Volume 3, Number 2 March 2026

ISSN 2760-1757 (Online)
ISSN 2760-3288 (Print)

CLINICAL MEDICINE & PHARMACOLOGY

https://jandoopress.com/journal/cmp

JANDOO PRESS
株式会社間渡出版

Issue

Volume 3, Number 2 (March 2026)

Publisher

株式会社間渡出版 (Jandoo Press Co., Ltd.)
Tokyo office: 1-53-13 Nishigahara, Kita City, Tokyo 114-0024, Japan
Email: contact@press.jandoo.ac

Journal info

Portal: https://jandoopress.com/journal/cmp
ISSN 2760-1757 (Online)
ISSN 2760-3288 (Print)

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Research article

https://doi.org/10.70731/0yk94f55

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

Xiongzhou Zhang [1,2,3,†], **Shujie Liu** [2,†], **Baojia Qi** [4], **Bin Li** [2,*], **Chaojun Duan** [1,3,5,6,†,*]

Received 26 January 2026

Accepted 2 March 2026

Published 31 March 2026

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

ISSN 2760-1757 (Online)
ISSN 2760-3288 (Print)

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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

[1] Department of Thoracic Surgery, Xiangya Hospital, Central South University, Changsha 410008, Hunan, China; [2] Department of Oncology, Xiangya Hospital, Central South University, Changsha 410008, Hunan, China; [3] Hunan Engineering Research Center for Pulmonary Nodules Precise Diagnosis & Treatment, Changsha 410008 Hunan, China; [4] Postgraduate Training Base Alliance of Wenzhou Medical University (Zhejiang Cancer Hospital), Hangzhou, China; [5] Xiangya Lung Cancer Center, Xiangya Hospital, Central South University, Changsha 410008, Hunan, China; [6] National Clinical Research Center for Geriatric Disease (Xiangya Hospital), Changsha 410008, Hunan, China.
† These authors contributed equally to this work.
* Corresponding author. Email: (Chaojun Duan) duancjxy@csu.edu.cn; (Bin Li) bincsuxy@csu.edu.cn

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-

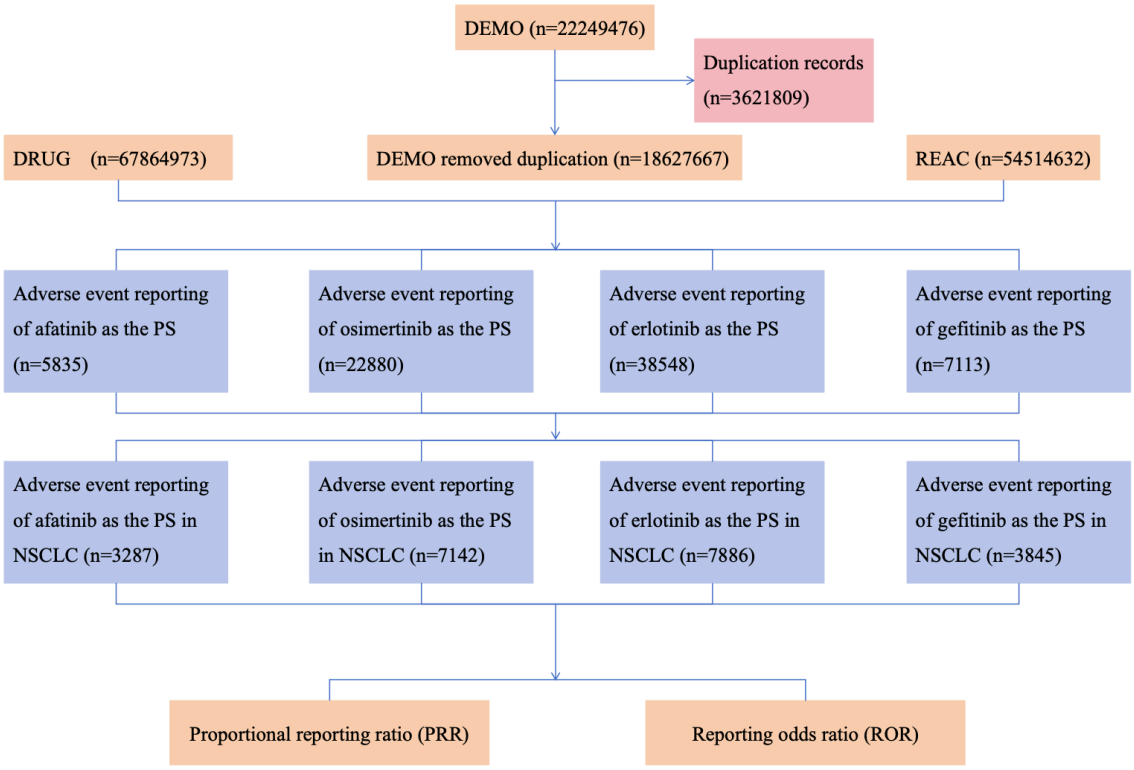


Figure 1 | Study Flowchart of FAERS Data Analysis

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

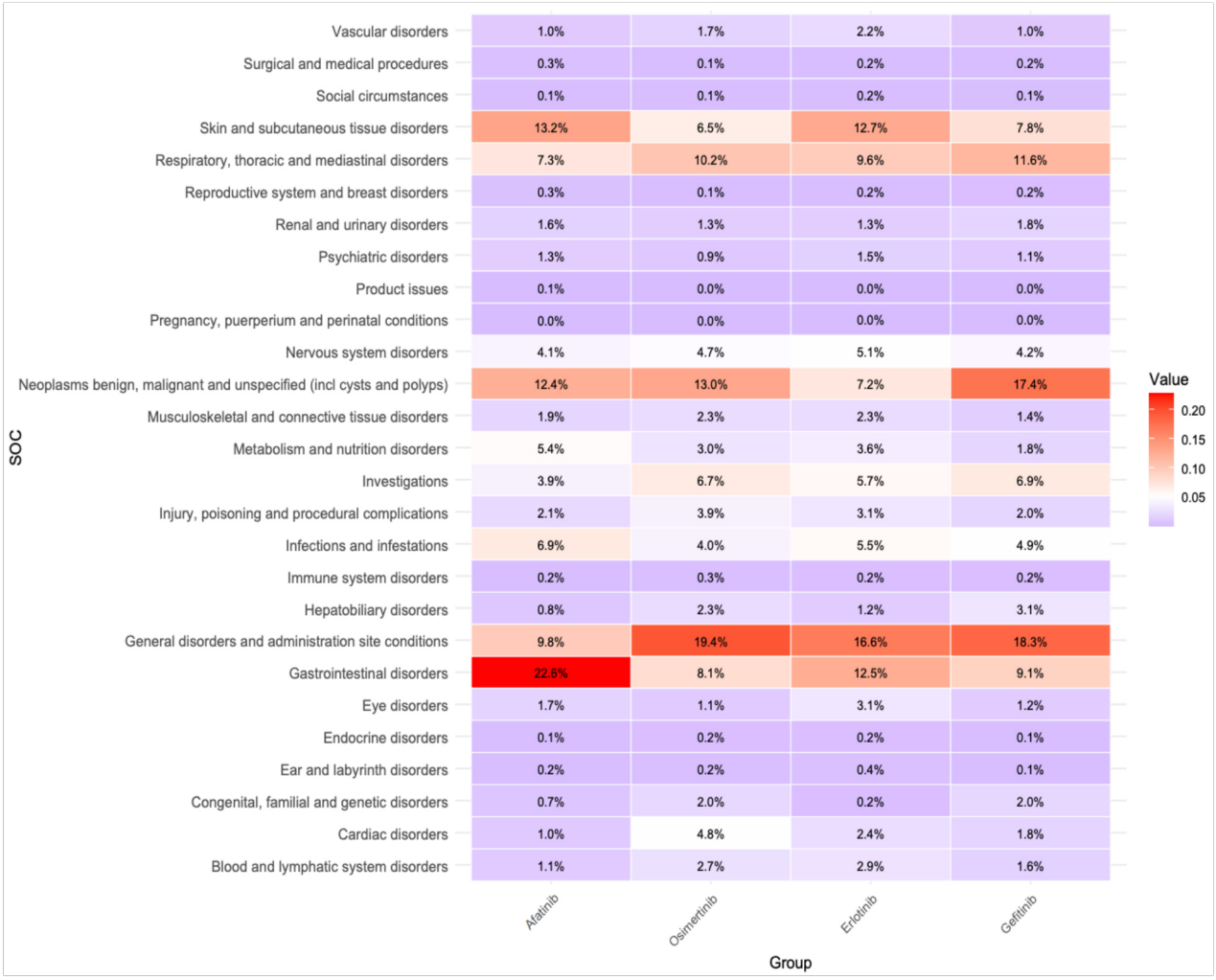


Figure 2 | System Organ Class (SOC) Distribution of EGFR-TKI-Related Adverse Events

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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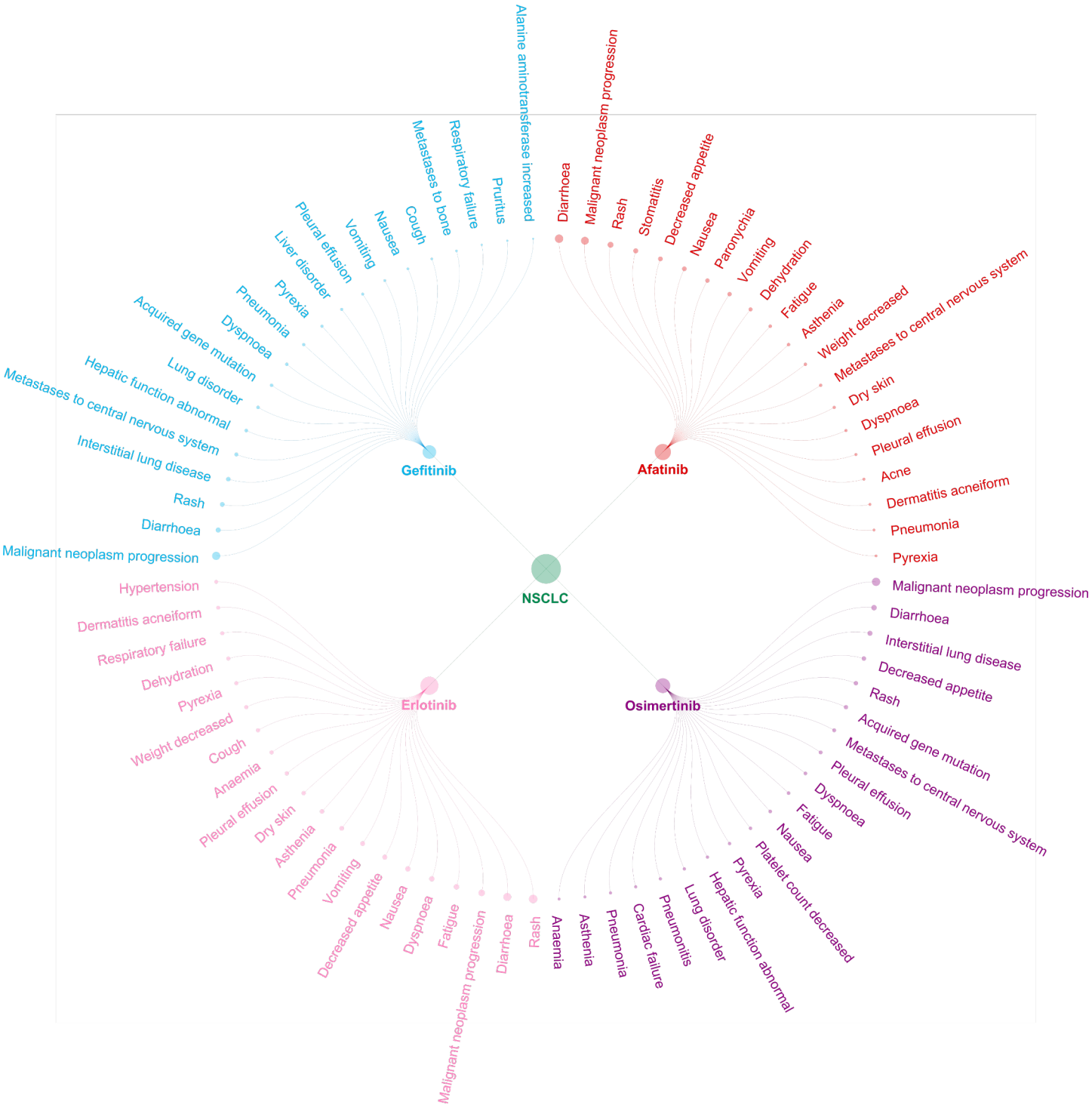


Figure 3 | Radial Network of EGFR-TKI-Associated Adverse Events in NSCLC

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.

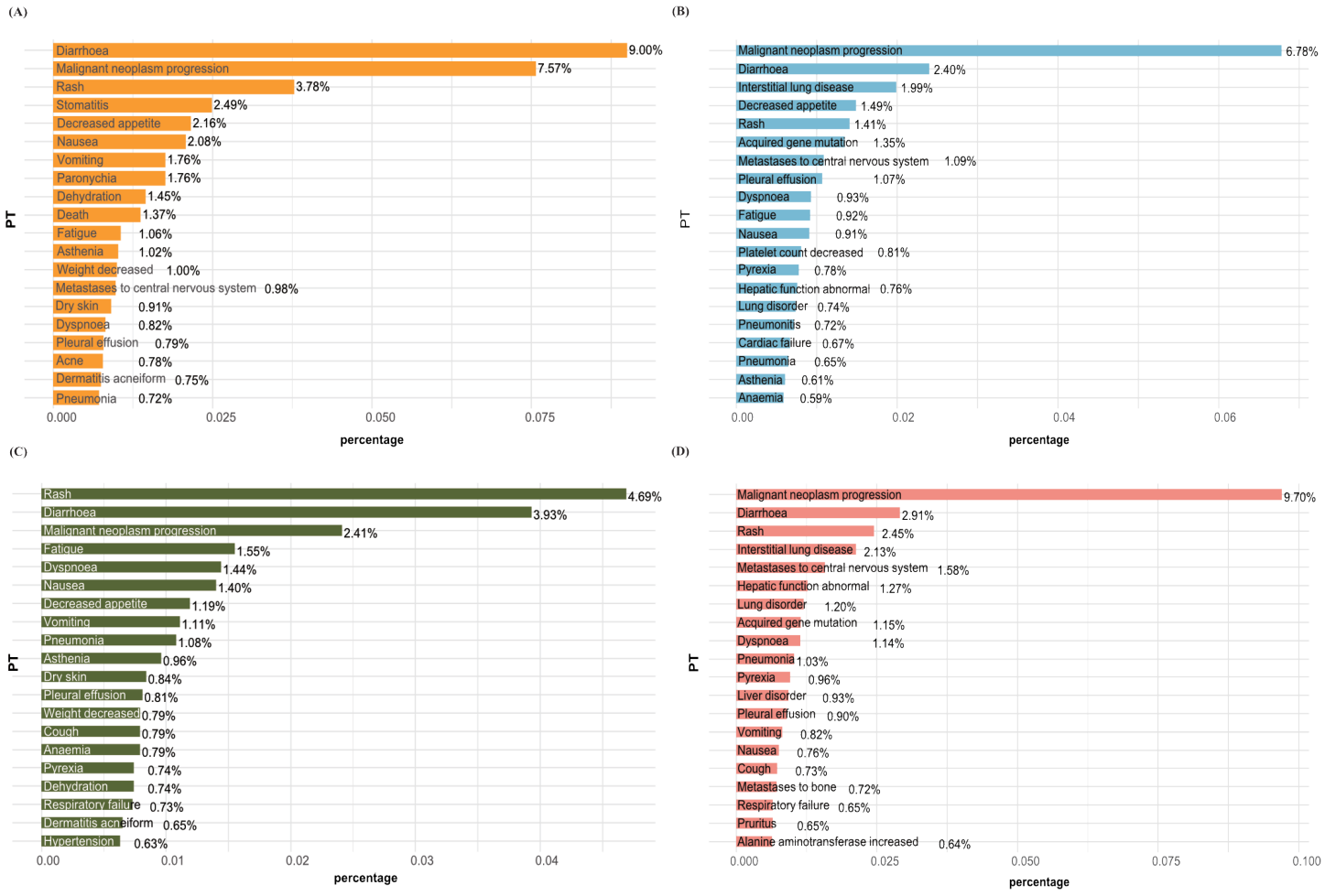


Figure 4 | Frequency Distribution of Top 20 Adverse Events (AEs) for Four EGFR-TKIs

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

https://doi.org/10.70731/0yk94f55

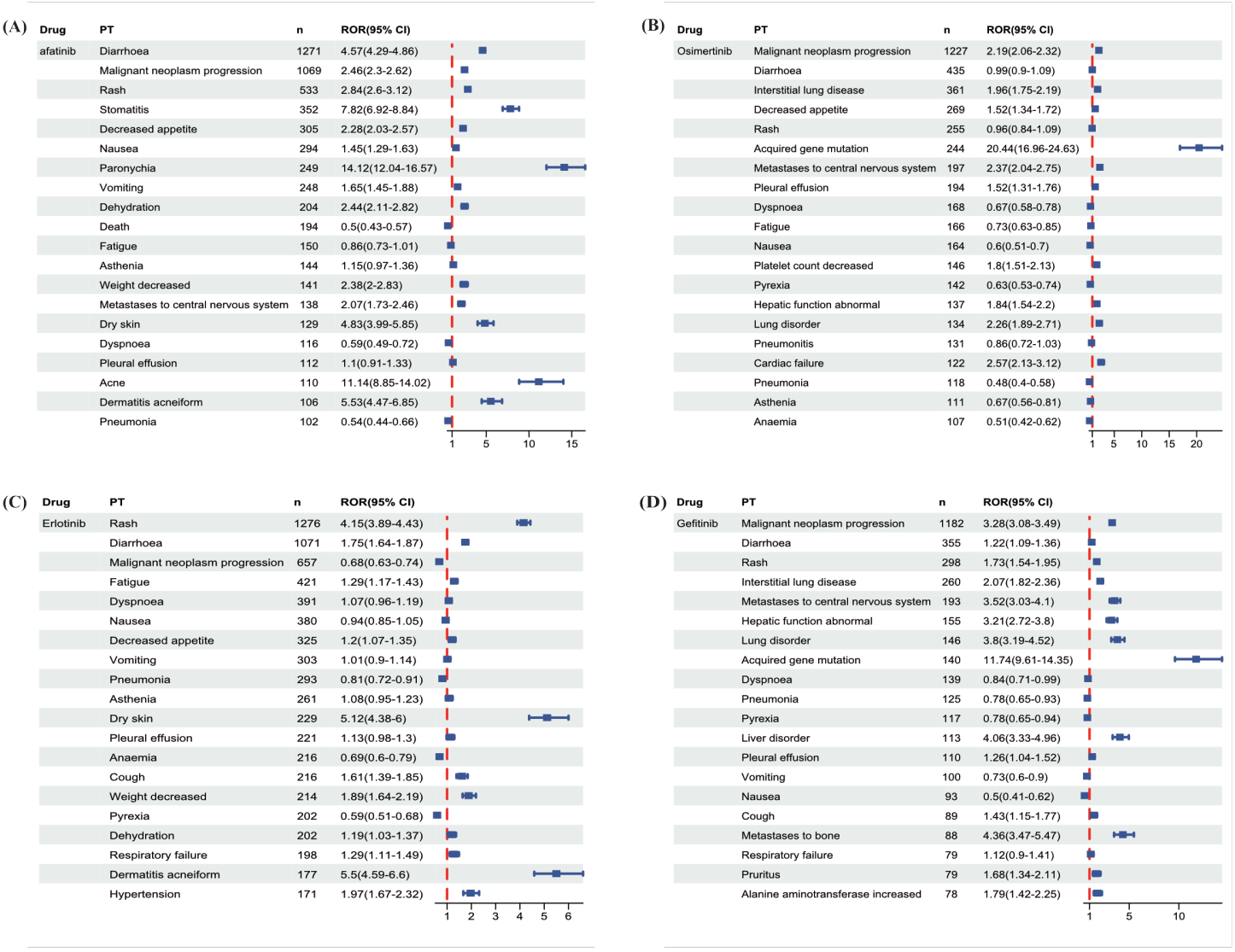


Figure 5 | Forest plots depicting the relative odds ratios (RORs) with 95% confidence intervals (CI) for adverse events associated with four EGFR-TKIs: (A) Afatinib, (B) Osimertinib, (C) Erlotinib, and (D) Gefitinib

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.

Acknowledgements: Not applicable.

Author contributions: CJD and LB designed and supervised the manuscript. XZZ and SJL drafted the initial manuscript. BJQ and SJL drew the figures. XZZ made the tables. XZZ and SJL searched and edited the references. XZZ, SJL and BJQ modified the manuscript. All authors reviewed and approved the final manuscript.

Fundings: This work was supported by the National Natural Science Foundation of China (No. 82372935, No. 81974367, No. 82003065, No. 82172655), the National Natural Science Foundation of Hunan Province (No.2024JJ5607, No.2023JJ30873, No.2021JJ70023, No.2023JJ41067), and National Multidisciplinary Cooperative Diagnosis and Treatment Capacity Building Project for Major Diseases (Lung Cancer, No. z027002).

Availability of data and materials: The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Data sharing statement: All the data generated or analyzed during this study are included in this published article and its supplementary files.

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Competing interests: Author CJD serves on the editorial board of this journal but had no role in the peer review or decision-making process for this article.

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

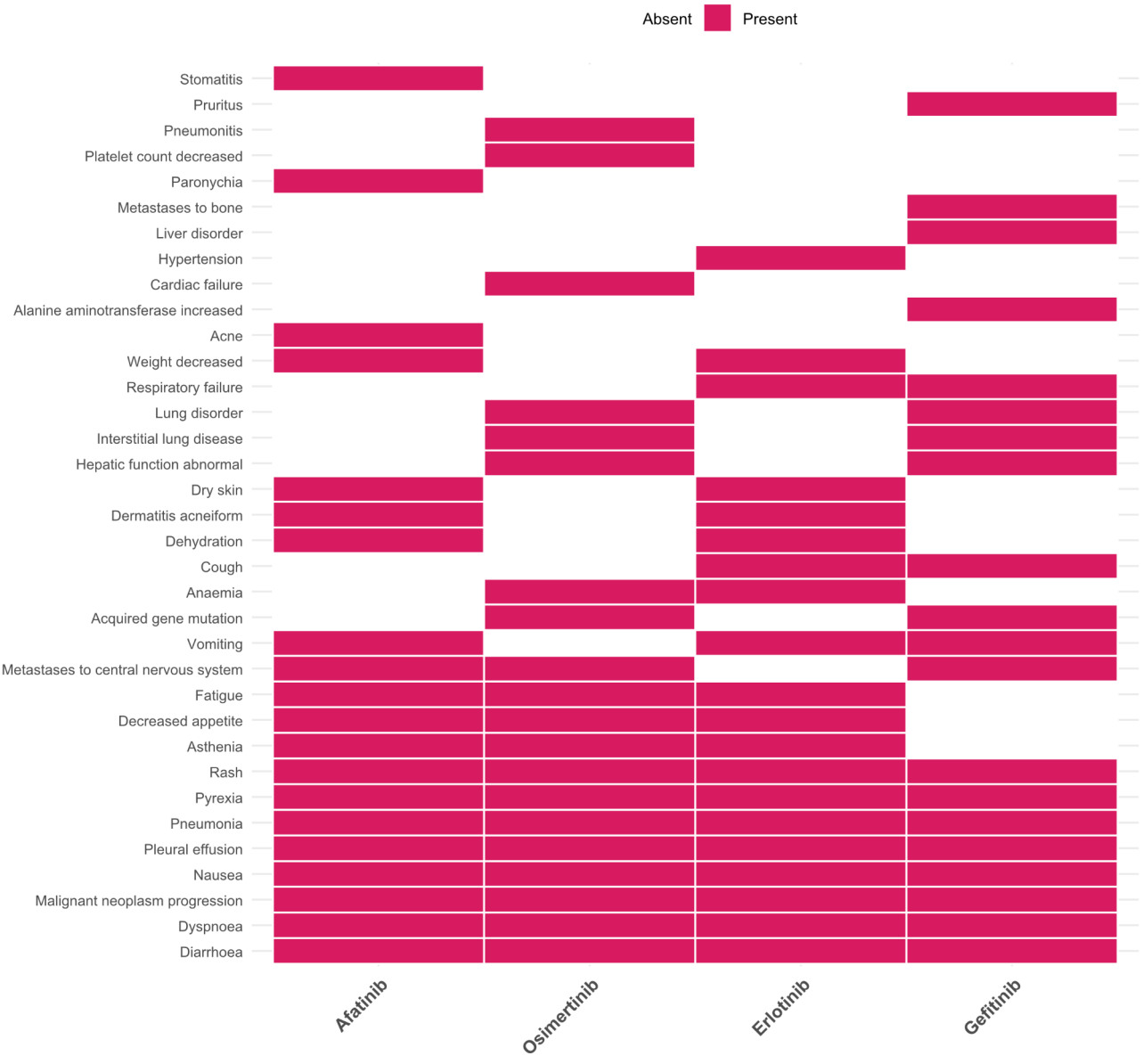
	Target AEs	Other AEs	Total
Target AEs	a	b	A + b
Other AEs	c	d	C + d
Total	A + c	B + d	N = a + b + c + d

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)

CLINICAL MEDICINE & PHARMACOLOGY

CMP

Research article

https://doi.org/10.70731/2nc8ac28

Potential Profile Analysis and Influencing Factors of Reproductive Quality of Life for Patients Treated with Assisted Reproductive Technology

Ruihong Guo [1], **Panpan Yang** [2], **Xiuping Zhang** [1], **Yongfang Wang** [1], **Fang Yan** [3,*]

Received 12 February 2026

Accepted 23 March 2026

Published 31 March 2026

Abstract:

Objective: To identify latent profiles of fertility quality of life (FertiQoL) in patients undergoing assisted reproductive technology (ART) and examine factors associated with different profiles, so as to inform individualized clinical interventions.

Methods: A convenience sample of 323 infertile patients receiving ART at the reproductive medicine department of a tertiary hospital in Jining, Shandong Province, was surveyed from December 2023 to November 2024. Data were collected using a general information questionnaire, the FertiQoL Scale, the Fertility Problem Inventory (FPI), and the Positive Psychological Capital Questionnaire (PPQ). Latent profile analysis was conducted in Mplus 8.3 with the six FertiQoL dimensions as manifest variables, and multivariate logistic regression was used to identify profile-related factors.

Results: The mean FertiQoL score was 71.71 ± 12.52. Three latent profiles were identified: physical and psychological distress group (n=43, 13.3%), moderate FertiQoL group (n=145, 44.9%), and high FertiQoL group (n=135, 41.8%). Social and sexual concerns, along with poor sleep quality, were risk factors for lower FertiQoL, whereas resilience and optimism were protective factors (all P<0.05). Compared with the high FertiQoL group, patients without biological children (OR=4.790) were more likely to be in the physical and psychological distress group, and urban residents (OR=2.398) were more likely to be in the moderate FertiQoL group (all P<0.05).

Conclusion: FertiQoL in ART patients was moderate overall and showed clear heterogeneity. Higher fertility-related stress, lower psychological capital, and poor sleep were associated with worse profiles. Clinical interventions should target high-risk groups and focus on stress management, psychological capital enhancement, and sleep improvement to improve FertiQoL.

Keywords: Assisted reproductive technology; Quality of life during reproduction; Potential profile analysis; Reproductive stress; Psychological capital; Sleep disorders

ISSN 2760-1757 (Online)
ISSN 2760-3288 (Print)

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Introduction

With the development of the social economy, the postponement of childbearing age and the influence of environmental factors [1, 2], the global incidence of infertility has continued to rise, becoming one of the key factors restricting fertility levels. The incidence of infertility in China has increased from 3% in the 1980s to 18% in 2020 [3]. Assisted Reproductive Technology (ART) is a key medical means to solve infertility and brings hope to patients. However, the treatment process is long and painful, and the results are uncertain [1, 4], which puts patients under great physiological and psychological pressure for a long time [5], seriously affecting their reproductive quality of life [4, 6–8]. Improving patients' reproductive quality of life is as important as disease

[1] Jining Medical University, Jining 272067, China; [2] Jining No. 1 People's Hospital, Jining 272100, China; [3] Xiangya School of Nursing, Central South University, Changsha 410000, China.
* Corresponding author. Email: yanfang_xy0804@csu.edu.cn

treatment [4, 9]. Existing research shows that the reproductive quality of infertile patients may be affected by a variety of factors such as age, education level, income, work status, and years of infertility [10, 11]. A positive psychological state and high-quality social support, especially the support between couples, are protective factors for patients' reproductive quality of life [11]. Most current studies focus on variables and explore the independent impact of various influencing factors on the quality of reproductive life. They fail to analyze the differences between individuals and ignore the differences in influencing factors between different categories, thus affecting the targeting of intervention measures. Therefore, this study uses Latent Profile Analysis (LPA) [12] to identify the potential profiles of the quality of reproductive life of patients treated with ART and explore the influencing factors of different profiles, in order to provide a basis for medical staff to formulate targeted intervention measures.

Objects and Methods

Object

This study is a cross-sectional design. Convenience sampling was used to select infertile patients who had visited the reproductive medicine department of a tertiary-level hospital in Jining City, Shandong Province from December 2023 to November 2024 and had entered the ART treatment cycle as the study subjects. Inclusion criteria: **1)** meeting the clinical diagnostic criteria for infertility; **2)** being able to independently read and fill out the questionnaire; **3)** giving informed consent and voluntarily participating in this study.

Exclusion criteria: **1)** having intellectual, hearing or visual impairments that affect questionnaire responses; **2)** suffering from serious physical or mental illnesses; **3)** experiencing major life events within the past 6 months; **4)** having confirmed pregnancy at the time of the questionnaire survey. The sample size for the study of variable influencing factors should be at least 5 to 10 times the number of independent variables [13]. In this study, there were 22 independent variables. Considering that there may be about 20% invalid questionnaires during the collection process, the required sample size was finally determined to be at least 132 cases. A total of 323 cases were effectively surveyed in this study . This project has been approved by the Ethics Committee of Jining Medical College (JNMC-YX-2025-168).

Survey tools

General information questionnaire

Designed by the researchers themselves, the study included basic personal information and infertility-related details. Basic personal information included age, education level, place of residence, annual personal income, whether the individual was an only child, marital status, daily exercise level, and sleep quality. Infertility details included whether the individual had biological children, duration of infertility, type of infertility, attribution, and history of ART treatment .

Fertility quality of life scale (FertiQoL)

It is an internationally recognized tool for assessing the quality of life of infertile patients [14]. The scale has 36 items, two of which are independent items used to assess living and physical conditions respectively, and the remaining items are divided into six dimensions: emotional state, physical and mental response, marital relationship, social relationship, environment and tolerance. The scale uses a 5-point scale (0–4 points) and is converted into a percentage standard score. The higher the score, the better the quality of life of fertility. The total Cronbach 's α coefficient of the scale is 0.940. In this study, the Cronbach 's α coefficient of the scale is 0.865.

Fertility problem inventory (FPI)

by Newton et al. [15] in 1999 to assess the level of fertility-related stress in infertile patients. In 2011, Peng et al. [16] translated the scale into Chinese. The scale has 46 items, covering five dimensions: social stress, sexual stress, marital relationship, parental role requirements, and stress of not having children. The Likert 6-point (1–6 points) scoring method was used, with a total score between 46 and 276 points. The higher the score, the greater the fertility stress felt by the individual. The Cronbach's α coefficient of the Chinese version of the FPI scale is 0.867. In this study , the Cronbach 's α coefficient of the scale is 0.813.

Positive psychological capital questionnaire (PPQ)

This study uses the Positive Psychological Capital Scale developed by Luthans [17] and translated and revised by Zhang Kuo et al. [18]. It consists of 26 items, divided into four dimensions: self-efficacy, resilience, optimism, and hope. The Likert 7-point (1–7) scoring method is used, with a total score between 26 and 182. The higher the score, the higher the reserve of positive psychological capital. The overall Cronbach's α coefficient of the scale is 0.900. In this study, the Cronbach 's α coefficient of the scale is 0.829.

Data collection methods and quality control

Prior to the survey, data collection personnel received standardized training. When distributing questionnaires, standardized instructions were used to explain the research purpose, significance, and completion requirements to patients. Participants were informed that the collected data would be used solely for research purposes and would be anonymized. Informed consent was obtained from all parties, and patients received one-on-one guidance in completing the paper questionnaires. Any questions raised during the completion process were answered objectively by the data collection personnel. After the questionnaires were collected , they were double-checked and entered into the database, removing invalid questionnaires with predictable answers or obvious logical contradictions. A total of 344 questionnaires were distributed, and 323 valid questionnaires were collected, resulting in a valid response rate of 93.9%.

Statistical methods

Data processing and statistical analysis were performed using SPSS 25.0 and Mplus 8.3 software. Multiple profile mod-

Table 1 | Reproductive quality of life, reproductive stress, and positive psychological capital scores of patients undergoing ART treatment (n = 323)

Project	Number of entries	Total score (points x̄±s)	Items are evenly divided (points x̄±s)
quality of life during pregnancy	34	71.71 ± 12.52	—
Emotional state	6	70.32 ± 17.48	—
physical and mental reactions	6	71.70 ± 20.41	—
marital relationship	6	70.55 ± 15.22	—
social relations	6	77.40 ± 14.87	—
environment	6	73.45 ± 13.93	—
Endurance	4	68.44 ± 20.11	—
fertility pressure	46	130.08 ± 31.01	2.83 ± 0.67
social pressure	10	23.17 ± 8.03	2.32 ± 0.80
Sexual pressure	8	18.41 ± 7.67	2.30 ± 0.96
marital relationship	10	22.19 ± 8.85	2.22 ± 0.89
Parent role requirements	10	37.79 ± 10.19	3.77 ± 1.02
No pressure from children	8	28.52 ± 8.82	3.56 ± 1.10
Positive psychological capital	26	122.39 ± 21.19	4.71 ± 0.82
Self-efficacy	7	31.83 ± 6.90	4.55 ± 0.98
toughness	7	29.12 ± 7.57	4.16 ± 1.08
hope	6	30.56 ± 5.86	5.09 ± 0.98
optimism	6	30.87 ± 5.83	5.15 ± 0.97

Note: The total score and scores for each dimension of the Reproductive Life Quality Scale are standard scores on a 100-point scale.

els were established sequentially using the scores of the six dimensions of fertility and quality of life of ART patients as explicit variables. The model fit indices [12] included: **1)** Aike Information Criterion (AIC), Bayesian Information Criterion (BIC), and sample-corrected BIC (aBIC). The smaller the value of the above indices, the better the model fit; **2)** Entropy, with a value range of 0 to 1. The closer to 1, the more accurate the model classification. A value greater than 0.8 is considered good; **3)** Röhler-Reuben Corrected Likelihood Ratio Test (LMRT) and Bootstrap-based Likelihood Ratio Test (BLRT). When $P < 0.05$, it indicates that the fit of the k profile models is significantly improved compared with the k -1 profile models. Combining the fit indices, interpretability, and clinical practice of each model, the optimal number of profiles was determined. Based on the posterior probability, all cases were assigned to the corresponding profiles and categorical variables were generated. Further statistical description and inference were performed based on the classification results. Quantitative data were described using cmean ± standard deviation based on the normality test results, while categorical data were expressed as frequency and percentage (%). The chi-square test or F- test was used to analyze differences between groups. Using the potential profile of fertility and quality of life of ART- treated patients as the dependent variable, variables with statistically significant differences in univariate analysis were included in multivariate logistic regression to explore the influencing factors of different potential profiles of fertility and quality of life of ART- treated patients. The significance level was set at $\alpha = 0.05$.

Results

Reproductive quality of life, reproductive stress, and positive psychological capital scores of ART patients

See **Table 1**.

Potential profile analysis results of ART treatment patients' reproductive quality of life

The standardized scores of six dimensions of reproductive quality of life were used as explicit variables for model fitting. A total of five models were fitted, and the goodness-of-fit indices of each model are shown in **Table 2**. When the number of potential profiles was 3, the entropy value was >0.8, and both LMRT and BLRT were statistically significant ($P < 0.05$). The AIC, BIC, and aBIC values were all low, indicating that the model fitting results of the 3 profiles were reliable. Individuals were classified according to their different characteristics on the explicit variables. Category 1 (C1) had low scores in all dimensions except for the environment dimension, especially in the emotional state, physical and mental response, and tolerance dimensions. Therefore, it was named the " Physical and Mental Distress Group " , with 43 cases (13.3%). Category 2 (C2) had moderate scores in all dimensions, with 145 cases (44.9%). It was named the " Medium Reproductive Quality of Life Group " . Category 3 (C3) had high scores in all dimensions, with 135 cases (41.8%). It was named the " High Reproductive Quality of Life Group " , as shown in **Figure 1**.

Differences in three potential profiles of fertility and quality of life in patients undergoing ART treatment

Differences in scores across explicit variables for the three potential profiles of reproductive quality of life were tested.

Table 2 | LPA fitting indexes for fertility and quality of life of patients treated with ART (n = 323)

Number of sections	AIC	BIC	aBIC	Entropy	LMR T	BLRT	Profile probability
1	16457.309	16502.641	16464.578	—	—	—	1
2	15868.822	15940.597	15880.331	0.887	0.002	<0.001	0.270/0.730
3	15592.588	15690.807	15608.338	0.853	0.012	<0.001	0.133/0.449/0.418
4	15505.666	15630.329	15525.657	0.848	0.101	<0.001	0.207/0.081/0.263/0.449
5	15468.182	15619.288	15492.413	0.869	0.159	<0.001	0.087/0.003/0.207/0.461/0.241

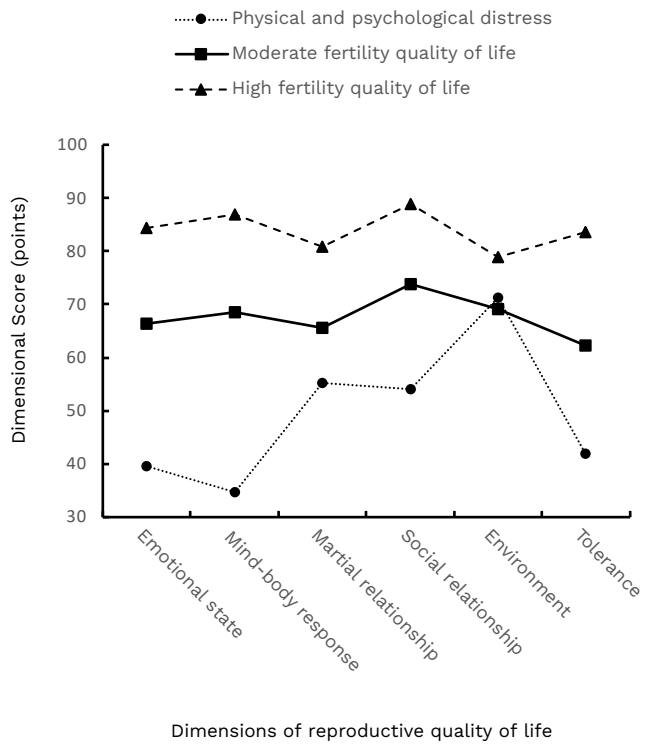
Note: **C1**: Mental and physical distress group; **C2**: Moderate quality of life with fertility group; **C3**: High quality of life with fertility group

Table 3 | Differences in total and dimension scores of fertility and quality of life among ART- treated patients across three profiles

Dimension	Overall	C1	C2	C3	F	P	Between groups
Overall score of reproductive quality of life	71.71 ± 12.52	50.15 ± 7.06	67.51 ±5 .09	83.09 ± 5.86	614.918	<0.001	C1 < C2 < C3
Emotional state	70.32 ± 17.48	39.53 ± 12.04	66.44 ± 9.39	84.29 ± 8.79	380.493	<0.001	C1 < C2 < C3
physical and mental reactions	71.70 ± 20.41	34.69 ± 13.51	68.53 ± 12.66	86.88 ± 9.43	342.915	<0.001	C1 < C2 < C3
marital relationship	70.55 ± 15.22	55.14 ± 15.90	65.60 ± 12.16	80.77 ± 10.52	95.440	<0.001	C1 < C2 < C3
social relations	77.40 ± 17.87	53.97 ± 14.00	73.76 ± 8.92	88.77 ± 7.99	243.357	<0.001	C1 < C2 < C3
environment	73.45 ± 13.93	71.22 ± 14.43	69.05 ± 12.48	78.89 ± 13.46	20.236	<0.001	C1 = C2 < C3
Endurance	68.44 ± 20.11	42.01 ± 17.43	62.24 ± 14.89	83.52 ± 11.97	166.062	<0.001	C1 < C2 < C3

Note: **C1**: Mental and physical distress group; **C2**: Moderate quality of life with fertility group; **C3**: High quality of life with fertility group.

Figure 1 | Category characteristics of three potential profiles of fertility quality of life in ART- treated patients



The results showed that, except for the environmental dimension, there were significant gradient differences in scores for all other dimensions and the total score among the three profiles (C1 < C2 < C3), and all differences were statistically significant (P < 0.001). In the environmental dimension, there was no significant difference between groups C1 and C2, but both were significantly lower than group C3 , supporting the validity of the potential profile classification . The results are shown in Table 3.

Univariate analysis of potential profiles of fertility and quality of life in patients undergoing ART treatment

The results showed that there were no statistically significant differences in age, education level, marital status, whether a patient was an only child, daily exercise volume, duration of infertility, cause of infertility, and history of ART treatment among different categories of reproductive quality of life (all P > 0.05). Items with statistically significant differences are shown in Table 4.

Multivariate logistic regression analysis of potential profiles of fertility and quality of life in ART- treated patients

Using the potential profile category of reproductive quality of life as the dependent variable and the high reproductive quality of life group (C3 group) as the reference group, multivariate logistic regression analysis was conducted with factors that had a p-value < 0.05 in the univariate analysis as independent variables. The independent variable assignments are as follows: Family residence: urban = 1, rural = 2; Annual income < 50,000 = 1, 50,000~ = 2, 100,000~ = 3; Poor sleep quality = 1, average = 2, good = 3; No biological children = 0, biological children = 1; Primary infertility = 1; Secondary infertility = 2; Original scores for each dimension of the reproductive stress and positive psychological capital scales were substituted. The likelihood ratio test value was 369.808, p < 0.001, indicating a good model fit. The results showed that, compared with the high fertility quality of life group, ART pa-

Table 4 | Basic information of patients receiving ART treatment and univariate analysis of different profiles

Project		Number of people	C1 (n = 43)	C2 (n = 145)	C3 (n=135)	x^2 / F	P
Place of residence [persons (%)]	town	233	27 (62.8)	117 (80.7)	89 (65.9)	9.737	0.008
	rural areas	90	16 (37.2)	28 (19.3)	46 (34.1)		
Annual personal income per 10,000 [person (%)]	<5	204	36 (83.7)	91 (62.8)	77 (57.0)	10.215	0.034*
	5~<10	90	6 (14.0)	40 (27.6)	44 (32.6)		
	>10	29	1 (2.3)	14 (9.7)	14 (10.4)		
Sleep quality [person (%)]	Poor	102	23 (53.5)	57 (39.3)	22 (16.3)	44.199	<0.001
	generally	157	18 (41.9)	70 (48.3)	69 (51.1)		
	very good	64	2 (4.7)	18 (12.4)	44 (32.6)		
Do you have any biological children? [persons (%)]	no	161	26 (60.5)	80 (55.2)	55 (40.7)	8.062	0.018
	yes	162	17 (39.5)	65 (44.8)	80 (59.3)		
Types of infertility [people (%)]	Primary	106	11 (25.6)	59 (40.7)	36 (26.7)	7.413	0.025
	Secondary	217	32 (74.4)	86 (59.3)	99 (73.3)		
Fertility pressure (points $\bar{x}$±s)	Total Score	130.08±31.01	162.28±31.28	136.21±25.41	113.25±25.52	63.793	<0.001
	social pressure	23.17±8.03	31.97±7.64	25.24±6.47	18.13±6.05	88.147	<0.001
	Sexual pressure	18.41±7.67	25.72±7.71	20.51±6.74	13.83±5.55	70.177	<0.001
	marital relationship	22.19±8.85	29.95±9.19	24.46±7.87	17.28±6.78	56.618	<0.001
	Parent role requirements	37.79±10.19	42.05±11.31	37.79±9.78	36.44±9.96	5.047	0.007
	No pressure from children	28.52±8.82	32.58±9.03	28.21±8.67	27.56±8.63	5.594	0.004
Positive psychological capital (points $\bar{x}$±s)	Total Score	122.39±21.19	102.44±17.99	117.80±16.18	133.67±20.44	55.728	<0.001
	Self-efficacy	31.83±6.90	27.60±6.42	30.79±6.08	34.30±6.98	20.625	<0.001
	toughness	29.12±7.57	21.56±6.14	27.42±5.47	33.36±7.35	64.725	<0.001
	hope	30.56±5.86	27.53±6.30	29.41±5.45	32.76±5.38	20.223	<0.001
	optimism	30.87±5.83	25.74±5.59	30.19±5.18	33.24±5.32	34.918	<0.001

Note: Categorical variables are expressed as frequencies (percentages), and numerical variables are expressed as mean ± standard deviation. **C1**: Mental and physical distress group; **C2**: Moderate quality of life with fertility group; **C3**: High quality of life with fertility group. ***** indicates Fisher's exact probability method.

tients with greater social and sexual stress, no biological children, and poorer sleep quality were more likely to enter the mental and physical distress group (all P < 0.05); ART patients with greater social and sexual stress, living in urban areas, and poorer sleep quality were more likely to enter the moderate fertility quality of life group (all P < 0.05), as shown in Table 5.

Discussion

Patients undergoing ART treatment have a moderate level of reproductive quality of life

The results of this study showed that the total score of fertility quality of life of patients treated with ART was (71.71±12.52), which is at a moderate level. It is higher than the scores of infertile patients in China who underwent frozen-thawed embryo transfer (64.5±14.1) [19] and in countries such as Switzerland (56.69) [20], Iran (62.57) and India (66.10) [11], and is close to the results of a study in Indonesia (72.7±14.9) [21]. This may be related to the fact that the group focused on in this study is patients who underwent ART treatment, which has increased their fertility expectations due to the application of technology, and that the psychological support for patients has been strengthened in domestic nursing work in recent years, thereby improving their psychological experience.

There is heterogeneity in the quality of life and fertility among patients undergoing ART treatment

This study identified three potential profiles of the reproductive quality of ART patients through potential profile analysis: the psychological distress group, the moderate reproductive quality of life group, and the high reproductive quality of life group, indicating that there is group heterogeneity in the reproductive quality of ART patients . The high reproductive quality of life group accounts for 41.8%. These patients adapt well to the treatment process, maintain a positive psychological state, and have less psychological distress. Stable psychological resources, effective social support, and good marital relationships may be the basis for maintaining this state. Encouraging these patients to share their personal experiences and convey positive beliefs to others can help other patients adjust their state and also enhance their own sense of value by helping others, further promoting the improvement of their reproductive quality of life. The moderate reproductive quality of life group accounts for 44.9%, which is at a moderate level in all aspects. This group has developed certain adaptive strategies, but is at the "critical point" of maintaining a fragile balance between challenges and coping resources. They have the potential to improve, but are also prone to falling into difficulties when encountering setbacks. Their core problem is insufficient coping resources [22] or lack of stress management ability. The focus of support

Table 5 | Multivariate logistic regression analysis of fertility quality of life in patients treated with ART

Project	Control group	β	SE	Wald s x^2	P	OR	95% CI
Group experiencing physical and mental distress vs. Group with high fertility and quality of life							
constant term		-4.815	3.003	2.572	0.109	—	—
social pressure		0.186	0.052	13.066	<0.001	1.205	1.089~1.333
Sexual pressure		0.146	0.057	6.615	0.010	1.158	1.035~1.294
toughness		-0.270	0.055	24.491	<0.001	0.763	0.686~0.849
optimism		-0.156	0.079	3.938	0.047	0.856	0.733~0.998
No biological children	Have biological children	1.566	0.748	4.386	0.036	4.790	1.106~2.749
Poor sleep quality	Good sleep quality	2.422	1.038	5.540	0.019	11.498	1.505~87.874
Medium quality of life with fertility group vs. high quality of life with fertility group							
constant term		-1.903	1.744	1.190	0.275	—	—
social pressure		0.101	0.032	9.670	0.002	1.106	1.038~1.178
Sexual pressure		0.075	0.035	4.516	0.034	1.078	1.006~1.155
toughness		-0.095	0.029	10.614	0.001	0.910	0.860~0.963
town	rural areas	0.875	0.386	5.142	0.023	2.398	1.126~5.107
Poor sleep quality	Good sleep quality	1.560	0.486	10.284	0.001	4.757	1.834~12.340

should be based on preventive mental health education, helping patients identify common negative emotions, improve stress management and communication skills, and assist patients in making life plans and maintaining connections with society [5], so as to enhance their overall coping ability. The proportion of the mental and physical distress group was 13.3%, and the scores of emotional state, mental and physical reaction and tolerance were significantly lower, showing severe anxiety, depression and physical symptoms, and the quality of reproductive life was seriously impaired. The proportion of those without biological children in this group was the highest. Under the background of traditional "filial piety" culture and family inheritance, they suffered greater psychological pressure and were prone to stigma and self-denial [9, 23]. Repeated treatment failures, insufficient social support, and loss of control over treatment all contributed to their emotional exhaustion. Active screening and key intervention for this group, with the focus of intervention being emotional relief and meaning reconstruction, can be used to help patients find and uphold their personal value in treatment, rather than just focusing on pregnancy outcomes, by using cognitive behavioral therapy [24], mindfulness-based stress reduction techniques [25–27].

Potential factors affecting the quality of reproductive life of ART patients

High fertility stress and poor sleep quality are common risk factors that prevent patients from maintaining a high quality of life for their children.

The results of this study show that, compared with the high fertility quality of life group, patients with high fertility stress scores and poor sleep quality are more likely to be classified into the mental and physical distress group and the moderate fertility quality of life group. Among them, the two dimensions of social stress (OR = 1.205 and 1.016) and sexual stress (OR = 1.158 and 1.078) in the fertility stress scale are statistically significant . Social stress is reflected in the worry about the outside world's gaze and social evaluation, the fear of being labeled, which leads to the patient's social withdrawal and impaired support system [28]; sexual stress is reflected in the impact of the fertility process on the intimate relationship between husband and wife, such as loss of interest in sex or feeling anxious, which damages the emotional connection and support between husband and wife [9, 29].

In addition, the results of this study show that poor sleep quality is a strong and common independent risk factor for the decline in reproductive quality of life in patients undergoing ART treatment (OR = 11.498 and 4.757) . Sufficient sleep is the basis for body repair, immune regulation and endocrine stability. Sleep disorders can lead to immune dysfunction, interfere with the hormonal rhythms related to reproduction [30], lead to fatigue, and reduce the tolerance and compliance of treatment. Sleep deprivation can also directly damage the function of the prefrontal cortex, weaken cognitive and emotional regulation abilities [31], increase susceptibility to treatment stress, easily fall into rumination, and significantly amplify negative emotions. Sleep deprivation leads to daytime functional impairment and reduced social activities, which not only reduces the patient's opportunities to obtain social support, but also deprives the patient of important psychological resources used to buffer stress, falling into a vicious cycle of "stress-sleep disorder-exacerbated physical and mental distress". As a sensitive early warning signal of declining reproductive quality of life, it also provides an operable intervention breakthrough for breaking the vicious cycle between stress and quality of life. By systematically monitoring the sleep quality index, patients with sleep problems can be identified early, and interventions such as sleep hygiene education, mindfulness training, and cognitive behavioral therapy can be implemented to improve sleep quality, thereby laying the foundation for coping with treatment stress and improving quality of life.

Positive psychological capital is a protective factor for maintaining a high quality of life for patients with high reproductive health

The results of this study show that positive psychological capital is a protective factor for the quality of life of patients undergoing ART treatment. Among them, the two dimensions that are statistically significant are resilience (OR = 0.763 and 0.910) and optimism (OR = 0.856) (among which the optimism dimension only has a statistically significant effect on the emotional distress group). Resilience is the ability of an individual to recover quickly from adversity and setbacks and maintain a positive state, avoiding being defeated by setbacks and failures; optimism helps pati ents see the positive side of things and maintain expectations for the future [18]. Self-efficacy and hope dimensions did not show statistical significance in this study, which may be because self-efficacy represents the belief that one is capable of achieving goals, but this belief is often constantly challenged in the face of reality; while hope is the individual's willingness to set goals and achieve them. Without the support of resilience and optimism, it is also easy to be exhausted in the face of setbacks. In the work, a systematic and hierarchical comprehensive intervention system can be established. At key nodes such as the start of treatment, before and after embryo transfer, and when the results are known, assessments of fertility stress and psychological capital can be carried out to achieve early identification and dynamic monitoring of risk factors. Structured psychological interventions can be provided to high-risk patients, such as using cognitive behavioral therapy to correct their irrational cognition of stigma and failure, accepting negative situations and thoughts that occur during treatment instead of being controlled by negative emotions; learning to call on social support systems [5], using mindfulness stress reduction techniques [25, 26] to cultivate and enhance the reserve of positive psychological capital and improve the ability to regulate emotions; intervening as a whole for couples, improving communication patterns, promoting emotional expression, enhancing the resilience of the couple's relationship, and strengthening the support between partners [32].

The absence of biological children is a specific risk factor for the "psychological distress group"

The results of this study show that the absence of biological children is a specific risk factor for ART patients to be classified into the mental and physical distress group (OR = 4.790) . The absence of biological children corresponds to the two dimensions of "parental role needs" and "stress of childlessness" in the reproductive stress scale. In the social culture, being a parent is a core component of adult identity [9]. The absence of children, especially when the status quo is not changed after actively seeking medical intervention, is more likely to trigger a deep crisis in terms of family inheritance, identity, self-worth, and meaning of life. This may lead to the blurring or loss of the sense of meaning in the future, causing patients to stagnate in life, lack goals, and develop a deep fear and resistance to the future. In response to this core risk that leads to mental and physical distress, intervention measures should focus on helping patients deal with the sense of loss, such as establishing peer support groups. The exchange between group members with similar experiences can effectively reduce the sense of isolation and gain unique understanding and resonance [33]. Accepting rather than resisting the painful feeling of not being able to have biological children, re-establishing personal value and meaning, and ensuring that a meaningful and dignified life can be maintained under any treatment outcome.

Urban residence is a specific risk factor for the "moderate fertility quality of life group," but it is not associated with the mental and physical distress group

The results of this study show that living in an urban area is a specific risk factor that makes ART patients more likely to be in the moderate quality of life group rather than the high quality of fertility group (OR = 2.398) . This may be related to the following factors: Although urban residents have a wider range of social interactions, their interpersonal relationships are relatively distant [34], making it difficult to obtain in-depth and stable emotional support and substantial help on fertility issues involving privacy; in addition, urban patients face a more diverse and higher standard of social evaluation system, resulting in a situation where high resources and chronic consumption coexist [35], which, although not causing serious physical and mental distress, makes it difficult to achieve an ideal life. For patients with high-risk factors living in urban areas, the choice of intervention measures should respect the patient's wishes and be based on dispelling their guard, such as providing institutional confidentiality and intervention methods involving only professional personnel; after the patient has achieved sufficient growth, more open intervention measures can be carried out.

Conclusion

ART treatment . High reproductive stress, low psychological capital, and poor sleep quality are common risk factors contributing to a decline in their quality of life. The absence of biological children is a specific high-risk factor for patients experiencing psychological and emotional distress, while urban residents are at higher risk of not achieving a high quality of life and remaining at a moderate level. This study aims to implement comprehensive interventions targeting different risk profiles, focusing on stress management, psychological capital development, and sleep improvement. Specialized and personalized psychosocial care should be provided to high-risk groups such as those without children or residing in urban areas, shifting from general support to targeted intervention. Limitations of this study include the difficulty in establishing causal relationships due to the cross-sectional design and the potential for selection bias in the sample. Future research could use longitudinal designs to track dynamic changes in patient profiles, verify the causal pathways between influencing factors and outcomes, further elucidate the psychosomatic mechanisms affecting the quality of life for fertility, and provide a basis for developing and validating targeted intervention programs.

Funding: 2025 Shandong Province Humanities and Social Sciences Project

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CLINICAL MEDICINE & PHARMACOLOGY

CMP

Review article

https://doi.org/10.70731/rd660x49

Epstein-Barr Virus Participates in the Development and Progression of Nasopharyngeal Carcinoma and its Application in Traditional Chinese and Western Medicine Integrated Treatment

Lin Chen [1,2], **Faqing Tang** [1,*]

Received 18 February 2026

Accepted 27 March 2026

Published 31 March 2026

Abstract: Nasopharyngeal carcinoma (NPC) is a epithelial tumor from the nasopharynx. Its pathogenesis is closely related to Epstein-Barr virus (EBV) infection, the patients account for over 95% of global NPC incidence. NPC is a highly malignant tumor, with over 70% of patients diagnosed at an intermediate or advanced stage. Over 90% of those diagnosed with undifferentiated NPC are infected with EBV. Currently, radiotherapy alone and concurrent chemoradiotherapy are the main treatment options for NPC. Early-stage NPC is primarily treated with radical radiotherapy, appropriately combined with chemotherapy, while locally advanced NPC is treated with concurrent chemoradiotherapy. However, long-term radiotherapy and chemotherapy can be difficult for NPC patients and can cause corresponding toxic side effects. Therefore, tumor immunotherapy is a promising treatment method for NPC, including vaccination, adoptive cell therapy, and immune checkpoint blockade. In addition, traditional Chinese medicine treatment can improve the immune status of NPC patients, reduce the toxic side effects of radiotherapy and chemotherapy, and improve survival time and quality of life. Therefore, the traditional Chinese and Western medicine treatment for NPC patients has shown remarkable efficacy; this also suggests that the traditional Chinese and Western medicine treatment of NPC has broad development prospects. Herin, we summarize mechanisms of EBV involved in NPC, and mainly elaborate the traditional Chinese and Western medicine treatment targeted EBV for NPC patients. This article provides some insights for future related research.

Keywords: Epstein-Barr virus; Nasopharyngeal carcinoma; Traditional Chinese medicine; Integrated treatment of traditional Chinese

ISSN 2760-1757 (Online)
ISSN 2760-3288 (Print)

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Introduction

Nasopharyngeal carcinoma (NPC) is a highly invasive head and neck malignant tumor originating from epithelial cells of nasopharyngeal mucosa. In high-incidence areas, more than 95% of nasopharyngeal carcinoma incidence is attributed to Epstein-Barr virus (EBV), a ubiquitous virus that causes lifelong asymptomatic infection in most populations worldwide[1, 2]. Common tumors associated with EBV infection include NPC, primary pulmonary lymphoepithelial carcinoma (PLELC), EBV-associated intrahepatic cholangiocarcinoma, and EBV-associated gastric cancer (EBVaGC) [3–7]. NPC accounts for up to 80 % of these tumors, and more than 90% of NPC patients have EBV infection[8, 9]. According to the latest global cancer statistics released by the International Agency for Research on Cancer (IARC) in 2022, the global incidence of NPC is estimated at 120,416 cases and the number of deaths is 73,476. The patients in Asia account for 83.3% (100,298 cases) of global NPC incidence and 83.6% (61,442 cases) of deaths. East Asia, southeast Asia, and central and south Asia are the endemic areas, and China has the highest incidence, at about 2.4/100,000 people/year (51,010 cases)[10]. NPC has a relatively hidden location and is sensitive to radiotherapy.

[1] Hunan Key Laboratory of Oncotarget Gene and Clinical Laboratory, The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University/ Hunan Cancer Hospital, Changsha 410013, China; [2] The First Clinical College of Traditional Chinese Medicine of Hunan University of Chinese Medicine, and Hunan Cancer Hospital, Changsha, 410007, China.
* Corresponding author. Email: tangfq@hnca.org.cn

Its clinical treatment is mainly radiotherapy, and chemotherapy can be combined for locally advanced stages . According to the latest CSCO guidelines for the treatment of head and neck tumors, concurrent chemoradiotherapy for NPC has good effects. The main treatment options are concurrent chemoradiotherapy, induction chemotherapy, and adjuvant chemotherapy. For patients with early-stage NPC, radiotherapy alone or combination therapy is the main treatment method [11, 12]. For locally advanced NPC, the main treatment modes have concurrent chemoradiotherapy, induction chemotherapy followed by concurrent chemoradiotherapy, and concurrent chemoradiotherapy followed by adjuvant chemotherapy. Although the combined chemoradiotherapy can improve the prognosis of patients with NPC, its efficacy is limited, and about 8-10% of patients still have experience recurrence or metastasis in the later stages [13–15]. Moreover, long-term concurrent chemoradiotherapy can lead to complications, such as dry mouth, trismus, and secondary tumors, which seriously affect the life quality of patients[16-20]. EBV infection is closely related to NPC, which makes EBV become a key target for tumor treatment. Immune cell infiltration and EBV antigen expression in NPC patients are the main research targets of immunotherapy [21, 22]. Traditional Chinese medicine has significant advantages in cancer treatment, with characteristics, such as reduced toxicity and enhanced efficacy, flexible formulation, and significant curative effect. Traditional Chinese medicine treatment not only prolongs disease-free survival but also reduces complications and adverse reactions associated with radiotherapy and chemotherapy, demonstrating significant clinical value. Here, we summarize research progress in the field of EBV and its relationship to NPC development and progression, as well as important research findings on the integration of traditional Chinese medicine in the treatment of NPC patients. This article provides promising directions for future research on NPC treatment.

Biological Characteristics of EBV

Isolated from the cells of a Burkitt lymphoma (BL) patient in Africa [23, 24], primary EBV infections are asymptomatic, with more than 95% of adults worldwide infected. It is mainly transmitted through bodily fluids, and its host cells mainly include epithelial cells and B cells. EBV causes as many as 200,000 deaths annually [25, 26]. EBV-induced diseases are mainly caused by an imbalance between the virus and the body's immune system after infection, which drives the host cells to undergo malignant transformation and cause disease. EBV is a herpesvirus with a bidirectional life cycle, including a latent phase and a replication phase [27]. The latent phase is mainly established after the host cells are infected with the virus. During this period, viral particles cease to be produced, and only a few essential viral genes are expressed [1, 28, 29]. EBV encodes eight latent genes, and naive B cells infected with EBV exhibit a latent phase III. Latent phase III genes include six EBV nuclear antigens (EBNA1, 2, 3A, 3B, 3C, LP), two latent membrane proteins (LMP1 and LMP2), EBV-encoded small RNAs (EBERs), and EBV-encoded microRNAs (miRNAs) [30]. The cells in this latent phase are highly immunogenic and can be rapidly captured by the host's EBV-specific T cells [31]. However, the "true latent phase" shows that in most individuals, EBV persists in a subset of memory B cells without expressing any viral genes in the latent phase 0 state [32]. Latent EBV genes can promote tumorigenesis, inhibit apoptosis, and suppress the recognition of infected cells by host immune cells [30]. After entering B cells, the viral genome usually exists in the nucleus in the form of circular fragments [33]. EBV latent proteins are generally considered to be key drivers of tumorigenesis in EBV-associated tumor. EBNA1 is a transcription factor that is essential for the maintenance and replication of EBV in vitro [34]. Similarly, EBV that knocks out EBNA1 loses its ability to latently infect cells in vitro. EBNA1 can upregulate proteins to involve in metastasis and oxidative stress in EBV-positive NPC cells [35]. EBNA1 is also the only EBV protein that is consistently expressed across all latent phases, making it become a key target for EBV-specific therapy in all EBV-associated tumors. The studies have shown that inhibiting EBNA1 can effectively suppress the proliferation of EBV-positive tumor cells [36]. EBNA2 is a transcriptional activator of cellular genes (such as CD21, CD23, and c-MYC) and viral genes (such as LMP1 and LMP2). LMP1, encoded by EBV, is an essential membrane protein. LMP1 mimics the cell CD40 receptor and is a member of the (TNFR) superfamily. It can drive the growth and differentiation of B cells by replacing the function of CD40 in vivo [37]. The LMP1 signaling pathway is mainly mediated by the interaction of host TNFR-related factors (TRAFs) or death domain protein TRADD with CTAR1 or CTAR2 to promote the activation of upstream regulators of multiple signaling pathways [38]. LMP1 is an oncogene of EBV and is crucial for the in vitro transformation of B cells. As a CD40 receptor, LMP1 affects the expression of cytokines such as IL-6 and IL-8, regulates immunity, and influences tumor cell proliferation, metastasis, and invasion by activating the NF-κB pathway [39] .

EBV and Tumorigenesis

EBV is associated with a variety of diseases and malignancies. For example, infectious mononucleosis (IM) is associated with primary EBV infection. Chronic active EBV infection (CAEBV), although rare, is life-threatening and is characterized by an abnormally high EBV DNA load [40]. EBV is also a major risk factor for immunocompromised patients. In HIV patients, the lack of antibodies that can effectively respond to EBV-specific T cells significantly increase the risk of developing EBV-related lymphoma [41, 42]. Post-transplant lymphoproliferative disorder (PTLD) is associated with the reactivation and replication of EBV in most cases [43]. EBV infection is also associated with the development of autoimmune diseases such as multiple sclerosis (MS) [44]. The incidence of EBV-related malignancies is slightly higher in men than in women [45]. In addition, EBV infection is associated with a variety of lymphomas, including Burkitt lymphoma (BL), Hodgkin lymphoma (HL), diffuse large B-cell lymphoma (DLBCL), NK/T-cell lymphoma and primary effusion lymphoma [46], and epithelial malignancies including NPC and GC. The

mechanisms of EBV-induced NPC were discussed in more detail below.

The Relationship between EBV with NPC Occurrence and Development

EBV infection is a key-risk factor for the development of NPC, and It plays an important role in NPC progression [47]. About 90% of malignant cells in NPC are undifferentiated or poorly differentiated squamous epithelial cells that typically express several EBV latency type II gene products [48]. These genes include EBER1/2, EBNA1, LMP1, LMP2, BARF1, and several other non-coding transcripts encoded by EBV. LMP1 is one of the key oncogenic drivers of NPC development, expressed in 20–60% of NPC and all precancerous or preinvasive lesions, and has become a major therapeutic target [49]. More than 50 mutations were found in each of 111 microscopically dissected EBV-positive tumor samples. Whole exome sequencing of NPCs has revealed a series of key cellular pathway gene mutations, including p53, HLA, NF-κB, MAPK and PI3K [50]. About 90% of EBV-positive NPCs have NF-κB inflammatory pathway activation characteristics, which may be due to somatic mutations or the expression of the LMP1 oncogene encoded by EBV [51]. LMP1 is usually expressed in NPC cells, and it can inhibit DNA repair in human epithelial cells through the c-terminal activation region 1 (CTAR1). The PI3K/Akt pathway is involved in LMP1-mediated DNA repair inhibition. DNA damage binding protein (DDB1) is involved in nucleotide excision repair. The LMP1/PI3K/Akt pathway can inactivate FOXO3a, inhibit DDB1 expression, and lead to genomic instability in human epithelial cells [52]. In addition, the weakened immune system of NPC patients is an important cause of its pathogenesis, and EBV has a variety of ways to evade the host's immune system attack. EBV infection and expression of various lysed EBV gene proteins may block the secretion of various antiviral cytokines. For example, EBV immediate early lysation proteins, including BZLF1 and BRLF1, inhibit the production of interferon response genes and type I interferon [53]. Lysed EBV proteins may also affect the host's innate immunity through interfering with intracellular NF-κB signaling by regulating TLR expression on the surface of virus-infected cells. Potential EBV gene products also play a role in regulating the host's immune response. The EBV-encoded gene product EBER is expressed at high levels in all latent EBV infections, and can inhibit interferon-stimulated gene activity by binding to double-stranded RNA-dependent protein kinase PKR [54]. EBV-infected cells can secrete exosomes to regulate immune activity [55, 56]. These exosomes have been shown to contain LMP1, galactoglobulin 9, and other immunomodulatory molecules, which may regulate the function of immune cells in NPC microenvironment [56]. LMP2A and LMP2B, encoded by EBV, inhibit type I IFN responses in epithelial cells by disrupting IFN-stimulated gene transcription and targeting IFN receptor degradation [57]. EBV-encoded miRNAs play an important role in immune evasion [58]. EBV-encoded BART-miRNAs are highly expressed in NPC cells. Cellular targets of BART-miRNAs identified in immune evasion include major histocompatibility complex class I related chain B (MICB). Decreased expression of MICB on the cell surface leads to a reduced cytolysis response following NKG2D activation, enabling EBV-infected cells to evade immune detection [59].

NPC Integrated-Treatment with Traditional Chinese

Because the onset of NPC is hidden, its clinical treatment is often based on radiotherapy. However, according to the latest CSCO treatment guidelines, the status of concurrent chemoradiotherapy for nasopharyngeal carcinoma has gradually increased. The main treatment strategies include concurrent chemoradiotherapy, induction chemotherapy, and adjuvant chemotherapy, their clinical efficacy is good. The patients with early and mid-stage NPC are mainly treated with radiotherapy or combined chemotherapy. NPC patients at Stage I (T1N0) is often treated with radiotherapy alone, and intensity-modulated radiotherapy (IMRT) is strongly recommended [60]. The treatment options for stage II NPC (T1N1/T2N0-1) are quite controversial. Concurrent chemoradiotherapy has certain advantages, but it is limited to two-dimensional irradiation techniques [61, 62].

Several retrospective studies have shown that radiotherapy alone using IMRT technology has a good therapeutic effect on intermediate NPC, but for patients with a high incidence of distant metastasis (T2N1), concurrent chemoradiotherapy seems to be more effective [63–65]. There are also prospective randomized controlled studies that have shown that for patients with stage II NPC, there is no difference between IMRT and concurrent chemoradiotherapy in overall survival terms, local control, or distant metastasis [66]. For low-risk stage II and stage III (T3N0M0) patients, there is no difference between IMRT and concurrent chemoradiotherapy on the primary endpoint of 3-year failure-free survival, while the results of secondary endpoints such as overall survival, local recurrence, and distant metastasis are still immature [67]. Concurrent chemoradiotherapy should be used for locally advanced NPC, cisplatin is the most commonly used drug [68, 69]. Randomized studies have shown that patients treated with weekly cisplatin regimens have a higher incidence of myelosuppression and hearing impairment [70–75]. For the patients who are intolerant to cisplatin, nedaplatin, carboplatin, etc. can be used as alternative treatments. For patients who are intolerant to chemotherapy, radiotherapy combined with cetuximab or nimotuzumab can be chosen. Although there is a lack of relevant randomized controlled trials [76], nimotuzumab significantly improved 5-year overall survival without significantly increasing toxicity when combined with concurrent chemoradiotherapy with cisplatin [77]. Induction chemotherapy followed by concurrent chemoradiotherapy is another treatment modality for locally advanced NPC. Previous meta-analyses have shown that induction chemotherapy helps improve local control, but does not improve overall survival [78, 79].

However, in two recent prospective randomized controlled trials of locally advanced NPC (excluding T3-4 N0), three cycles of the GP regimen or the modified TPF regimen significantly improved various endpoints, including overall survival, on top of concurrent chemoradiotherapy with IMRT and cisplatin [18, 80–82]. Concurrent chemoradiotherapy followed by adjuvant chemotherapy is another treatment option for locally advanced NPC, but previous studies have suggested that the completion rate is not ideal due to radiotherapy toxicity. Although the early randomized studies suggested that this mode could improve overall survival compared to radiotherapy alone, it cannot be ruled out that the benefit mainly comes from concurrent chemoradiotherapy [70–72]. The subsequent two randomized controlled trials using PF and GP regimens as adjuvant chemotherapy respectively had negative results, with the latter being more targeted at high-risk patients with residual EBV DNA after radiotherapy [83–85]. A prospective randomized controlled trial of capecitabine metronid chemotherapy showed improvement in all endpoints, including 3-year overall survival, and the benefit was independent of whether or not induction chemotherapy, but the results still need to be verified by long-term follow-up [86]. Two other prospective randomized controlled trials in patients with locally advanced disease who received concurrent chemoradiotherapy showed that 8 cycles of conventional capecitabine chemotherapy or 3 cycles of GP regimen could improve 3-year failure-free survival or progression-free survival [77, 87]. The optimal adjuvant chemotherapy regimen, chemotherapy cycle and benefit population still need to be determined, and the relationship between this treatment modality and induction chemotherapy on the overall efficacy still needs further research.

In recent years, immunotherapy has gradually emerged in the clinical management of tumors. Immunotherapy activates immune response in the tumor microenvironment by changing the biological characteristics of immune effector cells, thereby inhibiting or killing cancer cells. Modulated immunotherapy for NPC has shown good efficacy and safety, and has become a promising treatment method. Several types of immunotherapy, including adoptive cell transfer (ACT) and ICIs, have achieved durable clinical responses, but their efficacy varies. With the rapid development of immunotherapy, drugs that target immune checkpoint inhibitors (ICIs) are widely used in various solid tumors such as lung cancer, head and neck tumors, and cervical cancer. The occurrence and development of NPC are closely related to EBV infection. Therefore, a large number of EBV antigens, including latent membrane proteins and nuclear antigen-1, which can induce antitumor activity, have been detected in NPC diagnosis and efficacy evaluation. In addition, NPC is also known as "lymphoepithelioma". The microenvironment of inflammatory tumors is assembled with immune cell infiltration, which makes it a good basis for immunotherapy. Vaccination is the most effective treatment for preventing EBV infection [88]. Recently, nimotuzumab, a humanized monoclonal antibody targeting epidermal growth factor receptor (EGFR), has come into view. Many clinical trials have shown that nimotuzumab plus chemotherapy, radiotherapy or simultaneous radiotherapy and chemotherapy have certain therapeutic effects on patients with locally advanced and relapsed or metastatic NPC [89]. In terms of cell therapy, the main treatments include chimeric antigen receptor T-cell immunotherapy (CAR-T), tumor-infiltrating lymphocyte therapy, natural killer cell therapy and cytokine-induced killer cell (CIK) therapy. Clinically, the safety and preliminary efficacy of EBV CAR-T therapy to relapsed/refractory NPC are significant [90].

Traditional Chinese medicine can improve the immune function of tumor patients, prevent recurrence and metastasis, prevent or reduce the toxicity of radiotherapy and chemotherapy and improve the quality of life of patients. The specific mechanism of most Chinese medicines is still unclear, but many Chinese medicines have been found to effectively promote and stimulate the immune system, thereby improving the immune function of NPC patients and reducing toxic reactions. Chinese medicine compound treatment for symptoms, supporting the body's resistance and eliminating pathogens, helps the body restore the balance of yin and yang, enhance the body's anti-tumor ability, and thus effectively reduces the adverse reactions that occur after radiotherapy and chemotherapy in NPC patients. Jiang, et al. thought that the effective intervention of the Chinese medicine compound Yiqi Jiedu formula can reduce the proportion and activity of CD4+ CD25+ T regulatory cells of in the patients with mid-to-late stageNPC, increase the proportion and functional activity of immune effector cells Th17, help to reverse immune tolerance phenomenon in the tumor microenvironment of NPC, and thus enhance the anti-tumor ability of NPC patients [91]. Zhang Bei, et al. observed the correlation between TCM syndrome type and clinical stage and EBV-DNA concentration in newly diagnosed NPC patients. The results showed that the lung heat type had an earlier TNM stage and low EBV-DNA concentration in the four types. The blood stasis and phlegm coagulation type were all stage III and IV patients, and the highest EBV-DNA concentration was in the four types [92]. The results suggest that there is a certain correlation between TCM syndrome type and EBV-DNA concentration in NPC patients [92]. The peripheral blood T lymphocyte subset values of tumor patients are abnormal. The characteristic is that the CD3+ and CD4+ cells in the patient's body are significantly reduced, while the CD8 + cells are significantly increased. The CD4+/CD8+ ratio is significantly reduced, showing an immunosuppressive state [92]. Li, et al. explored the correlation between four syndrome types (phlegm accumulation type, qi and blood stagnation type, body fluid deficiency type, and spleen and stomach qi deficiency type) and T cell subsets pre- and post-treatment of NPC radiotherapy and chemotherapy. The results showed that the phlegm accumulation type and qi and blood stagnation type at pre-treatment transformed into spleen and stomach qi deficiency type at post-chemotherapy, and transformed into body fluid deficiency type posy-radiotherapy [93]. The expression level of CD4+ and CD4+/CD8+ at post-treatment was significantly higher than atpre-treatment, while the expression level of CD8 + was significantly lower than that at pre-treatment. This suggests that the expression levels of CD4+ and CD8+ and the CD4+/CD8+ ratio changed significantly in different TCM syndrome types at pre- and

post-treatment of NPC patients [93]. Compared with radiotherapy alone, it combined with TCM treatment significantly reduced adverse reactions, including acute oropharyngeal mucositis and acute skin radiation reaction [94]. Gao, et al. explored the effects of radiotherapy on acute oropharyngeal mucosal reaction and immune function caused by NPC. The results showed that the TCM syndrome score, degree of oral mucosal damage, CD8+ index, saliva flow rate, and amylase secretion rate of the observation group were all lower than those of the control group after treatment. Moreover, CD3+, CD4+ and CD4+/CD8+ indexes were higher than those of the control group after treatment. The results showed that the intervention of Qingre Liyan Decoction for radiotherapy patients can effectively prevent and treat acute oropharyngeal mucosal reaction and improve immune function, which has clinical promotion value [95]. Wang, et al. explored the use of blood-activating, qi-tonifying and yin-nourishing Chinese medicine to reduce acute toxic side effects of radiotherapy. Blood-activating, qi-tonifying and yin-nourishing formula can significantly reduce acute radiation damage to mucosa and skin and bone marrow suppression [96].

NPC treatment primarily includes radiotherapy and chemotherapy. Despite significant advancements in treatment options in recent years, local recurrence or/and distant metastasis are still main factors to lead to treatment failure. EBV activates tumor lymphocyte infiltration (TIL) and increased expression of programmed death receptor 1 (PD-1) or its ligand (PD-L1), all of which could potentially become therapeutic targets. Therefore, targeting EBV and immunotherapy to PD-1/PD-L1 may be an effect therapy for NPC. East Asia, southeast Asia, and central and south Asia have the highest incidence of NPC worldwide. Etiological and pathogenesis studies show that the occurrence of NPC is related to genetic factors, and EBV also plays a crucial role. Therefore, controlling EBV infection and activation in the population and reducing the levels of various EBV antibodies may prevent NPV or reduce its incidence. 5-year survival rate for radiotherapy in NPC is generally around 45%, and the side effects are significant; a small number of patients are not very sensitive to it. Therefore, searching anti-EBV drugs with non-toxic or low-toxicity from traditional Chinese medicine is an effective way to prevent and reduce NPC incidence. Yiqi Jiedu formula has played some role in the prevention, treatment, prognosis improvement of NPC, as well as in reducing the side effects of radiotherapy, but its effect and mechanism are not clear. Conducting research on the prevention and treatment of NPC using integrated traditional Chinese and Western medicine are still an urgent and important task in future, especially those working in areas with a high incidence of NPC.

Competing interests: Author FQT serves on the editorial board of this journal but had no role in the peer review or decision-making process for this article.

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Call for Papers

Scope

CMP particularly values clinician-led studies, practice-based evidence from primary care institutions, and collaborative contributions that translate emerging medical knowledge into improved patient outcomes. Our areas of interest include, but are not limited to:

Clinical Medicine and Specialties

- Precision oncology and individualized treatment strategies;
- Chronic disease management and multi-morbidity care;
- Rare diseases and therapeutics for special populations;
- Real-world studies and multicenter clinical practice analyses.

Pharmacology and Pharmaceutical Sciences

- Clinical evaluation of new and repurposed drugs;
- Pharmacokinetics, pharmacodynamics, and drug interaction research;
- Medication safety, pharmacovigilance, and adverse event monitoring;
- Interdisciplinary studies in oncology pharmacology, chronic medication regimens, and AI-assisted drug development.

Public and Global Health

- Evidence-based approaches to communicable and non-communicable diseases;
- Implementation research on clinical policies and treatment accessibility;
- Regional analyses of healthcare innovation and outcome disparities.

Biomedical Sciences and Emerging Technologies

- Applications of AI, big data, and machine learning in pharmacological analysis;
- Innovations in clinical diagnostics, precision medicine, and molecular testing;
- Translational research in imaging, regenerative medicine, and therapeutic devices.

Healthcare Systems and Practice

- Clinical decision support systems and electronic health record integration;
- Practice-based improvements in patient safety and treatment adherence;
- Models for managing chronic illness in complex healthcare settings.

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- Ethical conduct of clinical trials, patient autonomy, and informed consent;
- Social, cultural, and economic influences on clinical decision-making and patient care.

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- Real-world clinical research design and drug re-evaluation frameworks;
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ISSN 2760-1757 (Online)
ISSN 2760-3288 (Print)