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Cutaneous immune-related adverse events and survival during immune checkpoint inhibitor therapy: a pilot meta-analysis stratified by handling of immortal-time bias.

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Abstract

Importance:

Cutaneous immune-related adverse events (cirAEs) are read as a sign that checkpoint blockade is working, but a cirAE is recorded only in patients who survive long enough to develop it, so analyses that fix cirAE status at baseline credit the exposed group with immortal time.

Objective:

To describe the association of cirAEs with overall survival (OS) and progression-free survival (PFS) in estimates that handle immortal time, and to compare these with estimates that do not.

Methods:

Studies came from author-held reports and web searches seeded with known studies (17–18 October 2026); no bibliographic database was searched. Cohort studies reporting a hazard ratio (HR) for any cirAE versus none were included. Each estimate was classified as handling immortal time (Tier A: time-dependent Cox or landmark), partially (Tier B), or not (Tier C/D). Tier A estimates were read individually; random-effects pooling and between-tier meta-regression were exploratory. Certainty was rated with GRADE.

Results:

Thirteen studies were included. OS, immortal time handled: three cohorts (4,123 patients) gave HRs of 0.21 (95% CI 0.05–0.62), 0.52 (0.35–0.78) and 0.87 (0.79–0.98); pooled 0.57 (0.13–2.56; I^2 = 81%). OS, not handled: five cohorts pooled to 0.55 (0.43–0.70; I^2 = 1%). PFS, handled: 0.63 (0.21–1.87); not handled: 0.50 (0.12–2.06). The ratios of HRs between tiers (OS 1.29, 0.67–2.49; PFS 1.22, 0.40–3.71) were not significant, so these data neither show nor exclude inflation of uncorrected estimates. Certainty was very low for every outcome.

Conclusions and relevance:

Every cohort that handled immortal time found an OS HR below 1, but the size of the association is uncertain, and the gap from uncorrected studies may reflect tumour mix and adjustment.

Keywords. *Immune checkpoint inhibitors; cutaneous immune-related adverse events; immortal time bias; overall survival; meta-analysis.*
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Introduction

Skin toxicity is the most common and usually the earliest immune-related adverse event of PD-1, PD-L1 and CTLA-4 blockade. Three meta-analyses have reported that patients who develop it live longer, with pooled OS hazard ratios of 0.50 (9 studies), 0.61 (23 studies) and 0.54 (45 studies).[1–3] Those figures are increasingly quoted as reassurance that a rash is a good sign.

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The weakness is timing. Median onset of a cirAE is about two months after the first dose (2.2 months in Xu et al.; 57.5 days in Juan-Carpena et al.),[4,5] and a patient who dies or progresses earlier never has the chance to develop one. When cirAE status is entered as if it were known at baseline, the weeks before onset are counted as exposed, event-free time, and the analysis favours the exposed group even if the exposure does nothing (Figure 1).[6] The distortion can be large: for checkpoint-inhibitor thyroiditis in 6,596 patients the adjusted HR moved from 0.47 to 0.80 when the exposure was made time-varying,[7] and for vitiligo in melanoma from 0.20 to 0.53.[8]

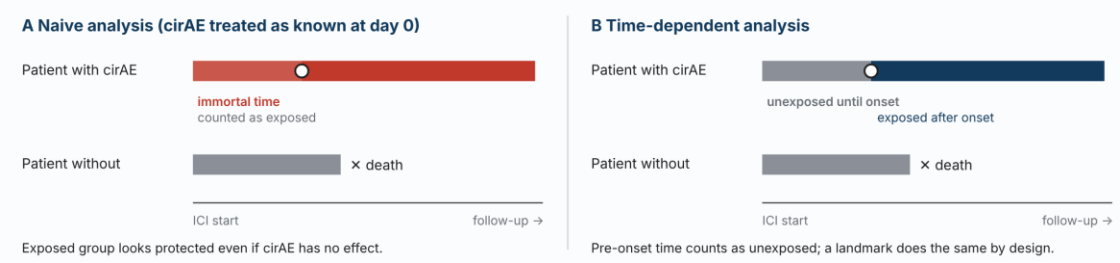


Figure 1. How immortal time inflates the apparent benefit of a cirAE.

Grey, unexposed person-time; red, person-time wrongly classified as exposed; navy, correctly exposed person-time; open circle, cirAE onset.

Methods

Design and eligibility

This is a pilot meta-analysis reported following PRISMA 2020 where applicable.[9] No protocol was registered. The tier framework and analysis plan were written before pooling but after the studies had been identified, so the analyses should not be read as prespecified. Eligible studies enrolled adults with any cancer treated with an immune checkpoint inhibitor, alone or combined; compared patients with any cirAE against patients without one; and reported an HR with 95% CI for OS or PFS. Studies reporting an HR for a single cutaneous phenotype only (such as vitiligo) formed a separate secondary category and were not pooled with any-cirAE estimates. Studies whose only comparator was other irAEs, studies reporting cutaneous irAEs only in combination with other organ systems, case series of fewer than 20 patients, and reports without an extractable HR were excluded; eligible cohorts without an extractable HR are listed in an evidence map in the supplementary workbook. Where cohorts overlapped (two Mass General Brigham/Dana-Farber cohorts[10,11] and two TriNetX cohorts[11,12]), the estimate with stronger immortal-time handling was kept, then the larger.

The two most recent meta-analyses reported a landmark subgroup (OS HR 0.69 and 0.59)[2,3] but defined it as any study applying a minimum six-week threshold. They did not separate time-dependent models from landmark analyses, did not grade adequacy of correction, and did not use studies that report both analyses on the same patients.

The objectives of this study were, first, to estimate the association between any cirAE and OS and PFS in cohorts that handle immortal time; second, to compare these estimates with those from cohorts that do not; and third, to map how the included studies handled exposure timing and how much usable corrected evidence exists.

The TriNetX estimate from one multi-organ irAE study[11] was placed in sensitivity analysis only. Its "cutaneous" group is a cluster of patients whose predominant irAE factor was cutaneous, which can include patients with other organ involvement, and the abstract does not state its comparator or size. Both points may conflict with the eligibility rules above, and the full text was not accessed.

Identification of studies

For this pilot, studies came from reports held by the first author and from targeted searching with a general web search engine on 17–18 October 2026, using queries that combined known study titles or first authors with terms for cutaneous irAEs, survival, landmark and time-dependent analysis; the query log is in the supplementary workbook (Figure 2). Seeding searches with studies already known is circular and selection-prone, and is not reproducible in the way a database search is. The PubMed string drafted for a database search, which was not run for this pilot, is:

("immune checkpoint inhibitors"[MeSH] OR "immune checkpoint"[tiab] OR "checkpoint inhibitor*"[tiab] OR "checkpoint blockade"[tiab] OR "PD-1"[tiab] OR PD1[tiab] OR "PD-L1"[tiab] OR PDL1[tiab] OR "programmed cell death"[tiab] OR "CTLA-4"[tiab] OR CTLA4[tiab] OR

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nivolumab[tiab] OR pembrolizumab[tiab] OR ipilimumab[tiab] OR tremelimumab[tiab] OR atezolizumab[tiab] OR durvalumab[tiab] OR avelumab[tiab] OR cemiplimab[tiab] OR dostarlimab[tiab] OR retifanlimab[tiab] OR spartalizumab[tiab] OR cosibelimab[tiab] OR relatlimab[tiab] OR toripalimab[tiab] OR tislelizumab[tiab] OR sintilimab[tiab] OR camrelizumab[tiab] OR penpulimab[tiab] OR serplulimab[tiab] OR zimberelimab[tiab] OR sugemalimab[tiab] OR adebrelimab[tiab] OR envafolimab[tiab] OR cadonilimab[tiab] OR ivonescimab[tiab] OR "immune-related adverse event*"[tiab] OR irAE*[tiab]) AND (cutaneous[tiab] OR skin[tiab] OR dermat*[tiab] OR rash[tiab] OR pruritus[tiab] OR vitiligo[tiab] OR lichenoid[tiab] OR psoriasi*[tiab] OR pemphigoid[tiab] OR bullous[tiab] OR eczema*[tiab] OR alopecia[tiab]) AND (survival[tiab] OR mortality[tiab] OR prognos*[tiab] OR "hazard ratio"[tiab])

Selection process

One reviewer (HSB) screened every record, comprising the author-held files and the hits from each web search, and then assessed every retrieved full-text report against the eligibility criteria. No second reviewer screened records or reports, so screening was not done independently or in duplicate, and no automation tools were used. Reasons for excluding reports at full-text assessment are given in Figure 2.

Extraction and classification

Every HR a report gave was extracted (univariable, multivariable, each landmark, time-dependent), with covariates, landmark time, median cirAE onset, analytic sample size, and overlap group. HRs coded as no-cirAE versus cirAE were inverted. The method of cirAE ascertainment was also recorded for each study (dermatologist confirmation, histology, CTCAE grading, and any adverse drug reaction causality scale such as WHO-UMC or Naranjo). Data extraction was done by the same single reviewer (HSB) without independent duplication.

Each estimate was described on four dimensions: time handling, adjustment (univariable or multivariable), exposure definition (any cirAE, a single phenotype, or a cutaneous-predominant cluster), and comparator (Table 1). The tier refers to time handling only:

- **A1**: cirAE as a time-dependent covariate in Cox regression or equivalent.
- **A2**: Landmark: exposure fixed by the landmark, earlier events excluded, follow-up from the landmark.
- **B**: Partial handling: pre-onset time removed from the exposed group only, or restriction by onset time without a landmark origin.
- **C**: cirAE as a fixed baseline covariate. **D**: Handling not reported.

A landmark analysis removes immortal time when exposure is classified only from information available by the landmark and follow-up starts there. It answers a narrower question, survival from the landmark among patients still alive and event-free, and its result depends on landmark timing. An early landmark classifies later-onset cirAEs as unexposed; this misclassification often pulls the HR toward 1, but not necessarily, because it may be related to prognosis. A late landmark restricts the sample to long survivors. Neither approach removes confounding by response or time on treatment. Formal risk-of-bias assessment with QUIPS was not done in this pilot; immortal-time handling, the bias of primary interest, was rated for every estimate and informed the certainty assessment below.

Synthesis

The analysis had four levels, set before pooling. (1) Primary: the Tier A cohorts, presented and interpreted study by study, with a pooled estimate reported as exploratory. (2) Secondary: a Tier C/D pool. (3) Exploratory: the comparison between tiers. (4) Separate: one estimate of uncertain eligibility,[11] one with partial handling,[12] one for a single phenotype[8] and one built from dependent estimates,[13] each added to the relevant pool as a sensitivity analysis.

HRs were log-transformed and standard errors derived from the 95% CI as (ln upper − ln lower)/3.92. This assumes a symmetric interval on the log scale; several reported intervals are asymmetric after rounding (for example, that of one landmark study[14]), so the derived standard errors are approximations. Estimates were pooled with REML random effects. Pooled 95% CIs are HKSJ intervals using the ad hoc variant, in which the variance scaling factor is truncated below at 1; Wald intervals and DerSimonian–Laird (DL) estimates are in Table 2. For two-study pools, the HKSJ interval, with one degree of freedom, is shown but is too wide to be informative. Prediction intervals are given where $k \geq 4$. I^2 is reported from the DL fit and τ^2 from REML. The difference between tiers was estimated by mixed-effects meta-regression with a tier indicator, a single τ^2 shared by both tiers, and Knapp–Hartung adjustment; because the shared τ^2 reweights studies, the ratio it gives is not the simple ratio of the two pooled HRs. With fewer than ten studies, this meta-regression has little power and was treated as exploratory. Analyses were run in custom Python code (NumPy, SciPy) and reproduced to two decimal places with

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the R package metafor 4.4 (rma, method = "REML", test = "adhoc"). Sensitivity analyses covered adding each of the four separately handled estimates in turn; leave-one-out; Tier A1 and A2 separately; adjusted-only estimates; and stratification by tumour. Funnel-plot methods were not applied: with eight OS estimates in the two main groups (nine with the dependent estimate), and tiers of different expected effect, such tests would be underpowered and confounded by tier.

Certainty assessment

Certainty in each pooled estimate (OS and PFS, Tier A and Tier C/D) was rated with the GRADE approach for prognostic factors,[15] under which a body of cohort evidence starts at high certainty and is rated down for risk of bias, inconsistency, indirectness, imprecision and publication bias. Because QUIPS was not applied, risk of bias was judged mainly from immortal-time handling and adjustment (Table 1). Inconsistency was judged from I^2, τ^2 and the spread of point estimates; imprecision from whether the HKSJ interval spanned both a clinically important association and no association; and publication bias from the seeded, non-systematic way studies were identified. Ratings were made by one reviewer (HSB).

Results

The 15 author-held files reduced to 11 unique reports after four exact duplicates were removed; five were excluded (two prior meta-analyses, a news report, a Spanish-language summary and a thyroiditis study), leaving six reports of five studies. Targeted searching led to 20 further reports, of which three could not be retrieved, and nine were excluded, leaving eight studies (Figure 2). Among the excluded reports, a cohort of US veterans reported thyroid and cutaneous irAEs only in combination and so could not contribute a skin-specific estimate.[16] Of the 13 included studies, 12 gave an HR for any cirAE and one, a vitiligo cohort,[8] for a single phenotype.

Gulati et al.[13] counted 871 treatment lines in 673 patients and reported mild and severe skin toxicity against a single shared comparator. Its fixed-exposure HRs were combined across strata but, because both the repeated lines and the shared comparator make the combined estimate dependent, it was analysed separately rather than in the Tier C/D pool. The authors also fitted multivariable time-dependent models but reported them only as P values (OS: mild P = .001, severe P = .037); the corresponding HRs were not available. Four estimates were therefore used in sensitivity analysis only: those of Gulati et al., Wan et al., Tang et al. (Tier B) and Dousset et al. (Table 1).

Table 1. Characteristics of included studies and extracted hazard ratios

Study	Setting; cancer	n	Analysis	Tier	OS HR (95% CI)	PFS HR (95% CI)
Immortal time handled (Tier A; primary evidence, read individually)						
Haratani et al.[14]	Japan; NSCLC, nivolumab	134[b]	6-week landmark, multivariable	A2	0.21 (0.05–0.62)	0.48 (0.23–0.91)
Chan et al.[17]	Australia; melanoma, anti-PD-1	82	Time-dependent Cox	A1	—	0.46 (0.23–0.91)[a]
Zhang et al.[10]	USA, MGB/DFCI; pan-cancer	3,731	Time-varying Cox, multivariable (6-month landmark 0.83)	A1	0.87 (0.79–0.98)	—
Xu et al.[4]	China; NSCLC	262	Time-dependent Cox, multivariable	A1	0.52 (0.35–0.78)	0.91 (0.65–1.28)
Fixed exposure or not reported (Tier C/D; secondary pool)						
Berner et al.[18]	Switzerland; NSCLC, prospective	73	Not reported	D	0.29 (0.12–0.71)	0.22 (0.09–0.49)
Cho et al.[19]	Taiwan; pan-cancer	468	Fixed, univariable (multivariable 0.69, 0.52–0.91, Tier B)[c]	C	0.58 (0.44–0.76)	—
Jurado et al.[20]	Spain; NSCLC	510	Fixed, multivariable	C	0.60 (0.44–0.80)	0.74 (0.56–0.99)

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Study	Setting; cancer	n	Analysis	Tier	OS HR (95% CI)	PFS HR (95% CI)
Lim et al.[21]	Singapore; melanoma, anti-PD-1	43	Fixed (log-rank/Cox); OS from stage IV diagnosis	C	0.29 (0.10–0.83)	—
Juan-Carpena et al.[5]	Spain; pan-cancer, prospective	189	Fixed, multivariable; no landmark	C	0.50 (0.32–0.76)	0.54 (0.38–0.77)
Sensitivity analyses only						
Gulati et al.[13]	USA, NYU; pan-cancer	673[d]	Fixed; mild + severe combined	C	0.49 (0.40–0.60)	0.42 (0.35–0.51)
Wan et al., TriNetX arm[11]	Global EHR network; pan-cancer	NR[f]	6-month landmark; cutaneous-predominant cluster	A2	0.62 (0.48–0.82)	—
Tang et al.[12]	TriNetX; anti-PD-(L)1	7,008[c]	Onset ≤ 3 months, no landmark origin	B	0.76 (0.70–0.82)	—
Dousset et al.[8] (vitiligo)	France; melanoma	457	Time-varying (fixed exposure: 0.20)	A1	0.53 (0.39–0.72)	0.27 (0.18–0.40)

[a]Progression or death. [b]Cohort size; the 6-week landmark analyses included 130 patients for OS and 105 for PFS.

Tier A totals in the text use the OS analytic sample (130 + 3,731 + 262 = 4,123). [c] Patients with a cirAE; total cohort not reported. [d]673 patients contributing 871 treatment lines; mild and severe strata share one comparator. [e]Cho et al., Table 2; the authors subtracted pre-onset time from the exposed group only. [Estimate] taken from the published abstract (full text not accessed). The TriNetX analytic cohort was 18,162 (5,538 with any irAE, 12,624 without); the size of the cutaneous cluster, its comparator, and any matching applied to it were not reported. MGB/DFCI, Mass General Brigham/Dana-Farber Cancer Institute; NR, not reported; NSCLC, non-small cell lung cancer.

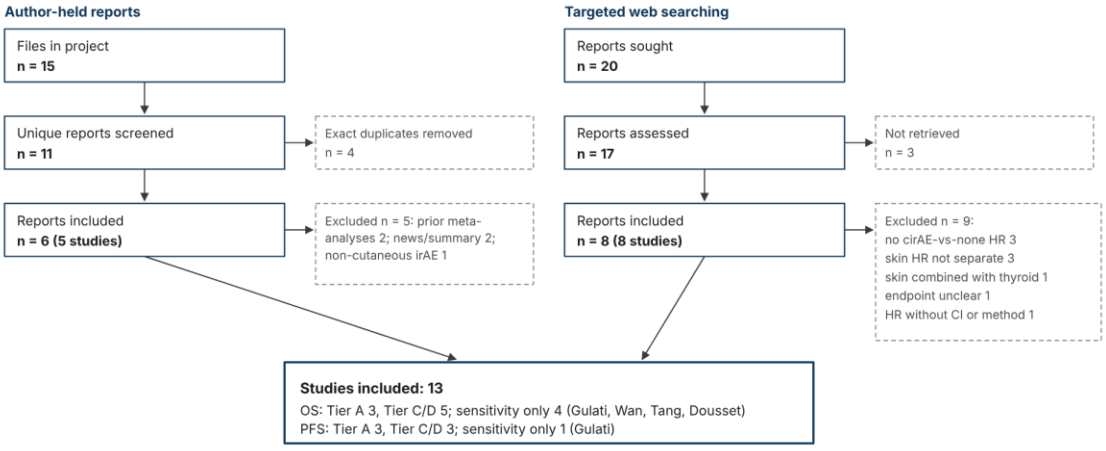


Figure 2. Flow of reports and studies (PRISMA-style).

No bibliographic database search was done. Reports not retrieved: Bottlaender et al. and Hirotsu et al. (paywalled full text) and Nardin et al. (repository access blocked). Excluded after assessment: Quach et al., Aso et al. and Oliveira Filho et al. (no HR for cirAE vs none; listed in the evidence map); Naqash et al., Cook et al. and an ESMO-IO 2023 abstract (no separate skin HR); Rehmani et al.[16] (thyroid and cutaneous combined; aHR 0.57, 0.46–0.71); Villa-Crespo et al. (endpoint unclear); Ricciuti et al. (HR without CI or confirmed method). Full citations for reports that were not retrieved or were excluded are given in the supplementary evidence map.

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Overall survival

The three Tier A cohorts (4,123 patients analysed) are the primary evidence. Haratani et al.[14] found 0.21 (0.05–0.62), Xu et al.[4] 0.52 (0.35–0.78) and Zhang et al.[10] 0.87 (0.79–0.98). All three point estimates are below 1, but they differ more than chance would explain ($I^2 = 81\%$; $\tau^2 = 0.227$). An exploratory pool gave 0.57 (95% CI 0.13–2.56), with Zhang carrying 45% of the weight, Xu 39% and Haratani 16%. The upper limit above 1 reflects disagreement among three studies, not evidence of harm. Tier C/D estimates (five cohorts, 1,283 patients) pooled to 0.55 (0.43–0.70) with no detectable heterogeneity ($I^2 = 1\%$) and a prediction interval of 0.41–0.73; adding Gulati gave 0.52 (0.44–0.62). In exploratory meta-regression, the ratio of HRs, Tier A to Tier C/D, was 1.29 (0.67–2.49; P = .39) (Figure 3). With eight studies, this comparison has little power, and a non-significant result is not evidence that the tiers agree.

Zhang et al.[10], the largest included time-varying study with detailed exposure phenotyping (dermatologist-adjudicated, across tumour types), found that its time-varying model and 6-month landmark (0.83) agreed. Dropping any one of the three Tier A studies left a two-study pool with a point estimate between 0.41 (without Zhang) and 0.70 (without Haratani); the HKSJ intervals of these pools (for example 0.03–17.7) carry no useful information (Table 2). Adding the Wan TriNetX arm gave 0.63 (0.33–1.20); adding Tang et al.[12] instead gave 0.69 (0.38–1.26).

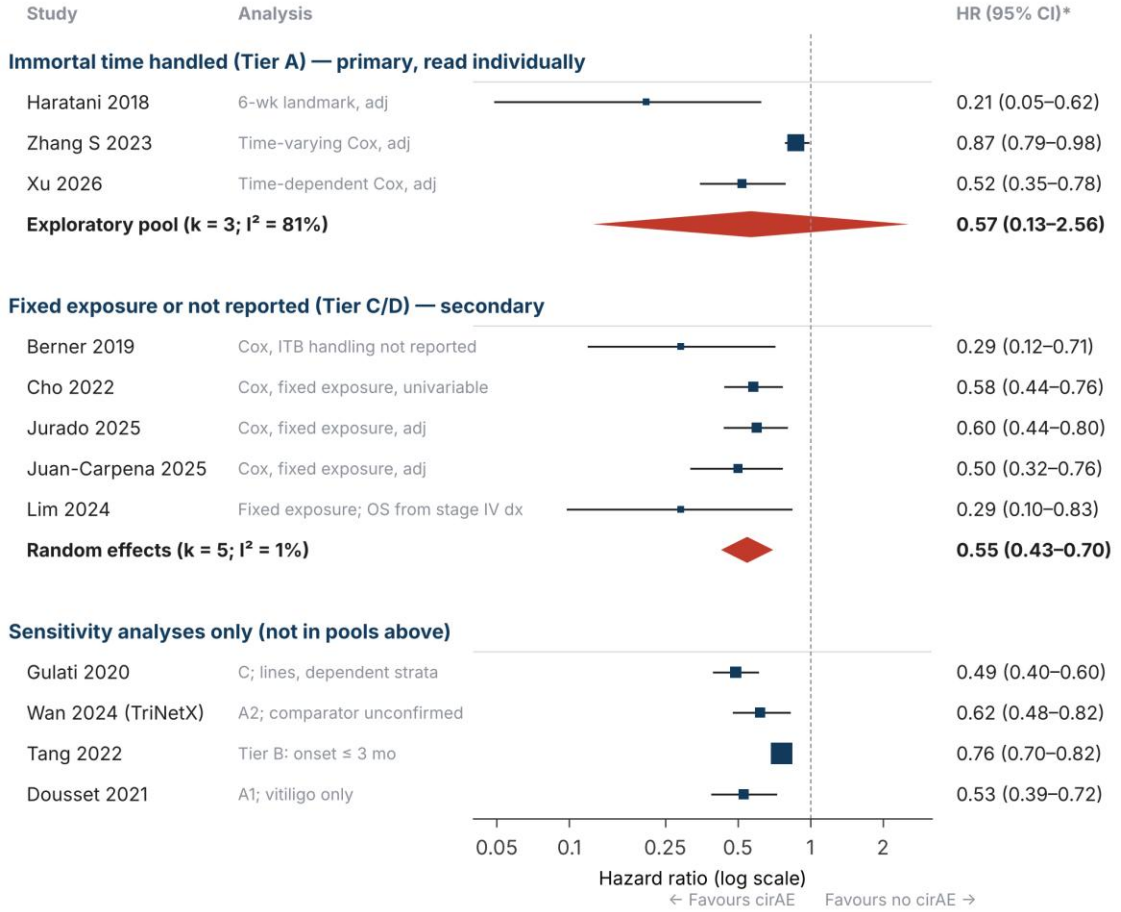


Figure 3. Overall survival in patients with versus without a cirAE, by handling of immortal time.

*Tier A studies are the primary evidence; their pooled diamond is exploratory. Squares are sized by inverse-variance weight; diamonds show REML pooled estimates with HKSJ 95% CIs (*study rows show each study's own*

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CI). Arrows mark intervals extending beyond the axis. Ratio of HRs, Tier A versus Tier C/D (exploratory meta-regression): 1.29 (0.67–2.49).

Progression-free survival

Tier A PFS estimates were 0.48 (Haratani), 0.46 (Chan), and 0.91 (Xu); exploratory pool 0.63 (0.21–1.87; I^2 = 59%). Tier C/D gave 0.50 (0.12–2.06; I^2 = 74%; three cohorts), or 0.49 (0.25–0.97) with Gulati; ratio of HRs 1.22 (0.40–3.71; P = .64). The largest corrected study found no constant PFS association (0.91) and, using a time-varying coefficient, an early benefit that faded, which its authors attribute partly to more intensive assessment of patients seen for skin problems.[4]

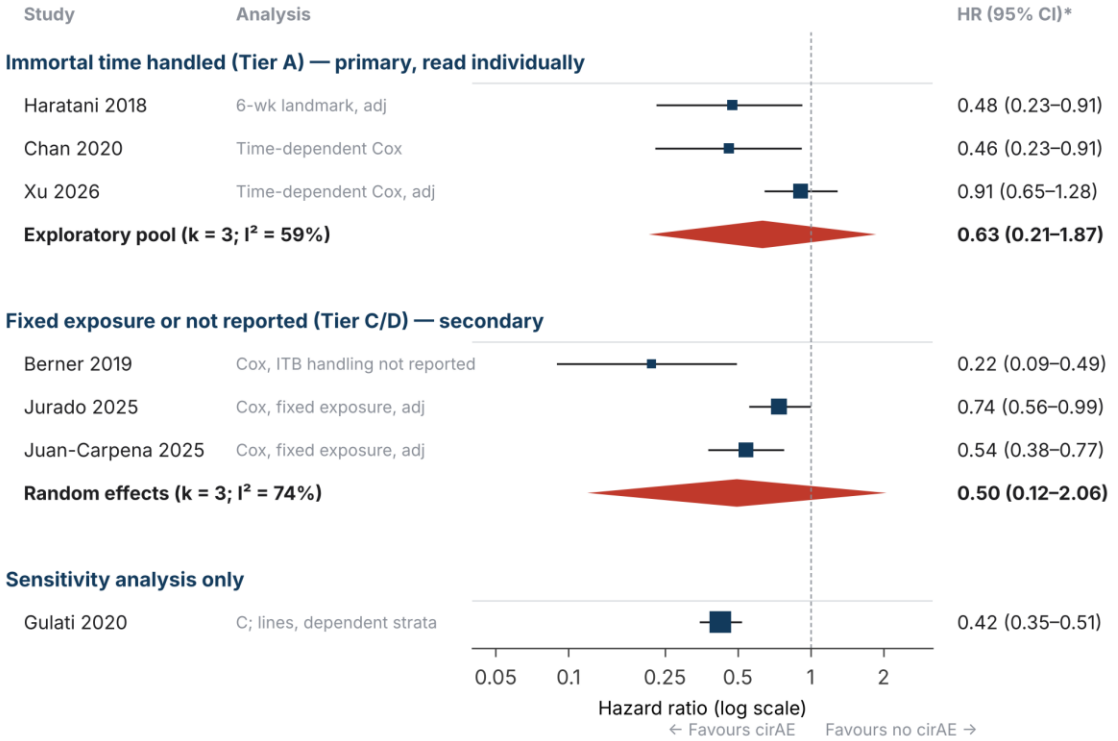


Figure 4. Progression-free survival in patients with versus without a cirAE, by handling of immortal time.

Tier A pooled diamond is exploratory. Diamonds show REML pooled estimates with HKSJ 95% CIs. Ratio of HRs, Tier A versus Tier C/D (exploratory meta-regression): 1.22 (0.40–3.71).

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Sensitivity analyses

Table 2. Pooled estimates and sensitivity analyses (REML random effects)

Analysis	k	HR (HKSJ 95% CI)	Wald 95% CI	95% PI	DL HR (95% CI)	I^2 (DL)
OS, Tier A exploratory pool (Haratani, Zhang, Xu)	3	0.57 (0.13–2.56)	0.30–1.07	—	0.58 (0.33–1.03)	81%
OS, Tier C/D secondary pool (without Gulati)	5	0.55 (0.43–0.70)	0.46–0.65	0.41–0.73	0.55 (0.46–0.65)	1%
OS, Tier C/D + Gulati et al. (lines; dependent strata)	6	0.52 (0.44–0.62)	0.46–0.60	0.43–0.63	0.52 (0.46–0.60)	0%
OS, Tier A + Wan et al. TriNetX arm	4	0.63 (0.33–1.20)	0.44–0.89	0.14–2.82	0.63 (0.44–0.89)	79%
OS, Tier A + Tang et al. (Tier B)	4	0.69 (0.38–1.26)	0.51–0.93	0.18–2.61	0.74 (0.61–0.89)	76%
OS, Tier A + Dousset et al. vitiligo (Tier A1)	4	0.59 (0.29–1.18)	0.40–0.87	0.11–3.20	0.58 (0.38–0.88)	83%
OS, Tier A without Haratani (= Tier A1 only: Zhang, Xu)	2	0.70 (0.03–17.7)†	0.42–1.15	—	0.70 (0.42–1.15)	83%
OS, Tier A without Zhang	2	0.41 (<0.01–70.8)†	0.18–0.90	—	0.41 (0.18–0.90)	45%
OS, Tier A without Xu	2	0.49 (<0.01–>1000)†	0.13–1.94	—	0.49 (0.13–1.94)	79%
OS, Tier A2 only (Haratani + Wan)	2	0.43 (<0.01–288.3)†	0.16–1.18	—	0.43 (0.16–1.18)	63%
OS, Tier C/D multivariable-adjusted only (Jurado, Juan-Carpena)	2	0.57 (0.11–2.79)†	0.44–0.72	—	0.57 (0.44–0.72)	0%
OS, Tier C/D without Berner (Tier D)	4	0.56 (0.42–0.75)	0.47–0.67	0.38–0.83	0.56 (0.47–0.67)	0%
OS, Tier C/D without Lim et al.	4	0.56 (0.42–0.74)	0.47–0.67	0.38–0.82	0.56 (0.47–0.67)	0%
OS, Tier C/D with Cho multivariable (Tier B)	5	0.57 (0.41–0.80)	0.47–0.70	0.37–0.91	0.56 (0.44–0.71)	31%
PFS, Tier A exploratory pool	3	0.63 (0.21–1.87)	0.39–1.04	—	0.63 (0.38–1.04)	59%
PFS, Tier C/D secondary pool (without Gulati)	3	0.50 (0.12–2.06)	0.27–0.91	—	0.52 (0.32–0.84)	74%
PFS, Tier C/D + Gulati et al.	4	0.49 (0.25–0.97)	0.33–0.71	0.09–2.67	0.49 (0.34–0.71)	78%

HKSJ, Hartung–Knapp–Sidik–Jonkman (ad hoc variant); PI, prediction interval ($k \geq 4$ only); DL, DerSimonian–Laird. †Two-study pool: the HKSJ interval has one degree of freedom and is uninformative; the point estimate is descriptive only. For the Cho et al. multivariable estimate, see Table 1, footnote e.

Splitting Tier A by method, the two time-dependent Cox studies (Tier A1: Zhang, Xu) gave a point estimate of 0.70 and the landmark studies (Tier A2: Haratani, plus Wan when added) 0.43, both with uninformative intervals. The single A2 study in the primary group, Haratani et al.[14], is also the outlier (0.21), so the A1/A2 split and the outlier cannot be separated with these data.

Stratifying by tumour changes the picture. Among NSCLC cohorts, the two corrected studies (Haratani 0.21, Xu 0.52; pooled point estimate 0.41) and the two uncorrected studies (Berner 0.29, Jurado 0.60; 0.47) gave similar results. In pan-cancer cohorts, the only primary corrected study (Zhang) found 0.87, or 0.75 with Wan added, against 0.56 for the two uncorrected pan-cancer cohorts in the secondary pool (Cho, Juan-Carpena; 0.52 with Gulati). The tier difference may therefore be largely a difference in cohort composition, resting on one large pan-cancer study, rather than an effect of immortal-time handling.

Restricting Tier C/D to multivariable-adjusted estimates (Jurado and Juan-Carpena) gave 0.57, and the ratio of HRs against Tier A fell to 1.12 (0.33–3.84). Part of the apparent tier gap may come from mixing unadjusted and adjusted HRs in Tier C/D.

Haratani et al.[14] gave the most extreme corrected estimate (0.21). Its 6-week landmark lies close to the median onset of skin irAEs in that cohort (5.7 weeks; range 0.4–36.2), so

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about half of the eventual cutaneous cases would have been classed as unexposed at the landmark. That misclassification would often move the HR toward 1, yet the estimate is the furthest from 1 of the three. Two explanations fit: patients with a cirAE by 6 weeks are the earliest-onset cases, who may have the strongest immune responses; and the landmark analysis included only 130 patients with few events in the exposed group, so the multivariable estimate is prone to sparse-data bias, which pushes HRs away from 1, as well as being imprecise (OS CI 0.05–0.62).

Benchmarks for the size of the bias

One cutaneous cohort reported both analyses on the same patients: in Dousset et al., the vitiligo HR rose from 0.20 to 0.53 when exposure was made time-varying.[8] Vitiligo is a single phenotype with a late median onset (6.9 months in that cohort), so its immortal time is longer than for early-onset rash or pruritus; the shift shows how large the distortion can be, but the vitiligo result may not generalize to cirAEs as a group. The earlier meta-analyses' overall and landmark pools, and this pilot's two tiers, compare different sets of studies rather than the same patients analysed two ways, so their differences (Figure 5B) do not measure the effect of correction.

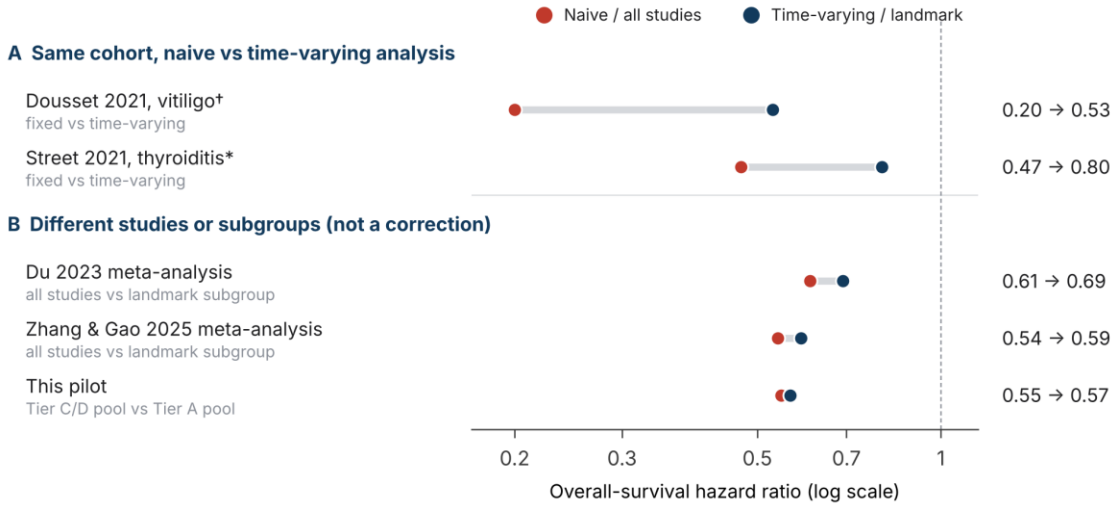


Figure 5. Overall-survival HRs from naive and immortal-time-handled analyses.

*A, within-cohort pairs: the same patients analysed with fixed and with time-varying exposure. B, comparisons between different studies or subgroups, which differ in tumour mix, adjustment, and setting as well as in time handling. *Thyroiditis is a non-cutaneous irAE, shown as a methodological benchmark only. †Vitiligo has late onset, so the shift may overstate the bias expected for cirAEs overall.*

Certainty of evidence

Certainty was very low for all four pooled estimates (Table 3). The pooled OS estimate from studies that handled immortal time was rated down for residual risk of bias, inconsistency, and imprecision. The pooled OS estimate from studies that did not handle immortal time was precise and consistent, but was rated down twice for risk of bias, because immortal time was not handled and most estimates were unadjusted or of unreported adjustment, and once for suspected publication bias arising from the seeded search. Both PFS pools were also inconsistent and imprecise.

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Table 3. Certainty of evidence for each pooled estimate (GRADE for prognostic factors)

Outcome and pool	Studies (patients)	HR (95% CI)	Reasons for rating down	Certainty
OS, immortal time handled (Tier A)	3 (4,123)	0.57 (0.13–2.56)	Risk of bias, serious (residual confounding by response and time on treatment); inconsistency, serious (I^2 81%; HRs 0.21–0.87); imprecision, serious	Very low
OS, immortal time not handled (Tier C/D)	5 (1,283)	0.55 (0.43–0.70)	Risk of bias, very serious (immortal time not handled; three of five estimates unadjusted or of unreported adjustment); publication bias, suspected (seeded, non-systematic search)	Very low
PFS, immortal time handled (Tier A)	3 (449)	0.63 (0.21–1.87)	Risk of bias, serious; inconsistency, serious (I^2 59%; HRs 0.46–0.91); imprecision, serious	Very low
PFS, immortal time not handled (Tier C/D)	3 (772)	0.50 (0.12–2.06)	Risk of bias, very serious; inconsistency, serious (I^2 74%); imprecision, serious	Very low

GRADE, Grading of Recommendations Assessment, Development and Evaluation. Cohort evidence on a prognostic factor starts at high certainty. Indirectness was not judged serious for any outcome. Publication bias was suspected for every outcome because studies were identified by a seeded, non-systematic search; it is listed only where it changed the rating. Ratings were made by one reviewer.

Discussion

The three included studies that handle immortal time all found HRs below 1, so these data do not suggest that the association disappears after correction. They do not agree on its size: 0.21 in a small NSCLC landmark cohort, 0.52 in an NSCLC time-dependent cohort and 0.87 in the largest pan-cancer cohort. Pooled, they give an imprecise and heterogeneous estimate. The uncorrected studies agree closely on about a halving of the hazard. A shared bias would produce that agreement, though with five studies it could also arise by chance, and the exploratory comparison between tiers was not statistically significant. For PFS, the picture is no clearer: the largest corrected study found 0.91 (0.65–1.28).

Correcting for immortal time does not make an association causal. Patients who respond stay on treatment longer and accumulate more opportunity for toxicity; more frequent visits for skin problems can change when progression is detected; and the more favourable of several models may be the one reported. Effect modification by tumour is plausible. In Zhang et al.[10] the association was statistically significant in melanoma (HR 0.67) but not in the other tumour groups, which suggests but does not demonstrate a difference between tumours; in this pilot the tier difference appeared only in pan-cancer cohorts, which rest on one large study. Gulati et al. fitted multivariable time-dependent models; these were significant (OS P = .001 for mild and .037 for severe toxicity), which suggests some association survives correction, but no HRs were reported. The HRs behind Gulati's P values and the full text of Wan et al.[11] were not available, so its cutaneous group and comparator are unconfirmed.

The clinical reading should be cautious. A cirAE may be weakly reassuring, but these data do not establish its prognostic usefulness for individual patients and are not a basis for decisions about continuing or stopping immunotherapy.

Limitations

This is a pilot. Studies were not identified by a bibliographic-database search but from author holdings and web searches seeded with known studies, so other cohorts that handled immortal time may exist; no protocol was registered, and the analysis plan followed study identification. Three of 20 sought reports were not retrieved, and two cohorts were excluded for lacking an HR without attempting reconstruction from Kaplan–Meier curves. Only three Tier A studies were available, and only one study gave a within-cohort naive-versus-corrected pair for a cutaneous exposure. Screening, extraction, and certainty rating were each done by a single reviewer, and risk of bias was not assessed with a formal tool such as QUIPS. Standard errors were derived from rounded, sometimes asymmetric CIs. The between-tier comparison rests on eight studies, is confounded by tumour type and adjustment, and is exploratory. The handling of immortal time in one Tier D

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cohort[18] could not be characterised; the dependent estimate[13] was excluded from the pools because it counts treatment lines and its strata share one comparator; and adjusted and unadjusted HRs were mixed in Tier C/D.

Conclusions

In this pilot, every included cohort that handled immortal time found an OS hazard ratio below 1, but the pooled association was imprecise and heterogeneous, and the largest well-phenotyped cohort found a modest association (HR 0.87). The precise estimates in circulation come mainly from analyses that do not handle immortal time. The gap between tiers was not statistically significant and may be explained by tumour mix and adjustment. Future cohorts should report both naive and time-dependent estimates, landmark sensitivity at several time points, and tumour-specific results.

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Author contributions.

HSB conceived the review, designed the classification framework, extracted the data, ran the analyses, and drafted the manuscript. PG contributed oncology expertise, SK dermatology expertise, and RK pharmacology expertise and supervision; all three critically revised the manuscript. All authors approved the final version. HSB is the guarantor.

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The authors declare no competing interests.

Conflict of interest.

The authors declare no conflict of interest.

Data and code.

The extraction workbook (including the search query log and evidence map) and analysis code (Python; REML with HKSJ, DerSimonian–Laird check; validated in R metafor 4.4) are available from the corresponding author.

List of abbreviations.

aHR, adjusted hazard ratio; CI, confidence interval; cirAE, cutaneous immune-related adverse event; CTCAE, Common Terminology Criteria for Adverse Events; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DL, DerSimonian–Laird; EHR, electronic health record; ESMO-IO, European Society for Medical Oncology Immuno-Oncology Congress; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HKSJ, Hartung–Knapp–Sidik–Jonkman; HR, hazard ratio; irAE, immune-related adverse event; MeSH, Medical Subject Headings; MGB/DFCI, Mass General Brigham/Dana-Farber Cancer Institute; NR, not reported; NSCLC, non-small cell lung cancer; NYU, New York University; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PI, prediction interval; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QUIPS, Quality In Prognosis Studies; REML, restricted maximum likelihood; tiab, title/abstract field; WHO-UMC, World Health Organization–Uppsala Monitoring Centre.

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References

1. Zhao F, Zhu J, Yu R, et al. Cutaneous adverse events in patients treated with PD-1/PD-L1 checkpoint inhibitors and their association with survival: a systematic review and meta-analysis. Sci Rep. 2022;12:20038. https://doi.org/10.1038/s41598-022-24286-3
2. Du Y, Wu W, Chen M, Dong Z, Wang F. Cutaneous adverse events and cancer survival prognosis with

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Original Article

immune checkpoint inhibitor treatment: a systematic review and meta-analysis. JAMA Dermatol. 2023;159:1093-101. https://doi.org/10.1001/jamadermatol.2023.3003

3. Zhang L, Gao Y. Cutaneous adverse events associated with the efficacy and benefit of immune checkpoint inhibitors: a systematic review and meta-analysis. Front Oncol. 2025;15:1689519. https://doi.org/10.3389/fonc.2025.1689519
4. Xu T, Li J, Zhao J, et al. Cutaneous immune-related adverse events independently predict overall survival with a grade-dependent association in ICI-treated advanced NSCLC: a time-dependent analysis. Front Oncol. 2026;16:1860717. https://doi.org/10.3389/fonc.2026.1860717
5. Juan-Carpena G, Martínez Banaclocha N, Palazón Cabanes JC, et al. 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. Acta Derm Venereol. 2025;105:adv42023. https://doi.org/10.2340/actadv.v105.42023
6. Lévesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. BMJ. 2010;340:b5087. https://doi.org/10.1136/bmj.b5087
7. Street S, Chute D, Strohbehn I, et al. The positive effect of immune checkpoint inhibitor-induced thyroiditis on overall survival accounting for immortal time bias. Ann Oncol. 2021;32:1050-1. https://doi.org/10.1016/j.annonc.2021.05.357
8. Dousset L, Pacaud A, Barnetche T, et al. Analysis of tumor response and clinical factors associated with vitiligo in patients receiving anti-programmed cell death-1 therapies for melanoma. JAAD Int. 2021;5:112-20. https://doi.org/10.1016/j.jdin.2021.09.002
9. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71
10. Zhang S, Tang K, Wan G, et al. Cutaneous immune-related adverse events are associated with longer overall survival in advanced cancer patients on immune checkpoint inhibitors: a multi-institutional cohort study. J Am Acad Dermatol. 2023;88:1024-32. https://doi.org/10.1016/j.jaad.2022.12.048
11. Wan G, Chen W, Khattab S, et al. Multi-organ immune-related adverse events from immune checkpoint inhibitors and their downstream implications: a retrospective multicohort study. Lancet Oncol. 2024;25:1053-69. https://doi.org/10.1016/S1470-2045(24)00278-X
12. Tang K, Seo J, Tiu BC, et al. Association of cutaneous immune-related adverse events with increased survival in patients treated with anti-PD-1 and anti-PD-L1 therapy. JAMA Dermatol. 2022;158:189-93. https://doi.org/10.1001/jamadermatol.2021.5476
13. Gulati N, Donnelly D, Qian Y, et al. Revisiting the association between skin toxicity and better response in advanced cancer patients treated with immune checkpoint inhibitors. J Transl Med. 2020;18:430. https://doi.org/10.1186/s12967-020-02612-5
14. Haratani K, Hayashi H, Chiba Y, et al. Association of immune-related adverse events with nivolumab efficacy in non-small-cell lung cancer. JAMA Oncol. 2018;4:374-8. https://doi.org/10.1001/jamaoncol.2017.2925 https://doi.org/10.1001/jamaoncol.2018.0751
15. Foroutan F, Guyatt G, Zuk V, et al. GRADE Guidelines 28: use of GRADE for the assessment of evidence about prognostic factors: rating certainty in identification of groups of patients with different absolute prognoses. J Clin Epidemiol. 2020;121:62-70. https://doi.org/10.1016/j.jclinepi.2019.12.023
16. Rehmani S, Higgins LM, Brinzevich D, et al. Heterogeneous survival impact of immune-related adverse events in US veterans. J Immunother Cancer. 2026. https://doi.org/10.1136/jitc-2025-014622
17. Chan L, Hwang SJE, Byth K, et al. Survival and prognosis of individuals receiving programmed cell death 1 inhibitor with and without immunologic cutaneous adverse events. J Am Acad Dermatol. 2020;82:311-6. https://doi.org/10.1016/j.jaad.2019.06.035
18. Berner F, Bomze D, Diem S, et al. Association of checkpoint inhibitor-induced toxic effects with shared cancer and tissue antigens in non-small cell lung cancer. JAMA Oncol. 2019;5:1043-7. https://doi.org/10.1001/jamaoncol.2019.0402
19. Cho YT, Lin YT, Yang CW, Chu CY. Cutaneous immune-related adverse events among Taiwanese cancer patients receiving immune checkpoint inhibitors link to a survival benefit. Sci Rep. 2022;12:7021. https://doi.org/10.1038/s41598-022-11128-5

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Original Article

20. Jurado JM, Gutiérrez V, Cantero A, et al. Association between cutaneous immune-related adverse events and efficacy of immune checkpoint inhibitors in advanced non-small cell lung cancer. J Clin Med. 2025;14:2499. https://doi.org/10.3390/jcm14072499

21. Lim AY-L, Chan JY, Oh CC. Cutaneous adverse reactions and survival outcomes of advanced melanoma treated with immune checkpoint inhibitors in an academic medical centre in Singapore. Diagnostics. 2024;14(15):1601. https://doi.org/10.3390/diagnostics14151601

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