

Research Paper

Prognostic Impact of TTF-1 Expression in Non-Squamous Non-Small-Cell Lung Cancer: A Meta-Analysis

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Abstract

Thyroid transcription factor-1 (TTF-1) is overexpressed in up to 95% of primary lung adenocarcinoma while negative for almost all squamous cell carcinomas. TTF-1 expression has been investigated as a prognostic factor in non-small-cell lung cancer (NSCLC) with conflicting results. We conducted this meta-analysis to gain a better insight into the prognostic role of TTF-1 in patients only with non-squamous (non-SQ) NSCLC. A systematic computerized search of the electronic databases including PubMed, PMC, EMBASE, Web of Science, and Cochrane Library was performed. From 21 studies, 6,451 patients were included in the combined analysis of hazard ratios (HRs) with 95% confidence intervals (CIs) for overall survival. Compared with patients with non-SQ NSCLC showing negative TTF-1 expression, those with tumors harboring TTF-1 overexpression had significantly better survival (HR = 0.49, 95% CI: 0.42-0.57, $p < 0.00001$). Subgroup analyses revealed that TTF-1 expression significantly correlated with a better prognosis in stage I (HR = 0.65, 95% CI: 0.50-0.84, $p = 0.0008$) as well as stage III-IV non-SQ NSCLC (HR = 0.38, 95% CI: 0.29-0.49, $p < 0.00001$). In conclusion, this meta-analysis demonstrates that TTF-1 overexpression is a favorable prognostic factor in patients with non-SQ NSCLC. The subgroup analyses indicate that TTF-1 is a good prognostic marker for survival not only in early-stage but also in advanced non-SQ NSCLC.

Key words: TTF-1; prognosis, non-small-cell lung cancer; meta-analysis

Introduction

Lung cancer remains the leading cause of cancer-related death worldwide [1,2], despite recent advances in diagnostic and therapeutic techniques. For patients with advanced or metastatic non-small-cell lung cancer (NSCLC), systemic chemotherapy can provide a modest but significant improvement of survival [3]. Systemic treatment for NSCLC has dramatically progressed with the introduction of molecular targeted agents in the last 15 years. Recently immune checkpoint inhibitors have emerged as a promising option in the treatment of

advanced NSCLC [4].

Several clinical and disease-related factors have been suggested as independent prognostic factors for survival in NSCLC: performance status (PS), age, sex, weight loss, stage, histologic subtypes, and gene expression profiles [5,6]. For most of these factors, however, the discriminant value is insufficient to guide the optimal therapeutic strategy for an individual.

Thyroid transcription factor-1 (TTF-1) is a master regulatory transcription factor for tissue specific genes

[7]. TTF-1 is normally expressed in the thyroid, lung, and brain during embryogenesis and plays a physiologic role in their development. In the normal lung, TTF-1 plays a decisive role in the maintenance of the functions of terminal respiratory unit cells [8]. TTF-1 expression by immunohistochemistry (IHC) in primary lung cancers is dependent on the histological subtypes, as demonstrated by 70-80% of adenocarcinomas (ADCs) and 80-90% of small-cell carcinoma while negative for virtually all squamous cell carcinomas (SQCCs). TTF-1 is commonly used to distinguish primary lung ADC from tumors of other sources that have metastasized to the lung. However, its role in the lung carcinogenesis remains unclear. An animal study demonstrated that upregulation of TTF-1 correlated with favorable survival and downregulation was linked to loss of differentiation, enhanced tumor seeding ability, and increased metastatic potential [9].

Although the role of TTF-1 as a marker for ADC in the differential diagnosis of primary lung cancers has been well documented, its prognostic significance in patients with NSCLC has still been inconclusive [11-36]. While Puglisi *et al.* observed a detrimental effect of TTF-1 expression in resected NSCLC [11], the relationship between TTF-1 and survival was not found in other observational studies [12, 14, 16-19, 23, 27, 31, 32, 37]. However, others investigators reported that TTF-1 positivity was associated with a better prognosis [13, 15, 20-22, 25, 26, 28-30, 33-36, 38]. These discrepant results indicate that the prognostic significance of TTF-1 in NSCLC remains controversial.

The previous meta-analyses reported that TTF-1 expression correlated with a better survival in NSCLC [39,40]. Although TTF-1 IHC staining is negative for almost all SQCCs, however, they included patients with this histological subtype of NSCLC in the analysis. Therefore, their results could not reflect exactly the prognostic significance of TTF-1 in non-squamous (non-SQ) NSCLC. We performed this updated meta-analysis to gain a better insight into the prognostic role of TTF-1 expression in patients only with non-SQ NSCLC.

Materials and Methods

Publication searching strategy

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [41]. A systematic computerized search of the electronic databases including PubMed, PMC, EMBASE, Web of Science, and Cochrane Library (up to July 2018) was performed. The search used the following terms

variably combined: "thyroid transcription factor-1" or "TTF-1" AND "non-small-cell lung cancer" or "NSCLC" or "lung cancer". The related articles function in the PubMed was used to identify all relevant articles. The references reported in the identified studies were also reviewed to complete the search.

Inclusion criteria

Eligible studies should meet the following inclusion criteria: (i) patients with non-SQ NSCLC (ii) IHC test of TTF-1 expression in the primary lung cancer tissue; (iii) the use of adequate IHC methods for positive TTF-1 staining; (iv) prospective or retrospective cohort studies investigating the correlation of TTF-1 expression with overall survival (OS); (v) sufficient data for hazard ratio (HR) with 95% confidence intervals (CI) for OS; (vi) articles written only in English.

Data extraction

Two investigators (BJK and HSK) extracted independently the data from each eligible article. If these two authors did not agree, the principle investigator (JHK) was consulted to settle the dispute through discussion.

The following data were extracted from the included studies: the first author, year of publication, country, inclusion period, sample size, disease stage, histology, cut-off criteria of TTF-1 expression, and survival data. When there were both univariate and multivariate analysis for survival, the data were extracted from multivariate analysis. If data were not reported in the original article, items were treated as "not available." We did not contact the authors of the primary study to request additional data.

Statistical analysis

The survival outcomes were stratified according to the status of TTF-1 expression (negative vs. positive). Statistical values were obtained directly from the original articles. When papers had no HR and its 95% CI, the Engauge Digitizer software was used to estimate them from Kaplan-Meier curves. The RevMan version 5.3 was used to combine the data. For quantitative aggregation of the survival outcomes, HRs and their 95% CIs were combined to give the effective value. Subgroup analysis was performed according to the disease stage (I or III-IV). The heterogeneity across studies was estimated by the Q statistics and I^2 inconsistency test. The fixed-effect model (Mantel-Haenszel method) was used for pooling homogeneous outcomes ($p \geq 0.1$ and $I^2 \leq 50\%$), and the random-effects model (DerSimonian-Laird method) was selected when significant

heterogeneity was detected ($p < 0.1$ or $I^2 > 50\%$). The significance of the pooled HR and OR was determined by the Z-test, and an observed HR < 1.0 implies better survival for patients with positive TTF-1 staining.

The possibility of publication bias was assessed with visual inspection of the funnel plot [42]. For quantitative analyses, Egger's linear regression test was performed using the statistical software packages R (www.r-project.org) [43]. Statistical significance was considered for a p-value of less than 0.05 for summary HR and publication biases.

Results

Results of search

A total of 880 potentially relevant articles were initially found, but 835 of them were excluded after careful screening of the titles and abstracts. Of the remaining 45 potentially eligible studies, 24 were further excluded by the inclusion criteria. Finally, 21 studies were included in the meta-analysis [18-38]. Figure 1 shows the search flow diagram of this meta-analysis.

Characteristics of the included studies

Table 1 summarizes the main characteristics and survival outcomes of the 21 studies. Except for eight with a prospective cohort [20-22,25,28,29,33,37], thirteen were retrospective studies. One study was conducted in two independent cohorts [21]. The IHC cut-off criteria for positive TTF-1 staining were variable across studies. Frequencies of TTF-1

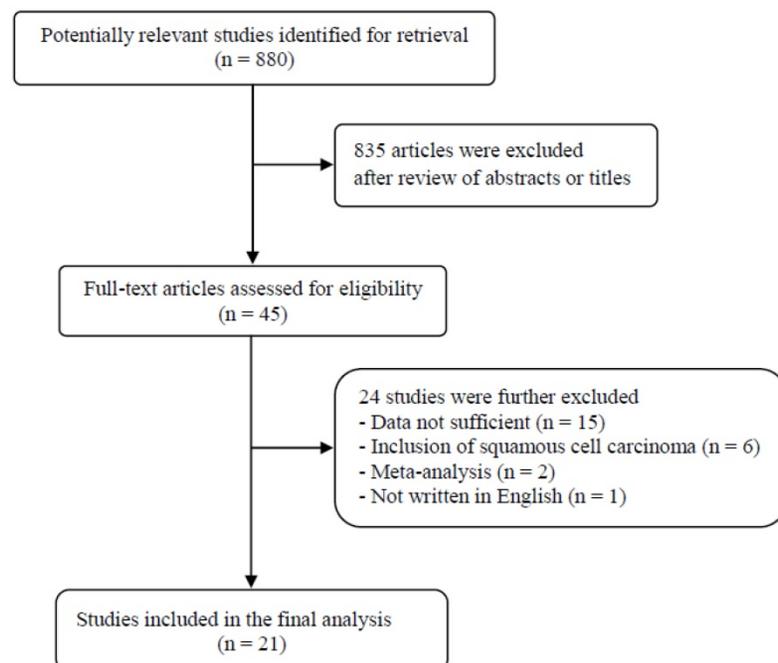


Figure 1. Flow diagram of search process

expression in the included studies ranged from 12.2% [23] to 95.5% [37]. While three studies contained non-SQ NSCLC [26,31,34], 18 studies only involved ADC [18-25,26-30,32,33,35-38]. Three studies involved patients only with stage I ADC [18,19,37] and nine involved patients with advanced (stage III-IV) [20, 22, 26,29,31,34,36,38]. Fourteen studies reported positive TTF-1 staining as a favorable prognostic factor [20-22,24-26,28-30,33-36,38] and the remaining 7 studies failed to observe statistically significant impact of TTF-1 expression on survival [18,19,23,27, 31,32,37].

Prognostic impact of TTF-1 expression

Impact of TTF-1 expression on survival

From 21 studies [18-38], a total of 6,451 patients were included in the meta-analysis of HRs for OS. There was a considerable heterogeneity among studies ($X^2 = 36.29$, $p = 0.02$, $I^2 = 42\%$). Compared with patients with non-SQ NSCLC showing negative TTF-1 staining, patients with non-SQ tumors harboring positive TTF-1 expression showed significantly better survival (HR = 0.49, 95% CI: 0.42-0.57, $p < 0.00001$, random-effects model) (Figure 2).

Subgroup-analyses according to the disease stage

When we pooled HRs for OS according to the stage, the combined HRs were 0.65 (95% CI: 0.50-0.84, $p = 0.0008$, $I^2 = 0\%$, fixed-effect model) for stage I (Figure 3A) and 0.38 (95% CI: 0.29-0.49, $p < 0.00001$, $I^2 = 48\%$, random-effects model) for stage III-IV (Figure 3B), indicating better prognosis in tumors showing TTF-1 expression not only in early-stage but also in advanced non-SQ NSCLC.

Publication bias

Visual inspection of the funnel plot for OS showed symmetry, indicating there was no substantial publication bias (Figure 4). Egger's test also indicated no evidence of substantial publication bias ($p = 0.145$).

Discussion

In clinical practice, TTF-1 is most commonly used to distinguish primary lung ADC from non-pulmonary cancers that have metastasized to the lung [44]. TTF-1 expression by IHC has been detected in up to 95% of ADC of the lung, depending on the techniques, cut-off value of positive staining, and stage [29,37]. However, the vast majority of SQ NSCLCs and most extrapulmonary tumors lack TTF-1 expression [45].

Table 1. Summary of the 21 included studies

First author (year) [ref]	Country	Study design	No. of pts	Inclusion period	Histology	Stage	IHC criteria for TTF-1 (+): nuclear staining	No. of pts with TTF-1 (+) (%)	HR for OS (95% CI)	Adjusted variables
Pelosi (2001) [18]	Italy	Retro	97	1987-1993	ADC	I	More intense to the internal control	70 (72.2%)	0.92 (0.48-1.73) p = 0.7854	Univariate
Saad (2004) [19]	USA	Retro	50	1996-2000	ADC	I	Percentage x intensity ≥ 50 positive tumor cells	30 (60%)	0.68 (0.45-1.01) p = 0.0583	Univariate
Barlesi (2005) [20]	France	Pro	106	2002-2004	ADC	III-IV	Sole nuclear staining	70 (66%)	0.40 (0.25-0.65) p = 0.0002	Univariate
Anagnostou, Cohort I (2009) [21]	USA	Pro	89 (43)	1995-2003	ADC	I-IV (I)	Nuclear AQUA score > 8.8	56 (62.9%) (30)	0.54 (0.29-7-0.98) p = 0.041 0.39 (0.14-1.11) p = 0.079	Age, sex, stage
Anagnostou Cohort II (2009) [21]	USA	Pro	98 (87)	1995-2003	ADC	I-IV (I)	Nuclear AQUA score > 8.8	72 (73.5%) (65)	0.53 (0.26-7-1.05) p = 0.07 0.48 (0.24-0.98) p = 0.043	Age, sex, stage
Martins (2009) [22]	Brazil	Pro	51	1997-1999	ADC	IIIB-IV	$> 40\%$ of tumor cells	20 (39.2%)	0.25 (0.11-0.57) p = 0.001	PS, MMP-9
Anami (2009) [23]	Japan	Retro	139	1993-2000	Small ADC (< 2 cm)	I-III	$\geq 50\%$ of tumor cells	17 (12.2%)	0.405 (0.10-1.69) p = 0.215	Univariate
Barletta (2009) [24]	USA	Retro	89	1997-1999	ADC	I-IV	No staining (0), weak staining (1), and strong staining (2) (positive: 1 or 2)	46 (51.7%)	0.39 (0.21-0.72)	Univariate
Hiramatsu (2010) [25]	Japan	Pro	193	1998-2001	ADC	I-IV	Stronger than xenograft staining	154 (79.8%)	0.28 (0.15-0.54) p < 0.001	Sex, stage, pAkt, pFKHR
Sun (2011) [26]	Korea	Retro	284	2007-2010	Non-SQCC	IIIB-IV	Percentage (0-100%) x intensity (0-2) ≥ 10	194 (68.3%)	0.55 (0.39-0.77) p = 0.0005	Age, sex, smoking, PS, histology
Solis (2012) [27]	USA	Retro	135	1997-2005	ADC with non-solid	I-IV	Percentage (0-100%) x intensity (0-4) > 160	59 (43.7%)	0.70 (0.48-1.04) p = 0.0749	Univariate
Li (2012) [28]	China	Pro	175	2000-2006	ADC	I-IV	$\geq 30\%$ of tumor cells with weak staining intensity	57 (32.6%)	0.41 (0.24-0.67) p < 0.001	Univariate
Chung (2013) [29]	China	Pro	496	2004-2009	ADC	IIIB-IV	Any definite nuclear staining	443 (89.3%)	0.45 (0.30-0.67)	Age, PS, stage, metastases, EGFR mutation, TKI treatment
Nagashio (2015) [30]	Japan	Retro	198	2002-2005	ADC	I-III	Moderate intensity in $\geq 10\%$ of tumor cells	161 (81.3%)	0.60 (0.42-0.85) p = 0.0044	Univariate
Elsamany (2015) [31]	Egypt	Retro	120	2011-2012	Non-SQCC	IIIB-IV	NA	100 (83.3%)	0.43 (0.16-1.18) p = 0.10	Sex, chemotherapy, EGFR mutations
Zhao (2015) [32]	Taiwan	Retro	200	2008-2013	ADC	I-IV	$\geq 10\%$ of tumor cells	163 (81.5%)	0.74 (0.39-1.41) p = 0.365 III-IV: 0.48 (0.24-0.95) p = 0.036	EGFR mutations
Zhang (2015) [33]	China	Pro	451	2008-2013	ADC	I-III	Any positive nuclear staining	332 (73.6%)	0.64 (0.42-0.99) P = 0.043	Sex, smoking, subtypes, stage, LN status, EGFR mutation
Nakahara (2016) [34]	Japan	Retro	26	2008-2013	Non-SQCC EGFR WT	IV	Evident nuclear staining	20 (76.9%)	0.10 (0.02-0.43) p = 0.002	Univariate
Piljić Burazer (2017) [35]	Croatia	Retro	118	2013-2014	ADC	I-IV	Homogeneous nuclear staining in any cell	96 (81.3%)	0.50 (0.29-0.85) p = 0.011	Univariate
Schilsky (2017) [36]	USA	Retro	479	2009-2011	ADC	IV	Any nuclear reactivity	383 (79.9%)	0.38 (0.29-0.51) p < 0.0001	Age, sex, smoking, PS, molecular subgroups, treatment
Zhou (2017) [37]	China	Pro	2,813	2010-2015	ADC	I	Sole nuclear staining	2,687 (95.5%)	0.60 (0.30 - 1.21) p = 0.152	Univariate
Doherty (2018) [38]	Ireland	Retro	44	2008-2013	ADC	IV	$\geq 1\%$ nuclear staining (not membranous or cytoplasmic)	9 (20.4%)	0.12 (0.04-0.35) p < 0.0001	Univariate

NSCLC, non-small-cell lung cancer; Pro, prospective; Retro, retrospective; ADC, adenocarcinoma; SQCC, squamous cell carcinoma; AQUA, automated quantitative analysis; MMP-9, matrix metalloproteinase-9; pAkt, phosphorylated Akt; pFKHR, phosphorylated forkhead transcription factor; EGFR, epidermal growth factor receptor; WT, wild type; PS, performance status; pts, patients; HR, hazard ratio; CI, confidence interval; OS, overall survival; IHC, immunohistochemistry; LN, lymph node; NA, not available

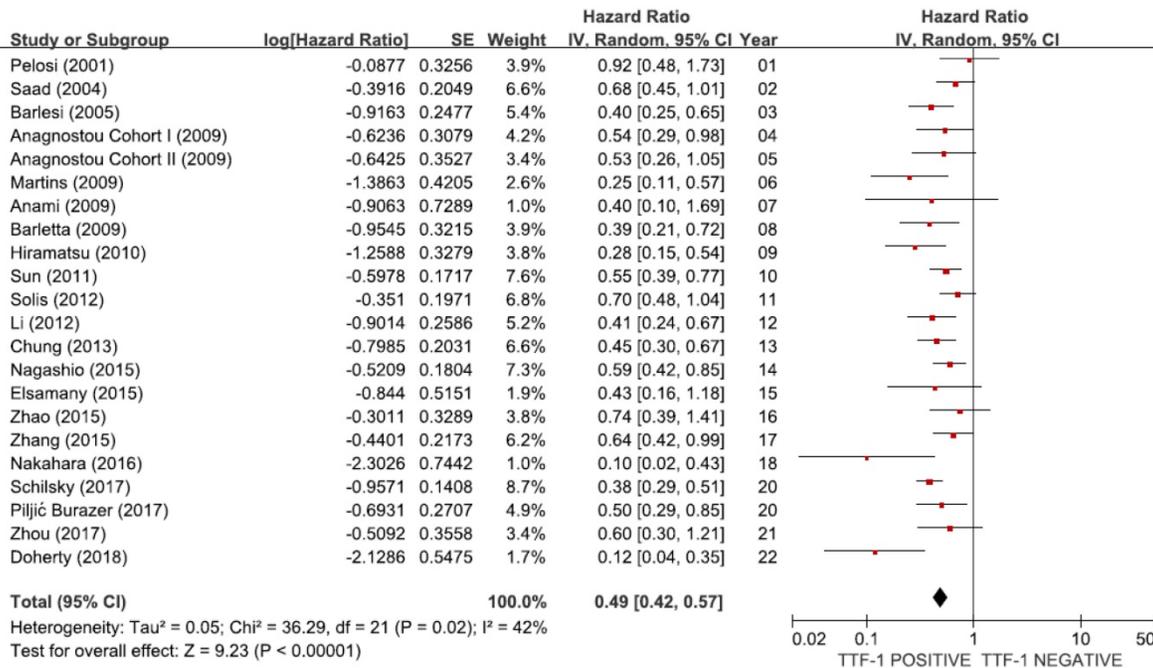


Figure 2. Meta-analysis (forest plot) of 21 studies assessing the prognostic impact of TTF-1 in non-SQ NSCLC.

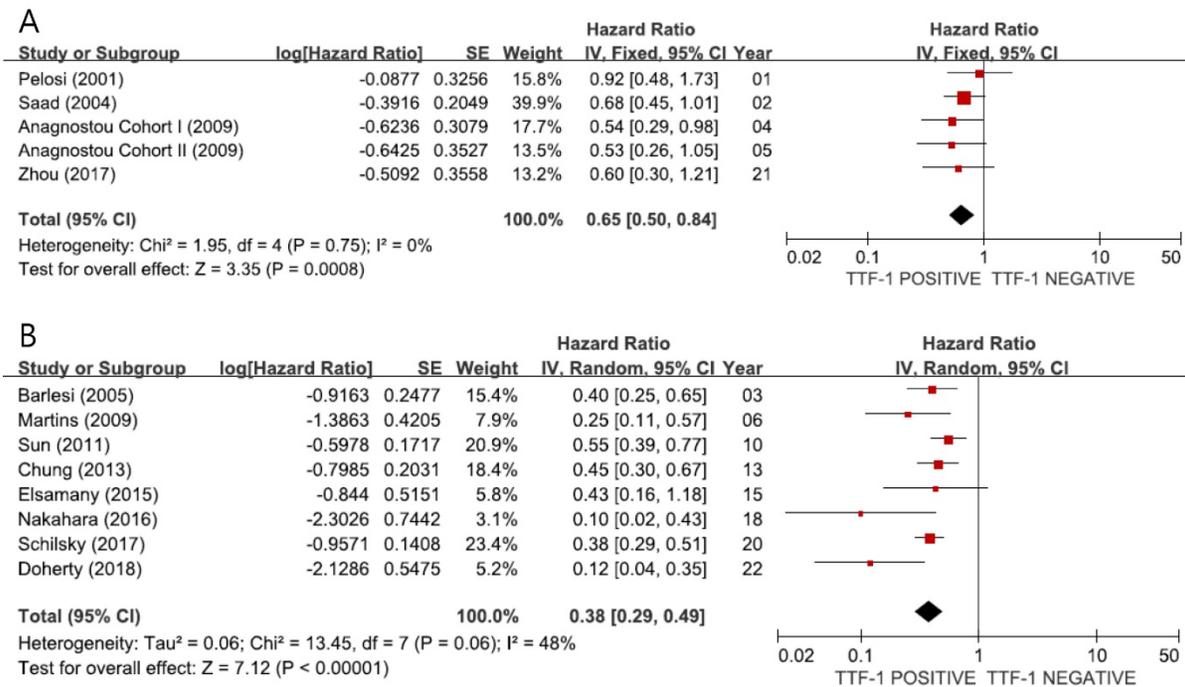


Figure 3. Subgroup meta-analyses (forest plots) assessing the prognostic impact of TTF-1 in stage I (A) and stage III-IV (B) non-SQ NSCLC

The first meta-analysis in 2006 by Berghmans *et al.* combined 8 studies [12,14-20] and observed that TTF-1 positivity was associated with better survival in NSCLC (HR = 0.64, 95% CI: 0.41-1.00) [39]. As there was one study incorporating stage IV, however, the prognostic impact of TTF-1 was demonstrated only in early or locally advanced stages (stage I-III). Qian *et al.* published in 2015 the second meta-analysis of 17

studies with 2,235 NSCLC patients [40]. They observed that TTF-1 overexpression had a favorable impact on survival of patients with NSCLC (HR = 0.49, 95% CI: 0.42-0.55, p = 0.001). The subgroup analysis showed that the favorable prognostic impact remained significant regardless of ethnicity: HR = 0.52 (95% CI: 0.42-0.63) for Asian and HR = 0.45 (95% CI: 0.38-0.52) for non-Asian. This effect was also

significant when the analysis was restricted to stage I (HR = 0.63, 95% CI: 0.39-0.86) or stage III-IV (HR = 0.43, 95% CI: 0.33-0.53). However, they included SQ NSCLC with virtually no potential of TTF-1 expression. Therefore, their results might not reflect the actual prognostic impact of TTF-1 in non-SQ NSCLC.

In the current meta-analysis, we investigated the prognostic value of TTF-1 expression in patients only with non-SQ NSCLC. We combined 21 published studies including 6,451 patients to yield summary statistics. The result revealed that TTF-1 expression had a significant correlation with favorable survival in patients with non-SQ NSCLC (HR = 0.49, $p < 0.00001$). Subgroup analysis demonstrated that TTF-1 overexpression had a significant favorable impact on survival in stage I (HR = 0.65, $p = 0.0008$). Because most patients included in our study did not receive adjuvant therapy, this finding indicates that TTF-1 can be an independent prognostic factor to delineate those who need to be further treated after surgery for patients with early-stage non-SQ NSCLC. In addition, when the analysis was restricted to stage III-IV, the prognostic impact of TTF-1 remained significant with the lower combined HR (0.38, $p < 0.00001$). These findings suggest that TTF-1 is a good prognostic marker for survival not only in early-stage but also in advanced non-SQ NSCLC. On the basis of the results from the current meta-analysis, TTF-1 needs to be selected for prospective studies with multivariate analysis including the known prognostic factors in NSCLC such as PS and stage.

The reasons why TTF-1 is associated with prognosis of patients with non SQ NSCLC (mainly ADC) are unclear. Myong reported that TTF-1 expression was inversely related to the proliferative activity evaluated through Ki-67 expression [16].

Some investigators have suggested that there is a relationship between epidermal growth factor receptor (*EGFR*) mutations and TTF-1 expression in lung ADCs [32,36,46-48]. The NEJ 002 clinical trial reported that the rate of *EGFR* mutations was significantly higher in ADC specimens with positive TTF-1 expression than in specimens with no TTF-1 expression [46]. Shanzhi *et al.* found that positive and partial positive TTF-1 expression has a significant positive correlation with *EGFR* mutations (exon 19 and 21) in lung ADCs [46]. Recently Zhao *et al.* also reported a significant association between TTF-1 positivity and *EGFR* mutations (exon 21) in the Chinese lung ADC patients [32]. Of 89 patients with *EGFR* mutations, 83 (93%) specimens were simultaneously positive for TTF-1 expression ($p < 0.001$ by the χ^2 test). In addition, patients with stage III-IV whose tumors were positive for TTF-1 expression and *EGFR* mutations had better postoperative survival than those with tumors harboring neither TTF-1 expression nor *EGFR* mutations (HR = 2.62, 95% CI: 1.09-6.31, $p = 0.027$). These results suggest that in clinical practice, TTF-1 expression combined with *EGFR* mutations can guide treatment timely for patients with lung ADCs.

Our study has several inherent limitations. First, the included studies showed considerable diversities in the techniques used for IHC. They used un-identical monoclonal antibodies at different concentration and dissimilar staining protocol. In addition, the cut-off criteria for positive TTF-1 staining was also various among studies. The wide range of incidence of TTF-1 positivity among studies (from 12.2% to 95.5%) might be attributable to the different IHC methods and criteria for TTF-1 overexpression. Therefore, it is still necessary to define the standardized methods to evaluate exactly the prognostic role of TTF-1 in non-SQ NSCLC. Second, this meta-analysis included the studies with non-SQ NSCLC regardless of *EGFR* mutation status. *EGFR* mutation is the strongest prognostic factor in non-SQ NSCLC. However, we could not evaluate the prognostic impact of TTF-1 according to the *EGFR* mutation status due to the insufficient data. Third, more than half studies were retrospectively performed and therefore might carry the biases of the retrospective design. Fourth, as we mentioned above, there were two meta-analyses regarding the prognostic impact of TTF-1 in NSCLC in the literature [39,40]. They included all subtypes of NSCLC from studies published between 1999 and 2012. However, we have improved upon the previous meta-analyses by adding

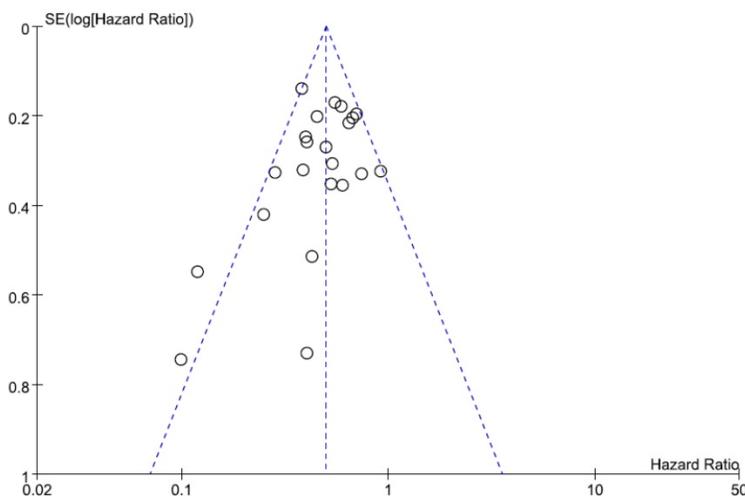


Figure 4. Funnel plot for publication bias regarding overall survival.

10 more recent studies published after 2013 [29-38] and the meta-analysis was performed in patients only with non-SQ NSCLC. Therefore, we assume that our results reflect more actually the prognostic impact of TTF-1 in non-SQ NSCLC. Finally, articles published only in English were included, which might bias the results.

In conclusion, this meta-analysis indicates that TTF-1 overexpression is a favorable prognostic factor in patients with non-SQ NSCLC. Its prognostic impact is also significant when the subgroup analysis is restricted to stage I or stage III-IV non-SQ NSCLC. However, large prospective studies using standardized IHC criteria based on the homogeneous populations are warranted to validate the prognostic value of TTF-1 expression in patients with non-SQ NSCLC.

Competing Interests

The authors have declared that no competing interest exists.

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