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Experience of patients with lung cancer and with targeted therapy-related skin adverse drug reactions: A qualitative study

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ABSTRACT

Objective: To explore the experience of non-small-cell lung cancer patients with targeted therapy-related skin adverse drug reactions.
Methods: This is a descriptive quantitative study conducted in a comprehensive hospital in Henan, China. Purposive sampling was used to recruit patients with non-small-cell lung cancer and with targeted therapy-related skin adverse drug reactions. In total, 23 patients were approached when the data were saturated. Face-to-face interviews were conducted by an independent researcher using a semi-structured interview guide. Interview data were transcribed and analyzed by qualitative inductive content analysis.
Results: Based on the analysis, four main categories were identified according to patients' descriptions of their experience: a lack of self-management ability, psychological and emotional problems, a barrier to social participation, and a need for social support. Suffering from persistent symptoms, insufficient knowledge, skills and strategies for skin adverse drug reaction management, psychological problems, social avoidance/withdrawal, and reduced willingness to work were core experiences that would affect patients' compliance with treatment, prognosis, and the overall quality of life.
Conclusions: This study revealed the real experience of patients with non-small-cell lung cancer and with targeted therapy-related skin adverse drug reactions which contributed to the development of targeted interventions to manage skin adverse reactions.

Introduction

Lung cancer is the main cause of cancer-related deaths accounting for a quarter of total cancer deaths. Globally, an estimated 2.22 million new lung cancer cases and 1.55 million deaths from lung cancer were reported in 2019.[1] Among the various types of lung cancer, non-small-cell lung cancer (NSCLC) accounts for 85% of the total cases in China. Significantly, in China, 75% of patients with NSCLC were in advanced stages when they were diagnosed, with 5-year survival rates of approximately 10% (stage III b) and 2%–5% (stage IV).[2,3] As a result, NSCLC-related theranostics and clinical care have gained great attention in recent years.

The rapid development of molecular biology has enabled the identification of molecular targets of particular cancer cells, thus providing a framework for targeted anticancer therapy.[4] Several studies had shown that targeted therapies could improve the overall survival, progression-free survival, and response rate of patients with cancer and contribute to better tolerance and quality of life (QoL).[5,6] The National Comprehensive Cancer Network guidelines confirmed that epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) can be used as the standard first-line treatment for patients with EGFR mutation-positive NSCLC.[7] Partly because of its oral administration, EGFR-TKIs have gained increasing popularity in recent years.[8] Although

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the incidence of lethal adverse reactions to targeted therapy is generally lower than that of chemotherapy due to the prolonged treatment time, an up to 80% adverse reaction incidence has been reported.[9] Particularly for skin adverse drug reactions (ADRs), as demonstrated by recent studies, an up to 80% patients receiving EGFR-TKIs have experienced skin ADRs within three months. This seriously affects their daily lives and treatment and highlights the importance of studying this group of drugs in clinical settings.[10,11]

The Common Terminology Criteria for Adverse Events 5.0 developed by the United States Department of Health and Human Services in 2017 is the most commonly used standard for skin ADR classification. Common Terminology Criteria for Adverse Events 5.0 provided a specific definition of each skin ADR and divided them into five grades according to the scope, symptoms, impact on life, and severity. However, this tool only explained the nature and intensity of skin ADRs, and the duration of ADRs and the suffering of patients were overlooked.[12] Another commonly used tool for ADR evaluation is the therapy-related symptoms checklist, which contains fourteen subscales corresponding to fourteen ADRs. However, this tool includes only two skin ADR (skin change and hair loss) assessments that focus on investigating the symptoms and severity of ADRs within a particular treatment cycle.[13] Moreover, in this tool, the assessments of skin change and hair loss were single items without a specific description of the symptoms of ADRs, making it unable to fully reflect the skin ADR situation. As a result, there is still space for the improvement of the existing assessment tools for skin ADRs.

For quantitative studies, several studies indicated that the status of various skin ADRs includes the incidence, clinical manifestations, location, time of occurrence, duration time, and accompanying symptoms.[14–16] Studies had shown that most patients occurred skin ADRs for the first time 1–2 weeks after taking medicine, while patients generally came to hospital 3–6 weeks after taking medicine due to severe skin rash with skin itching and dryness. At this time, patients may have serious skin ADRs without enough coping abilities.[17,18] Other studies had explored the factors affecting the occurrence and severity of skin ADRs. As shown by a study, male patients and elderly patients (over 65 years old) tended to experience more severe skin ADRs,[19] and patients with comorbidities had complicated disease conditions and took multiple medications, which easily led to severe skin ADRs or aggravation of ADRs.[20] In addition, the prolonged treatment period may also influence the degree of skin ADRs due to the toxicity of drugs accumulating over time.[21] However, as these factors are impossible to be improved, these studies have limited significance for guiding clinical and nursing decision-making and practice. A qualitative study explored the unmet needs of patients with cancer and with hand-foot skin reactions related to chemotherapy and targeted therapy, the results showed that patients had needs for symptom management, social participation, and coping with ADRs.[22] However, this study only involved one kind of ADR. And although the needs for managing ADR were mentioned, the experience, detailed problems, and difficulties of patients in ADR management were not explored. In addition, this study did not investigate patients' psychological conditions which are important indicators of ADRs. All these factors comprised the significance of the study for developing effective ADR management plans.

Severe skin ADRs can affect the QoL of patients and can cause damage to the physical, psychological, and social functions.[14,18] For example, the pain, pruritus, dryness, swelling, and numbness caused by skin ADRs could make patients physically uncomfortable, resulting in limited physical activity; moreover, the symptoms produced by skin ADRs could hurt patients psychologically and detrimentally affect their self-esteem and mental health. Importantly, with the increase in psychological distress, patients tend to show a desperate and evasive attitude when coping with skin ADRs.[23,24] Other studies had shown that skin ADRs could make patients feel rejected and ashamed, leading to patients' social participation barriers (social avoidance and isolation) and reduced self-identity.[25,26] Even worse, persistent painful symptoms caused by skin ADRs could reduce the treatment willingness of patients because they believed that the treatment compromises their QoL.[27] As shown in a previous research, the medication adherence of patients receiving EGFR-TKI-based targeted therapy was poor, with 76% of patients with NSCLC interrupting treatments and 32% of patients reducing drug dose or experiencing unplanned drug withdrawal,[28] which led to poor curative effects and poor prognosis (the recurrence and progression of cancer).[29,30] The practical guidelines for skin ADR management of patients with cancer also clearly put forward the impact of skin ADRs on QoL and clinical prognosis, and this impact had been generally underestimated by clinicians.[31,32]

Early skin ADR management enables patients to obtain relevant knowledge and skills, which can alleviate the severity of skin ADRs and reduce drug withdrawal and dose reduction.[33] Studies had confirmed that identifying, monitoring, and recording skin ADRs for timely evaluation of potential serious skin ADRs can contribute to improved skin ADR prevention and management, thereby reducing the suffering of patients, promoting the optimization of clinical decision-making, and improving clinical outcomes.[10,34] Another previous study showed that patients' activity ability, physical functions, and overall curative effect of treatment could be improved by skin ADR management.[35] Effective skin ADR management allowed patients to receive the maximum recommended dose of targeted therapy, which is very important for optimal treatment.[36]

As known, quantitative studies mostly explore the relationships between skin ADRs and relevant variables. However, simply identifying the influence factors of skin ADRs does not mean an effective management of skin ADRs can be achieved. This is because many of these factors are difficult to change, even though the impact of such factors on patients' QoL and disease prognosis is obvious. On the other hand, qualitative research can explore the subjective feelings of patients which contributes to focus on mild skin ADRs but have a significant impact on QoL. Besides, through qualitative research, we can identify the occurrence time, duration, progress, mitigation, and persistence factors of skin ADRs. Therefore, a well-designed qualitative research is necessary.

In this study, by investigating the experience of patients with advanced-stage NSCLC and with targeted therapy-related skin ADRs, we aimed to explore the patients' real experience with skin ADRs and the practical problems and difficulties in ADR management. Based on these findings, we can develop individual care plans, health education, and counseling and provide advice on coping skills to patients. Meanwhile, our findings may provide directions for developing intervention strategies for effective skin ADR management to benefit patients with cancer and with targeted therapy.

Methods

Design

This study was a descriptive qualitative study. A qualitative face-to-face interviews was applied, which is featured by semi-structured interview guidelines complying with the consolidated criteria for reporting qualitative research (COREQ) guideline (see supplementary file).[37]

Setting

The current study was performed in a private outpatient meeting room in a comprehensive hospital in Henan, China. NSCLC outpatients with targeted therapy-related skin ADRs were recruited from dermatology outpatients when they finished their clinic visit. The dermatology clinic was organized by the cooperation of the oncology and dermatology departments, and oncodermatologists provide services for patients with anticancer (chemotherapy, targeted therapy and immunotherapy) treatment-related skin problems every Wednesday. The most common reasons for visiting the clinic were rash, skin pruritus, paronychia, hair loss, and hand-foot syndrome. There are two oncodermatologists on duty, and a nurse is responsible for collecting patients' information,

keeping order and responding to patients' consultations. The clinic had established electronic medical records which contained detailed information about each patient. Therefore, researchers can review the electronic medical records of patients to screen potential participants.

Participants and samples

A purposive sampling technique was used based on a maximum variation among patients with NSCLC in terms of age, gender, education level, marital status, occupational status, and the type and classification of ADRs. This sampling technique enabled the researchers to capture a wide range of views and experiences from patients. From November 2021 to March 2022, we selected patients who visited the dermatology outpatient of the hospital due to skin ADRs at the first time. For these patients, the skin ADRs were more serious and/or they could not cope with by themselves; moreover, patients' problems and experience in these cases were generally very obvious for effective evaluation. Inclusion criteria for participation in the study were as follows: (1) the pathological diagnosis was NSCLC; (2) patients with EGFR-positive advanced NSCLC; (3) patients had been on EGFR-TKI treatment for at least four weeks (most skin ADRs occurred 1–4 weeks after medication[38]); (4) patients could communicate normally; (5) patients were able to give informed consent. The exclusion criteria were as follows: (1) patients who were seriously ill and unable to communicate and (2) patients with psychiatric illness or cognitive impairment. Skin ADRs related to EGFR-TKI treatment were identified based on the coexistence of adverse symptoms upon EGFR-TKI treatment.

In total, 32 patients who met the screening criteria consented to the qualitative interview. Five patients dropped out of the study because they were not interested in (3 patients) or because their diseases had progressed and required further treatment (2 patients). Open-ended and probing questions were used to gain adequate information from the interview. Data redundancy and information saturation were observed after 23 interviews.[39] Eligible patients were identified by a research assistant (a postgraduate: ZJZ) who reviewed patients' electronic medical records. Then, participants were met face-to-face by the assistant. If patients did not have time, we could also contact patients by telephone to arrange interviews according to patients' preferences. The participants were informed about the detailed information about the study orally by a researcher before the study, including the purpose, significance, and process of the study, and were asked to sign informed consent forms. When consent was obtained, a time and place for the interview were determined. Before the interview, the medical staff evaluated the physical status and disease conditions of the patients to confirm their eligibility to participate in the study. If the patients experienced any discomfort during the interview, the interview was suspended. No other persons were present during the interviews.

Data collection

The face-to-face semi-structured interview lasted 60–90 min, conducted in a private outpatient meeting room by an experienced interviewer (the study designer). The interviewer (DRF) is a female registered nurse who is a PhD candidate and she interned in the oncology department at the study hospital. There were no prior relationships between the interviewer and the interviewees. The interviewer introduced herself to all participants and chatted with them before the study; moreover, the interviewer explained that the information collected in this study could contribute to developing more effective measures to help and benefit them and patients with similar conditions. Therefore, a trusting relationship was established between the interviewer and the participants. In addition, the interviewer is interested in qualitative research and familiar with the methods and process of such a study by developing several similar studies previously. Notes were made to record important opinions, doubts, interviewees' expressions, and postures. Subsequently, one repeat interview was carried out to confirm and supplement the points to reach data saturation, and patients underwent repeat interviews were also included in the 23 samples mentioned above. All interviews were audio-recorded and transcribed verbatim by one of the authors (DRF).

A semi-structured interview guide (Table 1) was developed by the research team based on a comprehensive literature review and expert consultation. The preliminary interview list was tested in 5 pilot interviews for comprehensibility to ensure the rigor of the interview questions. Then, the interview guide was adapted according to specific issues raised during the implementation of the pilot interviews. The original interview outline started with "how much knowledge do you know about the drugs you take?"; however, in the pilot interviews, we found that the patients' answers were not related to the purpose of this study (skin ADRs), so we deleted this question. In addition, after pilot interviews, the patients' experience in managing skin ADRs was limited, and we did not obtain sufficient information to describe the problems and difficulties encountered during skin ADR management. Therefore, we added the following question: what factors do you think hinder or promote skin ADR management? All interviews were performed in Henan, China. The interview addressed topics including the patients' experiences with skin ADRs, how skin ADRs affect their lives, what they want to improve, how they cope with skin ADRs, the self-management of patients, and the barriers and facilitators for managing ADRs. Demographic data were obtained from their electronic medical records before the interview. To encourage participants to fully express their experiences or thoughts, the interview began with an open question: 'What skin ADRs do you suffer from?'

Data processing and analysis

The interviews were anonymized, and the record was transcribed into text by the computer software program NVivo 10 within 24 h. The identity information of all interviewees will be hidden during data analysis, and each interviewee will be represented by a code number. Meanwhile, the record, interview transcript and electronic field notes were stored in a dedicated computer after the interview for 1 year. The computer and folder are encrypted and only accessible to the researchers of this study.

Qualitative inductive content analysis of descriptive data was used to analyze the transcripts.[40] The inductive content analysis procedures were carried out: (1) read the transcript of the interview repeatedly and carefully until understanding the whole sense of text; (2) break up the data, analyze them line by line, determine the significant statements, and code them; (3) encode and classify repeated statements and phenomena to generate themes; (4) find the relationship between themes and form a theme group; (5) this cycle until saturation: there are no new themes and subthemes. The two researchers (DRF and ZHY) familiarized themselves with the data by reading, double checking, and summarizing the interview transcripts. First, we identified and classified the important information in the notes and marked different types of information with different colors. During this process, we divided the interview content into multiple-meaning units and each meaning unit expressed independent content. Then, open coding was performed, we summarized the keywords and repeated information in each meaning unit and schemes were identified. Additionally, other codes that emerged from the data

Table 1
Interview list.

	Open-ended questions
1	What skin adverse reactions do you suffer from?
2	How do you experience or feel about skin adverse reactions?
3	What factors aggravate or alleviate the adverse reactions?
4	How do these adverse reactions affect your life and what you suggest to improve?
6	What did you do when occurred skin adverse reactions?
7	What factors do you think hinder or promote your adverse reaction management?
8	What do you want medical staff, family and friends to do for you?

were added for more specific aspects. After that, we merged themes with similar meanings or separated themes containing different information according to the aim of the study to ensure theme optimization. Next, we decided which codes belonged to which theme and determined whether subthemes were necessary to explain themes further. To ensure reliability and rigor, the interview transcripts were coded and analyzed by each researcher independently. Differences between researchers were discussed until a consensus was reached. At this stage, a third researcher (WT) controlled the coding process to avoid subjective speculation and to solve disagreements that could not be solved. He compared the themes with the transcribed interviews to improve the trustworthiness of the results. Finally, transcripts were returned to participants to obtain the credibility of the data. In an iterative process, related themes were identified to structure the results section.

Ethical considerations

This study was approved by the Ethics Committee and permission was granted by the managers of each investigation ward. Information about the study was provided to all prospective participants, and we obtained informed consent from all participants prior to their inclusion in the study. In particular, the researchers emphasized that no form of discrimination would occur even if patients refused to join, and the participants volunteered to participate in the study and could withdraw at any time point. Moreover, the information patents provided were confidential and only used for research. The identity information of all interviewees was concealed, and we used ID numbers during the interview process.

Results

Patients were interviewed between November 2021 and March 2022. Thirty-two patients consented to the qualitative interview, data saturation was achieved after interviewing 23 patients. In total, 14 male and 9 female patients aged 49–80 years were interviewed. The demographic characteristics of the patients are presented in Table 2. There was consistency between the data presented and the findings as shown below:

Lack of self-management ability

Helplessness to persistent symptoms

Participants experienced persistent symptoms and changes in skin sensitivity that prevented them from performing daily activities and made them feel uncomfortable in maintaining a normal life. Some interviewees felt frustrated when skin ADRs seriously affected their daily lives and work; they did not know how to deal with the distress and to whom they could seek assistance.

A patient with skin swelling and pain on his hands said 'Anticancer medications caused more distress than surgery. Because of persistent numbness and pain, I hardly walked. I felt frustrated and stressed as hands are so important in daily life. For a long time, I did not know what to do.' (A5).

For a few patients, although they were informed about the side effects (skin itching) and were warned to avoid scratching, they could not tolerate the extreme itching. Worse still, they did not know any useful way to relieve itching except scratching. Meanwhile, insomnia and irritability caused by night itching almost overwhelmed them.

A patient with persistent skin pruritus for 2 months said 'Long-term pruritus makes me upset. I always scratched, the skin was scratched to bleed and swell, and finally, this piece of skin had turned hard and dark. Especially when itching at night, I cannot sleep at all.' (A6).

To alleviate skin cracking and bleeding, patients often need to use some skin care products. At present, many kinds of skin care products can be used for patients with skin ADRs, although these products show confirmed treatment effect, some patients were uncertain about long-term using skin protection products due to uncomfortability and unsatisfactory effect.

A woman with chapped skin said 'This skin cream I used is very sticky, it is very uncomfortable, it sticks everywhere, I have to wear gloves all the time. The high frequency of using the cream (3 times a day) truly affected my life and work severely. I do not know how to solve this problem. Sometimes I decided to not use it.' (A11).

The other patient with skin crack said 'My hands are getting darker and darker, swollen, and painful. Should I need to use hand cream and band-aids all the time? Which kind of skin cream should I choose? Most of the time, I had to wear gloves, but my hands become stiff and dull.'

Table 2
Characteristics of participants ($n = 23$).

Code	Gender	Age	Education level	Marital status	Occupational status	Types of ADR (most serious)	ADR grade
A1	Female	69	Senior school	Married	Unemployed	Rash	3
A2	Female	78	Primary school	Widowed	Unemployed	Rash	3
A3	Female	60	Senior school	Married	Unemployed	Hair loss	2
A4	Male	72	Junior school	Married	Unemployed	Rash	3
A5	Female	49	Senior school	Married	Unemployed	Hand-foot syndrome	3
A6	Male	80	Primary school	Widowed	Unemployed	Pruritus	2
A7	Male	66	College	Divorced	Unemployed	Hair loss	2
A8	Male	57	Senior school	Married	Employed	Xerosis	2
A9	Male	55	College	Divorced	Employed	Rash	1
A10	Male	73	Primary school	Married	Unemployed	Rash	2
A11	Female	71	Primary school	Divorced	Unemployed	Rash	3
A12	Male	56	Junior school	Married	Unemployed	Hair loss	1
A13	Male	64	Junior school	Married	Unemployed	Paronychia	1
A14	Female	62	Senior school	Married	Unemployed	Hair loss	2
A15	Male	70	Junior school	Married	Unemployed	Rash	3
A16	Female	54	College	Married	Unemployed	Hand-foot syndrome	3
A17	Male	77	Primary school	Widowed	Unemployed	Pruritus	2
A18	Male	63	College	Divorced	Unemployed	Pruritus	2
A19	Male	59	Senior school	Married	Employed	Xerosis	2
A20	Male	65	College	Married	Employed	Rash	1
A21	Male	70	Primary school	Married	Unemployed	Paronychia	2
A22	Female	61	Primary school	Divorced	Unemployed	Rash	3
A23	Female	49	Senior school	Married	Unemployed	Hand-foot syndrome	3

(A15).

Therefore, we can see that patients were helpless when they faced long-term symptoms caused by targeted anticancer medications.

Being unable to identify and record skin ADRs in a timely and effective manner

When giving health education to patients, it is important for patients to identify and record skin ADRs; however, without a detailed explanation, long-term follow-up, and supervision, the benefit of health education is limited. A few patients said that they could not distinguish whether some symptoms were skin ADRs.

A 78-year-old patient said 'The doctor informed me some information about recording ADRs, I tried to remember them, but it was truly difficult. When ADRs happened, I did not know what and how to do. It would be better to have a detailed checklist about what should I do (A2).

A male patient said 'I do not even remember when I had a rash on my face. When I found out, the rash turned more and began to be itchy. I thought I was allergic; now, my face is getting worse and worse.' (A4).

Without supervision, it was difficult for patients to perform regular skin ADR monitoring, and they neglected to record the dynamic changes in ADRs in time. As a result, they generally could not identify ADR alarm signals at the early stage.

One patient who always forgot to monitor skin ADRs said 'Someone should remind us how to identify ADRs, what should we pay attention to, and what factors may aggravate ADRs?' (A1).

Among these interviewees, some did not understand the importance of ADR monitoring and recording, and they thought it was unnecessary to record ADRs.

One patient neglected to record skin status: "I never thought about recording ADRs. If it is not very serious, I will not care. I think it is OK for me to take medicine according to the dosage on time. I do not know why I record this, what should be recorded and how should I record?" (A7).

However, identifying and recording the starting time, duration, aggravating factors, alleviating factors of ADR symptoms, and the effect of the anti-ADR medications could not only promote self-management but also provide valuable information to help clinical medical staff to improve treatment outcomes.

The need for knowledge, skills, and strategies for skin ADR prevention and management

Most patients who received EGFR-targeted therapy took medicine at home without the guidance of medical staff. Therefore, self-management played a significant role in the safety of the medication and effective ADR control. However, according to our study, self-management is generally not satisfactory among the interviewees. Almost all the interviewees said they were eager to improve their self-management ability to alleviate the severity of ADRs. Some patients dealt with skin problems by themselves, but the symptoms were not improved. They hoped medical staff could guide them to carry out effective ADR management to avoid unnecessary treatment and alleviate serious side effects. Information, precautions, and therapeutic measures should be provided to patients.

Some patients mentioned that they needed to know how to moisturize the skin. A patient with skin xerosis said 'I want to know how to prevent the aggravation of ADRs, what I can and cannot do to protect my skin' (A8).

A few patients want to know how to protect nails, for example, how to use gloves, nail cushions, and other protective equipment. A patient suffered from paronychia said 'How can I protect my nails? Do I need some instrument to protect my nails? Should I make nails wrapped or open?' (A13).

Patients need local or systemic application of multiple anti-inflammatory drugs to treat skin toxicities. Some patients need antibiotics, while others need steroid drugs. Other skin drugs used include antihistamines, pregabalin, and skin relaxants such as Vaseline, aloe gel, and hydrocolloid dressing. In these cases, patients need guidance and support to know the functions, usage of various drugs, and appropriate management of the medications.

A patient who needed prophylactic antibiotics said 'The doctor asked me to take oral antibiotics preventively, but I heard about drug resistance when taking too many antibiotics. Shall I use it all the time?' (A9).

Some patients wanted to know about the application of traditional Chinese medicine, such as the preparation of decoction, wet compress, boiling, and storage of drugs. Therefore, written instructions and video training should be provided to equip them with relevant skills.

A patient treated with traditional Chinese medicine said 'The decoction needs to be configured by myself. Moreover, there are requirements for temperature, time, and frequency when using it. I think it is very difficult for me.' (A12).

Additionally, some patients said they lacked the knowledge to judge whether they needed to go to the hospital or stop taking targeted drugs when skin ADRs occurred.

One patient who once stopped taking medication due to skin ADRs said 'When should I go to hospital, and when should I have to stop taking medicine? I think we need someone for consultation, and if we truly need to go to hospital, I hope someone can help us contact doctors.' (A22).

Psychological and emotional problems/issues

Due to the severity and persistence of ADR symptoms, accompanied by physiological harms, and an impact on life, the interviewees felt that they could do nothing even the easiest things. And with the accumulation of negative emotions, some of them showed psychological and emotional disorders.

Pressure

Most participants felt great burden and pressure, which resulted in psychological problems such as anxiety and irritability. Stress came from worrying about treatment interruption, affecting the overall treatment plan, poor treatment effect, limited daily life, poor prognosis and disease progression caused by skin ADRs.

Some patients with severe rash said 'I could not help to look at my face in the mirror, and I pay attention to my skin problems all the time. Sometimes I want to forget these problems, but the damages caused by skin ADRs always remind me of this, I feel a lot of pressure.' (A17); 'I am very worried that skin ADRs will affect my overall treatment plan. Once ADRs force me to stop or change medicine, the treatment effect will be affected.' (A10).

Depressed and losing hope

A few interviewees expressed their depression and despair. Primitively, they had great confidence in targeted therapy and believed that the targeted drugs had better effects and fewer adverse reactions than chemotherapy. However, they were very disappointed after a period of treatment because of serious skin ADRs. Some patients said many methods had been used while their skin problems never solved. As a result, some patients lost confidence and hope in treatment and did not even want to receive treatment anymore.

Two patients with serious skin ADRs said 'I was very sad and desperate. Before treatment, my doctor told me that the ADRs of the targeted drug were milder and may more effective than chemotherapy, which brought me great hope. But I did not expect that the skin ADRs of the targeted drug were so serious that I did not want to take the medicine anymore. I want to wait until the skin turns better.' (A16); 'To control symptoms, I had tried to take oral or external medicine, but my hands and feet are still painful and swollen and cannot be touched at all. I'm truly desperate, I think what I had done didn't work at all and I did not want to try.' (A23).

Low self-esteem

The manifestations of skin ADR include skin cracking, wrinkles, edema, blackening, rash, hair loss, etc. As the skin ADR occurred on visible parts of the body such as head, face, hands and limbs, the

appearance and image of patients could be greatly changed. The disorder of body image led to the impairment of patients' self-esteem and affected their intimate and interpersonal relationships.

A woman patient with facial skin damage said 'I do not want to see people peep at my skin. They point and whisper about my skin, which makes me feel malicious, and I am not respected. I feel I am not cared for but ridiculed. So I become self-pity and self-deprecation gradually and I do not want to go out, I become alienated from others.' (A22).

Some patients thought they couldn't do anything and had no contribution to family or society, and had lost their self-worth. Self-worth is a kind of expression of self-esteem in behavior and thought. People with low self-esteem often depreciate themselves, while those who lose self-worth also produce negative self-esteem.

A patient with obvious symptoms on hand said 'My hand skin had been desquamated, edematous and hardened. I cannot do anything, I even need help to complete my basic life, I feel like I am useless.' (A20).

Tension

Patients were anxious and nervous when skin ADR appeared constantly, and they would be more nervous if their skin condition deteriorated.

A worried patient said 'I'm very nervous about my skin condition. I'm afraid of further aggravation of skin symptoms. Once the skin cracks, it is hard to recover.' (A19).

A barrier to social participation

Social avoidance and withdrawal

Patients were reluctant or even refused to participate in social activities, which gradually led to social alienation. The main causes of social barrier included fear of discrimination or excessive sympathy.

One patient mentioned that 'I do not want to take part in any activities. I'm afraid that others will ask me why I turned like this, I'm afraid that others will care too much about me. I'm afraid that others will pity me.'

Patients feared socializing because they felt they looked terrible, and they had to cover their damaged skin. Moreover, they resisted social activities to avoid being stared at by others (A4, A15). Sometimes, patients refused social interaction to avoid repeatedly explaining skin problems to others (A 17, A20).

Reduced willingness to work

Patients said that they had to use their hands to work, but the skin symptoms hindered them from working, and caused reduced working efficacy. As a result, many patients quitted their jobs.

A resigned patient said 'Dealing with the uncomfortable symptoms and management of skin ADRs took me a lot of energy, and I have no motivation to work. Moreover, I am in a very upset mood and cannot calm down to work.' (A1).

Another patient said 'I feel that if I go to work, I only make trouble for others, and I cannot do anything at all.' (A12).

Need for social support

Effective social support from medical staff, family, and friends can help patients manage skin ADRs and alleviate patients' negative emotions. All patients expressed a strong desire to obtain information and emotional support from medical staff and believed that the instruction and the encouragement of medical professionals were authoritative and comforting.

A patient who took a targeted drug for a long time said 'I truly want to get support from medical staff because I trust them, they are professionals and their encouraging words can comfort me.' (A3).

One patient cared by his families more than three years said 'Now my family is my biggest dependence. My family's care and encouragement are the driving force for me to insist on treatment and maintain a positive attitude.' (A4).

Some patients received support from their friends and colleagues, which helped them overcome the difficulties.

A patient who received support from her friends said 'I hope that my friends can help me overcome difficult times. I just want to have an outlet to express my thoughts, and I hope someone can listen to my inner thoughts. It is easier and more relaxing for me to communicate with my friends. In addition, friends can enlighten me more, chatting with them, telling jokes, which make me feel better.' (A7).

Another patient said 'My colleagues and leaders supported me during work, which let me feel self-value. They only assign work that I am capable to complete. This way, I can also have the opportunity to make some contributions and get recognition from others.' (A8).

Discussion

This study revealed patients' experience with persistent skin symptoms and the difficulties and needs of patients undergoing targeted therapy during skin ADR management. One previous study found that 69% of patients with targeted therapy had skin ADRs. The most common symptom was rash, which coexisted with multiple skin symptoms.[41] It is quite clear that skin ADRs should be a great concern for patients with NSCLC undergoing targeted therapy.

The results of this study showed that skin ADR resulted in physical discomfort and psychological problems, which restricted patients' daily activities, impaired their social function, and led to a reduced QoL. A study reviewed 20 investigations on patients with breast cancer and with targeted therapy and concluded that patients' experience involved physical symptoms and emotional problems, which is consistent with our study.[42] The main reason for the impacts on physical and psychological conditions is the distress of skin symptoms, such as pain, swelling, numbness, itching, dryness, bleeding, exudation, hardening, and increased skin sensitivity. These symptoms may lead to abnormal sensation, sleep disorder, and restricted activity, all of these affect physical functions. At the same time, the persistence of symptoms, damage to body image, and negative impact on treatment and prognosis are the main factors leading to psychological problems. One study showed patients with skin ADRs suffered from obvious self-perceived burdens, which might not only aggravate psychological pressure and negative emotions but also complicate the relationship between patients and caregiver.[43] Therefore, effective symptom management and psychological intervention are necessary to improve patients' psychosomatic functions.

In this study, patients expressed urgent needs for knowledge, skills, and strategies for skin ADR prevention and management. Taking targeted drugs at home limits patients' access to medical services; meanwhile, the current hospital service model and the shortage of human resources cannot meet the needs of patients, all these highlighting the importance of improving patients' self-management. Self-management ability reflects the knowledge and skills of patients in managing ADRs. ADR management ability is an important predictor of drug safety in clinical practice.[44] Huang et al. showed that good self-management could effectively regulate the troubles and adverse effects caused by ADR symptoms of lung cancer treatment.[45] A meta-analysis indicated that patients with sufficient self-management ability were positive about learning knowledge and skills to deal with ADRs and showed less anxiety and better adaptability in stressful environments.[46] However, the results of this study showed that the self-management ability of patients should be improved. For this purpose, we can (1) provide support including carrying out customized health education to meet different requirements of patients; (2) provide skill training through videos, implementing online courses, and group discussions; (3) provide management manual for each patient. The manual will include detailed problem-solving methods and ADR coping strategies. Adequate and effective coping strategies and management measures are the premise of good self-management.[47] Importantly, the skill of identifying, monitoring, and recording skin ADRs dynamically should be provided to patients. The specific indicators required for the

self-identification of skin symptoms should be offered to patients.[25] Therefore, we should help patients develop a home medication record book and teach them how to monitor and record, such as the time, location, scope, duration, inducing factors, and mitigating factors of skin ADR. Furthermore, some protective measures should be notified to prevent skin ADR. For example, for the hand-foot syndrome, patients should pay attention to hand and foot moisturizing and avoid direct sunlight, extreme temperature, pressure, skin friction, and trauma.[48] In addition, specific coping strategies should be supplied, such as effective medication, nutritional support, detailed methods to alleviate symptoms, individualized drug dose adjustment by pharmacists, and traditional Chinese medicine treatment.[49] Larsen et al. used e-health to provide coping strategies for patients with cancer and with oral chemotherapy at home; in this way, they could adjust the drug dosage in a timely manner according to the severity of ADR and reduce the number of additional medical visits. The results showed that the e-Health system could effectively help patients improve medication compliance, ensure drug efficacy and security, and avoid serious ADRs.[50] Therefore, web-based or home-based measures may be effective methods to promote patients' self-management.

A study investigated the frequency of social interaction and the degree of social participation of patients with breast cancer. The results showed that the QoL of patients was improved along with better social participation.[51] Social participation can allow patients to communicate actively and seek help to alleviate skin ADRs. In addition, social participation can also enhance the enthusiasm and confidence of patients and, therefore, reduce their negative emotions.[52] In this study, patients showed obvious barriers to social participation; the main reasons included impaired body image, repeated interpretation of skin problems, limited mobility, and reduced work ability. Patients felt embarrassed and ashamed in social life and were unwilling to establish interpersonal relationships. Therefore, attention should be given to the social situation of patients with cancer undergoing targeted EGFR-TKI therapy, and we should encourage patients to participate in social activities by organizing activities for patients. Moreover, constructing a new "patient-family" and "patient-friend" interactive communication mode may allow patients to restore their social self-confidence in interpersonal relationships and social networks.[53]

The results showed patients expected social support to cope with difficulties during the management of skin ADRs. Social support can improve patients' cognition of skin ADR management and alleviate the negative emotions of patients.[54] Support from medical staff not only provides information and skills related to the treatment and management of skin ADRs but also provides emotional support to improve patients' confidence and motivation. Support from family and friends can encourage and comfort patients, reduce patients' self-perceived burden, and provide a platform for patients to express their emotions and feelings. Support from the public and policies increase patients' self-identity, make them feel accepted and respected. Therefore, support from family, friends, colleagues, society, and medical staff was needed.

To our knowledge, this is the first qualitative study to explore the experience of patients with lung cancer with EGFR-targeted therapy-related skin ADR and to understand the difficulties, barriers, and needs during skin ADR coping and management in China. At the same time, we analyzed the impact of skin ADR on patients, which was made up for the defect of quantitative research caused by imperfect evaluation tools. In addition, the research focused on patients undergoing targeted therapy. Previous studies have mainly focused on the mechanism and effect of targeted therapy, while few studies have investigated ADRs, especially skin ADRs, which have an important impact on the QoL, prognosis and treatment of patients. The findings of this study have specific significance for clinical practice. The research showed that patients' physical, psychological and social functions were affected by skin ADRs, which emphasized the importance of skin ADR prevention and management. Furthermore, the results showed the specific needs and defects of patients during ADR management which helped to identify some intervention directions, such as improving patients' skin ADR self-management, providing psychological counseling and social support, promoting social participation, developing targeted health education, and informing detailed ADR prevention and treatment strategies. Therefore, in the future, we can formulate effective intervention plans and implement intervention research based on the results of this study. However, this study has several limitations. Our sample was selected from a single institution. This might influence the universality of the results. Further studies including more areas should be carried out. In addition, most of our participants (71.6%) were older persons ($\geq$ 60 years); thus, we obtained limited information about the experience of skin ADR for younger patients so that the conclusions of our study might not be generalized.

Conclusions

This study revealed the experience of patients with cancer and with targeted therapy-related skin ADRs, which had been less investigated. The patient's experience was summarized into four themes and several subthemes. The symptoms of skin ADR seriously hindered patients' daily activities, including work and social functions, and decreased patients' QoL. In addition, the psychological burden caused by skin ADR even led to patients quitting cancer treatment. Given the lack of self-management ability of patients, targeted coping strategies should be given at the beginning of cancer therapy with the consideration of patients' expression and willingness. Furthermore, it is necessary to develop effective interventions to improve the awareness and ability of self-management and to provide social support.

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Author contributions

WT and CCY were responsible for the overall conception, design and quality control of the study as well as the communication with the hospital and departments investigated. DRF contributed to the implementation of the research and the training and management of interviewers. DRF, ZJZ and ZHY interviewed patients and contributed to the acquisition, analysis and interpretation of data. DRF, WT, MLX and MAG contributed drafting and critical revision of the manuscript and provided final approval of the manuscript.

Declaration of competing interest

None declared.

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Ethics statement

This study was approved by the Ethics Committee (Approval No. ZZUIRB-2020-97) in the College of Nursing and Health of Zhengzhou University and permission was granted by the managers of each investigation ward. In particular, the researchers emphasized that no form of discrimination would occur even if patients refused to join, and the information they provided was confidential and only used for research. Information about the study was provided to the participants, and we

obtained informed consent from all participants prior to their inclusion in the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.apjon.2022.100115.

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