Prognostic value of TTF-1 expression in patients with non-small cell lung cancer: a meta-analysis

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Background: Observational studies on the prognostic role of thyroid transcription factor 1 (TTF-1) in non-small cell lung cancer (NSCLC) are controversial.

Methods: To clarify the impact of TTF-1 in NSCLC survival, we performed this meta-analysis that included eligible studies. The combined hazard ratios and their corresponding 95% confidence intervals were calculated in terms of overall survival.

Results: A total of 17 studies with 2,235 patients were evaluable for this meta-analysis. The studies were categorized by histology, disease stage and patient race. Our results suggested that TTF-1 overexpression had a favorable impact on survival of patients with NSCLC, the HR (95% CI) was 0.49 (0.42 to 0.55) overall, 0.46 (0.38-0.54) in Asian patients, 0.52 (0.42-0.63) in non-Asian patients, 0.45 (0.38-0.52) in adenocarcinoma, 0.63 (0.39-0.86) in stage I NSCLC, 0.43 (0.33-0.53) in stage IIIb-IV NSCLC. The data collected were not sufficient to determine the prognostic value of VEGF in patients with squamous cell lung carcinomas. But there was a high heterogeneity between the studies.

Conclusions: TTF-1overexpression indicates a favorable prognosis for patients with NSCLC, this effect appears also significant when the analysis is restricted in lung AC patients, stage I and stage IIIb-IV NSCLC.

Key Words: Thyroid transcription factor 1; prognosis; lung cancer; meta-analysis

Introduction

Lung cancer remains the most lethal cancer worldwide, despite improvements in diagnostic and therapeutic techniques. Its incidence has not peaked in many parts of world, particularly in China, which has become a major public health challenge all the world (1). The prognosis for lung cancer patients is generally poor, with an overall 5 year survival rate of approximately 15%, and it has shown little improvement in recent decades (2,3). Several independent prognostic factors for survival have been identified: performance status (PS), disease stage, age, sex and amount of weight lost (4). Some of these factors are useful when

choosing treatment options for an individual, principally disease stage and PS. However, the discriminant value of most potential prognostic biological markers is insufficient to predict the optimal therapeutic course for an individual (5,6).

Thyroid transcription factor 1 (TTF-1), also known as Nkx2.1 or thyroid-specific enhancer-binding protein, is a 38-kDa nuclear protein encoded by a gene located on chromosome 14q13. TTF1 is a master regulatory transcription factor for tissue-specific genes (7). TTF-1 is expressed in the thyroid, the lung and the diencephalon during embryogenesis. In normal lung, TTF1 plays a decisive role in the maintenance of the functions of terminal respiratory unit cells, where

it regulates the expression of surfactant protein A (8), B (9), and C (10) and Clara cell secretory protein (11). Although the role of TTF1 as a lineage marker for terminal respiratory unit cells has been well documented (12), its role in carcinogenesis remains unclear.

The association between TTF-1 overexpression and survival in lung cancer patients has been studied for over a decade. However, no consensus has been reached; conflicting results have been reported from different laboratories. We therefore carried out a meta-analysis of data from published studies to quantitatively review the effect of TTF-1 overexpression in tumor tissue on survival in patients with non-small-cell lung cancer (NSCLC).

Materials and methods

Search strategy and study selection

The electronic databases PubMed, Embase, and CNKI (China National Knowledge Infrastructure) were searched for studies to include in our meta-analysis. An upper date limit of Jan 31, 2012 was applied; we used no lower date limit. Searches included the terms "lung cancer", "TTF-1", "thyroid transcription factor 1", and "prognosis". We also reviewed the Cochrane Library for relevant articles. The references reported in the identified studies were also used to complete the search.

Studies eligible for inclusion in this meta-analysis met the following criteria: (I) measure TTF-1 expression in the primary lung cancer tissue with IHC (immunohistochemistry) or other methods; (II) provide information on survival (studies investigating response rates only were excluded); (III) have a follow up time exceeding 5 years; and (IV) When the same author reported results obtained from the same patient population in more than one publication, only the most recent report, or the most complete one, was included in the analysis. Two reviewers (PZ and QQ) independently determined study eligibility. Disagreements were resolved by consensus.

Data extraction and quality assessment

The final articles included were assessed independently by two reviewers (PZ and QQ). Data retrieved from the reports included first author, publication year, patient source, histology, disease stage, test method, TTF-1 positive and survival data (*Table 1*). If data from any of the above categories were not reported in the primary study, items were treated as "not applicable". We did not contact the author of the primary study to request the information.

Statistical methods

For the quantitative aggregation of the survival results, hazard ratios (HR) and their 95% confidence intervals (CIs) were combined to give the effective value. When these statistical variables were not given explicitly in an article, they were calculated from available numerical data using methods reported by Parmar *et al.* (13).

Heterogeneity of the individual HRs was calculated with Chi-squared tests according to Peto's method (14). Meanwhile, Heterogeneity test with I^2 statistic and Q statistic was performed. All the studies included were categorized by patient race, histology, disease stage. Individual meta-analysis was conducted in each subgroup. If HRs were found to have fine homogeneity, a fixed effect model was used for secondary analysis; if not, a random-effect model was used. In this meta-analysis, DerSimonian-Laird random effects analysis (15) was used to estimate the effect of TTF-1 overexpression on survival. By convention, an observed HR >1 implies worse survival for the group with TTF-1 overexpression. The impact of TTF-1 on survival was considered to be statistically significant if the 95% confidence interval (CI) did not overlap with 1. Horizontal lines represent 95% CIs. Each box represents the HR point estimate, and its area is proportional to the weight of the study. The diamond (and broken line) represents the overall summary estimate, with CI represented by its width. The unbroken vertical line is set at the null value (HR =1.0).

Evidence of publication bias was sought using the methods of Egger *et al.* (16) and of Begg *et al.* (17). Moreover, contour-enhanced funnel plot (18) was performed to aid in interpreting the funnel plot. If studies appear to be missing in areas of low statistical significance, then it is possible that the asymmetry is due to publication bias. If studies appear to be missing in areas of high statistical significance, then publication bias is a less likely cause of the funnel asymmetry. Intercept significance was determined by the t-test suggested by Egger (P<0.05 was considered representative of statistically significant publication bias). All calculations were performed using STATA version 11.0 (Stata Corporation, College Station, TX).

Results

Study selection and characteristics

Seventeen studies (19-35) published between 1999 and 2012

Table 1 Main characteristics and results of the eligible studies

First author-year	Patients source	Histology	Stage	N pts	Method	Positive (%)	HR estimation	Survival results
Puglisi F-1999	Italy	NSCLC	I-III	88	IHC	38	Survival curves 1.58 (1.03-2.32)	Negative
Pelosi G-2001	Italy	AC	I	97	IHC	35	Survival curves 0.92 (0.32-1.73)	NS
Haque AK-2002	USA	NSCLC	I-III	57	IHC	46	Individual data 0.68 (0.30-1.38)	Positive
Tan D-2003	USA	NSCLC	I-III	126	IHC	45	HR and 95% CI 0.52 (0.32-0.92)	Positive
Myong NH-2003	Korea	NSCLC	I-III	65	IHC	35	Log-rank + n events 0.58 (0.28-1.09)	NS
Saad RS-2004	USA	AC	I	50	IHC	60	Survival curves 0.68 (0.33-1.01)	Positive
Shah L-2004	USA	NSCLC	I-III	63	IHC	59	HR and 95% CI 0.70 (0.32-1.5)	NS
Barlesi F-2005	France	AC	III-IV	106	IHC	66	Log-rank + n events 0.40 (0.25-0.65)	Positive
Wang CL-2007	China	BAC	I-III	81	IHC	80	HR and 95% CI 0.75 (0.58-0.98)	Positive
Anagnostou VK-2009	USA	AC	I-IV	98	IHC	73	HR and 95% CI 0.53 (0.26-1.05)	NS
			I	87	IHC	75	HR and 95% CI 0.48 (0.24-0.98)	Positive
Martins S-2009	Brazil	AC	IIIb-IV	51	IHC	40	HR and 95% CI 0.25 (0.11-0.57)	Positive
Anami Y-2009	Japan	BAC	I-III	70	IHC	16	Survival curves 0.26 (0.13-1.80)	
Hiramatsu M-2010	Japan	AC	I-IV	193	IHC	80	HR and 95% CI 0.24 (0.13-0.45)	Positive
Sun JM-2011	Korea	NSCLC nonSCC	IIIb-IV	284	IHC	68	HR and 95% CI 0.55 (0.39-0.77)	Positive
Solis LM-2012	USA	AC	I-IV	135	IHC	44	HR and 95% CI 0.70(0.51-1.04)	Positive
Li X-2012	Chian	AC	I-IV	175	IHC	33	Survival curves 0.41 (0.24-0.67)	Positive
Chung KP-2012	China	AC	IIIb-IV	496	IHC	89	HR and 95% CI 0.45 (0.30-0.67)	Positive

TTF-1, thyroid transcription factor 1; IHC, immunohistochemistry; NSCLC, non-small-cell lung cancer; AC, adenocarcinoma; Scc, squamous cell carcinoma; NS, not significant; HR, hazard ratio; N pts, number of patients

were eligible for this systematic review with meta-analysis. All reported the prognostic value of TTF-1 status for survival in NSCLC patients. The total number of patients included was 2,235, ranging from 57 to 496 patients per study (median 106). The major characteristics of the 17 eligible publications are reported in *Table 1*.

These publications followed several different patient cohorts. The NSCLC studies considered either all lung cancer subtypes (n=17) and adenocarcinomas (n=11). Three studies had information for stages I, 4 for stage IIIb-IV disease. All 17 studies used immunohistochemistry (IHC) to evaluate TTF-1 expression in NSCLC. Among the 17 studies evaluating TTF-1 expression in NSCLC, 7 studies (1,364 patients: 61%) were performed in Asian populations, and the remaining 10 studies (871 patients: 39%) followed European or American patients. Only one of the 17 studies identified TTF-1 overexpression as an indicator of poor prognosis, 4 studies showed no statistically significant impact of VEGF overexpression on survival, and the other 12 studies showed for favorable significance. The proportion of patients exhibiting TTF-1 overexpression in individual studies ranged from 16% to 89%.

Meta-analysis

The results of the meta-analysis are reported in *Table 2* and *Figure 1*. Overall, the combined HR for all eligible studies evaluated TTF-1 expression in NSCLC was 0.49 (95% CI: 0.42 to 0.55), indicating that TTF-1 overexpression was an indicator of favorable prognosis for NSCLC patients. However, highly significant heterogeneity was detected among these studies (I^2=59.4%, P=0.001). When grouped according to the geographic settings of individual studies, the combined HRs of Asian studies and non-Asian studies were 0.46 (95% CI: 0.38-0.54) and 1.61 (95% CI: 1.49-1.73), respectively (*Figure 1*).

The data extracted were adequate to aggregate the studies of stage I, stage IIIb-IV NSCLC, adenocarcinoma for subgroup analyses. When we aggregated eleven studies that reported results for adenocarcinoma, the combined HR was statistically significant: HR 0.45 (95% CI: 0.38-0.52, I^2=61.2%, P=0.004 for heterogeneity) (*Figure 2*).

Table 2 Meta-analysis: HR value in lung cancer subgroups according to histology and stage

	Nb	Patients	Combined HR (95% CI)	χ^2 heterogeneity test (P)
Overall	17	2235	0.49 (0.42-0.55)	0.001
Asian	7	1364	0.46 (0.38-0.54)	0.009
Non-Asian	10	871	0.52 (0.42-0.63)	0.010
Adenocarcinoma	11	1552	0.45 (0.38-0.52)	0.004
Stage I	3	234	0.63 (0.39-0.86)	0.506
Stage IIIb-IV	4	937	0.43 (0.33-0.53)	0.260
Abbreviations: HR, hazard ratio; Nb, number of studies; CIs, confidence intervals				
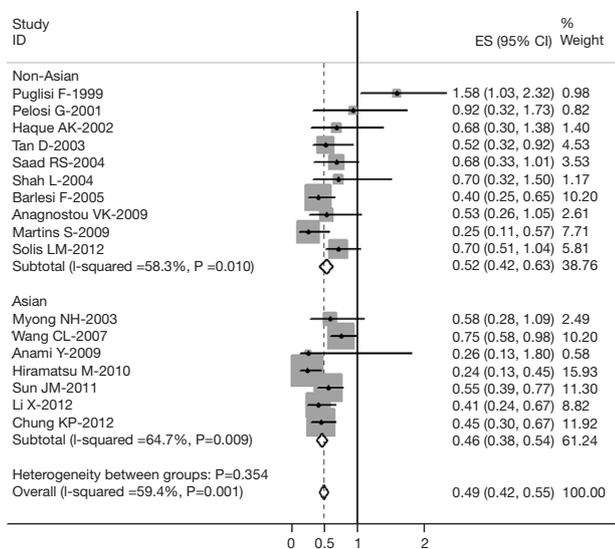
Figure 1 Meta-analysis (Forest plot) of the 17 evaluable studies assessing TTF-1 in NSCLC stratified by ethnic source
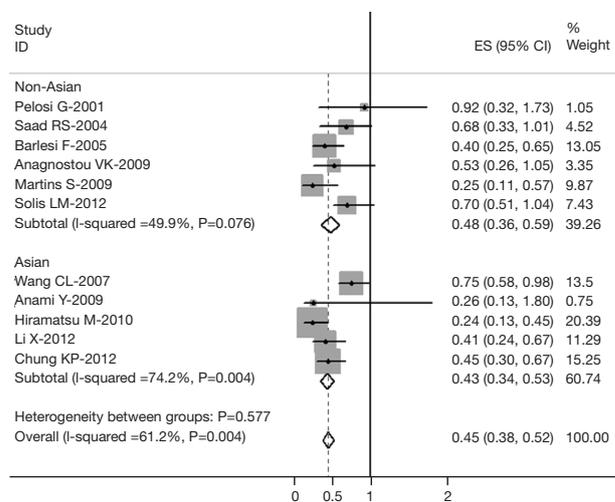
Figure 2 Meta-analysis (Forest plot) of the evaluable studies assessing TTF-1 in lung adenocarcinoma stratified by ethnic source
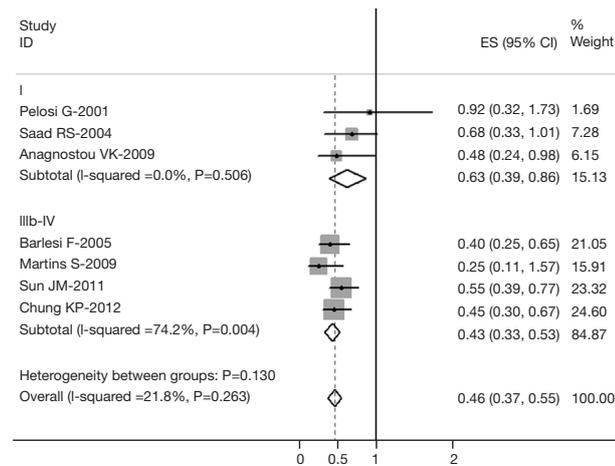
**Figure 3** Meta-analysis (Forest plot) of the evaluable studies assessing TTF-1 in lung stage I and IIIb-IV disease

We also observed a statistically significant effect of TTF-1 expression on survival in stage I patients with an HR of 0.63 (95% CI: 0.39-0.86, I^2=0%, P=0.506 for heterogeneity) (*Figure 3*) and in stage IIIb-IV patients with an HR of 0.43 (95% CI: 0.33-0.53, I^2=25.3%, P=0.260 for heterogeneity) (*Figure 3*). There were not adequate data to aggregate studies of stage II or III NSCLC.

Publication bias

Begg's funnel plot and Egger's test were performed to assess the publication bias in the literature. All 17 eligible studies investigating NSCLC patients yielded a Begg's test score of P=0.154 and an Egger's test score of P=0.126, meanwhile according to the contour-enhanced funnel plot (*Figure 4*), the absence of publication bias was found in all 17 studies. These results suggest that there is no publication bias at work.


Begg's funnel plot with pseudo 95% confidence limits
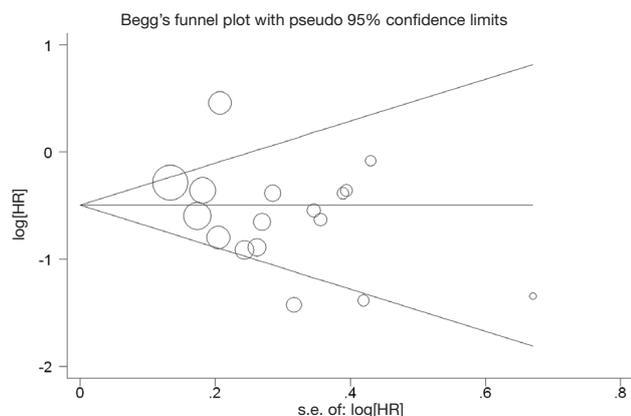
Figure 4 Funnel plot of the 17 evaluable studies assessing TTF-1 in NSCLC

Discussion

TTF-1 is a tissue-specific transcription factor expressed mainly in the epithelial cells of the lungs and thyroid. Identification and differential diagnosis of primary lung adenocarcinoma is sometimes difficult, and TTF-1 is most commonly used to distinguish primary lung adenocarcinoma from other sources that have metastasized to the lung (36). TTF-1 has also been a useful marker for differentiating primary lung adenocarcinoma from pleural mesothelioma (37). Positive TTF-1 staining by IHC has been described in as few as 25% to as many as 80% of primary adenocarcinomas, depending on the techniques used. However, the vast majority of squamous cell carcinomas and most extrapulmonary tumors (except for thyroid) lack TTF1 expression (38-40).

TTF-1 has been investigated as a potential prognostic indicator in NSCLC with conflicting results. Seventeen studies assessing the relationship between TTF-1 and survival have been published so far, only one (19) demonstrating a negative impact, four no impact of TTF-1 on survival (20,23,24,28), others positive impact. Pelosi *et al.* (20) showed that TTF-1 expression did not correlate with survival; however, a trend toward better outcome was observed for patients with tumors with more than 75% immunoreactive cells. However, Saad *et al.* (25) showed that moderate or strong TTF-1 expression was seen in 30 (60%) of 50 patients with conventional adenocarcinoma and was associated with significantly better survival compared with patients with weak or negative staining.

In the present meta-analysis, we have combined 17 published studies including 2,235 patients with NSCLC to yield summary statistics that indicate that TTF-1

overexpression has a significant correlation with favorable survival in NSCLC and AC patients. This correlation was observed in both Asian and non-Asian study populations. When analysis was restricted to stage I and stage IIIb-IV NSCLC, we observed a statistically significant effect of TTF-1 on favorable survival, suggesting that this good prognostic factor could be of importance not only in early-stage NSCLC but also in advanced staged NSCLC. Data were not sufficient to determine the prognostic value of VEGF expression in squamous cell carcinoma.

The effect of TTF-1 was more prominent in early and locally advanced disease (stages I-III) and in lung adenocarcinomas. The previous meta-analysis also observed that high TTF-1 protein expression is associated with better survival in NSCLC, mainly in early-stage NSCLC (41). The studies with early-stage NSCLC demonstrated that TTF1 can be a prognostic factor because most patients did not receive any adjuvant therapy, and subsequently survival was less likely to be affected by other treatments, as compared with surgical resection. In addition, 4 studies (26,30,32,35) of Stage IIIb-IV NSCLC included for our meta-analysis. When analysis was restricted to stage IIIb-IV NSCLC, we found that the combined HR (0.43) was lower than the combined HR (0.63) for studies of stages I NSCLC, suggesting that TTF-1 expression could be an important favorable prognostic factor for advanced-stage NSCLC.

Recently, several systematic reviews (42-50) with meta-analyses on other biological prognostic factors for NSCLC had been reported. P53, microvessel density, HER-2, Ki-67 and RAS might be poor prognostic factors for survival in NSCLC, however, Bcl-2 might be better prognostic factor for survival in NSCLC. In order to clarify the prognostic impact of other biological factors in lung cancer, our group has performed several systematic reviews of the literature with meta-analyses. We found that VEGF (51), E-cadherin (52) and matrix metalloproteinase 2 (53) might be poor prognostic factor in NSCLC, COX-2 (54) might be poor prognostic factor for stage I NSCLC, the ground glass opacity (GGO) area (55) had a favorable prognostic value of overall survival and relapse-free survival in small lung adenocarcinoma.

Our data were consistent with the results of a previous meta-analysis (41) published in 2006 that showed an association between TTF-1 overexpression and good survival of patients with NSCLC. This analysis included only 10 studies, and the data were insufficient to determine the prognostic value in lung adenocarcinoma, disease stage. In addition, that meta-analysis did not determine the combined HR for subgroups divided according to patient

ethnicity, histology, disease stage. We have improved upon that previous meta-analysis by including more recent related studies and by generally using a more comprehensive search strategy. Screening and study selection were performed independently and reproducibly by two reviewers. We also explored heterogeneity and potential publication bias in accordance with published guidelines.

This systematic review with meta-analysis was complicated by heterogeneity issues. We found highly significant heterogeneity among 17 studies of NSCLC. When the analysis was limited to 3 stage I studies of NSCLC and 4 studies of stage IIIb-IV NSCLC, but heterogeneity was detected. Therefore, disease stage was not a major source of heterogeneity.

Another potential source of bias is related to the method of HR and 95% CI extrapolation. If these statistics were not reported by the authors, we calculated them from the data available in the article. If this was not possible, we extrapolated them from the survival curves, necessarily making assumptions about the censoring process. Data for multivariate survival analysis reported in the article were included in the present systematic review with meta-analysis; if these data were not available, data calculated from survival curves by univariate analysis were included. These results should be confirmed by an adequately designed prospective study. Furthermore, the exact value of TTF-1 overexpression status needs to be determined by appropriate multivariate analysis. Unfortunately, few prospectively designed prognostic studies concerning biomarkers have been reported; thus, our collection of many retrospective studies revealed more significance.

Publication bias (56) is a major concern for all forms of meta-analysis; positive results tend to be accepted by journals, while negative results are often rejected or not even submitted. The present analysis does not support publication bias; the obtained summary statistics likely approximate the actual average. However, it should be noted that our meta-analysis could not completely exclude biases. For example, the study was restricted to papers published in English and Chinese, which probably introduced bias.

In conclusion, TTF-1 overexpression is associated with a favorable prognosis in patients with NSCLC in present meta-analysis, but there is a high heterogeneity between the studies. Interestingly, our meta-analysis suggests that TTF-1 is a favorable prognostic factor in stage I and stage IIIb-IV NSCLC and lung AC patients. These results should be confirmed by an adequately designed prospective study.

Acknowledgments

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.3978/j.issn.2218-676X.2013.02.08). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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