Original Article

Fatal toxic effects related to EGFR tyrosine kinase inhibitors based on 53 cohorts with 9,569 participants

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Background: To estimate the incidence and susceptible factors of fatal toxic effects related to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs).

Methods: PubMed and Embase were thoroughly searched for clinical trials based on the following terms and corresponding Medical Subject Heading ones: "erlotinib", "gefitinib", "afatinib", "dacomitinib", "osimertinib", and "non-small-cell lung cancer (NSCLC)". A total of 53 eligible cohorts with 9,569 participants were collected.

Results: A total of 105 cases of fatal toxic effects related to EGFR-TKIs occurred in 53 cohorts. The overall incidence was 1.33% [95% confidence interval (CI): 1.08–1.63%]. The odds and incidence were apparently higher in Japanese group (compared with non-East Asian group) [2.72 *vs.* 1.30, P=0.015; odds ratio (OR): 2.26, 95% CI: 1.17–4.37, P=0.015], in first-line treatment group (compared with EGFR-TKI retreatment group) (1.54 *vs.* 0.69, P=0.028; OR: 2.41, 95% CI: 1.10–5.26, P=0.028), and in the trial phase II (compared with trial phase III) (1.82% *vs.* 1.11%, P=0.009; OR: 1.73, 95% CI: 1.15–2.62, P=0.009). Notably, the Japanese group was higher than non-East Asian group after controlling for the treatment-line and trial phase (OR: 2.16, 95% CI: 1.12–4.16, P=0.022). Interstitial lung disease (ILD) was predominant in 29 fatal causes followed by pneumonia, respiratory failure and diarrhea.

Conclusions: The overall incidence of fatal toxic effects related to EGFR-TKIs was 1.33%, and the major fatal cause was ILD, followed by pneumonia, respiratory failure and diarrhea. The susceptible factor of fatal toxic effects related to EGFR-TKIs was the Japanese group. This study provided a capability for clinicians to predict and detect high-risk populations of fatal toxic effects.

Keywords: Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs); fatal toxic effects; meta-analysis

Submitted Dec 13, 2019. Accepted for publication Mar 12, 2020.
doi: 10.21037/jtd-19-4000A
View this article at: http://dx.doi.org/10.21037/jtd-19-4000A

Introduction

Lung cancer is the most frequent malignancy and the leading cause of cancer death (1). Over the decade, the management of treatment options for non-small cell lung cancer (NSCLC) has continually evolved. Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), comprising erlotinib, gefitinib, afatinib, dacomitinib and osimertinib, were primary regimens for NSCLC with EGFR mutation, which has significantly prolonged progression-free survival compared with platinum-based chemotherapy (2,3) and generally coupled with tolerable adverse events like rash and diarrhea (4,5). Despite these benefits, however, fatal toxic effects might occasionally occur in individuals treated with EGFR-TKIs.

The majority of prior studies on severe toxic effects involved pulmonary toxicities, especially interstitial lung disease (ILD), and the incidence was approximately 0.20–1.00% (6-8). The minority of prior studies provided various severe causes, including hepatotoxicity, dyspnea, sepsis, and unknown cause (9,10). Additionally, a meta-analysis on both lung cancer and other cancers exhibited that the overall incidence of fatal toxic effects was 1.9% (11). However, the aforementioned studies hardly provided the precise incidence, the comprehensive spectrum and the susceptible factors of fatal toxic effects related to EGFR-TKIs in patients with NSCLC. Consequently, it is imperative to systematically estimate the incidence and provide a detailed spectrum as well as susceptible factors of fatal toxic effects related to EGFR-TKIs through extensive databases.

Herein, we performed a meta-analysis of patients with NSCLC treated with EGFR-TKIs, comprising erlotinib, gefitinib, afatinib, dacomitinib and osimertinib, to determine the accurate incidence, comprehensive spectrum and susceptible factors of fatal toxic effects related to EGFR-TKIs.

Methods

Literature search

PubMed and Embase were thoroughly searched for clinical trials based on the following terms and corresponding Medical Subject Heading ones: “erlotinib”, “gefitinib”, “afatinib”, “dacomitinib”, “osimertinib” and “NSCLC” before October 25, 2018.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (I) study on NSCLC treated with EGFR-TKIs, including erlotinib, gefitinib, afatinib, dacomitinib and osimertinib; (II) availability of fatal toxicity results; (III) articles published in English. On the contrary, the exclusion criteria were as follows: (I) fatal toxic effects related to EGFR-TKIs unavailable; (II) trial phase undefined; (III) full texts unavailable; (IV) other agents combined; (V) retrospective articles.

Data extraction

The type of EGFR-TKIs, generation of drugs, trial phase of studies, treatment-line, EGFR status, study regions, average age, the number and type of fatal causes, and the total number of patients were extracted from eligible articles. Defining 63 as a cut-off age since it was the median age of eligible studies. The treatment-line was assigned into three groups as follows: (I) first-line treatment group: without any systematic treatment; (II) prior chemotherapy group: treated with EGFR-TKI following chemotherapy; (III) EGFR-TKI retreatment group: treated with distinct types of EGFR-TKI following EGFR-TKI therapy. Fatal toxic effects related to EGFR-TKIs were defined as that death was merely attributed to drugs rather than disease progression or ambiguous reasons. To accommodate the different terminology used in various studies, pneumonitis and interstitial pneumonitis were categorized into ILD, aspirational pneumonia and lung infection into pneumonia and respiratory decompensation into respiratory failure.

Screening of eligible articles and extracting of data was conducted individually by two reviewers, conforming to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (12). Any discrepancy was resolved by a third researcher.

Statistical methods

The study was focused on the evaluation of rare events (the incidence of fatal toxic effects was far below 20%). Thus, the raw data was conformed to a normal distribution by logit transformation for improving the validity of the analysis (13). Mixed-effects logistic regression was used for calculating pooled incidence and corresponding 95% confidence intervals (CI) of fatal toxic effects related to EGFR-TKIs. Subgroup analyses were performed based on EGFR-TKI agents, generation of the drug, trial phase of studies, treatment-line, EGFR status, study regions and average age ($P<0.05$ indicated statistical significance). Heterogeneity was assessed by Higgins inconsistency index

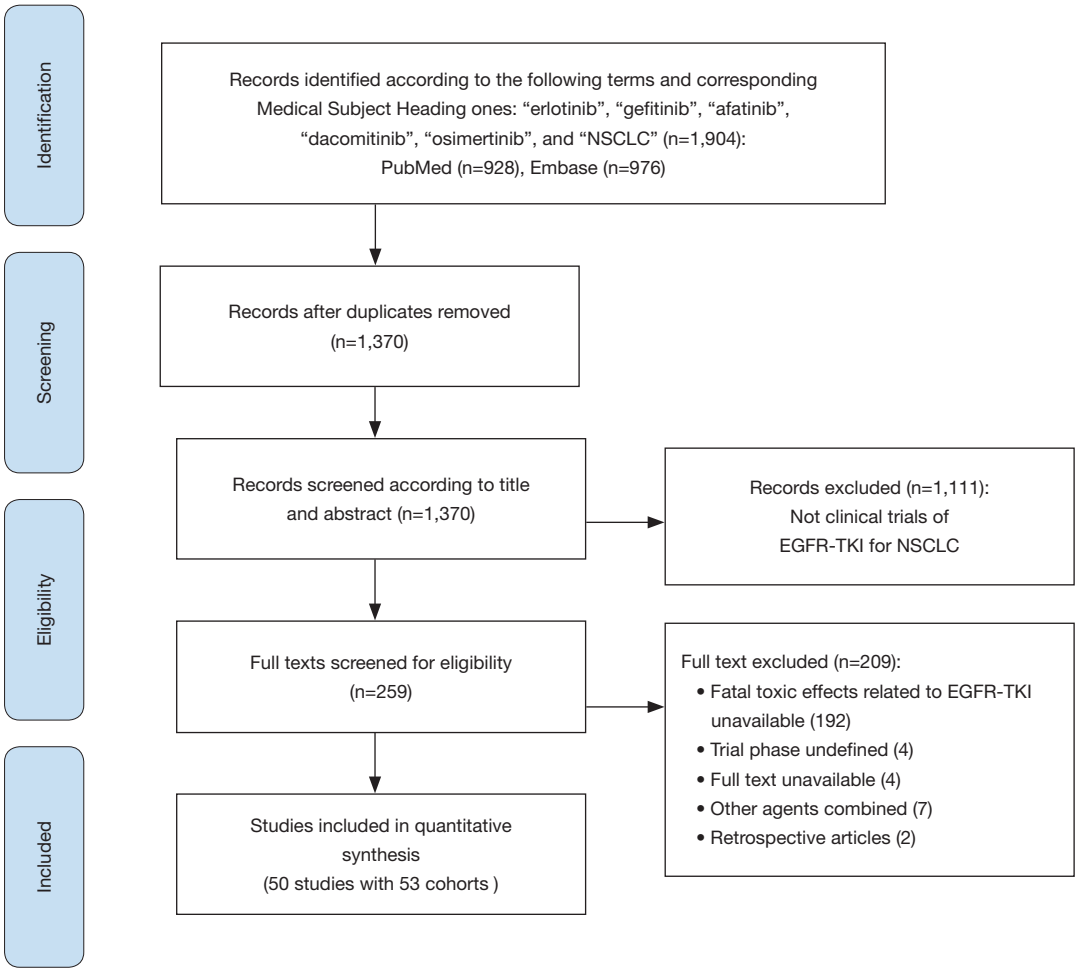

Figure 1 Flow diagram of study inclusion. NSCLC, non-small-cell lung cancer; EGFR-TKIs, epidermal growth factor receptor tyrosine kinase inhibitors.

(I^2) test and values higher than 50% implied substantial heterogeneity (14). The univariate meta-regression analysis was carried out to estimate the correlation between various covariates and the incidence of fatal toxic effects related to EGFR-TKIs. The multivariate meta-regression analysis was performed to distinguish susceptible factors from diverse variables, comprising a value of $P<0.05$ that occurred in univariate meta-regression analysis and important clinical factors. Publication bias was evaluated by funnel plot and Egger's or Begg's tests (15). Potential outliers were identified by the value of externally studentized residuals, which greater than 2 indicated outliers (16), and influential studies would be marked with red in the influence plot.

Pooled analyses were conducted by the “metafor” and “meta” packages in R version 3.4.4 (R foundation).

Results

Eligible studies and characteristics

A total of 1,904 records were screened and evaluated for eligibility, and 50 studies, involving erlotinib (17-39), afatinib (40-45) and other EGFR-TKIs (3,46-65). Finally, 53 cohorts with 9,569 participants were identified (*Figure 1*). Totally, 105 cases of fatal toxic effects related to EGFR-TKIs occurred in 53 cohorts. All studies were prospective clinical trials.

A study with phase II/III was categorized into phase III study (44), which had two deaths related to afatinib.

Table 1 Characteristics of eligible trial cohorts

Study characteristics	Contents	Cohorts of first-line treatment, prior chemotherapy and EGFR retreatment (n=53), n (%)
EGFR-TKI agents	Erlotinib	25 (47.17)
	Gefitinib	15 (28.30)
	Afatinib	5 (9.43)
	Dacomitinib	4 (7.55)
	Osimertinib	4 (7.55)
Generation	First	40 (75.47)
	Second	9 (16.98)
	Third	4 (7.55)
Treatment line	First-line	24 (45.28)
	Prior chemotherapy	23 (43.40)
	EGFR retreatment	5 (9.43)
	Mixed[†]	1 (1.89)
Trial phase	II	28 (52.83)
	III	24 (45.28)[‡]
	I	1 (1.89)
EGFR status	Mixed[§]	32 (60.38)
	Mutation	18 (33.96)
	No mutation	3 (5.66)
Study regions	Japan	10 (18.87)
	China	1 (1.89)
	Korea	2 (3.77)
	Mixed[¶]	24 (45.28)
	Non-East Asia[¶¶]	16 (30.19)
Average age	>63 years	26 (49.06)
	≤63 years	25 (47.17)
	Unknown	2 (3.77)

[†], studies comprised the participants from prior chemotherapy and first-line therapy group; [‡], one study with phase II/III was categorized into phase III study; [§], studies included the following three status: mutation, no mutation, and unknown; [¶], studies included at least one of the following countries: Japan, China, Korea; [¶¶], studies excluded countries as follows: Japan, China, Korea. EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor.

Besides, 18 cases of fatal toxic effects related to EGFR-TKIs occurred in three studies incorporating six cohorts (42,49,62). Only one study was phase I (46), which possessed one death related to osimertinib. Erlotinib was dominantly used, and first-generation EGFR-TKI composed of erlotinib and gefitinib was frequently used in 53 cohorts. Detailed characteristics of 53 eligible cohorts were presented in *Table 1*.

Incidence of fatal toxic effects related to EGFR-TKIs

The overall incidence of fatal toxic effects related to EGFR-

Table 2 Subgroup analyses and univariate meta-regression of fatal toxic effects

Study characteristics	Contents	Fatal toxic effects		P
		Incidence (%) (95% CI)	OR (95% CI)	
Overall	–	1.33 (1.08–1.63)	NA	–
EGFR-TKI agents	Gefitinib	1.55 (0.93–2.57)	2.17 (0.84–5.61)	0.111
	Erlotinib	1.47 (1.11–1.96)	1.98 (0.79–4.96)	0.147
	Afatinib	1.18 (0.70–1.98)	1.51 (0.53–4.33)	0.442
	Dacomitinib	0.83 (0.43–1.59)	1.12 (0.37–3.44)	0.841
	Osimertinib	0.73 (0.30–1.76)	Ref	–
Generation	First	1.51 (1.18–1.94)	2.04 (0.84–4.99)	0.117
	Second	1.02 (0.67–1.54)	1.33 (0.51–3.52)	0.561
	Third	0.73 (0.30–1.76)	Ref	–
Treatment line	First-line	1.54 (1.07–2.22)	2.41 (1.10–5.26)	0.028*
	Prior chemotherapy	1.30 (0.99–1.70)	1.90 (0.88–4.10)	0.102
	Mixed[†]	0.63 (0.20–1.93)	0.91 (0.23–3.61)	0.891
	EGFR-TKI retreatment	0.69 (0.34–1.40)	Ref	–
Trial phase	II	1.82 (1.30–2.56)	1.73 (1.15–2.62)	0.009*
	I	0.40 (0.06–2.75)	0.36 (0.05–2.68)	0.318
	III	1.11 (0.87–1.41)	Ref	–
EGFR status	No mutation	2.41 (0.91–6.25)	2.43 (0.79–7.47)	0.122
	Mixed[‡]	1.42 (1.09–1.85)	1.44 (0.88–2.34)	0.145
	Mutation	1.02 (0.69–1.50)	Ref	–
Study regions	Japan	2.72 (1.53–4.77)	2.26 (1.17–4.37)	0.015*
	China	2.04 (0.66–6.13)	1.58 (0.46–5.46)	0.469
	Korea	1.60 (0.40–6.18)	1.24 (0.28–5.39)	0.778
	Mixed[§]	1.07 (0.83–1.36)	0.82 (0.49–1.37)	0.440
	Non-East Asia[¶]	1.30 (0.83–2.03)	Ref	–
Average age	>63 years	1.38 (1.03–1.86)	1.10 (0.71–1.72)	0.668
	Unknown	1.37 (0.52–3.60)	1.11 (0.36–3.44)	0.862
	≤63 years	1.21 (0.86–1.70)	Ref	–

*, a value of P<0.05 indicated statistical significance; [†], studies comprised the participants from prior chemotherapy and first-line therapy group; [‡], studies included the following three status: mutation, no mutation, and unknown; [§], studies included at least one of the following countries: Japan, China, and Korea; [¶], studies excluded countries as follows: Japan, China, and Korea. CI, confidence interval; OR, odds ratio; NA, not available; Ref, reference group; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor.

TKIs was 1.33% (95% CI: 1.08–1.63%). Heterogeneity was not observed in our study (I^2=0%, P=0.60). Subgroup analyses were performed based on EGFR-TKI agents, generation of the drug, trial phase of studies, treatment-line, EGFR status, study regions and average age. The results were presented in *Table 2*. Notably, the incidence was apparently higher in the Japanese group (compared with the non-East Asian group) (2.72% *vs.* 1.30%, P=0.015),

Table 3 Results of multivariate meta-regression of fatal toxic effects

Variables	Contents	OR (95% CI)	P
Study regions	Japan	2.16 (1.12–4.16)	0.022*
	China	2.25 (0.62–8.17)	0.219
	Korea	1.45 (0.32–6.45)	0.629
	Mixed§	1.13 (0.63–2.01)	0.689
	Non-East Asian¶	Ref	–
Trial phase	II	1.48 (0.92–2.39)	0.108
	I	0.65 (0.08–5.38)	0.687
	III	Ref	–
Treatment-line	First-line	2.01 (0.85–4.73)	0.110
	Prior chemotherapy	1.70 (0.74–3.92)	0.211
	Mixed†	1.03 (0.26–4.12)	0.965
	EGFR retreatment	Ref	–

*, a value of P<0.05 indicated statistical significance; §, studies included at least one of the following countries: Japan, China, and Korea; ¶, studies excluded countries as follows: Japan, China, and Korea; †, studies comprised the participants from prior chemotherapy and first-line therapy group. OR, odds ratio; CI, confidence interval; Ref, reference group; EGFR, epidermal growth factor receptor.

in first-line treatment group (compared with EGFR-TKI retreatment group) (1.54% *vs.* 0.69%, P=0.028), and in the trial phase II (compared with trial phase III) (1.82% *vs.* 1.11%, P=0.009). No significant distinction was observed for the incidence among Asian groups without Japanese, the type of EGFR-TKIs, generation of drugs, EGFR status, and average age.

The results of univariate meta-regression analysis showed that the odds were evidently higher in the Japanese group than non-East Asian group [odds ratio (OR): 2.26, 95% CI: 1.17–4.37, P=0.015], higher in first-line treatment group than EGFR-TKI retreatment group (OR: 2.41, 95% CI: 1.10–5.26, P=0.028), and higher in the trial phase II than trial phase III (OR: 1.73, 95% CI: 1.15–2.62, P=0.009). No significant distinction for the odds among the type of EGFR-TKIs, generation of drugs, EGFR status and average age. The detailed results were showed in *Table 2*.

The three factors (study regions, the trial phase, and the treatment-line) were included in multivariate meta-regression analysis for identifying susceptible factors. The detailed results were presented in *Table 3*. Impressively, the Japanese group had a markedly higher incidence than non-East Asian group after controlling the treatment-line and trial phase (OR: 2.16, 95% CI: 1.12–4.16, P=0.022). However, no significant discrepancy existed in the trial phase II and phase III after adjusting to the treatment-line and study regions. Additionally, a similar trend was found in different treatment-line group following controlling for study regions and the trial phase.

A potential outlier was noted by the forest plot of the overall incidence presented in *Figure 2*. The value of externally studentized residuals of the study (8) was larger than 2 (z=4.05). Thus, it was regarded as a potential outlier. To determine whether the study might impact the overall incidence, we performed a plot of influence and the influential study would be marked with red (*Figure 3*). Thus, the study (52) was regarded as influential, and the re-estimated incidence was 1.25% when the study (52) was removed from the 53 cohorts.

The spectrum of fatal toxic effects related to EGFR-TKIs

To provide a comprehensive spectrum of fatal toxic effects related to EGFR-TKIs, we thoroughly evaluated the types among 105 fatal cases. A total of 29 fatal causes were documented, among which ILD was highly predominant. Subsequent fatal causes were as follows: pneumonia, respiratory failure, diarrhea, hemoptysis, pulmonary infiltrates, hepatic and renal failure, heart failure and unknown cause. Moreover, we noted the respiratory system was most frequently involved, followed by the digestive system. A detailed spectrum of fatal toxic effects related to

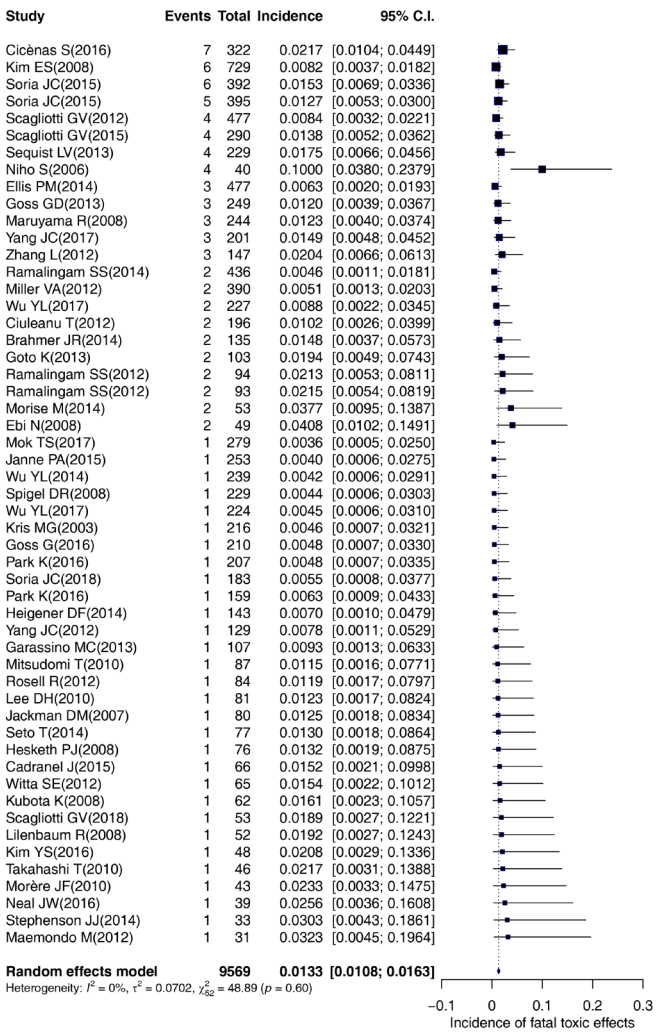

Figure 2 Forest plot of the overall incidence of fatal toxic effects related to EGFR-TKIs. EGFR-TKIs, epidermal growth factor receptor tyrosine kinase inhibitors; CI, confidence interval.

EGFR-TKIs was presented in *Table 4*. Notably, ILD was the most frequent fatal cause regardless of various regimens.

Publication bias

The funnel plot of the incidence of fatal toxic effects related to EGFR-TKIs was asymmetric (*Figure 4*). However, no evidence of publication bias was provided for the incidence of fatal toxic effects according to Egger's test (P=0.144).

Discussion

To the best of our knowledge, this study provided the most comprehensive analysis of fatal toxic effects related to EGFR-TKIs through widespread databases. The overall incidence was 1.33%, which was significantly higher in the Japanese group (compared with the non-East Asian group), in the first-line treatment group (compared with the EGFR-TKI retreatment group), and in the trial phase II (compared with trial phase III). The susceptible factor of fatal toxic effects related to EGFR-TKIs was the Japanese group. ILD was predominant fatal cause regarding different agents.

Despite the number of fatal toxic effects related to EGFR-TKIs was notable (n=105), the incidence was rare for patients with NSCLC (1.33%). The result was different from the prior study including 15 trials whose incidence was 1.7% (66), which might derive from diverse amounts of eligible studies. Moreover, dominant fatal cause was ILD,

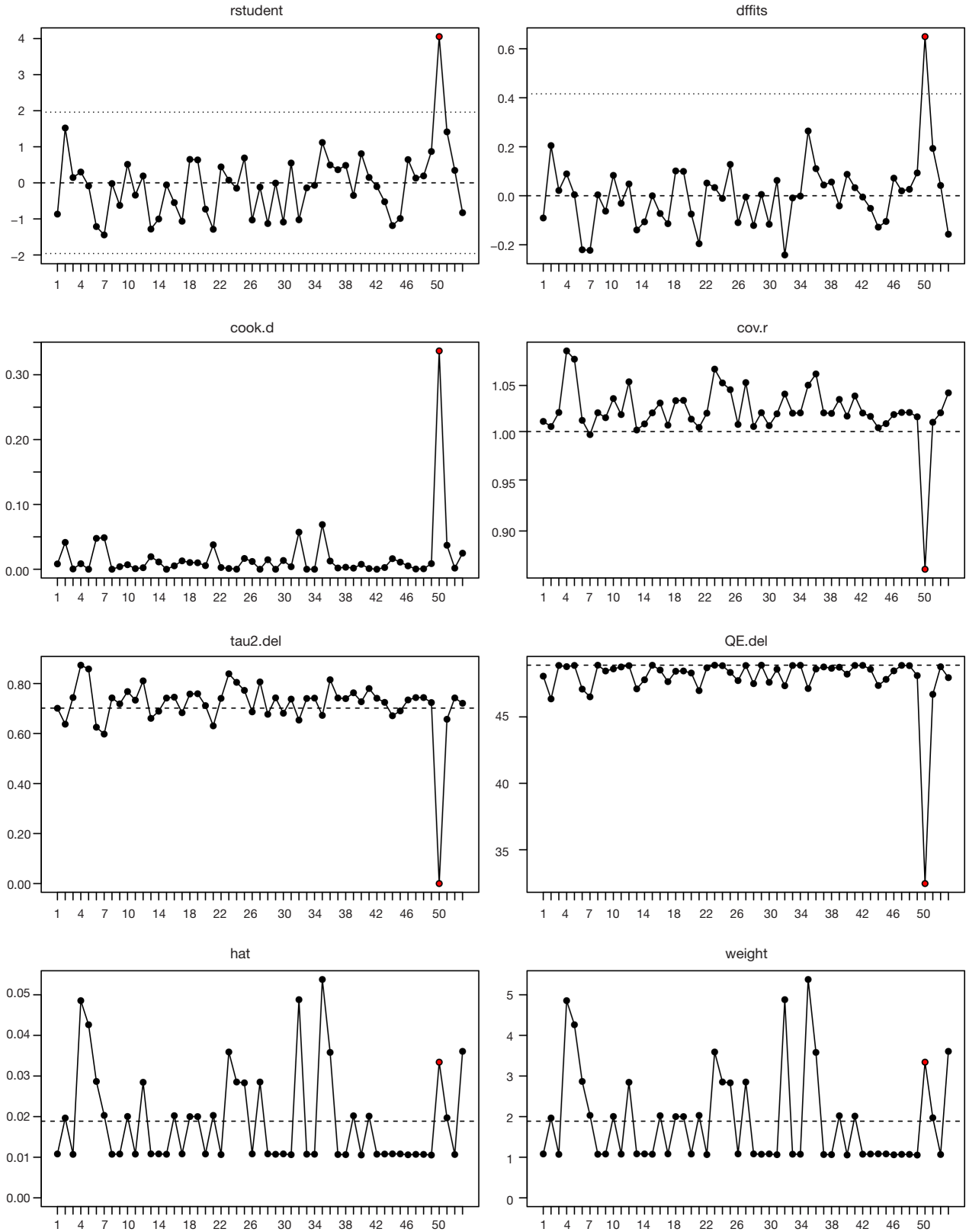

Figure 3 The plot of influential study. The influential study was marked with red.

Table 4 Complete spectrum of fatal toxic effects related to EGFR-TKIs

Fatal toxic types	Fatal causes	No.
Respiratory system (N=67)	ILD	39
	Pneumonia	12
	Respiratory failure	8
	Hemoptysis	2
	Pulmonary infiltrates	2
	Pulmonary embolism	1
	Allergic alveolitis	1
	Dyspnea	1
	Pulmonary hemorrhage	1
Digestive system (N=10)	Diarrhea	3
	Peritonitis	1
	Intestinal obstruction	1
	Cholelithiasis/Liver disease	1
	Intestinal ischemia	1
	Jaundice	1
	Hepatotoxicity	1
	Sigmoid colon diverticulitis/rupture	1
Others (N=13)	Hepatic and renal failure	2
	Heart failure	2
	Acute renal failure	1
	General physical health deterioration	1
	Cardiac arrest	1
	Drown	1
	Bullous dermatitis	1
	Pneumonia aspiration/renal failure/ acute cardiac arrest	1
	Sudden death	1
	Sepsis	1
	Subdural hemorrhage	1
Unknown (N=15)	NA	15
Total	–	105

No., the case of fatal causes; NA, not available; EGFR-TKIs, epidermal growth factor receptor tyrosine kinase inhibitors; ILD, interstitial lung disease.

which was analogous to that of prior study (10). However, this study firstly provided the most detailed spectrum and susceptible factors of fatal toxic effects related to EGFR-TKIs based on widespread databases.

Although the precise interpretation of a higher incidence of fatal toxic effects for the Japanese group remained unclear, the result might be attributed to environmental factors and genetic polymorphisms (67). Consequently, it was crucial to further explore the underlying mechanism. Compared with the first-line treatment group, we found that individuals repeatedly used EGFR-TKIs might less likely to suffer from a drug-related death. Intriguingly, participants enrolled in the trial phase II possessed a higher incidence than trial phase III. The possible interpretation was that the design of subsequent trials was optimized according to the experience of early trials to facilitate the contraction of incidence. Additionally, we scrutinized the 53 cohorts and found that the majority of studies on the Japanese group were trial phase II (8/10). Thus, it should be cautious to interpret the result. Furthermore, we also noted the respiratory system was most frequently involved. Therefore, pulmonary adverse events occurring in patients with EGFR-TKIs treatment were needed to be handled as soon as possible. Further researches should be taken to minimize the fatal toxic effects related to EGFR-TKIs.

Regardless of the outlier that was observed in this study, we remained to enroll the study (52) which included potential predisposing factors of fatal toxic effects related to EGFR-TKIs (Japanese group, first-line treatment group and the trial phase II). The incidence of fatal toxic effects on a single study was 10%, which significantly higher than the overall incidence (1.33%). Therefore, if we deleted the study (52), the credibility of the results might be undermined.

Some limitations we encountered were as follows: firstly, these events we estimated were rare and incidence was far below 20%, thus we thoroughly screened and evaluated eligible studies via widespread database; secondly, the causality between drugs and fatal toxic effects was not clearly stated in several studies, hence we had to select the studies that definitely stated fatal causes were attributed to drugs rather than disease progression or ambiguous reasons; finally, as unknown cause occurred in several studies, which hindered detailed analysis of fatal toxic effects.

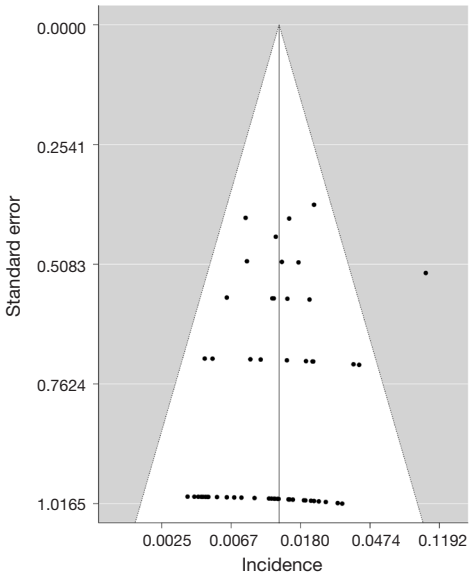

Figure 4 Funnel plot of publication bias in the meta-analysis.

In conclusion, the overall incidence of fatal toxic effects related to EGFR-TKIs was 1.33%, and the major fatal cause was ILD followed by pneumonia and respiratory failure. The pulmonary system was the most frequently involved. The susceptible factor of fatal toxic effects related to EGFR-TKIs was the Japanese group. The study provided a capability for clinicians to predict and detect high-risk populations of fatal toxic effects.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-19-4000A). 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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Cite this article as: Xie X, Wang X, Wu S, Yang H, Liu J, Chen H, Ding Y, Ling L, Lin H. Fatal toxic effects related to EGFR tyrosine kinase inhibitors based on 53 cohorts with 9,569 participants. J Thorac Dis 2020;12(8):4057-4069. doi: 10.21037/jtd-19-4000A

