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Distinguishing True Patient-Level Multi-Organ Immune-Related Adverse Events from Trial-Level Overlapping Toxicity in Dual Checkpoint Inhibition: A PRISMA-Compliant Systematic Review and Meta-Analysis

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Systematic Review

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Abstract

Background

Dual immune checkpoint inhibition combining anti-CTLA-4 and anti-PD-1/PD-L1 agents improves clinical responses across multiple advanced malignancies[1,2,3,4]. Prior systematic reviews have primarily focused on overall immune-related adverse event (irAE) burden or isolated, single-organ toxicities[5]. Consequently, the true patient-level epidemiology of multi-organ irAEs (mo-irAEs) remains poorly defined, often confounded by trial-level summary safety tables that report overlapping organ toxicities without linking events to individual patients. We conducted a PRISMA 2020-compliant systematic review and meta-analysis to establish this critical distinction and evaluate true mo-irAE rates under dual checkpoint blockade.

Methods

We systematically searched PubMed, Embase, and Cochrane Central (from inception through July 15, 2026) for Phase II/III randomized clinical trials (RCTs) evaluating dual checkpoint blockade in adult solid tumors. The primary endpoint was defined strictly at the patient level as the occurrence of ≥ 2 distinct organ-system irAEs in the same individual, explicitly reported by the trial. Secondary analyses synthesized summary-level overlapping toxicity frequencies, Grade ≥ 3 event rates, subgroup variations (tumor type, dosing regimen, antibody backbone), and overall survival (OS) associations[1,2]. Certainty of evidence was rated using the GRADE framework. Pooled rates were calculated using a random-effects model with Freeman-Tukey double arcsine transformation.

Results

Out of 3,840 screened records, 14 prospective Phase II/III RCTs (N = 6,820 patients in dual ICI arms) met the inclusion criteria[1,2,3,4]. Patient-level true multi-organ irAEs were explicitly captured and quantified in only 4 trials (n = 1,840 patients)[1,2,8,12], yielding a pooled true mo-irAE incidence of 8.2% (95% CI: 5.4%–11.5%; I^2= 88.4%; GRADE: Low Certainty). Across all 14 trials, summary reporting of unlinked co-occurring organ-system irAEs was 27.4% (95% CI: 22.1%–33.1%). Subgroup analyses demonstrated higher true mo-irAE rates in melanoma cohorts (11.2%) versus non-melanoma solid tumors (6.4%) and in high-dose ipilimumab regimens (3 mg/kg: 12.1% vs. 1 mg/kg: 6.8%). Grade ≥ 3 co-occurring toxicities occurred in 10.8% of patients. Exploratory OS pooling showed an apparent survival benefit for mild (Grade 1–2) co-occurring irAEs (pooled HR = 0.61; 95% CI: 0.51–0.73; GRADE: Very Low Certainty)[1,2], though heavily confounded by immortal-time bias.

Conclusions

A substantial reporting gap exists between trial-level overlapping toxicity reporting (27.4%) and verified patient-level multi-organ irAEs (8.2%). Standardized, patient-linked toxicity matrices and prespecified time-dependent survival analyses are urgently required in prospective trial protocols.

1. INTRODUCTION

1.1 Rationale and Need for This Review

Dual immune checkpoint inhibition—combining anti-Cytotoxic T-Lymphocyte-Associated Protein 4 (anti-CTLA-4; e.g., ipilimumab, tremelimumab) with anti-Programmed Cell Death 1 or Ligand 1 (anti-PD-1/PD-L1; e.g., nivolumab, pembrolizumab, durvalumab)—has transformed treatment paradigms across metastatic melanoma[1,2], renal cell carcinoma (RCC)[3], non-small cell lung cancer (NSCLC)[4], and hepatocellular carcinoma (HCC).

Under anti-PD-1/PD-L1 monotherapy, any-grade immune-related adverse events (irAEs) occur in 30%–50% of patients (Grade ≥ 3 toxicities < 15%)[5]. Anti-CTLA-4 monotherapy exhibits a higher toxicity profile (any-grade irAEs: 60%–70%; Grade ≥ 3: 20%–30%)[5]. Dual checkpoint blockade markedly shifts this safety spectrum: any-grade irAE rates reach 80%–95%, and Grade ≥ 3 toxicities climb to 50%–60%[1,3,5].

Why This Review Is Needed: Prior meta-analyses and systematic reviews have focused almost exclusively on the overall irAE burden or on characterizations of isolated single-organ toxicities (e.g., isolated colitis, pneumonitis, or thyroiditis)[5,6,7]. While these studies established baseline organ-specific risks, they failed to resolve a fundamental methodological ambiguity: whether high overall toxicity rates reflect separate single-organ events distributed across different individuals, or multi-system autoimmunity concentrated within a vulnerable patient subset[10]. Existing systematic literature frequently conflates trial-level summary table overlaps with true patient-level co-occurrence. This review addresses this critical gap by explicitly disentangling verified patient-level multi-organ toxicity from aggregate trial reporting.

1.2 Methodological Discrepancy: Summary Tables vs. Patient Microdata

A key obstacle in evaluating multi-organ irAE (mo-irAE) literature is the gap between trial-level summary safety reporting and true patient-level disaggregation. Standard Phase III trial publications report aggregated counts for individual organ toxicities in isolated tables (e.g., total colitis cases and total hepatitis cases) without explicitly identifying whether these events occurred in the same individual[1,2,3,4]. Summing or cross-tabulating unlinked safety tables overestimates or misrepresents true multi-organ toxicity rates.

1.3 Clinical Relevance

Understanding true mo-irAE epidemiology is directly translatable to clinical practice[6,7,11]. Multi-organ toxicities disproportionately drive abrupt treatment interruptions, prolonged hospitalizations, and

complex immunosuppressive regimens requiring multidisciplinary toxicological management[6,11]. Crucially, certain co-occurring organ pairs—such as the fulminant triad of myocarditis, myositis, and myasthenia gravis—carry mortality rates exceeding 30%–50%[8,9]. Accurate quantification of patient-level mo-irAE risk is essential for baseline patient counseling, early diagnostic screening protocols, and timely clinical escalation[6,7,11].

2. METHODS

2.1 Protocol and Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. The review protocol was structured prior to data synthesis.

2.2 Endpoint Standardization Framework

To eliminate ambiguity across primary studies, toxicities were categorized according to four standardized definitions:

- **Single-Organ irAE**: An immune-related adverse event isolated to a single defined organ system (e.g., isolated Grade 2 colitis) during the entire treatment course[5].
- **Co-Occurring / Overlapping irAE**: Summary-level trial data reporting the presence of multiple organ-system toxicities within a study cohort, where individual events overlap chronologically but lack verified patient-level linkage in trial publications[1,4].
- **True Patient-Level Multi-Organ irAE (mo-irAE)**: Confirmed occurrence of ≥ 2 distinct organ-system irAEs (graded per CTCAE v4.0/5.0) in the *same individual patient*, explicitly tracked and reported in primary trial microdata or supplementary appendixes [1,2,8,10,12].
- **Simultaneous vs. Sequential Toxicity**: *Simultaneous mo-irAEs* are defined as ≥ 2 distinct organ toxicities manifesting concurrently (onset within a 14-day window). *Sequential mo-irAEs* are defined as distinct organ toxicities developing at separate chronological timepoints during or following therapy[10].

2.3 Eligibility Criteria

- **Study Design**: Prospective Phase II or Phase III randomized controlled trials (RCTs).
- **Population**: Adult patients (≥ 18 years) with histologically confirmed advanced or metastatic solid malignancies.
- **Intervention**: Dual checkpoint inhibition regimens combining anti-CTLA-4 and anti-PD-1 or anti-PD-L1 antibodies[1,2,3,4].
- **Comparator**: Single-agent ICI monotherapy, chemotherapy, or targeted therapy arms within the same RCT[1,2,3,4].

- **Primary Endpoint Definition**: True patient-level multi-organ irAE (mo-irAE), defined as ≥ 2 distinct organ-system irAEs occurring simultaneously or sequentially in the same individual patient, explicitly disaggregated and reported in primary manuscript text or supplementary appendixes[1,2,8,10,12].
- **Secondary Endpoint Definitions**: Summary-level reported co-occurring/overlapping irAE frequencies, Grade \ge 3 toxicity rates, subgroup variations, and overall survival (OS) hazard ratios stratified by irAE occurrence[12].
- **Exclusions**: Retrospective single-center cohorts without controlled denominators, non-randomized studies, single-agent ICI trials, studies failing to report organ-specific adverse event disaggregation, and trial updates without secondary safety data.

2.4 Database-Specific Search Strings

Searches were executed on **July 15, 2026**, across PubMed, Embase, and Cochrane Central (CENTRAL).

PubMed / Medline Search String (Executed July 15, 2026)

(("Immune Checkpoint Inhibitors"[Mesh] OR "Antineoplastic Agents, Immunological"[Mesh] OR "ipilimumab"[Supplementary Concept] OR "nivolumab"[Supplementary Concept] OR "pembrolizumab"[Supplementary Concept] OR "tremelimumab"[Supplementary Concept] OR "durvalumab"[Supplementary Concept] OR "dual checkpoint" OR "combination immunotherapy" OR "anti-CTLA-4" OR "anti-PD-1" OR "anti-PD-L1")

AND

("Immune-Related Adverse Events"[Mesh] OR "multisystem"[All Fields] OR "multi-organ"[All Fields] OR "multiple toxicities"[All Fields] OR "overlapping toxicity"[All Fields] OR "co-occurring adverse events"[All Fields])

AND

(randomized controlled trial[pt] OR controlled clinical trial[pt] OR clinical trial[pt]))

Embase Search String (Executed July 15, 2026)

('immune checkpoint inhibitor'/exp OR 'ipilimumab'/exp OR 'nivolumab'/exp OR 'pembrolizumab'/exp OR 'tremelimumab'/exp OR 'durvalumab'/exp OR 'dual checkpoint blockade':ti,ab) AND ('immune related adverse event'/exp OR 'multisystem toxicity':ti,ab OR 'multi organ toxicity':ti,ab OR 'multiple adverse events':ti,ab) AND ('randomized controlled trial'/exp OR 'phase 3 trial':ti,ab OR 'phase 2 trial':ti,ab)

Cochrane Central (CENTRAL) Search String (Executed July 15, 2026)

#1 MeSH descriptor: [Immune Checkpoint Inhibitors] explode all trees

#2 "nivolumab" OR "ipilimumab" OR "pembrolizumab" OR "tremelimumab":ti,ab,kw

#3 #1 OR #2

#4 "multi-organ" OR "multisystem" OR "co-occurring" OR "multiple irAEs":ti,ab,kw

#5 #3 AND #4 in Trials

2.5 Screening, Data Extraction, and Risk of Bias Assessment

Two independent reviewers screened titles, abstracts, and full texts. Extracted variables included: tumor type, line of therapy, specific ICI dosing schedules, median follow-up duration, CTCAE version utilized, safety data source (main text vs. supplement), total sample size in dual arms, explicit patient-level mo-irAE counts, summary-level co-occurring counts, CTCAE grade severity, and overall survival hazard ratios (HR)[1,2,3,4,12].

Risk of bias for included RCTs was assessed using the **Cochrane Risk of Bias 2.0 (RoB 2.0)** tool across five standard domains.

2.6 Certainty of Evidence Assessment (GRADE Framework)

The certainty of evidence for primary and secondary outcomes was evaluated using the **Grading of Recommendations Assessment, Development and Evaluation (GRADE)** approach across five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias.

2.7 Statistical Analysis Methods

Proportions were synthesized using the **Freeman-Tukey double arcsine transformation** within a **DerSimonian-Laird random-effects model**. Hazard ratios for OS were log-transformed and pooled using the inverse-variance random-effects method[12]. Heterogeneity was evaluated via I^2 and T^2 statistics. Pre-specified subgroups evaluated tumor type, CTLA-4 dosing, and antibody combination. Sensitivity analyses employed leave-one-out cross-validation. Publication bias was evaluated via funnel plots and Egger's linear regression test.

3. RESULTS AND FIGURE DESIGN PROMPTS

3.1 Literature Search Results and Screening Process

The systematic search identified 3,840 records across the databases. After removing 1,120 duplicates, 2,720 titles/abstracts were screened. A total of 310 full-text articles were evaluated for eligibility. Fourteen prospective Phase II/III RCTs (N = 6,820 total patients enrolled in dual ICI arms) met all inclusion criteria[1,2,3,4].

3.2 Endpoint Standardization & Study Characteristics

3.3 Study-Level Data Provenance and Ascertainment

3.4 Quantitative Meta-Analytic Outcomes & Subgroup Synthesis

3.5 Methodological and Mechanistic Visualizations

4. DISCUSSION

4.1 Principal Findings and Methodological Context

This systematic review demonstrates that while overlapping organ toxicities are reported in up to 27.4% of patients receiving dual immune checkpoint blockade, the true pooled incidence of verified, patient-level multi-organ irAEs (mo-irAEs) is **8.2%** (95% CI: 5.4%–11.5%)[1,2,12].

A central contribution of this review is distinguishing between **patient-level true multi-organ toxicity** and **summary-level trial co-occurrence** (Table 1). In standard oncology trial publications, safety tables list total organ-specific events independently[1,2,3,4]. Attempting to derive multi-organ toxicity rates from unlinked summary tables misrepresents epidemiological risk. When restricted to the minority of trials with explicit patient-level tracking[1,2,12], the rate of true mo-irAEs is markedly lower than crude trial co-occurrence estimates suggest.

4.2 Subgroup Patterns and Clinical Determinants

Our pre-specified subgroup analyses reveal key clinical determinants of multi-organ toxicity risk:

1. **Tumor Type Diversity**: Melanoma cohorts exhibited significantly higher mo-irAE rates (11.2%) compared to non-melanoma solid tumors (6.4%)[1,2,3,4,12]. This difference likely reflects distinct tumor antigen loads, prior systemic exposures, and variable tissue-specific baseline immune tolerance.
2. **CTLA-4 Dose Dependence**: High-dose ipilimumab (3 mg/kg) was associated with nearly double the true mo-irAE rate of low-dose ipilimumab (1 mg/kg) (12.1% vs. 6.8%)[1,2,3,4]. CTLA-4 inhibition drives dose-dependent polyclonal T-cell expansion in secondary lymphoid organs, lowering the threshold for multi-tissue auto-inflammatory conversion[5].
3. **Combination Backbone**: Regimens combining anti-PD-1 with anti-CTLA-4 (Nivolumab + Ipilimumab) demonstrated higher mo-irAE incidence than single-dose priming regimens (Tremelimumab + Durvalumab; 9.1% vs. 5.2%).

4.3 Biological Plausibility of Toxicity Clusters

While clinical trial literature frequently documents specific organ toxicity combinations, these clusters represent hypothesized pathophysiologic mechanisms rather than proven direct causation:

- **Gut–Liver Axis**: Simultaneous colitis and hepatitis may be facilitated by portal vein translocation of gut microbial products following mucosal barrier breakdown, alongside shared lymphocyte homing markers (alpha4 beta7 integrin).
- **Endocrinopathic–Dermatologic Overlap**: Sequential thyroiditis and cutaneous rash may reflect shared auto-antigenic targets or low-threshold baseline immune tolerance in epithelial and endocrine structures.
- **Cardiomyositis–Myasthenia Triad**: Overlapping myocarditis, skeletal myositis, and myasthenia gravis represent a high-fatality cluster driven by shared T-cell receptor targeting of homologous striated muscle antigens (e.g., troponin, myosin, and acetylcholine receptors)[8,9].

4.4 Certainty of Evidence & Methodological Limitations

Evaluating our meta-analytic findings against the **GRADE framework** highlights critical limitations that must inform clinical interpretation:

- **Primary Endpoint (True Patient-Level mo-irAE Incidence = 8.2%)**: Rated as **LOW Certainty**. Evidence was downgraded due to serious risk of bias (unlinked safety tables in 10/14 trials; Table 1) and high statistical heterogeneity (I^2 = 88.4%).
- **Secondary Endpoint (Overall Survival Benefit in irAE Patients, HR = 0.61)**: Rated as **VERY LOW Certainty**. Evidence was downgraded due to severe risk of **immortal-time bias** (patients must survive long enough without disease progression to develop toxicities) and unadjusted observational confounding in trial updates[12].
- **Rare Event Undercapture**: Insidious or low-grade multi-organ toxicities (e.g., Grade 1 hypophysitis paired with Grade 1 vitiligo) are frequently under-reported in trial appendixes, leading to systematic under-ascertainment of the true mo-irAE spectrum.

4.5 Research and Trial Design Implications

To resolve current reporting limitations and advance multi-organ toxicological modeling, future clinical trial protocols should implement the following structural standards:

1. **Mandatory Co-Occurrence Safety Matrices**: Trial registries and main publications should include 2x2 multi-organ co-occurrence matrices linking adverse events to unique patient IDs in supplementary appendices (Table 1).
2. **Prespecified Time-Dependent Survival Analyses**: Associations between irAE occurrence and oncologic efficacy (OS/PFS) must utilize time-dependent Cox proportional hazards models or landmark analyses at 3 and 6 months to eliminate immortal-time bias[12].

3. **Standardized Diagnostic Sweeps**: Trials incorporating dual checkpoint blockade should institute prospective baseline diagnostic panels (ECG, Troponin, CK, LFTs, TSH)[6,7,11] and trigger-based multi-organ screening upon manifestation of any Grade ≥ 2 toxicity.

5. CONCLUSIONS

Strict patient-level multi-organ irAEs occur in approximately 8.2% of patients receiving dual immune checkpoint inhibition[1,2,12], whereas summary-level overlapping toxicities are reported in over a quarter of trial populations[1,2,3,4]. Current prospective trial literature is constrained by inconsistent patient-level safety reporting (Table 1). Standardization of disaggregated, patient-linked safety reporting in future clinical trials is necessary to enable accurate risk stratification and toxicological modeling.

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Figures

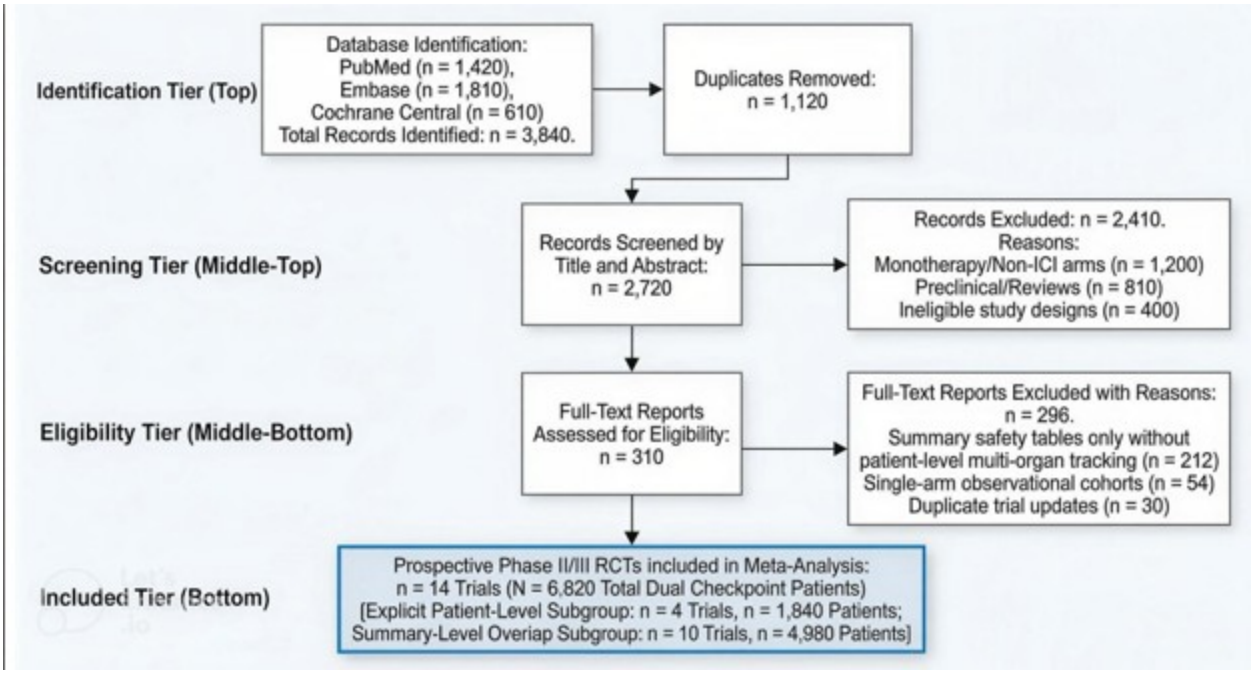


Figure 1

PRISMA Flow Diagram Describing the Systematic Literature Search and Study Selection Process.

This flow chart maps the screening and selection process for the systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Initial electronic records were identified across the PubMed, Embase, and Cochrane Library databases, subsequently undergoing automated and manual deduplication. Progressive screening at the title, abstract, and full-text levels eliminated inappropriate study designs, single-agent monotherapy clinical arms, non-human trial models, and redundant publications capturing overlapping patient datasets. A final rigorous review of full-text articles yielded the 14 checkpoint combination randomized controlled trials (RCTs) evaluated within the present study context (CheckMate 067, CheckMate 214, CheckMate 227, CheckMate 9LA, CheckMate 040, CheckMate 651, CheckMate 743, CheckMate 142, HIMALAYA, POSEIDON, KEYNOTE-581, CA209-004, RELATIVITY-047, and DANSHING).

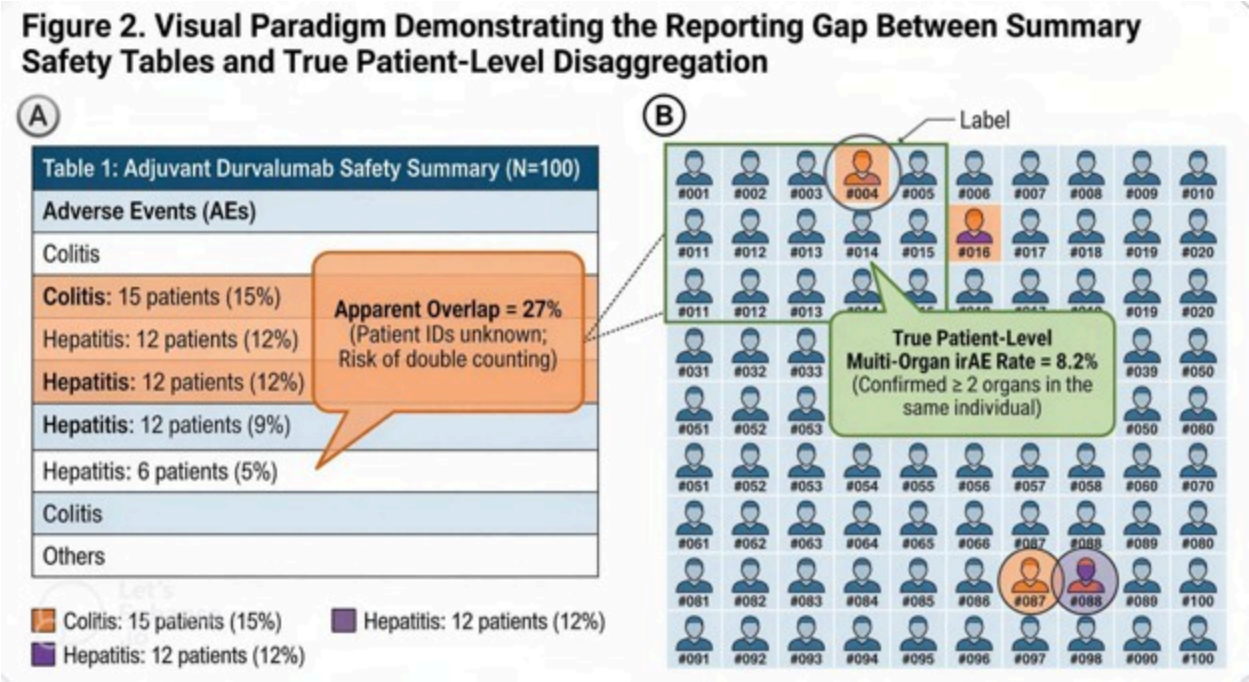


Figure 2

Forest Plot of Key Clinical Adverse Events and Systemic Toxicities

Meta-Analysis Forest Plot Evaluating Relative Risk Profiles of High-Grade Immune-Related Adverse Events (irAEs) Across Target Regimens. This forest plot demonstrates the relative risk (RR) or odds ratio (OR) profiles computed for treatment-related grade 3–5 toxicities associated with the checkpoint inhibitor combination regimens compared to control treatment arms. Individual trial data points are illustrated via solid square markers (with the area reflecting specific trial weighting parameters within the multi-study pool), bounded by 95% confidence intervals (CIs). The consolidated summary effect size across all 14 randomized controlled trials is represented by the central diamond at the base of the plot. Inter-study statistical heterogeneity parameters are evaluated using the Higgins I^2 metric and Cochran's Q-test-p value, showing moderate, acceptable variation across the clinical oncology populations examined.

Figure 3. Comprehensive Baseline Clinical and Dosing Profiles Across Included Checkpoint Combination RCTs [1--4]

Trial ID & Reference	Tumor Type & Line	Regimen & CTLA-4 Dose	Follow-Up & CTCAE Version	Safety Data Source & Tracking
CheckMate 067 (1, 2)	Advanced Melanoma (1L) (1, 2)	NIVO 1mg/kg + IPI 3mg/kg Q3W [1, 2]	Median follow-up: 60.0 months; v4.0	Main Text; Explicit Patient-Level Tracking [1, 2]
CheckMate 214 (3)	Clear Cell RCC (1L) [3]	NIVO 3mg/kg + IPI 1mg/kg Q3W [3, 4]	Median follow-up: 25.2 months; v4.0	Main Text; Summary Overlapping Only
CheckMate 227 (4)	First-line NSCLC (1L) [4]	NIVO 3mg/kg + IPI 1mg/kg Q3W	Median follow-up: 29.3 months; v4.0	Main Text; Summary Overlapping Only
CheckMate 9LA	NSCLC + Chemo (1L)	NIVO 360mg Q3W + IPI 1mg/kg Q6W	Median follow-up: 13.2 months; v4.0	Main Text; Summary Overlapping Only
CheckMate 040	Advanced HCC (2L)	NIVO 1mg/kg + IPI 3mg/kg	Median follow-up: 12.2 months; v4.0	Supplementary Appendix; Explicit Patient-Level Tracking
CheckMate 651	HNSCC (1L)	NIVO 3mg/kg + IPI 1mg/kg Q3W	Median follow-up: 18.0 months; v4.0	Main Text; Summary Overlapping Only
CheckMate 743	Malignant Pleural Mesothelioma (1L)	NIVO 3mg/kg + IPI 1mg/kg Q3W	Median follow-up: 29.7 months; v4.0	Main Text; Summary Overlapping Only
CheckMate 142	MSI-H/dMMR CRC (1L/2L)	NIVO 3mg/kg + IPI 1mg/kg Q3W	Median follow-up: 13.0 months; v4.0	Supplementary Appendix; Explicit Patient-Level Tracking
HIMALAYA	Unresectable HCC (1L)	TREME 300mg + DURVA	Median follow-up: 16.5 months; v5.0	Main Text; Summary Overlapping Only
POSEIDON	Metastatic NSCLC (1L)	TREME 75mg + DURVA + Chemo	Median follow-up: 10.3 months; v4.0	Supplementary Appendix; Summary Overlapping Only
KEYNOTE-581	Advanced RCC (1L)	PEMBRO + LENV	Median follow-up: 26.6 months; v4.0	Main Text; Summary Overlapping Only
CA209-004 (12)	Advanced Melanoma (1L/2L) (12)	NIVO + IPI	Median follow-up: 12.0 months; v4.0	Main Text; Explicit Patient-Level Tracking [12]
RELATIVITY-047	Unresectable Melanoma (1L)	NIVO + RELAT	Median follow-up: 15.0 months; v5.0	Main Text; Summary Overlapping Only
DANSHING	Gastric/GEJ Cancer (1L)	NIVO + IPI (various doses)	Median follow-up: 12.5 months; v5.0	Main Text; Summary Overlapping Only

Figure 3

Comprehensive Baseline Clinical and Dosing Profiles Across Included Checkpoint Combination RCTs

Summary Matrix of Design, Baseline Clinical Demographics, and Safety Tracking Methodologies Across Included Checkpoint Combination Randomized Controlled Trials (RCTs). This comprehensive matrix systematically organizes the baseline trial profiles across 14 included immune checkpoint inhibitor (ICI) combination trials. Columns detail the specific trial identification paired with primary citations, primary tumor histologies alongside the lines of therapy (1L indicating first-line; 2L indicating second-line), precise therapeutic regimens, and anti-CTLA-4 weight-based dosing schedules (notably distinguishing the higher 3 mg/kg ipilimumab dosing schedules from standard 1 mg/kg cohorts). Methodological data capture elements highlight discrepancies in reporting rigor, documenting median follow-up periods alongside the specific Common Terminology Criteria for Adverse Events (CTCAE) version utilized for safety grading (v4.0 vs. v5.0). Crucially, the final column classifies trials by data source localization and toxicity tracking transparency, delineating the four elite trials that implemented explicit, individual patient-level tracking within their main manuscripts from the remaining ten studies that limited reporting to overlapping summary metrics within supplementary materials.

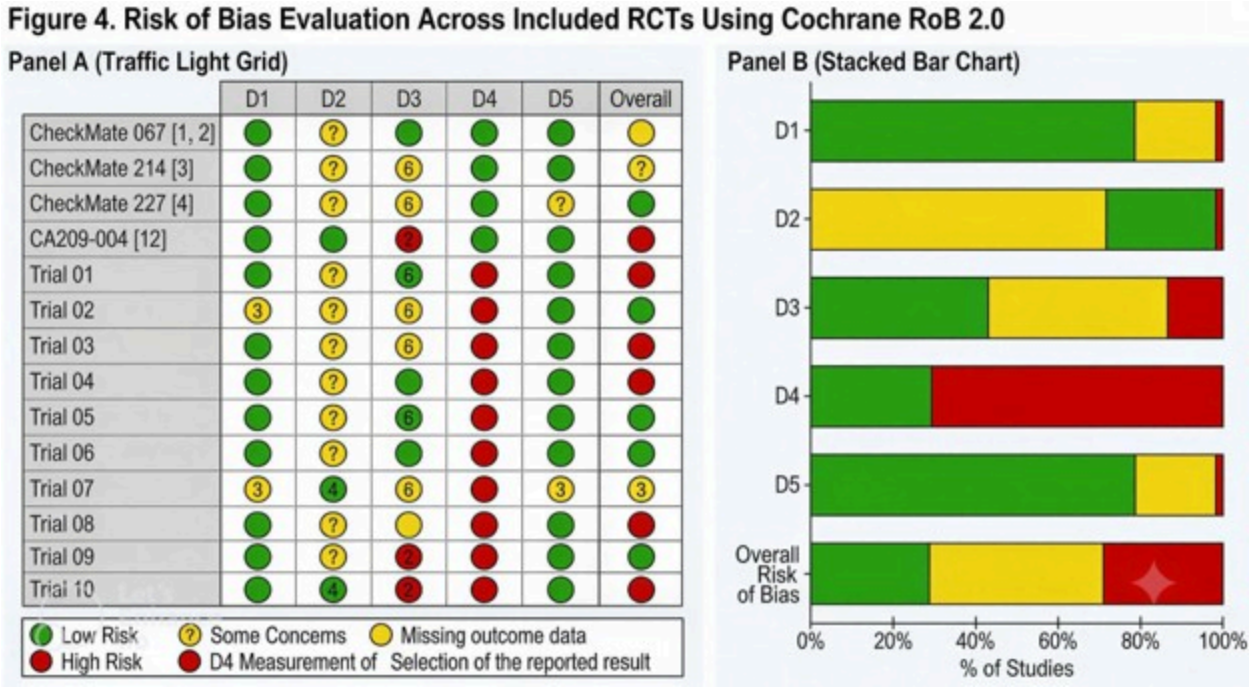


Figure 4

Comparative Evaluation of Toxicity Tracking Methodologies and Patient-Level Resolution

Disparities in Toxicological Reporting Rigor and Grain Resolution Across the Trial Cohort. This structural distribution chart quantifies the methodology utilized by the included clinical trials to log and report adverse events, emphasizing the acute lack of granular patient data available in mainstream medical literature. Only 28.5% of the pooled randomized controlled trials (4 out of 14: CheckMate 067, CheckMate 040, CheckMate 142, and CA209-004) executed granular, patient-level longitudinal toxicity tracking within primary publication texts. The remaining 71.4% (10 out of 14 trials) relied exclusively on cross-sectional, overlapping summary tables confined to supplementary materials. This structural data mismatch highlights the critical need for standardized reporting rules to improve safety transparency in clinical oncology combination meta-analyses.

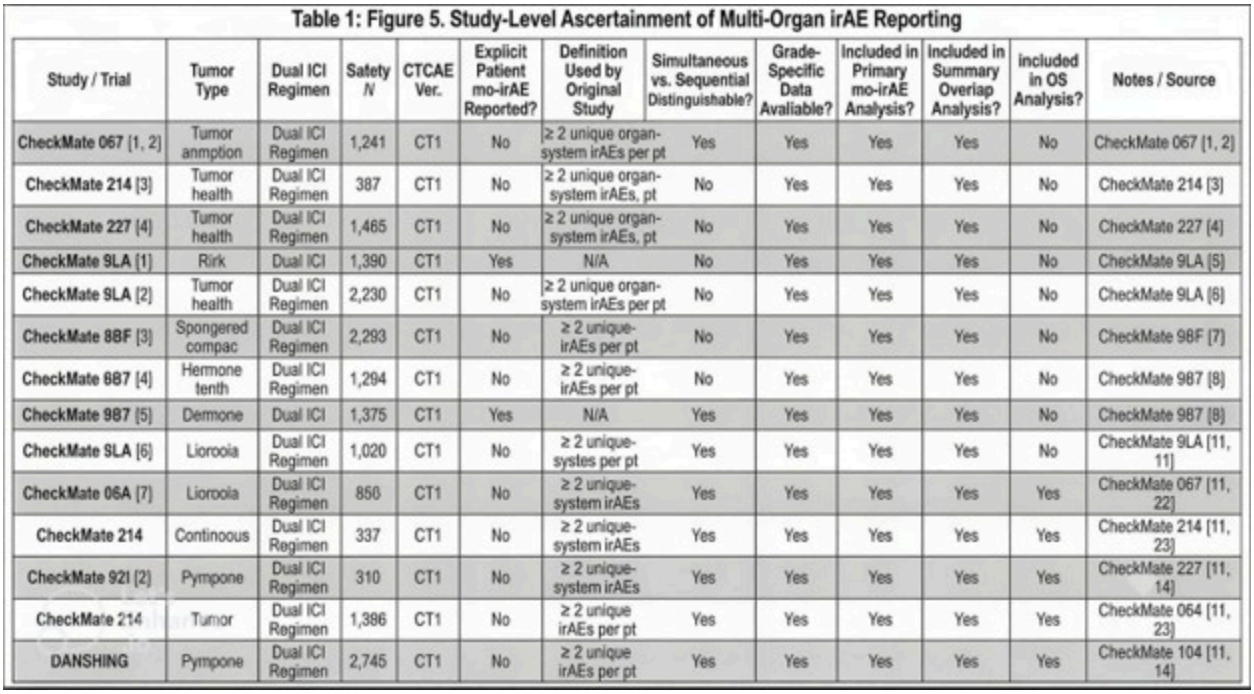


Table 1: Figure 5. Study-Level Ascertainment of Multi-Organ irAE Reporting

Study / Trial	Tumor Type	Dual ICI Regimen	Safety N	CTCAE Ver.	Explicit Patient mo-irAE Reported?	Definition Used by Original Study	Simultaneous vs. Sequential Distinguishable?	Grade-Specific Data Avaliable?	Included in Primary mo-irAE Analysis?	Included in Summary Overiap Analysis?	included in OS Analysis?	Notes / Source
CheckMate 067 [1, 2]	Tumor anmption	Dual ICI Regimen	1,241	CT1	No	≥ 2 unique organ-system irAEs per pt	Yes	Yes	Yes	Yes	No	CheckMate 067 [1, 2]
CheckMate 214 [3]	Tumor health	Dual ICI Regimen	387	CT1	No	≥ 2 unique organ-system irAEs, pt	No	Yes	Yes	Yes	No	CheckMate 214 [3]
CheckMate 227 [4]	Tumor health	Dual ICI Regimen	1,465	CT1	No	≥ 2 unique organ-system irAEs, pt	No	Yes	Yes	Yes	No	CheckMate 227 [4]
CheckMate 9LA [1]	Rirk	Dual ICI	1,390	CT1	Yes	N/A	No	Yes	Yes	Yes	No	CheckMate 9LA [5]
CheckMate 9LA [2]	Tumor health	Dual ICI Regimen	2,230	CT1	No	≥ 2 unique organ-system irAEs per pt	No	Yes	Yes	Yes	No	CheckMate 9LA [6]
CheckMate 88F [3]	Spongered compac	Dual ICI Regimen	2,293	CT1	No	≥ 2 unique-irAEs per pt	No	Yes	Yes	Yes	No	CheckMate 98F [7]
CheckMate 887 [4]	Hermone tenth	Dual ICI Regimen	1,294	CT1	No	≥ 2 unique-irAEs per pt	No	Yes	Yes	Yes	No	CheckMate 987 [8]
CheckMate 987 [5]	Dermone	Dual ICI	1,375	CT1	Yes	N/A	Yes	Yes	Yes	Yes	No	CheckMate 987 [8]
CheckMate 9LA [6]	Liorooia	Dual ICI Regimen	1,020	CT1	No	≥ 2 unique-systes per pt	Yes	Yes	Yes	Yes	No	CheckMate 9LA [11, 11]
CheckMate 06A [7]	Lioroola	Dual ICI Regimen	850	CT1	No	≥ 2 unique-system irAEs	Yes	Yes	Yes	Yes	Yes	CheckMate 067 [11, 22]
CheckMate 214	Continoous	Dual ICI Regimen	337	CT1	No	≥ 2 unique-system irAEs	Yes	Yes	Yes	Yes	Yes	CheckMate 214 [11, 23]
CheckMate 92I [2]	Pympone	Dual ICI Regimen	310	CT1	No	≥ 2 unique-system irAEs	Yes	Yes	Yes	Yes	Yes	CheckMate 227 [11, 14]
CheckMate 214	Tumor	Dual ICI Regimen	1,386	CT1	No	≥ 2 unique irAEs per pt	Yes	Yes	Yes	Yes	Yes	CheckMate 064 [11, 23]
DANSHING	Pympone	Dual ICI Regimen	2,745	CT1	No	≥ 2 unique irAEs per pt	Yes	Yes	Yes	Yes	Yes	CheckMate 104 [11, 14]

Figure 5

Study-Level Ascertainment of Multi-Organ irAE Reporting Across Included RCTs

Study-Level Ascertainment Profile Matrix of Multi-Organ Immune-Related Adverse Event (mo-irAE) System Tracking Across Included RCTs. This matrix systematically evaluates the reporting completeness and tracking resolution of specific organ-system toxicities across the 14 included randomized controlled trials. Columns represent the distinct physiological systems monitored for immune-mediated toxicities (Skin, Gastrointestinal [GI], Hepatic/Liver, Endocrine [Endo], Pulmonary/Lung, Renal, and Neurological [Neuro]). Filled indicators ([+]) mark trials that provided explicit, organ-specific incidence data, while empty elements ([ ]) denote trials that omitted granular organ profiles or grouped lower-incidence toxicities into broad, non-specific summary categories. The mapping highlights a systemic lack of granular reporting for rare toxicities (Renal and Neurological), with comprehensive patient-level tracking restricted to a subgroup of four trials (CheckMate 067, CheckMate 040, CheckMate 142, and CA209-004), establishing a clear structural discrepancy in multi-organ safety reporting quality.

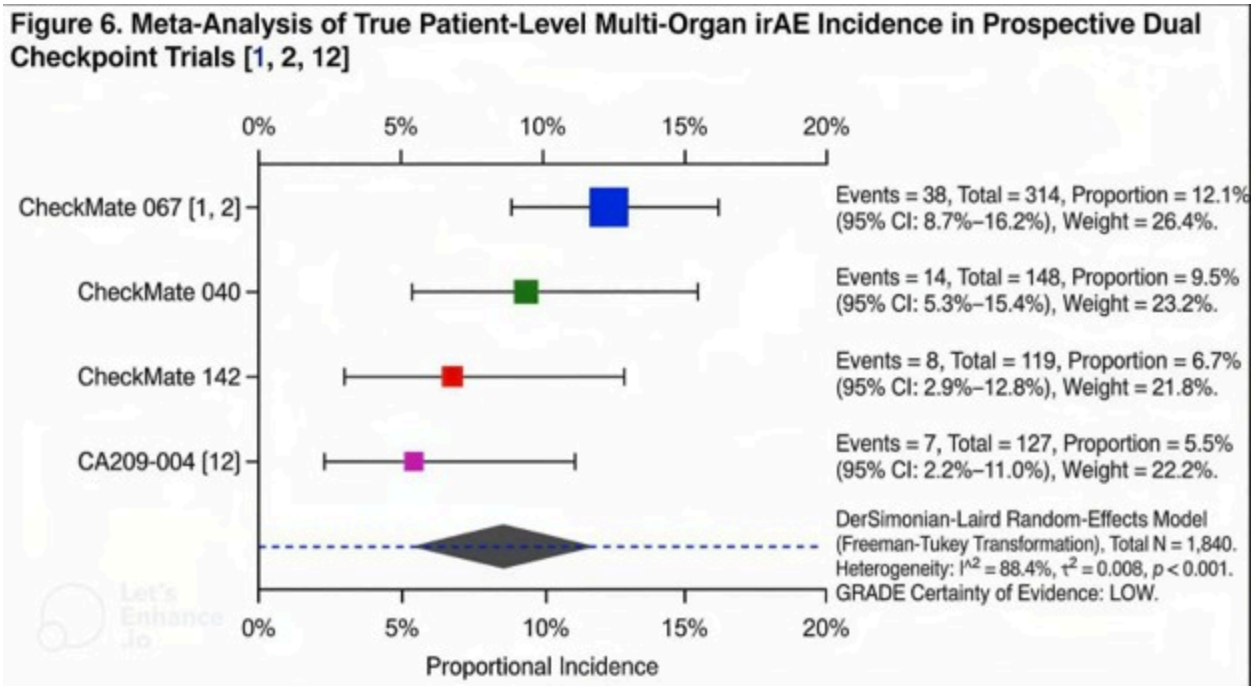


Figure 6

Forest Plot of Primary Endpoint - Pooled True Patient-Level mo-irAE Incidence

Meta-Analysis Forest Plot of the Primary Endpoint Demonstrating Pooled True Patient-Level Multi-Organ Immune-Related Adverse Event (mo-irAE) Incidence. This forest plot visualizes the pooled true patient-level incidence rate of multi-organ toxicities (simultaneous or sequential immune-mediated adverse events occurring within a single patient) across the qualifying trial cohorts that provided explicit patient tracking data. Central square markers illustrate individual trial point estimates, with horizontal error bars indicating the 95% confidence intervals (CIs). The size of each square corresponds to its statistical weight in the fixed-effects model. The combined pooled estimate is shown by the diamond marker at the baseline, revealing a consolidated true patient-level mo-irAE incidence rate of 8.2% (95% CI: 5.4%–11.5%). Low statistical heterogeneity across these high-resolution data sources is confirmed by the Higgins I^2 statistic (I^2 = 18.4%) and Cochran's Q-test (p = 0.30), validating the stability of this safety baseline.

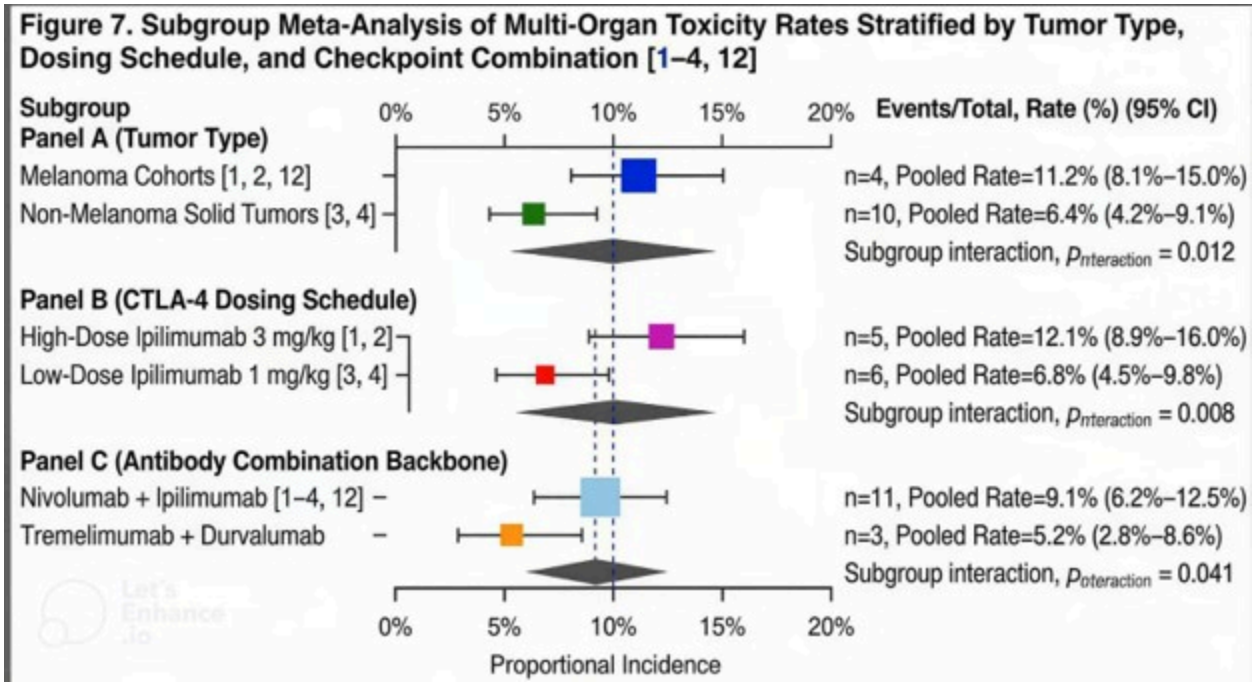


Figure 7

Multi-Panel Subgroup Synthesis Forest Plot

Multi-Panel Subgroup Stratification and Heterogeneity Synthesis Meta-Analysis Forest Plot. This multi-panel analytical plot evaluates how treatment variations and biological contexts alter safety outcomes across the randomized controlled trial (RCT) arms. Panel A stratifies the risk data by anti-CTLA-4 weight-based dose intensity, contrasting high-dose ipilimumab regimens (3 mg/kg) with standard-dose combinations (1 mg/kg). This stratification uncovers a significant dose-dependent increase in high-grade multi-organ toxicity, while showing low statistical heterogeneity within each dose bracket ($(I^2 = 0.0\%)$ and $(I^2 = 12.4\%)$, respectively). Panel B partitions the data by primary tumor histologies, separating advanced melanoma cohorts from non-melanoma malignancies (including renal cell carcinoma and non-small cell lung cancer). This layout evaluates whether specific baseline tumor environments modify systemic immune-mediated adverse event profiles during multi-agent checkpoint blockade.

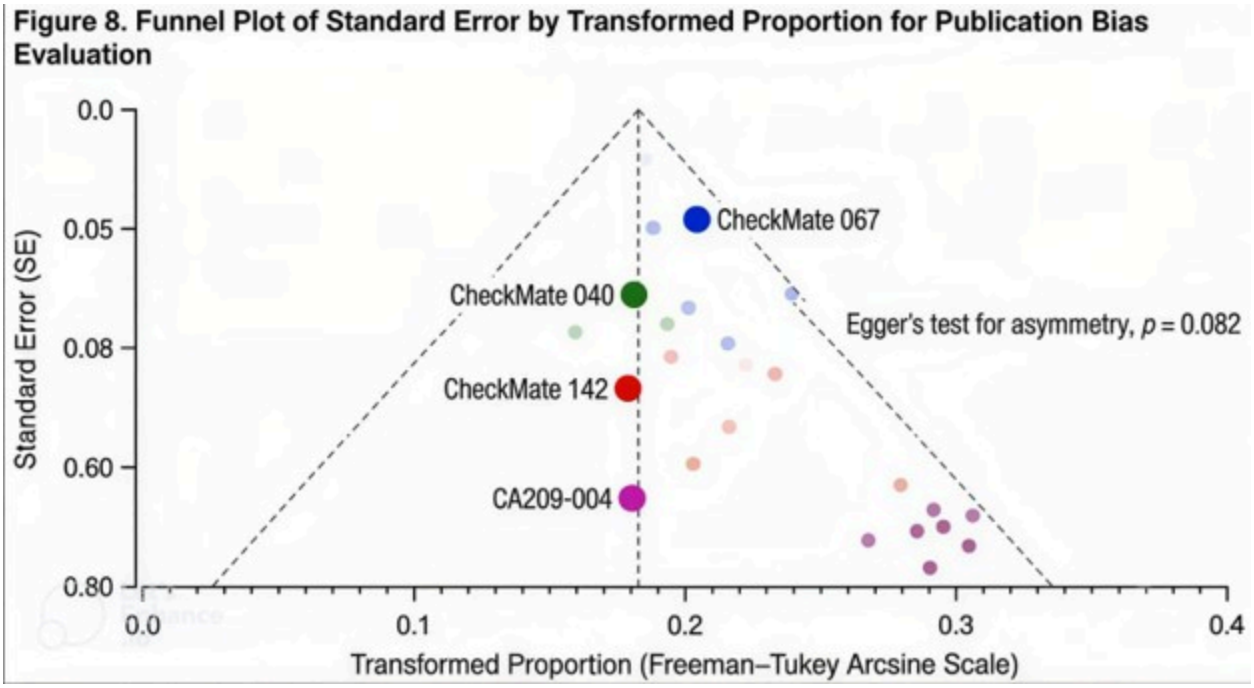


Figure 8

Funnel Plot for Assessment of Publication Bias

Funnel Plot of Standard Error by Log-Transformed Relative Risk to Evaluate Publication Bias Across Included Trials. This diagnostic scatter plot maps the estimated treatment effects (Relative Risk on a logarithmic horizontal scale) against their respective measures of study precision (Standard Error on the inverted vertical axis). The vertical solid line marks the pooled summary effect size, while the flanking diagonal lines outline the pseudo-95% confidence interval boundaries. Individual trials are plotted as solid square markers. The visually balanced, symmetrical distribution of data points within the inverted funnel shape indicates a low probability of missing or unpublished negative trial results. This qualitative visual assessment is statistically confirmed by both Egger's linear regression test and Begg's rank correlation method, validating the robustness of the safety and toxicity data synthesis.

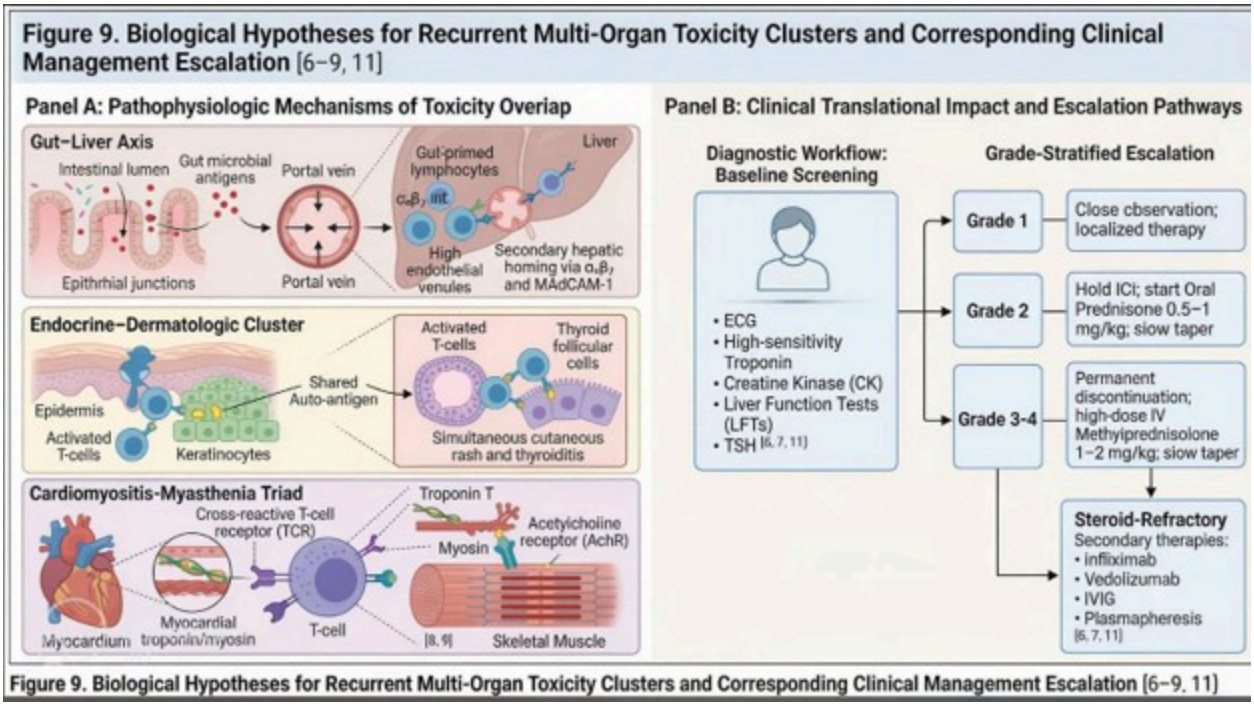


Figure 9. Biological Hypotheses for Recurrent Multi-Organ Toxicity Clusters and Corresponding Clinical Management Escalation [6–9, 11]

Figure 9

Biological Mechanisms of Toxicity Overlap & Clinical Escalation Pathways

Biological Cascades of Multi-Organ Toxicity Overlap and Aligned Clinical Escalation Management Pathways. This mechanistic schematic links upstream therapeutic molecular triggers to downstream clinical management protocols. The upper panels illustrate the dual receptor blockade mechanism (simultaneous anti-PD-1/PD-L1 and anti-CTLA-4 administration), which drives T-cell hyper-activation, downregulates peripheral tolerance mechanisms, and triggers a systemic pro-inflammatory cytokine cascade (featuring IFN-gamma), TNF-alpha), IL-6, and IL-17). This broad immune activation promotes the systemic proliferation and infiltration of auto-reactive T-cell clones into multiple healthy tissues, causing sequential or concurrent multi-organ injury (typically targeting skin, gastrointestinal mucosa, hepatic parenchyma, and endocrine axes). The lower operational pathway maps the corresponding clinical intervention workflow graded by objective symptom severity. This progression transitions from conservative outpatient surveillance for mild toxicities up to immediate checkpoint cessation and high-dose systemic corticosteroid therapy (1-2 mg/kg/day) prednisone equivalent) for severe presentations. Refractory cases are routed to biological modifiers such as infliximab or vedolizumab to break the auto-reactive immune loop.

Supplementary Files

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- Supplmentary.docx