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Research article

Characterizing immune checkpoint inhibitor-related cutaneous adverse reactions: A comprehensive analysis of FDA adverse event reporting system (FAERS) database

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ABSTRACT

Background: The increasing adoption of immune checkpoint inhibitors (ICIs) in clinical settings highlights their efficacy in treating diverse conditions, while also emphasizing the potential for common cutaneous adverse reactions to arise. The aim of this study is to investigate a multitude of impacting factors and determinants among patients presenting with ICI-associated cutaneous adverse reactions.

Methods: We conducted a comprehensive analysis of ICI-associated cutaneous adverse reactions using data from the FAERS. Our study spans from January 1, 2015, to March 31, 2023, focusing on ICIs, including anti-PD-1, anti-PD-L1, and anti-CTLA-4 agents.

Findings: Among the 334,293 reported irAR, 17,431 were identified as cutaneous adverse reactions (ARs). Predominant cutaneous ARs included rash (21.01 %), pruritus (11.22 %), and pemphigoid (3.90 %). Stevens-Johnson syndrome emerged as the most reported severe cutaneous adverse reaction (SCAR) (2.08 %). Anti-CTLA-4 agents exhibited higher cutaneous toxicity compared to anti-PD-1 and anti-PD-L1 agents. Anti-PD-1 agents demonstrated an elevated mortality rate. The combined use of ICIs with chemotherapy amplified the risk of SCAR and mortality. Targeted therapy was a risk factor for cutaneous ARs but was associated with reduced mortality. The median onset day for cutaneous toxicity was 21 days, while for SCAR, it was 23 days. Weight and age were identified as predictors of SCAR, cutaneous toxicity, and mortality. Skin cancer increased skin toxicity, while lung cancer heightened SCAR formation. The number of administered ICIs positively correlated with SCAR, skin toxicity, and mortality.

Interpretation: This study highlights the significance of early identification and effective management of cutaneous toxicities, along with personalized follow-up care, as essential strategies for minimizing risks and preventing treatment disruptions.

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1. Research in context

1.1. Evidence before this study

We searched PubMed, Scopus, and Web of Science with keywords including "immune checkpoint inhibitors" and "cutaneous adverse reactions" and their synonyms to evaluate the existing body of literature. Numerous studies have extensively reported cutaneous adverse reactions associated with specific immune checkpoint inhibitors (ICIs) by focusing on individual ICIs or a particular category of ICI, such as PD-1 inhibitors. Furthermore, they predominantly examined isolated aspects of these reactions, like demographics and incidence rates, with limited exploration of multiple dimensions simultaneously, including risk factors, mortality determinants, combined ICI with other treatments, and a comprehensive assessment of clinical impact. The remaining literature has primarily relied on narrative reviews, a limited number of systematic reviews, and meta-analyses predominantly focusing on managing individual skin reactions.

1.2. Added value of this study

Our research significantly contributes to the current literature by emphasizing the need for more comprehensive investigations into ICI-associated cutaneous reactions. Instead of concentrating solely on a single ICI or limited aspects, we adopt a holistic approach by utilizing the FAERS database. We integrate demographic data, incidence rates, onset times, mortality determinants, and the intricate interactions between various ICI and combined treatments. By addressing these factors collectively, we advance the understanding of the clinical impact of cutaneous adverse reactions to ICI and highlight the importance of more comprehensive studies in this field. In contrast to prior studies, our research delves into the roles of targeted therapy and chemotherapy, alongside immunotherapy, in the occurrence of each skin adverse reaction, SCAR development, and mortality. We conducted a comparison among patients receiving varying numbers of ICI, targeted therapy, and chemotherapy. Each group was divided into monotherapy, dual therapy, and triple therapy categories. We stand out as one of the few studies that significantly emphasize mortality as a primary focus. We also employed immune-related adverse reactions as a comparative group to gain deeper insights into individual risk factors for cutaneous adverse reactions and associated mortality rates.

2. Implications of all available evidence

Our findings emphasize the critical need for personalized management of patients undergoing ICI therapies. Individual risk profiles, including patient demographics, prior treatments, and specific cancer diagnoses, must guide therapeutic approaches, especially since different ICI regimens—particularly those combined with chemotherapy or targeted therapies—significantly affect the incidence and severity of irCARs. High-risk groups such as older adults, those with lower body weight, or patients with melanoma, are particularly vulnerable and require vigilant monitoring due to their increased risk of severe reactions and higher mortality rates.

Early intervention is crucial for these high-risk patients, with the initial weeks of treatment being critical for managing potential skin toxicities. The onset of these reactions can vary based on treatment type and patient demographics, such as age, sex, and weight, necessitating tailored monitoring strategies to manage these variables effectively. Our findings provide valuable insights that can guide clinicians in understanding how different factors influence the onset day of adverse reactions. By considering these factors, clinicians can optimize monitoring strategies to ensure timely and effective management of skin toxicities, thereby improving patient care and outcomes.

Management plans should include proactive skincare regimens, immediate dermatological consultation at the first sign of symptoms, and educational sessions to help patients recognize early signs of adverse reactions. These strategies, grounded in a thorough understanding of risk factors and onset patterns, will enable healthcare providers to optimize care and improve outcomes.

Ongoing education for healthcare providers on managing irCARs and continuous research into more effective treatment strategies are essential for advancing patient care in this field. By integrating comprehensive patient data and refining treatment approaches, clinicians can further mitigate risks associated with ICIs.

3. Introduction

Immune checkpoint inhibitors (ICI) present a groundbreaking milestone in facilitating individualized patient care and have been recognized for reconstructing the therapeutic landscape in the field of immuno-oncology [1,2]. ICI are monoclonal antibodies that target cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed cell death 1 (PD-1), or its ligand (PD-L1) by blocking signals that suppress the activity of T cells and promote an anti-tumor immune response [3]. Despite being a new mainstay of cancer therapy, ICI can set a cascade of life-threatening reactions, termed immune-related adverse reactions (irARs), that require further attention [4,5].

Amongst the wide array of adverse reactions that ICI therapy can manifest, cutaneous adverse reactions are one of the most frequently occurring [6]. Most are typically mild to moderate in severity and can be successfully controlled with early diagnosis and supportive treatment [7]. Although rare, certain patients can experience severe cutaneous adverse reactions (SCAR), which involve systemic symptoms and may necessitate the immediate discontinuation of therapy [8]. The existing body of knowledge regarding such cutaneous adverse reactions occurring in combination with ICI therapy, as reported by the FDA Adverse Event Reporting System (FAERS), is limited. Given the multitude of diverse factors that influence the treatment trajectory of patients, early recognition of risk factors can be paramount for successful management, prevention of cutaneous reactions, and enhancement of overall quality of life

[9].

By surpassing expected outcomes, the use of ICIs is anticipated to increase over time [10]. However, the limitations of this constantly progressing field underscore the need for a more comprehensive and structured analysis of specific adverse side effects. To address this gap and provide a broader perspective, we used a vast number of parameters, including demographics, clinical characteristics, onset day, ICI regimen, treatment strategies, and additional therapies alongside immunotherapy to analyze the pool of patients with immune-related cutaneous adverse reactions (irCAR) reported by FAERS concerning all current ICI therapy.

4. Methods

4.1. Data source

In this study, we focused on characterizing the clinical features of irCAR using the FAERS database, which is a publicly accessible database that collects adverse event reports submitted by consumers, healthcare professionals, and drug manufacturers globally, supporting the FDA's post-marketing safety surveillance program. The database includes detailed information such as drug information (DRUG), therapy start and end dates for the reported drug (THER), adverse event terms (REAC), report sources (RPSR), patient demographics (DEMO), outcomes (OUTC), and indications for use (INDI), which facilitates the detection and quantification of drug-associated adverse events. This comprehensive data allows for robust analysis of the clinical features associated with immune checkpoint inhibitors. Input data were downloaded from the public release of the FAERS database, covering the period from January 1, 2015, to March 31, 2023.

We included FDA approved 10 ICI agents, which are anti-PD-1 agents (nivolumab, pembrolizumab, and cemiplimab), anti-PD-L1 agents (atezolizumab, avelumab, and durvalumab), and anti-CTLA-4 agents (ipilimumab and tremelimumab) to retrieve relevant report data of ICI from the FAERS database.

Furthermore, adverse reactions reported in the FAERS database are entered using preferred term (PT) codes derived from the Medical Dictionary for Regulatory Activities (MedDRA). MedDRA is an outcome of collaboration under the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, designed as a detailed and standardized medical terminology. MedDRA is structured into hierarchical levels. The PTs are distinct descriptors for an individual's medical notions, such as symptoms, side effects, and disease diagnosis. These PTs are further organized into higher categories: "high-level terms" (HLTs) and "high-level group terms" (HLGTs), which are ultimately grouped into broader "system organ classes" (SOCs) based on causation, presentation site, or purpose. Differing PTs are grouped into different SOCs. While PTs may be relevant to multiple SOCs due to MedDRA's multiaxiality, each PT is primarily associated with the SOC most relevant to its clinical presentation. In this study, we specifically included adverse reactions categorized under the 'Skin and subcutaneous tissue disorders' SOC, focusing on PTs where this was designated as the primary SOC. The filtered PTs in MedDRA (version 26.0) were obtained and used for the subsequent analysis, thus ensuring that the analyzed PTs were actual cutaneous adverse reactions from a clinical point of view. The PTs selected from the MedDRA and included in this study are provided in Supplementary Table S1. We also employed the standardized MedDRA queries (SMQs) to identify cases related to SCAR from the FAERS database. SMQs serve as predefined search filters that facilitate the systematic extraction of relevant adverse event reports, thereby enhancing the accuracy and specificity of our research findings. These SMQs consist of validated, pre-determined collections of PTs that are compiled following thorough review, testing, analysis, and discussions among experts. The complete list of PTs within relevant SMQs is provided in Supplementary Table S2.

4.2. Data processing procedure

The FAERS database initially yielded 13,283,781 cases. After deduplication, conducted per FDA guidelines, we selected the most recent FDA_DT for identical CASEIDs to ensure that the analysis reflected the latest outcome of each case. This process was necessary because one case can be reported multiple times as its outcome may change over time. By also opting for the higher PRIMARYID when both identifiers matched, we ensured the selection of the most recent report, leaving a total of 11,543,991 unique cases remaining for analysis. These cases collectively reported a total of 33,359,333 adverse events. Inclusion criteria mandated that ICI be listed as the "primary suspect" in the ROLE_COD section. Monotherapy was defined as using a single ICI coded as "primary suspect". This approach was adopted to ensure more precise results, focusing our analysis exclusively on cases where ICIs were identified as the primary contributing factor to adverse events. At the same time, polytherapy was characterized by the concurrent use of multiple ICIs, one of which was classified as "primary suspect" and others labeled as "second suspect" "concomitant" or "interacting" The time intervals between the onset of adverse events (EVENT_DT) and the ICI treatment start date (START_DT) were analyzed for various adverse effects. Reports containing erroneous or inconsistent entries were excluded from the study. Specific exclusion criteria included cases where the event date was recorded as earlier than the start date, cases with erroneous treatment start dates, and reports with implausible or incorrect age or weight data. We further categorized the cases to explore the additional toxic effects of other therapies used alongside ICI. Four distinct groups emerged based on the types of different treatments: Only ICI, ICI plus chemotherapy, ICI plus targeted therapy, and ICI plus chemotherapy and targeted therapy. We sourced the International Nonproprietary Names of the chemotherapies, targeted therapies, and immunotherapies from the WHO Collaborating Centre for Drug Statistics Methodology, specifically under the "L01 ANTINEOPLASTIC AGENTS" class. Supplementary Tables S3 and S4 contain the list of chemotherapies and targeted therapies examined in this study.

Table 1
Demographics and clinical characteristics of patients with adverse reactions following immune checkpoint inhibitor administration reported in the FAERS database.

Clinical characteristics	Total patients (n = 128320)	Patients with cutaneous adverse reactions (n = 13222)	Patients with non-cutaneous adverse reactions (n = 115098)	p-value
Sex				
Male	70560 (62.35 %)	7250 (59.67 %)	63310 (62.68 %)	<0.0001
Female	42559 (37.65 %)	4902 (40.33 %)	37657 (37.32 %)	
Missing	15201	1070	14131	..
Age (years)				
Mean (standard deviation)	64.41 (12.72)	65.03 (12.09)	64.34 (12.79)	<0.0001
Median (min - max)	66 (0–109)	67 (3–97)	66 (0–109)	..
Age Group				
65 years ≥	47364 (55.86 %)	5388 (57.44 %)	41976 (55.64 %)	0.0008
<65 years	37484 (44.14 %)	3992 (42.56 %)	33492 (44.36 %)	
Missing	43472	3842	39630	..
Weight (kg)				
Mean (standard deviation)	71.4 (20.44)	70.22 (21.13)	71.54 (20.35)	0.0002
Median (min - max)	68.6 (0.59–246.4)	67 (20–225)	69 (0.59–246.4)	..
Weight group				
70 kg ≥	18278 (47.90 %)	1706 (43.74 %)	16572 (48.33 %)	<0.0001
<70 kg	19890 (52.10 %)	2194 (56.26 %)	17696 (51.67 %)	
Missing	90152	9322	80830	..
Reporter type				
Healthcare worker	93606 (73.69 %)	9434 (71.76 %)	84172 (73.96 %)	<0.0001
Consumer	33365 (26.25 %)	3717 (28.24 %)	29648 (26.04 %)	
Missing	1349	71	1278	..
Income level by country				
High income	111581 (92.28 %)	12238 (95.94 %)	99343 (92.70 %)	<0.0001
Upper-middle income	7451 (6.16 %)	470 (3.68 %)	6981 (6.52 %)	
Lower-middle and low income	1885 (1.56 %)	47 (0.37 %)	1838 (1.71 %)	
Missing	7403	467	6936	..
Received year				
2023 Q1	6572 (5.15 %)	813 (6.71 %)	5759 (5.01 %)	<0.0001
2022	22348 (17.50 %)	2666 (22.03 %)	19682 (17.15 %)	
2021	19240 (15.07 %)	2108 (17.41 %)	17132 (14.92 %)	
2020	17389 (13.62 %)	1766 (14.59 %)	15623 (13.60 %)	
2019	19067 (14.93 %)	1886 (15.57 %)	17181 (14.96 %)	
2018	16288 (12.75 %)	1635 (13.51 %)	14653 (12.76 %)	
2017	13496 (10.57 %)	1240 (10.24 %)	12256 (10.67 %)	
2016	9364 (7.33 %)	768 (6.34 %)	8596 (7.48 %)	
2015	4540 (3.55 %)	337 (2.78 %)	4203 (3.66 %)	
Missing	16	3	13	..
Indication				
Lung	38942 (35.21 %)	4026 (34.10 %)	34916 (35.17 %)	<0.0001
Skin	22246 (20.11 %)	3335 (28.23 %)	18911 (19.05 %)	
Urogenital	16373 (14.81 %)	1925 (16.31 %)	14448 (14.55 %)	
Gastrointestinal	7238 (6.54 %)	493 (4.17 %)	6745 (6.79 %)	
Hepatopancreatobiliary	5847 (5.29 %)	373 (3.16 %)	5474 (5.51 %)	
Head and neck	4002 (3.62 %)	357 (3.02 %)	3645 (3.67 %)	
Gynecologic	3825 (3.46 %)	424 (3.59 %)	3401 (3.43 %)	
Breast	2823 (2.55 %)	217 (1.84 %)	2606 (2.62 %)	
Hematopoietic and lymphoid	2488 (2.25 %)	192 (1.63 %)	2296 (2.31 %)	
Other thoracic (cardiac, mesothelioma, thymus)	1310 (1.18 %)	121 (1.02 %)	1189 (1.20 %)	
Musculoskeletal	804 (0.73 %)	33 (0.28 %)	771 (0.78 %)	
Central nervous system	993 (0.90 %)	27 (0.23 %)	966 (0.97 %)	
Endocrine	382 (0.35 %)	24 (0.20 %)	358 (0.36 %)	
Other indications	4117 (3.72 %)	341 (2.89 %)	3776 (3.80 %)	
Missing	16930	1334	15596	..
Number of different immune checkpoint inhibitors used				
Monotherapy	107208 (83.55 %)	10538 (79.7 %)	96670 (83.99 %)	<0.0001
Dual therapy	20726 (16.15 %)	2543 (19.23 %)	18183 (15.8 %)	
Triple therapy	286 (0.22 %)	90 (0.68 %)	196 (0.17 %)	
Quadruple therapy or more	100 (0.08 %)	51 (0.39 %)	49 (0.04 %)	
Number of different targeted therapy agents used				
None	113685 (88.59 %)	11325 (85.65 %)	102360 (88.93 %)	<0.0001
One	13409 (10.45 %)	1716 (12.98 %)	11693 (10.16 %)	
Two	1068 (0.83 %)	153 (1.16 %)	915 (0.79 %)	
Three or more	158 (0.12 %)	28 (0.21 %)	130 (0.11 %)	
Number of different chemotherapy agents used				

(*continued on next page*)

Table 1 (*continued*)

Clinical characteristics	Total patients (n = 128320)	Patients with cutaneous adverse reactions (n = 13222)	Patients with non-cutaneous adverse reactions (n = 115098)	p-value
None	112102 (87.36 %)	11533 (87.23 %)	100569 (87.38 %)	0.044
One	4081 (3.18 %)	408 (3.09 %)	3673 (3.19 %)	
Two	10735 (8.37 %)	1161 (8.78 %)	9574 (8.32 %)	
Three or more	1402 (1.09 %)	120 (0.91 %)	1282 (1.11 %)	
Management strategies				
Only immunotherapy	100385 (78.23 %)	10043 (75.96 %)	90342 (78.49 %)	<0.0001
Immunotherapy + chemotherapy	13300 (10.36 %)	1282 (9.7 %)	12018 (10.44 %)	
Immunotherapy + targeted therapy	11717 (9.13 %)	1490 (11.27 %)	10227 (8.89 %)	
Immunotherapy + chemotherapy + targeted therapy	2918 (2.27 %)	407 (3.08 %)	2511 (2.18 %)	
Outcomes of cases				
Non-serious	15595 (12.15 %)	2663 (20.14 %)	12932 (11.24 %)	<0.0001
Serious	112725 (87.85 %)	10559 (79.86 %)	102166 (88.76 %)	
Death	33451 (26.07 %)	1377 (10.41 %)	32074 (27.87 %)	..
Hospitalization	52151 (40.64 %)	5152 (38.97 %)	46999 (40.83 %)	..
Life-threatening	7878 (6.14 %)	737 (5.57 %)	7141 (6.2 %)	..
Disability	2668 (2.08 %)	333 (2.52 %)	2335 (2.03 %)	..
Required intervention to prevent permanent impairment/damage	148 (0.12 %)	21 (0.16 %)	127 (0.11 %)	..
Other serious outcomes	86079 (67.08 %)	8893 (67.26 %)	77186 (67.06 %)	..

The number of cases and their respective percentages are displayed for each category, with the exception of missing data, which is presented solely as the number of cases.

4.2.1. Signal mining

In our study, disproportionality analysis was employed to investigate the potential associations between ICIs and cutaneous adverse events, utilizing the reporting odds ratio (ROR). The ROR measures the likelihood of reporting a specific adverse event for a particular drug compared to all other events, relative to other drugs in the FAERS database. This approach, a cornerstone in pharmacovigilance, helps identify signals that warrant further clinical investigation [11]. Both PTs and HLTs were employed in the ROR analyses. Our methodology involved creating a contingency table that outlines drug-adverse reaction pairs, available for review in Supplementary Table S5. The formula for ROR calculation is shown in detail in Supplementary Table S6. A signal for cutaneous toxicity was considered significant and strongly correlated with ICI therapy if it met two specific criteria: 1) the number of reports on irCAR was not less than three, and 2) the lower limit of the 95 % Confidence Interval (CI) for the ROR (ROR025) was greater than 1. PTs and HLTs that met these conditions were classified as irCAR. Reports featuring these specified cutaneous adverse events were selected for further detailed analysis. Additionally, our disproportionality analysis was chiefly focused on reports involving ICI alone as a treatment strategy. These were then compared with reports that included other treatment combinations: specifically, ICI combined with chemotherapy, ICI combined with targeted therapy, and ICI used in conjunction with both chemotherapy and targeted therapy.

4.3. Statistical analysis

To comprehensively analyze the incidence and clinical characteristics of irCAR, we employed a multi-tiered statistical approach. Our descriptive analysis summarized key patient attributes, including sex, age, weight, country, outcome, year of FDA acceptance, ICI regimen, treatment strategy, and treatment indication, and compared these attributes between two groups: patients with irCAR and those without. In Supplementary Table S7, we delineated the respective income level categories attributed to each country. Chi-square or Fisher's exact tests were utilized for categorical variables in the descriptive analysis, depending on sample size and theoretical frequencies. Specifically, Fisher's exact test was chosen for instances where the sample size was smaller than 4 when at least one cell in a contingency table had an expected frequency of less than 1, or when 20 % of the cells in the contingency table had expected frequencies of less than 5. Otherwise, the chi-square test was employed [12]. For continuous, normally distributed samples, which were age and weight, t-tests were used. Additionally, we employed the Kaplan-Meier estimator to calculate the probabilities of remaining event-free over time until the onset of irCAR. Cumulative distribution curves were used to present these findings and compared using Mann–Whitney tests for dichotomous variables and Kruskal-Wallis tests for more than two independent samples. Interquartile ranges (IQRs) and p-values were also reported. Further, univariate logistic regression analyses were conducted to assess the odds ratios (ORs) for mortality and the occurrence of irCAR and SCARs under various exposures like treatment strategy, regimen, age, weight, sex, and indication. All statistical analyses were conducted using Software R (version 4.3.1), with a significance level set at $p < 0.05$.

5. Results

5.1. Descriptive analysis

A total of 334,293 irAR from 128,320 cases were reported. Of these, 13,222 cases were explicitly related to irCAR, while the remaining 115,098 cases were associated with other types of ARs. Comprehensive demographic and clinical characteristics of these

cases are presented in Table 1.

Sex-based differences were observed in the frequency of irCAR, with males representing a more significant proportion (59.67 %) than females (40.33 %). However, this difference was less pronounced when comparing the frequency of male patients among patients with other ARs. (59.67 % vs. 62.68 %, $p < 0.0001$). Age-wise stratification revealed that patients aged 65 years and above were more prone to reporting irCAR (57.44 %) than other types of ARs (55.64 %) ($p = 0.0008$). Among the patients with irCAR, the majority had indications for lung cancer (34.10 %), skin cancer (28.23 %), and urogenital cancer (16.31 %). The prevalence of irCAR varied depending on the indication site ($p < 0.0001$) (Table 1).

The majority of patients (79.7 %) received ICI monotherapy, while 19.23 % were on dual ICI therapy. Triple therapy was

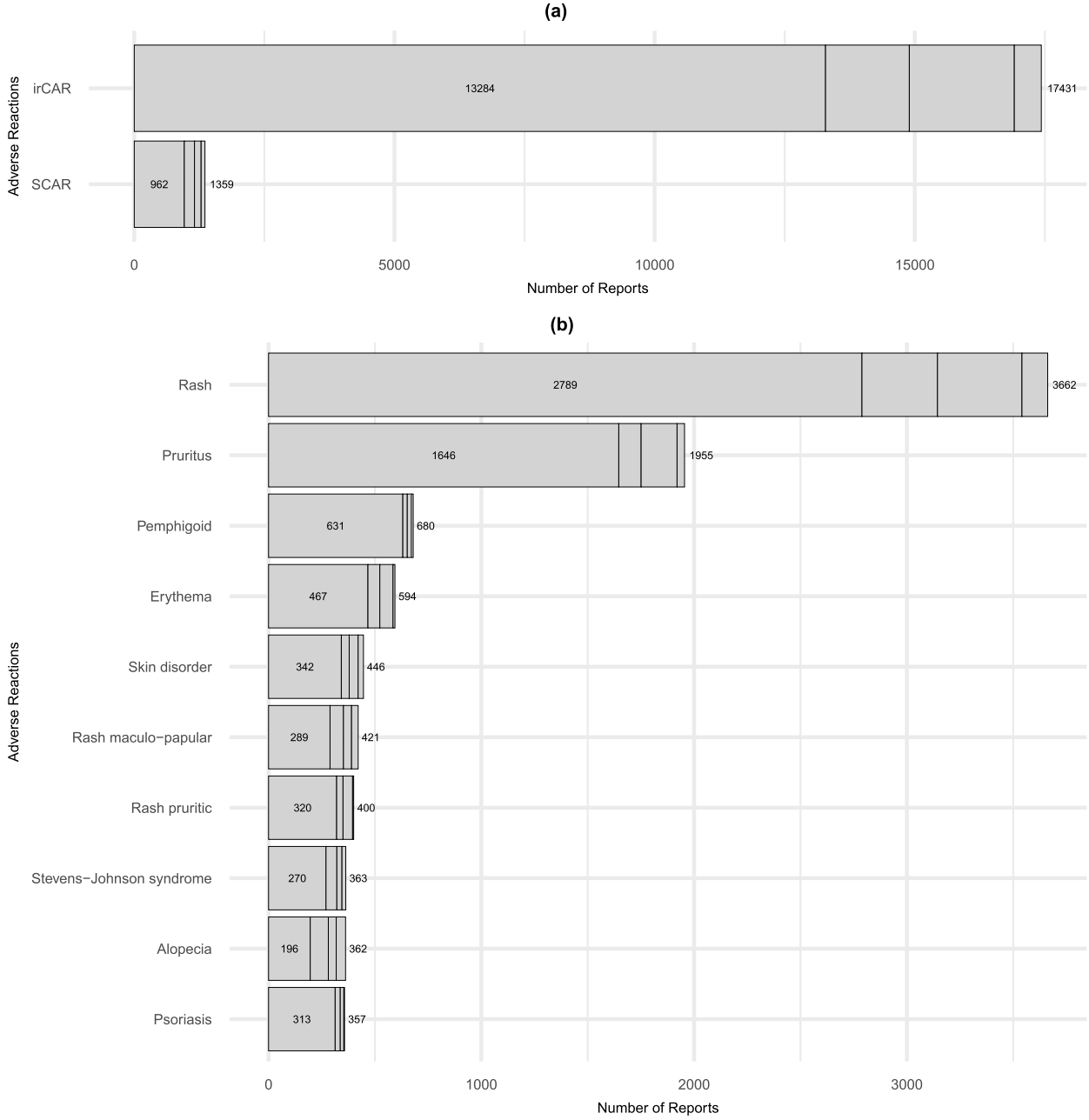


Fig. 1. Number of patients with irCAR and signal profiles under various treatment strategies. (A) The bar plots show the number of patients with irCAR and SCAR. (B) The bar plots illustrate the number of reported cases for the 10 most frequently reported categories of irCAR. From left to right, each box on the bar plots represents the number of reported cases that had undergone immunotherapy only, the combination of immunotherapy and chemotherapy, and the combination of immunotherapy and targeted therapy, followed by the total reported irCARs. (C) irCAR and SCAR signal profiles associated with different ICI treatment strategies.

(c)

	irCAR	SCAR
Only ICI	0.94	**2.08**
Monotherapy	0.90	**1.85**
Anti−PD−1	0.92	**1.95**
Nivolumab	0.87	**1.69**
Pembrolizumab	0.97	**2.09**
Cemiplimab	**1.15**	**2.46**
Anti−PD−L1	0.64	**1.37**
Atezolizumab	0.65	**1.55**
Durvalumab	0.59	**1.09**
Avelumab	0.51	
Anti−CTLA−4	**1.02**	0.68
Ipilimumab	**1.02**	0.68
Dual Therapy	**1.01**	**2.61**
Nivolumab + Ipilimumab	**1.02**	**2.62**
Nivolumab + Pembrolizumab	0.91	
Pembrolizumab + Ipilimumab	0.93	**1.25**
Durvalumab + Tremelimumab	0.20	**1.10**
Triple Therapy	**1.95**	**2.13**
Nivolumab + Pembrolizumab + Ipilimumab	**1.13**	**1.49**
Nivolumab + Pembrolizumab + Atezolizumab	**2.28**	
ICI + Chemotherapy vs. Only ICI	0.82	**1.25**
ICI + Targeted Therapy vs. Only ICI	**1.05**	0.79
ICI + Chemotherapy + Targeted Therapy vs. Only ICI	**1.08**	**1.83**

Fig. 1. (*continued*).

administered in 0.68 % of cases, and quadruple therapy or more was infrequent, accounting for only 0.39 %. In our assessment of ICI, chemotherapy, and targeted therapy combinations, 75.96 % of cases received immunotherapy alone, 9.7 % were treated with a combination of ICI and chemotherapy, 11.27 % underwent ICI plus targeted therapy, and a combined approach involving ICI, chemotherapy, and targeted therapy was observed in 3.08 % of cases. Outcomes in our study were stratified into 'serious' and 'non-serious' adverse events. While the precise etiology of these outcomes, whether attributable to cancer or treatment toxicity, remained undetermined, 79.86 % of cases were labeled as 'serious' and 20.14 % as 'non-serious.' Various subtypes were identified within the 'serious' outcomes: death was reported in 10.41 % of all cases, and hospitalization was 38.97 %. The remaining serious outcomes involved life-threatening events, disability, and interventions required to prevent permanent impairment or damage (Table 1). Notably, cases with SCAR exhibited a higher mortality rate, reaching 22.62 %.

Nivolumab was the most frequently reported agent in monotherapy cases, utilized in 4284 cases. Pembrolizumab was the second most commonly used agent, with 3816 cases, and atezolizumab was the third, with 1211 cases. Tremelimumab was the least widely used, appearing in only one monotherapy case. However, in polytherapy settings, tremelimumab was often combined with durvalumab, with 33 reported cases. The most commonly used dual therapy combined nivolumab and ipilimumab, with 2393 reported cases (Supplementary Table S8).

Of 17,431 reports with irCAR, 13,284 were reported from cases exclusively receiving immunotherapy (Fig. 1A). Among the reported irCAR, the most prevalent were rash (N = 3662, 21.01 %), followed by pruritus (N = 1955, 11.22 %), pemphigoid (N = 680, 3.90 %), and erythema (N = 594, 3.41 %). Other commonly reported skin conditions included skin disorder (N = 446, 2.56 %), rash maculo-papular (N = 421, 2.42 %), rash pruritic (N = 400, 2.29 %), alopecia (N = 362, 2.08 %), and psoriasis (N = 357, 2.05 %) (Fig. 1B). For SCAR, 1359 ARs were reported, of which 962 originated from cases undergoing only immunotherapy (Fig. 1A). Among SCARs, Stevens-Johnson syndrome (SJS) was the most frequently reported (N = 363, 2.08 %), followed by erythema multiforme (N = 284, 1.63 %), toxic epidermal necrolysis (N = 222, 1.27 %), toxic skin eruption (N = 111, 0.64 %), dermatitis bullous (N = 103, 0.59 %), and drug reaction with eosinophilia and systemic symptoms (DRESS) (N = 101, 0.58 %).

Cemiplimab exhibited the strongest signal for both irCAR and SCARs in the monotherapy setting, with ROR025 of 1.15 and 2.46,

	Only ICI vs. All Database	Nivolumab	Pembrolizumab	Cemiplimab	Atezolizumab	Durvalumab	Avelumab	Ipilimumab	Nivolumab + Ipilimumab	Nivolumab + Pembrolizumab	Pembrolizumab + Ipilimumab	Durvalumab + Tremelimumab	Nivolumab + Pembrolizumab + Ipilimumab	Nivolumab + Pembrolizumab + Atezolizumab	ICI + Chemotherapy vs. Only ICI	ICI + Targeted Therapy vs. Only ICI	ICI + Chemotherapy + Targeted Therapy vs. Only ICI
Rash	**1.51**	**1.13**	**1.47**	**1.36**	0.90	0.95	0.80	**2.91**	**1.84**		0.58		0.65	**4.07**	0.82	0.92	**1.09**
Pruritus	**1.09**	**1.00**	**1.04**	**1.27**	0.58	0.48	0.42	**1.53**	**1.17**		0.49			0.91	0.37	0.63	0.45
Pemphigoid	**21.37**	**30.75**	**13.00**	**25.81**	**4.89**	**5.89**		**3.05**	**7.88**	**160.58**		**9.78**			0.15	0.14	0.22
Erythema	0.46	0.48	0.42	0.43	0.30	0.11	0.41	0.24	0.44						0.65	0.73	0.30
Skin disorder	**2.20**	**1.82**	**1.83**	0.57	0.90	0.70		0.58	**2.77**		**1.80**			**17.91**	0.55	0.64	**1.46**
Rash maculo−papular	**3.18**	**1.79**	**1.67**	**4.04**	**4.21**	0.29		**1.71**	**6.01**		**6.66**				**1.19**	0.67	**2.22**
Rash pruritic	**1.40**	0.90	**1.54**	0.39	0.19	0.56		**2.02**	**1.74**						0.46	0.74	0.19
Stevens−Johnson syndrome	**3.82**	**2.94**	**4.46**	**1.25**	**2.42**	**2.35**		0.67	**3.52**						**1.00**	0.42	**1.24**
Alopecia	0.17	0.15	0.15	0.08	0.13	0.12	0.11	0.11	0.13						**2.41**	0.96	**4.87**
Psoriasis	0.46	0.55	0.48		0.33	0.31		0.03	0.16						0.36	0.24	0.09
Dry skin	0.33	0.42	0.22	0.13	0.14	0.08		0.07	0.30						0.40	**1.67**	0.41
Drug eruption	**3.18**	**2.22**	**3.27**		**1.00**	0.60		0.32	**4.74**		**4.09**				**1.35**	0.79	**1.10**
PPE	0.39	0.56	0.06		0.51				0.14						0.71	**25.71**	**5.37**
Dermatitis	**2.65**	**1.78**	**2.04**		**1.04**	0.44		**5.56**	**2.78**						0.68	0.39	0.89
Urticaria	0.32	0.21	0.33	0.19	0.24	0.34		0.26	0.30				0.65		0.58	0.60	0.68
Vitiligo	**34.93**	**17.89**	**40.15**		**3.19**			**26.90**	**26.01**		**80.82**		**134.20**		0.18	0.14	0.11
Blister	0.77	0.78	0.77	**1.47**	0.56	0.36			0.52						0.29	**2.00**	
Erythema multiforme	**4.62**	**2.83**	**4.02**		**1.59**				**8.33**						**1.61**	**1.12**	**3.68**
Skin exfoliation	0.34	0.32	0.37		0.05	0.17		0.11	0.26						0.49	**1.91**	**2.03**
Hyperhidrosis	0.33	0.25	0.33	0.24	0.22	0.10	0.45	0.16	0.31						0.22	0.41	0.15
Toxic epidermal necrolysis	**2.93**	**1.56**	**3.95**	**3.35**	**1.45**	0.72		0.60	**3.23**						0.88	0.25	0.57
Immune−mediated dermatitis	**141.55**	**11.68**	**115.14**						**188.43**						**1.89**	0.35	0.58
Skin toxicity	**6.55**	**3.72**	**6.56**	**8.19**	**6.04**	**3.16**		**1.47**	**4.19**				**19.96**	**80.54**	0.79	0.51	0.18
Eczema	0.87	0.87	0.80	0.59	0.45	0.27	0.78	0.15	0.52						0.91	0.38	0.70
Lichenoid keratosis	**20.29**	**20.10**	**18.24**		**5.26**	**3.23**	**22.59**	**2.70**	**6.97**						0.35	0.22	
Rash erythematous	0.61	0.40	0.76		0.39	0.23		0.43	0.42						0.45	0.76	
Skin lesion	0.96	0.95	**1.07**	**3.07**	0.26				0.54						0.23	0.64	
Skin ulcer	0.53	0.52	0.56			0.34			0.23						0.64	**3.29**	**1.07**
Lichen planus	**14.04**	**17.71**	**15.96**		**7.63**				0.95						0.15	0.09	
Skin discolouration	0.43	0.36	0.46			0.26		0.35	0.36						0.14	0.75	
Skin reaction	**1.46**	0.75	**1.46**	**2.10**	**1.26**	0.40		0.34	**1.20**					**10.20**	0.27	0.31	
Rash macular	0.51	0.27	0.43					0.58	0.71						0.31	0.87	
Night sweats	0.60	0.47	0.28		0.22	0.19		0.44	0.99						0.25	0.35	0.47
Toxic skin eruption	**1.87**	**2.00**	0.50		**1.05**	**1.01**			**2.28**						0.61	0.44	0.33
Dermatomyositis	**7.32**	**8.41**	**3.81**		**2.96**	**2.52**		**7.28**	**2.96**						0.94		0.35
Dermatitis bullous	**2.37**	**2.47**	0.81	**8.53**	**1.07**	**1.41**			**1.21**						0.48	0.36	**1.50**
DRESS	0.45	0.30	0.13		0.32			0.36	0.80						0.21	**1.65**	
Leukoderma	**155.80**	**125.83**	**5.87**						**155.74**							0.12	
Rash papular	0.60	0.40	0.89						0.45						0.26	0.32	
Dermatitis psoriasiform	**8.36**	**9.34**	**7.70**		**3.70**	**8.81**			0.66							0.09	
Dermatitis acneiform	**1.55**	**1.29**	0.79					**5.37**	0.89						0.76	**1.06**	**2.36**
Angioedema	0.26	0.31	0.12		0.16	0.30		0.18	0.03						0.95	0.24	
Hair colour changes	0.50	0.31	0.39					0.26	0.71							0.72	
Purpura	**1.05**	**1.02**	0.82		0.95				0.48						0.75	0.54	0.66
Acne	0.06	0.03	0.06					0.07	0.08							**1.90**	
Photosensitivity reaction	0.43	0.24	0.19					0.46	0.58						0.67	0.79	
Decubitus ulcer	0.68	0.59	0.52						0.68						0.73	0.74	
Rash vesicular	**1.49**	0.69	**3.20**						0.28						0.28	0.28	
Pemphigus	0.48	0.57	0.07						0.25						0.18	0.18	
SCLE	**2.66**	**2.48**	**3.38**		**2.02**				0.56						0.55	0.31	

(caption on next page)

Fig. 2. Heatmap analysis of the interplay between irCAR and diverse treatment strategies. The heatmap shows the ROR_{025} (lower end of the 95 % confidence interval of ROR, exceeded one, with at least three records) for all reported cutaneous adverse reactions in the FAERS database under different ICI treatment strategies. Grayed boxes indicate ROR_{025} values higher than 1, white boxes indicate ROR_{025} values less than 1, and empty boxes indicate ROR_{025} values could not be calculated. (Abbreviations: PPE, palmar-plantar erythrodysesthesia; DRESS, drug reaction with eosinophilia and systemic symptoms; SCLE, subacute cutaneous lupus erythematosus; ICI, immune checkpoint inhibitor).

respectively. In contrast, monotherapies involving an anti-PD-L1 showed the lowest signal, with ROR025 values of 0.64 for irCARs and 1.37 for SCARs. Among the dual therapies, only nivolumab with ipilimumab showed a signal for both irCARs and SCARs. Triple therapies yielded strong ROR025 values for both categories, 1.95 for irCARs and 2.13 for SCARs. Interestingly, while ICI with chemotherapy vs. only ICI did not show significant signal strength for irCARs (ROR025 = 0.82), it did for SCARs (ROR025 = 1.25). On the other hand, ICI therapy with targeted therapy vs. only ICI showed a robust signal for irCARs (ROR025 = 1.05) but not for SCARs (ROR025 = 0.79) (Fig. 1C).

The occurrence of rash and pruritus demonstrated signals for exclusive ICI use, nivolumab, pembrolizumab, cemiplimab, ipilimumab, and the combination of nivolumab and ipilimumab (ROR025 for rash 1.51, 1.13, 1.47, 1.36, 2.91, 1.84; for pruritus 1.09, 1.00, 1,04, 1.27, 1.53, 1.17, respectively). Pemphigoid has shown strong signals for nivolumab (ROR025 = 30.75), pembrolizumab (ROR025 = 13.00), cemiplimab (ROR025 = 25.81), atezolizumab (ROR025 = 4.89), durvalumab (ROR025 = 5.89), the combination of nivolumab and pembrolizumab (ROR025 = 160.58) and the combination of durvalumab and tremelimumab (ROR025 = 9.78). The maculopapular rash had a prominent signal with exclusive ICI use (ROR025 = 3.18), cemiplimab (ROR025 = 4.04), atezolizumab (ROR025 = 4.21), nivolumab-ipilimumab (ROR025 = 6.01), and pembrolizumab-ipilimumab (ROR025 = 6.66) combination. Vitiligo has also shown a robust signal for ipilimumab (ROR025 = 26.90), nivolumab (ROR025 = 17.89), pembrolizumab (ROR025 = 40.15), and the combination of pembrolizumab with ipilimumab (ROR025 = 80.82), or both nivolumab and ipilimumab (ROR025 = 26.01). Chemotherapy use and ICI were found to have a signal for maculopapular rash (ROR025 = 1.19), alopecia (ROR025 = 2.41), and SJS (ROR025 = 1.00). Psoriasis and erythema were not specifically linked to any of the ICIs. Remarkably, targeted therapy has no signal for

Table 2
Univariate logistic regression analysis of demographic and clinical variables for irCAR, mortality, and SCAR.

Variables	Reference group	OR [95 % CI]	p-value
Immune-related cutaneous adverse reactions (irCAR)			
Age ≥65 years	Age <65 years	1.08 [1.03–1.13]	0.0008
Weight <70 kg	Weight ≥70 kg	1.20 [1.13–1.29]	<0.0001
Male	Female	0.88 [0.85–0.91]	<0.0001
Skin cancer	Non-skin cancer indications	1.66 [1.59–1.74]	<0.0001
ICI + chemotherapy	Only ICI	0.96 [0.90–1.02]	0.19
ICI + targeted therapy	Only ICI	1.31 [1.24–1.39]	<0.0001
ICI + chemotherapy + targeted therapy	Only ICI	1.46 [1.31–1.62]	<0.0001
Polytherapy[a]	Monotherapy	1.33 [1.27–1.40]	<0.0001
Anti-PD-L1[b]	Anti-PD-1	0.63 [0.58–0.68]	<0.0001
Anti-CTLA-4[b]	Anti-PD-1	1.10 [1.01–1.20]	0.032
Anti-CTLA-4[b]	Anti-PD-L1	1.75 [1.57–1.96]	<0.0001
Mortality			
Age ≥65 years	Age <65 years	1.20 [1.06–1.36]	0.0048
Weight <70 kg	Weight ≥70 kg	1.59 [1.32–1.91]	<0.0001
Male	Female	1.42 [1.26–1.60]	<0.0001
Skin cancer	Non-skin cancer indications	0.85 [0.74–0.96]	0.013
ICI + chemotherapy	Only ICI	1.31 [1.10–1.56]	0.0023
ICI + targeted therapy	Only ICI	0.78 [0.64–0.95]	0.014
ICI + chemotherapy + targeted therapy	Only ICI	1.22 [0.89–1.63]	0.20
Polytherapy[a]	Monotherapy	1.16 [1.00–1.34]	0.053
Anti-PD-1[b]	Anti-PD-L1	1.41 [1.08–1.87]	0.014
Anti-CTLA-4[b]	Anti-PD-L1	0.71 [0.46–1.09]	0.12
Anti-PD-1[b]	Anti-CTLA-4	1.98 [1.42–2.86]	<0.0001
Severe cutaneous adverse reactions (SCAR)			
Age ≥65 years	Age <65 years	0.97 [0.86–1.10]	0.65
Weight <70 kg	Weight ≥70 kg	1.97 [1.63–2.39]	<0.0001
Male	Female	0.92 [0.82–1.04]	0.18
Skin cancer	Non-skin cancer indications	1.13 [0.99–1.30]	0.074
ICI + chemotherapy	Only ICI	1.53 [1.30–1.79]	<0.0001
ICI + targeted therapy	Only ICI	1.19 [0.98–1.43]	0.076
ICI + chemotherapy + targeted therapy	Only ICI	2.77 [2.15–3.51]	<0.0001
Polytherapy[a]	Monotherapy	1.85 [1.59–2.13]	<0.0001
Anti-PD-L1[b]	Anti-PD-1	1.35 [1.07–1.73]	0.016
Anti-CTLA-4[b]	Anti-PD-1	0.59 [0.36–0.94]	0.034
Anti-PD-L1[b]	Anti-CTLA-4	1.69 [1.06–2.81]	0.034

(Abbreviations: ICI, immune checkpoint inhibitor; OR, odds ratio; CI, confidence interval).

[a] This analysis was performed by the exclusion of cases receiving chemotherapy and/or targeted therapy.

[b] This analysis was performed by the exclusion of cases receiving chemotherapy, targeted therapy, and/or polytherapy.

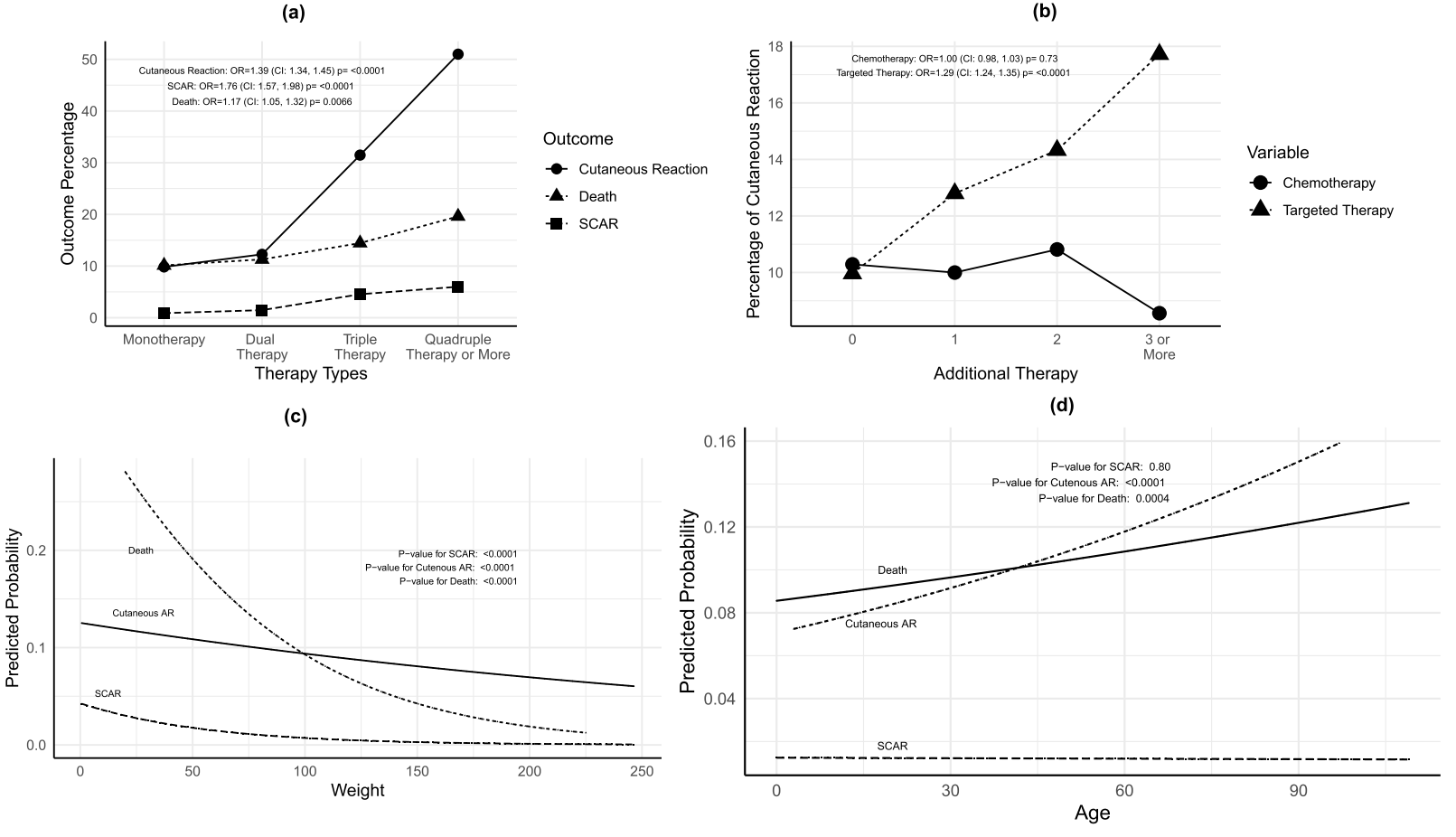


Fig. 3. Influence of additional treatment regimens, age, and weight on skin toxicity incidence, mortality, and SCARs. (A) Distribution of outcome percentage of death, SCAR, and irCAR according to different immunotherapy types. (B) The distribution of skin toxicity percentage in relation to additional therapy. (C, D) Logistic regression analysis showing the impact of weight and age on predicted probabilities of death, irCAR, and SCAR.

most reactions. The signal for palmar-plantar erythrodysesthesia was potent (ROR025 = 25.71). The other reactions showing a signal for targeted therapy were dry skin (ROR025 = 1.67), blister (ROR025 = 2.00), erythema multiforme (ROR025 = 1.12), skin exfoliation (ROR025 = 1.91), and DRESS (ROR025 = 1.65) (Fig. 2). The extended version of the heatmap is provided in Supplementary Table S9.

Our logistic regression analysis revealed that being male reduced the incidence of irCAR (OR = 0.88 [0.85–0.91], p < 0.0001) but increased the risk of death (OR = 1.42 [1.26–1.60], p < 0.0001), with no significant effect on SCAR (OR = 0.92 [0.82–1.04], p = 0.18) (Table 2). When stratifying the data by cancer type, only skin (OR = 1.66 [1.59–1.74], p < 0.0001) and urogenital cancers (OR = 1.14 [1.08–1.20], p < 0.0001) were found to increase the risk of cutaneous toxicity significantly (Supplementary Table S10). Intriguingly, lung cancer was the only indication significantly associated with an increased risk of SCAR (OR = 1.21 [1.08–1.36], p = 0.0014), whereas both skin (OR = 1.13 [0.99–1.30], p = 0.074) and urogenital cancers (OR = 0.91 [0.77–1.07], p = 0.26) showed no significant impact on SCAR. For the risk of death, lung cancer was associated with an increased risk (OR = 1.48 [1.31–1.66], p < 0.0001). Skin cancer, on the other hand, demonstrated a decreased risk (OR = 0.85 [0.74–0.96], p = 0.013), as did urogenital cancer (OR = 0.77 [0.65–0.91], p = 0.0024) (Table 2, Supplementary Table S10).

In cases where only monotherapy was administered, anti-CTLA-4 agents were associated with higher skin toxicity compared to both anti-PD-1 agents (OR = 1.10 [1.01–1.20], p = 0.032) and anti-PD-L1 agents (OR = 1.75 [1.57–1.96], p < 0.0001). In contrast, anti-PD-L1 agents were less toxic than anti-PD-1 agents (OR = 0.63 [0.58–0.68], p < 0.0001). Regarding mortality, anti-PD-1 agents were more lethal than both anti-PD-L1 (OR = 1.41 [1.08–1.87], p = 0.014) and anti-CTLA-4 agents (OR = 1.98 [1.42–2.86], p < 0.0001). There was no significant difference between anti-CTLA-4 and anti-PD-L1 agents in terms of mortality (OR = 0.71 [0.46–1.09], p = 0.12). The most significant risk factor for SCAR was anti-PD-L1, followed by anti-PD-1, and finally anti-CTLA-4. Anti-PD-L1s were a greater risk factor compared to anti-PD-1s (OR = 1.35 [1.07–1.73], p = 0.016), and anti-CTLA-4s showed less SCAR compared to anti-PD-1s (OR = 0.59 [0.36–0.94], p = 0.034) (Table 2). The addition of chemotherapy alongside immunotherapy had no substantial impact on the incidence of irCAR (OR = 0.96 [0.90–1.02], p = 0.19), but it did increase the risk for both death (OR = 1.31 [1.10–1.56], p = 0.0023) and SCAR (OR = 1.53 [1.30–1.79], p < 0.0001). Targeted therapy was found to be a risk factor for irCAR (OR = 1.31 [1.24–1.39], p < 0.0001) but was associated with a reduced risk of death (OR = 0.78 [0.64–0.95], p = 0.014) and had no significant relationship with SCAR (OR = 1.19 [0.98–1.43], p = 0.076) (Table 2).

The complexity of the treatment regimen was identified as a substantial factor. An increase in the number of ICI used correlated with a statistically significant rise in the incidence of irCAR (OR = 1.39 [1.34–1.45], p < 0.0001), SCAR (OR = 1.76 [1.57–1.98], p < 0.0001), and mortality (OR = 1.17 [1.05–1.32], p = 0.0066) (Fig. 3A). Additionally, an increased number of targeted therapies was associated with a higher incidence of irCAR (OR = 1.29 [1.24–1.35], p < 0.0001). Interestingly, the quantity of chemotherapy agents administered did not significantly affect the incidence of irCAR (OR = 1.00 [0.98–1.03], p = 0.73) (Fig. 3B).

Weight decline was correlated with a significant increase in the incidence of both irCAR and SCAR (p < 0.0001), as well as an

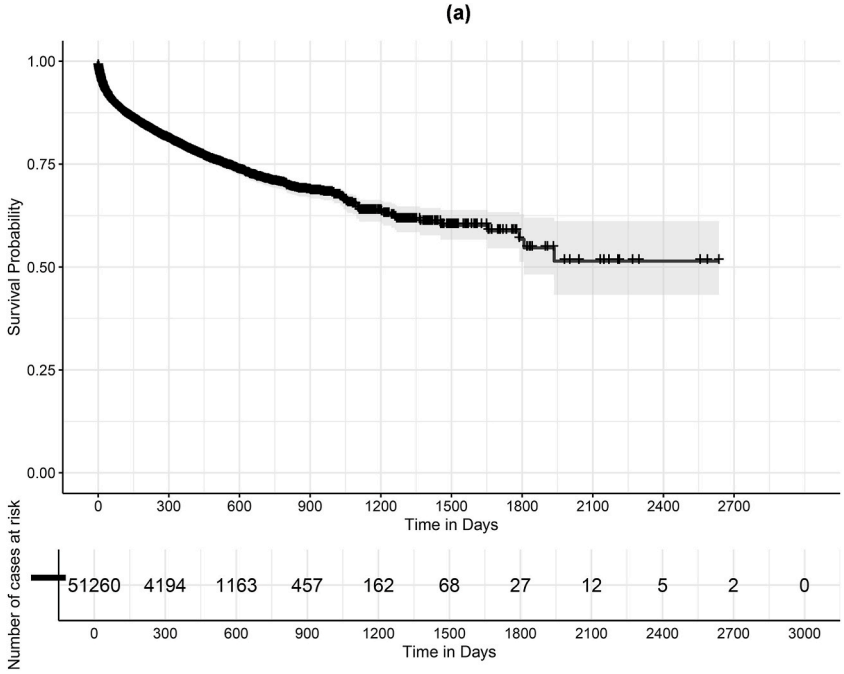


Fig. 4. Onset and impact of irCAR in ICI therapy. (A) Kaplan Meier survival curve displays the estimated percent survival of patients with irCAR. (B) From left to right, the cumulative distribution curves demonstrate the onset time of irCAR according to age group (1), non-fatal vs. fatal outcome (2), therapy type (3), sex (4), skin cancer (5), and weight group (6), and the onset time of adverse reactions according to irCAR (7). (C) This figure depicts four violin plots illustrating the onset timing of irCAR in four distinct treatment groups. (D) The onset of irCAR was demonstrated and compared among PD-1, PD-L1, and CTLA-4 using violin plots.

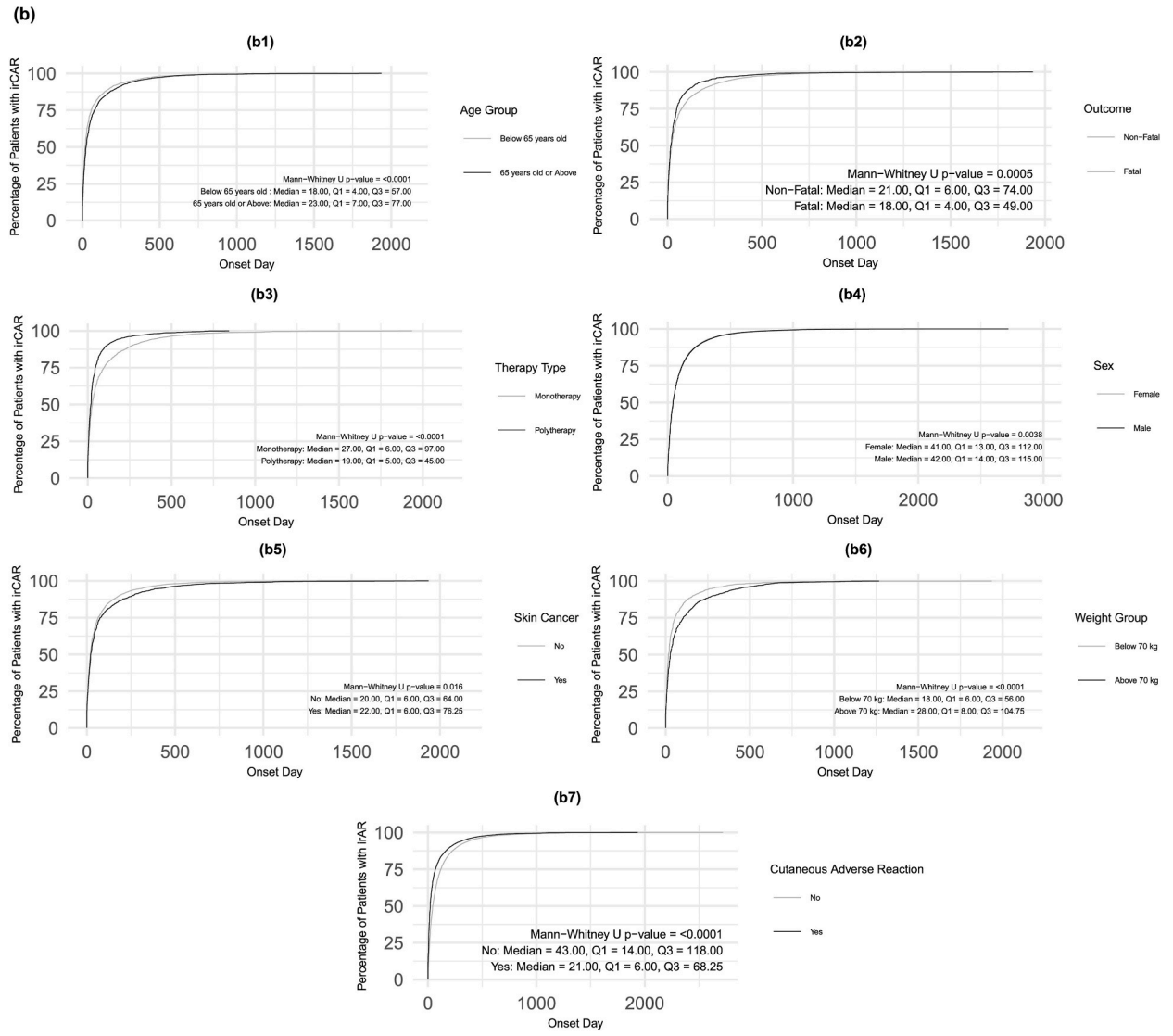


Fig. 4. (*continued*).

elevated risk of death ($p < 0.0001$) (Fig. 3C). In terms of age, an increase was associated with a significant uptick in the incidence of death ($p = 0.0004$) and irCAR ($p < 0.0001$). However, age did not demonstrate a statistically significant trend in affecting the incidence of SCAR ($p = 0.80$) (Fig. 3D).

The onset of adverse reactions varied significantly across groups. The median onset day for cutaneous toxicity was 21 days (IQR 6–68.25), while for SCAR, it was 23 days (IQR 8–66.75). Significant variations in onset days were evident among the most commonly reported PTs. Rash had a median onset of 14 days (IQR 3–43), pruritus at 14 days (IQR 1–54.25), and rash maculo-papular showed a median onset at 16 days (IQR 6–54), while SJS were observed to start around 24 days (IQR 7.75–56.25). Other conditions like pemphigoid and vitiligo had later onset, with medians of 201 days (IQR 57–399.5) and 88.5 days (IQR 33.25–208.75), respectively (Supplementary Table S11). The median onset day of the top 10 most common HLTs was shown in Supplementary Table S12.

Kaplan-Meier estimates demonstrated that about 10 % of patients will experience irCAR by day 63 (95 % CI: 58–68 days) and 25 % by day 531 (95 % CI: 486–584 days) (Fig. 4A).

The median onset time for adverse outcomes was significantly shorter in the group aged less than 65 compared to those aged 65 and older (18 vs. 23 days, $p < 0.0001$). Regarding mortality, the fatal group exhibited a median onset time of 18 days, which was shorter than the 21 days observed in the non-fatal group ($p = 0.0005$). The monotherapy group had a longer median onset time of 8 days compared to polytherapy (27 vs. 19 days, $p < 0.0001$). Females had a 3-day longer median onset than males (21 vs. 18 days, $p = 0.0038$). Skin cancer cases had a 2-day longer median onset than other indications (22 vs. 20 days, $p = 0.016$). irCAR had a shorter median onset than other cases (21 vs. 43 days, $p < 0.0001$). Finally, weight also influenced onset; those under 70 kg had a 10-day shorter median onset than those 70 kg or more (18 vs. 28 days, $p < 0.0001$) (Fig. 4B).

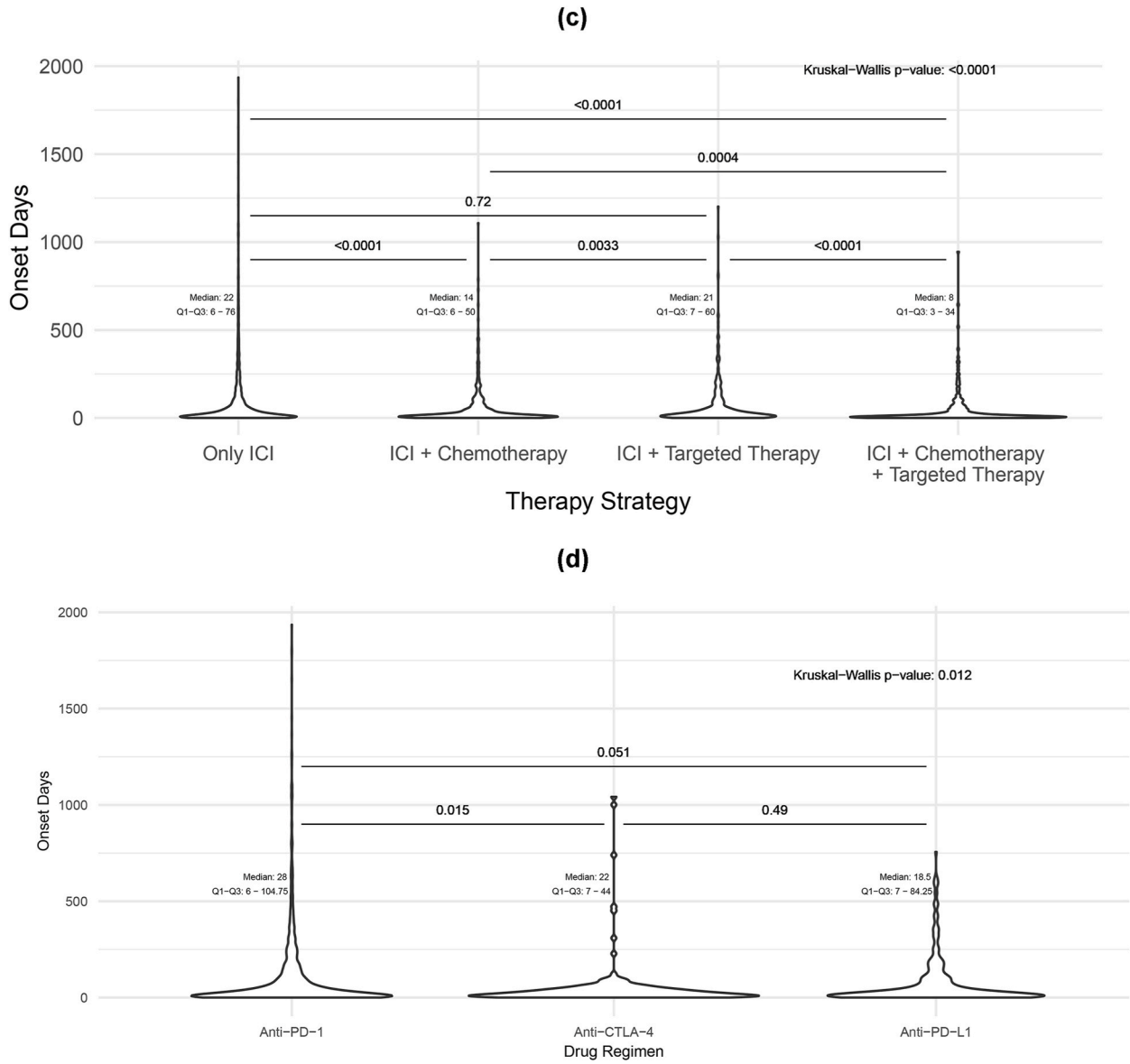


Fig. 4. (*continued*).

Regarding therapy strategies, different median onset days were observed for various treatment combinations. The median onset day for only ICI therapy was 22 days (IQR 6–76). For the combination of ICI and chemotherapy, it was 14 days (IQR 6–50). The combination of ICI and targeted therapy was 21 days (IQR 7–60); for the combination of all three, it was 8 days (IQR 3–34). A noteworthy finding was that the median onset for ICI plus chemotherapy was 8 days shorter than for only ICI (14 vs. 22 days, $p < 0.0001$). Interestingly, the difference in median onset days between the combination of ICI and targeted therapy versus only ICI was not statistically significant ($p = 0.72$) (Fig. 4C). Among those receiving only monotherapy, the median onset days differed by the type of immune checkpoint inhibitor used. For anti-PD-1, the median onset was 28 days (IQR 6–104.75). For anti-CTLA-4, it was 22 days (IQR 7–44); and for anti-PD-L1, it was 18.5 days (IQR 7–84.25). Notably, anti-PD-1 demonstrated a significantly delayed onset compared to anti-CTLA-4 ($p = 0.015$). However, the difference in median onset days between anti-CTLA-4 and anti-PD-L1 was not statistically significant ($p = 0.49$) (Fig. 4D).

6. Discussion

Existing literature on the dermatologic toxicities associated with ICI has primarily relied on narrative reviews and a limited number of systematic reviews and meta-analyses focusing on managing individual skin reactions. However, there has been a notable absence of original research utilizing large databases such as FAERS. In an effort to bridge this gap, our study seeks to elucidate the demographic

characteristics, potential risk factors, the impact of individual ICI on cutaneous reactions, and determinants of mortality among patients presenting with irCAR following ICI administration.

Skin reactions have previously been reported to occur in about one-third of patients receiving ICI therapies [13–15], with a higher prevalence among males and the elderly [16,17]. Similarly, we observed that both immune-related and dermatological adverse effects were primarily observed in males or elderly individuals. Inexplicably, more irCAR and higher mortality were observed as the patients' weight decreased. This correlation might be attributed to patients with advanced or aggressive forms of cancer and who are particularly affected by the adverse effects of their antitumor treatment are more likely to experience weight loss. A similar study has shown the impact of BMI on survival previously [18]. Our data indicates a lower mortality rate in patients with irCAR, adding to existing literature on this topic [19]. Furthermore, skin toxicity was more commonly observed in patients with skin cancer, and mortality rates were also lower in this group. A higher incidence of skin and gastrointestinal toxicities in melanoma patients was previously reported [20]. This is presumably due to the potent immunogenic properties of melanoma and the similarity of antigens in skin cells. Additionally, most ICIs were first approved in the treatment of melanoma, making a reporting bias likely. The combination of different ICI in the melanoma treatment might also increase the skin-related side effects [13]. As in line with the literature [13], varieties of ICIs were associated with higher frequency and earlier onset of adverse events compared to monotherapy. Higher rates of mortality were also observed in the patients with polytherapy, presumably due to a higher frequency of overall adverse reactions, advanced-stage cancers, and potential refractory or non-responsive cancers to treatment. The higher mortality observed in our patients receiving chemotherapy is likely attributed to the severe and systemic adverse effects, which can lead to complications. Conversely, targeted therapies, associated with specific and localized adverse reactions, might tend to be better tolerated, presumably leading to lower mortality rates. Another point worth mentioning is that there were significantly more reports from high-income countries in our data, showing that it is crucial to promote reporting of adverse reactions in low-income countries to provide a more inclusive approach to adverse reaction management.

irCAR might have a widespread clinical manifestation profile, most common ones including eczematous, morbilliform, vitiligo and lichenoid lesions but also relatively rarer SCARs and bullous conditions might be seen [9,21–23]. Rare adverse events also extend up to hair conditions, ICI-induced scleroderma, vasculitis [24]. Oral/mucosal involvement has been reported but relatively overlooked and requires further elucidation [13,24]. Another pharmacovigilance study conducted using data from the FAERS analyzed 1882 reports of cutaneous adverse events associated with ICIs from January 2011 to September 2020 [25]. Among these reactions, the most prevalent were maculopapular rash, vitiligo, Stevens-Johnson syndrome, and toxic epidermal necrolysis. On the other hand, our study revealed that rash (21.01 %), pruritus (11.22 %), and pemphigoid (3.90 %) were the most commonly seen reactions. Again, another pharmacovigilance study utilizing data from VigiBase [26], global repository of individual case safety reports curated by the World Health Organization, revealed that 27 specific skin eruptions exhibited conspicuous signals of disproportionality, among the spectrum of cirAEs.These identified cirAEs comprised vitiligo, drug eruption, Stevens–Johnson syndrome, eczematous dermatitis, lichenoid dermatitis, bullous pemphigoid, erythema multiforme, and toxic epidermal necrolysis. A retrospective cohort study in Taiwan examining 468 cancer patients receiving ICI revealed that maculopapular eruption and pruritus being the most common events. Additionally, the incidence was highest with pembrolizumab and was further elevated when combined with molecular-targeted therapy [27].

irCAR shows variable onset intervals, ranging from one week to a year, depending on lesion type [24,28]. Most complaints start at 3–8 weeks after initiating the ICI treatment [16]. We found this onset time to have a median of 21 days for all irCARs. More specifically, rashes and maculopapular eruptions were identified as one of the most early cutaneous reactions in the literature and our findings [24]. The onset time of maculopapular rash was reported as 3–6 weeks after starting ICI therapy [24], while it was 14 days in our results. The other early presenting reactions were pruritus, erythema, pruritic rash, and urticaria. In this study, pruritus typically began around the 14th day. Still, the literature reveals a wide range of onset times for pruritus, occurring promptly as well as 2–8 cycles into ICI therapy, sometimes preceding or following the development of a rash or even presenting without a rash altogether. Pemphigoid, vitiligo, psoriasis, lichenoid keratosis, and lichen planus were presented later compared to other reactions. The onset time was reported as 6 weeks to 5–6 months for pemphigoid and several months for vitiligo in previous studies [29,30] consistently, we found a median of 201 and 89 days, respectively. Pemphigoid typically exhibits one of the most prolonged delays in presentation among all cutaneous reactions, as reported both in the literature and in our study [29]. In addition, lichenoid keratosis demonstrates significant variability on presentation onset while vitiligo-like depigmentation might develop gradually, resulting in delayed-onset presentation profiles. The onset of presentation of overall irCAR was delayed as the patient's age increased, which may be attributed to the weakening of the immune system associated with the aging process. Interestingly, the rapid onset of developing cutaneous adverse reactions was also linked to higher mortality. Individual lesion types are often considered a major factor influencing onset timing. However, our data also revealed a noteworthy delay in cutaneous adverse reactions with PD-1 inhibitors compared to CTLA-4 inhibitors. Similar results were also reported before [30]. However, this could be linked to the delayed appearance of cutaneous lesions such as vitiligo, pemphigoid, and lichenoid conditions, which are specifically associated with PD-1 inhibitors.

Skin reactions appeared earlier with chemotherapy and ICI, while targeted therapy had no observable effects. This may be attributed to the wide-ranging cytotoxic impacts of chemotherapeutics and the more specific targeting of targeted therapies [31]. ICI and targeted therapies usually align in their mechanisms, reducing the likelihood of early skin toxicity due to immune system hyperactivation. Patients with skin cancer exhibit delayed onset of skin toxicities associated with ICI therapy, and this could be attributed to the immunosuppressive microenvironment of the skin induced by cancer. However, the precise cause remains unclear. Timing differences in skin toxicities between ICI monotherapy and polytherapy may result from enhanced immune system activation and vigilant lesion monitoring in the polytherapy group.

More vitiligo cases were reported in patients receiving pembrolizumab. On the contrary, vitiligo was previously reported more

commonly in patients treated with nivolumab compared to pembrolizumab [24]. Previously, another study reported a significant association between vitiligo and combination therapy involving anti-PD-1/L1 and anti-CTLA-4 agents [26]. Although the combination of nivolumab and pembrolizumab was not found to be linked with the overall occurrence of dermatological adverse events, the combination had significant associations with pemphigoid and bullous conditions based on our analysis, which is also in line with the other reports in the literature [28]. On the other hand, cemiplimab use was found to be associated with higher rates of cutaneous adverse reactions and SCAR in our study. Cemiplimab significantly enhances immune activity against skin cells, resulting in its primary effectiveness against cutaneous squamous cell carcinoma [32]; however, it often leads to common dermatological adverse effects. Furthermore, the primary patient group for cemiplimab usage primarily comprises individuals with skin cancer, potentially resulting in significantly higher rates of cutaneous reactions. Previous studies investigating the safety profile of cemiplimab noted the occurrence of maculopapular rash, pruritus, and rash among the patients who received cemiplimab [33,34]. However, unlike our findings, SCARs are not frequently associated with cemiplimab in the literature.

Our findings have shown that the occurrence of SCAR was linked to decreased body weight, female sex, and increased ICI combinations. The onset of presentation of individual SCARs, especially SJS and TEN (24 days for both), was earlier compared to 47 and 48 days, respectively reported in the literature [4]. The comprehensive and systemic impact of chemotherapy on the entire body, combined with short but intense treatment regimens, may increase the likelihood of SCAR. In contrast to chemotherapy, targeted therapy, which is frequently administered at low doses with extended exposure, may contribute to a reduced possibility of causing severe reactions. Lung cancer also demonstrated an elevated incidence of SCARs, presumably due to its frequent utilization of combination therapy involving chemotherapy alongside ICI. A recent extensive database analysis delved into the correlation between SCARs and ICI using FAERS data [35]. The findings uncovered notable RORs for SJS, TEN, and DRESS, demonstrating statistical significance when contrasting ICI with both all drugs in FAERS and a reference group of pooled anticancer drugs. Furthermore, elevated mortality rates were observed for ICI compared to anticancer medications across these SCARs, implying a potentially heightened risk associated with ICI therapy regardless of cancer status. Most studies concluded that ICIs are associated with a heightened risk of SJS/TEN [8,36]. The median onset time for these conditions was reported to be around 25 days, leading to discontinuation of ICIs in the majority of cases. Moreover, a considerable proportion of SJS/TEN cases resulted in fatalities, emphasizing the severity of these adverse events and the critical need for ongoing monitoring and management [8].

This study has several limitations. First, we could not independently assess the dermatologic adverse event profile of drugs like tremelimumab, commonly used in combination therapy. Secondly, side effects reported for newly introduced ICIs, like avelumab and tremelimumab, may not be directly comparable to widely used ICIs. Thus, it remains to be seen whether this is due to lower reporting rates or better dermal safety profiles for the newer ICI. It necessitates ongoing monitoring and reporting of cutaneous adverse reactions in patients receiving these agents to enhance our understanding of their safety profiles. Thirdly, the FAERS database's heterogeneity, with data from both healthcare and non-healthcare practitioners, introduces reporting bias and the potential for data duplication and missing information. These issues undermine the ability to accurately assess adverse event incidence or establish clear causal relationships. Fourthly, controlling for confounders such as pre-existing dermatological conditions and comorbidities poses a significant challenge due to the limited clinical detail in the FAERS database. This complicates our ability to definitively attribute cutaneous reactions to ICIs. Future research could improve these limitations by incorporating detailed patient data from electronic health records or designing prospective studies. Lastly, some cutaneous reactions such as "skin disorders" or "skin toxicities" were ambiguously labeled, highlighting the challenges and lack of awareness in characterizing specific skin lesions.

7. Conclusion

irCARs are common but rarely severe enough to warrant treatment discontinuation. However, improper management can affect the quality of life and potentially halt therapy. Simple lesions may indicate serious skin toxicities and require close monitoring. Timely identification and management and personalized follow-ups can minimize risks and avoid treatment interruption. Specifically, monitoring SCAR is critical due to their high mortality rates.

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Data availability statement

Data supporting the findings of this study are available at the FDA Adverse Event Reporting System (FAERS) Public Dashboard. The data can be accessed and downloaded directly from https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html.

Ethics and informed consent

Given that the FAERS database is publicly accessible and contains anonymized and de-identified patient information, the requirement for ethical approval and informed consent does not apply to this study.

CRediT authorship contribution statement

Buğra Han Esen: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Laşin Özbek:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Formal analysis, Conceptualization. **Sinem Oğuz:** Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Fatih Selçukbiricik:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e33765.

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