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Clinicopathological and prognostic significance of thyroid transcription factor-1 expression in small cell lung cancer: A systemic review and meta-analysis

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ABSTRACT

Purpose: To explore the association of thyroid transcription factor-1 (TTF-1) expression status with clinicopathological characteristics and survival of patients with small cell lung cancer (SCLC).
Methods: A comprehensive literature search was conducted to identify potentially relevant studies in several electronic databases, including EMBASE, PubMed, Web of Science, CNKI and WanFang. The relative risks (RRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) were used to assess the relation of TTF-1 with clinicopathological parameters and prognosis, respectively. Sensitivity analysis was performed to assess the stability of the pooled results. Begg's funnel plot and Egger's test were applied to detect the publication bias. All statistical analyses were performed by STATA 12.0 version software.
Results: A total of 11 studies involving 1786 SCLC patients were included in our study. No significant relationship between TTF-1 and any clinicopathological features was observed. However, the pooled results demonstrated that TTF-1 expression indicated prolonged overall survival (OS) (HR = 0.56, 95% CI: 0.45-0.70; $P < 0.001$) and progression-free survival (PFS) (HR = 0.41, 95% CI: 0.28-0.62; $P < 0.001$). Subgroup analysis stratified by the country manifested that the significant prognostic value of TTF-1 expression status was only observed in SCLC patients who from China.
Conclusion: TTF-1 might be an independent prognostic factor in SCLC patients, especially patients who were from China. More well-designed prospective studies are needed to further testify our findings.

1. Introduction

Small cell lung cancer (SCLC) is a subtype of lung cancer with neuroendocrine differentiation, which accounts for about 13% of all lung carcinoma cases [1]. Although SCLC is more responsive to chemoradiotherapy than other types of lung carcinoma, its prognosis is the poorest among all histological subtypes with 5-year overall survival (OS) rate of only 5–15%, comparing with 57.7% of squamous cell carcinoma and 49.6% of adenocarcinoma [2,3]. How to accurately predict the prognosis of SCLC patients and develop appropriate treatment strategies is an urgent problem needing to be solved.

Thyroid transcription factor-1 (TTF-1) was initially regarded as a thyroid-specific gene transcription activator and also known as TITF-1 or Nkx2-1 [4]. It is mainly expressed in the thyroid glands, lungs and brain [5]. In normal adult lungs, it is restricted to express in type II pneumocytes and Clara cells [6]; it has also been reported that TTF-1 plays a crucial role in regulating the expression of several genes such as the Clara cell protein and surfactant [7,8].

Previous reports have indicated that the expression of TTF-1 differs among different histological types of lung cancer [9–11]. TTF-1 expression is frequent in adenocarcinoma and SCLC, whereas it is rare in squamous or large cell carcinomas [9–11]. In SCLC, TTF-1 expression was found in 85–90% cases [12]. However, non-pulmonary small cell carcinoma can also express TTF-1 because of their neuroendocrine differentiation [13]. Thus, the diagnostic value of TTF-1 in SCLC remains limited.

In recent years, more and more studies focused on the clinicopathological and prognostic role of TTF-1 in lung cancer. As for non-small cell lung cancer (NSCLC), there are already several meta-analyses which have demonstrated that the loss of TTF-1 expression is significantly related with more aggressive tumor behavior and poorer survival [14,15]. However, the clinical pathological and prognostic

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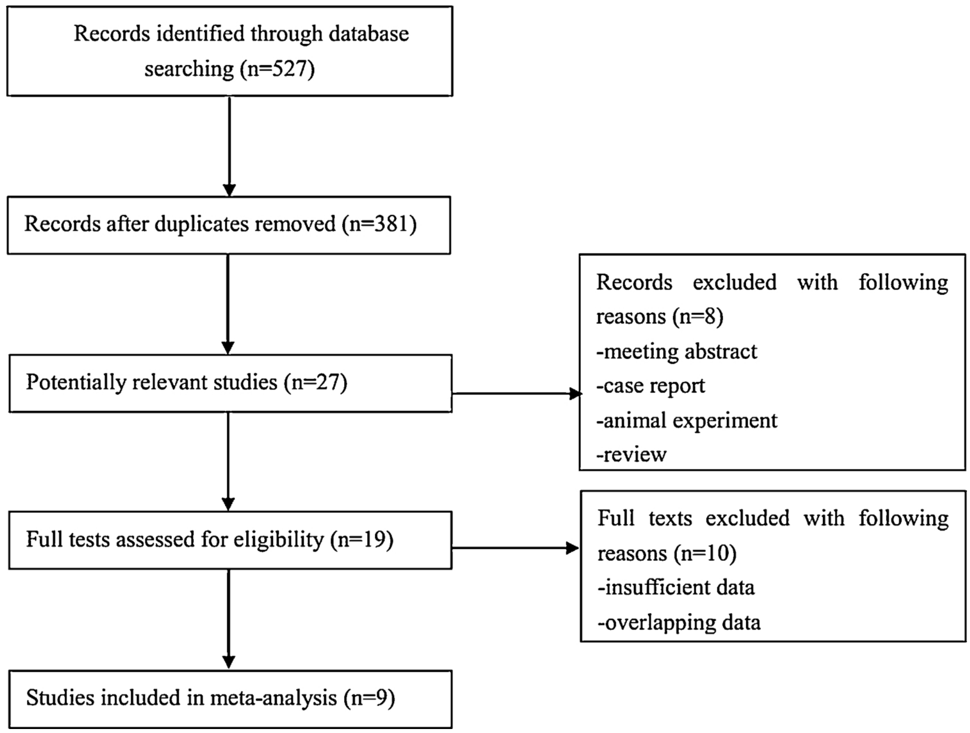

Fig. 1. Flow diagram of the literature review.

value of TTF-1 in SCLC is still unclear.

Therefore, we conducted this systemic review and meta-analysis to further determine clinical significance of TTF-1 expression status in SCLC, which may contribute to the prediction of prognosis and formulation of therapy strategy for SCLC patients.

2. Materials and methods

The current systemic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [16].

2.1. Literature search strategy

A systematic and comprehensive search was conducted in five electronic databases, including the PubMed, EMBASE, Web of Science, CNKI and WanFang, from January 1966 to August 11, 2019. The following terms were used, “thyroid transcription factor-1″, “TTF-1″, “small cell lung cancer” and “SCLC”. The MeSH terms and free-texts words were both used to increase sensitivity.

2.2. Inclusion and exclusion criteria

The following inclusion criteria were used: 1) patients were diagnosed with SCLC pathologically; 2) patients were divided into two groups (TTF-1 positive vs TTF-1 negative) according to the TTF-1 expression status and the prognosis of patients was compared between the two groups; 3) sufficient information was provided to calculate the hazard ratio (HR) with 95% confidence interval (CI) of the interest outcome when they were not directly reported in the articles.

The following exclusion criteria were used: 1) letters, reviews, animal trials, case reports and meeting abstracts; 2) when the data was duplicated or overlapped, only the latest publication was included.

The literature search and selection were conducted by two independent investigators (Yan Wang and Yanming Wu). Any disagreement was resolved by team discussion until consensus was reached.

2.3. Data extraction

The following information was extracted from each included studies by two authors (Yan Wang and Yanming Wu) independently: the name of the first author, publication year, country where the study was performed, sample size, number of patients who were TTF-1 positive, sex, age, lymph node metastasis status, tumor-node-metastasis (TNM) stage, smoking history, therapy strategy and HR with 95% CI of each interest outcome.

2.4. Quality assessment

The quality of each included study was assessed according to the Newcastle-Ottawa quality assessment scale (NOS) [17]. Studies which earned a score of 6 or higher were considered as high-quality studies.

2.5. Statistical analysis

All statistical analyses were performed by the STATA 12.0 software. The relation of TTF-1 with clinicopathological characteristics was assess by the pooled relative risks (RRs) with 95% CIs and the association of TTF-1 with prognosis was evaluated by the pooled HRs with 95% CIs. HRs with 95% CIs from multivariable models were used whenever available; and if they were not reported directly, then they would be estimated from the Kaplan-Meier curves using the method described by Tierney et al. [18]. The Chi-square based Q-test and I^2 statistic were applied to assess the heterogeneity among included studies [19]. If significant heterogeneity was observed representing as $P < 0.10$ or/and $I^2 > 50\%$, the random-effect modes was used; otherwise the fixed-effect model was used [20]. Subgroup analyses based on the country, treatment strategy and source of HR were performed to further verify the overall results of meta-analysis for OS. The stability of pooled results was assessed by the sensitivity analysis. The potential publication bias was detected by the Begg’s funnel plot and Egger’s test [21]. A log-rank P value < 0.05 was considered significant.

3. Results

3.1. Literature search process

As shown in Fig. 1, 2051 records were yielded from the five databases. After removing 664 duplicates, titles and abstracts of 1387 records were reviewed. Forty-five records of 69 relevant publications were excluded for the following reasons: meeting abstract (n = 23), case report (n = 3), animal experiment (n = 9) and review (n = 10). Twenty-four full-texts were assessed for eligibility and 13 publications were exclude for the following reasons: insufficient data (n = 10) and overlapping data (n = 3). Eventually, a total of 11 studies involving 1786 patients met the inclusion criteria and were included in our systemic review and meta-analysis.

3.2. Basic characteristics of included studies

All included studies were retrospective and earned a NOS score of 6 or higher. Among the 11 included studies, most of them (8/11) were from China. The proportion of TTF-1 positive patients in the study population ranged from 62% to 90%, with the sample size ranged from 65 to 396. Furthermore, the immunohistochemical method was used for the detection of TTF-1 expression status in all included studies. Other characteristics were presented in Table 1 in detail.

3.3. Association of TTF-1 with clinicopathological parameters in SCLC

Based on the data provided by included studies, we explored the relation of TTF-1 expression status with sex, age (≥ 60 vs < 60), lymph node metastasis, TNM stage (IV,III vsII,I) and smoking history (Table 2). However, no significant association between TTF-1 and these parameters was observed.

3.4. Association of TTF-1 with prognosis in SCLC

A total of 10 studies involving 1689 patients reported the relation between TTF-1 and OS and the pooled results manifested that TTF-1 expression indicated prolonged OS in SCLC patients (HR = 0.56, 95% CI: 0.45–0.70; P < 0.001) with significant heterogeneity (I^2 = 46.7%, P = 0.051) (Table 3; Fig. 2). Then we performed subgroup analysis stratified by the country, treatment and source of HR, which indicated that the race may have an impact on the prognostic value of TTF-1 in SCLC. The significant association of TTF-1 with OS was only observed in Chinese patients (HR = 0.55, 95% CI: 0.46–0.66; P < 0.001) with low heterogeneity (I^2 = 9.2%, P = 0.359) (Table 3).

Only 2 studies involving 241 patients reported the relation of TTF-1 with progression-free survival (PFS) and the pooled results demonstrated that TTF-1 expression indicated improved PFS in SCLC patients (HR = 0.41, 95% CI: 0.28–0.62; P < 0.001) with low heterogeneity (I^2 = 0.0%, P = 0.547) (Table 3; Fig. 3).

3.5. Sensitivity analysis

The sensitivity analysis was conducted through excluding each study from the meta-analysis at each time, which showed that the pooled results were stable (Fig. 4).

3.6. Publication bias

The Begg's funnel plot was symmetrical (Fig. 5) and the P value for Egger's test was 0.330, which both indicated that no significant publication bias existed in this systemic review and meta-analysis.

4. Discussion

TTF-1 is usually applied as an immunohistochemical marker which contributes to differentiate primary lung cancer from non-pulmonary cancers in clinics. TTF-1 expression has been reported to be frequent in SCLC, with TTF-1 positive proportion of 62 to 90% according to included studies [22–32]. Actually, TTF-1 also expressed in some other organs or tissues, such as the thyroid glands, brain and prostate small cell carcinoma [4]. Yao et al. found that TTF-1 expressed in 83% of small cell prostate carcinoma and Ordonez et al. reported that TTF-1 only expressed in 7% of cases [12,13]. So, TTF-1 is not an exclusively pulmonological biomarker, which is proved by the fact that non-pulmonary small cell carcinomas also express other neuroendocrine markers as well as SCLC, such as the neuro-specific enolase (NSE), CD56 and chromogranin A [33–37]. Therefore, the value of TTF-1 for diagnosis of SCLC remains questionable.

Then, more researchers focused on the clinical significance of TTF-1 on tumor behavior and prognosis of SCLC patients. Several studies reported that TTF-1 expression was a protective factor in SCLC and TTF-1-negative patients had poorer survival than TTF-1-positive patients did [22,23,27–29 31,32], which were consistent with our results. It is suspected that tumor cells with TTF-1 positive-expression remain the ability to differentiate normally and TTF-1may play a potential role in controlling the differentiation and metastasis of tumor cells or could reduce the expression of cell proliferation antigen (Ki-67) [38,39]. However, some other studies manifested that there was no significant relation between TTF-1 expression status and prognosis of SCLC patients [24,25,30]. We supposed there may be several reasons why they got inconsistent conclusions. First, the sample sizes of most included studies are less than 200, which increases the risk of bias. Second, among the eight studies which are from China, most of them reported positive results except Jiang et al. and Jiang et al. only analyzed 79 SCLC patients in their research [30]. Furthermore, among the studies which are from non-China countries, two of them reported negative results [25,26]. This indicated that TTF-1 may show high prognostic

Table 1
Basic characteristics of included studies.

Author	Year	Country	Sample size	Positive, n (%)	Treatment	TNM stage	Outcome	Source of HR	NOS score
Lv [22]	2012	China	65	40 (62)	Surg	I- III	OS	E	7
Yu [23]	2015	China	90	72 (80)	Mixed	I- IV	OS	R	7
Liu [24]	2015	China	97	76 (78)	CRT	NR	PFS	R	8
Misch [25]	2015	Germany	221	183 (83)	CRT	III- IV	OS	E	7
Miyauchi [26]	2015	Japan	96	79 (82)	Mixed	I- IV	OS	R	6
Ji [27]	2017	China	144	120 (83)	CRT	III- IV	OS/PFS	E	7
Wang [28]	2017	China	198	145 (73)	CRT	II- IV	OS	R	8
Iida [29]	2018	Japan	135	101 (75)	CRT	NR	OS	E	6
Jiang [30]	2018	China	79	71 (90)	Surg	I- III	OS	E	7
Yang [31]	2018	China	265	201 (76)	Mixed	NR	OS	R	8
Han [32]	2019	China	396	290 (73)	CRT	II- IV	OS	R	7

TNM: tumor-node-metastasis; OS: overall survival; PFS: progression-free survival; HR: hazard ratio; Surg: surgery; CRT: chemoradiotherapy; Mixed: surgery and (or) chemoradiotherapy; NR: not reported; R: reported; E: estimated; NOS: Newcastle-Ottawa quality assessment scale.

Table 2
Associations of TTF-1 expression with clinicopathological characteristics in small cell lung cancer.

Author	Sex (M vs F)	Age (≥60 vs <60)	Lymph node metastasis (N + vs -)	TNM (IV,III vsII,I)	Smoking history (yes vs no)
Lv [22]	0.853 (0.582–1.249)	–	0.792 (0.545–1.150)	0.746 (0.506–1.100)	0.795 (0.548–1.156)
Yu [23]	–	–	–	–	–
Liu [24]	1.063 (0.832–1.358)	1.002 (0.813–1.236)	–	–	1.024 (0.821–1.278)
Misch [25]	0.998 (0.880-1.133)	–	–	–	–
Miyauchi [26]	–	–	–	–	–
Ji [27]	0.909 (0.790–1.047)	0.884 (0.767–1.020)	–	–	0.904 (0.777–1.051)
Wang [28]	1.123 (0.884–1.426)	0.908 (0.768–1.073)	–	1.049 (0.693–1.588)	0.996 (0.820–1.209)
Iida [29]	1.038 (0.819–1.315)	–	–	–	1.155 (0.651–2.050)
Jiang [30]	0.972 (0.835–1.131)	1.058 (0.918–1.220)	1.194 (0.963–1.480)	–	–
Yang [31]	–	–	–	–	–
Han [32]	0.891 (0.752–1.055)	0.908 (0.807–1.022)	–	1.049 (0.782–1.406)	0.996 (0.868–1.142)
Overall	0.97 (0.91–1.03); P = 0.348	0.94 (0.88–1.02); P = 0.078	1.00 (0.67–1.49); P = 0.994	0.95 (0.78–1.17); 0.658	0.97 (0.89–1.05); P = 0.388

TTF-1: thyroid transcription factor-1; M: male; F: female; TNM: tumor-node-metastasis.

Table 3
Meta-analyses for the association of TTF-1 expression with survival of small cell lung cancer.

Analysis	No. of studies	HR (95% CI)	Log-rank *P* value	I^2 (%)	*P* value
Overall survival	10	0.56 (0.45-0.70)	< 0.001	46.7	0.051
Country					
China	7	0.55 (0.46-0.66)	< 0.001	9.2	0.359
Non-China	3	0.70 (0.34-1.42)	0.318	78.6	0.009
Treatment					
Surgery	2	0.38 (0.20-0.73)	0.004	0.0	0.759
Chemoradiotherapy	5	0.58 (0.48-0.70)	< 0.001	7.5	0.364
Source of HR					
Estimated	5	0.49 (0.37-0.65)	< 0.001	12.7	0.333
Reported	5	0.63 (0.46-0.86)	0.004	61.9	0.033
Progression-free survival	2	0.41 (0.28-0.62)	< 0.001	0.0	0.547

TTF-1: thyroid transcription factor-1; HR: hazard ratio; CI: confidence interval.

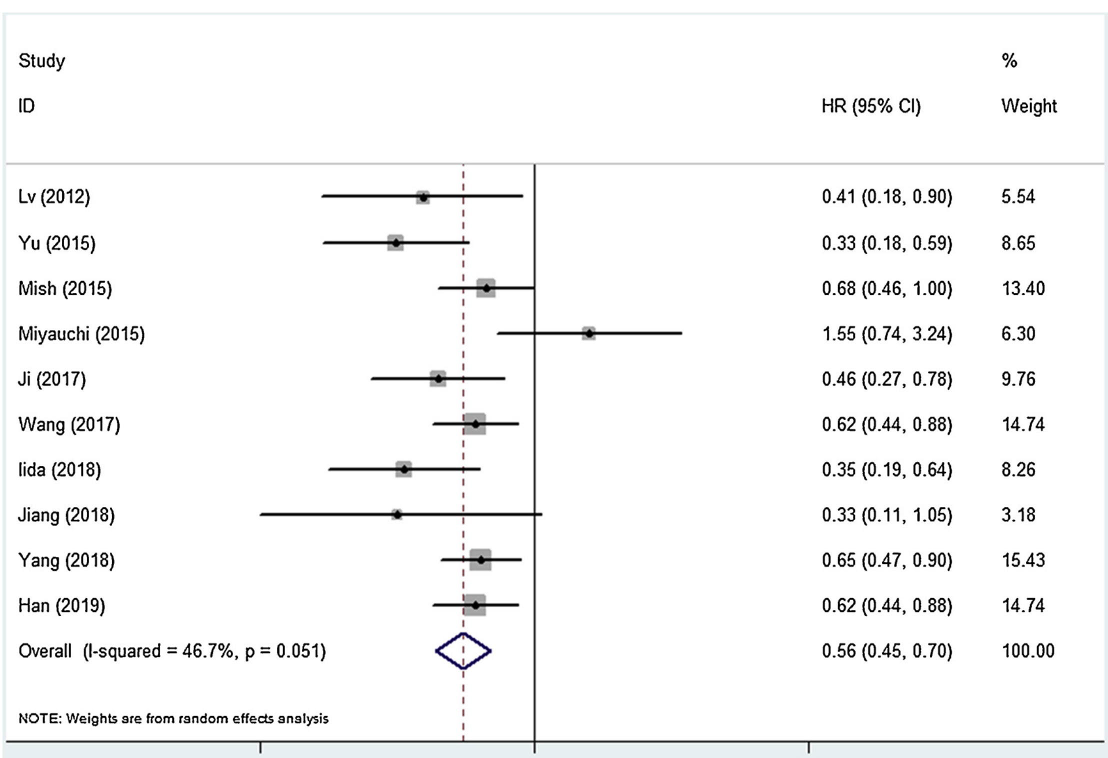

Fig. 2. Forest plot of the association between TTF-1 and overall survival.

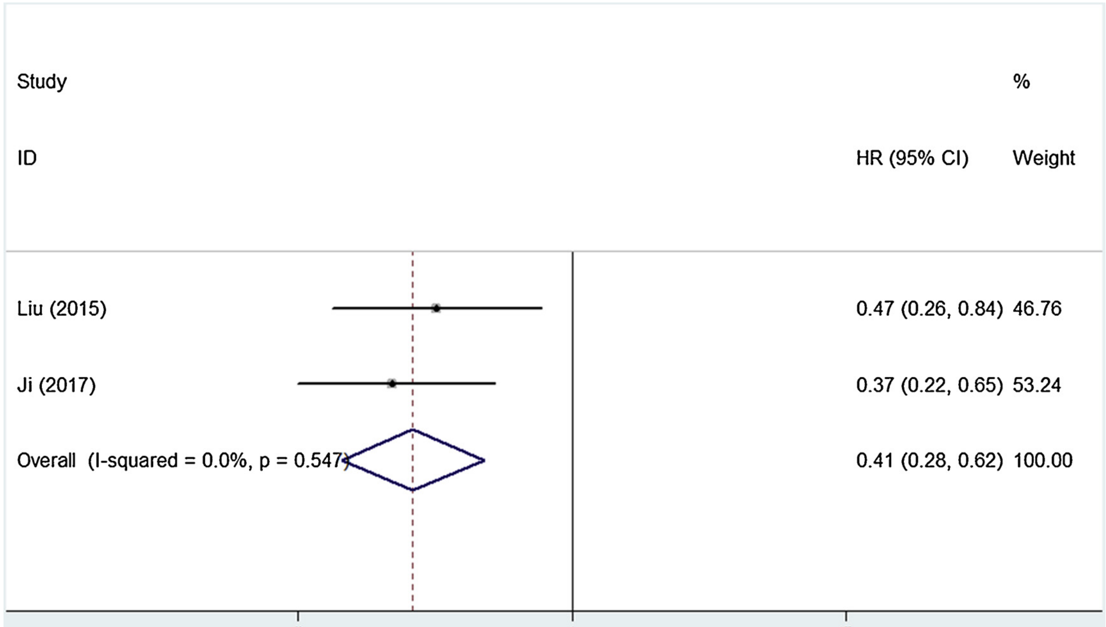

Fig. 3. Forest plot of the association between TTF-1 and progression-free survival.

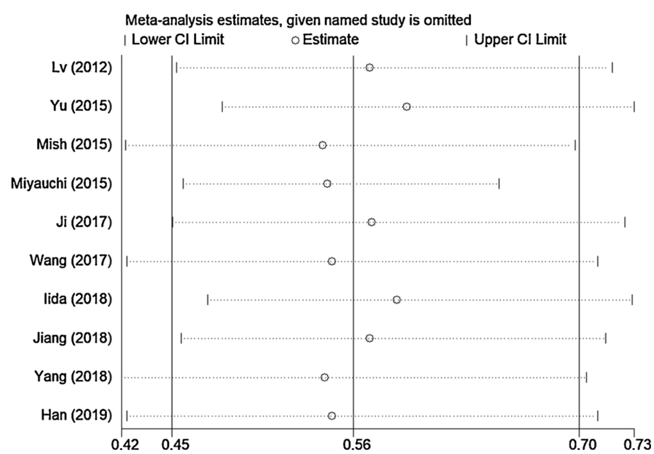

Fig. 4. Sensitivity analysis of the association between TTF-1 and overall survival.

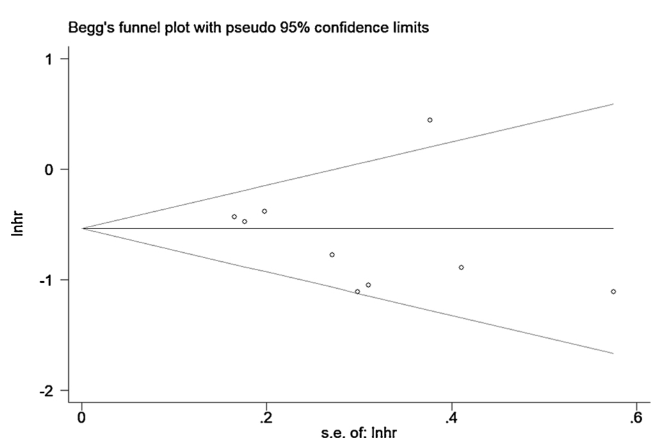

Fig. 5. Begg's funnel plot of the association between TTF-1 and overall survival.

value only in Chinese SCLC patients and the results of our meta-analysis are consistent with this conjecture; however, this should to be further clarified and more researches from non-China countries are still needed.

As for the clinicopathological significance of TTF-1 in SCLC patients, none of included studies reported significant relation between TTF-1 expression status and clinicopathological parameters including the sex, age, lymph node metastasis, TNM stage and smoking history. Thus, TTF-1 may not play a role in the development and progression of SCLC. Ji et al. reported that TTF-1 expression was significantly associated with response rate in advanced stage SCLC patients who received first-line platinum-based chemotherapy [27]. This may explain one of the mechanisms by which TTF-1 expression status affect the survival of SCLC patients. Furthermore, Iida et al. reported that TTF-1 expression status was significantly correlated with the expression of synaptophysin and chromogranin A which were both proved to be independent factors for SCLC patients [40]. So, TTF-1 may cause an indirect influence on the survival of SCLC patients.

Actually, there are still some fields worth further investigation about clinical role of TTF-1 in SCLC. It is unclear whether TTF-1 has high prognostic value in all SCLC patients despite of the TNM stage. As mentioned above, compared with TTF-1-negative patients, patients with TTF-1 expression are more sensitive to chemotherapy [27]. So, is it more necessary for TTF-1-negative patients to receive surgical treatment under the same conditions? Furthermore, only 2 and 3 studies reported the relation of TTF-1 with lymph node metastasis and TNM stage with negative results, respectively. We believe that it is still necessary to further confirm the relationship between them. Besides, the mechanisms by which TTF-1 affect the survival of SCLC patients remain unclear.

There are some limitations in our study. First, all of included researches are retrospective with small sample sizes. Second, most of included studies are from China and no significant association between TTF-1 and OS in SCLC patients who were from non-China regions was observed. Therefore, the prognostic role of TTF-1 in SCLC patients who are from other countries or regions is still needed to further testify. Third, although all included studies used the immunohistochemical method to detect the expression status of TTF-1, the definitions of "positive" they applied were very different, which may be a confounding factor. Four, due to the lack of detailed information about some important prognostic factors such as the TNM stage, age and diagnosis method, we were unable to conduct subgroup analysis based on these factors. Five, we did not verify the results of this meta-analysis using the original data about SCLC patients of our hospital.

In conclusion, our study manifested that TTF-1 may serve as a novel prognostic factor in SCLC, especially for Chinese patients. However, more prospective studies with bigger sample sizes are needed to verify our findings.

Author contributions

Guowei Che made the substantial contributions to the conception and design of the work; Yan Wang, Yanming Wu, Jue Li and Jialong Li searched, selected materials and extracted data; Yan Wang and Yanming Wu wrote this manuscript; Jue Li and Jialong Li revised the paper carefully and also contributed to the statistical analysis. All authors have read and approved the final manuscript.

Declaration of Conflicting Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval

All procedures performed in studies which involved human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

References

[1] A. Tartarone, P. Giordano, R. Lerose, M.G. Rodriquenz, R. Conca, M. Aieta, Progress and challenges in the treatment of small cell lung cancer, Med. Oncol. 34 (2017) 110.
[2] L.E. Gaspar, E.G. Gay, J. Crawford, et al., Limited-stage small-cell lung cancer (stages I-III): observations from the National Cancer data Base, Clin. Lung Cancer 6 (2005) 355–360.
[3] X.G. Xiong, J.H. He, D.K. Yang, et al., Prognostic role of histologic type in non-small cell lung cancer according to different tumor sizes, Tumor. 32 (9) (2012) 703–708.
[4] S. Guazzi, M. Price, M. De Felice, et al., Thyroid nuclear factor 1 (TTF-1) contains a homeodomain and displays a novel DNA binding specificity, EMBO J. 9 (1990) 3631–3639.
[5] C.D. Bingle, Thyroid transcription factor-1, Int. J. Biochem. 29 (1997) 1471–1473.
[6] L. Zhou, L. Lim, R.H. Costa, et al., Thyroid transcription factor-1, hepatocyte nuclear factor-3beta, surfactant protein B, C, and Clara cell secretory protein in developing mouse lung, J. Histochem. Cytochem. 44 (1996) 1183–1193.
[7] C.D. Bingle, Thyroid transcription factor-1, Int. J. Biochem. Cell Biol. 29 (12) (1997) 1471–1473.
[8] S.K. Lau, D.J. Luthringer, R.N. Eisen, Thyroid transcription factor-1: a review, Appl. Immunohistochem. Mol. Morphol. 10 (2) (2002) 97–102.
[9] J. Zamecnik, R. Kodet, Value of thyroid transcription factor-1 and surfactant apoprotein A in the differential diagnosis of pulmonary carcinomas: a study of 109 cases, Virchows Arch. 440 (4) (2002) 353–361.
[10] C. Di Loreto, V. Di Lauro, F. Puglisi, G. Damante, D. Fabbro, C.A. Beltrami, Immunocytochemical expression of tissue specific transcription factor-1 in lung carcinoma, J. Clin. Pathol. 50 (1) (1997) 30–32.
[11] Y. Yatabe, T. Mitsudomi, T. Takahashi, TTF-1 expression in pulmonary adenocarcinomas, Am. J. Surg. Pathol. 26 (6) (2002) 767–773.
[12] N.G. Ordonez, Value of thyroid transcription factor-1 immunostaining in distinguishing small cell lung carcinomas from other small cell carcinomas, Am. J. Surg. Pathol. 24 (9) (2000) 1217–1223.
[13] J.L. Yao, R. Madeb, P. Bourne, J. Lei, X. Yang, S. Tickoo, et al., Small cell carcinoma of the prostate: an immunohistochemical study, Am. J. Surg. Pathol. 30 (6) (2006) 705–712.
[14] T. Berghmans, M. Paesmans, C. Mascaux, et al., Thyroid transcription factor 1—a new prognostic factor in lung cancer: a meta-analysis, Ann. Oncol. 17 (2006) 16731–16736.
[15] H.H. Qian, T.S. Xu, X.Q. Cai, T.L. Ji, H.X. Guo, Prognostic value of TTF-1 expression in patients with non–small cell lung cancer: a meta-analysis, Clin. Chim. Acta 451 (2015) 208–214.
[16] D. Moher, L. Shamseer, M. Clarke, D. Ghersi, A. Liberati, M. Petticrew, et al., Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement, . Syst. Rev. 4 (2015) 1.
[17] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eurjepidemiol. 2010; 25:603-605...
[18] J.F. Tierney, L.A. Stewart, D. Ghersi, S. Burdett, M.R. Sydes, Practical methods for incorporating summary time-to-event data into meta-analysis, Trials. 7 (2007) 8–16.
[19] J. Lau, J.P. Ioannidis, C.H. Schmid, Quantitative synthesis in systematic reviews, Ann. Intern. Med. 127 (November 9) (1997) 820–826.
[20] E. Zintzaras, J.P. Ioannidis, HEGESMA: genome search meta-analysis and heterogeneity testing, Bioinformatics 21 (18) (2005) 3672–3673.
[21] J.L. Peters, A.J. Sutton, D.R. Jones, K.R. Abrams, L. Rushton, Comparison of two methods to detect publication bias in meta-analysis, JAMA. 295 (February 6) (2006) 676–680.
[22] X. Lv, L. Sun, Z. Zhan, et al., Expression and prognostic value of TTF-1 and CK in small cell lung carcinoma, Chin. J. Clin. Oncol. 39 (5) (2012) 273–277.
[23] H. Yu, R. Qin, C. Liang, et al., Immunohistochemical characteristics and prognosis study of 90 small cell lung cancer patients, J. Clin. Exp. Pathol. 31 (1) (2015) 62–69.
[24] J. Liu, Analysis of the Correlation Between TTF-1、CgA and PFS in Small Lung Cancer [D], Dalian Medical University., Dalian, 2015.
[25] D. Misch, T. Blum, C. Boch, et al., Value of thyroid transcription factor (TTF)-1 for diagnosis and prognosis of patients with locally advanced or metastatic small cell lung cancer, Diagn. Pathol. 10 (21) (2015) 1–7.
[26] E. Miyauchi, N. Motoi, H. Ono, et al., Distinct characteristics of small cell lung Cancer Correlate with central or peripheral origin: subtyping based on location and expression of transcription factor TTF-1, Medicine (Baltimore) 94 (51) (2015) e2324.
[27] Y. Ji, S. Shen, C. Lu, et al., Correlation analysis between TTF-1 expression and chemosensitivity and prognosis of advanced small cell lung cancer patients treated with first-line platinum-based chemotherapy, Chin. J. Cancer Prev. Treatment 24 (22) (2017) 1578–1583.
[28] X. Wang, Y. Zhang, M. Hu, et al., Prognostic and predictive value of thyroid transcription Factor-1, CD56, P40 and other clinical characteristics in small cell lung Cancer patients, Chin. J. Lung Cancer. 20 (8) (2017) 522–527.
[29] Y. Iida, S. Masuda, Y. Nakanishi, et al., Clinicopathological characteristics of thyroid transcription factor 1-negative small cell lung cancers, Hum. Pathol. 79 (2018) 127–134.
[30] Z. Jiang, L. Huang, G. Cui, et al., Expression and clinical significance of TTF - 1 in small cell lung cancer and lung adenocarcinoma, J. Mod. Oncol. 26 (20) (2018) 3232–3236.
[31] J. Yang, The prognostic value of the TTF-1 expression in patients with small cell lung cancer, Chin. J. Coal Ind. Med. 21 (1) (2018) 70–73.
[32] S. Han, Prognostic value of TTF-1, CD56, P40 and serum NSE, ProGRP and LDH in small cell lung cancer, Chin. Remedies Clin. 19 (1) (2019) 97–99.
[33] B.S. Wilson, R.V. Lloyd, Detection of chromogranin in neuroendocrine cells with a monoclonal antibody, Am. J. Pathol. 115 (3) (1984) 458–468.
[34] V.E. Gould, I. Lee, W.H. Warren, Immunohistochemical evaluation of neuroendocrine cells and neoplasms of the lung, Pathol. Res. Pract. 183 (2) (1988) 200–213.
[35] J.W. Said, S. Vimadalal, G. Nash, I.P. Shintaku, R.C. Heusser, A.F. Sassoon, et al., Immunoreactive neuron-specific enolase, bombesin, and chromogranin as markers for neuroendocrine lung tumors, Hum. Pathol. 16 (3) (1985) 236–240.
[36] S. Lantuejoul, D. Moro, R.J. Michalides, C. Brambilla, E. Brambilla, Neural cell adhesion molecules (NCAM) and NCAM-PSA expression in neuroendocrine lung tumors, Am. J. Surg. Pathol. 22 (10) (1998) 1267–1276.
[37] K. Kontogianni, A.G. Nicholson, D. Butcher, Sheppard MN. CD56: a useful tool for the diagnosis of small cell lung carcinomas on biopsies with extensive crush artefact, J. Clin. Pathol. 58 (9) (2005) 978–980.
[38] N.R. Foster, S.J. Mandrekar, S.E. Schild, et al., Prognostic factors differ by tumor stage for small cell lung cancer: a pooled analysis of North Central Cancer treatment Group trials, Cancer. 115 (12) (2009) 2721–2731.
[39] K. Hiroshima, A.T. Iyoda, K. Shibuya, et al., Distinction of pulmonary large cell neuroendocrine carcinoma from small cell lung carcinoma: a morphological, immunohistochemical, and molecular analysis, Mod. Pathol. 19 (10) (2006) 56.
[40] W. Hamanaka, N. Motoi, S. Ishikawa, et al., A subset of small cell lung cancer with low neuroendocrine expression and good prognosis: a comparison study of surgical and inoperable cases with biopsy, Hum. Pathol. 45 (5) (2014) 1045–1056.