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REVIEW ARTICLE

Relationships between quality of life and skin toxicities of epidermal growth factor receptor inhibitors in cancer patients: A literature review

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Abstract

Aim: Epidermal growth factor receptor (EGFR) inhibitors are used as treatments for various cancers, but the associated skin toxicities affect quality of life (QoL). The aim of this review is to document the relationship between skin toxicity and QoL of cancer patients, and to identify implications for clinical practice and subjects for future studies.

Methods: Electronic databases were searched systematically and all studies examining aspects of health-related QoL in patients receiving EGFR inhibitor treatments for cancer.

Results: A total of 25 published studies met the criteria for inclusion. Some cancer patients maintained their health conditions by recognizing that skin toxicities are correlated with the efficacy of EGFR inhibitor therapy, yet QoL declined in all functional evaluations. In particular, QoL was low in patients above 81 years of age and in those under 50 years of age.

Conclusion: Improved understanding of the pain due to skin toxicity is required in all age groups, particularly in elderly and young cancer patients. In addition, further studies are required to define long-term changes in QoL among patients receiving EGFR inhibitors for cancer. Healthcare professionals need to help patients to maintain subjective health conditions by understanding relationships between skin toxicity and therapeutic effects. To this end, assessments of patients who are prone to QoL decline due to skin toxicity are critical so that skin management can be started during early stages.

KEYWORDS

cancer, epidermal growth factor receptor, quality of life, skin, toxicity

1 | INTRODUCTION

In recent years, molecular-targeted agents have become important and prevalent therapeutic options for cancer patients, and are increasingly used to treat advanced solid tumors (Forde & Ettinger, 2013; Kirstein et al., 2014). Among molecular-targeted agents, epidermal growth factor receptor inhibitors (EGFRIs) include the anti-EGFR monoclonal antibodies cetuximab and panitumumab, and the EGFR tyrosine kinase inhibitors gefitinib, erlotinib, afatinib, lapatinib, and osimertinib. EGFRIs are indicated for the treatment of advanced and metastatic non-small

cell lung cancer, pancreatic cancer, breast cancer, colon cancer, and head and neck cancer (Tischer, Huber, Kraemer, & Lacouture, 2017).

These agents have led to improved response rates and survival in comparison with cytotoxic chemotherapies (Cohen, Kim, & DeMatteo, 2017). However, despite these benefits, skin toxicity is the most common adverse effect of EGFRIs, and occurs in more than 80% of patients (Peuvrel et al., 2012). EGFRIs are thought to affect basal keratinocytes, leading to the development of some skin toxicities. The inhibition of EGFR-mediated signaling pathways affects keratinocytes, resulting in distinctive cutaneous manifestations (Lacouture, 2006). Typical symptoms include skin rash, xerosis, pruritus, and paronychia. Skin rash is the most common symptom of skin toxicity, usually occurring 1 week after cancer treatment and reaching its maximum intensity after 2–3 weeks (Hidalgo et al., 2001). Xerosis is defined as dry, flaking skin and is seen in approximately 35% of patients treated with EGFRIs. Pruritus is defined as an unpleasant sensation that leads to itching of the skin and occurs in response to the release of histamine (Abdullah, Haigentz Jr., & Piperdi, 2012). Paronychia is a swelling beside the nail, which presents later than the skin rash, seen after 4-8–weeks after the start of cancer treatment (Bianchini, Jayanth, Chua, & Cunningham, 2008). These symptoms affect patients' daily lives and may lower the quality of life (QoL) (Haley et al., 2011; Ra et al., 2013; Wagner & Lacouture, 2007), and several studies show correlations between the incidence and severity of skin toxicities and overall survival (Bonner et al., 2010; Peeters et al., 2009; Wacker et al., 2007). Hence, it is advisable to prevent or ameliorate skin toxicities using appropriate and timely management (Kiyohara, Yamazaki, & Kishi, 2013). Although previous studies lack evidence-based guidelines on how to prevent or treat EGFRI-induced skin toxicity (Baas et al., 2012), recommending prophylactic management such as gentle cleansing, skin care with moisturizing cream and lotion, and sunlight protection, has been indicated (Hofheinz et al., 2016).

Over the past few years, many researchers have shown interest in health-related QoL (HRQoL) in addition to therapeutic effects. HRQoL is a multi-dimensional concept that is assessed in terms of physical, mental, emotional, and social functions. Relationships between skin toxicities and HRQoL during treatments with EGFRIs have been demonstrated in many studies, and negative effects of skin disease have been described in terms of physical, functional, emotional, and social well-being. Furthermore, there are no published studies comprehensively assessing the consistency of skin management recommendations (Brown, Su, Nelleson, Shankar, & Mayo, 2016). Hence, the impacts of EGFRIs on HRQoL have not been adequately evaluated yet, warranting further discussion of HRQoL and skin toxicities induced by EGFRIs in cancer patients.

The objective of this literature review is to summarize demonstrated relationships between skin toxicities of EGFRIs and patients' QoL. Herein, we summarize the factors through which skin diseases affect QoL, and discuss the implications for clinical practice and for future studies.

2 | METHODS

2.1 | Data sources and searches

This literature review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2009). The articles published until May 2018 were searched and retrieved from electronic databases including PubMed, MEDLINE, and CINAHL. The MeSH terms used to retrieve the articles were; ("neoplasms" OR "cancer") AND ("quality of life" OR ["quality" AND "life"]) AND ("skin" AND "toxicity") OR ("exanthema" OR ["skin" AND "rash" OR "skin rash"]) OR ("skin" AND "reaction").

2.2 | Inclusion and exclusion criteria

Studies of (a) patients undergoing cancer treatments with EGFRIs and (b) reporting EGFRI-induced skin toxicity as an adverse event, (c) using at least one HRQoL instrument were included; and (d) only English language articles were included. Studies were excluded if they were not reported in English or were literature or systematic reviews.

2.3 | Search outcomes

A total of 1,197 studies were initially identified in the three databases. Among these, 566 were duplicates, 474 were not focused on EGFRIs, 103 did not report skin toxicity or QoL, and two were not published in English language journals. The remaining 52 studies were retrieved for further analysis. In further assessments of eligibility, 14 studies were excluded because they were review articles and seven were excluded because they evaluated adverse events that were not related to skin toxicity. Further, two studies suggested that the therapeutic agents used were not just EGFRIs, two more were not original articles, one surveyed the value of QoL instruments for EGFRIs, and one did not meet the criteria. These studies did not meet

the criteria and were excluded, leaving a final set of 25 research studies. A flowchart of the study selection procedure is presented in Figure 1.

2.4 | Quality appraisal of the selected studies

All the included studies were critically appraised according to the instrument of the Joanna Briggs Institute using the critical appraisal tools (Joanna Briggs Institute, 2017). Assessments of randomized controlled trials (RCTs), cohort studies, analytical cross-sectional studies, and case series are presented in Tables 1–4, respectively. Because this review was a survey of HRQoL, the measurement range was limited to circumstances in which health improvements were expected from medical interventions (Guyatt, Feeeny, & Patrick, 1993). Therefore, overall well-being was comprehensively evaluated in terms of global health status and QoL, and functional states of physical,

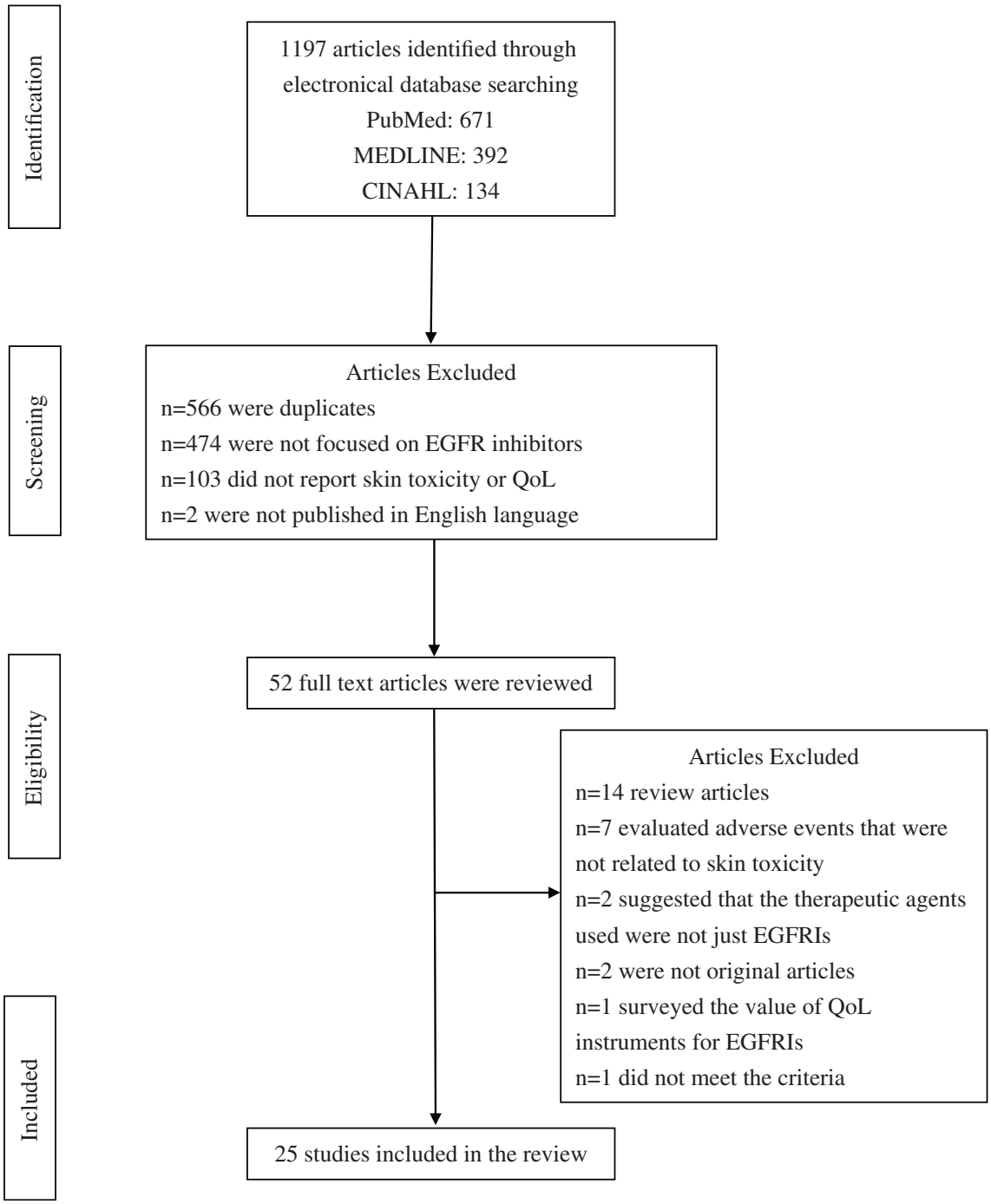

FIGURE 1 Flowchart of the study retrieval and selection process

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TABLE 1 Assessment of the randomized controlled trials

Appraisal criteria	Deplanque et al. (2016)	Hofheinz et al. (2018)	Jatoi et al. (2008)	Jatoi et al. (2010)	Koukakis, Gatta, Hechmati, & Siena (2016)	Kripp et al. (2017)	Lacouture et al. (2010)	Peeters et al. (2009)	Siena et al. (2016)	Sommeijer et al. (2014)
Was true randomization used for assignment of participants to treatment groups?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was allocation to treatment groups concealed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were treatment groups similar at the baseline?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were participants blind to treatment assignment?	Yes	Yes	Yes	Yes	No	No	No	No	No	Unclear
Were those delivering treatment blind to treatment assignment?	No	Unclear	Unclear	Unclear	N/A	N/A	N/A	N/A	N/A	Unclear
Were outcomes assessors blind to treatment assignment?	Unclear	Yes	Yes	Yes	No	No	No	No	No	Unclear
Were treatment groups treated identically other than the intervention of interest?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were participants analyzed in the groups to which they were randomized?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were outcomes measured in the same way for treatment groups?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

(Continues)

TABLE 1 (Continued)

Appraisal criteria	Deplanque et al. (2016)	Hofheinz et al. (2018)	Jatoi et al. (2008)	Jatoi et al. (2010)	Koukakis, Gatta, Hechmati, & Siena (2016)	Kripp et al. (2017)	Lacouture et al. (2010)	Peeters et al. (2009)	Siena et al. (2016)	Sommeijer et al. (2014)
Were outcomes measured in a reliable way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was appropriate statistical analysis used?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the trial design appropriate for the topic, and any deviations from the standard RCT design accounted for in the conduct and analysis?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Abbreviation: N/A, not applicable; RCT, randomized controlled trial.

psychological, social, economic, spiritual elements were classified (Spilker, 1996). These domains were investigated as defined by the World Health Organization (World Health Organization, 2006).

3 | RESULTS

3.1 | Characteristics of included studies

The findings across all the included studies are presented in narrative and tabular forms (Table 5). Studies of QoL in cancer patients with skin toxicities due to EGFRIs included 10 RCTs, eight cohort studies, six cross-sectional studies, and one case series. Among these articles, there were nine intervention studies on the treatment of skin toxicities and HRQoL, whereas the others evaluated HRQoL as a secondary item in cancer treatment. We included 15 studies of colorectal cancer, one of lung cancer, and nine studies of various types of cancer. Numerous studies of colorectal cancer have used anti-EGFR monoclonal antibodies such as panitumumab or cetuximab, whereas in studies of other cancer types EGFR tyrosine kinase inhibitors such as gefitinib or erlotinib have been used as therapeutic agents.

3.2 | HRQoL instruments

Generic HRQoL evaluations among reviewed studies included four cases of the European Profile of Quality of Life (EUROQoL) Health Index (EQ-5D) and one case of The Short-Form Health Survey (SF-36). Reported disease-specific scales included The European Organization for Research and Treatment of Cancer QoL Questionnaire-C30 (EORTC QLQ-C30) in eight studies, the Functional Assessment of Cancer Therapy-General (FACT-G), the Functional Assessment of Cancer Therapy-Colorectal (FACT-C), and the Functional Assessment of Cancer Therapy-Epidermal Growth Factor Receptor-18 (FACT-EGFR-18) in one study each, the Dermatology Life Quality Index (DLQI) in 10 studies, Skindex29 or Skindex16 in six studies, and original scales in two studies. In these measurements, EORTC QLQ-C30 and FACT instruments are considered specific for cancers, and DLQI and Skindex29 or Skindex16 instruments are specifically relevant to skin diseases.

3.3 | Validated global health status/QoL and total scores of HRQoL

Overall well-being of cancer patients receiving EGFRI treatments was analyzed using EORTC QLQ-C30 item

TABLE 2 Assessment of the cohort studies

Appraisal criteria	Clabbers et al. (2015)	De Tursi et al. (2017)	Grande et al. (2013)	Láng et al. (2013)	Pinto et al. (2016)	Thaler et al. (2012)	Unger et al. (2013)	Yamaguchi et al. (2017)
Were the two groups similar and recruited from the same population?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the exposure measured in a valid and reliable way?	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Were confounding factors identified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were strategies to deal with confounding factors stated?	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes
Were the groups/ participants free of the outcome at the start of the study (or at the moment of exposure)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the outcomes measured in a valid and reliable way?	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Was the follow-up time reported and sufficient to be long enough for outcomes to occur?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was follow up complete, and if not, were the reasons for loss to follow up described and explored?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were strategies to address incomplete follow up utilized?	Yes	N/A	N/A	Yes	Yes	N/A	No	No
Was appropriate statistical analysis used?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Abbreviation: N/A, not applicable.

Global Health Status/QoL (GHS/QoL) and the generic HRQoL measures EQ-5D and SF-36. Among the intervention studies of treatments for skin toxicity, one report showed no changes in GHS/QoL after 12-week cancer treatments (Hofheinz et al., 2018), and in another study, GHS/QoL scores decreased over time (Kripp et al., 2017). In four longitudinal studies of the relationship between skin toxicities of EGFRIs and QoL, GHS/QoL and EQ-5D scores decreased (Peeters et al., 2009; Pinto et al., 2016; Unger et al., 2013; Yamaguchi et al., 2017), whereas five longitudinal studies reported no changes in these measures (Koukakis et al., 2016; Láng et al., 2013; Siena et al., 2016; Sommeijer et al., 2014; Thaler et al., 2012). In three of these five conflicting studies, no changes were observed in GHS/QoL scores and degrees of skin toxicity were classified according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) as grades 0–2 versus grade 3+, and grade 0 or 1 versus grade

TABLE 3 Assessment of the analytical cross-sectional studies

Appraisal criteria	Joshi et al. (2010)	Osio et al. (2009)	Romito et al. (2010)	Rosen et al. (2013)	Tischer, Bilang, Kraemer, Ronga, & Lacouture (2018)	Yagasaki et al. (2018)
Were the criteria for inclusion in the sample clearly defined?	Yes	Yes	Yes	Yes	Yes	Yes
Were the study subjects and the setting described in detail?	Yes	Yes	Yes	Yes	Yes	Yes
Was the exposure measured in a valid and reliable way?	Yes	Yes	Yes	Yes	Yes	Yes
Were objective, standard criteria used for measurement of the condition?	Yes	Yes	Yes	Yes	Yes	Yes
Were confounding factors identified?	Yes	Yes	No	Yes	Yes	Yes
Were strategies to deal with confounding factors stated?	Yes	Unclear	No	Yes	Yes	Yes
Were the outcomes measured in a valid and reliable way?	Yes	Yes	Yes	Yes	Yes	Yes
Was appropriate statistical analysis used?	Yes	N/A	Yes	Yes	Unclear	Yes

TABLE 4 Assessment of the case series

Appraisal criteria	Vaccaro et al. (2016)
Were there clear criteria for inclusion in the case series?	Yes
Was the condition measured in a standard, reliable way for all participants included in the case series?	Yes
Were valid methods used for identification of the condition for all participants included in the case series?	Yes
Did the case series have consecutive inclusion of participants?	Yes
Did the case series have complete inclusion of participants?	Yes
Was there clear reporting of the demographics of the participants in the study?	No
Was there clear reporting of clinical information of the participants?	Unclear
Were the outcomes or follow-up results of cases clearly reported?	Yes
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Yes
Was statistical analysis appropriate?	Yes

2+ (Koukakis et al., 2016; Siena et al., 2016; Sommeijer et al., 2014). However, no effects on overall well-being due to the degree of skin toxicity were reported.

Numerous studies refer to total scores from disease-specific scales, such as FACT-G, FACT-C, FACT-EGFR-18, DLQI, Skindex29 or Skindex16, and QoL, and suggest that HRQoL deteriorates due to skin toxicity for 4–12 weeks from the start of cancer treatments. However, three studies report no significant differences (Clabbers et al., 2015; Sommeijer et al., 2014; Unger et al., 2013), and no relationships between QoL and age, gender, degree of skin toxicity, or time after the start of cancer treatments. Among the studies of treatments for skin toxicity that show deterioration of total QoL scores (Joshi et al., 2010; Osio et al., 2009; Pinto et al., 2016; Romito et al., 2010; Rosen et al., 2013; Yagasaki et al., 2018), one showed that declines in QoL could be prevented by starting skin treatments before the onset of skin toxicity (Lacouture et al., 2010), and another showed that oral tetracyclines ameliorate skin toxicities (Deplanque et al., 2016). In addition, QoL was lower in patients aged ≤50 years than in patients aged >50 years (Joshi et al., 2010), and patients of greater than 81 years of age experiencing higher impacts on QoL than those of the mean age range between 61 and 70 years (Clabbers et al., 2015).

3.4 | Descriptions of QoL in physical and symptom domains

The incidence of skin toxicity has been related directly with functional and symptomatic aspects of QoL in

TABLE 5 Studies about the impact of skin toxicity induced with EGFR inhibitors on quality of life

Author/ year	Research design	Indication/(samples)	EGFR inhibitors	Skin treatment	QoL instruments	Main findings
Clabbers et al. (2015)	Cohort study	Colorectal Lung ($N = 77$)	Panitumumab Erlotinib		FACT-EGFR-18 FACT-G SF-36 Skindex-16	• Physical domain was significantly higher during all 6 weeks compared to baseline. • In patients with grades 1/2, the dispersion in functional domains is relatively low; however, the social–emotional domain did show significant changes within the grades 3/4 sample. • There were no significant differences between FACT-EGFR-18 scores for gender or cancer type. • Patients younger than 50 years scored significantly lower on the functional domain QoL. • Patients above 81 years experienced more impact on the physical domain and total score, compared to patients in the mean age range between 61 and 70 years. • Patients with pruritus showed a trend of higher scores on Skindex-16 and FACT-EGFRI-18 (indicating a lower HRQoL) than patients with papulopustular eruption or xerosis.
Deplanque et al. (2016)	RCT	Lung ($N = 147$)	Erlotinib	Prophylactic doxycycline ($N = 73$) vs. control ($N = 74$)	DLQI	• The severity (grade >2) of folliculitis was lower in the doxycycline than in the control arm. • The percentage of patients with the DLQI global score of 0 to 1 (indicating no effect of skin alterations on QoL) was significantly higher in the doxycycline arm (day 14 and day 28).
De Tursi et al. (2017)	Cohort study	Colorectal ($N = 30$)	Cetuximab (+oxaliplatin or irinotecan)		Skindex-29	• A positive correlation was found between HRQoL (psychosocial and symptoms domains) and the severity of dermatological toxicities.
Grande et al. (2013)	Cohort study	Colorectal Lung ($N = 51$)	CetuximabPanitumumabErlotinib	Pre-emptive skin moisturizers and lymecycline	DLQI	• QoL did not show a significant difference from the beginning and the end of skin treatment. (after 3 months)

(Continues)

TABLE 5 (Continued)

Author/ year	Research design	Indication/(samples)	EGFR inhibitors	Skin treatment	QoL instruments	Main findings
Hofheinz et al. (2018)	RCT	Colorectal($N = 126$)	Cetuximab(+FOLFIRI)	Prophylactic doxycycline and vitamin K1 cream ($n = 66$) vs. prophylactic doxycycline ($n = 60$)	EORCT QLQ C-30DLQI	• Starting in week 5 and increasing over time patients treated with vitamin K1 cream had less severe rash and fissures. • EORCT QLQ C-30 global health status in both arms did not change over the 12 weeks. • Total scores of DLQI worsened in both arms over time.
Jatoi et al. (2008)	RCT	All ($N = 61$)	All	Tetracycline ($n = 31$) vs. Placebo ($n = 30$)	Skindex-16	• By week 4, physician-reported grade 2 skin rash occurred in 17% of tetracycline arm and in 55% of placebo arm ($p = .04$) • Tetracycline-treated patients reported better scores such as skin burning or stinging, skin irritation. (+4 weeks) • Tetracycline arm had positive effects on physical subdomains but had negative effects on emotion scores (+8 weeks)
Jatoi et al. (2010)	RCT	ColorectalLung ($N = 110$)	PanitumumabCetuximabErlotinib	Sunscreen ($n = 54$) vs. placebo ($n = 56$)	Skindex-16	• No significant differences in skin rash severity between 8 weeks in both arms. • QoL scores declined for 8 weeks but remained comparable between arms. • Patients reported >30% drop in QoL with respect to itching and burning/stinging over time. • Patients reported >30% change to indicate worry and embarrassment about their skin condition.
Joshi et al. (2010)	Cross-sectional	All ($N = 67$)	All		Skindex-16	• The highest scores were for the emotions domain, which was significantly higher than the functioning domain but not different from the symptoms domain. • There was significant difference between patients aged ?50 years and patients aged >50 years with regard to all domains and overall score; younger patients had higher scores.

(Continues)

TABLE 5 (Continued)

Author/ year	Research design	Indication/(samples)	EGFR inhibitors	Skin treatment	QoL instruments	Main findings
Koukakis et al. (2016)	RCT	Colorectal ($N = 485$)	Panitumumab (+FOLFOX) vs. (+FOLFIRI) vs. (+BSC)		EQ-5D	• No significant differences in QoL outcomes between patients with worst skin toxicity grade <3 and those with grade >3.
Kripp et al. (2017)	RCT	Colorectal ($N = 80$)	Panitumumab	Prophylactic erythromycin ointment 2% followed by doxycycline ($n = 39$) vs. prophylactic doxycycline ($n = 41$)	EORCT QLQ C-30DLQI	• Patients in the erythromycin arm suffered from skin toxicity of grade ≥2 vs. in the standard arm. • The mean values of global health score amount to 59 in the erythromycin arm and declined to 47 points in the doxycycline arm (at the beginning of cycle 4). • No relevant differences between both arms were noticed as per the DLQI. • In the DLQI subscale, "symptoms and feelings" deteriorated over time.
Lacouture et al. (2010)	RCT	Colorectal ($N = 95$)	Panitumumab	Pre-emptive treatment (skin moisturizers, sunscreen, topical steroid, and doxycycline) ($n = 48$) vs. reactive treatment (physician determined) ($n = 47$)	DLQI	• Incidence of grade ≥2 skin toxicities were decreased with preemptive vs. reactive skin treatment. • QoL was less impaired in the pre-emptive group compared with the reactive group. • Mean DLQI changes in score from baseline at week 3 for patients in the pre-emptive and reactive groups were 1.3 points and 4.2 points.
Láng et al. (2013)	Cohort study	Colorectal ($N = 627$)	Cetuximab (+FORFIRI) vs. FOLFIRI		EORTC QLQ-C30	• No significant differences for GHS/QoL ($p = .12$) and social functioning scores ($p = .43$) between the cancer treatment arms. (+8 weeks)
Osio et al. (2009)	Cross-sectional	Colorectal Lung ($N = 16$)	PanitumumabCetuximabErlotinib		DLQI	• Two patients, DLQI score was more than 10 points. • DLQI evaluation showed a moderate to strong impact on QoL in 25% patients. (DLQI scores between 6 and 20).
Peeters et al. (2009)	RCT	Colorectal ($N = 463$)	Panitumumab (+BSC) vs. BSC		mDLQIEQ-5DEORTC QLQ-C30	• The minimum post-baseline observed value for the mDLQI was inversely correlated with the median post-baseline observed value for

(Continues)

TABLE 5 (Continued)

Author/ year	Research design	Indication/(samples)	EGFR inhibitors	Skin treatment	QoL instruments	Main findings
						the EQ-5D index ($p = .0003$) and the EQ-VAS. (+4 to 8 weeks) • A nonsignificant trend for an inverse correlation between mDLQI and EORTC QLQ-C30 global health status/QoL scale (+4 to 8 weeks)
Pinto et al. (2016)	Cohort study	Colorectal ($N = 225$)	Cetuximab (+chemotherapy)	Prophylactic ($n = 160$) vs. reactive ($n = 37$) vs. usual clinical practice ($n = 28$)	DLQIEORTC QLQ-C30	• DLQI scores increased at the first post-baseline visit, which corresponds to a small effect in both arms for skin treatment in prophylactic and reactive. • Reactive skin treatment arm had lower QoL than prophylactic arm. • EORTC QLQ-C30 scores decreased for all functional scales, including GHS/QoL, indicating slight worsening during chemotherapy combined with cetuximab (+8 weeks).
Romito et al. (2010)	Cross-sectional	Colorectal ($N = 80$)	Cetuximab		FACT-C	• Psychological distress and social avoidance were not correlated to skin rash, but only to QoL. • Fact-C subscales (physical, social/familiar, emotional, functional, additional concerns) were measured to understand which factor was more strongly correlated with psychological distress.
Rosen et al. (2013)	Cross-sectional	All ($N = 237$)	All		Skindex-16	• Significant differences between patients treated with targeted vs. non-targeted therapy with regard to total Skindex-16 ($p = .02$) and emotion subdomain ($p = .02$) scores were observed. (+3 months) • Patients who experienced skin rash and pruritus had higher Skindex-16 scores in symptom ($p < .001$), emotion ($p = .01$), and function ($p = .001$) subdomains than patients without this adverse event.

(Continues)

TABLE 5 (Continued)

Author/ year	Research design	Indication/(samples)	EGFR inhibitors	Skin treatment	QoL instruments	Main findings
Siena et al. (2016)	RCT	Colorectal ($N = 1,183$)	Panitumumab (+FOLFOX) vs. FOLFOX		EQ-5D	• 38% of patients receiving panitumumab +FOLFOX4 and 2% of patients receiving FOLFOX4 alone experienced grade 3+ skin toxicity. • No significant differences in QoL outcomes in patients with grades 0–2 skin toxicity and those with grade 3+ skin toxicity.
Sommeijer et al. (2014)	RCT	Colorectal ($N = 572$)	Cetuximab vs. BSC		EORTC QLQ-C30	• Changes in global health status from baseline to week 8 and 16 did not differ between patients with grade 0/1 rash and grade 2+. • No consistent trend was observed for the association of severity of rash and quality of life.
Thaler et al. (2012)	Cohort study	Colorectal ($N = 154$)	Panitumumab (+FOLFIRI)		EQ-5DEORTC QLQ-C30	• Objective responses occurred more commonly in patients with grade 2+ skin toxicity (56%) than in those with grade 0/1 toxicity (29%). • EQ-5D health state index and health rating scores between the two skin toxicity groups (grade 0/1 or 2+) were not statistically significant. • EORTC QLQ-C30 global health status scores or functioning and symptoms scores remained stable throughout the study. (+8 weeks).
Tischer et al. (2018)	Cross-sectional	ColorectalHead and neckLungPancreatic ($N = 195$)	All		Original	• Dermatologic adverse events had an impact on social–emotional and functional aspects of patients' lives. • Female patients reported significantly more often than males that dermatologic adverse events had an emotional or social impact.
Unger et al. (2013)	Cohort study	Colorectal ($N = 40$)	Cetuximab (+chemotherapy) vs. chemotherapy		Original	• General QoL and HRQoL scores were continuously decreasing from baseline to course III (after 85 days) but no significant main effect of time in both groups. • The severity of the skin reactions had a significant influence on HRQoL.

(Continues)

TABLE 5 (Continued)

Author/year	Research design	Indication/(samples)	EGFR inhibitors	Skin treatment	QoL instruments	Main findings
Vaccaro et al. (2016)	Case series	Colorectal ($N = 12$)	Cetuximab	Clindamycin phosphate 1.2%-benzoyl peroxide 5% gel	DLQI	• A clindamycin phosphate-benzoyl peroxide gel may be an effective in skin treatment of cetuximab-associated acneiform eruptions. • DLQI values decreased 13.64 ± 2.01 before skin treatment to 6.45 ± 1.37 after 8 weeks.
Yagasaki et al., 2018	Cross-sectional	LungColonPancreatic ($N = 34$)	ErlotinibOsimertinibAfatinibOthers		DLQI	• Mean DLQI score was 4.59 indicating a small effect on a patient's life. • The symptom and feelings domains showed the highest scores among DLQI domain scores.
Yamaguchi et al. (2017)	Cohort study	Colorectal ($N = 351$)	Cetuximab (+FOLFIRI) vs. FORFIRI		EORTC QLQ-C30	• Skin reaction had an influence on GHS/QoL and social functioning from baseline to week 8.

Abbreviations: BSC, best supportive care; DLQI, dermatology life quality index; EORCT QLQ C-30, The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30; EQ-5D, EuroQol-5D; FACT-C, functional assessment of cancer therapy-colorectal; FACT-EGFR-18, functional assessment of cancer therapy-epidermal growth factor receptor-18; FACT-G, functional assessment of cancer therapy-general; FOLFIRI, Folinic acid + Fluorouracil + Irinotecan; FOLFOX, Folinic acid + Fluorouracil + Oxaliplatin; GHS/QoL, the Global Health Status/quality of life; HRQoL, health-related quality of life; RCT, randomized controlled trials; SF-36, Short-Form Health Survey.

cancer patients. In all but one of these studies, skin toxicities affected patients' QoL (Clabbers et al., 2015; De Tursi et al., 2017; Jatoi et al., 2008; Kripp et al., 2017; Rosen et al., 2013; Unger et al., 2013; Yagasaki et al., 2018). One study showed deterioration of QoL due to high degrees of skin toxicity, and severe pruritus had greater effects on QoL scores than papulopustular eruptions or xerosis. This study also shows that patients above 81 years of age suffer greater impacts on the physical domain than those aged between 61 and 70 years (Clabbers et al., 2015). The results of intervention studies on the use of antibiotic oral medications and ointment for the treatment of skin toxicities show that three out of four were effective (Deplanque et al., 2016; Jatoi et al., 2008; Vaccaro et al., 2016). Furthermore, in the management of prophylactic point of view for skin toxicities, studies were conducted in which vitamin K1 cream (Hofheinz et al., 2018), erythromycin (Kripp et al., 2017), and sunscreen (Jatoi et al., 2010) have been added to the recommended skin management. Some of these studies have been shown to reduce the extent of skin toxicities.

3.5 | Emotional and social domains of QoL

In studies relating skin toxicities to emotional and social domains of QoL, cancer patients receiving EGFRIs had deficiencies in scores of the emotion domain (De Tursi et al., 2017; Jatoi et al., 2008; Joshi et al., 2010; Kripp et al., 2017; Rosen et al., 2013; Tischer et al., 2018; Yagasaki et al., 2018; Yamaguchi et al., 2017). Although effects on social domains were similar between studies (De Tursi et al., 2017; Tischer et al., 2018; Yamaguchi et al., 2017), only one study reported no changes in QoL (Láng et al., 2013). Finally, decrements in emotional and social domains were proportional to the degree of skin toxicity (Rosen et al., 2013), and women suffered greater emotional and social adversities than men (Tischer et al., 2018). However, there has been no research from the viewpoint of how much emotional and social aspects of QoL improves by intervention research in the treatment of skin toxicities.

4 | DISCUSSION

4.1 | Suggestions for nursing practice

The aim of this literature review was to summarize the relationship between skin toxicity and QoL in cancer patients receiving EGFRI treatments. Some studies

suggest that overall well-being of cancer patients with skin toxicity decreases with time. Although studies of overall well-being report differing results, declines in QoL were consistent across functional areas of physical, emotional, social, and symptom domains.

Differences in reported changes in overall well-being and reductions in health conditions may reflect varying skin toxicities and deterioration of symptoms between studies. Several studies show that the incidence and severity of skin toxicities are correlated with therapeutic effects (Bonner et al., 2010; Peeters et al., 2009; Wacker et al., 2007), suggesting that health conditions are supported by patient awareness that the efficacy of cancer treatments is related to the incidence of the skin toxicities. As suggested by Charles et al. (2016), the perception that cancer treatment efficacy is related to the impact of skin toxicity independently affects QoL. In this regard, overall well-being may be maintained by explaining to patients that skin toxicity and therapeutic effects are related from the start of cancer treatment.

Because declines in QoL have been observed in all functional areas, it is critical that patients strengthen self-care and continue skin management so that pruritus does not become severe. Severe pruritus has a large influence on physical and symptom components of QoL scores, and these influences may spread to emotional and social aspects. In addition, in this study, there was only one article in which the therapeutic agent was EGFR tyrosine kinase inhibitors; therefore, we did not conduct a review comparing anti-EGFR monoclonal antibodies. However, because previous research has shown that skin rash appears to be more severe in anti-EGFR monoclonal antibodies than in EGFR tyrosine kinase inhibitors (Sipples, 2006), cancer patients who receive anti-EGFR monoclonal antibodies may have a lower QoL with respect to physical aspects. Moreover, among elderly patients, physical aspects were more prevalent, and these patients are at higher risk of poor self-management due to various functional shortcomings and complicated social backgrounds. In addition, moisture contents of skin decrease naturally with aging, and the resulting dry skin likely exacerbates the symptoms of skin toxicity. Thus, it is necessary to provide information and support for emotional and social aspects in addition to physical and symptomatic aspects. Some of the studies included in this review suggest that skin toxicities affect emotional and social parameters (De Tursi et al., 2017; Joshi et al., 2010; Rosen et al., 2013; Tischer et al., 2018; Yamaguchi et al., 2017), and the specific quantitative influence of skin toxicity on these is an important area of enquiry. In the question items on emotional and social aspects in DLQI (Finlay & Khan, 1994), Skindex29 (Chren, Lasek, Flocke, & Zyzanski, 1997), and Skindex16 scales (Chren, Lasek, Sahay, & Sands, 2001), which were frequently used in the present studies were embarrassment and changes in human relations, and concerns about deteriorating symptoms. QoL was low in patients under 50 years of age, suggesting that patients who engage daily in social activities suffer more from skin toxicities, and this tendency was stronger in women. In particular, QoL reportedly decreases more with higher severity of pruritus. Persistence of pruritus leads to irritability, which may affect emotional parameters. Thus, improvements in emotional parameters of QoL can be expected following appropriate management of skin toxicity.

The results from this literature review indicate that although all aspects of QoL decrease due to skin toxicity, patients receiving EGFRI treatments can maintain overall health conditions by recognizing the correlation between skin toxicity and therapeutic effects. In addition, as shown in the intervention studies on the treatment of skin toxicities, it is important to continue prophylactic skin management to prevent the severity of symptoms from the start of cancer treatment to minimize the decrease in terms of physical and symptom aspects. Further clarification of the skin conditions that influence QoL components in elderly people and women may inform supporting interventions that can reduce the impact on QoL.

4.2 | Issues of future research

In this review, we discuss research trends in the area of EGFRI-mediated skin toxicity and QoL. Efforts to maintain QoL in patients using EGFRIs can help to sustain therapy for as long as possible. Thus, assessments of the effects of molecular-targeted agents on QoL are crucial for optimizing outcomes. The present studies collectively indicate that skin toxicity affects QoL, although various gaps in knowledge remain. In the context of nursing practices, further studies are necessary to define the precise QoL components that are subject to deterioration, such as physical, psychological, social, and symptomatic aspects so that efforts to maintain and improve QoL can be optimal. Skin toxicities have a high incidence rate and it is difficult to prevent them from appearing. It is important to maintain a physical QoL, because preventing the severity of symptoms improves cancer treatment compliance. In particular, the emergence of severe symptoms of grade 3 or higher in the NCI-CTCAE classification may interfere with the continuous treatment of cancer and oral treatment compliance (Boone et al., 2007); therefore, it is necessary to investigate QoL evaluation in skin

toxicities of grades 0–2 in more detail. Moreover, few studies investigate the long-term effects of EGFRIs in patients, and most report effects over the cancer treatment period of 4–12 weeks, with inconsistent durations, as previously stated (Charles et al., 2016). Although characterization of skin toxicities is worthwhile from the outset, some patients continue EGFRI treatments for a long time, warranting study durations of about 1 year. Furthermore, treatment combinations with other cytotoxic chemotherapies likely contribute a broader range of adverse events that affect QoL. The present results may also vary with degrees of tumor progression and differences in therapeutic drugs.

Finally, skin toxicities are generally investigated in terms of skin rash, xerosis, pruritus, and paronychia, whereas other skin symptoms have been reported in patients, including hair growth abnormalities such as alopecia and trichomegaly (Potthoff et al., 2011). Patients with these symptoms likely suffer greater impacts on QoL, especially in terms of emotional and social parameters. These skin toxicities are compulsory subjects of future studies.

The results from this study indicate that continuous prophylactic self-skin management by cancer patients helps maintaining QoL in terms of physical and symptom aspects, leading to compliance with cancer treatment, which contributes to the improvement of survival prognosis. In addition, it is necessary not to reduce the emotional and social QoL by practicing the assessment of skin toxicities and individualized treatment in the medical team.

5 | CONCLUSIONS

Among cancer patients with skin toxicities due to treatments with EGFRIs, some do not suffer reductions in overall well-being with cancer treatments; however, QoL decreases have been reported in all areas, as indicated by physical, emotional, social, and symptomatic measures. Support is required for emotional and social influences of skin toxicity, in addition to those relating to physical declines, and the required support will vary depending on age and gender, and according to experiences of pain. The results from this literature review indicate the need for more studies of pain due to skin toxicities in elderly patients, and in younger patients with active social lives. In addition, changes of QoL over the long term need to be investigated, particularly to improve the understanding of typical symptoms of skin toxicity, such as skin rash, xerosis, pruritus, and paronychia, and in terms of characteristic adverse events such as hair growth abnormalities.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Conception and design of this study by K. H. and M. C.; published work search and data analysis by K. H., Y. S. and M. I.; critically reviewed the manuscript by Y. S. and M. Y.

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