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INPLASY

Factors associated with cutaneous immune-related adverse events during immune checkpoint inhibition for melanoma: a retrospectively registered systematic review protocol

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ADMINISTRATIVE INFORMATION

Support - No specific funding was received for the conduct of this review or the preparation of the manuscript. There was therefore no funder role in the design, conduct, analysis, interpretation, or dissemination of the review.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202690123

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 September 2026 and was last updated on 29 September 2026.

INTRODUCTION

Review question / Objective To systematically evaluate patient, disease, treatment and biological factors associated with the development of cutaneous immune-related adverse events (cirAEs) in adults with melanoma receiving immune checkpoint inhibitors (ICIs), while distinguishing melanoma-specific cutaneous evidence from contextual evidence and pretreatment measurements from on-treatment or later observations. A secondary objective was to examine associations between cirAEs and oncological outcomes within the retained studies.

Rationale At the time of retrospective registration, related reviews address overlapping but different clinical questions. A pan-cancer scoping review catalogues candidate cirAE risk factors, a melanoma review focuses principally on the clinical spectrum of reported cutaneous events, and another systematic review addresses treatment of established cirAEs. The present review provides a melanoma-specific comparative synthesis because skin phenotype, treatment setting and the timing of factor measurement determine whether an association can inform risk assessment. It evaluates which reported associations can be interpreted for a defined cutaneous phenotype at a clinically relevant prediction time.

Condition being studied Melanoma treated with immune checkpoint inhibition, with a focus on cutaneous immune-related adverse events. CirAEs include pruritus, inflammatory eruptions, pigmentary changes such as vitiligo, lichenoid or psoriasiform reactions, blistering disorders and other treatment-associated cutaneous toxicities.

METHODS

Search strategy PubMed, Scopus and Embase were searched using immune-checkpoint-inhibitor, cutaneous-toxicity and factor/biomarker concepts; Scopus and Embase additionally included melanoma terms. Exact historical execution dates are not documented in the available records. Historical search syntax is reproduced below without retrospective rewriting. PubMed used the PubMed (NCBI) interface. The Scopus syntax is retained as recorded. The specific Embase platform was not documented; the recorded /exp and :ti,ab,kw syntax is therefore preserved without assigning an inferred interface.

PubMed:

(("immune checkpoint inhibitor*" OR "checkpoint inhibitor*" OR "immune checkpoint blockade" OR "PD-1 inhibitor*" OR "PD-L1 inhibitor*" OR "CTLA-4 inhibitor*" OR "anti-PD-1" OR "anti-PD-L1" OR "anti-CTLA-4" OR nivolumab OR pembrolizumab OR ipilimumab OR relatlimab OR atezolizumab OR durvalumab OR avelumab OR cemiplimab OR tremelimumab OR "Immune Checkpoint Inhibitors"[Mesh]) AND ("cutaneous adverse event*" OR "cutaneous immune-related adverse event*" OR "cutaneous irAE*" OR "dermatologic adverse event*" OR "dermatological adverse event*" OR "skin toxicity" OR rash OR pruritus OR dermatitis OR vitiligo OR lichenoid OR psoriasiform OR pemphigoid) AND (predict* OR biomarker* OR baseline OR pretreatment OR "pre-treatment" OR "risk factor*" OR predictor* OR "predictive factor*" OR "associated"))

Filters: in the last 10 years, English, Humans

Scopus:

TITLE-ABS-KEY((melanoma* OR "advanced melanoma" OR "metastatic melanoma") AND ("immune checkpoint inhibitor*" OR "checkpoint inhibitor*" OR "immune checkpoint blockade" OR "PD-1 inhibitor*" OR "PD-L1 inhibitor*" OR "CTLA-4 inhibitor*" OR "anti-PD-1" OR "anti-PD-L1" OR "anti-CTLA-4" OR nivolumab OR pembrolizumab OR ipilimumab OR relatlimab OR atezolizumab OR durvalumab OR avelumab OR cemiplimab OR tremelimumab) AND ("cutaneous adverse event*" OR "cutaneous immune-related adverse event*" OR "cutaneous irAE*" OR "dermatologic adverse event*" OR "dermatological adverse event*" OR "skin toxicity" OR rash OR pruritus OR dermatitis OR vitiligo OR lichenoid OR psoriasiform OR pemphigoid) AND (predict* OR biomarker* OR baseline OR pretreatment OR "pre-treatment" OR "risk factor*" OR predictor* OR "predictive factor*")) AND LIMIT-TO(LANGUAGE, "English") AND (LIMIT-TO(EXACTKEYWORD, "Humans") OR LIMIT-TO(EXACTKEYWORD, "Human")) AND LIMIT-TO(DOCTYPE, "ar") AND PUBYEAR > 2015

Embase:

(
'melanoma'/exp
OR melanoma*:ti,ab,kw
OR 'advanced melanoma':ti,ab,kw
OR 'metastatic melanoma':ti,ab,kw
OR 'cutaneous melanoma':ti,ab,kw
)
AND
(
'immune checkpoint inhibitor'/exp
OR 'immune checkpoint blockade':ti,ab,kw
OR 'immune checkpoint inhibitor*':ti,ab,kw
OR 'checkpoint inhibitor*':ti,ab,kw
OR 'pd-1 inhibitor*':ti,ab,kw
OR 'pd-l1 inhibitor*':ti,ab,kw
OR 'ctla-4 inhibitor*':ti,ab,kw
OR 'anti-pd-1':ti,ab,kw
OR 'anti-pd-l1':ti,ab,kw
OR 'anti-ctla-4':ti,ab,kw
OR nivolumab/exp
OR pembrolizumab/exp
OR ipilimumab/exp
OR relatlimab/exp
OR atezolizumab/exp
OR durvalumab/exp
OR avelumab/exp
OR cemiplimab/exp
OR tremelimumab/exp
OR nivolumab:ti,ab,kw
OR pembrolizumab:ti,ab,kw
OR ipilimumab:ti,ab,kw
OR relatlimab:ti,ab,kw
OR atezolizumab:ti,ab,kw
OR durvalumab:ti,ab,kw
OR avelumab:ti,ab,kw
OR cemiplimab:ti,ab,kw
OR tremelimumab:ti,ab,kw
OR opdualag:ti,ab,kw
)
AND
(
'cutaneous adverse event*':ti,ab,kw
OR 'cutaneous immune-related adverse event*':ti,ab,kw
OR 'cutaneous irAE*':ti,ab,kw
OR 'dermatologic adverse event*':ti,ab,kw
OR 'dermatological adverse event*':ti,ab,kw
OR 'skin toxicity':ti,ab,kw
OR 'skin toxicities':ti,ab,kw
OR 'skin adverse event*':ti,ab,kw
OR ((cutaneous OR dermatolog* OR skin) NEAR/3 ('adverse event*' OR toxicit* OR irAE* OR reaction*)):ti,ab,kw

OR rash*:ti,ab,kw
OR pruritus:ti,ab,kw
OR pruritic:ti,ab,kw
OR dermatitis:ti,ab,kw
OR vitiligo:ti,ab,kw
OR lichenoid:ti,ab,kw
OR psoriasiform:ti,ab,kw
OR pemphigoid:ti,ab,kw
)
AND
(
predict*:ti,ab,kw
OR predictor*:ti,ab,kw
OR 'predictive factor*':ti,ab,kw
OR biomarker*:ti,ab,kw
OR baseline:ti,ab,kw
OR pretreatment:ti,ab,kw
OR 'pre-treatment':ti,ab,kw
OR 'risk factor*':ti,ab,kw
OR associat*:ti,ab,kw
OR correlat*:ti,ab,kw
OR 'clinical characteristic*':ti,ab,kw
OR 'baseline characteristic*':ti,ab,kw
)
AND [2016-2026]/py
AND [english]/lim
AND [humans]/lim
AND [article]/lim.

Participant or population Adults receiving immune checkpoint inhibitors for melanoma. Mixed-cancer populations were eligible only as contextual evidence unless a melanoma-specific cutaneous comparison was separately extractable.

Intervention This is not primarily an intervention-effect review. The treatment context is immune checkpoint inhibition for melanoma, including PD-1, PD-L1 and CTLA-4 inhibitors and eligible combinations, including nivolumab–relatlimab. The focal exposures are patient, disease, treatment and biological factors evaluated for association with cutaneous toxicity.

Comparator There was no single universal comparator. Comparators were the study-defined reference categories for each candidate factor, such as demographic groups, disease characteristics, treatment regimens or biomarker levels. For treatment comparisons, a separable ICI-treated stratum was required for direct interpretation.

Study designs to be included Original peer-reviewed studies evaluating associations between candidate factors and cutaneous or relevant immune toxicity in adults with melanoma treated with ICIs. Eligible evidence included retrospective and prospective observational cohorts, cross-sectional studies and exploratory biomarker studies where the relevant association could be assessed.

Eligibility criteria Original, peer-reviewed English-language studies of adults receiving ICIs for melanoma were eligible if they analysed patient, disease, treatment or biological factors in relation to cutaneous or relevant immune toxicity. Mixed-cancer or overall-irAE analyses were treated as contextual unless a melanoma-specific cutaneous comparison was separable. Reviews, editorials, case reports, mini case series, and studies lacking a relevant population, treatment, outcome or factor analysis were excluded. A numerical threshold used historically to distinguish mini case series was not recoverable from the available documentation. Known or suspected overlapping cohorts were retained as separate publications where eligible but were not treated as independent replication in the synthesis.

Information sources PubMed, Scopus and Embase were the historical electronic database sources. No systematic supplementary-search procedure or author-contact procedure was documented for the original review. During manuscript preparation, targeted citation/reference follow-up identified Dousset 2021. This record underwent dual screening, eligibility assessment, consensus extraction and QUIPS assessment and was integrated on 26 September 2026. This supplementary branch did not alter the historical database counts and did not constitute a complete database search update.

Main outcome(s) The primary outcomes were associations between candidate factors and cutaneous immune-related adverse events in ICI-treated melanoma. Source-defined outcomes included any cutaneous event, individual cutaneous phenotypes, event severity and time to first cutaneous event. Candidate factors included demographic, clinical, disease-related, treatment-related, laboratory, genetic and immune variables. Source-reported effect estimates, precision, reference groups, adjustment and measurement timing were retained.

Additional outcome(s) Secondary outcomes were oncological outcomes associated with the occurrence of cutaneous events, including treatment response, overall survival, melanoma-specific mortality, progression-related endpoints and time to next treatment or death. These analyses treated the skin event as the exposure and retained information on comparator,

adjustment and temporal modelling. This secondary prognosis synthesis was confined to the studies retained for the primary review and was not an exhaustive independent systematic search of prognostic evidence.

Data management Covidence was used for record management and screening. Covidence removed 358 duplicates and one additional duplicate was removed manually. Two human reviewers independently screened titles/abstracts and assessed full texts, with disagreements adjudicated by a third reviewer and additional senior consultation where required. A standardized extraction template was developed and refined by the team. Two reviewers independently extracted each included study and resolved discrepancies by discussion and consensus. Extracted variables included population, design, treatment, observation period, skin phenotype, event frequency and onset, factor comparisons, measurement timing, effect estimates, precision and adjustment. No AI or machine-learning screening or prioritization was used. OpenAI ChatGPT was subsequently used during manuscript preparation for grammatical and language editing, editorial refinement, selected data summarization and statistical calculations, and cross-file consistency checks. All such outputs were reviewed and verified by the authors. AI was not used to make study-selection, data-extraction, risk-of-bias or scientific-interpretation decisions. The final structured dataset is supplied as Online Resource 1.

Quality assessment / Risk of bias analysis Risk of bias was assessed using the Quality In Prognosis Studies (QUIPS) tool across six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis/reporting. Two human reviewers independently performed the original assessments, reconciled disagreements and obtained third-reviewer confirmation/adjudication. Subsequent source verification retained 86 original judgments, corrected 72 and completed 22 previously unrecorded fields. Six additional human-consensus judgments were added for Dousset 2021. Corrected or completed historical values are not represented as original duplicate-human consensus. No overall numerical study score or formal certainty-of-evidence grade was calculated.

Strategy of data synthesis A narrative synthesis was conducted. Evidence was grouped by clinical domain and by direct melanoma cutaneous, mixed-cancer, overall-irAE or mechanistic scope. Measurement timing was classified as baseline, on-treatment or concurrent/post-event. A reporting map allowed at most one entry per study and standardized factor, preferentially retaining clearly reported adjusted estimates. Results were classified as increased, decreased, no statistically significant association, mixed, or no defensible directional summary. Counts were descriptive and unweighted. Heterogeneity in phenotype, exposure definitions, thresholds, measurement windows, comparators and effect measures prevented clinically interpretable meta-analysis; therefore, no pooled effect estimate was calculated. Missing results were not coded as nonsignificant. Known overlapping cohorts were not treated as independent replication. Odds ratios and time-to-event estimates, and baseline versus concurrent measurements, were not combined.

Subgroup analysis No formal inferential subgroup analysis was undertaken. Findings were descriptively stratified where relevant by cutaneous phenotype, measurement timing, clinical domain and evidence scope.

Sensitivity analysis No formal quantitative sensitivity analysis was performed.

Language restriction Yes. Historical database searches and study inclusion were restricted to English-language reports, consistent with the documented historical search limits.

Country(ies) involved Australia.

Other relevant information This registration is retrospective and was submitted on 29 September 2026. The review originated as a student-led educational project. Initial project documentation was developed as internal working material within the student project framework rather than as a formal publicly registered systematic-review protocol, and prospective registration was therefore not undertaken at project inception. As the project subsequently developed into a full systematic review intended for journal publication, the authors elected to register it retrospectively to provide a transparent public record of the methods implemented. By the time of registration, database searching, screening, data extraction, risk-of-bias assessment, synthesis, manuscript preparation and journal submission had been completed. Exact dates for the original database searches and historical screening/extraction are not recoverable from the available records and have not been retrospectively inferred. During manuscript preparation, targeted citation/reference checks identified Dousset 2021, which was integrated on

26 September 2026 after dual screening, eligibility assessment, consensus extraction and QUIPS assessment; the historical database branch was unchanged. The evidence grouping, reporting-map structure and secondary prognosis synthesis were developed during the review and were not prospectively prespecified; study-level findings were available when these later synthesis refinements were finalized. This registration documents the implemented methods transparently and should not be interpreted as evidence of prospective prespecification.

Keywords Melanoma; Immune Checkpoint Inhibitors; Cutaneous Immune-Related Adverse Events; Risk Factors; Prognosis; Systematic Review; Retrospective Registration.

Dissemination plans The completed systematic review has been submitted for consideration to the International Journal of Dermatology. The review findings, study characteristics, extracted evidence, search strategies, QUIPS assessments, exclusion documentation and prognostic analyses are intended to be disseminated through the journal article and its supplementary structured dataset. The final publication will be linked to the INPLASY registration once available.

Contributions of each author

Author 1 - Lecheng Li - Conceived and coordinated the review; developed methodology and synthesis framework; conducted the literature search; contributed to screening and extraction; led data curation, synthesis and verification; assessed risk of bias; prepared tables, figures and supplements; interpreted findings; drafted and revised the manuscript.
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