Original Article

Retrospective clinical study analysis of skin adverse reactions related to epidermal growth factor receptor inhibitors

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Background: Epidermal growth factor receptor inhibitors (EGFRIs) represent a cornerstone in the targeted therapy of malignant tumors. While effective, dermatological adverse events (dAEs) associated with EGFRIs pose a significant challenge, often necessitating treatment discontinuation due to their severity and potential to impede the continuity of cancer therapy. Despite extensive research, the specific mechanisms and predictors of these adverse events remain poorly understood, particularly in diverse populations. This gap in knowledge underscores the need for targeted studies to better predict and manage these events, enhancing patient outcomes and adherence to life-saving therapies.

Methods: This observational study was conducted at The First Affiliated Hospital of Guangxi Medical University, covering cancer patients treated with EGFRIs from 2020 to 2022. We analyzed clinical data including patient demographics, treatment specifics, and the development and timing of dAEs. The study employed SPSS 26.0 software for data analysis, focusing on the incidence of dAEs and factors influencing their occurrence. We used Kaplan-Meier and Cox regression methods to establish a predictive model for dAEs, tracking their onset and impact on treatment continuity.

Results: In our study of 120 patients treated with EGFR inhibitors at The First Affiliated Hospital of Guangxi Medical University, we found a high prevalence of dAEs, with 84.2% of patients experiencing such effects. The most common manifestations were papulopustular rashes, observed as pustules in 52.5% and papules in 57.4% of cases, followed by nail lesions in 62.4% of patients, oral or other mucosal ulcers in 34.7%, and hair changes in 26.7%. The median incubation time (MIT) for dAEs was 5 weeks. We identified drug type, ethnicity, and occupation as statistically significant risk factors ($P<0.05$ for all) that influenced the MIT, which the Cox regression model further identified as protective factors. Nomograms were developed to assess the risk of dAEs, although it is important to note that these models have only been internally validated, lacking external validation data at this stage.

Conclusions: The study highlights the high incidence of EGFRIs-associated dAEs, with specific dermatological manifestations posing significant challenges in cancer therapy. The identification of drug type, ethnicity, and occupation as influential factors on the MIT for dAEs informs clinical decisions. Our prediction model serves as a practical tool for evaluating the risk of developing dAEs over time, aiming to optimize patient management and mitigate treatment interruptions.

Keywords: Epidermal growth factor receptor inhibitors (EGFRIs); dermatological adverse events (dAEs); risk factors; prediction model

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Introduction

Epidermal growth factor receptor (EGFR)-related signaling pathways regulate tumor cell proliferation and differentiation. Epidermal growth factor receptor inhibitors (EGFRIs) and EGFRI-containing regimens are commonly used as targeted therapeutic agents in treating various malignant tumors. EGFRIs are associated with a variety of dermatological adverse events (dAEs) including papulopustular rashes, nail lesions, hair changes, dry skin, itchy skin, chapped skin, and oral/other mucosal lesions (1).

Many factors, such as calcium imbalance, hyperkeratosis, immune dysregulation, apoptosis imbalance, epidermal barrier dysfunction, oxidative stress, lipid metabolism disorders, inflammatory response, pharmacologic agent and individual differences, may contribute to the pathogenesis of dAEs (2-5). Other possible factors include: (I) genetic factors: such as specific human leukocyte antigen (HLA) alleles and other immune-related genes, which may increase the risk of EGFRIs-associated dAEs; (II) immune factors: EGFRIs can affect the immune system, leading to changes in the number and function of immune cells [e.g., T cells, B cells, and natural killer (NK) cells], which may trigger the occurrence of dAEs; and (III) environmental factors: such as external temperature, humidity, and ultraviolet radiation may have an impact on the development of dAEs. The above factors may also affect each other, thus raising the risk of EGFRIs-associated dAEs (2,6-16).

Despite numerous international investigations, the mechanisms, diagnosis, and treatment options of EGFRIs-associated dAEs remain unclear. In addition, there are also controversies about the effectiveness and safety of the currently available treatments.

In some studies, the anti-tumor activities of EGFRIs are related to the occurrence and severity of EGFRIs-associated dAEs. Studies on cetuximab-related dAEs revealed that higher incidence of skin toxicities was associated with longer progression-free survival (PFS), or a significantly prolonged median survival period (17-19).

In Guangxi Zhuang Autonomous Region of China, the Han Chinese have genetic differences with other ethnic minorities (e.g., Zhuang), which offers valuable population resources for research on the potential correlations of human diseases with genes, heredity, and other factors (20-22). For example, some studies have found that genetic variants associated with diseases such as skin cancer and vitiligo are related to ethnicity and geographic distribution (23-26).

Unfortunately, few studies have explored EGFRIs-associated dAEs in Guangxi. In the present study, we analyzed the effects of factors associated with the median incubation time (MIT) of EGFRIs-associated dAEs. In addition, we established a prediction model for the quantitative prediction of EGFRIs-associated dAEs in clinical setting.

According to clinical trial report prior to the approval of EGFRIs, the incidence of all types of skin adverse reactions of any grade varies from 34% to 90% (27). Other influencing factors may vary due to differences in gender, age, ethnicity, and type of medication.

Factors that increase the risk of skin adverse reactions related to erlotinib include non-smokers, those with fair skin, and individuals over the age of 70. In a study involving patients treated with cetuximab, severe rashes

Highlight box

Key findings

- Research reveals ethnic and occupational disparities in the median onset time of skin adverse reactions to epidermal growth factor inhibitors in Guangxi's Han and minority populations. Longer onset times suggest better medication tolerance, with treatment duration potentially affecting outcomes. A newly created nomogram aids clinicians in quickly assessing these reactions.

What is known and what is new?

- High skin reaction rates (>90%) to epidermal growth factor receptor inhibitors (EGFRIs) have been confirmed. Skin reactions are one of the most common side effects during EGFRIs treatment.
- The study identifies factors influencing the onset times of EGFRIs-related skin adverse reactions in cancer patients treated with EGFRIs at The First Affiliated Hospital of Guangxi Medical University. The study provides new insights into the management of EGFRIs-related skin adverse reactions, helping improve patient care for those receiving EGFRIs therapy.

What is the implication, and what should change now?

- Evidence suggests a link between skin reaction onset to inhibitors and patients' ethnicity and occupation in Guangxi, assisting oncologists in anticipating reactions and adjusting treatment to improve patient longevity.

were more common in males and younger patients, with males experiencing more severe skin adverse reactions than females. Among these risk factors, the risk of severe rash in males over the age of 70 years was 8% (28). Another study of elderly patients treated with erlotinib showed similar progression-free survival to younger patients, but higher skin toxicity in the elderly. Severe (grade 3 and 4) toxicity rates were 18% in younger patients and 35% in older patients, with a relatively lower relative dose intensity, and they were more likely to discontinue treatment due to treatment-related toxicity (11). Additionally, compared to low molecular weight tyrosine kinase inhibitors (5–9%), monoclonal antibodies have a higher incidence of serious skin adverse reactions (10–17%) (6).

Some studies suggest potential links with ethnicity and mutation sites. For example, the occurrence of EGFR mutations is higher in Japanese than in Caucasians (29). The HLA-A2 expression rates in Japanese and Caucasians are respectively 22.2–36.0% and 49.6% (30,31). These findings suggest that EGFR mutations may occur in tumors with specific HLA types. On the other hand, research shows that EGFR mutations in lung adenocarcinoma patients are more common in females and non-smokers than in their peers (8). Since EGFRIs are associated with side effects due to their role in inhibiting the activity of the EGFR signaling pathway, it can be speculated that EGFR mutations may also cause abnormalities in the EGFR signaling pathway (32-35), thus leading to associated skin adverse reactions.

A study in China has shown a strong association between the genetic model of the EGFR signaling pathway, the drug metabolism/transport pathway, and miRNAs, and the adverse reactions to erlotinib, suggesting that treatment and adverse reactions may be related to single nucleotide polymorphisms (SNPs) associated with these genetic foundations in certain populations (36).

The above studies indicate that factors such as skin color, gender, age, lifestyle (such as smoking), and type of medication can also affect the inhibition of the EGFR signaling pathway, potentially leading to EGFRIs-related skin adverse reactions.

In the context of this study, the term 'minority ethnic groups' refers to the various ethnic groups in China that are not part of the Han majority. China is home to 56 different ethnic groups, with the Han being the largest. The 'minority ethnic groups' in our study predominantly include those residing in the Guangxi Zhuang Autonomous Region, an area known for its ethnically diverse population. These groups have distinct cultural, linguistic, and historical characteristics, differentiating them from the Han majority. Understanding this diversity is crucial for interpreting our study's findings, as these ethnic backgrounds can influence health outcomes and responses to medical treatments. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-486/rc).

Methods

Samples and sources

The clinical data of some tumor patients admitted to The First Affiliated Hospital of Guangxi Medical University and treated with EGFRIs or EGFRI-containing regimens from 2020 to 2022 were analyzed. The inclusion criteria were as follows: (I) cancer patients treated with EGFRIs or retrospectively EGFRI-containing regimens in the outpatient or inpatient facilities of our hospital; and (II) willing to participate in this study. The exclusion criteria were as follows: (I) refusal to be involved in this study; and (II) with other skin diseases including psoriasis, atopic dermatitis, and eczema before using EGFRIs. The data collected mainly included ethnicity, occupation, gender, age, type of EGFRIs [the third-generation EGFRIs, and others (general term for EGFRIs other than the third-generation drugs and EGFRI-containing regimens)], time-to-onset of dAEs, and types of dAEs. The diagnostic criteria for assessing the types of skin adverse reactions in study subjects were based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0 standard (37).

Due to the lack of external funding for this study, we adopted a retrospective research design. This design allowed us to utilize existing medical records data, but it also limited our ability to collect more extensive data and conduct more complex analyses.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board (IRB) of The First Affiliated Hospital of Guangxi Medical University (No. 2023-E476-01) and individual consent for this retrospective analysis was waived.

Statistical analysis

Statistical methods applied in this study included descriptive analysis, Chi-squared test, Kaplan-Meier survival analysis, and nomograms. Purpose of analyses: descriptive analysis

Table 1 Basic information of the samples

Variables	Values, n (%)
Gender	
Males	50 (41.7)
Females	70 (58.3)
Ethnic group	
Han	78 (65.0)
Ethnic minorities	42 (35.0)
Occupation	
Manual workers	66 (55.0)
Non-manual workers	54 (45.0)
Age group, years	
≤54	42 (35.0)
55–65	39 (32.5)
≥66	39 (32.5)
Drug type	
Third-generation EGFRIs	93 (77.5)
Others	27 (22.5)

EGFRIs, epidermal growth factor receptor inhibitors.

was used to summarize patient demographics and clinical characteristics. The Chi-squared test was employed to assess the association between categorical variables and the presence of dAEs. Kaplan-Meier analysis was conducted to estimate the time-to-onset of dAEs, and Cox regression was used to identify significant risk factors influencing the MIT for dAEs. Nomograms were developed to provide a visual representation of the probability of dAE occurrence based on significant risk factors identified. These models were internally validated to assess their predictive accuracy using a bootstrap resampling method. Statistical analysis was performed using the SPSS 22.0 software package (IBM Corp., Armonk, NY, USA), and graphs were created using R's ggplot2 package. A two-sided P value of less than 0.05 was regarded as statistically significant.

Data processing and quality control

The raw data was cleaned, including deletion of missing values, outliers, duplicate data, etc. Raw data were converted into an analyzable format and summarize the data according to the above requirements.

Data accuracy was verified by comparing it to electronic records, ensuring patients' basic information was accurate and checking for any underreporting of adverse reactions. Data consistency was checked by verifying the absence of duplicate data and ensuring data format consistency. Raw data were more complete, with no obvious gaps or omissions.

Results

A total of 145 samples were observed and 135 samples with complete information were collected, of which 120 samples (82.8%) met the quality requirements and were included in this study. There were 70 females (58.3%) and 50 males (41.7%). The females aged 57.5±13.5 years and the males aged 59.4±10.7 years, showing no significant difference (P>0.05). About 2/3 (65.0%) of the cases were Han Chinese, and manual workers accounted for 55.0%. Cases with an age of ≤54 years accounted for 35.0%, and the third-generation EGFRIs accounted for 77.5% (*Table 1*). We reviewed the medical records of relevant patients in our hospital system. Inclusion criteria for selection of these 145 patients were based on the manifestation of cutaneous adverse reactions associated with EGFRIs, including the stage of the associated cutaneous adverse reactions, prior treatment, and continuation of dermatologic therapy. Patients' informed consent was also a key factor in conducting the study. We primarily conducted telephone follow-up visits to collect data. This approach allowed us to collect real-time, real-world data that provided insight into the clinical manifestations of EGFRI-associated cutaneous adverse reactions. The main tumor types are non-small cell lung cancer, small cell lung cancer and colorectal cancer.

Types of dAEs

We observed dAEs in 101 (84.2%) of 120 samples. The most common dAEs included papulopustular rashes (pustules 52.5% and papules 57.4%), oral/other mucosal ulcers (34.7%), nail lesions (62.4%), and hair changes (26.7%) (*Table 2*).

Incidence of dAEs in different subgroups

Overall, the incidence of dAEs showed no significant difference in terms of gender [χ^2=0.002, odds ratio (OR) =0.979, 95% confidence interval (CI): 0.363–2.642, P=0.97], age (χ^2=1.133, P=0.57), and drug type (χ^2=1.856, OR =0.358,

Table 2 Types of dAEs

Type	Values, n (%)
Pustules	
Yes	53 (52.5)
No	48 (47.5)
Acne	
Yes	1 (1.0)
No	100 (99.0)
Papules	
Yes	58 (57.4)
No	43 (42.6)
Erythema	
Yes	20 (19.8)
No	81 (80.2)
Erosions	
Yes	2 (2.0)
No	99 (98.0)
Oral/other mucosal ulcers	
Yes	35 (34.7)
No	66 (65.3)
Crusting	
Yes	1 (1.0)
No	100 (99.0)
Scars	
Yes	2 (2.0)
No	99 (98.0)
Dried skin	
Yes	20 (19.8)
No	81 (80.2)
Chapped skin	
Yes	11 (10.9)
No	90 (89.1)
Wheal	
Yes	2 (2.0)
No	99 (98.0)
Eczema	
Yes	4 (4.0)
No	97 (96.0)
Blisters	
Yes	3 (3.0)
No	98 (97.0)
Subcutaneous nodules	
Yes	1 (1.0)
No	100 (99.0)
Hyperpigmentation or hypopigmentation	
Yes	2 (2.0)
No	99 (98.0)
Seborrheic keratosis	
Yes	1 (1.0)
No	100 (99.0)
Scales	
Yes	2 (2.0)
No	99 (98.0)
Atrophy	
Yes	1 (1.0)
No	100 (99.0)
Nail lesions	
Yes	63 (62.4)
No	38 (37.6)
Hair changes	
Yes	27 (26.7)
No	74 (73.3)
Toothache, periodontitis, and/or bleeding gums	
Yes	3 (3.0)
No	98 (97.0)

dAEs, dermatological adverse events.

95% CI: 0.077–1.657, P=0.17). However, the incidence of dAEs for Han Chinese was 91.0%, significantly higher than that for ethnic minorities (71.4%) (χ^2=7.867, OR =4.057, 95% CI: 1.455–11.310, P=0.005). The non-manual workers had an incidence of dAEs of 96.3%, which was significantly higher than that of the manual workers (74.2%) (χ^2=10.840, OR =6.955, 95% CI: 1.680–28.781, P=0.001) (*Table 3*).

Factors that were statistically significant in the univariate analysis were included in the logistic multivariate model,

Table 3 Results of univariate analysis of the risk factors for dAEs in different subgroups

Variables	dAEs, n (%)		Sample size	Log-rank χ^2	P value	OR (95% CI)
	Yes	No				
Gender						
Male	42 (84.0)	8 (16.0)	50	0.002	0.97	0.979 (0.363–2.642)
Female	59 (84.3)	11 (15.7)	70	–	–	1.000
Ethnicity						
Han	71 (91.0)	7 (9.0)	78	7.867	0.005	4.057 (1.455–11.310)
Ethnic minorities	30 (71.4)	12 (28.6)	42	–	–	1.000
Occupation						
Non-manual workers	52 (96.3)	2 (3.7)	54	10.840	0.001	6.955 (1.680–28.781)
Manual workers	49 (74.2)	17 (25.8)	66	–	–	1.000
Age group, years						
≤54	37 (88.1)	5 (11.9)	42	1.133	0.57	–
55–65	33 (84.6)	6 (15.4)	39	–	–	–
≥66	31 (79.5)	8 (20.5)	39	–	–	–
Drug type						
Third-generation EGFRIs	76 (81.7)	17 (18.3)	93	1.856	0.17	0.358 (0.077–1.657)
Others	25 (92.6)	2 (7.4)	27	–	–	1.000

dAEs, dermatological adverse events; OR, odds ratio; CI, confidence interval; EGFRIs, epidermal growth factor receptor inhibitors.

Table 4 Results of multivariate analysis of the risk factors for dAEs in different subgroups

Variables	β	SE	Wald χ^2	AOR (95% CI)	P value
Occupation					
Non-manual workers	2.159	0.785	7.573	3.859 (1.317–11.311)	0.006
Manual workers	–	–	–	–	–
Ethnicity					
Han	1.350	0.549	6.059	8.665 (1.862–40.333)	0.01
Ethnic minorities	–	–	–	–	–
Constant	–3.853	0.796	23.424	–	0.02

dAEs, dermatological adverse events; SE, standard error; AOR, adjusted odds ratio; CI, confidence interval.

which revealed that the risk factors included non-manual workers [adjusted odds ratio (AOR) =3.859, 95% CI: 1.317–11.311, P=0.006] and Han Chinese (AOR =8.665, 95% CI: 1.862–40.333, P=0.01) (*Table 4*).

MIT of dAEs

The Kaplan-Meier model was established to evaluate the median time to onset of dAEs in different subgroups. The MIT of dAEs in 101 samples was 5.0 weeks (95% CI: 2.644–7.356) (*Figure 1A*), and the cumulative risk is shown in *Figure 1B*.

MIT of dAEs in drug type subgroups

The MIT of dAEs was 9.0 weeks (95% CI: 5.0–12.9) for the third-generation drugs, which was significantly longer than that for "others" (2.0 weeks) (95% CI: 1.5–2.5; log-rank χ^2=10.320, P=0.001) (*Table 5* and *Figure 2*).

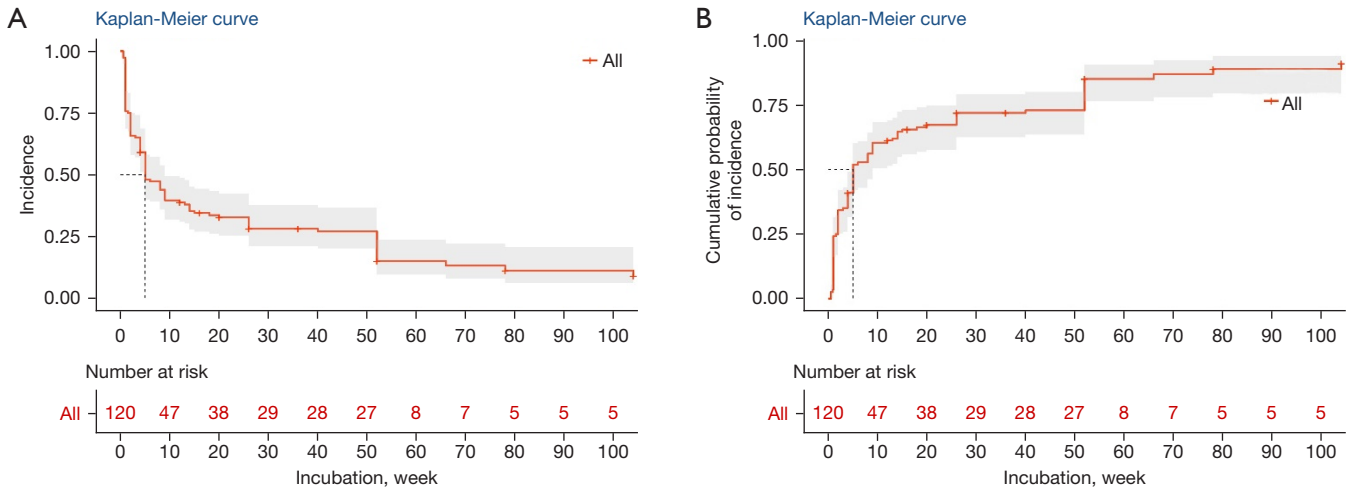

Figure 1 Survival curves of dAEs and cumulative risk curves for the whole sample. dAEs, dermatological adverse events.

Table 5 Difference in the MIT of dAEs between two drug type subgroups

Subgroups	MIT (weeks)	95% CI	Log-rank χ^2	P value
Third-generation EGFRIs	9.0	5.0–12.9	10.320	0.001
Others	2.0	1.5–2.5	–	–
Total	5.0	2.6–7.4	–	–

MIT, median incubation time; dAEs, dermatological adverse events; CI, confidence interval; EGFRIs, epidermal growth factor receptor inhibitors.

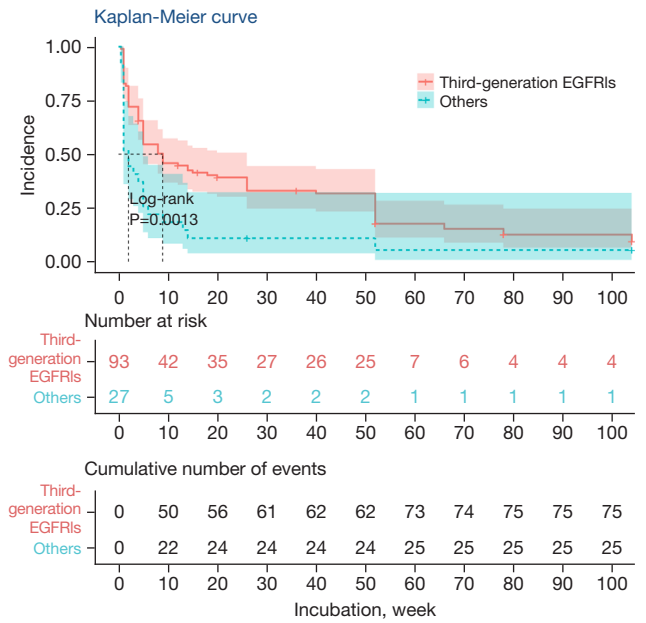

Figure 2 MIT of dAEs between two drug type subgroups. MIT, median incubation time; dAEs, dermatological adverse events; EGFRIs, epidermal growth factor receptor inhibitors.

MIT of dAEs in gender subgroups

The MIT of dAEs was 4.0 weeks (95% CI: 1.7–6.3) for women, showing no significant difference when compared with men (8.0 weeks) (95% CI: 4.0–12.0; log-rank χ^2=1.482, P=0.22) (*Table 6* and *Figure 3*).

MIT of dAEs in ethnic group subgroups

The MIT of dAEs was 5.0 weeks (95% CI: 3.8–6.2) for Han Chinese, which was significantly shorter than that for ethnic minorities (15.0 weeks) (95% CI: 0.5–29.5; log-rank χ^2=6.483, P=0.01) (*Table 7* and *Figure 4*).

MIT of dAEs in occupation subgroup

The MIT of dAEs was 9.0 weeks (95% CI: 0.0–19.0) for manual workers, which was significantly longer than that for non-manual workers (4.0 weeks) (95% CI: 2.7–5.3; log-rank χ^2=7.254, P=0.007) (*Table 8* and *Figure 5*).

MIT of dAEs among different age subgroups

The MIT of dAEs in the ≤54 years subgroup, 55–65 years subgroup, and ≥66 years subgroup was 2.0 weeks (95% CI: 0.3–3.7), 14.0 weeks (95% CI: 0.6–27.4), and 8.0 weeks (95% CI: 4.9–11.1), respectively, showing no statistically significant difference (log-rank χ^2=2.704, P=0.26) (*Table 9* and *Figure 6*).

Table 6 Difference in the MIT of dAEs between two gender subgroups

Subgroups	MIT (weeks)	95% CI	Log rank χ^2	P value
Females	4.0	1.7–6.3	1.482	0.22
Males	8.0	4.0–12.0	–	–
Total	5.0	2.6–7.4	–	–

MIT, median incubation time; dAEs, dermatological adverse events; CI, confidence interval.

Table 7 Difference in the MIT of dAEs between Han Chinese and ethnic minorities

Subgroups	MIT (weeks)	95% CI	Log-rank χ^2	P value
Han Chinese	5.0	3.8–6.2	6.483	0.01
Ethnic minorities	15.0	0.5–29.5	–	–
Total	5.0	2.6–7.4	–	–

MIT, median incubation time; dAEs, dermatological adverse events; CI, confidence interval.

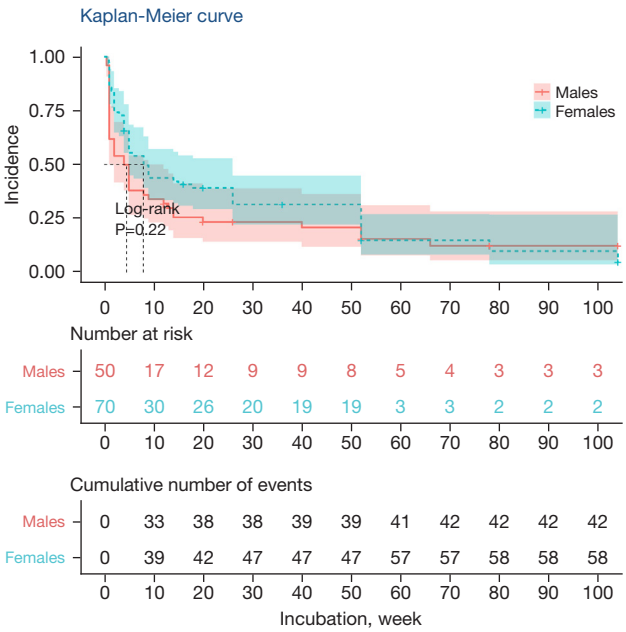

Figure 3 MIT of dAEs between two gender subgroups. MIT, median incubation time; dAEs, dermatological adverse events.

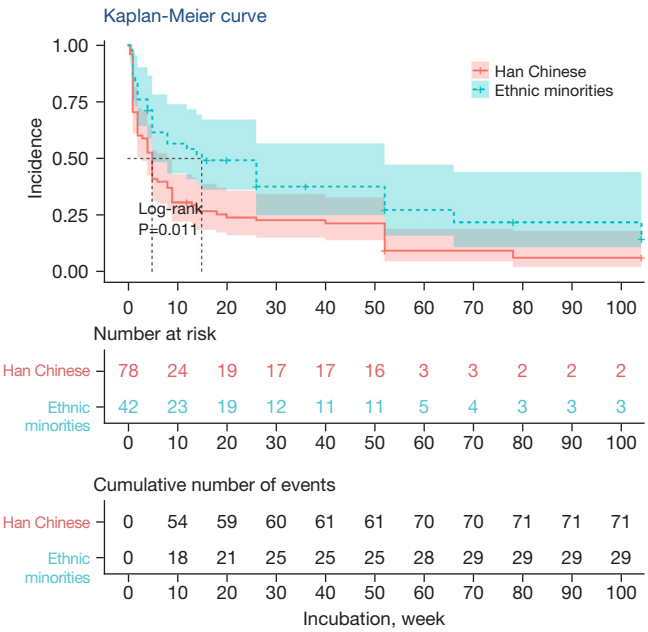

Figure 4 MIT of dAEs between Han Chinese and ethnic minorities. MIT, median incubation time; dAEs, dermatological adverse events.

Cox regression analysis

The Cox regression model revealed that the protective factors for the MIT of dAEs included third-generation drugs (AOR =0.429, 95% CI: 0.266–0.690, P<0.001), ethnic minorities (AOR =0.551, 95% CI: 0.353–0.860, P=0.009), and manual workers (AOR =0.645, 95% CI: 0.434–0.958, P=0.03) (*Table 10*).

Nomogram prediction

Statistically significant variables identified by the Cox regression model were included in the nomogram to build a visualization model. Occupation, ethnicity, and drug type were assigned with corresponding scores (points), and the total points were calculated to evaluate the probability that patients may develop dAEs within 1, 3, 5, 10, and 20 weeks, to improve clinical applicability (*Figure 7*).

The Cox regression model and the nomogram were internally calibrated and then tested at 1, 3, 5, 10, and 20 weeks. It was found that the fitting effect was relatively good at 1, 3, 5, and 10 weeks, whereas deviation occurred at 20 weeks (*Figure 8*).

Discussion

EGFRIs are a class of targeted anticancer drugs mainly used for the treatment of malignant tumors such as lung cancer,

Table 8 Difference in the MIT of dAEs between manual workers and non-manual workers

Subgroups	MIT (weeks)	95% CI	Log-rank χ^2	P value
Manual workers	9.0	0.0–19.0	7.254	0.007
Non-manual workers	4.0	2.7–5.3	–	–
Total	5.0	2.6–7.4	–	–

MIT, median incubation time; dAEs, dermatological adverse events; CI, confidence interval.

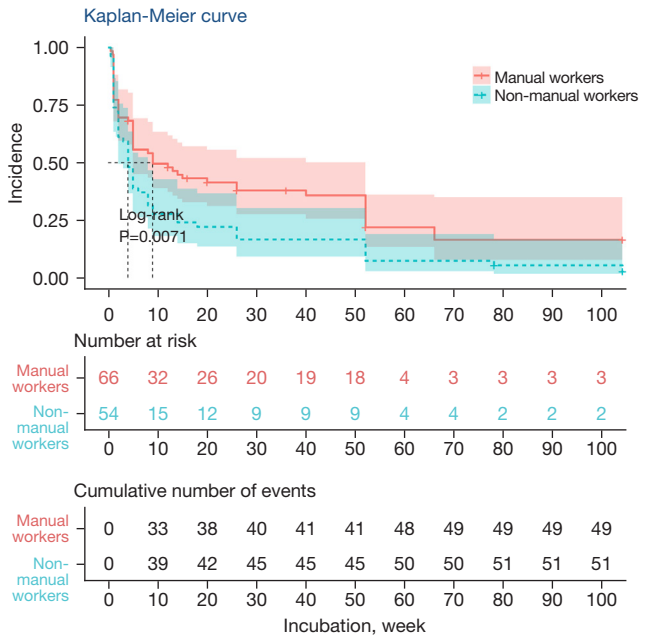

Figure 5 MIT of dAEs between manual workers and non-manual workers. MIT, median incubation time; dAEs, dermatological adverse events.

Table 9 Difference in the MIT of dAEs among different age subgroups

Subgroups	MIT (weeks)	95% CI	Log-rank χ^2	P value
≤54 years	2.0	0.3–3.7	2.704	0.26
55–65 years	14.0	0.6–27.4	–	–
≥66 years	8.0	4.9–11.1	–	–
Total	5.0	2.6–7.4	–	–

MIT, median incubation time; dAEs, dermatological adverse events; CI, confidence interval.

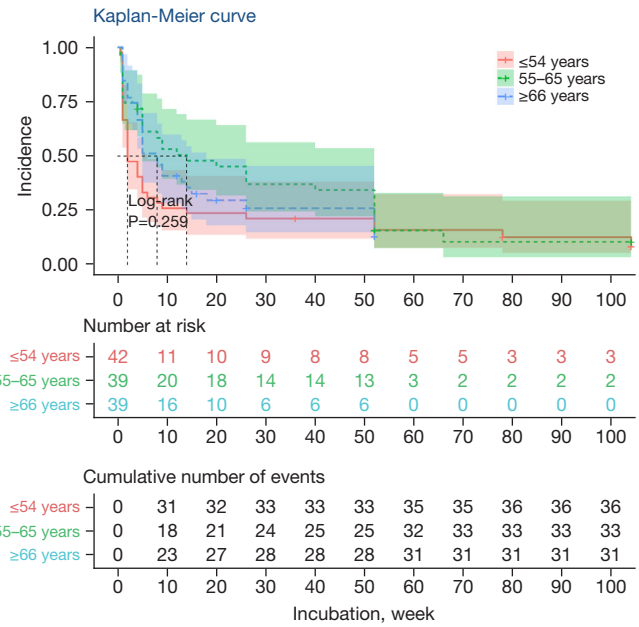

Figure 6 Time to onset of dAEs among different age subgroups. dAEs, dermatological adverse events.

Table 10 Cox regression analysis of median time-to-onset of dAEs

Variables	β	SE	Wald χ^2	AOR (95% CI)	P value
Drug					
Third-generation EGFRIs	−0.847	0.243	12.153	0.429 (0.266–0.690)	<0.001
Others	–	–	–	–	–
Ethnicity					
Ethnic minorities	−0.596	0.227	6.898	0.551 (0.353–0.860)	0.009
Han Chinese	–	–	–	–	–
Occupation					
Manual workers	−0.439	0.202	4.708	0.645 (0.434–0.958)	0.03
Non-manual workers	–	–	–	–	–

dAEs, dermatological adverse events; SE, standard error; AOR, adjusted odds ratio; CI, confidence interval; EGFRIs, epidermal growth factor receptor inhibitors.

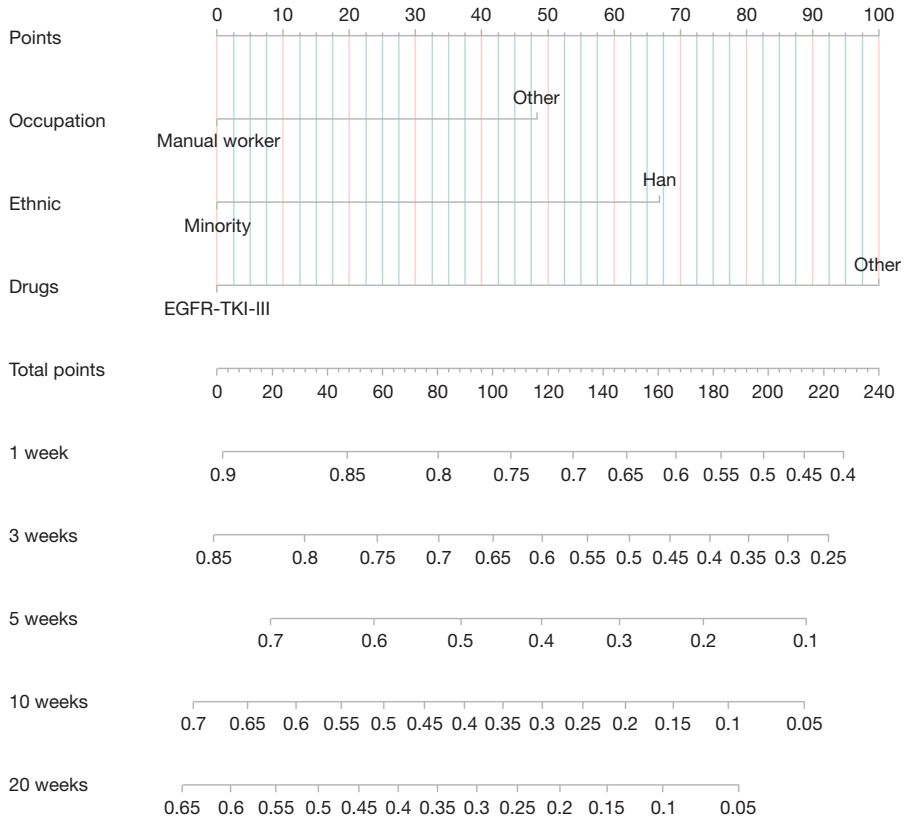

Figure 7 Nomogram of the Cox regression model. EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

colorectal cancer, and head and neck cancer. Epidermal growth factor receptors are found in the keratinocytes of the epidermis and skin appendages. Studies have shown that the lack of epidermal growth factor receptors can lead to obstruction in the progression of the hair cycle, indicating that epidermal growth factor receptors play a key role in the development of hair follicles (38-41). The inhibitory effect of EGFRIs on normal skin cells has an impact on the growth, differentiation, and repair of epidermal cells, leading to the manifestation of dAEs. Other factors, such as inflammatory reactions, abnormal follicular keratinization, dysfunction in the skin barrier, and immune-mediated reactions, can also influence the pathophysiology of normal epidermal cells.

EGFRIs can cause side effects such as skin rash, oral ulcers, diarrhea, nausea/vomiting, anorexia, fatigue, high blood pressure, infections, bleeding, and heart problems, among which skin toxicities are the most common. In the current study, dAEs were observed in 84.2% (101 out of 120) of the samples. The incidence of all grades of dAEs ranged between 34% and 90% in pre-approval clinical trials of EGFRIs. The variability in rates may stem from diverse factors such as age, gender, ethnicity, and drug mechanism (2,27-28,42-43). Common EGFRIs-associated dAEs include manifestations such as a papulopustular rashes, onychomycosis/nail changes, mucosal ulceration, hair changes, dry skin, itchy skin, and pigmentation abnormalities (44). Similarly, the present study found a diversity of skin lesions after EGFRI use, with papulopustular rashes (pustules 52.5% and papules 57.4%), oral/other mucosal ulcers (34.7%), nail lesions (62.4%), and hair changes (26.7%) being the most common.

Although the mechanism and pathophysiology of EGFRIs-associated dAEs have not yet been fully elucidated, four potential causes may contribute to them: damaged physical barrier after the destruction of the epidermis; damage to hair follicles; disruption of skin homeostasis (by inflammatory response and host immune activation); and radiation therapy (45).

EGFRIs-associated dAEs may also have some special manifestations.

A female Romanian patient developed purpuric skin

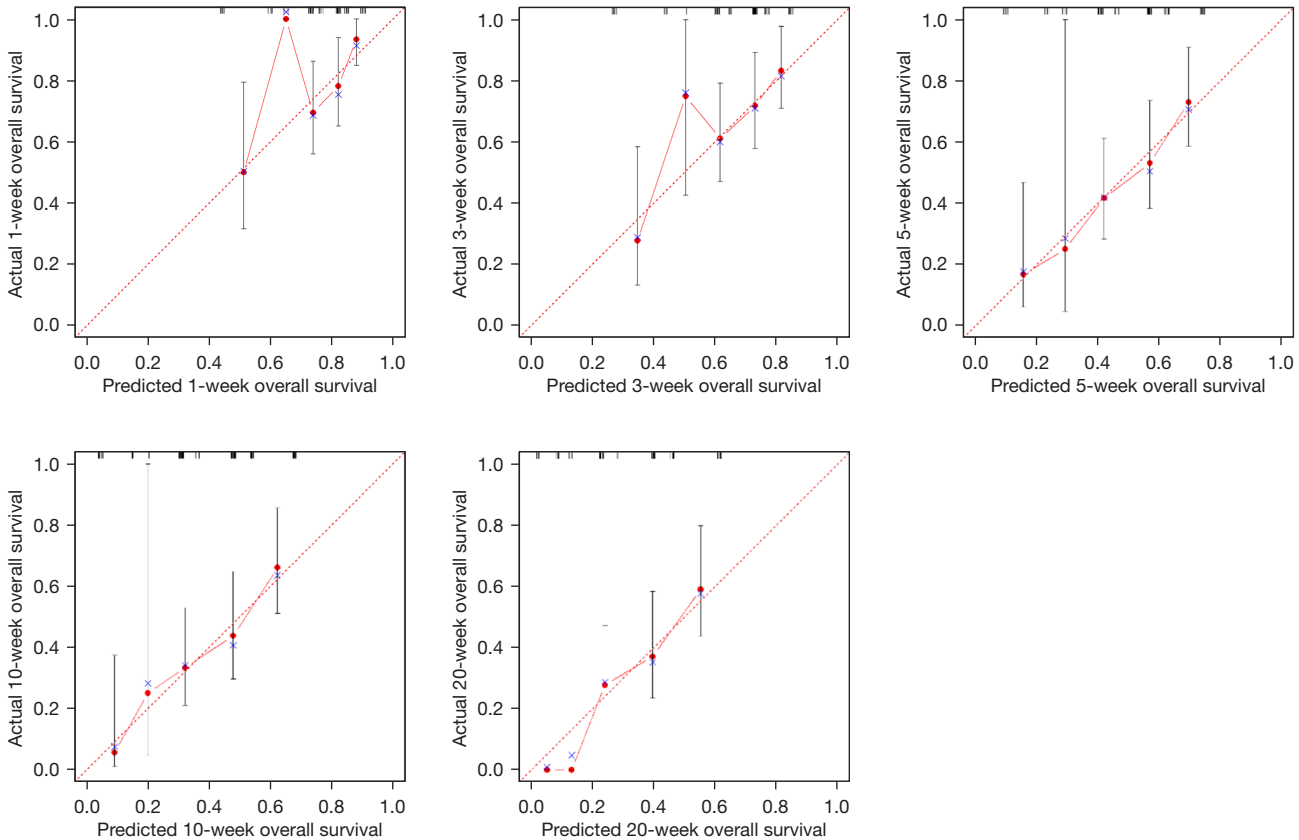

Figure 8 Internally calibrated diagram of the model.

lesions after 8 months of erlotinib monotherapy, and the condition was diagnosed as cutaneous leukocytoclastic vasculitis by skin histopathology (46).

Two Korean males presented with yellowish papuloplaques and acneiform eruption on the face after having received erlotinib therapy for lung cancer. In 1 patient, xanthomatous change was suggested by skin histopathology, and the condition gradually disappeared as the acneiform eruption improved. It was believed that the xanthomatous change was associated with the acneiform eruption (47).

Among 20 Chinese cancer patients with dAEs associated with erlotinib treatment, none of the above specific manifestations were described (48), which might be explained by ethnographic differences however this needs to be investigated in future research.

As shown in the present study, non-manual workers and Han Chinese individuals were more likely to develop dAEs during EGFRI treatment, which may be related to genetic factors, environmental factors, and lifestyle, but evidence is limited. It is also possible that manual workers may be less likely to observe their skin lesions due to roughness and thickening of the skin as a result of physical exertion and lack of awareness of the associated adverse effects, which needs to be further investigated. However, our present study is of clinical significance to improve the prevention and monitoring of EGFRIs-associated dAEs in Han Chinese and non-manual workers.

This study is a real-world clinical investigation, primarily based on medical records data from The First Affiliated Hospital of Guangxi Medical University. Although this research design provides preliminary insights into the actual clinical scenarios of EGFRIs-related dAEs, it inevitably has some limitations. Firstly, due to its retrospective design, we cannot completely eliminate the possibility of record bias and selection bias. Secondly, due to the lack of funding, the data set may not cover a broader population and variables. These limitations could affect the generalizability of our findings.

In response to these limitations, future studies should consider adopting a prospective cohort design and expanding the sample size to more systematically assess and validate the risk factors and mechanisms associated with

EGFRIs-related dAEs. Furthermore, more comprehensive funding support would enable more complex analyses, including genetic and biomarker analysis, which would deepen our understanding of these adverse events.

Conclusions

We used the Kaplan-Meier survival model to evaluate the median time to the occurrence of adverse drug events (ADEs) in different subgroups, and analysis of the MIT of all dAEs in each risk factor showed statistically significant differences by drugs, ethnicity, and occupation. A Cox regression model was developed to evaluate the factors affecting the MIT of EGFRIs-associated dAEs, based on the 3 protective factors including third-generation drugs, ethnicity, and manual workers. As previously reported (2,6,49-51), later onset of dAEs may lead to a delay in tapering or discontinuing EGFRI treatment due to skin lesion intolerance; accordingly, the longer treatments are associated with more favorable outcomes of the primary diseases (e.g., tumors), including longer survivals and smaller impacts on the patient's physical and psychological well-being. Therefore, we assume that the MIT of EGFRIs-associated dAEs is a protective factor for patients.

The Cox regression model was implemented in this research to identify statistically significant variables (i.e., occupation, ethnicity, and drug type) for inclusion in Norman plots. The corresponding scores were assigned to these variables, and the total score was calculated to assess the likelihood that patients might develop dAEs within 1, 3, 5, 10, and 20 weeks. This method provided clinicians with visual models, which may improve the clinical applicability and enable the quick and simple diagnosis of EGFRIs-associated dAEs. Further research is necessary to clarify the specific mechanisms by which occupation, ethnicity, and drug type act as protective factors as well as the signaling pathways that regulate EGFRIs-associated dAEs. This will provide a deeper theoretical foundation for the prevention and treatment of such adverse events. Most importantly, this study needs to be validated in an independent cohort in order to solidify these parameters as predictive markers of dAEs. In summary, EGFRIs-associated dAEs are common conditions. Some patients may develop skin complications of varying severity, which may hinder the continuation of drug therapy and impact the physical and psychological well-being of the patients. The MIT model of EGFRIs-associated dAEs and the Norman diagram of the protective factors have furnished clinicians with visual aids that could enhance clinical usability and facilitate the prompt and simple detection of EGFRIs-associated dAEs. Moreover, it is imperative that clinicians utilizing EGFRIs in practice consider inter-population disparities and proactively take measures towards averting or intervening with adverse reactions.

Although this study provides valuable insights into dAEs related to EGFR inhibitors, its retrospective and observational design limits the generalizability of the results. Future research should focus on validating these preliminary findings through a prospective design and exploring more unknown factors. This requires not only broader geographic and demographic coverage but also methodological and financial support to ensure more accurate and comprehensive results. We hope these efforts will enhance the safety and effectiveness of EGFR inhibitor treatments, ultimately improving patient treatment experiences and quality of life.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-486/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-486/coif). 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board (IRB) of The First Affiliated Hospital of Guangxi Medical University (No. 2023-E476-01)

and individual consent for this retrospective analysis was waived.

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