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Safety Evaluation of EGFR-TKI Therapy in Patients with Non-Small Cell Lung Cancer: A Real-World Study Based on the FAERS Database

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Abstract:

Background: Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR-TKIs) have been widely employed in the treatment of non-small cell lung cancer (NSCLC) patients harboring EGFR mutations. However, systematic comparative studies assessing the adverse events (AEs) associated with various EGFR-TKI agents remain relatively scarce.

Method: This study conducted a real-world analysis of the safety profile of EGFR-TKI treatment in NSCLC patients, utilizing data from the FDA Adverse Event Reporting System (FAERS) database. A total of 22,160 AE reports pertaining to afatinib, osimertinib, erlotinib, and gefitinib were included. The safety profiles were evaluated through disproportionality analysis (including ROR and PRR) alongside descriptive statistics.

Results: This study analyzed 22,160 reports of adverse events (AEs) associated with EGFR-TKIs. The incidence of AEs was significantly higher for Osimertinib (7,142 cases) and Erlotinib (7,886 cases), compared to Afatinib (3,287 cases) and Gefitinib (3,845 cases). Females constituted 58.3% of the cohort; notably, Osimertinib exhibited the highest proportion of patients over 85 years old (3.2%). Disproportionality analysis revealed specific drug-related risks: Afatinib was particularly associated with Paronychia (PRR=13.89, ROR=14.12), Osimertinib with Acquired gene mutations (PRR=20.18, ROR=20.44), Erlotinib with Dermatitis acneiform (PRR=5.47, ROR=5.50), and Gefitinib also with Acquired gene mutations (PRR=11.62, ROR=11.74). Cross-drug surveillance should prioritize common risks such as Malignant neoplasm progression and Interstitial lung disease.

Conclusion: There are significant discrepancies in the safety profiles among different EGFR-TKIs. In clinical practice, it is crucial to closely monitor the high-incidence AEs associated with specific drugs in order to facilitate individualized treatment while minimizing potential risks.

Keywords: Adverse Event; EGFR-TKIs; NSCLC; FAERS

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Introduction

Non-small cell lung cancer (NSCLC) represents a heterogeneous group of malignant tumors that originate from lung epithelial cells, accounting for over 85% of all lung cancer cases. It is one of the leading causes of cancer-related mortality worldwide [1]. The incidence of NSCLC continues to rise globally, particularly in smoking populations and individuals exposed to environmental carcinogens such as air pollution or occupational hazards. Epidemiological data indicate that the annual incidence of NSCLC varies by region, with approximately 400,000–500,000 cases reported annually in Asian

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Abbreviations	
AE	Adverse Event
CI	Confidence Interval
EGFR-TKI	Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
ILD	Interstitial Lung Disease
ISRs	Individual Safety Reports
MedDRA	Medical Dictionary for Regulatory Activities
NSCLC	Non-Small Cell Lung Cancer
OS	Overall Survival
PRR	Proportional Reporting Ratio
PT	Preferred Term
PFS	Progression-Free Survival
ROR	Reporting Odds Ratio
SOC	System Organ Class

populations and around 200,000–300,000 cases in Western populations [2]. Current treatment strategies for NSCLC encompass surgical resection, radiotherapy, chemotherapy, and targeted therapies aimed at epidermal growth factor receptor (EGFR) gene mutations. Among these approaches, EGFR tyrosine kinase inhibitors (EGFR-TKIs) have emerged as the cornerstone treatment regimen for late-stage NSCLC patients harboring EGFR mutations, particularly in Asian populations where the detection rate of EGFR mutation reaches 40–50%, significantly higher than the 10–15% observed in Western cohorts, resulting in their widespread application [3].

However, therapy with EGFR-TKI presents notable challenges including frequent adverse drug reactions and the development of acquired resistance; median resistance duration is only 10–14 months [4] . These issues constrain the long-term efficacy of this treatment modality and underscore the urgent for further research into safety profiles and mechanisms underlying resistance. Since gefitinib became the first approved EGFR-TKI in 2003, targeted therapy has transformed the therapeutic landscape for NSCLC characterized by sensitive EGFR mutations. This advancement has substantially extended both progression-free survival (PFS) and overall survival (OS) rates among affected for patients [5].

However, with the advent of second and third-generation EGFR-TKIs, an increasing number of clinical cases have reported drug-related toxicities, including diarrhea, acneiform rash, and mucositis, among other adverse reactions [6]. These side effects not only hinder patient adherence to treatment but may also necessitate treatment discontinuation or dose adjustments. Consequently, there is an urgent need for systematic comparison of the safety profiles of EGFR-TKIs across different generations. This study aims to address this knowledge gap by elucidating the deficiencies in the real-world safety data concerning EGFR-TKI drugs post-marketing and by clarifying their risk differences. Ultimately, this research seeks to provide evidence-based guidance for optimizing clinical treatment strategies. Currently, safety data for EGFR-TKIs are primarily derived from phase III clinical trials [7]. However, these studies often employ stringent inclusion and exclusion criteria (for instance, excluding patients with hepatic or renal impairment or comorbidities), which fail to fully capture the complexities encountered in real-world complexities [8]. Furthermore, existing literature predominantly focuses on the adverse event (AE) profiles of individual agents without conducting systematic cross-generational comparisons. For example, Jones et al. identified a significant association between gefitinib use and the risk of interstitial lung disease (ILD) [9], while Park et al. [10] reported that 9% of patients treated with afatinib experienced skin toxicities such as rash or acneiform eruptions. Nevertheless, these studies remain limited to single-drug analyses and do not explore variations in AE types, severity levels, or demographic correlations across different EGFR-TKIs. Additionally, analyses utilizing the FDA Adverse Event Reporting System (FAERS) have similarly concentrated on individual drugs without systematically uncovering safety spectra and their potential influencing factors across generations. This research gap hinder a comprehensive understanding of the toxicity profiles associated with EGFR-TKI and highlights the urgent need for more extensive real-world evidence to inform clinical practice.

The U.S. Food and Drug Administration's (FDA) Adverse Event Reporting System (FAERS) is the largest spontaneous reporting database in the world, capable of capturing rare or long-term toxicity signals that may not be identified during in clinical trials, thereby providing a unique perspective for pharmacovigilance research [11]. This study, utilizing data from the FAERS database, systematically compares the safety profiles of four commonly used EGFR-TKIs (gefitinib, erlotinib, afatinib, and osimertinib) for the first time. Its objective is to elucidate differences in risks among these agents as well as their associations with demographic factors, dosages, or concomitant medications. Through proportionality analysis techniques such as the reporting odds ratio (ROR), this investigation quantifies the patterns of major adverse events (AEs) for each drug exploring their severity and potential safety signals. The findings are anticipated to provide evidence-based guidance for clinicians, facilitating personalized drug selection and strategies for monitoring toxicity. In doing so, this study aims to maximize therapeutic efficacy while minimizing the adverse reactions risk, ultimately achieving an optimal balance between safety and effectiveness in treating NSCLC.

Methods

Data sources and processing

This study extracted data from FAERS database, covering the period from the approval of each drug up to the fourth quarter of 2024. **Figure 1** illustrates a multi-step process that includes data extraction, processing, and evaluation. We collected specific clinical characteristics from each adverse event (AE) report, including individual safety reports (ISRs), outcomes, drug names, role codes, dosages, indications, adverse event details, case identifiers, gender, reporter's country, and age information. Since the FAERS database integrates data from multiple sources, duplicate reports may occur [12]. To address this, we used case IDs and ISRs as key criteria for screening. If duplicate case IDs were found, we retained the record with the higher ISR. Additionally, to minimize con-

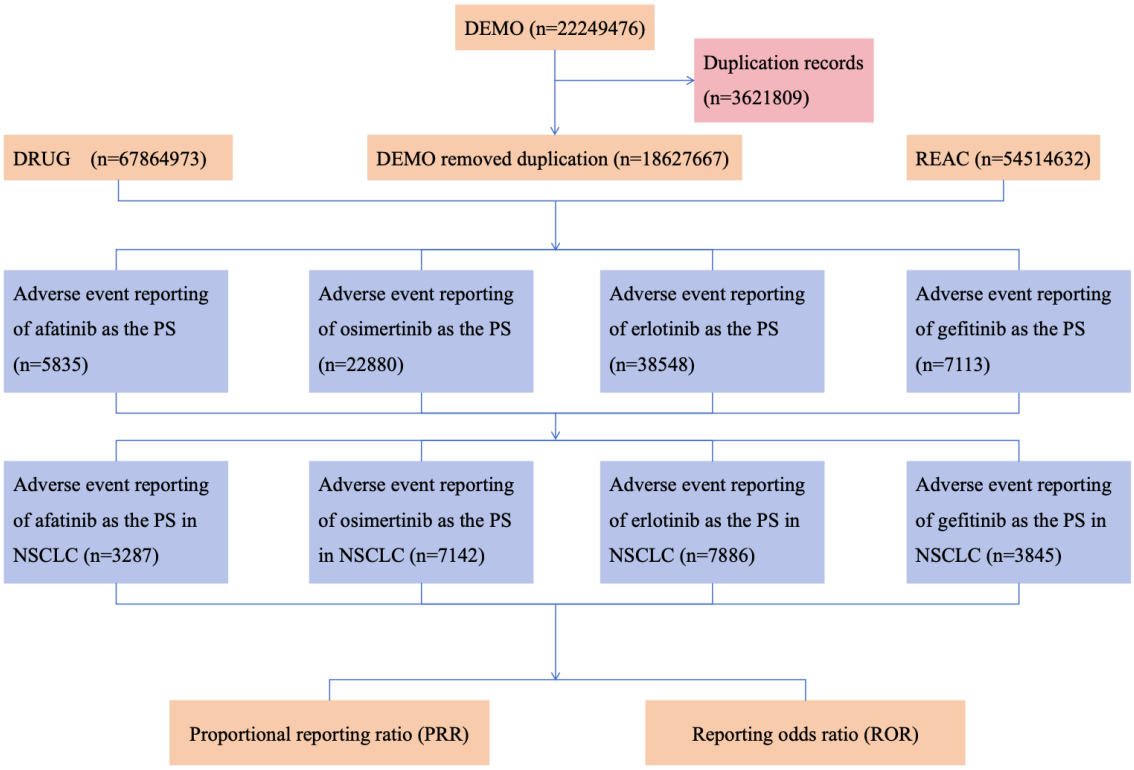

Figure 1 | Study Flowchart of FAERS Data Analysis

Flowchart of data extraction and processing for the analysis of adverse events (AEs) associated with EGFR-TKIs (afatinib, osimertinib, erlotinib, and gefitinib) using the FAERS database. The flow includes steps from data collection, screening of duplicate records, and exclusion of irrelevant terms, to the final dataset used for disproportionality analysis.

founding effects, we excluded primary terms (PTs) related to indications, off-label use, and product issues [13].

Adverse event and drug identification

This study focuses on epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), including afatinib (Afatinib, Gilotrif), osimertinib (Osimertinib, Tagrisso), erlotinib (Erlotinib, Tarceva), and gefitinib (Gefitinib, Iressa). By searching for adverse event (AE) records using both the generic and brand names of the drugs, we filtered out reports where the target drug was identified as the primary suspect drug to enhance the accuracy of the analysis. Adverse events were encoded according to the Medical Dictionary for Regulatory Activities (MedDRA, version 24.0) and categorized by System Organ Class (SOC) [14].

Statistical analysis

We summarize the clinical characteristics of adverse event (AE) reports, including event distribution, outcomes, gender, age, and reporting countries. To investigate the relationship between the target drugs and target adverse events, we employed disproportionality analysis. The reporting odds ratio (ROR) and proportional reporting ratio (PRR) were calculated to generate signals of disproportionate reporting. The specific algorithms for disproportionality analysis are outlined in **Supplementary Table 1**, with the formulas and criteria listed in **Table 1** [15]. A significant safety signal was identified when the ROR or PRR indicated statistical significance (ROR 95% confidence interval lower bound >1, PRR chi-square value ≥4). The strength of the signal was positively correlated with the ROR or PRR value. Additionally, we conducted new signal analysis to identify any significant adverse events related to the four EGFR-TKIs under discussion in this study. A new signal was defined as a significant adverse event not listed on the drug label. Furthermore, following FDA standards, we categorized AE outcomes as serious (death, life-threatening, disability, or hospitalization) or non-serious and determined the most common serious AE for each EGFR-TKI. All data processing and statistical analyses were performed using R language, version 4.2.

Results

Descriptive analysis

As the fourth quarter of 2024, this study included 22,160 adverse event (AE) reports associated with EGFR-TKIs. Osimertinib (7,142 cases) and erlotinib (7,886 cases) demonstrated significantly higher frequencies of AE compared to afatinib (3,287 cases) and gefitinib (3,845 cases). A consistent female predominance was observed across all drugs regarding gender distribution: For Afatinib-females accounted for 55.4% of reports; males represented 32.9%; unknown gender

Table 1 | ROR and PRR methods, formulas, and thresholds

Method	Formula	Threshold
ROR	$ROR = \frac{a/c}{b/d}$ $SE(\ln ROR) = \sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}$ $95\%CI = e^{\ln(ROR)\pm 1.96se}$	$a \geq 3$ ROR>1 95%CI (lower limit) > 1
PRR	$RRR = \frac{a/(a+b)}{b/c+d}$ $x^2 = \frac{[(a\times d - b\times c)^2]\times(a+b+c+d)}{(a+b)\times(c+d)\times(a+c)\times(b+d)}$	$a \geq 3$ ROR>1 $x^2 \geq 4$

Abbreviations: 95% CI, 95% confidence interval; x^2, chi-squared

Table 2 | Characteristics of AE reports for different EGFR-TKIs

Characteristics	Subcategories	Afatinib (n=3287)	Osimertinib (n=7142)	Erlotinib (n=7886)	Gefitinib (n=3845)
Age (year)	<18	1 (0.0%)	0 (0%)	9 (0.1%)	0 (0%)
	18–64.9	1014 (30.8%)	1085 (15.2%)	2184 (27.7%)	1140 (29.6%)
	65–85	1357 (41.3%)	2040 (28.6%)	3000 (38.0%)	1346 (35.0%)
	>85	68 (2.1%)	229 (3.2%)	174 (2.2%)	81 (2.1%)
	Missing	847 (25.8%)	3788 (53.0%)	2519 (31.9%)	1278 (33.2%)
Gender	Female	1821 (55.4%)	3875 (54.3%)	3730 (47.3%)	2186 (56.9%)
	Male	1081 (32.9%)	2159 (30.2%)	3217 (40.8%)	1449 (37.7%)
	Unknown	385 (11.7%)	1108 (15.5%)	939 (11.9%)	210 (5.5%)
Reported Region	United States	682 (20.7%)	1376 (19.3%)	2613 (33.1%)	457 (11.9%)
	Japan	745 (22.7%)	2357 (33.0%)	547 (6.9%)	865 (22.5%)
	China	143 (4.4%)	496 (6.9%)	967 (12.3%)	1080 (28.1%)
	United Kingdom	50 (1.5%)	71 (1.0%)	2227 (28.2%)	54 (1.4%)
	Other	1184 (36.0%)	2842 (39.8%)	1452 (18.4%)	1388 (36.1%)
	Unknown	483 (14.7%)	0 (0%)	80 (1.0%)	1 (0.0%)
Outcome of AEs	Death	732 (22.3%)	2364 (33.1%)	2839 (36.0%)	765 (19.9%)
	Disability	26 (0.8%)	49 (0.7%)	60 (0.8%)	66 (1.7%)
	Hospitalization	883 (26.9%)	1366 (19.1%)	1731 (22.0%)	786 (20.4%)
	Life-threatening	110 (3.3%)	241 (3.4%)	146 (1.9%)	158 (4.1%)
	Other outcomes	1212 (36.9%)	2474 (34.6%)	2171 (27.5%)	1853 (48.2%)
	Unknown	324 (9.9%)	648 (9.1%)	939 (11.9%)	217 (5.6%)

Notes: EGFR-TKIs: Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors; AEs: Adverse Events. “Missing” and “Unknown” indicate incomplete or unrecorded data.

comprised 11.7%. For osimertinib-females constituted 54.3%; males made up 30.2%; unknown gender accounted 15.5%. Erlotinib: The demographic distribution revealed that females constituted 47.3%, males 40.8%, and individuals with unknown gender accounted for 11.9%. In the case of gefitinib, females represented the highest proportion at 56.9%, while male comprised 37.7%, with an additional 5.5% classified as unknown. Age-related analysis indicated that adverse events AEs associated with osimertinib were most prevalent among patients aged ≥85 years (3.2%), whereas gefitinib predominantly reported in the age of 18–64 age group (29.6%). The percentage of missing age data varied significantly, ranging from 25.8% for afatinib to as high as 53.0% for osimertinib. Geographically, reports related to afatinib primarily originated from Japan (22.7%) and the United States (20.7%). Osimertinib reports were largely sourced from Japan (33.0%), while erlotinib reports came mainly from the U.S. (33.1%) and the United Kingdom (28.2%). Gefitinib was predominantly reported in China (28.1%) and Japan (22.5%). The most frequently reported outcomes included "other" categories at (34.79%), followed by death at 30.23%, hospitalization at 21.51%, unknown outcomes at 9.6%, life-threatening events at 2.96%, and disability cases at 0.91%. Detailed characteristics of AE reporting stratified by EGFR-TKI are presented in Table 2.

Disproportionate analysis

Signal of system organ class

At the System Organ Class (SOC) level, a total of 27 SOCs were involved in the adverse event signals. The proportion of cases reported for different EGFR-TKIs at the SOC level is shown in Figure 2. The analysis identified the most commonly reported SOC for each EGFR-TKI. For Afatinib, the top three SOCs were Gastrointestinal disorders (3,190 cases, 22.6%), Skin and subcutaneous tissue disorders (1,863 cases, 13.2%), and Neoplasms benign, malignant and unspecific (1,744 cases, 12.4%). For Osimertinib, the top three SOCs were General disorders and administration site conditions

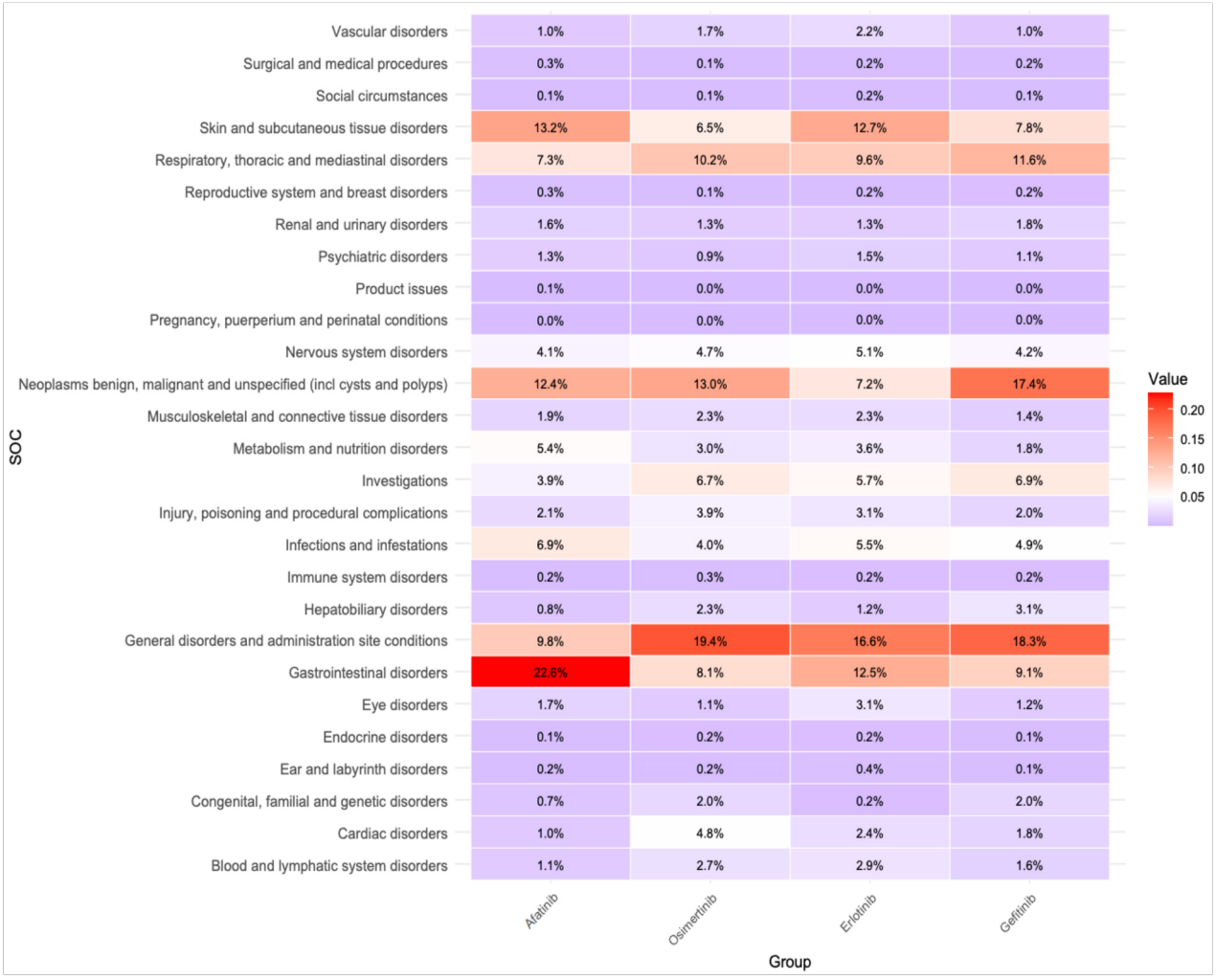

Figure 2 | System Organ Class (SOC) Distribution of EGFR-TKI-Related Adverse Events

Heatmap displaying the percentage distribution of AEs across 26 System Organ Classes for four EGFR-TKIs. Color intensity reflects AE frequency, with gastrointestinal disorders predominating in afatinib (22.6%) and general disorders in osimertinib (19.4%). Shared high-frequency SOCs include respiratory disorders (osimertinib 11.6%, gefitinib 11.6%) and neoplasms (gefitinib 17.4%). Data derived from 22,160 AE reports.

(3,520 cases, 19.4%), Neoplasms benign, malignant and unspecific (2,360 cases, 13.0%), and Respiratory, thoracic and mediastinal disorders (1,851 cases, 10.2%). For Erlotinib, the most reported SOCs were General disorders and administration site conditions (4,524 cases, 16.6%), Skin and subcutaneous tissue disorders (3,455 cases, 12.7%), and Gastrointestinal disorders (3,405 cases, 12.51%). Lastly, for Gefitinib, the top three SOCs were General disorders and administration site (2,230 cases, 18%), Neoplasms benign, malignant and unspecific (2,127 cases, 17.45%), and Respiratory, thoracic and mediastinal disorders (1,411 cases, 11.6%). In terms of signal values, Afatinib showed the strongest signals for Skin and subcutaneous tissue disorders (ROR=2.65, PRR=2.43) and Gastrointestinal disorders (ROR=2.47, PRR=2.14), with a notable risk for Congenital, familial and genetic disorders (ROR=2.25, PRR=2.24). Osimertinib had a particularly high signal for Congenital, familial and genetic disorders (ROR=9.35, PRR=9.18), and Neoplasms benign, malignant and unspecific (ROR=1.78, PRR=1.68) and Cardiac disorders (ROR=1.59, PRR=1.56). Erlotinib had the strongest signals for Skin and subcutaneous tissue disorders (ROR=2.68, PRR=2.47) and Eye disorders (ROR=3.17, PRR=3.1), while Respiratory, thoracic and mediastinal disorders had weaker signals (ROR=0.94, PRR=0.94). Gefitinib showed significant risks for Congenital, familial and genetic disorders (ROR=7.90, PRR=7.76) and Neoplasms benign, malignant and unspecific (ROR=2.53, PRR=2.27), with strong signals for Hepatobiliary disorders (ROR=1.26, PRR=1.25).

Signal of preferred terms

At the Preferred Term (PT) level, we identified the top 20 adverse event (AE) signals for each drug (Figure 3). The details of the five most common AEs for each drug are as follows: For Afatinib (N=14,115) （Figure 4A）, the most frequent AEs were Diarrhea (1,271 cases, 9.00%), Malignant neoplasm progression (1,069 cases, 7.57%), Rash (533 cases, 3.78%), Stomatitis (352 cases, 2.49%), and Decreased appetite (305 cases, 2.16%). For Osimertinib (N=18,108) (Fig-

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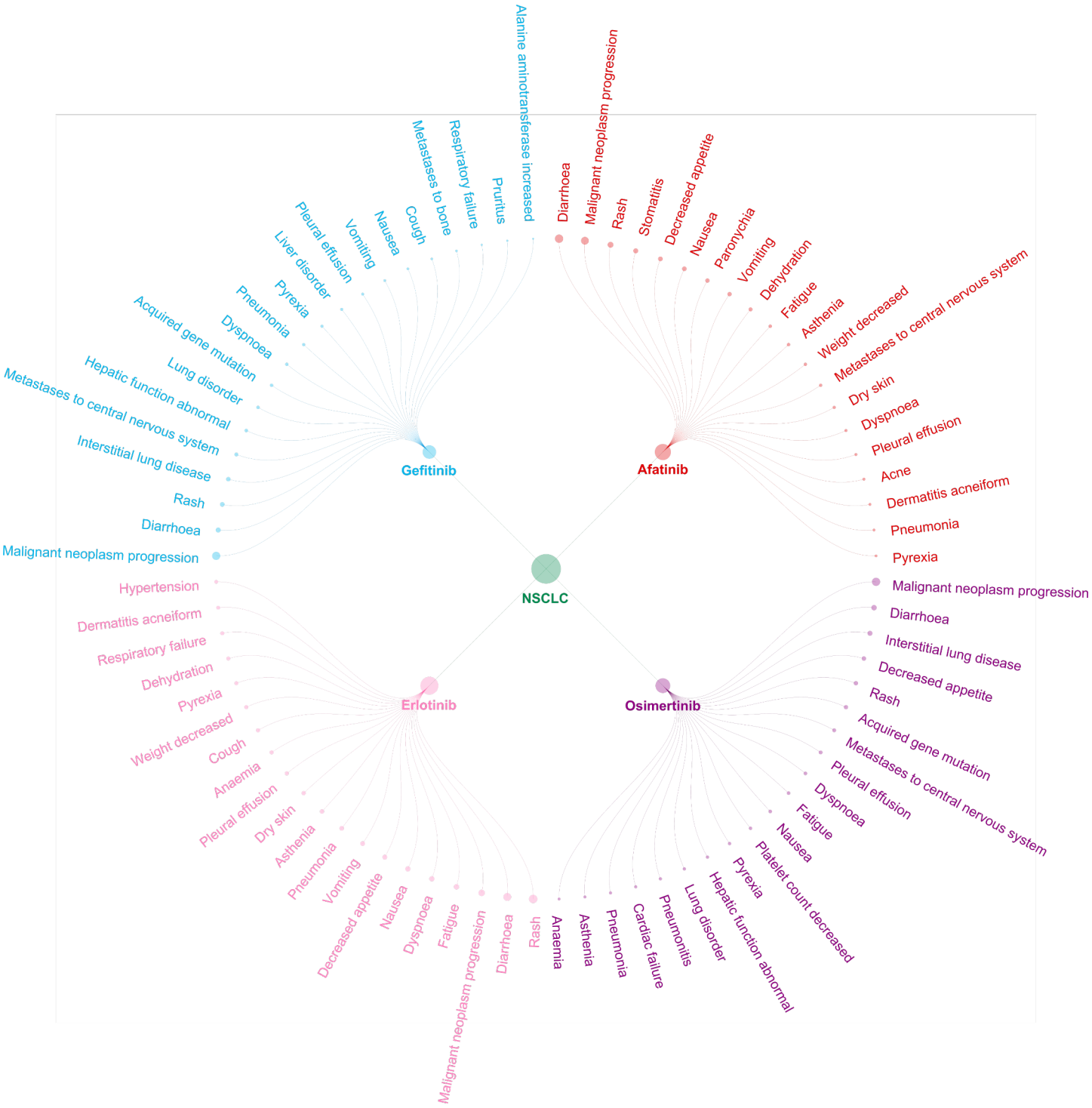

Figure 3 | Radial Network of EGFR-TKI-Associated Adverse Events in NSCLC

Radial network diagram mapping the associations between four EGFR-TKIs (afatinib, osimertinib, erlotinib, gefitinib) and their corresponding adverse events (AEs) in non-small cell lung cancer (NSCLC) treatment. Central Node: NSCLC (green) as the disease anchor. Drug Nodes(color-coded): Afatinib (red): Primarily linked to Diarrhoea, Malignant neoplasm progression, and Rash. Osimertinib (purple): Strongly associated with Malignant neoplasm progression, Diarrhoea, and Interstitial lung disease. Erlotinib(pink): Correlated with Rash, Diarrhoea, and Malignant neoplasm progression. Gefitinib (light blue): Predominant risks include Malignant neoplasm progression, Diarrhoea, and Rash. AE Nodes: Size reflects reporting frequency.

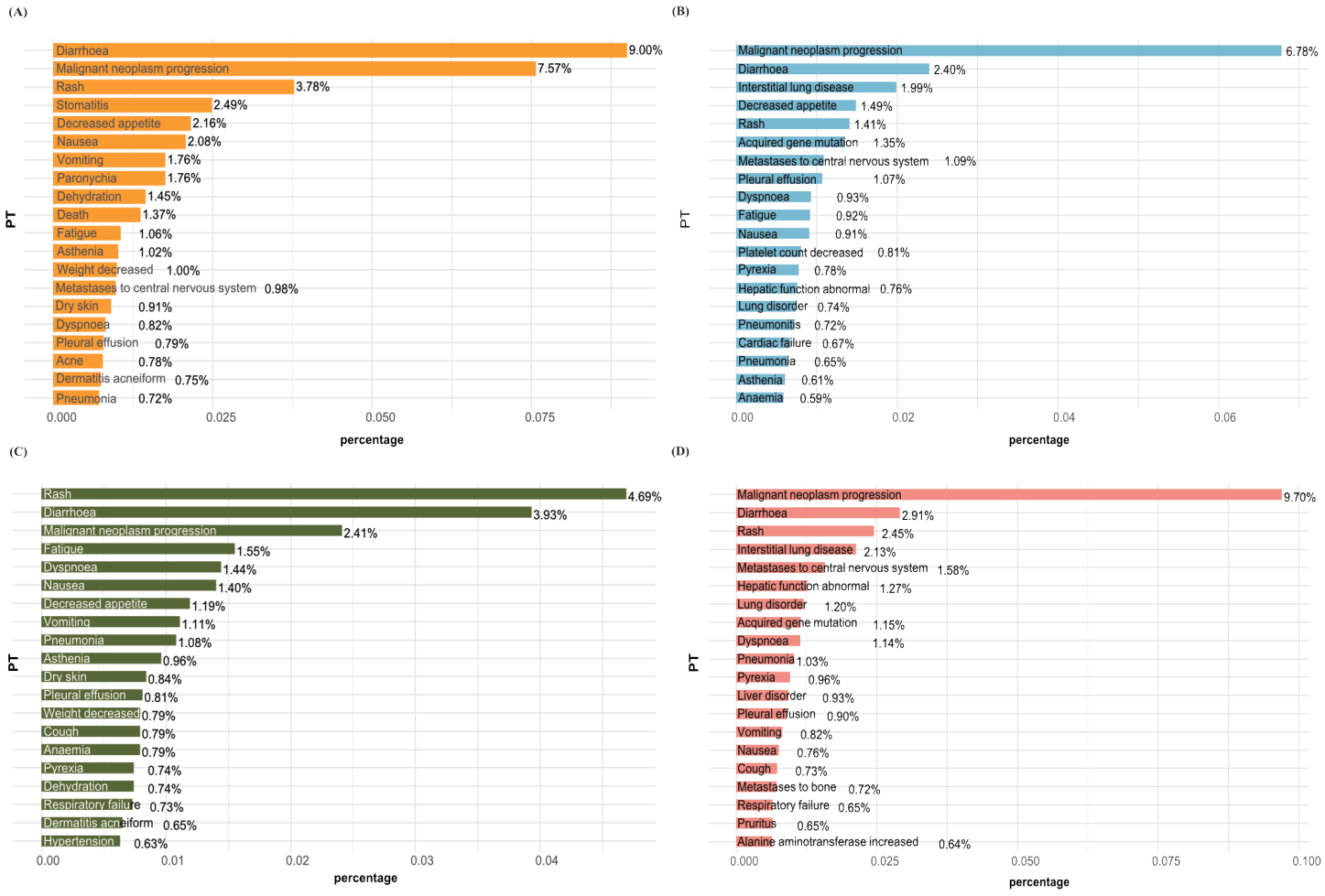

Figure 4 | Frequency Distribution of Top 20 Adverse Events (AEs) for Four EGFR-TKIs

Subfigures **(A)** afatinib (N=14,115), **(B)** osimertinib (N=18,108), **(C)** erlotinib (N=27,226), and **(D)** gefitinib (N=12,187) display the top 20 most frequently reported AEs for each drug, ranked by absolute case counts within the FDA Adverse Event Reporting System (FAERS) database. AE frequencies are expressed as percentages of total reports for each agent.

ure 4B), the most reported AEs were Malignant neoplasm progression (1,227 cases, 6.78%), Diarrhea (435 cases, 2.40%), Interstitial lung disease (361 cases, 1.99%), Decreased appetite (269 cases, 1.49%), and Rash (255 cases, 1.41%). For Erlotinib (N=27,226) (Figure 4C), the top AEs were Rash (1,276 cases, 4.69%), Diarrhea (1,071 cases, 3.93%), Malignant neoplasm progression (657 cases, 2.41%), Fatigue (421 cases, 1.55%), and Dyspnoea (391 cases, 1.44%). For Gefitinib (N=12,187) (Figure 4D), the most frequent AEs included Malignant neoplasm progression (1,182 cases, 9.70%), Diarrhea (355 cases, 2.91%), Rash (298 cases, 2.45%), Interstitial lung disease (260 cases, 2.13%), and Metastasis to central nervous system (193 cases, 1.58%). By comparing the common and distinct adverse events (AEs) (Supplementary Figure 1), eight AE signals were detected in all four drugs. These include Diarrhea, Malignant neoplasm progression, Rash, Dyspnea, Nausea, Pleural effusion, Pneumonia, and Pyrexia.

In the analysis of the top 20 most common adverse event (AE) signals, we identified varying significant signals for each EGFR-TKI (defined as the lower limit of the 95% confidence interval for the ROR >1 and the PRR chi-square value ≥4). The number of significant signals for each drug were as follows: afatinib (14 signals), osimertinib (10 signals), erlotinib (11 signals), and gefitinib (14 signals) (Figures 5). Specifically, afatinib showed prominent signals for Paronychia (PRR=13.89, ROR=14.12, 95% CI:12.04–16.57), Acne (PRR=11.06, ROR=11.14, 95% CI:8.85–14.02), and Stomatitis (PRR=7.65, ROR=7.82, 95% CI:6.92–8.84) (Figures 5A). Osimertinib was linked to significant signals for Acquired gene mutations (PRR =20.18, ROR=20.44, 95% CI:16.96–24.63), Interstitial lung disease (PRR=1.94, ROR=1.96, 95% CI:1.75–2.19), and Cardiac failure (PRR=2.56, ROR=2.57, 95% CI:2.13–3.12) (Figures 5B). Erlotinib presented strong signals for Dermatitis acneiform (PRR=5.47, ROR=5.50, 95% CI: 4.59–6.60), Rash (PRR=4.00, ROR=4.15, 95% CI:3.89–4.43), and Dry skin (PRR=5.09, ROR=5.12, 95%CI:4.38–6.00) (Figures 5C). Gefitinib was associated with significant signals for Metastasis to bone (PRR=4.33, ROR=4.36, 95% CI: 3.47–5.47), Liver disorder (PRR=4.03, ROR=4.06, 95% CI:3 .33–4.96), and

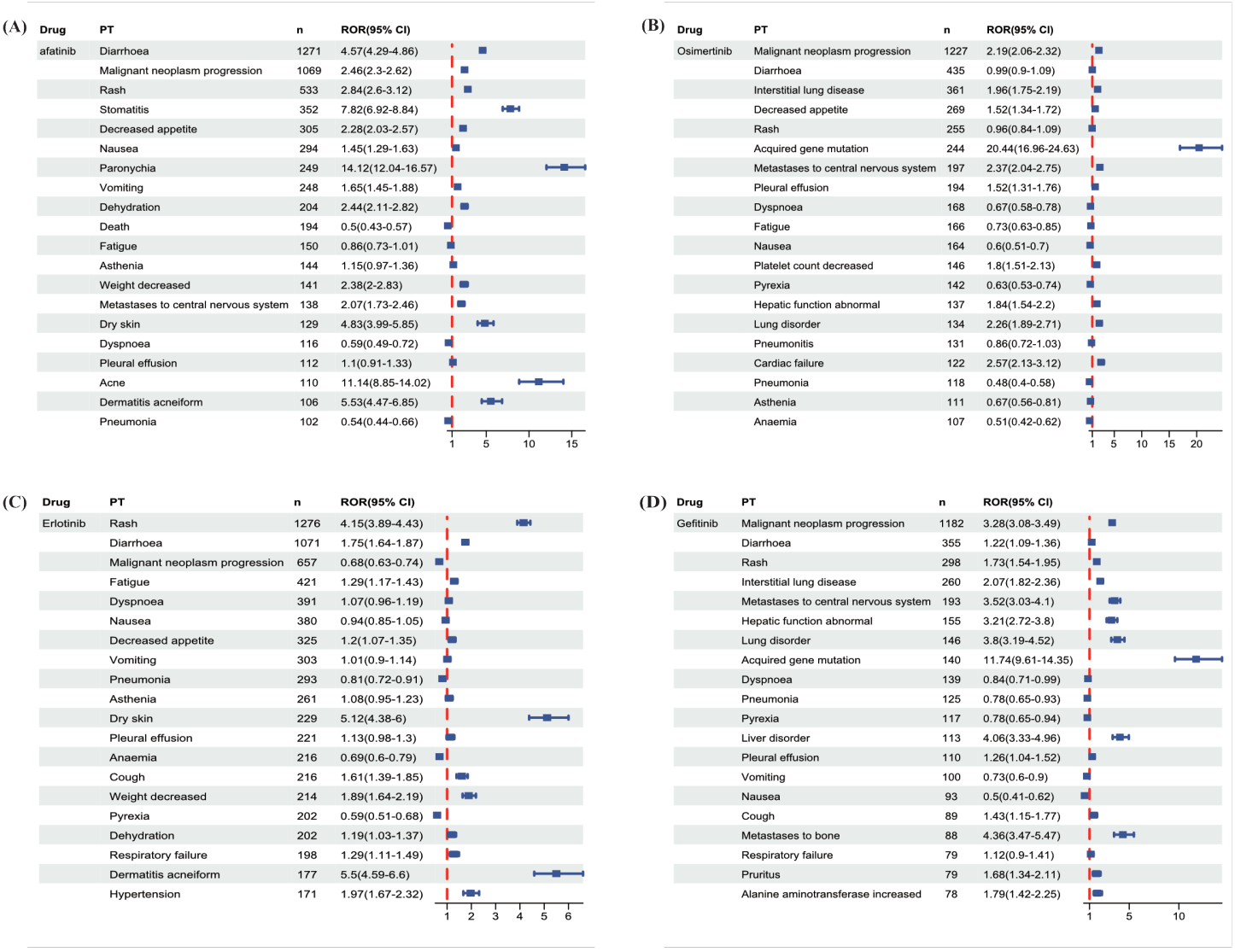

Figure 5 | Forest plots depicting the relative odds ratios (RORs) with 95% confidence intervals (CI) for adverse events associated with four EGFR-TKIs: (A) Afatinib, (B) Osimertinib, (C) Erlotinib, and (D) Gefitinib

ROR values >1 indicate a higher reporting likelihood of the adverse event with the drug, while ROR <1 suggests a reduced reporting. The number of reported cases (n) is provided for each drug. Vertical dashed lines mark ROR thresholds (5, 10, 15, 20) for ease of comparison. Data are presented to show the associations between the drugs and the adverse events.

Acquired gene mutations (PRR=11.62, ROR=11.74, 95% CI:9.61–14.35) (Figures 5D).

Overall, afatinib is characterized by skin toxicity (Paronychia, Acne) and mucosal damage (Stomatitis); osimertinib is strongly associated with genetic mutations and cardiopulmonary toxicity; erlotinib is commonly linked to skin inflammatory reactions (Dermatitis acneiform, Rash); and gefitinib stands out for its risks in liver injury and tumor metastasis. Among the co-occurring signals, Malignant neoplasm progression and Interstitial lung disease (ILD) were significantly observed with both osimertinib and gefitinib, suggesting the need for cross-drug monitoring of common risks.

New signals

After conducting the search, new safety signals were identified for afatinib, osimertinib, erlotinib, and gefitinib. Specifically, two new signals were detected for afatinib, while osimertinib, erlotinib, and gefitinib each had one new signal. The newly identified safety signals for each EGFR-TKI are listed in Supplementary Table 2. For afatinib, the significant adverse event (AE) signals not included in the drug label were Paronychia (PRR=13.89, ROR=14.12) and Acne (PRR=11.06, ROR=11.14). For osimertinib, the newly detected signal was Acquired gene mutation (PRR=20.18, ROR=20.44). Erlotinib was associated with Hypertension (PRR=1.96, ROR=1.97), while the newly identified signal for gefitinib was Metastasis to bone (PRR=4.33, ROR=4.36).

Discussion

This study analyzed 22,160 reports of adverse events (AEs) associated with EGFR-TKIs, revealing the diversity of toxicity profiles and potential underlying mechanisms of afatinib, osimertinib, erlotinib, and gefitinib. Afatinib demonstrated significant skin toxicity, with the highest signal intensities observed for Paronychia (ROR=14.12, 95% CI: 12.04–16.57), Acne (ROR=11.14, 95% CI: 8.85–14.02), and Stomatitis (ROR=7.82, 95% CI: 6.92–8.84). This finding is consistent with afatinib's irreversible binding to EGFR and its persistent inhibition of keratinocyte repair [16]. Joly-Tonetti et al. reported that EGFR-TKIs suppress basal keratinocyte proliferation and induce differentiation, which leads to impaired skin barrier function [17], aligning closely with our findings. However, it remains unclear whether specific toxicities such as Paronychia are entirely driven by this mechanism alone; Further investigation into the potential involvement of local microenvironment or inflammatory mediators is warranted through in vitro and clinical investigations. Liver disorder emerged as a notable signal for gefitinib in this analysis (ROR=4.06, 95% CI: 3.33–4.96), corroborating previous literature [18] . Luo et al. proposed that gefitinib may induce hepatocyte apoptosis by downregulating the anti-apoptotic factor COX6A1 (cytochrome c oxidase subunit 6A1), thereby impairing mitochondrial respiratory chain complex IV function [19]. While this molecular mechanism offers a plausible explanation for Liver disorder associated with gefitinib use, our study did not identify similarly strong signals related to metabolic disorder; this suggests that variations in drug-metabolizing enzymes, such as CYP3A4 or alternative pathways leading to liver injury may also play a role [20]. This discrepancy underscores the necessity for larger-scale metabolomic studies aimed at elucidating the full spectrum of gefitinib-induced hepatotoxicity. Osimertinib demonstrated a significant association with Acquired gene mutations (ROR=20.44, 95% CI: 16.96–24.63), indicating its relationship with drug resistance and corroborating reports of limited long-term efficacy [21-23]. Previous studies have demonstrated that osimertinib-resistant patients not only develop EGFR-dependent mutations (such as C797S) but also acquire mutations in non-EGFR genes, including ARID1A, NTRK1, and ZRSR2 [24], along with bypass activation events such as RET fusion and BRAF V600E mutations [25]. The high-frequency gene mutation signal observed in our study supports these findings. Erlotinib was primarily associated with skin inflammation, exhibiting significant signals for Dermatitis acneiform (ROR=5.50, 95% CI: 4.59–6.60) and Rash (ROR=4.15, 95% CI: 3.89–4.43). These epidermal reactions are consistent with EGFR inhibition; however, they displayed lower signal intensity compared to afatinib, further underscoring afatinib's irreversible binding characteristics [26].

Interstitial lung disease (ILD) was frequently reported in conjunction with osimertinib and gefitinib (PRR=1.96 and 2.07, respectively), while the ILD-related mortality associated with osimertinib (1.99%) exceeded expectations, consistent with previous clinical studies [27]. Nonetheless, the underlying mechanisms of ILD remain contentious; some evidence points to direct alveolar epithelial injury [28], whereas others suggest an immune-mediated inflammatory response [29]. Our study data do not provide conclusive support for either hypothesis, highlighting the necessity for large-scale case-control studies to studies the pathogenesis of EGFR-TKI-associated ILD.SOC-level analysis revealed that adverse event (AE) signals related to the four EGFR-TKIs encompassed 27 SOC categories, reflecting the systemic nature of their toxic effects. Afatinib was primarily associated with Gastrointestinal disorders (3,190 cases, 22.6%, ROR=2.47) and Skin and subcutaneous tissue disorders (1,863 cases, 13.2%, ROR= 2.65). These findings are consistent with its irreversible inhibition properties that lead to mucosal and epidermal damage. In contrast, osimertinib demonstrated a significant proportion of reports related to General disorders and administration site conditions (3,520 cases, 19.4%), Neoplasms benign, malignant and unspecified (2,360 cases, 13.0%, ROR= \1.78), as well as Respiratory, thoracic and mediastinal disorders (1,851 cases, 10.2%). Notably, the signal for congenital familial and genetic disorders was pronounced (ROR=9.35, 95% CI: 8.23-10.61), potentially linked to the accumulation of resistance-related gene mutations [30]. Erlotinib was predominantly associated with General disorders and administration site conditions (4,524 cases, 16.6%), Skin and subcutaneous tissue disorders (3,455 cases, 12.7%, ROR=2.68), along with Gastrointestinal disorders (3,405 cases, 12.5%). A significant signal was observed for Eye disorders (ROR=3.17, 95% CI: 2.93–3.42), likely resulting from corneal or conjunctival reactions induced by local EGFR inhibition [31]. Gefitinib exhibited a high prevalence of General disorders and administration site conditions (2,230 cases, 18%), Neoplasms benign, malignant and unspecified (2,127 cases, 17.5%, ROR=2.53), in addition to Respiratory, thoracic and mediastinal disorders (1,411 cases, 11.6%). A strong signal for hepatobiliary disorders was also noted (ROR=1.26, 95% CI: 1.13–1.40), aligning with its hepatotoxicity profile. The SOC-level analysis underscored that skin and tumor-related toxicities were consistently prominent across all four drugs in accordance with the fundamental effects of EGFR inhibition [32] . However, differences in signal intensity warrant careful consideration.

Afatinib and erlotinib demonstrated more pronounced skin-related signals (ROR=2.65 and 2.68, respectively) compared to osimertinib (ROR=1.15), likely due to their broader inhibition of EGFR family receptors, including HER2 [26]. Although osimertinib and gefitinib reported higher proportions of Respiratory, thoracic and mediastinal disorders (10.2% and 11.6%, respectively), their signal values at SOC level were relatively low (ROR= 1.00 and 0.94). This is in contrasts to the significant ILD signals observed at the PT level (PRR = 1.96 and 2.07, respectively), which may be attributed to the broad classification of SOC categories or potential reporting bias. Such heterogeneity indicates that SOC-level analyses may have limitations in accurately specific toxicities; therefore, these findings should be interpreted alongside PT-level data. The study identified several novel signals, with Acquired genetic mutations associated Osimertinib exhibiting a particularly high risk ratio (ROR= 20.44, 95% CI: 16.96–24.63), as well as bone metastasis linked to gefitinib (ROR= 4.36, 95%

CI: 3.47–5.47). These signals are not comprehensively documented in the drug labels, suggesting a possible underestimation of risks during clinical use. The genetic mutations related to osimertinib are associated with resistance mechanisms that may arise from selective pressure exerted by its targeting of EGFR mutations [33]. It is advisable to regularly monitor circulating tumor DNA for early detection of resistance mutations [34, 35]. Gefitinib-associated bone metastasis could be linked to the potential effects of EGFR-TKIs on the tumor microenvironment or bone metabolism [36], especially among long-term users, underscoring the importance of vigilance regarding the risk of bone metastasis. Additionally, new signals for afatinib, including Paronychia (ROR=14.12) and Acne (ROR=11.14), further emphasize its characteristic skin toxicity. The identification of these new signals suggests that the toxicity profile of EGFR-TKIs may evolve with their expanded real-world application, necessitating enhanced monitoring and revision to clinical guidelines.

Gender and age were found to have a significant influence on adverse event (AE) reporting. The proportion of female patients was generally higher than that of male patients (47.3%-56.9%), with osimertinib exhibiting a greater risk for severe AEs (OR =1.68). The mortality rate among female patients (33.1%) was notably higher than that in males, potentially linked to increased drug metabolism toxicity via estrogen receptor signaling [37] . This gender disparity indicates that female patients may require dose adjustments or more rigorous monitoring. Regarding age distribution, osimertinib had the highest representation among patients aged over 85 years (3.2%), while gefitinib was more prevalent in patients aged 18-64 years (29.6%).Elderly patients, due to polypharmacy and declining organ function, may be at an elevated risk for interstitial lung disease (ILD) or cardiotoxicity [38, 39] . The ILD mortality rate associated with osimertinib (1.99%) in this study supports this perspective. Additionally, the higher reporting rate among younger patients may be attributed to the widespread use of gefitinib within Asian populations (22.5% in Japan, 28.1% in China), underscoring the necessity to consider population-specific factors.

The four EGFR-TKIs exhibit both commonalities and distinct characteristics within their toxicity profiles. Common features include eight high-frequency adverse events (AEs)—diarrhea, malignant tumor progression, rash, dyspnea, nausea, pleural effusion, pneumonia, and fever—which are significantly observed across all drugs. At the SOC level, both general diseases as well as benign or malignant tumors are frequently noted; this reflects the shared effects resulting from EGFR inhibition. In terms of individuality, afatinib is most strongly associated with skin and mucosal toxicities (Paronychia ROR= 14.12, Stomatitis ROR= 7.82). Osimertinib stands out in relation to genetic mutations (ROR= 20.44) and cardiopulmonary toxicity (ILD ROR= 1.96, Cardiac failure ROR=2.57). Erlotinib is primarily linked to skin inflammation (Dermatitis acneiform ROR= 5.50), while gefitinib is notably associated with liver disorder (ROR= 4.06) and Metastasis to bone (ROR= 4.36). These differences may be attributed to their binding properties or target selectivity [40].

Clinical outcomes indicate that mortality (30.23%) and hospitalization (21.51%) are the predominant serious adverse events associated with treatment. Osimertinib demonstrates a notable ILD-related mortality rate of 1.99%, while gefitinib-associated hepatotoxicity may significantly contribute to severe outcomes, with mortality rates at 19.9% and hospitalization rates at 20.4%. In contrast, erlotinib-related is primarily skin reactions, exhibiting a mortality rate of 36.0%, which is lower than that observed for osimertinib (33.1%), suggesting relatively better safety profiles for this agent. Afatinib presents moderate rates of mortality (22.3%) and hospitalization rates (26.9%); however, its potential for skin toxicity may adversely affect patient adherence to treatment regimens. Safety assessments should take into account baseline patient characteristics, including pulmonary and liver function status. Erlotinib may be superior due to lower cardiopulmonary risk, nevertheless further validation is needed. This study possesses has several notable strengths. First, it utilizes real-world data from a substantial cohort of 22,160 cases, encompassing a wide range of adverse events (AEs) related to four EGFR-TKIs. This approach addresses the limitations inherent in clinical trials that often exclude complex patient populations due to stringent inclusion and exclusion criteria [41]. Second, the dual analysis employing both SOC and PT provides a systematic and specific perspective that facilitates the identification of new signals, specifically Paronychia and Acquired genetic mutations, thereby enriching pharmacovigilance research. Third, unlike studies focusing on a individual drugs, this investigation systematically compares the toxicity profiles of four EGFR-TKIs for the first time. The combined application of Proportional Reporting Ratio (PRR) and Reporting Odds Ratio (ROR) enhances signal detection reliability, offering valuable insights for individualized clinical treatment. However, there are certain limitations to consider. The FAERS spontaneous reporting system may overestimate severe AEs while underreporting mild events [42], necessitating cautious interpretation due to potential reporting biases. Furthermore, the causality of newly identified signals has yet to be validated through prospective cohort studies or in vitro experiments [43]. Additionally, the high proportion of Asian data—33.0% for osimertinib and 28.1% for gefitinib—may limit the generalizability of these findings [44] . Future research endeavors should aim to integrate electronic health records alongside multi-omics data to dynamically monitor the evolution of toxicity and elucidate underlying mechanisms, thereby providing robust support for precision medicine initiatives[45, 46]. In conclusion, this study systematically analyzes the AE characteristics associated with EGFR-TKIs, identifies novel signals and risks, and establishes a foundation for optimizing clinical monitoring strategies.

Conclusion

This study systematically compares the toxicity profiles of four EGFR-TKIs (afatinib, osimertinib, erlotinib, and gefitinib) by analyzing 22,160 adverse event reports. The results indicate that afatinib is primarily associated with gastrointestinal diseases as well as skin and subcutaneous tissue dis-

orders; osimertinib is linked to general diseases, administration site reactions, and genetic disorders; erlotinib is related to skin and subcutaneous tissue disorders with eye disorders; while gefitinib is connected to benign, malignant, and unspecified neoplasms in addition to hepatobiliary disorders. At the PT level, afatinib exhibits the most significant signal for paronychia; osimertinib shows a notable signal for acquired genetic mutations; erlotinib indicates a strong association with dermatitis acneiform; and gefitinib presents a significant risk for bone metastasis. These signals elucßidate specific toxicity characteristics unique to each drug and identify new signals, such as afatinib-related paronychia and acne, osimertinib-associated acquired genetic mutations, and gefitinib-linked bone metastasis, that have been less emphasized in previous studies or inadequately documented in drug labels. This suggests that existing labels may underestimate certain toxicity risks.

The findings provide compelling evidence for optimizing individualized treatment strategies for clinicians. For example, the high risk of resistance associated with Osimertinib alongside ILD-related mortality underscore the necessity necessitates increased attention to skeletal health among long-term users, whereas afatinbib's skin toxicity calls for improvement function assessment. The potential risk of bone metastasis associated with Gefitinib necessitates increased attention to skeletal health among long-term users, while afatinib's skin toxicity calls for improvements in local management strategies. These insights could prompt updates to drug labels as well as enhancements in monitoring guidelines, significantly improving both safety and efficacy within EGFR-TKI treatments. Future prospective cohort studies will be essential in validating these new signals by integrating multi-omics data alongside real-world evidence to further clarify toxicity mechanisms and patient-specific risks ultimately achieving an optimal balance of benefits and risks associated with EGFR-TKI.

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Supplementary Table 1 | 2 × 2 fourfold table of disproportionality method

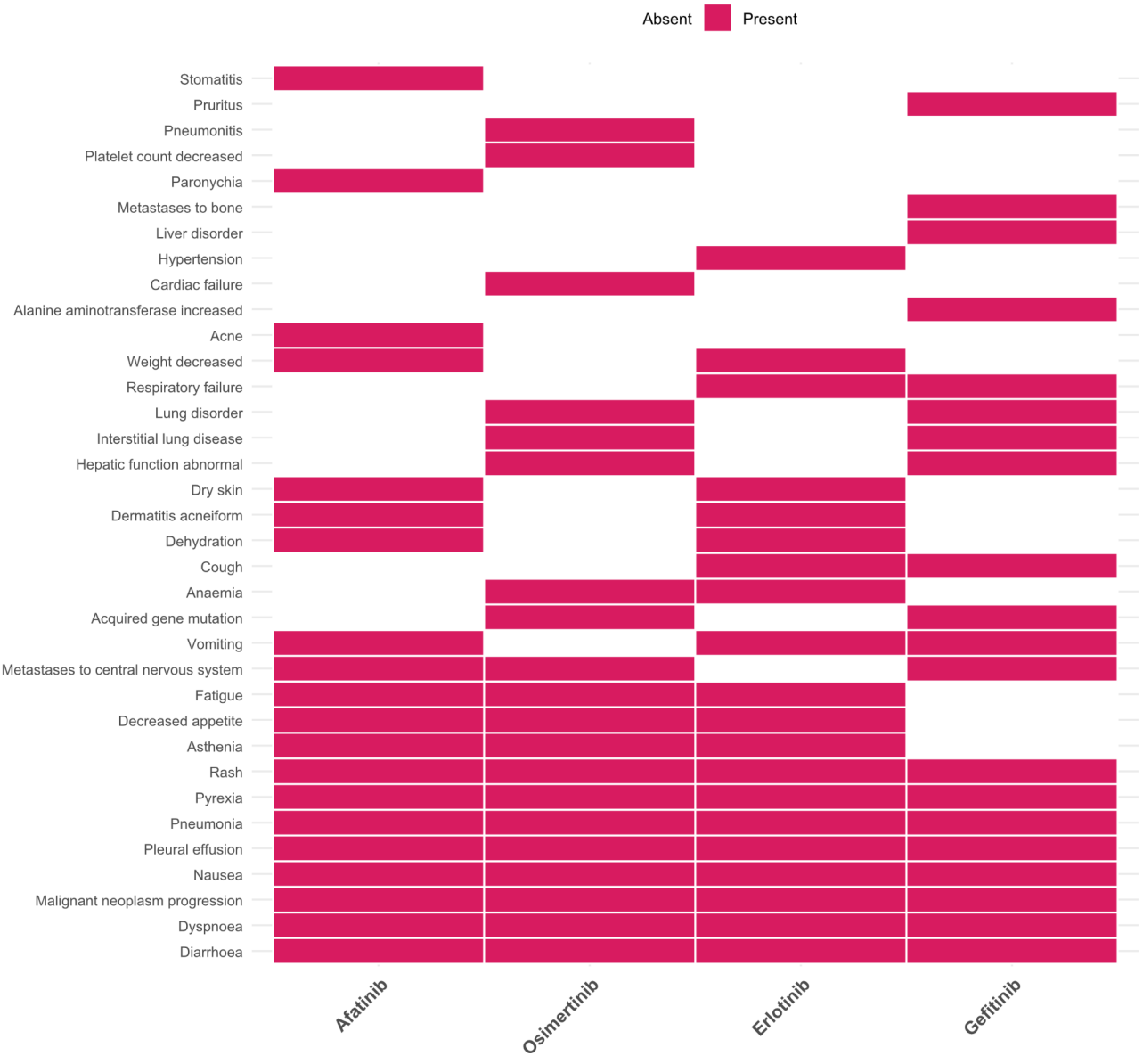
	Target AEs	Other AEs	Total
Target AEs	a	b	A + b
Other AEs	c	d	C + d
Total	A + c	B + d	N = a + b + c + d

Abbreviations: AEs: Adverse Events

Supplementary Table 2 | New signals of AE reports for different EGFR-TKIs

Drug	New signals	PRR/POR (95%CI)
Afatinib	Paronychia	13.89/14.12 (95% CI: 12.04–16.57)
	Acne	11.06/11.14 (95% CI: 8.85–14.02)
Osimertinib	Acquired gene mutation	20.18/20.44 (95% CI: 16.96–24.63)
Erlotinib	Hypertension	1.96/1.97 (95% CI: 1.67–2.32)
Gefitinib	Metastases to bone	4.33/4.36 (95% CI: 3.47–5.47)

Abbreviations: PRR: Proportional Reporting Ratio; ROR: Relative Odds Ratio; 95% CI: 95% confidence interval



Supplementary Figure 1 | Drug Adverse Events (Sorted by Commonality)