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Research Article

Skin Adverse Events Linked to Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors: A Disproportionality Analysis Using FAERS and Drug–Gene Interaction Network Analyses

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Abstract

Background: While tyrosine kinase inhibitors (TKIs) targeting the epidermal growth factor receptor (EGFR) have improved outcomes for non-small cell lung cancer (NSCLC) patients, these inhibitors also cause skin adverse events (AEs). Moreover, real-world, data driven studies on EGFR-TKI-related AEs remain limited. In particular, the mechanisms underlying EGFR-TKI-induced skin AEs remain unclear. **Methods:** EGFR-TKI AE reports from the FDA Adverse Event Reporting System (FAERS) (Q1 2004 to Q3 2024) involving skin and subcutaneous tissue were analyzed using the reporting odds ratio (ROR) and multi-item gamma Poisson shrinker (MGPS) methods. The onset time was assessed using the Weibull Shape Parameter (WSP). Drug-gene network analyses and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment were conducted to explore the underlying mechanisms. **Results:** A total of 13,786 skin and subcutaneous tissue AE reports were identified as associated with EGFR-TKI use. Significant signals were detected using both ROR and MGPS. Disproportionality signals for severe skin AEs were observed for erlotinib, afatinib, and osimertinib. All EGFR-TKIs showed early failure patterns. Gene analysis revealed key nodes in the network associated with skin AEs, including *PIK3CA*, *PIK3R1*, and *PIK3CB*. KEGG-enriched pathways included the MAPK signaling pathway, the proteoglycans in cancer pathway, and the phosphoinositide 3-kinase (PI3K)–protein kinase B (Akt) signaling pathway. **Conclusion:** This study underscores significant associations between EGFR-TKIs and skin AEs, including Stevens–Johnson syndrome. This study also identifies potential mechanisms and provides valuable mechanistic insights, although further studies are needed to confirm the findings.

Keywords: epidermal growth factor receptor; tyrosine kinase inhibitors; FAERS database; pharmacovigilance; drug-gene analysis

1. Introduction

According to data from the International Agency for Research on Cancer (IARC), lung cancer was the most commonly diagnosed cancer worldwide in 2022, accounting for approximately one in eight cancer cases globally (12.4% of all cancers). Lung cancer also had the highest mortality rate, accounting for 18.7% of all cancer deaths [1]. Approximately 80–85% of all lung cancer cases are non-small cell lung cancer (NSCLC) [2]. Treatment strategies for NSCLC include surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy [3]. However, patients with advanced-stage disease may be unable to undergo surgery. Furthermore, the prognosis of advanced NSCLC remains unsatisfactory due to various chemotherapy-related adverse events (AEs) and the development of tumor resistance [4]. In recent years, targeted therapy has achieved success in the treatment of advanced NSCLC [5].

Epidermal growth factor receptor (EGFR), a member of the receptor tyrosine kinase family, activates multiple signaling pathways that promote cell growth, differentiation, proliferation, and survival [6]. EGFR mutations are the most common oncogenic drivers in NSCLC, prompting considerable research into targeted therapies aimed at these mutations [7]. EGFR tyrosine kinase inhibitors (TKIs) have been shown to significantly improve the survival and clinical outcomes of NSCLC patients with EGFR mutations, establishing them as the recommended first-line treatment for these patients [8,9]. While EGFR-TKIs are typically associated with fewer AEs compared to traditional chemotherapy, they can still cause severe AEs that adversely affect treatment efficacy and patient quality of life [10].

A frequent AE associated with EGFR-TKIs is skin reaction. A meta-analysis indicated that EGFR-TKIs significantly increase the risk of skin AEs, with rash being the most prevalent form [11]. Recent pharmacovigilance evidence has characterized the overall spectrum of dermatologic toxicities associated with EGFR inhibitors [12]. However, a more focused evaluation of skin AEs related specifically to EGFR-TKIs, together with the potential molecular mechanisms, is warranted. The occurrence of skin AEs can lead to adjustments in EGFR-TKI treatment, including dose

reduction or even discontinuation in severe cases. They can also negatively affect the patient's quality of life and medication adherence [11,13]. Therefore, it is important to understand the characteristics of EGFR-TKI-induced skin AEs and to explore the underlying mechanisms so that personalized treatment and management strategies can be developed. Unfortunately, there is a lack of large-scale, real-world data-based studies on EGFR-TKI-related skin AEs. The FDA Adverse Event Reporting System (FAERS) from the U.S. is an extensive, real-world database that collects individual case safety reports (ICSRs) on AEs linked to drugs and biological products [14,15]. It is based on the spontaneous reporting system (SRS) and contains vast amounts of information on AE reports. ICSRs are based on individual patient reports and provide baseline information about the patient, details of medication use, description of the AEs, and timing of the AEs [16], thus helping researchers understand the characteristics of AEs. Therefore, the aim of this study was to explore the characteristics of skin AEs associated with different EGFR-TKIs using real-world data from the FAERS database.

Recently, the integration of signal mining from the FAERS database with drug-gene interaction analysis has opened new directions for pharmacovigilance research [17,18]. The investigation of drug-gene interactions contributes to a deeper understanding of drug toxicity. Since the underlying mechanisms of skin AEs caused by EGFR-TKIs are still unclear, we extracted gene data relating to EGFR-TKIs and skin diseases from public gene databases. By constructing a drug-gene interaction network and conducting functional enrichment analysis of these genes, our aim was to reveal the mechanisms linking drugs, genes, and AEs.

2. Methods

2.1 Data Source and Data Cleaning

Data from AE reports spanning the timeframe from the first quarter of 2004 (Q1 2004) to the third quarter of 2024 (Q3 2024) were retrieved from the FAERS database in December 2024. This timeframe was based on the dates for market approval of EGFR-TKIs by the U.S. FDA, including gefitinib, erlotinib, afatinib, dacomitinib, and osimertinib. Data preprocessing followed the U.S. FDA guidelines, including deduplication and quality assurance measures. Specifically, when multiple reports shared the same CASEID, the most recent record was retained based on FDA_DT. Python (version 3.11; Python Software Foundation, Beaverton, OR, USA) was employed during preliminary text analysis to harmonize the naming conventions of drugs under investigation. EGFR-TKIs flagged as "primary suspect (PS) drugs" were then subjected to detailed identification using R (version 4.4.2; R Foundation for Statistical Computing, Vienna, Austria). The Medical Dictionary for Regulatory Activities (MedDRA, version 27.0) served as the framework to identify AEs affecting the skin and subcutaneous tissue. The MedDRA® trademark is registered by the International Council for Harmonization (ICH). To further identify disproportionality signals for severe skin AEs, a targeted investigation of serious skin adverse reactions was conducted through the application of a narrow query using Standardized MedDRA Queries (SMQs). The preferred terms (PTs) related to these reactions are presented in **Supplementary Table 1**.

2.2 Data Mining of Disproportionality Signals for Skin AEs

The primary method currently used for disproportionality signals for mining skin AEs is disproportionality analysis (DPA) based on a 2 × 2 contingency table (see **Supplementary Table 2**). This method can quickly identify target signals and provide valuable information about drug safety [19,20,21,22]. The approach includes two main methods, with one relying on frequency-based calculations and the other utilizing Bayesian principles. Each method has unique advantages and can be used in a complementary manner to enhance the reliability of signal detection [23,24]. The present study employed signal mining using the reporting odds ratio (ROR) method, which relies on frequency, as well as the multi-item gamma Poisson shrinker (MGPS) method, which is based on Bayesian principles [25,26,27]. **Supplementary Table 3** summarizes the details of the calculation processes, detection criteria, and evaluation metrics for these methods. For signal detection, a positive ROR signal was defined as having a lower limit for the 95% confidence interval (CI) of >1 with at least three reports. A positive MGPS signal was defined as a lower one-sided 95% confidence limit of the empirical Bayes geometric mean ($EBGM_{05}$) >2. AE identification, signal mining, and result visualization were performed using R (version 4.4.2; R Foundation for Statistical Computing, Vienna, Austria).

2.3 Time-to-Onset Analysis

The onset time was assessed using the Weibull Shape Parameter (WSP) assessment. The β shape parameter and its 95% CI determine the classification of onset time patterns. When β is <1 with a 95% CI <1, the AE onset pattern is classified as an early failure type. When β is equal to or approximately 1, and its 95% CI includes 1, the pattern is considered a random failure type. When β is >1 with a 95% CI that excludes 1, the AE onset pattern is identified as a wear-out failure type [28,29,30]. The time-to-onset analysis was conducted using R software (version 4.4.2; R Foundation for Statistical Computing, Vienna, Austria).

2.4 Interaction Networks for EGFR-TKIs Linked to Skin Disease Genes

The SwissTargetPrediction (http://www.swisstargetprediction.ch), SuperPred (https://prediction.charite.de), and ChEMBL (https://www.ebi.ac.uk/chembl) databases were

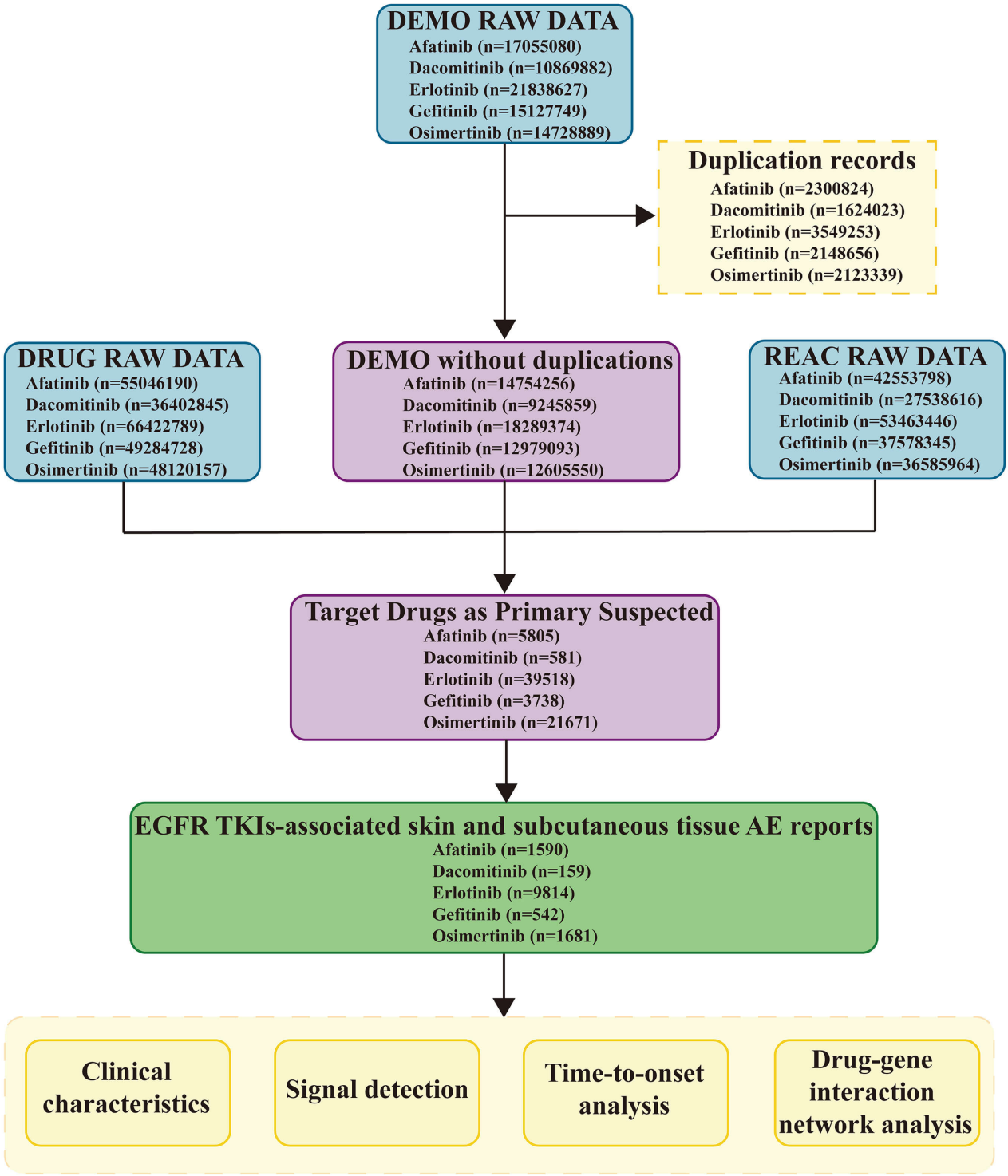

Fig. 1. Flow diagram for identifying skin and subcutaneous tissue AE reports related to EGFR-TKIs. AE, adverse event; EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors.

used to predict drug-related genes, including the involved EGFR-TKIs. The DisGeNET (https://disgenet.com) and GeneCards (https://www.genecards.org) platforms were utilized to identify genes associated with skin diseases. After separating duplicates from the genes related to drugs and diseases, the genes associated with EGFR-TKIs and skin diseases were combined to determine the target gene list. Target genes were imported into the STRING database (https://string-db.org) to predict protein-protein interactions (PPI) for the target genes, focusing on data scoring >0.9. After exporting the data, Cytoscape (version 3.10.3; Cytoscape Consortium, San Diego, CA, USA) was used to

Table 1. Clinical features of patients with skin and subcutaneous tissue AEs related to EGFR-TKIs.

Baseline information	Number of reports (%)				
	Gefitinib	Erlotinib	Afatinib	Dacomitinib	Osimertinib
Total	542	9814	1590	159	1681
Sex					
Female	347 (64.0%)	5555 (56.6%)	1015 (63.8%)	84 (52.8%)	1166 (69.4%)
Male	174 (32.1%)	3899 (39.7%)	524 (33.0%)	73 (45.9%)	388 (23.1%)
Missing	21 (3.9%)	360 (3.7%)	51 (3.2%)	2 (1.3%)	127 (7.6%)
Age group					
<18	0 (0%)	12 (0.1%)	3 (0.2%)	0 (0%)	0 (0%)
18–64	138 (25.5%)	1814 (18.5%)	533 (33.5%)	81 (50.9%)	242 (14.4%)
65–85	196 (36.2%)	2700 (27.5%)	704 (44.3%)	67 (42.1%)	485 (28.9%)
>85	16 (3.0%)	207 (2.1%)	30 (1.9%)	0 (0%)	39 (2.3%)
Missing	192 (35.4%)	5081 (51.8%)	320 (20.1%)	11 (6.9%)	915 (54.4%)
Reporter					
Consumer	146 (26.9%)	6500 (66.2%)	470 (29.6%)	91 (57.2%)	651 (38.7%)
Physician	175 (32.3%)	1665 (17.0%)	921 (57.9%)	29 (18.2%)	624 (37.1%)
Pharmacist	23 (4.2%)	369 (3.8%)	43 (2.7%)	6 (3.8%)	68 (4.0%)
Other health-professional	57 (10.5%)	1124 (11.4%)	146 (9.2%)	31 (19.5%)	109 (6.5%)
Missing	141 (26.0%)	156 (1.6%)	10 (0.6%)	2 (1.3%)	229 (13.6%)
Outcome					
Congenital anomaly	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)
Death	74 (13.7%)	1680 (17.1%)	235 (14.8%)	22 (13.8%)	160 (9.5%)
Disability	5 (0.9%)	78 (0.8%)	20 (1.3%)	3 (1.9%)	11 (0.7%)
Hospitalization-initial or prolonged	105 (19.4%)	1211 (12.3%)	488 (30.7%)	30 (18.9%)	373 (22.2%)
Life-threatening	10 (1.8%)	93 (0.9%)	40 (2.5%)	2 (1.3%)	63 (3.7%)
Other serious	296 (54.6%)	1927 (19.6%)	534 (33.6%)	71 (44.7%)	614 (36.5%)
Required intervention to prevent permanent impairment/damage	0 (0%)	10 (0.1%)	1 (0.1%)	31 (19.5%)	1 (0.1%)
Missing	52 (9.6%)	4815 (49.1%)	272 (17.1%)	22 (13.8%)	458 (27.2%)

AE, adverse event; EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors.

build the interaction network, with scores calculated using the maximal clique centrality (MCC) method in the cytoHubba app.

2.5 Kyoto Encyclopedia of Genes and Genomes (KEGG) Enrichment Analysis

KEGG enrichment analysis was performed in R (version 4.4.2; R Foundation for Statistical Computing, Vienna, Austria) using the BiocManager and clusterProfiler packages to investigate the biological significance of target genes. The study concentrated on the top 100 genes, ranked by their MCC scores. Pathways were prioritized based on their adjusted *p*-values (adjusted *p*-values < 0.05 were considered statistically significant), and the top 20 pathways were selected for detailed analysis. Visualization of the enriched pathways was carried out using the ggplot2 R package (version 3.5.1; Posit, PBC, Boston, MA, USA). This methodology offers a comprehensive understanding of the biological roles of target genes and their involvement in critical signaling pathways.

3. Results

A total of 13,786 skin and subcutaneous tissue AE reports were identified as being associated with EGFR TKI therapy, categorized as the "Primary Suspect (PS) Drug" based on the FAERS database (Fig. 1). Analysis of the AE reports for five EGFR-TKIs revealed variations in demographics and outcomes (Table 1). Female patients were more commonly reported, especially for osimertinib and gefitinib. Across the five EGFR TKIs, the proportion of reports involving patients aged 18–64 years was highest for dacomitinib (50.9%), followed by afatinib (33.5%). Regarding reporter type, consumer reports accounted for the highest proportion for erlotinib (66.2%), whereas physician reports accounted for the highest proportion for afatinib (57.9%). With regard to reported outcomes, the highest proportions of death, initial or prolonged hospitalization, and life-threatening events were observed for erlotinib (17.1%), afatinib (30.7%), and osimertinib (3.7%), respectively.

In terms of system organ class (SOC) level, the ROR method detected signals of skin and subcutaneous tissue AEs for all five EGFR-TKIs, whereas the MGPS method

identified positive signals for only three drugs (erlotinib, afatinib, and dacomitinib). Dacomitinib had the strongest signal (ROR of 4.19, EBGM of 3.73), followed by erlotinib (ROR of 3.06, EBGM of 2.75) and afatinib (ROR of 2.59, EBGM of 2.39), with all three showing positive disproportionality signals for these AEs (Table 2).

Table 2. The skin and subcutaneous tissue disproportionality signals associated with EGFR-TKIs for SOC level.

Drugs	ROR (95% CI)	EBGM ($EBGM_{05}$)
Gefitinib	1.63 (1.52, 1.75) *	1.58 (1.49)
Erlotinib	3.06 (3.01, 3.11) *	2.75 (2.71) *
Afatinib	2.59 (2.49, 2.7) *	2.39 (2.31) *
Dacomitinib	4.19 (3.70, 4.74) *	3.73 (3.36) *
Osimertinib	1.09 (1.05, 1.14) *	1.09 (1.05)

EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; SOC, system organ class; ROR, reporting odds ratio; CI, confidence interval; EBGM, empirical Bayesian geometric mean; $EBGM_{05}$, the lower 95% one-sided CI of EBGM.

*: The signal is considered with statistically significant.

At the PT level, the ROR method identified 48 skin and subcutaneous tissue disproportionality signals related to afatinib, 18 for dacomitinib, 70 for erlotinib, 20 for gefitinib, and 38 for osimertinib (Fig. 2). The strongest signal was PRIDE syndrome associated with gefitinib (ROR of 866.7, 95% CI: 244.5–3071.7). The MGPS method identified 52 skin and subcutaneous tissue disproportionality signals for afatinib, 24 for dacomitinib, 54 for erlotinib, 24 for gefitinib, and 34 for osimertinib (Fig. 3). Again, the most prominent signal was PRIDE syndrome linked to gefitinib (EBGM of 693.36). **Supplementary Table 4** lists the overlapping AE positive signals in skin and subcutaneous tissue associated with EGFR-TKIs, as identified by both ROR and MGPS.

SMQ narrow query was used to further explore the signals for serious skin adverse reactions. Table 3 summarizes the serious skin adverse reaction signals associated with EGFR-TKIs. Erlotinib was linked to significant signals for exfoliative rash and cutaneous vasculitis. Afatinib showed substantial associations with Stevens-Johnson syndrome (SJS) and severe cutaneous adverse reactions. Osimertinib was notably associated with erythema multiforme, SJS, and toxic epidermal necrolysis.

Table 4 presents the Weibull distribution analysis of onset times for skin and subcutaneous tissue AEs linked to EGFR-TKIs. The median onset times differ across the drugs, with afatinib having the shortest median onset time (9 days, interquartile range (IQR) 4–28 days) and dacomitinib the longest (49 days, IQR 26–270 days). The minimum onset time was 1 day for all drugs except dacomitinib (2 days), while the maximum onset time ranged from 723 days for dacomitinib to 3737 days for erlotinib. All drugs exhibited an early failure type, with $\beta < 1$.

A total of 798 target genes were identified, representing the intersection of EGFR-TKI-associated genes and skin disease-related genes (see **Supplementary Table 5**). The PPI network illustrates the connections between EGFR-TKIs and genes associated with skin diseases (Fig. 4). The size of each node indicates its degree value, while the color reflects the MCC score, with darker colors (red and dark orange) signifying higher MCC scores. Central nodes such as PIK3CA, PIK3R1, PIK3CB, PIK3CD, and SRC are highlighted in red, indicating their high degree of connectivity and pivotal role in the network.

KEGG pathway enrichment analysis of the top 100 genes ranked by MCC scores identified significant enrichment in several pathways, including the MAPK signaling pathway, proteoglycans in cancer, and the phosphoinositide 3-kinase (PI3K)-protein kinase B (Akt) signaling pathway. Other enriched pathways include Hepatitis B, human cytomegalovirus infection, and EGFR TKI resistance (Fig. 5).

4. Discussion

EGFR is extensively expressed in the skin, making skin toxicity one of the most frequent AEs associated with EGFR TKI therapy. EGFR-TKIs can cause diverse cutaneous toxicities, highlighting the need for close attention and standardized management [31]. However, there are still only limited studies of skin AEs associated with EGFR-TKIs based on real-world evidence. The current study leveraged the FAERS database to perform a comprehensive analysis of skin reaction disproportionality signals associated with EGFR-TKIs, including those related to severe skin reactions. Furthermore, we investigated the potential mechanisms underlying these events through drug-gene interaction analysis and KEGG pathway enrichment approaches, providing a deeper understanding of the biological pathways involved in developing these skin-related AEs.

A total of 13,786 skin and subcutaneous tissue AE reports associated with EGFR-TKIs were identified in the FAERS database. At the system organ class (SOC) level, the ROR method detected skin and subcutaneous tissue disproportionality signals for all five EGFR-TKIs, whereas the MGPS method identified positive signals for only three (erlotinib, afatinib, and dacomitinib). Dacomitinib displayed the strongest signal, followed by erlotinib and afatinib, indicating relatively stronger disproportionality signals for these AEs. Our findings suggest potential differences in the dermatologic safety profiles of EGFR-TKIs at the SOC level, with dacomitinib, erlotinib, and afatinib showing relatively stronger disproportionality signals, while gefitinib and osimertinib showed weaker signals and did not meet the positive signal threshold by MGPS. Positive signals that are consistently detected by different methods may

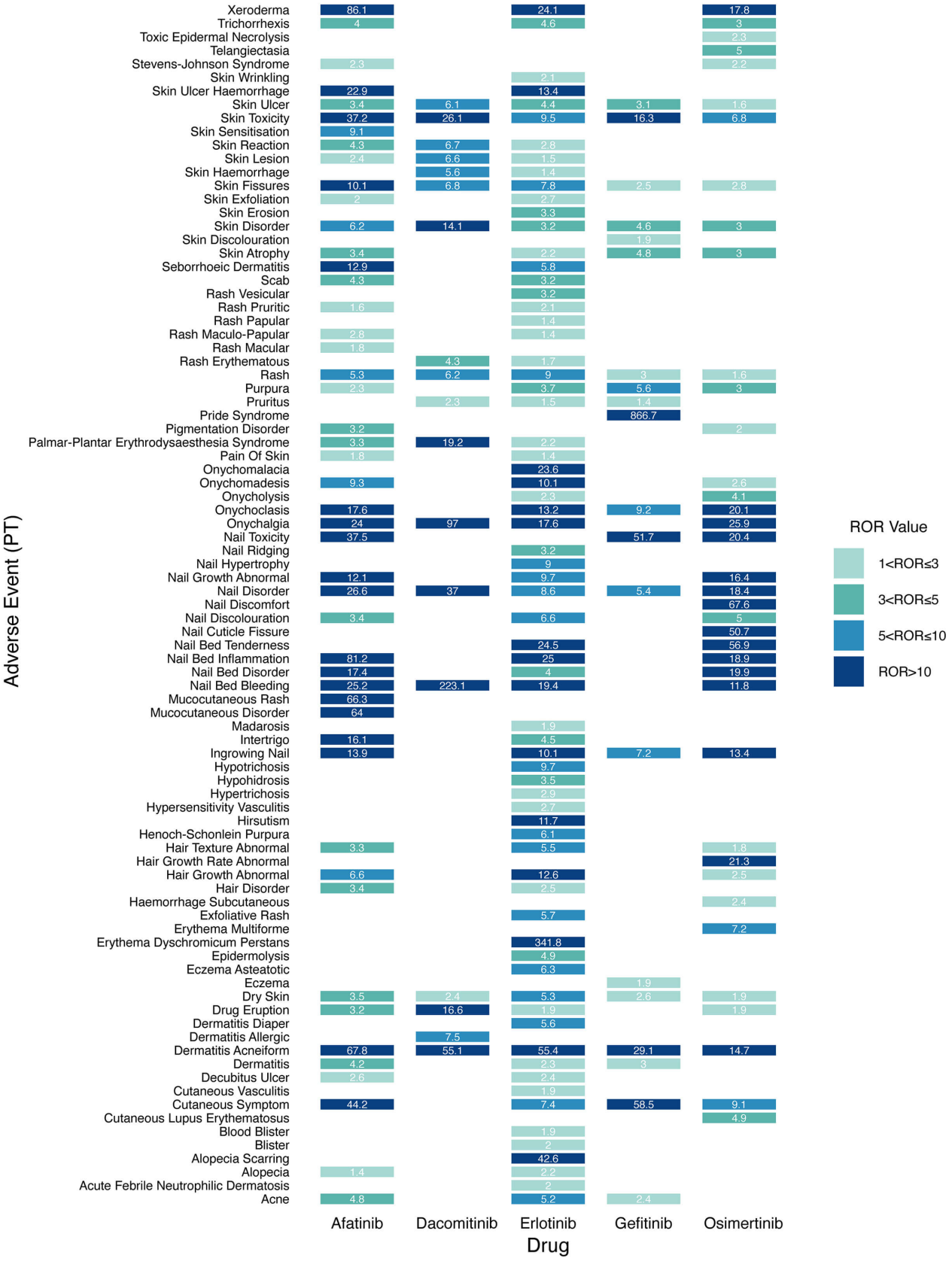

Fig. 2. The skin and subcutaneous tissue disproportionality signals of the reporting odds ratio (ROR) related to EGFR-TKIs of preferred term (PT).

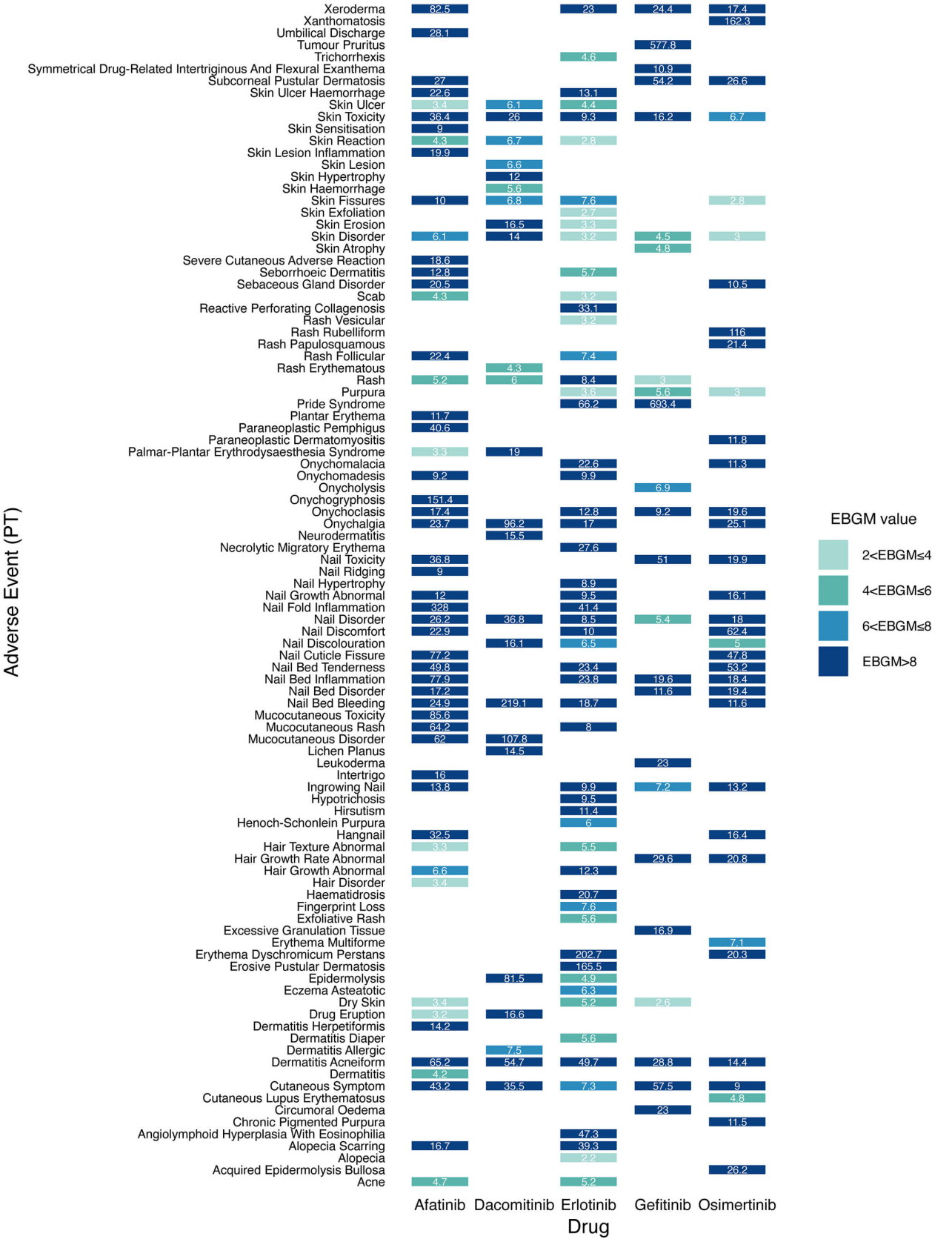

Fig. 3. The skin and subcutaneous tissue disproportionality signals of the multi-item gamma Poisson shrinker (MGPS) related to EGFR-TKIs of preferred term (PT).

Table 3. The serious skin adverse reaction signals associated with EGFR-TKIs.

Drug	PT	a	ROR (95% CI)	EBGM ($EBGM_{05}$)
Erlotinib	Exfoliative rash	26	5.66 (3.85–8.34) *	5.61 (4.06) *
Erlotinib	Cutaneous vasculitis	10	1.9 (1.02–3.53) *	1.89 (1.13)
Afatinib	Stevens-Johnson syndrome	13	2.29 (1.33–3.94) *	2.28 (1.45)
Afatinib	Severe cutaneous adverse reaction	1	18.73 (2.61–134.26)	18.57 (3.57) *
Osimertinib	Erythema multiforme	40	7.18 (5.26–9.81) *	7.12 (5.49) *
Osimertinib	Stevens-Johnson syndrome	25	2.22 (1.5–3.29) *	2.22 (1.6)
Osimertinib	Toxic epidermal necrolysis	22	2.28 (1.5–3.47) *	2.28 (1.6)

a: number of AE reports.

*: The signal is considered with statistically significant.

Table 4. The Weibull distribution of onset time of skin and subcutaneous tissue AEs related to EGFR-TKIs.

Drug	Cases (N)	Median (IQR) (days)	Min-max (days)	Scale parameter: α (95% CI)	Shape parameter: β (95% CI)	Failure type
Gefitinib	112	38 (14–124)	1–1894	100.40 (67.60–133.21)	0.60 (0.52–0.68)	Early failure
Erlotinib	2535	25 (8–92)	1–3737	67.81 (63.09–72.54)	0.59 (0.58–0.61)	Early failure
Afatinib	665	9 (4–28)	1–1300	27.15 (23.26–31.04)	0.56 (0.53–0.59)	Early failure
Dacomitinib	65	49 (26–270)	2–723	130.10 (87.71–172.50)	0.79 (0.64–0.94)	Early failure
Osimertinib	517	16 (6–62)	1–1261	47.29 (39.82–54.76)	0.58 (0.54–0.62)	Early failure

N, number of cases with available onset time; CI, confidence interval; IQR, interquartile range.

suggest a more robust association. However, variations in signal strength across drugs should still be interpreted cautiously, since disproportionality estimates from FAERS may be affected by reporting behaviors, patient characteristics, indication-related differences, and other unmeasured confounders. Rare cases of purpuric drug eruptions have been reported in patients treated with EGFR-TKIs [32]. Severe skin reaction signals were detected for erlotinib, afatinib, and osimertinib, highlighting the importance of close monitoring of these serious skin AEs. Disproportionality signals for the SJS AE were identified for afatinib and osimertinib in this study. Cases of SJS have previously been reported in patients using these drugs [33,34], consistent with the present findings.

Research has demonstrated a significant correlation between the severity and onset timing of rashes caused by EGFR-TKIs and the therapeutic efficacy of this treatment. However, there is currently no comprehensive comparison of the onset time of skin and subcutaneous tissue AEs associated with EGFR-TKIs [35]. The present study examined the onset time characteristics and Weibull distribution parameters for these AEs. We found significant variation in the median onset times, with afatinib and osimertinib having shorter median onset times (9 days and 16 days, respectively), while dacomitinib had a longer median onset time (49 days). All drugs displayed early failure characteristics, with afatinib ($\beta = 0.56$) exhibiting the most prominent early onset. These findings emphasize the need for early monitoring and personalized treatment, particularly for high-risk, early-onset drugs such as afatinib and osimertinib. Long-term follow-up is also necessary for drugs with broader time spans, like dacomitinib, to minimize AE risks.

The high expression level of EGFR in skin promotes the proliferation and differentiation of keratinocytes, thereby maintaining the skin barrier function [36]. The occurrence of skin AEs is associated with the use of EGFR-TKIs, which leads to disruption of the skin barrier and inflammatory responses. However, the detailed mechanisms underlying the skin AEs remain largely unknown. The present study identified PIK3CA, PIK3R1, PIK3CB, PIK3CD, and SRC as key nodes in the network. A previous study reported that genetic variations in *PIK3CA* may serve as important pharmacogenomic markers for predicting the occurrence of EGFR inhibitor-related skin rash [37]. Another study found that carriers of the *PIK3R1* 326I variant are more susceptible to rashes and tend to have better survival rates [38]. However, there is still only limited research on the roles of *PIK3CB*, *PIK3CD*, and *SRC* in EGFR TKI-related skin and subcutaneous tissue AEs. These genes may indicate potentially novel molecular mechanisms that warrant further attention.

The KEGG pathway enrichment results highlight the significant involvement of key signaling and disease-related pathways in the context of EGFR-TKIs and skin diseases. Prominent pathways include the MAPK signaling pathway, proteoglycans in cancer, and the PI3K-Akt signaling pathway, all of which showed the highest gene counts and significance. These results suggest that signaling transduction, immune regulation, and metabolic processes are central to the interaction between EGFR-TKIs and skin-related genes. The use of EGFR inhibitors in cancer treatment is limited by skin toxicity caused by inhibition of the MAPK pathway [39], consistent with the present findings. Upon phosphorylation, EGFR can initiate multi-

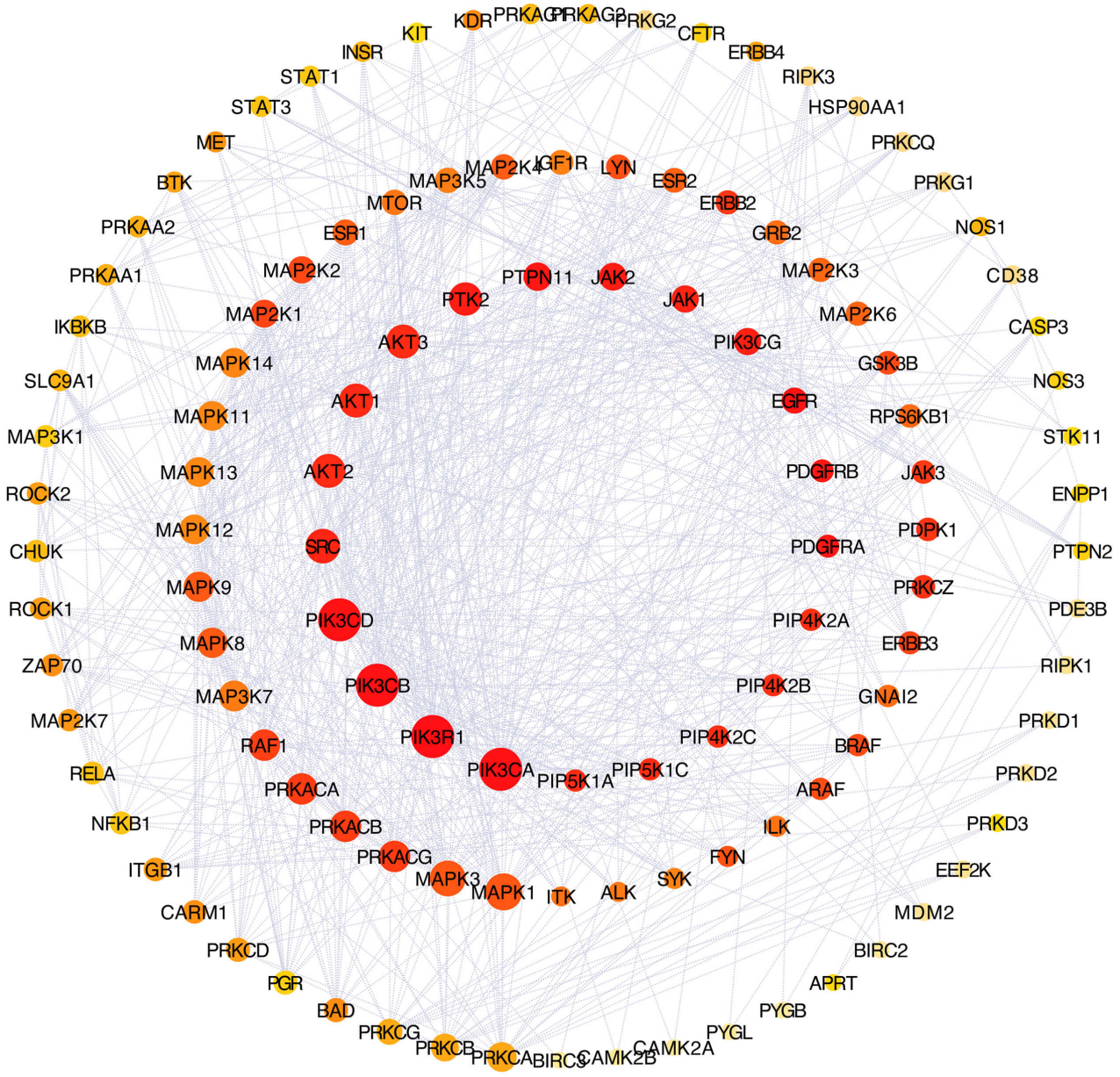

Fig. 4. The Protein–protein interaction network of EGFR-TKIs associated with skin disease genes. Note: Nodes denote proteins encoded by the overlapping genes, whereas edges represent the interactions among these proteins. The size of each node is proportional to its degree value, and node color reflects the maximal clique centrality (MCC) score, with darker colors representing higher MCC values.

ple downstream signaling cascades, notably the parallel Akt and MAPK pathways [40,41]. The PI3K signaling pathway plays a vital role in regulating key cellular processes, and the use of PI3K inhibitors has been linked to severe cutaneous AEs [42]. This indicates the PI3K pathway could be a key contributor to EGFR TKI-induced skin and subcutaneous tissue AEs, although the exact mechanisms remain to be explored. A previous study found that exposure to EGFR inhibitors can activate the PI3K/Akt pathway in keratinocytes, thereby promoting cellular senescence and differentiation while impairing epidermal barrier formation [43]. This observation provides a plausible biological explanation for EGFR TKI-related cutaneous AEs. Recent evidence has shown that EGFR-TKIs may induce acneiform rash and xerosis through Caspase-3/GSDME-mediated pyroptosis of keratinocytes and sebocytes, suggesting that epidermal cell injury may contribute to the development of cutaneous AEs [44]. Osimertinib and afatinib have been reported to affect keratinocyte barrier function and inflammatory regulation through the EGFR-STAT3 signaling pathway [45]. These findings are consistent with our results and provide further support for the proposed mechanism.

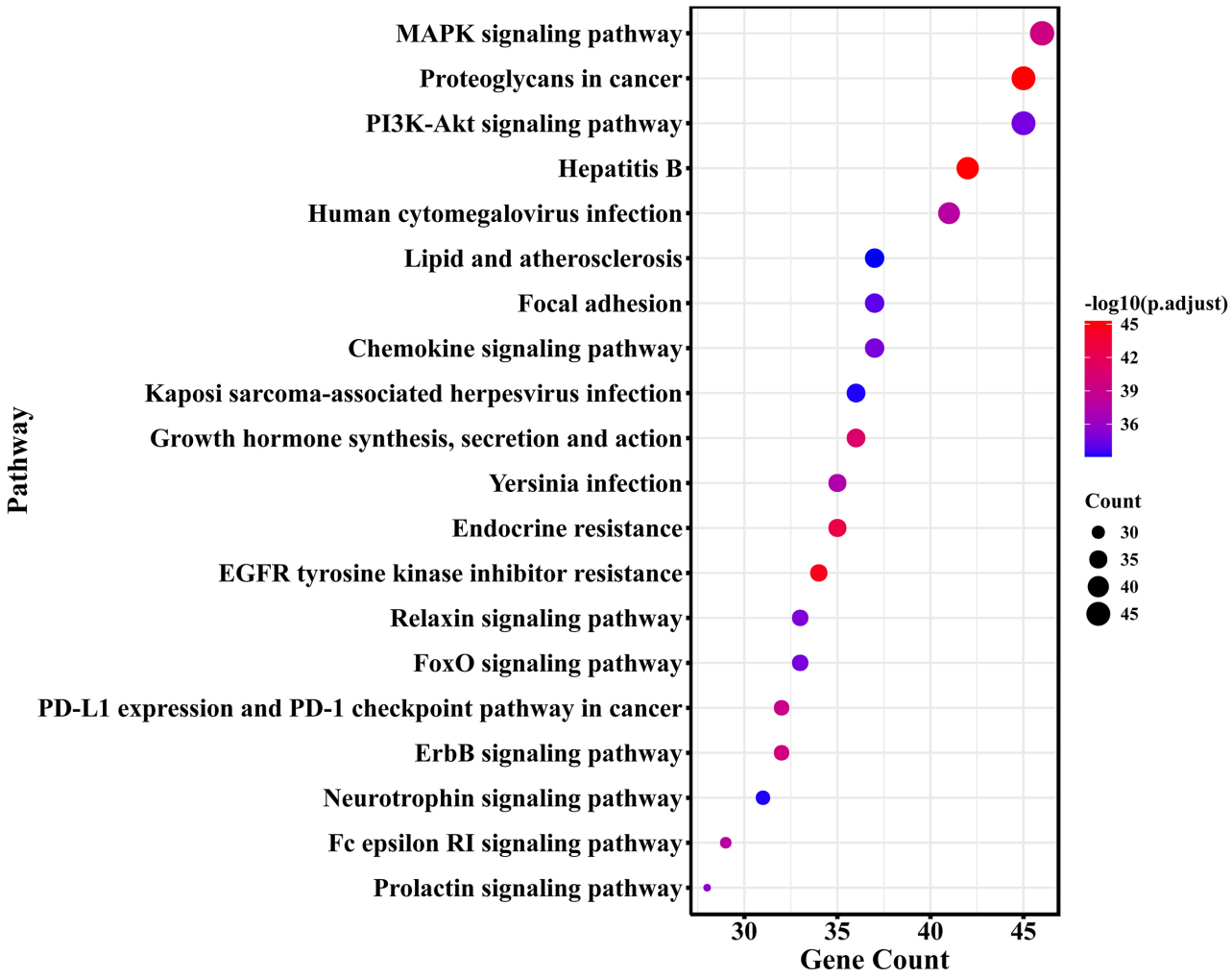

Fig. 5. The Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis of EGFR-TKIs related to skin disease genes. Note: Each circle denotes a significantly enriched KEGG pathway. Circle size reflects the number of enriched genes, while circle color represents the enrichment significance as –log10(adjusted *p*-value), with darker or warmer colors indicating greater statistical significance.

Notably, ethnic diversity contributes to genetic variations that can affect susceptibility to drug-induced AEs, including those linked to EGFR-TKIs. However, due to limitations in the available data, this issue could not be fully addressed in the current study. Further research that integrates population-specific pharmacogenomic data will be crucial for gaining a deeper understanding of ethnic variability in EGFR-TKI-induced skin AEs.

Limitations

This study has certain limitations that should be acknowledged. Although FAERS data is a free and publicly accessible database, it is based on a spontaneous reporting system, which inevitably leads to missing data and the use of inconsistent terminology [46]. Some variables in Table 1 had a relatively high proportion of missing data, which is a common limitation of spontaneous reporting databases and may affect the completeness of descriptive analyses. The lack of complete data for all patients using a targeted drug makes it challenging to accurately determine the incidence of AEs. Although we restricted our analysis to PS drugs, confounding by concomitant medications cannot be completely excluded. This represents an inherent limitation of FAERS data and a potential focus for future research. Indication bias could also affect signal detection, as the underlying disease and treatment context may influence reporting patterns. Although we applied standard deduplication procedures, residual duplicate reports may still exist. Furthermore, in the absence of a control group of non-users, it is not possible to clearly establish a causal relationship between the drug and its AEs. Therefore, disproportionality signals do not imply causality and should be interpreted with caution. It should also be noted that the identified genes represent potential associations detected through

database-derived intersections. The tissue-specific expression of these genes and their functional relevance in normal skin tissue remain to be fully elucidated and warrant further validation through expression analysis and functional studies. Although we have begun to investigate the underlying mechanisms, further animal studies and clinical trials are required to confirm these preliminary findings.

5. Conclusion

This study employed the FAERS database to obtain a detailed analysis of skin and subcutaneous tissue AEs associated with EGFR-TKIs. Our findings suggest potential associations between EGFR-TKIs and skin and subcutaneous tissue AEs, including severe AEs like Stevens-Johnson Syndrome. The present study also identified variations in the onset time of these AEs, suggesting the need for early monitoring and personalized treatment. Furthermore, analysis of the molecular mechanisms suggested potential involvement of the PI3K-Akt and MAPK pathways in the development of EGFR-TKI-induced skin toxicity. However, further clinical studies are needed to validate these findings and gain a deeper understanding of the underlying mechanisms.

Availability of Data and Materials

The original data can be accessed from the U.S. FDA Adverse Event Reporting System database (https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases/). The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

XL and WT led the study's conceptualization and the design of the research protocol, establishing a strong foundation for the investigation. YH, SW and ZW were responsible for standardizing drug nomenclature and cleaning the data to ensure its accuracy and consistency. XL and ZG managed gene-related data processing and analysis. LL, WT and CQ concentrated on summarizing the data and visualizing the results. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/IJP50806.

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