

## The Impact of Immune Checkpoint Inhibitors-Induced Skin Toxicity on Patients Quality of Life and the Role of Dermatologic Intervention

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**Key words:** checkpoint inhibitors, skin toxicity, skin rash, quality of life, patient reported outcomes

**Citation:** Kemanetzi C, Lallas K, Lazaridou E, et al. The Impact of Immune Checkpoint Inhibitors-Induced Skin Toxicity on Patients Quality of Life and the Role of Dermatologic Intervention. *Dermatol Pract Concept*. 2024;14(3):e2024118. DOI: <https://doi.org/10.5826/dpc.1403a118>

**Accepted:** January 14, 2024; **Published:** July 2024

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**Funding:** None.

**Competing Interests:** None.

**Authorship:** All authors have contributed significantly to this publication.

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**ABSTRACT Introduction:** Data regarding quality of life (QoL) of oncologic patients experiencing dermatologic immune-related adverse events (dirAEs) and their course after dermatologic intervention are scarce.

**Objectives:** To assess the impact of dirAEs on patients QoL and to investigate the correlation between dermatologic and oncologic indexes used for estimating QoL.

**Methods:** We enrolled oncologic patients with dirAEs managed in two supportive onco-dermatology outpatient clinics in Greece. Patient-reported outcomes included DLQI, EORTC-QLQ-C30 and Numerical Rating Scale for pruritus (pNRS).

**Results:** Overall, 110 patients were enrolled in the study. Mean (standard deviation) DLQI and pNRS scores were 15.54 (5.44) and 7.25 (2.95), correspondingly, while functional, symptom and summary scores of EORTC-C30 were 79.17 (2.11), 17.66 (3.60) and 80.67 (3.08), respectively. After therapeutic interventions, there was a statistically significant decrease in DLQI scores after first intervention compared to baseline, and second intervention compared to first (mean decrease 4.38 (2.91),  $P < 0.001$  and 5.16 (3.99),  $P < 0.001$ , respectively). DLQI showed no correlation with global health status/QoLs ( $\rho$  0.01,  $P = 0.90$ ) of EORTC-C30.

**Conclusions:** DirAEs negatively affect QoL. Dermatologic intervention improves patients QoL, facilitating an unimpaired oncologic treatment. Poor correlation between DLQI and EORTC-QLQ-C30 highlights the need for adapted QoL measurement tools in the context of immune checkpoint inhibitors treatment.

## Introduction

The introduction of immune checkpoint inhibitors (ICIs) (CTLA-4, PD-1, PD-L1) in the therapeutic armamentarium of oncologists was a major breakthrough in cancer therapy. Due to their unique mechanism, ICIs induce a new spectrum of adverse events that are described with the term immune related adverse events (irAEs) and practically represent a class effect of these drugs. Among them, dermatologic irAEs (dirAEs) are the most common, affecting up to 50% of treated patients [1-5].

DirAEs include eczematous, lichenoid and psoriasiform-rashes, pruritus, vitiligo-like rash, auto-immune bullous diseases-like rash, as well as other less common skin toxicities [2,3,5-7]. Importantly, cumulative data suggest that development of certain skin toxicities linked to a better oncologic outcome, as indicated by the longer progression-free and overall survival in these patients [8-10].

The Quality-of-Life (QoL) Index is a multidimensional concept that describes the impact of a person health status on QoL. It involves many aspects of life, including physical and mental health [11,12]. From the limited available literature data, it appears that skin toxicities triggered by ICIs have a significant impact on patients QoL. The use of tools evaluating QoL and the collection of patient-reported outcomes (PROs) before and after therapeutic interventions, is of paramount importance in modern medicine. PROs reflect patients needs and their perspective regarding treatment outcome and should be considered in treatment decision-making [13].

The Dermatology Life Quality Index (DLQI) is a 10-question questionnaire used to gauge the impact of skin diseases on the patients QoL. Each question receives a score from 0 ("not at all") to 3 ("very much"). The sum gives the total score that ranges from 0-30. A score over 10 indicates that the patient QoL is being severely affected by the skin disease [14-15].

The numerical rating scale for pruritus (pNRS) is a widely used ten-point numerical scale, in which 0 represents "no" itch and 10 represents "maximum" itch.

The EORTC-QLQ-C30 is a specialized questionnaire, developed in 1988 to capture the QoL of oncologic patients. It includes 9 sections: 5 functional sections (physical condition, posture, perceptual ability, emotional and social functioning), 3 symptom-related sections (fatigue, pain and nausea) and 1 section regarding the patient general health status (GHS) [11,12]. Scores range from 0 to 100, with a 10-point score shift corresponding to a clinically meaningful change [16]. A high score in functional scales suggests a high/healthy level of functioning, which translates to a higher overall health status/QoL. In contrast, a higher score on a physical symptom scales indicates a higher level of problems [17].

## Objectives

In this study we aimed to record the impact of dirAEs on patient QoL, using DLQI, pNRS and EORTC-QLQ-C30 and the modification of these scores after therapeutic interventions by specialized dermatologists. We also attempted to correlate baseline patients and toxicity characteristics with QoL. Furthermore, we tested the correlation between the dermatology QoL index and EORTC-QLQ-C30, in order to clarify whether the latter can adequately capture the QoL impairment induced by skin toxicity.

## Methods

The study was conducted in two supportive onco-dermatology outpatient clinics in Greece. Oncologic patients who developed dirAEs from July 2020 to July 2022 and were referred for dermatologic consultation were enrolled for the aims of the study. The study received approval from the Institutional Ethical Committee (6296/01-Jul-2020)

and it was conducted in accordance with the provisions of Helsinki Declaration and good clinical practice guidelines. All participants provided written informed consent before undergoing any procedure related to the study. Inclusion criteria were age >18 years and the appearance of at least one dirAEs due to ICIs. Exclusion criteria were co-morbidities and co-medications that could result in development of skin rashes similar to dirAEs, as well as individuals who did not have adequate level of Greek language, or were mentally and physically unable to complete the questionnaires.

The patients first visit included the clinical assessment of the skin rash, the evaluation of its severity based on the CTCAE v4.0 criteria, the completion of the DLQI, pNRS and EORTC-QLQ-C30 questionnaires and the administration of treatment according to standard clinical practice [18,19]. IrAEs, including dirAEs, were recorded during follow-up visits, scheduled at 4 and 12 weeks from baseline. During the follow-up visits, the severity of irAEs based on CTCAE was evaluated and EORTC-QLQ-C30, DLQI, and pNRS were collected. Additional recorded data included the evolution of the underlying neoplasm and the impact of the dermatologic adverse event on the oncologic treatment. Topography of the rash was documented with the use of digital imaging at baseline and follow-up visits.

## Statistics

A descriptive analysis with mean and standard deviation for continuous variables and frequencies for categorical was conducted. Following normality considerations, Mann-Whitney t-test (or ANOVA Kruskal-Wallis) and Wilcoxon rank test were used for comparisons in unpaired and paired variables, respectively. In order to investigate possible correlation among QoLs scores, Spearman rho was preferred. Also, for DLQI and pNRS, a change in score  $\geq 4$  was considered as clinically significant, while for global health and Summary score the change was set  $\geq 10$ .<sup>20,21</sup> Moreover, linear mixed models were used to evaluate the change of QoLs after therapeutic interventions and to compare change in score between patients with and without pruritus. All statistical

tests were two-sided,  $P < 0.05$  was considered significant and the analysis was conducted with the Statistical Package for Social Sciences statistical software (version 28.0, IBM SPSS Statistics for Windows).

## Results

### Demographic and Baseline Characteristics

Overall, 110 patients with a mean age of 67 years (range 37-86) who received ICIs for various oncologic indications were included in the analysis. The most common type of primary cancer was NSCLC (53 patients, 48.2%) followed by melanoma (25 patients, 22.7%). Most of the patients were treated with anti-PD1 (93 patients, 84.5%). The epidemiological and clinical characteristics of the patients at baseline can be found in the supplement table.

The most prevalent dirAE was psoriasis-like rash (35 out of 110, 31.8%), followed by eczema-like rash (22 patients, 20%) and pruritus (15 patients, 13.6%). Fifteen individuals experienced two different types of dirAE. The most common dirAE in the latter group was vitiligo (6 out 15 patients, 5.5%).

### Responsiveness Analysis

At baseline, mean (standard deviation, SD) DLQI score was 15.54 (5.44), pNRS was 7.25 (2.95), while functional, symptom and summary scores of EORTC-C30 were 79.17 (2.11), 17.66 (3.60) and 80.67 (3.08), respectively. After therapeutic interventions, there was a statistically significant decrease in DLQI scores between the first intervention compared to baseline, and between the second intervention compared to the first [mean (SD) decrease 4.38 (2.91),  $P < 0.001$  and 5.16 (3.99),  $P < 0.001$ , respectively]. The same statistically significant difference was seen for pNRS scores after each intervention (Table I). Regarding Summary score of EORTC-C30, a significant increase in mean scores was detected after the first (mean increase 1.34 (2.64),  $P < 0.001$ ) and the second intervention (mean increase 0.96 (2.26),  $P < 0.001$ ), but the same significant association was not detected for functional

**Table 1. Mean of main QoLs scores and their change after each intervention.**

	Baseline	1 <sup>st</sup> intervention	P	2 <sup>nd</sup> intervention	P
DLQI	15.54 (5.44)	11.15 (6.07)	$P < 0.001$	5.99 (4.70)	$P < 0.001$
Global health-QoL	59.16 (13.4)	65.90 (10.1)	$P < 0.001$	66.4 (9.71)	$P = 0.47$
pNRS	7.25 (2.95)	5.25 (3.11)	$P < 0.001$	3.47 (2.79)	$P < 0.001$
Functional score	79.17 (2.11)	79.04 (1.85)	$P = 0.46$	79.07 (1.95)	$P = 0.98$
Symptom score	17.66 (3.60)	16.1 (3.56)	$P < 0.001$	14.6 (3.99)	$P < 0.001$
EORTC-QLQ-C30 Summary score	80.67 (3.08)	82.01 (2.33)	$P < 0.001$	83.0 (2.59)	$P < 0.001$

DLQI = Dermatology Quality of Life Index; pNRS = numerical rating scale for pruritus; QoL = Quality-of-Life.

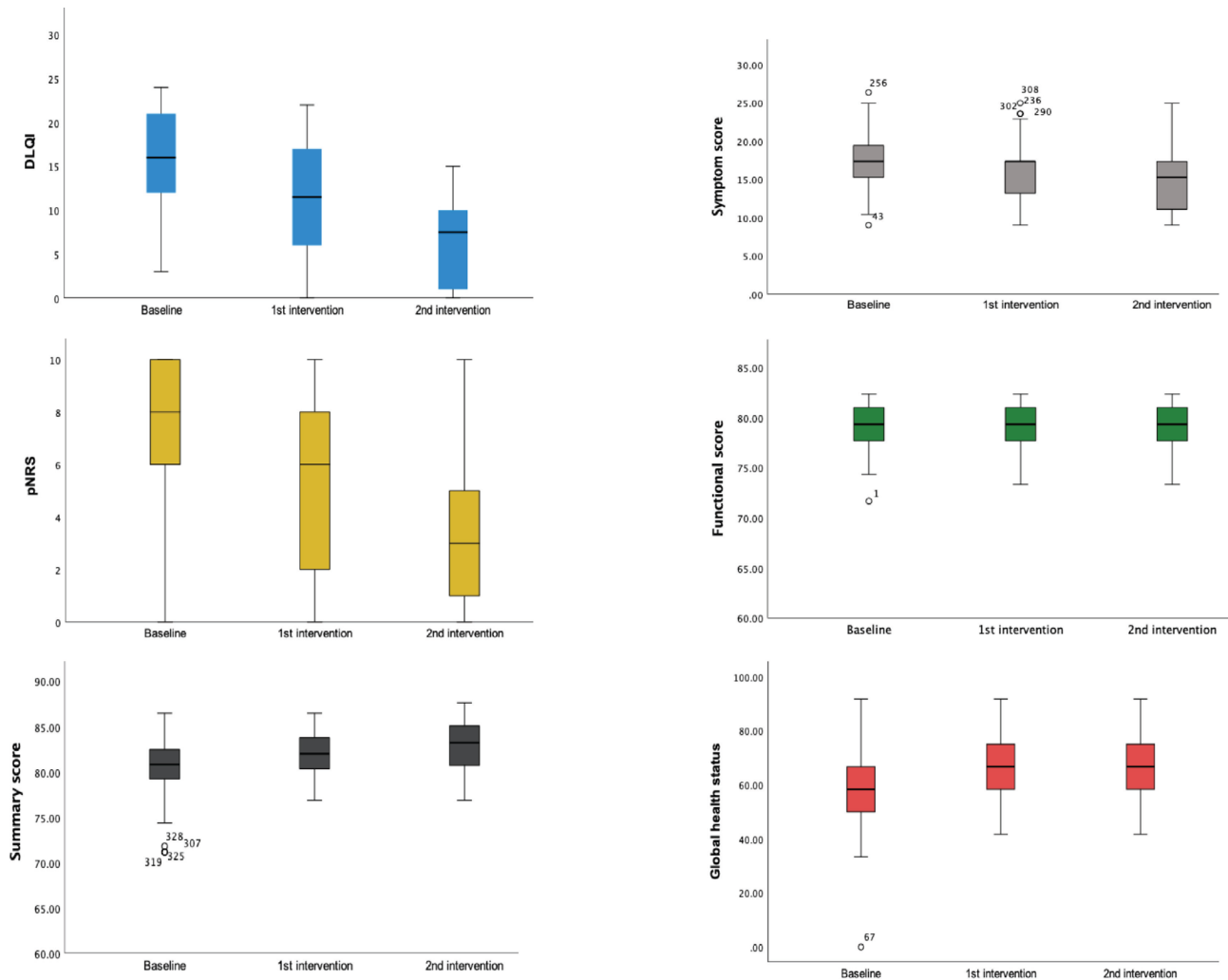


Figure 1. Boxplots demonstrating QoL scores at baseline and after first and second intervention.

### Barplots with change of QoL scores between baseline and after treatment

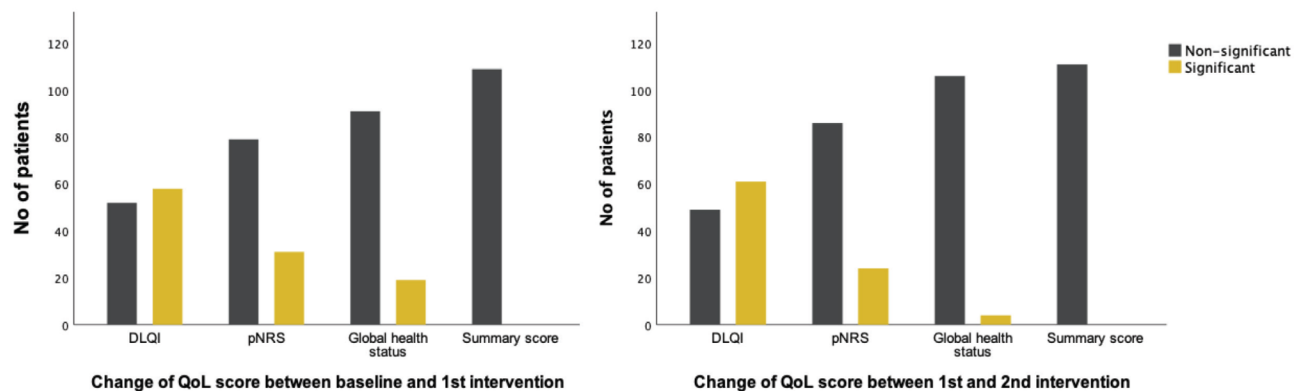
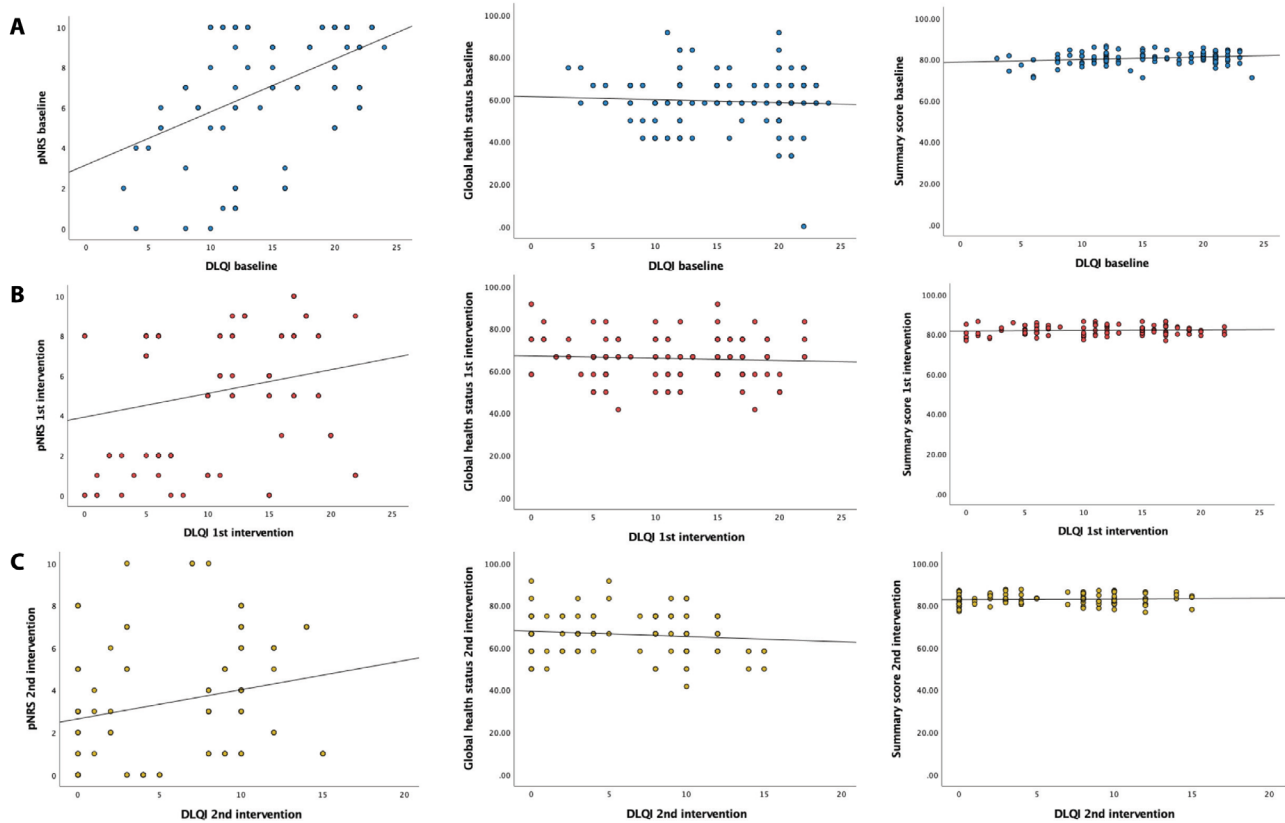


Figure 2. Barplots showing significant and non-significant changes in quality of life scores after each intervention.

symptoms (Table 1). Also, global health status/QoLs significantly change only after first intervention (Figure 1).

As regards to a change in DLQI score  $\geq 4$  and pNRS score  $\geq 4$  (thresholds that are widely considered as clinically meaningful changes) 58 (52.7%) and 31 (28.2%) individuals achieved this level of response in DLQI and pNRS, accordingly after the first intervention, respectively. These rates

further increased after the second intervention, as compared to first. On the other hand, considering the global QoL score, a significant change was detected in 19 patients (17.3%) after the first and in 4 (3.6%) patients after second intervention. Based on Summary score, that change was found in 2 (1.8%) patients after second intervention as compared to baseline (Figure 2).



**Figure 3.** Scatterplots showing the correlation between Dermatology Life Quality Index and Numerical Rating Scale for pruritus, Global health status and Summary score a) at baseline, b) after 1<sup>st</sup> intervention and c) after 2<sup>nd</sup> intervention.

**Table 2.** Correlation analysis between DLQI and other QoL scores.

	Baseline		1 <sup>st</sup> intervention		2 <sup>nd</sup> intervention	
	Rho	P	Rho	P	Rho	$\nu$
DLQI						
Global Health	0.012	0.90	-0.056	0.56	-0.129	0.17
pNRS	0.441	<0.001	0.227	0.02	0.260	0.01
EORTC-QLQ-C30 Summary score	0.197	0.04	0.064	0.50	0.066	0.49
Functional scale	-0.140	0.14	0.056	0.56	-0.061	0.52
Symptom scale	-0.177	0.06	-0.047	0.62	-0.074	0.44

DLQI = Dermatology Quality of Life Index; pNRS = numerical rating scale for pruritus; QoL = Quality-of-Life.

### Correlation Analysis

At baseline, DLQI and pNRS were moderately correlated ( $\rho$  0.44,  $P < 0.001$ ), while DLQI showed weak correlation with summary score of EORTC-C30 ( $\rho$  0.19,  $P = 0.04$ ), functional ( $\rho$  -0.14,  $P = 0.14$ ) and symptom scores ( $\rho$  -0.17,  $P = 0.06$ ), and no correlation with global health status/QoLs ( $\rho$  0.01,  $P = 0.90$ ) (Figure 3). After the first and the second intervention, a weak correlation between DLQI and pNRS remained ( $\rho$  0.20,  $P = 0.02$  and  $\rho$  0.23,  $P = 0.01$ , respectively), whereas summary score, functional or symptoms scores were not correlated with either DLQI or pNRS (Table 2).

### QoLs Scales and Baseline Characteristics

QoLs scores did not significantly differ in terms of gender, number of doses and personal history of skin disease. The mean (SD) BSA of the patients was 0.41 (0.18) and was not significantly correlated with either QoL scores at baseline. Moreover, individuals experiencing dirAE of higher grades at baseline had more impaired DLQI, pNRS and Summary score as compared to those with lower grades. Analytically, patients with grade 4 toxicities had mean DLQI, pNRS and Summary score 20, 10, 81.2 respectively, while for grade 1 toxicities the corresponding scores were 13, 4.57 and 79.8. There was a significant correlation between age and pNRS

score at baseline, with an increase of 0.04 in pNRS for every added year of age ( $b = 0.04$ , 95% confidence interval [CI] 0.005 – 0.08). Regarding type of primary cancer, there was a statistically significant difference in pNRS and global health QoLs, and from pairwise comparisons, patients with melanoma had a significantly lower mean pNRS score at baseline, compared to patients with head and neck SCC (mean difference 2.82,  $P = 0.03$ ) and a higher mean Global health QoLs, respectively.

In relation to type of ICI treatment, patients treated with combination therapy had higher DLQI score at baseline (mean DLQI 22.0) compared to patients treated with anti-PD1 (mean 15.1 [5.57],  $P = 0.001$ ) and patients treated with anti-PDL1 (mean 15.9 [3.18],  $P = 0.002$ ).

### Analysis for Patients with Pruritus

Patients with pruritus had a higher mean baseline DLQI (mean 20.27 [3.06]) and pNRS score (mean 8.93 [1.16]) compared to all other individuals (Mann-Whitney t-test,  $P < 0.001$  and  $P < 0.034$ , respectively). All other scores, including summary EORTC-C30, functional and symptom scales and global health, did not significantly differ in patients with pruritus, as compared to all other participants. From mixed models, after each intervention, patients with pruritus had higher DLQI score compared to all other patients (4.67, 95%CI 2.07 – 7.28,  $P < 0.001$ ).

DLQI was significantly impaired at baseline, but rapidly improved after adequate therapeutic intervention, as shown in follow-up visits. In a similar manner, pNRS significantly improved from baseline. PNRS moderately correlated with DLQI. Individuals experiencing pruritus reported worse quality of life (higher mean DLQI and mean pNRS compared to all other patients at baseline), highlighting that pruritus is a key symptom in QoL.

## Conclusions

Skin toxicities occur in up to 50% of patients treated with ICIs. However, publications reporting skin-related QoL in this group are lacking. In this study we evaluated the impact of dirAEs on patients QoL, based on DLQI and pNRS in conjunction with EORTC-QLQ-C30, as well as the role of dermatologic intervention towards improvement of QoL. Our main finding was that dirAEs significantly impair patients QoL, with moderate and severe dirAEs resulting in greater impact compared to mild skin toxicities.

Furthermore, we showed that adequate dermatologic intervention improved DLQI and pNRS. In a retrospective cohort study, Chen et al pointed out that patients with dirAEs when managed by dermatologists were less likely to receive systemic immunosuppression and less likely to require ICI discontinuation due to skin toxicity, as compared

to individuals managed by non-dermatologists [22]. The aforementioned observations highlight the crucial role of the dermatologist in early diagnosis and successful treatment of dirAEs, towards improvement of patients status and unimpaired oncologic therapy [22]. In addition, the use of the aforementioned scores was useful in detecting clinically significant changes in QoL after appropriate treatment, in contrast to the EORTC- C30 and the global health status that appeared insufficient to capture changes related to skin QoL.

Data regarding QoL of the oncologic patients treated with ICIs mostly emerge from phase III trials testing efficacy and safety of certain immunotherapies [13,18,23-25]. A meta-analysis assessed the difference in QoL between patients under chemotherapy versus ICIs and found that ICIs are associated with a better QoL and a longer time to clinical deterioration as compared to chemotherapeutics [25]. QoL in the majority of cancer-drugs trials is assessed by oncology-derived, generic questionnaires, such as the EORTC-QLQ-C30. However, ICIs-derived toxicities differ from those traditionally reported with conventional oncologic drugs, rendering the measurement of QoL in the context of ICI treatment particularly challenging. In particular, the impact of cutaneous rash and pruritus that are the most common irAEs, is poorly represented in generic indexes, like SF-36 questionnaire or EORTC-QLQ-C30. Taking into account the aforementioned limitations and considering that real-life data about dermatology QoL of patients experiencing dirAEs are scarce in the literature, we decided to use both, dermatology-derived (DLQI, pNRS) and oncology-derived (EORTC-QLQ-C30) PROs and investigate the correlation between them [13]. Our findings, based on DLQI and pNRS scores, clearly indicate an impairment of patients QoL related to the development of cutaneous adverse events. However, this observation is not clearly reflected in the EORTC-QLQ-C30. Our findings are in line with the conclusions of a systematic review by Frances et al suggesting that data in existing literature regarding the impact of ICIs on health-related QoL do not adequately capture the impact of cutaneous adverse reactions. The latter indicates that conventional oncologic QoL assessment tools like EORTC-QLQ-30, once developed for capturing the impact mostly of chemotherapy, may be insufficient to capture the impact of newer oncologic treatments. Therefore, dermatology derived questionnaires, like DLQI, pNRS, Skindex<sup>7</sup> and ItchyQoL should be integrated in clinical practice to better cover this aspect of QoL. Towards overcoming the aforementioned limitations, adapted measurement scales are being developed to improve the assessment of the impact of these life-changing treatments on patients QoL [13,23,24,27,28].

A significant observation was that pruritus appears to be a decisive factor in most patients perceived QoL. Mean pNRS in our sample was particularly high at baseline and

correlated with DLQI, indicating that pruritus plays a key role in QoL. Given that currently available treatments can only moderately control severe ICI-derived pruritus, the development of new therapeutic interventions, or combined treatment strategies for pruritus, are highly needed.

Interestingly, a recent study showed that regular recording of PROs demonstrated a 5-month overall survival benefit for patients with metastatic solid tumors, as compared to patients receiving standard care [29,20]. The latter highlights the benefits of incorporating tools that adequately capture patients health status in our daily practice and the need of a more patient-centric medicine. Although correlating overall survival with QoL monitoring was not in the aims of the current study, we strongly believe that outlining the patients profile with the use of PROs improves treatment-decision making.

In conclusion, our study confirmed the significant impact of dirAEs on patients QoL and the important role of the dermatologist in managing ICI-derived skin toxicities. Incorporation of dermatology QoL indexes in the context of ICIs treated individuals is expected to better serve towards improved identification of dirAEs impact on patients QoL.

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