ORIGINAL REPORT

Association of Cutaneous Immune-related Adverse Events with Overall Survival and Progression-free Survival in Oncology Patients Receiving Immune Checkpoint Inhibitors: A Prospective Study of 189 Patients in a Spanish Tertiary Care Hospital

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Cutaneous immune-related adverse events (cirAEs) may be associated with tumoral response and survival in patients using immune checkpoint inhibitors, but this relationship remains unclear because previous reports on the topic have various limitations. The purpose of this study was to examine the association of cirAEs with overall survival and progression-free survival in patients starting immune checkpoint inhibitors. A prospective observational study was conducted in a Spanish tertiary care hospital, including participants between March 2020 and May 2022. The statistical analysis involved the Kaplan–Meier method, log-rank test, and multivariable Cox proportional hazards regression models. At total of 189 patients were included, of whom 82 (43.4%) presented cirAEs. Most participants (56.6%) were diagnosed with non-small cell lung cancer (NSCLC). Mortality and progression rates were lower in patients with vs without cirAEs ($p < 0.0001$). Cox models showed that cirAEs were a protective factor for overall survival (adjusted HR 0.50; $p < 0.0001$) and progression-free survival (adjusted HR 0.54; $p = 0.001$) independently of cancer type, tumour stage or immune checkpoint inhibitor category. There were similar results for extracutaneous irAEs. A limitation was the single-centre design. CirAE occurrence is positively associated with longer survival and less cancer progression among immune checkpoint inhibitor recipients independently of other factors.

Key words: overall survival; progression-free survival; cutaneous immune-related adverse events; immune checkpoint inhibitors; dermatologic toxicity; immunotherapy.

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SIGNIFICANCE

Among patients receiving immune checkpoint inhibitors, those who experienced cutaneous immune-related adverse events showed better overall survival and progression-free survival, independently of cancer type or drug category. Cutaneous toxicity may be a protective factor for survival and could therefore influence the management of this population.

Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of cancer and are currently prescribed to more than one-third of oncology patients. Two groups of ICIs are available: cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitors (ipilimumab and tremelimumab) and programmed cell death protein 1 (PD-1) or ligand 1 (PD-L1) inhibitors (pembrolizumab, nivolumab, cemiplimab, atezolizumab, avelumab, and durvalumab) (1–5).

ICIs stimulate the immune system and activate tumour-destroying T cells. However, this stimulus can trigger diverse autoimmune or autoinflammatory events in any organ or tissue. Cutaneous immune-related adverse events (cirAEs) are among the most frequent types of toxicity, affecting more than one-third of people on these drugs (6–8).

Several studies have associated the occurrence of cirAEs with tumour response to ICIs and longer survival rates. However, these results should be interpreted with caution, as they are based on retrospective reports (often with small sample sizes), subanalyses of clinical trials, and studies on a particular type of tumour, cirAE, or ICI (4, 9–14). Further research is needed to confirm or refute the protective effect of cirAEs.

We aimed to examine the influence of cirAEs on overall survival (OS) and progression-free survival (PFS) in ICI recipients through a real-world prospective study, controlling for confounding factors.

MATERIAL AND METHODS

We performed a prospective observational study in the Department of Dermatology of Dr. Balmis University General Hospital, a Spanish tertiary care hospital with a catchment population of 280,000 people. We included all adults who were starting ICI monotherapy or combination therapy (more than one ICI or ICI plus a traditional

cancer drug) for any type of cancer between March 2020 and May 2022, and who provided their informed consent to participate. The ICIs had to be approved for each participant's cancer type; we excluded people initiating ICIs as part of a clinical trial.

We planned a 12-month follow-up schedule. Patients were referred from the Department of Oncology to the Dermatology Outpatient Clinic for an initial comprehensive evaluation 14 days before the first dose of oncologic therapy, then attended follow-up visits at months 1, 3, 6, and 12. They also came for urgent consultations when necessary. One of 2 dermatologists (GJC or MBM) attended all participants. Study surveillance continued until March 2023; however, follow-up was extended (beyond 12 months or beyond March 2023) in individuals with skin toxicity when required. Participants who did not adhere to the follow-up protocol remained in the study regardless, as they could be referred to the Department of Dermatology if they presented any cirAE (**Fig. 1**).

At the initial study visit, we collected participants' epidemiologic variables and clinical variables through history-taking, physical examination, and review of medical records. We recorded participant age, sex, comorbidities, and oncologic history.

At later visits, we recorded data on the appearance, onset date, and features of cirAEs to determine to which category they belonged. Based on the current literature (15–17), we established 4 categories of cirAE: inflammatory dermatosis, immunobullous eruptions, alterations of epidermal keratinocytes, and pigmentary changes (Table SI). We performed cutaneous biopsies of any participants with an uncertain clinical diagnosis or a severe dermatosis needing histological confirmation. The pathologist was initially blinded to clinical manifestations, although cases were sometimes discussed to achieve the correct diagnoses through clinicopathologic correlation. We took clinical pictures in all cases of cutaneous toxicity. All cirAEs were managed as per usual clinical practice.

The institutional Review Board of our Health Department approved this study (reference numbers PI2021-003; 2020-0323), which was part of a multidisciplinary project (TOXIREL-immunoRELated TOXIcity, protocol number NMB-ATE-2019-01) promoted by the Department of Oncology of Dr. Balmis University General Hospital.

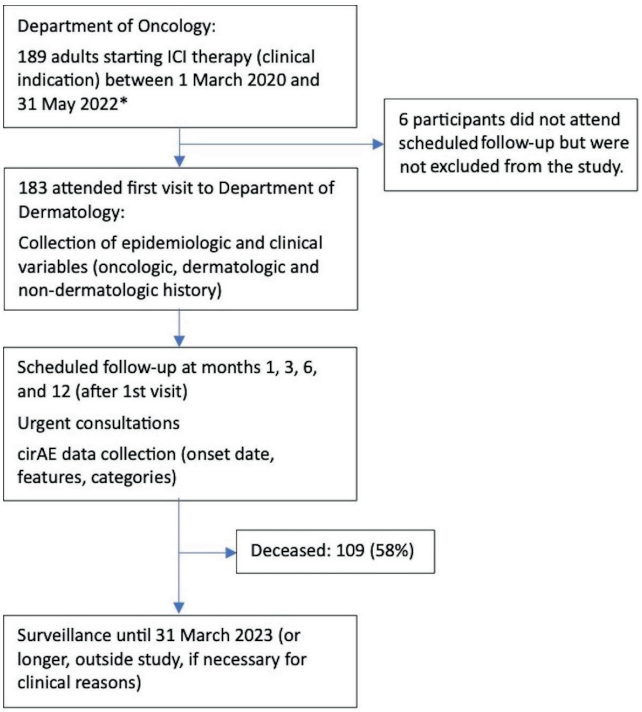

Fig. 1. Study flow diagram. *All participants provided their informed consent to participate. cirAE: cutaneous immune-related adverse event; ICI: immune checkpoint inhibitor.

Statistical analysis

We entered the study data into an anonymized database before performing a descriptive analysis. We described qualitative variables as frequencies and proportions, and quantitative variables as measures of central tendency and dispersion. We used the χ^2 test to calculate overall response (OR) to ICIs (complete response, partial response, or stable disease) in participants with and without cirAE occurrence, and to compare baseline features between participant survival and progression status.

We defined OS as the interval from the time of cancer diagnosis to death from any cause, with censoring at the last available information of the patient (last documented clinical visit or study closing date, 31 March 2023) when death did not occur. We defined PFS as the interval from ICI initiation to either disease progression or death, with censoring at the last documented clinical visit or study closing date when progression did not occur. Starting new oncologic treatment other than ICIs was not considered censoring, as cirAEs may appear after ICI interruption. To compare OS and PFS among participants with and without cirAEs, we used Kaplan–Meier curves and the log-rank test. To analyse the relationship of cirAEs with OS and PFS and determine possible confounders, we used a bivariable and multivariable Cox proportional hazards regression model, obtaining adjusted hazard ratios (HRs). *P* values under 0.05 were considered statistically significant. All statistical analyses were performed using Stata version 18 (StataCorp LLC, College Station, TX, USA).

RESULTS

We included 189 adults starting ICI treatment, of whom 82 (43.4%) experienced cutaneous toxicity. **Table I** presents demographic features, oncologic baseline characteristics, and the cumulative incidence of cirAEs for the total sample and according to death and disease progression status. The mean time from ICI initiation to onset of the first (or unique) cirAE was 89.4 (standard deviation 12.6) days. The most frequent category of cirAEs was inflammatory dermatoses (38.6%), and the most frequent types were pruritus (18.5%) and eczema (10.6%) (Table SI). Some 65 (34.2%) participants experienced extracutaneous toxicity and the main types of extracutaneous irAEs were digestive (13.8%) and endocrine (12.7%) toxicity (**Tables I, II and III**; legend).

Of the 189 participants, 112 (59.3%) achieved OR. OR was more frequent in participants with vs without cirAEs ($n=58$, 70.7% vs $n=54$, 50.5%; $p=0.005$).

Overall survival: mortality analysis

The χ^2 test showed a relationship between the following characteristics and mortality: non-small cell lung cancer (NSCLC; $p=0.001$), tumour stage IV ($p=0.005$), low performance status (PS) ($p=0.003$), negative PD-L1 tumour expression ($p<0.0001$), and use of PD-1 inhibitors ($p=0.023$). However, survival was higher in participants

Table I. Baseline characteristics and cutaneous toxicity variables for all participants and according to death and disease progression status

Variable	Total ($n = 189$)	Deceased			Progression		
		No ($n = 80$)	Yes ($n = 109$)	p-value	No ($n = 46$)	Yes ($n = 143$)	p-value
Age, years, mean (SD)	64.1 (11.4)	62.9 (12.4)	65.0 (0.6)	NS	63.3 (11.8)	64.4 (11.4)	NS
Sex, male, *n* (%)	138 (73.0)	54 (67.5)	84 (77.1)	NS	29 (63.0)	109 (76.2)	NS
Comorbidities[a], *n* (%)	46 (24.3)	22 (27.5)	24 (22.0)	NS	13 (28.3)	33 (23.1)	NS
Cancer type, *n* (%)				**0.001**			**0.001**
NSCLC	107 (56.6)	33 (41.2)	74 (67.9)		17 (37.0)	90 (62.9)	
Melanoma	18 (9.5)	13 (16.2)	5 (4.6)		7 (15.2)	11 (7.7)	
Kidney/urinary	27 (14.3)	14 (17.5)	13 (11.9)		5 (11.0)	22 (15.4)	
Others[b]	37 (19.6)	20 (25.0)	17 (15.6)		17 (37.0)	20 (14.0)	
Tumour stage, *n* (%)				**0.005**			**0.015**
I–II	8 (4.2)	6 (7.5)	2 (1.8)		5 (10.9)	3 (2.1)	
III	35 (18.5)	21 (26.2)	14 (12.8)		11 (23.9)	24 (16.8)	
IV	146 (77.2)	53 (66.2)	93 (85.3)		30 (65.2)	116 (81.1)	
Performance status, *n* (%)				**0.003**			**0.001**
Low (0–1)	157 (83.1)	74 (92.5)	83 (76.1)		45 (97.8)	113 (78.3)	
High (2–4)	32 (16.9)	6 (7.5)	26 (23.8)		1 (2.2)	31 (21.7)	
ICI category				**0.023**			**0.036**
Anti PD-L1	64 (33.9)	22 (27.5)	42 (38.5)		10 (21.7)	54 (37.8)	
Anti PD-1	114 (60.8)	50 (62.5)	65 (59.6)		31 (67.4)	84 (58.7)	
Anti CTLA-4/PD-1	10 (5.3)	8 (10.0)	2 (1.8)		5 (10.9)	5 (3.5)	
Previous CTx (yes), *n* (%)	91 (48.1)	34 (42.5)	57 (52.3)	NS	19 (41.3)	72 (50.3)	NS
Treatment line, *n* (%)				NS			NS
First	114 (60.3)	51 (63.7)	63 (57.8)		29 (63.0)	85 (59.4)	
Second or successive	75 (39.7)	29 (36.2)	46 (42.2)		17 (37.0)	58 (40.6)	
Treatment type, *n* (%)				NS			NS
Monotherapy	125 (66.1)	48 (60.0)	77 (70.6)		29 (63.0)	96 (67.1)	
Combination	64 (33.9)	32 (40.0)	32 (29.4)		17 (37.0)	47 (32.9)	
PD-L1 level, *n* (%)				**< 0.0001**			**0.001**
< 1% (negative)	58 (30.7)	19 (23.7)	39 (35.8)		7 (15.2)	51 (35.7)	
1–49%	26 (13.8)	11 (13.7)	15 (13.8)		8 (17.4)	18 (12.6)	
≥ 50%	31 (16.4)	6 (7.5)	25 (22.9)		3 (6.5)	28 (19.6)	
No value	74 (39.1)	44 (55.0)	30 (27.5)		28 (60.9)	46 (32.2)	
cirAEs, *n* (%)	82 (43.4)	50 (62.5)	31 (28.4)	**< 0.0001**	28 (60.9)	53 (37.1)	**0.005**
Category of cirAEs							
Inflammatory dermatoses	72 (38.1)	44 (55.0)	28 (25.7)	**< 0.0001**	23 (50.0)	49 (32.3)	0.056
Alteration of keratinocytes	12 (6.3)	8 (10.0)	4 (3.7)	NS	6 (13.0)	6 (4.2)	**0.032**
Pigmentary changes	5 (2.6)	3 (3.7)	2 (1.8)	NS	2 (4.3)	3 (2.1)	NS
Immunobullous eruptions	1 (0.5)	—	1 (0.9)	NS	—	1 (0.7)	NS
No. of cirAEs, *n* (%)				**< 0.0001**			**0.044**
None	108 (57.1)	30 (37.5)	78 (71.6)		19 (41.3)	89 (62.2)	
1	55 (29.1)	33 (41.2)	22 (20.2)		18 (39.1)	37 (25.9)	
≥ 2	26 (13.8)	17 (21.2)	9 (8.3)		9 (19.6)	17 (12.0)	
Extracutaneous irAEs[c], *n* (%)	65 (34.2)	45 (56.2)	20 (18.3)	**< 0.0001**	28 (60.9)	37 (25.9)	**< 0.0001**

[a]Chronic kidney disease, autoimmune disease, chronic viral infection (human immunodeficiency virus, hepatitis B virus, hepatitis C virus), and chronic liver failure. [b]Digestive tract cancer, lymphoma, head and neck cancer, cutaneous epidermoid carcinoma, small cell lung cancer, mesothelioma, hepatocarcinoma, and breast cancer. [c]Fever (2.1%), endocrine (12.7%), rheumatologic (7.9%), digestive (13.8%), pulmonary (6.9%), cardiological (1.1%), kidney (3.2%), neurologic (0.5%), and haematological (0.5%) irAEs were detected.
cirAE: cutaneous immune-related adverse event; CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; CTx: chemotherapy; ICI: immune checkpoint inhibitor; irAE: immune-related adverse event; *n*: number of participants; NS: non-significant; NSCLC: non-small cell lung cancer; PD-1: programmed cell death protein 1; PD-L1: programmed cell death protein ligand 1; SD: standard deviation. Statistically significant results are shown in bold.

without PD-L1 level data and in participants with extracutaneous irAEs and cirAEs, specifically inflammatory dermatosis ($p < 0.0001$) (Table I).

A total of 109 patients died after starting ICI therapy. Median OS time was reached at 27 months (2.3 years) of follow-up (Fig. S1), and the overall mortality rate was 24.2 per 100 patient-years. Mortality was lower in patients with vs without cutaneous toxicity (13.3 vs 35.9 per 100 patient-years; $p < 0.0001$; Table SII; **Fig. 2**A). In contrast, mortality was significantly higher in participants with NSCLC (37.4 per 100 patient-years; Table SII) than in those with kidney and urinary cancers, melanoma, or other tumours ($p < 0.0001$; Fig. S2). Melanoma showed lower rates of mortality compared with the remaining tumour types (9.4 vs 26.2 per 100 patient-years; $p = 0.021$; Table SII; Fig. S3).

Table II presents the results of the bivariable and multivariable analyses. Significant risk factors for mortality in the multivariable analysis were NSCLC (HR 3.21, 95% CI 1.89–5.45), kidney and urinary cancers (HR 2.49, 95% CI 1.54–5.36), tumour stage IV (HR 1.75, 95% CI 1.01–3.05), and high PS (HR 1.70, 95% CI 1.03–2.80). Protective factors for mortality were prior chemotherapy (HR 0.32, 95% CI 0.19–0.54), combination treatment (ICI and chemotherapy; HR 0.52, 95% CI 0.31–0.89), extracutaneous toxicity (HR 0.30, 95% CI 0.18–0.50), and cutaneous toxicity (HR 0.50, 95% CI 0.32–0.76). Some factors positively associated with survival in the bivariable analysis showed no association in the multivariable analysis (ICI use as second line of treatment, inflammatory dermatoses, appearance of 2 or more cirAEs, no PD-L1 level data).

Table II. Risk factors for mortality in patients receiving immune checkpoint inhibitors (multivariable Cox proportional hazards regression model)

Variable	Bivariable analysis HR (95% CI; *p*-value)	Multivariable analysis HR (95% CI; *p*-value)
Age, years, mean (SD)	1.00 (0.98–1.02; 0.901)	
Sex, female	0.80 (0.51–1.25; 0.332)	
Comorbidities[a]	0.70 (0.44–1.10; 0.126)	
Cancer type		
Others[b]	1	1
Melanoma	1.09 (0.52–2.30; 0.815)	—
Kidney/urinary	0.65 (0.23–1.79; 0.401)	**2.49 (1.54–5.36; 0.020)**
NSCLC	**2.43 (1.38–4.28; 0.002)**	**3.21 (1.89–5.45; < 0.0001)**
Tumour stage		
I–II	1	1
III	2.81 (0.63–12.5; 0.174)	—
IV	**5.11 (1.25–20.9; 0.023)**	**1.75 (1.01–3.05; 0.046)**
Performance status		
Low (0–1)	1	1
High (2–4)	1.57 (0.98–2.49; 0.057)	**1.70 (1.03–2.80; 0.036)**
ICI category		
Anti PD-L1	1	
Anti PD-1	0.81 (0.55–1.21; 0.311)	
Anti CTLA-4/PD-1	0.27 (0.07–1.13; 0.074)	
Previous chemotherapy (yes)	**0.63 (0.43–0.93; 0.020)**	**0.32 (0.19–0.54; < 0.0001)**
Treatment line		
First	1	
Second or successive	**0.63 (0.42–0.93; 0.022)**	
Treatment type		
Monotherapy	1	1
Combination	1.29 (0.85–1.97; 0.232)	**0.52 (0.31–0.89; 0.001)**
PD-L1 level		
< 1% (negative)	1	
1–49%	0.82 (0.45–1.50; 0.528)	
≥ 50%	1.41 (0.85–2.33; 0.183)	
No value	**0.43 (0.26–0.70; 0.001)**	
cirAEs	**0.39 (0.26–0.59; < 0.0001)**	**0.50 (0.32–0.76; 0.001)**
Category of cirAEs		
Inflammatory dermatoses	**0.43 (0.28–0.66; < 0.0001)**	
Alteration of keratinocytes	0.53 (0.19–1.44; 0.214)	
Pigmentary changes[c]	0.53 (0.13–2.16; 0.379)	
Immunobullous eruptions	0.57 (0.08–4.21; 0.580)	
No. of cirAEs		
None	1	
1	**0.42 (0.26–0.67; < 0.0001)**	
≥ 2	**0.35 (0.17–0.69; 0.003)**	
Extracutaneous irAEs[d]	**0.32 (0.20–0.52; < 0.0001)**	**0.30 (0.18–0.50; < 0.0001)**

[a]Chronic kidney disease, autoimmune disease, chronic viral infection, and chronic liver failure. [b]Digestive tract cancer, lymphoma, head and neck cancer, cutaneous epidermoid carcinoma, small cell lung cancer, mesothelioma, hepatocarcinoma, and breast cancer. [c]Pigmentary changes were observed in 5 patients (3 patients with NSCLC and 2 patients with melanoma). [d]Fever (2.1%), endocrine (12.7%), rheumatologic (7.9%), digestive (13.8%), pulmonary (6.9%), cardiological (1.1%), kidney (3.2%), neurologic (0.5%), and haematological (0.5%) irAEs were detected. CI: confidence interval; cirAE: cutaneous immune-related adverse event; CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; HR: hazard ratio; ICI: immune checkpoint inhibitor; irAE: immune-related adverse event; NSCLC: non-small cell lung cancer; PD-1: programmed cell death protein 1; PD-L1: programmed cell death protein ligand 1; SD: standard deviation. Statistically significant results are shown in bold.

Table III. Risk factors for progression in patients receiving immune checkpoint inhibitors (multivariable Cox proportional hazards regression model)

Variable	Bivariable analysis HR (95% CI; *p*-value)	Multivariable analysis HR (95% CI; *p*-value)
Age, years, mean (SD)	1.00 (0.99–1.02; 0.638)	
Sex, female	0.69 (0.47–1,02; 0.061)	
Comorbidities[a]	0.79 (0.53–1.16; 0.232)	
Cancer type		
Others[b]	**1**	**1**
Kidney/urinary	1.78 (0.97–3.26; 0.064)	**1.97 (1.18–3.30; 0.001)**
Melanoma	1.1 (0.52–2.29; 0.806)	—
NSCLC	**2.04 (1.25–3.31; 0.004)**	—
Tumour stage		
I–II	**1**	
III	2.41 (0.72–8.03; 0.151)	
IV	**3.70 (1.17–11.7; 0.026)**	
Performance status		
Low (0–1)	1	1
High (2–4)	**2.11 (1.41–3.15; < 0.0001)**	**2.02 (1.33–3.07; 0.001)**
ICI category		
Anti PD-L1	1	
Anti PD-1	**0.68 (0.48–0.96; 0.030)**	
Anti CTLA-4/PD-1	0.50 (0.20–1.26; 0.142)	
Previous chemotherapy (yes)	1.15 (0.83–1.60; 0.402)	
Treatment line		
First	1	
Second or successive	1.03 (0.74–1.44; 0.853)	
Treatment type		
Monotherapy	1	
Combination	0.95 (0.67–1.34; 0.760)	
PD-L1 level		
< 1% (negative)	1	**1**
1–49%	0.62 (0.36–1.07; 0.085)	**0.51 (0.30–0.86; 0.012)**
≥ 50%	0.99 (0.62–1.57; 0.961)	—
No value	**0.50 (0.33–0.75; 0.001)**	**0.39 (0.26–0.58; < 0.0001)**
cirAEs	**0.51 (0.36–0.72; < 0.0001)**	**0.54 (0.38–0.77; 0.001)**
Category of cirAEs		
Inflammatory dermatoses	**0.60 (0.42–0.84; 0.004)**	
Alteration of keratinocytes	**0.42 (0.18–0.96; 0.039)**	
Pigmentary changes[c]	0.55 (0.17–1.72; 0.304)	
Immunobullous eruptions	0.78 (0.11–5.62; 0.810)	
No. of cirAEs		
No	1	
1	**0.59 (0.40–0.86; 0.007)**	
≥ 2	**0.45 (0.27–0.76; 0.003)**	
Extracutaneous irAEs[d]	**0.35 (0.24–0.51; < 0.0001)**	**0.36 (0.24–0.54; < 0.0001)**

[a]Chronic kidney disease, autoimmune disease, chronic viral infection, chronic liver failure. [b]Digestive tract cancer, lymphoma, head and neck cancer, cutaneous epidermoid carcinoma, small cell lung cancer, mesothelioma, hepatocarcinoma, and breast cancer. [c]Pigmentary changes were observed in 5 patients (3 patients with NSCLC and 2 patients with melanoma). [d]Fever (2.1%), endocrine (12.7%), rheumatologic (7.9%), digestive (13.8%), pulmonary (6.9%), cardiological (1.1%), kidney (3.2%), neurologic (0.5%), and haematological (0.5%) irAEs were detected. CI: confidence interval; cirAE: cutaneous immune-related adverse event; CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; HR: hazard ratio; ICI: immune checkpoint inhibitor; irAE: immune-related adverse event; NSCLC: non-small cell lung cancer; PD-1: programmed cell death protein 1; PD-L1: programmed cell death protein ligand 1; SD: standard deviation. Statistically significant results are shown in bold.

Progression-free survival

Progression was significantly more frequent in participants with NSCLC ($p=0.001$), tumoral stage IV ($p=0.015$), low PS ($p=0,001$), and anti-PD-1 therapy ($p=0.036$). However, progression was less frequent in participants without PD-L1 level data ($p=0.001$) and in those with extracutaneous irAEs ($p<0.0001$) and cirAEs ($p=0.005$), specifically alterations of keratinocytes ($p=0.032$) (Table I).

A total of 143 participants showed disease progression after starting ICI therapy. The maximum surveillance time was 38.9 months (3.24 years). Median PFS time was reached at 5.4 months (0.45 years) of follow-up (Fig. S4). Participants with cirAEs showed a lower progression rate than those without (69.0 vs 146.2 per 100 patient-years; $p=0.001$; Fig. 2B). Progression also varied significantly according to tumour type; participants with NSCLC were most likely to experience disease progression (130.9 per 100 person-years; $p=0.011$; Fig. S5). The difference in disease progression between people with melanoma and those with other tumours was nonsignificant (60.9 vs 109.1 per 100 patient-years; $p=0.147$; Fig. S6).

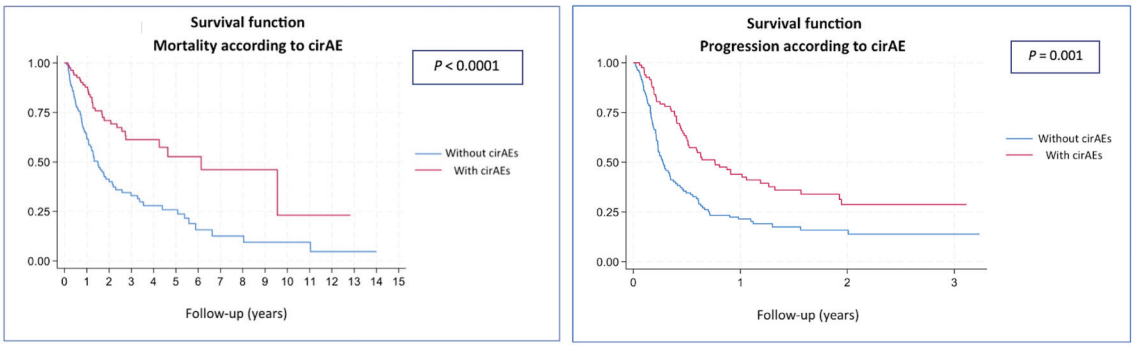

Fig. 2. (A) Survival function for mortality (overall survival) according to appearance of cutaneous immune-related adverse events (cirAEs). Mortality rates were lower in participants with cirAEs vs without cirAEs (13.3 vs 35.0 per 100 patient-years; $p < 0.0001$). (B) Survival function for progression (progression-free survival) according to appearance of cutaneous immune-related adverse events (cirAEs). Progression rates were lower in participants with cirAEs vs. without cirAEs (69.0 vs 146.2 per 100 person-years; $p = 0.001$).

Table III presents the results of the bivariable and multivariable analyses. Significant risk factors for progression in the multivariable analysis were kidney and urinary cancers (HR 1.97, 95% CI 1.18–3.30) and high PS (HR 2.02, 95% CI 1.33–3.07); the effect observed for NSCLC and tumoral stage in the bivariable analysis were nonsignificant in the multivariable analysis. Protective factors for disease progression were cutaneous toxicity (HR 0.54, 95% CI 0.38–0.77), extracutaneous toxicity (HR 0.36, 95% CI 0.24–0.54), PD-L1 levels of 1% to 49% (HR 0.51, 95% CI 0.30–0.86), and lack of PD-L1 level data (HR 0.39; 95% CI 0.26–0.58). Some factors associated with better PFS in the bivariable analysis showed no relationship in the multivariable analysis (anti PD-1 therapy, inflammatory dermatoses, alteration of keratinocytes, appearance of 2 or more cirAEs).

DISCUSSION

Different from retrospective analyses, reports with small samples, and studies focused on a specific type of cancer or ciRAE, we conducted a real-world prospective observational study and reported survival data in a considerable sample of patients with different types of cancer on ICI therapy with and without cirAEs, adjusting for confounders such as cancer type, tumour stage, and ICI category. In general, our results confirm the positive association of cirAE occurrence with oncologic response to ICI, OS, and PFS.

Different authors have reported that cutaneous toxicity is associated with tumoral response and longer survival in patients treated with ICIs (9–14, 18–25), but, owing to the limitations of these reports, their results should be interpreted with caution (26–29).

A small number of prospective studies have reported the relationship between cirAEs and survival outcomes in patients receiving ICI therapy (20, 22). However, 1 included only people with advanced (stage III or IV) melanoma who were receiving nivolumab or pembrolizumab as part of a clinical trial or on compassionate grounds (22), and another selected participants from 2 (national and single-centre) databases (20). In contrast, we included all people with cancer who were starting an ICI approved for their tumour type, and participants attended scheduled follow-up visits in a real-world setting.

Multiple retrospective studies have found a positive association between cutaneous toxicity (especially vitiligo) and positive oncologic outcomes in advanced melanoma patients on ICI therapy (12–14, 18, 24, 25, 30). However, this association is controversial in people with NSCLC. Some authors have reported longer survival in NSCLC patients who experience any kind of irAE (cutaneous or extracutaneous) (4, 9), while others have observed no difference in PFS or OS according to cirAE occurrence (29). Our multivariable analysis suggested that cutaneous toxicity was associated with better OS and PFS, and was therefore a protective factor for mortality and progression independently of cancer type, tumour stage, and ICI category.

Some studies have associated bullous disorders with tumoral response (11, 31), and others have associated specific cirAE types other than vitiligo (e.g., rash, isolated pruritus, eczematous, lichenoid, psoriasiform, and acneiform eruptions) with better survival (21, 22). Although we did not assess the influence of specific cirAE types on survival, we studied categories of dermatosis, and found no relationship between any single category and OS or PFS. Although pigmentary changes were not associated with survival, people with melanoma showed longer OS than those with other cancer types in the log-rank test. In this sense, we believe there is a need for further research into the association between vitiligo and survival in people with melanoma on ICI therapy, as studies reporting positive associations were published before the widespread use of immunotherapy (32–34).

We also studied the influence of extracutaneous irAEs on OS and PFS, and found that extracutaneous toxicity behaved as an independent protective factor for mortality and progression, in line with previous studies (4, 14, 35). However, the occurrence of multiple (≥2) cirAEs

showed no association with survival outcomes in the multivariable analysis.

In our study, kidney and urinary cancers, NSCLC, tumour stage IV at baseline, and high PS were associated with worse OS; but only kidney and urinary cancers and high PS were negatively associated with PFS. Kidney and urinary cancers have relatively poor 5-year survival rates, and clinicians tend to prescribe ICIs for these cancer types later in disease evolution, often as second-line therapy (36). This could explain why kidney and urinary cancers remained a significant risk factor for progression as well as mortality, unlike other tumours such as NSCLC. One possible reason for the better OS in people with previous chemotherapy is that we calculated OS from the date of cancer diagnosis, and participants with previous chemotherapy had been alive for longer with active disease before ICI initiation. We have no explanation for the positive association of low PD-L1 levels and lack of PD-L1 level data with better PFS. It is possible that PD-L1 level does not have a clear influence on survival in patients receiving ICI.

Strengths and limitations

We performed a real-world prospective observational study confirming the positive relationship between cirAE appearance with OS and PFS. One limitation of our study is the single-centre design, with the sample restrictions that entails; nevertheless, we included more patients than many other studies (10, 12, 13, 18, 22–25, 37, 38). There were few participants with severe cirAEs and receiving systemic therapies to treat cirAEs, hence we did not study the association between these factors with OS and PFS because the statistical power of this analysis would have been low. Another possible limitation is that we did not perform a landmark analysis (4, 12, 18, 21, 22, 24). However, the median latency time until the first cirAE in our population was 57.5 (interquartile range 15–126) days, shorter than the median PFS time of 0.45 years (5.4 months). This means the risk of guarantee-time bias was low, as more than 75% of patients with cirAEs had this exposure (occurrence of cirAEs) before half of the patients experienced tumour progression. Additionally, in line with other authors (29), we believe that the landmark approach could introduce a selection bias, as it considers only the fraction of cirAE emerging by certain time points.

Conclusions

In our real-world prospective study of people receiving ICIs, cirAE occurrence showed a positive association with OR, OS, and PFS, and acted as a protective factor for mortality and progression independently of cancer type, tumoral stage, ICI therapy, and other factors. The findings were similar for extracutaneous irAEs. Specific categories of dermatosis had no effect on OS or PFS. These findings are relevant for the management of patients on ICI therapy. Further prospective multicentre studies or multiple cohort studies with broader samples are needed to confirm this relationship.

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Patient consent on file: All patients signed the informed consent form to participate in this study.

*Ethical statement***:** This research has been performed according with principles stablished in the Declaration of Helsinki about medical research involving human subjects and Declaration of Taipei of research on health databases, big data and biobanks

The authors have no conflicts of interest to declare.

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