



Prognostic and clinicopathological significance of *FGFR1* gene amplification in resected esophageal squamous cell carcinoma: a meta-analysis

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Background: Previous studies about the prognostic and clinicopathological significance of fibroblast growth factor receptor 1 (FGFR1) amplification in resected esophageal squamous cell carcinoma (ESCC) are controversial. Therefore, the aim of the current meta-analysis was to determine the association of FGFR1 amplification with prognosis and clinicopathological characteristics of resected ESCC patients.

Methods: The PubMed, EMBASE, Web of Science, The Cochrane Library, CNKI, Wanfang, VIP and SinoMed databases were searched systematically from the establishment date of databases to April 1, 2019 to identify related studies. The correlations of FGFR1 amplification of prognosis and clinicopathological characteristics in ESCC were assessed by the combined hazard ratio (HR) with 95% confidence interval (CI) and combined odds ratio (OR) with 95% CI, respectively. All statistical analyses were performed by the Stata 12.0 software.

Results: A total of nine retrospective studies involving 2,326 patients who received the surgery were included into the current meta-analysis. The results indicated that FGFR1 amplification was significantly correlated with worse overall survival (OS) (HR =1.50, 95% CI: 1.25–1.81, P<0.001), disease-free survival (DFS) (HR =1.58, 95% CI: 1.27–1.96, P<0.001), lymph node metastasis (OR =1.45, 95% CI: 1.13–1.86, P=0.004), higher TNM stage (OR =1.33, 95% CI: 1.03–1.72, P=0.027) and poorer differentiation (OR =1.10, 95% CI: 1.07–1.13, P<0.001).

Conclusions: The current meta-analysis strongly demonstrates that FGFR1 amplification is an independent prognostic risk factor for resected ESCC patients and more prevalent among patients with advanced tumor stage and poorer differentiation.

Keywords: Fibroblast growth factor receptor 1 (FGFR1); esophageal squamous cell carcinoma (ESCC); surgery; prognosis; clinicopathological characteristics; meta-analysis

Submitted Jul 18, 2019. Accepted for publication Sep 24, 2019.

doi: 10.21037/atm.2019.10.69

View this article at: <http://dx.doi.org/10.21037/atm.2019.10.69>

Introduction

In esophageal squamous cell carcinoma (ESCC), tyrosine kinase inhibitors (TKIs) mainly target the vascular endothelial growth factor receptor (VEGFR) and

epidermal growth factor receptor (EGFR), which displays important significance in clinical practice (1). The FGFR1 is one member of the FGFR family which consists of four tyrosine kinase receptors: FGFR1, FGFR2, FGFR3 and

FGFR4 and they have been found to be another potential target of TKIs. Actually, their inner structures are similar to those of some pharmacologic therapeutic targets such as VEGFRs, EGFRs and platelet-derived growth factor receptors (PDGFRs) (2); which may indicate their great clinical value.

According to previous reports, FGFRs could initiate many intracellular events to activate major proliferative and survival signal pathways; furthermore, they could affect many biological processes such as the neovascularization, wound repair and embryonic development (3). In recent years, increasing reports manifested that FGFRs play a key role in the tumorigenesis and development of several cancers (4-6). Among three main deregulation form, including the point mutation, translocation and amplification, the amplification is the most common one.

FGFR1 gene amplification has been demonstrated to show high prognostic value in several kinds of cancers such as squamous cell lung cancer (7), head and neck squamous cell carcinoma (8) and breast cancer (9). Besides, Xie *et al.* (10) proved that *FGFR1* amplification was significantly correlated with some clinicopathological characteristics like the smoking, sex and histology in non-small cell lung cancer (NSCLC), especially in squamous cell cancer (SCC). However, its association with prognosis and clinical pathological parameters of ESCC patients remains unclear now. Although there are already several studies which explored clinical significance of *FGFR1* amplification in resected ESCC, their results are different among each other (11-19).

Therefore, we conducted this meta-analysis to further determine the correlation of *FGFR1* amplification with survival and clinicopathological characteristics of ESCC patients who underwent the operation and contribute to clinical application of *FGFR1*.

Methods

Literature search

We searched the PubMed, EMBASE, Web of Science, Cochrane Library, CNKI, VIP, Wanfang and SinoMed databases for related articles published from the establishment date of databases to April 1, 2019 with the following terms “*FGFR1*”, “fibroblast growth factor receptor 1”, “esophageal”, “esophagus”, “tumor”, “cancer”, “carcinoma” and “neoplasm”. Besides, the references cited in the included studies were also identified for eligibility.

Inclusion criteria and exclusion criteria

Inclusion criteria were: (I) patients were diagnosed as ESCC pathologically and the amplification of *FGFR1* was detected by the monoclonal antibody (MA), fluorescent *in situ* hybridization (FISH) or quantitative reverse transcription polymerase chain reaction (QRT-PCR); (II) the studies described the association of *FGFR1* amplification with ESCC patient prognosis [overall survival (OS) or disease-free survival (DFS)] using the hazard ratio (HR) with 95% confidence interval (CI) or by Kaplan-Meier curves and clinicopathological characteristics of patients; (III) all patients receive the surgical therapy; (IV) the articles were published with full-texts; (V) if the data were duplicated or overlapped, only the most recent publication was included; (VI) articles were written in English or Chinese.

Exclusion criteria were as following: (I) letters, reviews, animal trials, meeting abstracts and case reports; (II) articles did not provide enough information to calculate the HR with 95% CI when HRs with 95% CIs for survival and Kaplan-Meier curves were not reported.

The literature selection was performed by two independent authors (Y Wang and Y Wu) and disagreements were resolved by discussion.

Data extraction and quality assessment

The data were extracted using an excel sheet (Microsoft Corporation) and the following information were collected: name of the first author, publication year. Country, number of patients with *FGFR1* amplification, gender, age, tumor depth, lymph node metastasis, TNM stage, differentiation status, drinking history, smoking history, treatment method, detection method, definition of *FGFR1* amplification, clinical outcomes, source of HR and HR with 95% CI.

In our study, the Newcastle-Ottawa quality assessment scale (NOS) was applied for the quality evaluation of included publications (20). Studies earning a score of 6 or higher were regarded as high-quality studies.

The process of data extraction and quality evaluation was also performed by two researchers (Y Wang and Y Wu) independently.

Statistical analysis

Correlations of *FGFR1* gene amplification with clinicopathological parameters of resected ESCC patients were estimated by the pooled odds ratios (ORs) with 95%

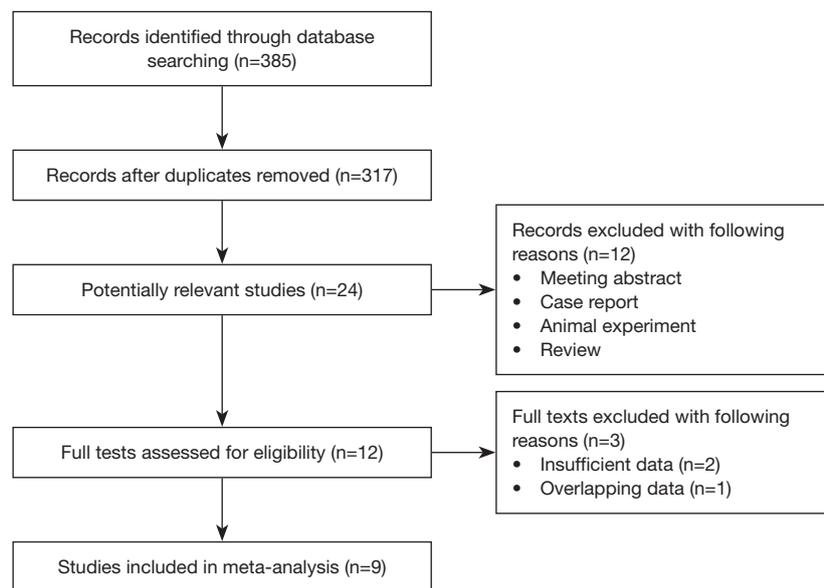


Figure 1 Flow diagram of the literature review.

CI) and correlations between *FGFR1* amplification and prognosis were assessed by the pooled HRs with 95% CIs. HRs from multivariate models were applied whenever available; if they were not reported directly, then they would be calculated from Kaplan-Meier curves with the method described by Tierney *et al.* (21). The heterogeneity among included studies was calculated using the Chi-square based Q-test and I^2 statistic (22). When significant heterogeneity was observed representing as $P < 0.10$ or/and $I^2 > 50\%$, the random effect model was applied to calculate the ORs and HRs with corresponding 95% CIs; otherwise the fixed effect model was adopted (23). Subgroup analyses based on the country and detection method were performed to explore the influence of these two factors on the prognostic value of *FGFR1* gene amplification in ESCC or potential causes of heterogeneity; and the sensitivity analysis was conducted to assess the stability of the pooled results. Begg's funnel plot and Egger's test were used to assess potential publication bias (24). P values < 0.05 were considered significant and all the statistical analyses were conducted using the Stata 12.0 software (Corporation, TX, USA).

Results

Literature search process and basic characteristics of included studies

Specific flow diagram of the current meta-analysis was

shown in *Figure 1*. A total of 9 retrospective studies (11-19) involving 2,326 resected ESCC patients were enrolled eventually according to the criteria and exclusion criteria. Among included patients, 381 (16.4%) patients were with *FGFR1* gene amplification; and the ratios of positive *FGFR1* amplification in included articles ranged from 8.6% to 64.9%. All patients received the surgery and all included studies reported the relation of *FGFR1* amplification with OS in ESCC. In most of the included studies (6/9), the FISH method was applied to measure the status of *FGFR1* gene amplification; the MA and QRT-PCR methods were used in 2 and 1 studies, respectively. Other detailed information was presented in *Table 1*.

Correlations of FGFR1 amplification with prognosis in resected ESCC

The results of meta-analyses for OS demonstrated that *FGFR1* amplification was an independent risk factor for OS of ESCC patients (HR =1.50, 95% CI: 1.25–1.81, $P < 0.001$) with low heterogeneity ($I^2 = 3.3\%$, $P = 0.407$) (*Figure 2*). Subgroup analyses for OS based on the country and detection method further verified above results with one exception (*Table 2*). There was no significant relation between *FGFR1* amplification and poor OS in ESCC patients who were detected for *FGFR1* amplification status with the MA method (HR =0.64, 95% CI: 0.34–1.22,

Table 1 Basic characteristics of included studies

Author	Year	Country	Sample size	Positive, n (%)	TNM stage	Detection method	Definition of FGFR1 amplification	Outcome	Source of HR	NOS score
Sugiura K (11)	2007	Japan	79	47 (59.5)	I–IV	MA	Stained cytoplasm of cancer cells >30%	OS	E	7
Wang D (12)	2014	China	82	13 (15.9)	I–III	FISH	FGFR1 copy number ≥ 6 or FGFR1/CEN8 ratio ≥ 2.0	OS	R	8
Kim HS (13)	2015	Korea	526	45 (8.6)	I–III	FISH	FGFR1 copy number ≥ 6 or FGFR1/CEN8 ratio ≥ 2.0 or percentage of tumor cells containing ≥ 15 or large cluster in $\geq 10\%$ cells	OS/DFS	R	8
Shimada Y (14)	2015	Japan	57	37 (64.9)	I–IVa	MA	Scores for intensity and distribution of expression ≥ 4	OS	R	7
von Loga K (15)	2015	Germany	202	18 (8.9)	I–IV	FISH	FGFR1/CEN8 ratio ≥ 2.0	OS	E	8
Kwon D (16)	2016	South Korea	173	37 (21.4)	I–III	FISH	FGFR1 copy number ≥ 6 or FGFR1/CEN8 ratio ≥ 2.0 or percentage of tumor cells containing ≥ 15 or large cluster in $\geq 10\%$ cells	OS	R	7
Wang D (17)	2017	China	556	67 (12.1)	I–III	FISH	FGFR1 copy number ≥ 6 or FGFR1/CEN8 ratio ≥ 2.2	OS/DFS	R	7
Song Q (18)	2017	China	506	44 (8.7)	I–IV	FISH	FGFR1 copy number ≥ 6 or FGFR1/CEN8 ratio ≥ 2.0 or percentage of tumor cells containing ≥ 15 or large cluster in $\geq 10\%$ cells	OS/DFS	R	7
Chen B (19)	2018	China	145	73 (50.3)	II–III	QRT-PCR	Median mRNA expression	OS/DFS	R	7

TNM, tumor-node-metastasis; MA, monoclonal antibody; FISH, fluorescent *in situ* hybridization; QRT-PCR, quantitative reverse transcription polymerase chain reaction; FGFR1, fibroblast growth factor receptor 1; CEN, centromere; OS, overall survival; DFS, disease-free survival; HR, hazard ratio; R, reported; E, estimated; NOS, Newcastle-Ottawa quality assessment scale.

$P=0.175$) without any heterogeneity ($I^2=0.0\%$, $P=0.742$).

Four articles involving 1,733 patients explored the predictive role of FGFR1 amplification on DFS in ESCC. The combined HR (95% CI) was 1.58 (1.27–1.96) without any heterogeneity ($I^2=0.0\%$, $P=0.900$), which indicated that FGFR1 amplification was a negative predictor for DFS of ESCC patients (Figure 3).

Correlations of FGFR1 amplification with clinicopathological parameters in resected ESCC

The associations between FGFR1 amplification and main clinicopathologic features such as the gender, age, tumor depth, lymph node metastasis, metastasis, TNM stage, tumor differentiation status, history of drinking and smoking. Overall, the FGFR1 amplification was

significantly associated with lymph node metastasis (N1–3 *vs.* N0) (OR =1.45, 95% CI: 1.13–1.86, $P=0.004$), TNM stage (TNM III, IV *vs.* TNM I, II) (OR =1.33, 95% CI: 1.03–1.72, $P=0.027$) and differentiation (moderate or poor *vs.* well) (OR =1.10, 95% CI: 1.07–1.13, $P<0.001$). While, no significant correlation of FGFR1 amplification with sex (male *vs.* female), age (≥ 60 *vs.* <60), tumor depth (T3, 4 *vs.* T1, 2), metastasis (positive *vs.* negative), drinking history (drinking *vs.* no drinking) or smoking history (smoking *vs.* no smoking) (Table 3).

Sensitivity analysis

To assess the stability of the pooled results, we conducted the sensitivity analysis; and it indicated that there was no single study which showed a significant influence on our

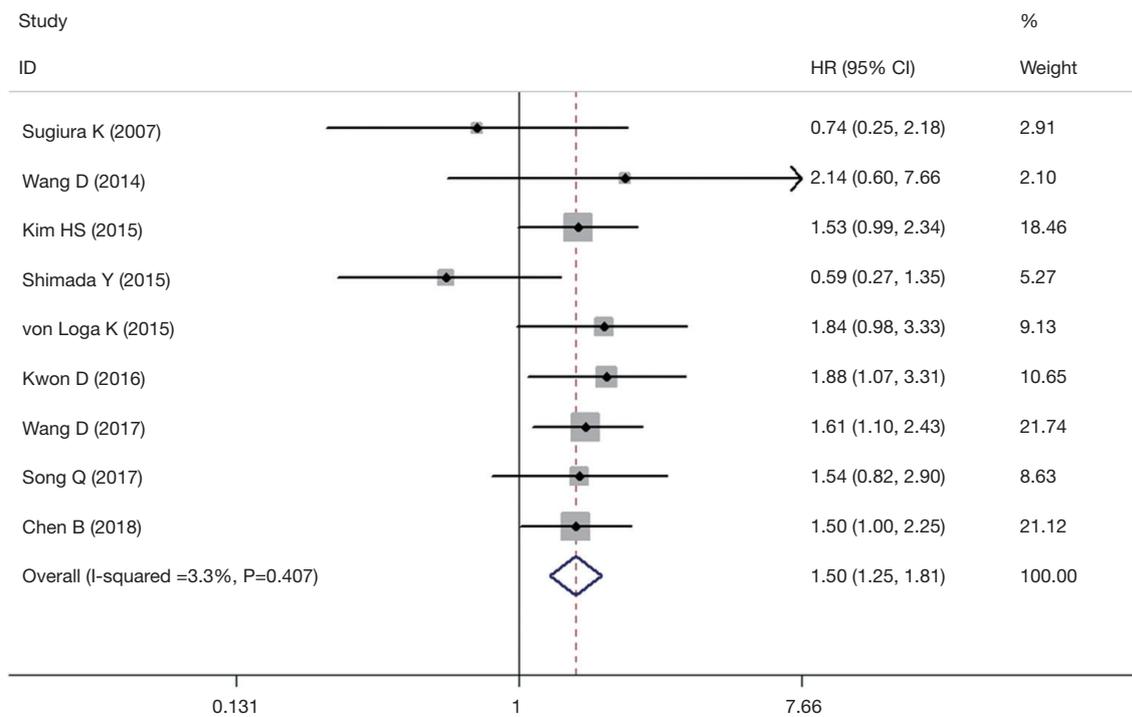


Figure 2 Forest plot of the association between FGFR1 amplification and overall survival. FGFR1, fibroblast growth factor receptor 1; HR, hazard ratio; CI, confidence interval.

Table 2 Meta-analyses for the association of FGFR1 amplification with survival of ESCC patients

Analysis	No. of studies	HR (95% CI)	Log-rank P value	I ² (%)	P value
Overall survival	9	1.50 (1.25–1.81)	<0.001	3.3	0.407
Country					
China	4	1.57 (1.22–2.03)	<0.001	0	0.962
Non-China	5	1.43 (1.09–1.87)	0.01	48.2	0.103
Detection method					
MA	2	0.64 (0.34–1.22)	0.175	0	0.742
FISH	6	1.66 (1.33–2.07)	<0.001	0	0.985
QRT-PCR	1	1.502 (1.005–2.246)	0.047	–	–
Disease-free survival	4	1.58 (1.27–1.96)	<0.001	0	0.900

FGFR1, fibroblast growth factor receptor 1; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; CI, confidence interval; MA, monoclonal antibody; FISH, fluorescent *in situ* hybridization; QRT-PCR, quantitative reverse transcription polymerase chain reaction.

results (Figure 4).

Publication bias

To detect potential publication bias, the Begg's funnel plot

and Egger's test were both applied in our study. The Begg's funnel plot was relatively symmetrical ($P=0.602$) and the P value of Egger's test was 0.319; which manifested that no significant publication bias existed in our meta-analyses (Figure 5).

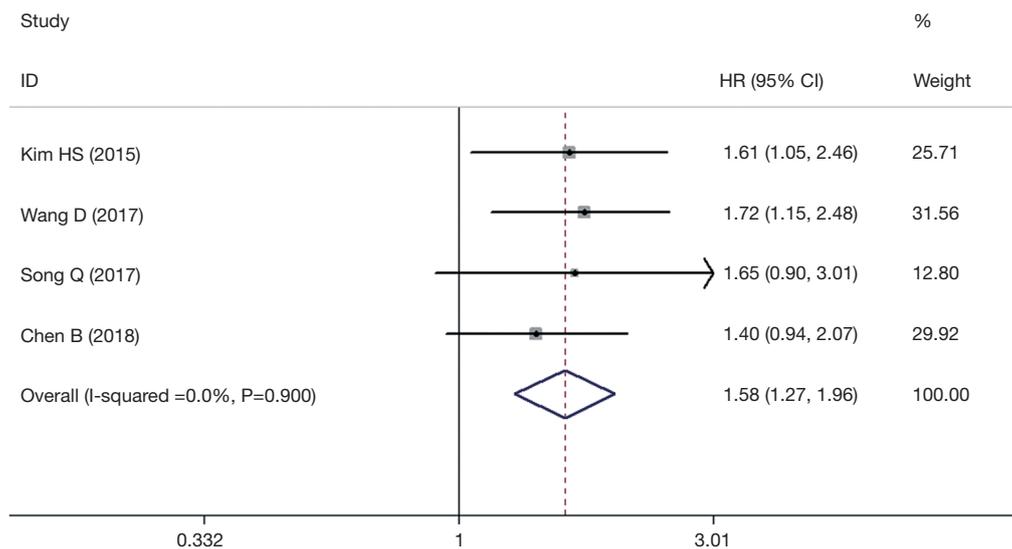


Figure 3 Forest plot of the association between FGFR1 amplification and disease-free survival. FGFR1, fibroblast growth factor receptor 1; HR, hazard ratio; CI, confidence interval.

Table 3 Correlations of FGFR1 amplification with clinicopathological characteristics

Author	Gender (M vs. F)	Age (≥ 60 vs. < 60)	Tumor depth (T3,4 vs. T1,2)	Lymph node metastasis (N+ vs. N-)	Metastasis (+ vs. -)	TNM (IV, III vs. II, I)	Differentiation (moderate or poor vs. well)	Drinking history (+ vs. -)	Smoking history (+ vs. -)
Sugiura K (11)	3.01 (0.80–11.31)	0.96 (0.39–2.38)	1.47 (0.60–3.64)	1.46 (0.57–3.72)	0.44 (0.14–1.42)	1.08 (0.44–2.70)	1.13 (0.35–3.62)	–	–
Wang D (12)	0.52 (0.15–1.82)	1.01 (0.31–3.31)	0.83 (0.23–2.99)	5.92 (1.63–21.53)	–	0.36 (0.04–3.01)	0.70 (0.17–2.94)	3.33 (0.68–16.20)	0.57 (0.16–1.95)
Kim HS (13)	1.69 (0.39–7.26)	–	0.94 (0.51–1.73)	1.02 (0.55–1.87)	–	1.28 (0.68–2.39)	0.87 (0.44–1.75)	–	14.14 (1.93–103.78)
Shimada Y (14)	0.92 (0.15–5.50)	–	1.40 (0.43–4.53)	1.95 (0.58–6.53)	3.68 (0.41–32.95)	2.36 (0.77–7.28)	2.89 (0.56–14.95)	–	–
von Loga K (15)	1.27 (0.40–4.05)	–	0.70 (0.26–1.86)	1.17 (0.44–3.10)	2.47 (0.86–7.08)	0.96 (0.36–2.52)	1.10 (1.05–1.15)	–	–
Kwon D (16)	–	0.47 (0.21–1.01)	1.42 (0.69–2.94)	1.36 (0.66–2.83)	–	1.23 (0.58–2.62)	1.84 (0.66–5.14)	–	0.78 (0.30–2.01)
Wang D (17)	1.73 (0.72–4.15)	–	1.39 (0.81–2.36)	1.38 (0.80–2.39)	–	1.29 (0.71–2.33)	0.88 (0.51–1.51)	1.15 (1.11–1.19)	1.98 (0.95–4.12)
Song Q (18)	1.43 (0.59–3.49)	0.88 (0.47–1.63)	1.72 (0.92–3.21)	1.99 (1.05–3.78)	1.49 (0.63–3.52)	1.86 (1.00–3.47)	1.10 (1.07–1.13)	–	0.80 (0.42–1.53)
Chen B (19)	1.20 (0.38–3.77)	–	0.80 (0.36–1.76)	1.21 (0.63–2.35)	–	1.28 (0.67–2.46)	4.24 (0.46–38.85)	3.13 (1.57–6.26)	0.75 (0.35–1.62)
Overall	1.37 (0.91–2.06)	0.77 (0.52–1.15)	1.20 (0.94–1.55)	1.45 (1.13–1.86)	1.37 (0.78–2.40)	1.33 (1.03–1.72)	1.10 (1.07–1.13)	1.99 (0.85–4.66)	1.11 (0.61–2.00)

FGFR, fibroblast growth factor receptor; F, female; M, male; TNM, tumor-node-metastasis.

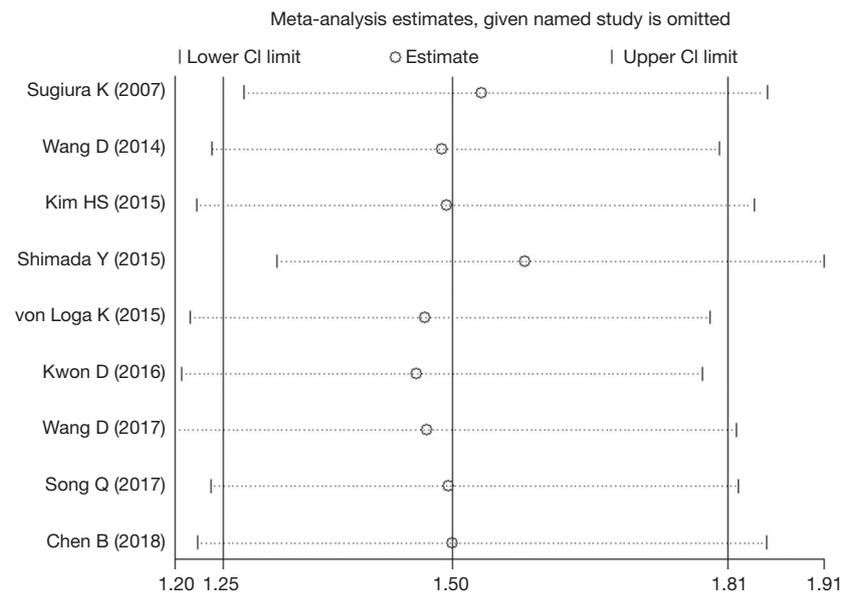


Figure 4 Sensitivity analysis of the association between FGFR1 amplification and overall survival. FGFR1, fibroblast growth factor receptor 1; CI, confidence interval.

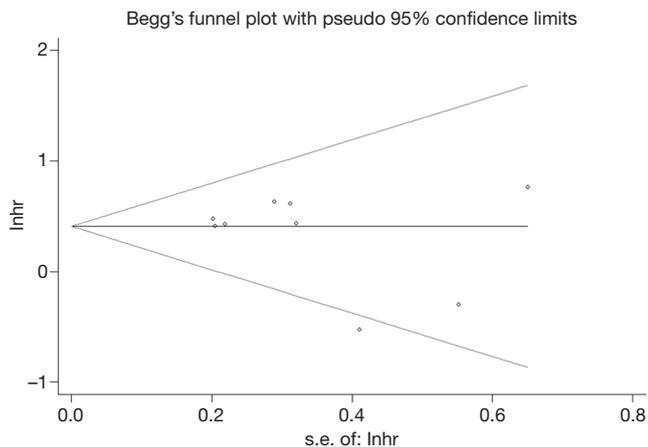


Figure 5 Begg's funnel plot of the association between FGFR1 amplification and overall survival. FGFR1, fibroblast growth factor receptor 1.

Discussion

Esophageal cancer, as one of the most aggressive malignancies globally, consists of two main histological subtypes, ESCC and esophageal adenocarcinoma (25,26). In Asian countries, ESCC accounts for the majority of all esophageal cancer cases (25,26). Although there are several kinds of novel therapy methods such as the targeted therapy,

the main treatments of ESCC are still traditional surgery and chemoradiotherapy and the prognosis remains poor.

Our research demonstrated that overexpression of *FGFR1* gene was significantly associated with higher tumor stage, poorer differentiation and worse survival after the surgery in resected ESCC. According to previous studies, there are some potential mechanisms by which FGFR1 amplification is related to development and prognosis of ESCC. FGFR1, activated by fibroblast growth factor, was considered to play a role in provoking the signal transduction and activator of transcription (STAT) pathway directly or indirectly through Janus kinases (JAKs) and then inducing cellular proliferation and survival (27,28). However, Chen *et al.* (19) reported that the inhibition of mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK) pathway may mostly contribute to suppression of FGFR1 expression and the MEK/ERK pathway may be the major signaling pathway which is mediated by FGFR1 in the progression of ESCC cells. Besides, another signaling pathway, epithelial-mesenchymal transition (EMT) which is modulated by the FGF1-FGFR1 axis, has been demonstrated to contribute to the metastasis of tumor cells in multiple cancers (29-31). Jiao *et al.* (29) found that after blocking the FGF1-FGFR1 axis through FGFR1 specific siRNAs, the role of FGF1 in promoting

Cal27 cells migration and invasion abilities through the FGFR1 would be obviously inhibited, which indicated that FGFR1 amplification has an effect on the metastasis of tumor cells. Furthermore, FGFR1 was found to play a role in affecting the stem cell-like phenotype through regulating the expression and activity of GLI2 via the ERK pathway in lung SCC (32), which may indicate the role of *FGFR1* gene in the differentiation of cancers; and our meta-analysis did demonstrate the significant association between *FGFR1* gene amplification and differentiation in ESCC.

Based on these mechanisms mentioned above, some small molecular inhibitors targeting FGFR, such as the AZD4547, JNJ-42756493 and PRN1371, have been invented and applied in preclinical or clinical trials with obvious anti-tumor effect (33-37). However, there is no definite report that anti-FGFR1 therapy could be beneficial for ESCC patients with FGFR1 amplification significantly up to now.

Although there were a few articles which explored prognostic and clinicopathological significance of FGFR1 amplification in resected ESCC patients, their results were inconsistent. For example, among nine included studies, only three articles (16,17,19) reported that FGFR1 amplification was an independent prognostic risk factor for ESCC patients and Song *et al.* (18) reported that FGFR1 amplification was significantly associated with TNM stage, which are consistent with our results. Therefore, the current meta-analysis is urgently needed to determine the association of FGFR1 with prognosis and clinicopathological parameters in resected ESCC and we did verify the significant correlation between FGFR1 amplification and lymph node metastasis status, TNM stage, differentiation status, OS and DFS of ESCC patients. We did not find the significant relation between FGFR1 amplification and drinking after combining the three eligible studies (12,17,19), although Wang *et al.* (17) and Chen *et al.* (19) both indicated a significant correlation between drinking and FGFR1 amplification. Therefore, more researches are still needed to further testify the correlation of drinking and FGFR1 amplification. Similarly, Kim *et al.* (13) manifested a strongly significant association between smoking and FGFR1 amplification, but we came up with a negative result after combining several other studies which also reported negative results.

Actually, for FGFR1 amplification in ESCC, there are many fields which deserve further researches. First of all, how to predict the FGFR-targeted therapy response is still a big challenge for now, although increasing evidence

indicates that FGFR1 mRNA expression may serve as a promising biomarker in predicting treatment outcomes of FGFR inhibitors (38). Whether the anti-FGFR therapy is suitable for patients who cannot receive the surgery due to the advanced tumor stage or other causes, better than chemoradiotherapies as postoperative adjuvant treatment or beneficial for patients with recurrent ESCCs remains unclear. Besides, according to the results of our meta-analysis, FGFR1 amplification was not an independent prognostic factor for patients who were detected by the MA method (16,19), but Sugiura *et al.* (11) and Shimada *et al.* (14) used different thresholds to define FGFR1 amplification. Therefore, it is necessary to compare the role of MA in predicting prognosis of resected ESCC patients with those of the other two methods and further determine the definition of overexpression of *FGFR1* gene when using the MA method.

There are some limitations in our study. First, all included studies are retrospective studies with relatively small sample sizes, which may cause some bias. Second, due to the lack of original data, we were unable to perform subgroup analyses for OS based on other important factors such as sex, age and TNM stage. Third, it is well-known that the occurrence of ESCC is related to diet and race; unfortunately, none of the included studies reported the association of FGFR1 amplification with these factors.

In conclusion, our study demonstrated that FGFR1 amplification was significantly correlated with prognosis, tumor stage and differentiation status of resected ESCC patients. More well-designed prospective studies are still needed to clarify the real value of our findings.

Acknowledgments

None.

Footnote

Conflicts of Interest: 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. 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.

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Cite this article as: Wang Y, Wu Y, Li J, Lai Y, Zhou K, Che G. Prognostic and clinicopathological significance of *FGFR1* gene amplification in resected esophageal squamous cell carcinoma: a meta-analysis. *Ann Transl Med* 2019;7(22):669. doi: 10.21037/atm.2019.10.69