

$$O-E=\frac{\sqrt{Total\ \ observed\ \ events\times Analyzed\ \ research\times Analyzed\ \ control}}{(\text{Analyzed research}+\text{Analyzed control})}\times(\text{Z score for } P \text{ value}/2)$$

$$V=\frac{\text{Total observed events}\times\text{Analyzed research}\times\text{Analyzed control}}{(\text{Analyzed research}+\text{Analyzed control})^2}$$

$$HR=\text{Exp}\left(-\frac{O-E}{V}\right)$$

where O – E is the log rank Observed minus Expected events and V is the log rank Variance.[26] We then extracted the associated details by Engauge Digitizer 4.1 (http://sourceforge.net) from the K-M curves to measure the accuracy of estimated HRs. We extracted basic characteristics, including first author (year), primary treatment, country, study period, study design, number of patients, number of patients with evaluated PTEN expression and/or survival data, stage, method, cut-off/scoring categories, antibody, median follow-up, patients' average age when diagnosed with lung cancer, histology, and attitude conclusion from eligible articles.

Statistical analysis

The log HR was chosen as the appropriate summary statistic because it was the only summary statistic that allowed for both censoring and time to an event.[27] However, these relevant statistical variables were not explicitly provided in most studies; therefore, we extracted associated data from K–M survival curves. We carried out meta-analysis on PTEN expression in NSCLC cells for OS and DFS. We also analyzed correlations between PTEN expression and clinical characteristics, including age, gender, grade, smoking history, histology, primary tumor (pT) stage, TNM stage, lymph node metastasis, and other characteristics. According to clinical characteristics, stages I and II, stages III and IV, T2, T3, and T4 were combined, while well-differentiated (G1) and moderately differentiated (G2) were combined and poorly differentiated (G3) was separated. Their correlations were described by odds ratio (OR). The effects of PTEN expression on survival outcome (OS/DFS) and correlations between PTEN expression and clinical characteristics were estimated by forest plots. Heterogeneity was defined as $P < 0.10$ or $I^2 > 50\%$. When homogeneity was good ($P > 0.10$, $I^2 < 50\%$), a fixed effect model was used to combine effective sizes, otherwise a random effect model was used. Subgroup analyses were performed to investigate the potential causes of heterogeneity according to region, sample size, follow-up period, test methods, and NOS scores. Meta-regression was also used to identify the source of heterogeneity. An observed HR > 1 indicated a worse outcome for the positive group compared with the negative group and was considered significant if the 95% CI did not overlap 1. The potential publication bias was evaluated by Begg's rank correlation and Egger's test, with $P > 0.05$ indicating no potential publication bias.[28] Meta-analysis and publication biases were both performed by STATA 13.0 (STATA Corporation, College Station, TX, USA).

Results

Reference retrieval

After primary retrieval, a total of 231 potentially relevant studies were initially incorporated into our study, including 121 from MEDLINE, 89 from Embase, 17 from CBM, 1 from CENTRAL, and 3 from reference lists. Forty were excluded as duplicates and 151 were excluded by title/abstract screening. Full texts were retrieved for the remaining 40 studies. Nineteen retrospective trials finally met all of the criteria for inclusion in the analysis, which included 3071 patients with a median number of 161.6 patients per study (Fig 2).

Characteristics and qualities of the included studies

The clinical characteristics of the patients are listed in Table 1. All of the studies were published after 2005. Only one study was a multinational study undertaken in 30 different countries, while the other 18 studies were single-center studies (14 in Asian countries and 4 in Western countries).[39] NSCLC trials included either all histological subtypes[29–33,35–41,43–47] ($n = 17$), or adenocarcinoma (ADC) ($n = 2$).[34,42] Data related to local advanced disease (stages I–III) comprised three of the 19 NSCLC trials,[32,36,42] while

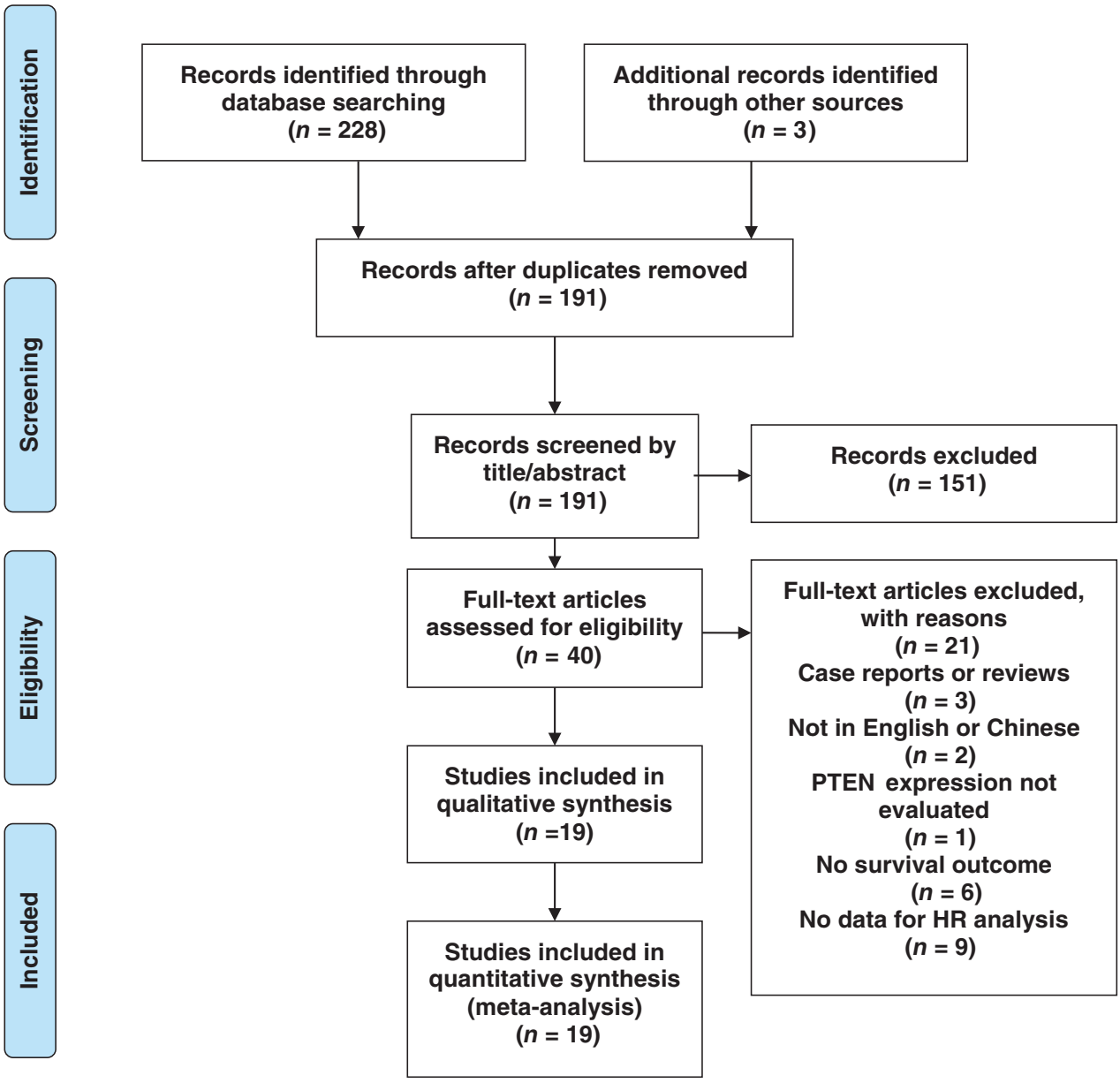

Figure 2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for selection of studies. HR, hazard ratio; PTEN, phosphatase and tensin homolog.

13 studies dealt with any stage (I–IV).[29,31,33–35,37,38,40,41,43,44,46,47] Shin *et al.* assessed local early disease stage (I).[30] O'Byrne *et al.* only involved patients with stages III–IV disease and the patients were separated into to two groups according to different treatments (chemotherapy and chemotherapy + cetuximab).[39] In Lim *et al.*'s study, patients were divided into two groups on the basis of different stage and treatment (stage I treated with surgery and stage IV treated with gefitinib).[45]

Quality assessments of individual studies are shown in Table S1. We used the NOS for cohort studies to assess included studies, which included three aspects (selection, comparability, and outcome) and eight items. All studies scored either six or seven.

Correlation between phosphatase and tensin homolog (PTEN) expression and clinicopathological characteristics

The studies that referred to a correlation between PTEN expression and clinical characteristics were gathered to evaluate the combined ORs. We found that PTEN

Table 1 Baseline characteristics of included studies

Study (year)	Country	Study period	Study design	NOS	N	n	Primary treatment	Stage	Histology			Method	Cut-off/ scoring categories	Antibody	Follow-up (months)	Age (years)	Survival Outcome	Attitude
									ADC	SCC	Other							
Wang *et al.* 2015[29]	China	2004–2010	ROS	7	92	92	Surgery	I–IV	52	34	6	IHC	Scoring = 2	Monoclonal, mouse anti-human PTEN	28	23–83	OS	Positive
Shin *et al.* 2015[30]	Korea	2000–2005	ROS	6	408	250	Surgery	I	250	158	-	IHC	Scoring = 1	NR	NR	62.1	OS	Positive
Li *et al.* 2015[31]	China	2004–2006	ROS	6	68	68	Surgery	I–IV	32	36	-	IHC	74%	Monoclonal, rabbit anti-human PTEN	15.8	64	OS	Positive
Ji *et al.* 2014[32]	China	2007–2008	ROS	6	67	67	Surgery	I–III	31	28	8	IHC	5%	Monoclonal, mouse anti-human PTEN	NR	39–80	OS	Positive
Yoo.*et al.* 2013[33]	Korea	2003–2009	ROS	6	41	41	Surgery	I-IV	36	2	3	IHC	50%	NR	NR	59	DFS	Positive
Yanagawa *et al.* 2012[34]	Canada	2005–2009	ROS	6	152	152	Surgery	I–IV	94	44	14	IHC	0%	Monoclonal, rabbit anti-human PTEN	28.6	66.9	DFS	Positive
Wang *et al.* 2012[35]	China	2006–2007	ROS	6	78	78	Surgery	I–IV	34	44	–	IHC	Scoring = 2	Polyclonal, rabbit anti-human PTEN	NR	NR	DFS	Positive
Kim *et al.* 2012[36]	Korea	NR	ROS	7	245	245	Surgery	I–III	154	91	–	IHC	Scoring = 2	Monoclonal, rabbit anti-human PTEN	39	64	OS	Negative
Hu *et al.* 2012[37]	China	2006–2007	ROS	6	114	114	Surgery	I–IV	74	40		IHC	50%	Monoclonal, rabbit anti-human PTEN	40.1	NR	OS	Positive
An *et al.* 2012[38]	China	2004–2006	ROS	6	98	98	Surgery	I–IV	62	24	12	IHC	Scoring = 0	Monoclonal, rabbit anti-human PTEN	53.9	56.7	OS	Positive
O'Byrne *et al.* 2011†[39]	Multi-Center	2004–2006	ROS	7	155	155	CT	III-IV	69	52	27	FISH	–	–	NR	NR	OS,DFS	Negative
O'Byrne *et al.* 2011‡[39]	Multi-Center	2004–2006	ROS	7	148	148	CT+ Cet	III–IV	63	59	33	FISH	–	–	NR	NR	OS,DFS	Negative
Zolota *et al.* 2010[40]	Greece	2000–2006	ROS	7	128	46	Surgery	I–IV	64	46	–	IHC	50%	NR	23	63	OS	Negative
Yoshizawa *et al.* 2010[41]	USA	NR	ROS	6	300	252	Surgery	I–IV	135	132	–	IHC	Scoring = 2	Monoclonal, rabbit anti-human PTEN	40.8	64.5	OS	Negative
Wang *et al.* 2009[42]	China	NR	ROS	6	249	249	Surgery	I–III	249	–	–	IHC	5%	Monoclonal, rabbit anti-human PTEN	NR	59.4	OS	Positive
Regina *et al.* 2009[43]	France	2002–2005	ROS	6	53	49	Surgery	I–IV	32	13	8	PCR	–	-	35	66	OS	Negative
Zheng *et al.* 2007[44]	Japan	1993–2006	ROS	7	155	143	Surgery	I–IV	86	37	32	IHC	5%	Monoclonal, mouse anti-human PTEN	20.6	69.5	OS	Positive
Lim *et al.* 2007 I[45]	Singapore	1998–2000	ROS	6	69	34	Surgery	I	13	20	1	IHC	Scoring = 2	Polyclonal, rabbit anti-human PTEN	NR	67	/	/
Lim *et al.* 2007 IV[45]	Singapore	2000–2004	ROS	6	270	25	Gefitinib	IV	9	10	6	IHC	Scoring = 2	Polyclonal, rabbit anti-human PTEN	NR	67	OS,DFS	Positive
Tang *et al.* 2006[46]	China	1997–1998	ROS	7	102	102	Surgery	I–IV	51	51	–	IHC	Scoring = 2	Monoclonal, mouse anti-human PTEN	NR	59	OS	Positive
Endoh *et al.* 2006[47]	Japan	2002–2004	ROS	6	79	78	Surgery + Gefitinib	I–IV	68	6	4	PCR	–	–	NR	61.9	OS	Negative

†Patients treated with chemotherapy. ‡Patients treated with chemotherapy + cetuximab. ADC, adenocarcinoma; Cet, cetuximab; CT, chemotherapy; DFS, disease-free survival; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; N, number of patients included in the study; n, number of tests of PTEN to analyze survival outcome; NR, no referred; NOS, Newcastle–Ottawa Scale; OS, overall survival; PTEN, phosphatase and tensin homolog; ROS, retrospective observational study; RT, reverse transcription; SCC, squamous cell carcinoma.

Table 2 Meta-analyses of PTEN expression classified by clinicopathological characteristics

Clinical characteristics	N	Patients	Heterogeneity (I-squared, *P*) (%)	Model	OR (95% CI)	*P*	Conclusion
Gender (male vs. female)	10	1628	13.0	Fixed	0.59 (0.47–0.75)	0.000	Significant
Age (> 60 vs. ≤ 60)	5	608	0.0	Fixed	0.90 (0.60–1.35)	0.619	Not significant
Smoking history (yes vs. no)	4	707	50.0	Fixed	2.22 (1.57–3.14)	0.000	Significant
Histology (ADC vs. SCC)	12	1763	63	Random	1.53 (1.03–2.29)	0.037	Significant
TNM stage (I–II vs. III–IV)	9	1220	70.9	Random	1.96 (1.13–3.40)	0.017	Significant
Grade (G3 vs. G1–G2)	7	880	73.6	Random	0.76 (0.37–1.57)	0.455	Not significant
pT stage (T1 vs. T2–T4)	5	816	51	Random	1.41 (0.79–2.49)	0.244	Not significant
N status (N0 vs. N1–N3)	8	963	69.7	Random	2.22 (1.31–3.76)	0.003	Significant
Distant metastasis (M0 vs. M1)	3	272	0.0	Fixed	6.47 (2.19–19.14)	0.001	Significant
Vascular invasion (yes vs. no)	1	155	–	–	0.27 (0.10–0.68)	0.001	Significant
Pleural involvement (yes vs. no)	1	155	–	–	3.60 (1.36–9.55)	0.001	Significant

ADC, adenocarcinoma; CI, confidence interval; N, reference count; N status, lymph node metastasis status; OR, odds ratio; pT, primary tumor; PTEN, phosphatase and tensin homolog; SCC, squamous cell carcinoma; TNM, tumor node metastasis; –, no data.

expression was significantly correlated with gender (male vs. female: OR 0.59, 95% CI 0.47–0.75; $P = 0.000$), smoking history (yes vs. no: OR 2.22, 95% CI 1.57–3.14; $P = 0.000$), histology (ADC vs. squamous cell carcinoma [SCC]: OR 1.53, 95% CI 1.03–2.29; $P = 0.037$), TNM stage (I–II vs. III–IV: OR 1.96, 95% CI 1.13–3.40; $P = 0.017$), N status (N0 vs. N1–N3: OR 2.22, 95% CI 1.31–3.76; $P = 0.003$), and distant metastasis (M0 vs. M1: OR 6.47, 95% CI 2.19–19.14; $P = 0.001$) (Table 2).

Correlation between PTEN expression and survival outcomes

All articles, including 2486 patients, listed the relationship between PTEN expression and survival outcome in NSCLC.[29–47] The combined HR was 0.51 (95% CI 0.42–0.62; $P = 0.000$, $I^2 = 59.5\%$) for OS in 16 studies (Fig 3),[29–32,36–47] but was 0.82 (95% CI 0.26–2.60; $P = 0.733$, $I^2 = 84.7\%$) for DFS in three studies (Fig 4; Table 3).[33–35] Negative PTEN expression was a predictor of poor OS (but not DFS) in NSCLC patients. We also conducted subgroup analysis according to region, sample size, follow-up period, test methods, and NOS scores (Table 4). Interestingly, we found that the patients with positive PTEN tended to have favorable OS in Asian countries (HR 0.46, 95% CI 0.40–0.53; $P = 0.027$) compared with Western countries (HR 0.82, 95% CI 0.52–1.30; $P = 0.319$). Four trials for ADC and three for SCC were assessable for OS (Fig 3, Table 3). The combined HR for OS in ADC (95% CI) was 0.61 (0.44, 0.85; $I^2 = 0.0\%$, $P = 0.003$); however, the combined HR for OS in SCC (95% CI) was 0.78 (0.54, 1.12; $I^2 = 40.7\%$, $P = 0.178$). Moderate heterogeneity was found in the meta-analysis for HR (OS) of the prognostic role of PTEN expression. Univariable meta-regression was used to identify the source of heterogeneity, and we found that different regions (Asian vs. Western countries) could explain 53.1% of the heterogeneity ($P = 0.039$), which is consistent with the earlier result in OS subgroup analysis. However, published year ($P = 0.942$), NOS score ($P = 0.506$), and TNM stage ($P = 0.388$) could not explain the heterogeneity.

Assessment of publication bias

Publication bias is a major concern for all forms of meta-analyses, because positive results tend to be accepted by journals while negative results are often rejected or are not even submitted. Two methods, including Begg's funnel plot and Egger's test, were used to evaluate publication bias of the meta-analysis. No publication bias of the prognostic value of PTEN for OS in NSCLC was discovered (Fig 5). Both the Begg's test ($P = 0.112$) and the Egger's test ($P = 0.272$) found little publication bias. Although little publication bias was detected in our study, we caution the poor sensitivity of Begg's and Egger's tests when the number of eligible articles is fewer than 20.

Discussion

Phosphatase and tensin homolog, regarded as a tumor suppressor gene, regulates many cellular processes, including proliferation, survival, energy metabolism, cellular architecture, and motility.[48] PTEN inactivation is frequently found in many tumors, including lung, endometrial, bladder, renal, and breast cancers.[49] We found that PTEN expression was markedly lower in patients with certain clinicopathological characteristics, including men, SCC (vs. ADC), late N status (N1–N3), distant metastasis, and late TNM stage (stage III–IV), which implied that a loss of PTEN expression tended occur in late NSCLC stage and indicated a poor prognosis. No association was found between PTEN expression and age, grade, or primary tumor stage.

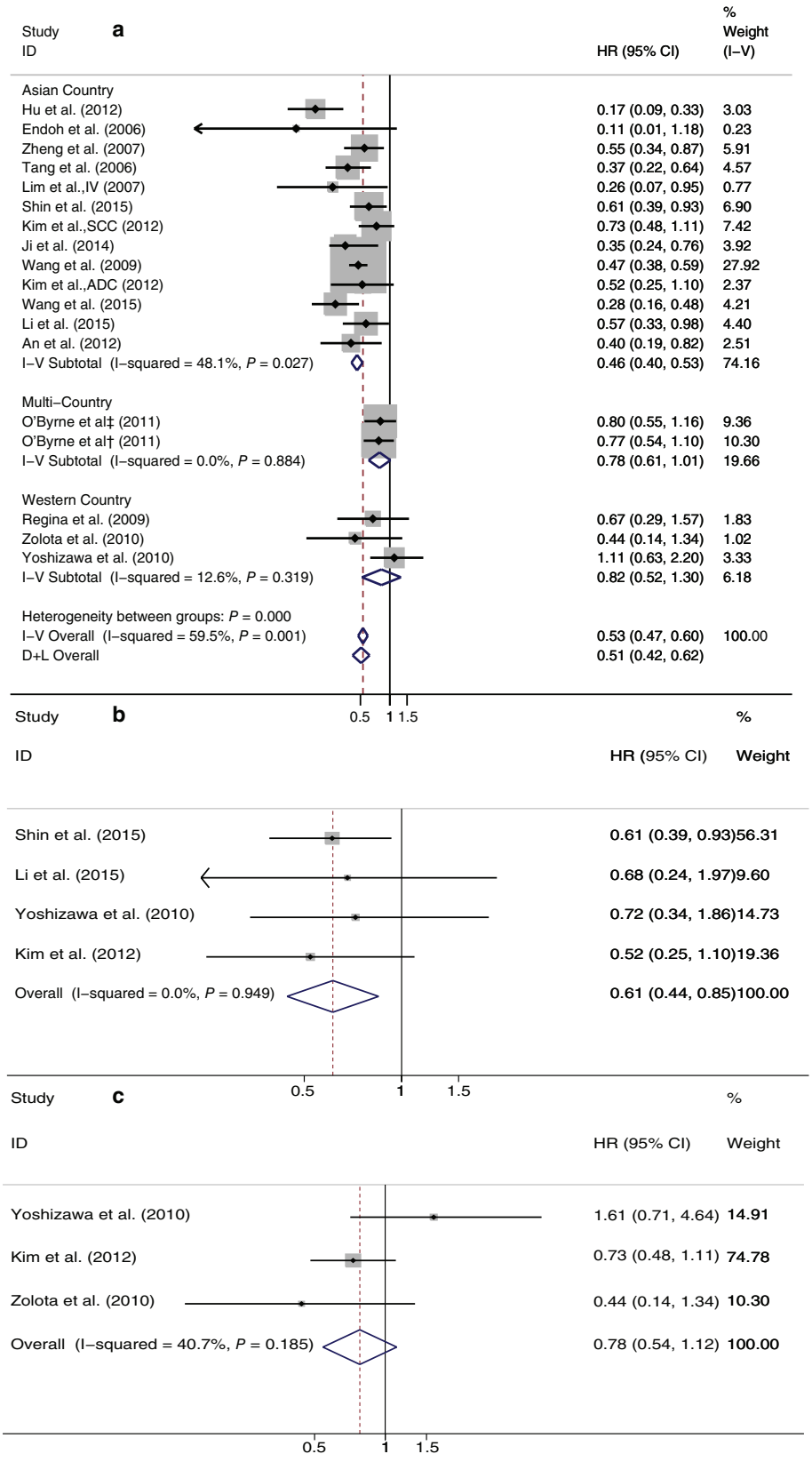

Figure 3 Pooled hazard ratios (HRs) for assessing the prognostic value of phosphatase and tensin homolog expression for overall survival in (**a**) non-small cell lung cancer, (**b**) adenocarcinoma, and (**c**) squamous cell carcinoma. †Patients treated with chemotherapy; ‡patients treated with chemotherapy + cetuximab. CI, confidence interval; D+L, DerSimonian & Laird; I–V, inverse variance.

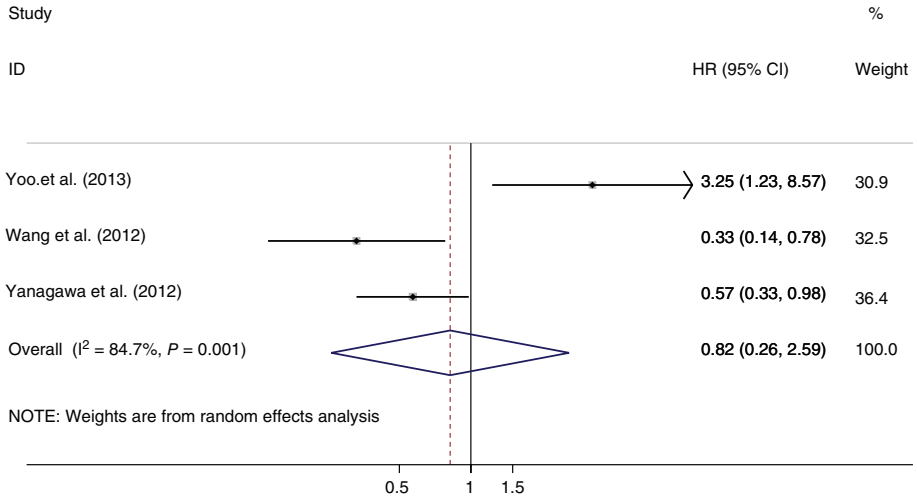

Figure 4 Pooled hazard ratios (HRs) for assessing the prognostic value of PTEN expression for DFS in surgical patients.

Table 3 Meta-analyses of PTEN expression to predict survival outcome in NSCLC patients

Tumor type	Outcome	N	Patients	Heterogeneity (I^2, *P*)	Model	HR (95% CI)	*P*	Conclusion
NSCLC	OS	16	2181	59.5%, 0.001	Random	0.53 (0.47,0.60)	0.000	Positive
	DFS	3	271	84.7%, 0.001	Random	0.82 (0.26,2.60)	0.733	Negative
ADC	OS	4	504	0.0%, 0.949	Fixed	0.61 (0.44,0.85)	0.003	Positive
SCC	OS	3	321	40.7%, 0.185	Fixed	0.78 (0.54,1.12)	0.178	Negative

ADC, adenocarcinoma; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; NSCLC, non-small cell lung cancer; N, reference count, OS, overall survival; PTEN, phosphatase and tensin homolog; SCC, squamous cell carcinoma.

In the present meta-analysis, we combined 19 published studies including 2486 patients with NSCLC to yield summary statistics, which indicate that negative expression of PTEN has a significant correlation with poorer OS in NSCLC; however, it is not an unfavorable prognostic factor for DFS in NSCLC patients. In subgroup analysis, we found that loss of PTEN expression only predicted adverse clinical outcomes in ADC patients. Interestingly, when we investigated survival by different regions, the poorer OS associated with PTEN loss was only observed in Asian

Table 4 Subgroup analyses of the relationships between PTEN expression and overall survival

Comparison variables	Number of studies (I^2 statistics %)	HR (95% CI), *P*	Heterogeneity between sub-groups (*P*)
Total	16 (59.5%)	0.51 (0.42–0.62), 0.000	NA
Regions			0.000
Asian countries	12 (48.1%)	0.49 (0.40–0.53), 0.000	
Western countries	3 (12.6%)	0.82 (0.52–1.30), 0.399	
Multi-countries	1 (NA)	0.78 (0.61–1.01), 0.064	
Sample size			0.017
>100	8 (69.7%)	0.57 (0.50–0.64), 0.000	
≤100	8 (0.0%)	0.40 (0.31–0.52), 0.000	
Follow-up period			0.565
Referred	7 (74.3%)	0.56 (0.46–0.67), 0.000	
Not referred	9 (37.6%)	0.52 (0.45–0.60), 0.000	
Test method			0.001
IHC	13 (55%)	0.48 (0.42–0.55), 0.000	
Others	3 (0%)	0.76 (0.59–0.97), 0.027	
NOS score			0.053
≤6	10 (59.2%)	0.48 (0.41–0.56), 0.000	
>6	6 (56.6%)	0.60 (0.51–0.71), 0.000	

CI, confidence interval; HR, hazard ratio; ICH, immunohistochemistry; NA, not applicable; NOS, Newcastle–Ottawa Scale; PTEN, phosphatase and tensin homolog.

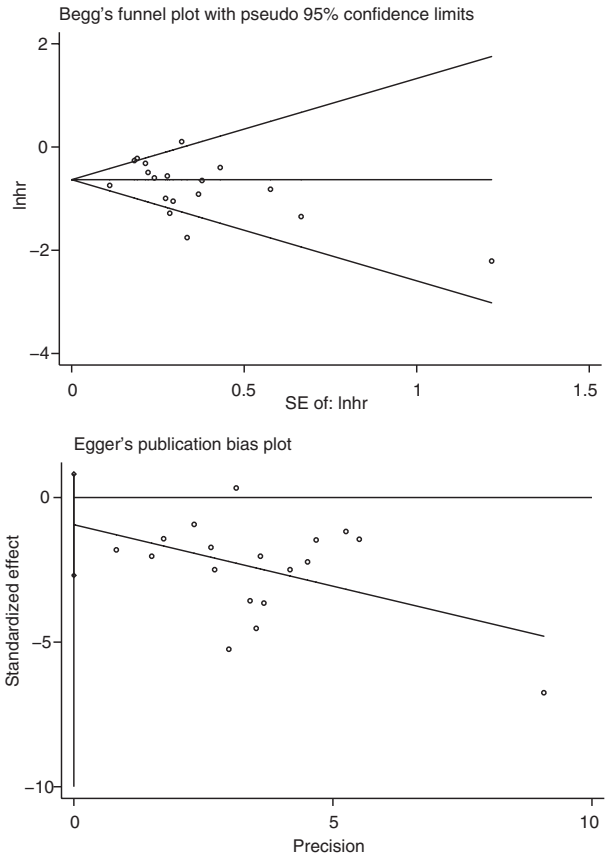

Figure 5 Publication bias of the prognostic value of phosphatase and tensin homolog for overall survival in non-small cell lung cancer on Begg's and Egger's plots. SE, standard error.

patients. Thus, our results suggest that loss of PTEN expression was a more appropriate prognostic marker for ADC or Asian patients than for SCC or Western patients. However, further studies are required to address this issue.

Our study has several limitations. First, the findings of a meta-analysis depend on the quality of the individual studies, as their potential problems and biases may affect the pooled data. According to the NOS quality assessment performed, 10 of the 16 involved studies scored six, and the other six scored seven, which indicated moderate quality of all of the studies. Second, the method of HR extrapolation is potentially biased. If the authors did not report the required statistics, we calculated them from the data available in the article; if this was not possible, we extrapolated them from the survival curves; therefore some subjective data may affect the final conclusion. Third, we did not search unpublished and grey literature databases, which may lead to potential publication bias. Furthermore, there is also a language bias, as we only screened English and Chinese literature.

In conclusion, this meta-analysis implied that a loss of PTEN expression, which is associated with gender, smoking history, histology, TNM stage, N status, and distant metastasis, might play an unfavorable prognostic role for overall survival in NSCLC patients, especially Asian or ADC patients. However, there is moderate heterogeneity between the studies and further rigorous and high-quality investigation of the effectiveness of PTEN as a therapeutic target for NSCLC is warranted.

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Disclosure

No authors report any conflict of interest.

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Supporting Information

Additional Supporting Informationmay be found in the online version of this article at the publisher's website:

Table S1 Quality assessment of individual studies using the Newcastle-Ottawa Scale for cohort studies

