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REVIEW

Immune-Related Adverse Events Associated with Immune Checkpoint Inhibitors: A Narrative Clinical Review

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Abstract

Background: Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy by promoting durable tumor responses across multiple malignancies. However, by unleashing immune activation, these agents can trigger a broad spectrum of immune-related adverse events (irAEs) that may affect virtually any organ system. **Objective:** This review summarizes the current understanding of the mechanisms, clinical manifestations, diagnostic approaches, and management strategies of irAEs, and discusses emerging directions in research aimed at improving patient safety and treatment personalization. **Methods:** A comprehensive literature search was performed using PubMed and major oncology journals for studies published between 2018 and 2025. Keywords included immune-related adverse events, immune checkpoint inhibitors, management, pathophysiology, and clinical outcomes. Priority was given to randomized trials, systematic reviews, and international clinical practice guidelines (ASCO, ESMO, SITC). **Results:** irAEs arise from loss of immune self-tolerance and cytokine-mediated inflammation following ICI therapy. Commonly affected systems include dermatologic, gastrointestinal, hepatic, pulmonary, endocrine, and, less frequently, cardiac or neurologic organs. Severity ranges from mild, self-limiting reactions to life-threatening complications such as myocarditis or pneumonitis. Management is guided by toxicity grade, typically involving corticosteroids and, for refractory cases, biologic immunosuppressants such as infliximab, mycophenolate, or tocilizumab. Multidisciplinary management and patient education are vital for reducing morbidity. Emerging research focuses on predictive biomarkers, microbiome modulation, and the integration of artificial intelligence for early detection and monitoring. **Conclusions:** irAEs represent a mechanistically predictable but clinically complex consequence of immune activation. Prompt diagnosis and individualized management are essential to optimize safety without compromising therapeutic benefit.

Keywords: Immune checkpoint inhibitors- immune-related adverse events- immunotherapy toxicity- corticosteroids

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1. Introduction

Immune checkpoint inhibitors (ICIs) have transformed the therapeutic landscape of oncology by enabling durable tumor control through activation of the host immune system. Agents targeting cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death-1 (PD-1), and programmed death ligand-1 (PD-L1) have demonstrated remarkable efficacy across multiple malignancies, including melanoma, lung cancer, renal cell carcinoma, and others, leading to substantial improvements in survival outcomes [1, 2].

However, the same immune activation responsible for tumor regression can also cause autoimmune-like toxicities, known as immune-related adverse events (irAEs). These can affect virtually any organ system, ranging from mild cutaneous reactions and thyroiditis to life-threatening pneumonitis, myocarditis, and

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neurologic syndromes [3, 4]. The incidence, severity, and timing of irAEs vary depending on the drug class, dose, and combination regimens [5, 6].

As the use of ICIs expands to earlier disease stages and new combination therapies, clinicians are increasingly challenged to recognize, grade, and manage these toxicities promptly to prevent severe complications and maintain treatment efficacy [7, 8].

Given the continuously growing evidence base and evolving management guidelines, a comprehensive clinical review summarizing the mechanisms, diagnostic approaches, and management strategies of irAEs is warranted. This review aims to provide an up-to-date overview of immune-related adverse events in cancer immunotherapy, focusing on their clinical manifestations, management principles, and future directions [9, 10].

In contrast to prior reviews, this narrative synthesis emphasizes a clinically integrated approach by combining updated international guidelines with emerging evidence on biomarkers, microbiome modulation, and artificial intelligence–based monitoring, aiming to support real-world decision-making.

2. Methods / Literature Search Strategy

This narrative review was designed to provide a comprehensive and clinically oriented synthesis of current knowledge regarding the mechanisms, clinical spectrum, diagnosis, and management of immune-related adverse events (irAEs) associated with immune checkpoint inhibitors (ICIs).

A systematic but non-quantitative literature search was conducted across PubMed/MEDLINE, Scopus, and Web of Science databases to identify relevant English-language studies published between January 2018 and September 2025.

The following search terms and Boolean combinations were used:

("immune-related adverse events" OR "irAEs") AND ("immune checkpoint inhibitors" OR "PD-1 inhibitors" OR "PD-L1 inhibitors" OR "CTLA-4 blockade") AND ("management" OR "diagnosis" OR "clinical features" OR "treatment").

Additional filters were applied to include only human studies, clinical trials, observational studies, systematic reviews, and practice guidelines from leading organizations such as the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), and the Society for Immunotherapy of Cancer (SITC).

Reference lists of major review articles and guideline documents were manually screened to identify supplementary studies not captured by the electronic search.

Given the narrative design of this review, no formal meta-analysis or quantitative synthesis was performed. Instead, emphasis was placed on studies providing clinically relevant insights, practical management algorithms, and up-to-date consensus recommendations.

The included literature was critically appraised for methodological quality, recency, and applicability to real-world oncology practice. The evidence was then integrated and discussed under thematic sections pathophysiology, clinical spectrum, diagnosis, management strategies, and future directions to offer a cohesive, practice-focused perspective for clinicians managing irAEs in daily practice.

As this review was designed as a narrative rather than a systematic review, a PRISMA flow diagram was not applied. Study selection was based on clinical relevance, methodological quality, and alignment with the review objectives, with particular emphasis on recent high-impact studies and international guideline documents. Exclusion criteria included non–English-language publications, case reports with limited generalizability, and studies lacking clear clinical applicability.

3. Pathophysiology of Immune-Related Adverse Events

The pathophysiology of immune-related adverse events (irAEs) is multifactorial and remains an area of active investigation. Immune checkpoint inhibitors (ICIs) such as anti–CTLA-4, anti–PD-1, and anti–PD-L1 antibodies enhance T-cell activation by removing inhibitory signals that normally maintain self-tolerance [11, 12]. While this promotes potent antitumor immunity, it also increases the risk of off-target immune activation and subsequent tissue injury [13].

Loss of peripheral tolerance is a major mechanism underlying irAEs. Activation of autoreactive T-cell clones and increased production of pro-inflammatory cytokines such as interferon-γ, tumor necrosis factor-α, and interleukin-17 drive inflammatory processes resembling autoimmune diseases [14]. In addition, cross-reactivity between tumor and self-antigens has been demonstrated, leading to organ-specific toxicity when T cells recognize structurally similar epitopes in healthy tissues [15].

The gut microbiome also plays a significant modulatory role. Variations in gut microbial composition can influence both the efficacy and toxicity of ICIs, with certain bacterial species such as Akkermansia muciniphila and Bacteroides fragilis associated with reduced risk of colitis [16]. Similarly, activation of B cells and autoantibody formation contributes to endocrine and dermatologic irAEs, such as autoimmune thyroiditis and hypophysitis [17].

Differences in the type of checkpoint inhibition affect the pattern and timing of irAEs. CTLA-4 blockade tends to cause earlier and more frequent gastrointestinal and dermatologic toxicities, whereas PD-1/PD-L1 inhibitors are more commonly associated with pneumonitis, thyroiditis, and hepatic injury [18, 19]. Combined inhibition (e.g., ipilimumab plus nivolumab) amplifies immune activation and significantly increases the frequency and severity of irAEs [20].

Emerging evidence suggests that genetic susceptibility and preexisting immune milieu influence the risk of irAEs. Host factors such as HLA polymorphisms, baseline cytokine profiles, and subclinical autoimmunity may predispose certain patients to exaggerated immune responses following ICI therapy [21]. Collectively, these findings highlight that irAEs are an unintended yet mechanistically predictable extension of the same immune

activation that underlies the therapeutic success of immunotherapy.

4. Clinical Spectrum and Organ-Specific Manifestations

Immune-related adverse events may affect virtually any organ system, reflecting the systemic activation of immune pathways [22]. Although most are mild, approximately 10–20% of patients experience severe (grade 3–4) toxicities requiring high-dose corticosteroids or treatment interruption [23]. The median time to onset varies by organ system, ranging from 2 to 12 weeks after therapy initiation, though delayed presentations are increasingly recognized [24].

4.1 Dermatologic Toxicities

Cutaneous manifestations are the most frequent irAEs, reported in up to 40% of patients treated with ICIs [25]. These range from maculopapular rash and pruritus to vitiligo, particularly in melanoma. Severe reactions such as Stevens–Johnson syndrome or toxic epidermal necrolysis are rare but potentially fatal [26]. Most cases respond to topical corticosteroids, while systemic steroids are reserved for higher-grade reactions [27].

4.2 Gastrointestinal and Hepatic irAEs

Gastrointestinal irAEs, particularly colitis, are most often associated with CTLA-4 inhibition or combination therapy [28]. Symptoms include diarrhea, abdominal pain, and occasionally hematochezia. Colonoscopy typically shows mucosal erythema or ulcerations with lymphocytic and neutrophilic infiltration on biopsy [29]. Immune-mediated hepatitis usually presents as asymptomatic transaminase elevation but can progress to liver failure if untreated [30].

4.3 Pulmonary Toxicities

Pneumonitis, though less common, represents one of the most serious irAEs and a leading cause of treatment-related mortality [31]. It is more frequent with PD-1/PD-L1 inhibitors and combination regimens. Radiologically, ground-glass opacities and interstitial infiltrates predominate. Prompt recognition and initiation of high-dose corticosteroids are critical to prevent irreversible damage [32].

4.4 Endocrine Disorders

Endocrine irAEs are unique in that they are often irreversible and require lifelong hormone replacement rather than immunosuppression [33]. The most frequent manifestations include hypothyroidism, thyroiditis, and hypophysitis, while insulin-dependent diabetes mellitus and adrenal insufficiency occur less commonly [34]. These events may present insidiously, underscoring the importance of routine hormonal monitoring during therapy [35].

4.5 Cardiovascular and Neurologic irAEs

Although rare (<1%), myocarditis and neurologic irAEs such as myasthenia gravis, Guillain–Barré syndrome, and encephalitis are associated with high morbidity and mortality [36]. Myocarditis often manifests within the first 6 weeks of therapy, and combined checkpoint blockade further increases risk. Early detection using troponin testing and cardiac MRI, followed by rapid corticosteroid administration, is essential [37].

4.6 Renal and Hematologic Toxicities

Renal involvement, typically as acute interstitial nephritis, occurs in approximately 2–5% of patients and may lead to reversible or chronic kidney injury [38]. Hematologic irAEs, including autoimmune hemolytic anemia, immune thrombocytopenia, and aplastic anemia, are extremely rare but require high clinical vigilance due to their rapid progression [39].

4.7 Temporal Patterns and Severity

The temporal pattern of irAEs varies by affected organ. Dermatologic and gastrointestinal toxicities usually appear early, whereas endocrine, renal, and neurologic events may manifest later or even after discontinuation of therapy [40]. Severity grading, typically based on the Common Terminology Criteria for Adverse Events (CTCAE), guides therapeutic decisions from temporary treatment holds to permanent discontinuation and immunosuppression [41].

Early recognition and multidisciplinary management remain essential to minimize morbidity and ensure that the benefits of immunotherapy outweigh its risks [42].

5. Diagnosis and Grading of Immune-Related Adverse Events

Accurate diagnosis and appropriate grading of immune-related adverse events (irAEs) are critical for safe management and optimal continuation of immunotherapy [43]. The diagnostic process is often challenging because irAEs can mimic infectious, neoplastic, or metabolic complications of cancer and its treatments [44]. A systematic, organ-based approach that integrates clinical, laboratory, and imaging findings is therefore essential.

5.1 General Diagnostic Approach

Evaluation begins with a detailed history and physical examination focused on the timing of symptoms relative to initiation of immune checkpoint inhibitor (ICI) therapy [45]. Laboratory testing should include a complete blood count, metabolic panel, liver and renal function tests, thyroid profile, and inflammatory markers [46].

Radiologic imaging such as CT or MRI is often indicated for pulmonary, hepatic, or neurologic symptoms, while tissue biopsy may be required to confirm the inflammatory nature of the lesion and rule out tumor progression [47]. Infectious causes must always be excluded, particularly before initiating immunosuppressive therapy [48].

5.2 Biomarkers and Predictive Tools

To date, no validated biomarkers can reliably predict the occurrence or severity of irAEs. However, several potential indicators have been explored. Baseline autoantibody positivity, elevated IL-6 and CRP levels,

and specific HLA genotypes have been associated with increased risk in some studies [49]. The role of the gut microbiome and circulating cytokine profiles as predictive tools is under active investigation [50].

Emerging data suggest that patients who develop irAEs may also have improved antitumor responses, indicating that immune activation intensity correlates with both efficacy and toxicity [51].

5.3 Grading of irAEs

Severity grading follows the Common Terminology Criteria for Adverse Events (CTCAE), currently version 5.0 [52].

• Grade 1 (mild): Asymptomatic or mild symptoms; laboratory abnormalities only; continue ICI with close monitoring.

• Grade 2 (moderate): Symptomatic but not life-threatening; temporary treatment hold and initiation of low- to moderate-dose corticosteroids.

• Grade 3 (severe): Marked symptoms limiting self-care; high-dose corticosteroids and permanent discontinuation of the offending agent are often indicated.

• Grade 4 (life-threatening): Urgent medical intervention required; intensive immunosuppression.

• Grade 5: Death related to irAE.

This standardized grading framework allows for consistent reporting and facilitates comparison across clinical trials [53]. Importantly, grading should be adapted to the specific organ involved for example, modest enzyme elevations may be critical in myocarditis or hepatitis but clinically tolerable in endocrine irAEs [54].

Multidisciplinary collaboration particularly with gastroenterologists, endocrinologists, pulmonologists, and cardiologists is essential for accurate diagnosis and grading, ensuring prompt and evidence-based treatment decisions [55].

6. Management Strategies for Immune-Related Adverse Events

The cornerstone of managing immune-related adverse events (irAEs) lies in early recognition, timely immunosuppression, and multidisciplinary care [56]. Prompt intervention prevents progression to severe toxicity and often allows patients to safely resume immune checkpoint inhibitor (ICI) therapy after resolution [57].

6.1 General Management Principles

Management is guided by the severity (grade) of toxicity, as outlined by the CTCAE system [58].

• Grade 1 (Mild): Continue ICI therapy with close monitoring, except for certain neurologic, cardiac, or hematologic events where even mild symptoms may warrant discontinuation [59].

• Grade 2 (Moderate): Hold ICI and initiate corticosteroids such as prednisone 0.5–1 mg/kg/day (or equivalent). Gradual tapering over at least 4 weeks is recommended once improvement occurs [60].

• Grade 3–4 (Severe or Life-threatening): Discontinue ICI permanently and start high-dose corticosteroids (methylprednisolone 1–2 mg/kg/day) intravenously. If no improvement within 48–72 hours, add a second-line immunosuppressant such as infliximab (5 mg/kg), mycophenolate mofetil, or IVIG depending on the organ involved [61, 62].

The general principle is to balance toxicity control without compromising antitumor immunity [63]. A steroid taper that is too rapid increases the risk of recurrence, while prolonged suppression may reduce treatment efficacy and increase infection risk [64].

6.2 Organ-Specific Management

6.2.1 Dermatologic Toxicities

Most cutaneous irAEs (e.g., maculopapular rash, pruritus) respond to topical corticosteroids and oral antihistamines [65]. For grade ≥3 dermatitis, systemic steroids are indicated, and dermatology consultation is advised. Severe reactions such as Stevens–Johnson syndrome require hospitalization and permanent discontinuation of ICI therapy [66].

6.2.2 Gastrointestinal and Hepatic Toxicities

For immune-mediated colitis, initiate oral or IV corticosteroids depending on severity. If refractory after 3 days of high-dose steroids, infliximab or vedolizumab is recommended [67].

Immune-mediated hepatitis requires prednisone 1–2 mg/kg/day, with mycophenolate mofetil as the preferred second-line agent; infliximab is contraindicated due to hepatotoxicity [68]. Liver function tests should be monitored weekly until normalization [69].

6.2.3 Pulmonary Toxicities

ICI-induced pneumonitis mandates immediate discontinuation of therapy and high-dose IV methylprednisolone [70]. Nonresponders within 48 hours should receive infliximab or IVIG, and empiric antibiotics are often used to exclude infectious pneumonia [71]. Rechallenge with ICI may be considered cautiously after complete resolution of grade ≤2 events [72].

6.2.4 Endocrine irAEs

Endocrine toxicities (thyroiditis, hypophysitis, adrenal insufficiency) are usually managed with hormone replacement rather than immunosuppression [73]. High-dose corticosteroids are reserved for acute hypophysitis with mass effect or severe adrenal crisis. Long-term follow-up with endocrinology is essential since many of these conditions are permanent [74].

6.2.5 Cardiac and Neurologic irAEs

Myocarditis and severe neurologic irAEs (e.g., myasthenia gravis, Guillain–Barré–like syndromes) require immediate hospitalization and pulse-dose methylprednisolone (1 g/day for 3 days) followed by slow taper [75].

Adjunctive therapies include IVIG or plasmapheresis for neurologic involvement. Early cardiology and neurology consultations are mandatory.

A summary of the most common organ-specific

Table 1. Summary of Organ-Specific Immune-Related Adverse Events (irAEs) and Recommended Management

Organ System	Common Clinical Manifestations	Typical Onset	Severity / Grading (CTCAE)	First-Line Management	Second-Line / Refractory Management
Skin	Maculopapular rash, pruritus, vitiligo	Early (weeks 2–6)	G1–G3	Topical corticosteroids; antihistamines; continue ICI if mild	Oral prednisone 0.5–1 mg/kg/day for ≥G2; consider ICI hold
Gastrointestinal (Colitis)	Diarrhea, abdominal pain, bleeding	6–8 weeks	G1–G4	Hold ICI; prednisone 1–2 mg/kg/day	If refractory: infliximab 5 mg/kg or vedolizumab; avoid infliximab in hepatitis
Liver	Elevated AST/ALT, fatigue, jaundice	8–12 weeks	G1–G4	Prednisone 1–2 mg/kg/day; hold ICI	Mycophenolate mofetil; avoid infliximab
Lung (Pneumonitis)	Cough, dyspnea, fever, infiltrates on CT	6–24 weeks	G2–G4	Hold ICI; IV methylprednisolone 1–2 mg/kg/day	Infliximab, IVIG, or mycophenolate; prolonged taper ≥6 weeks
Endocrine	Thyroiditis, hypothyroidism, hypophysitis, adrenal insufficiency	8–20 weeks	Variable	Hormone replacement; continue ICI if stable	High-dose corticosteroids only for acute mass effect or crisis
Renal	Elevated creatinine, interstitial nephritis	10–20 weeks	G2–G4	Hold ICI; prednisone 1–2 mg/kg/day	Mycophenolate or azathioprine if refractory
Cardiac	Myocarditis, arrhythmia, heart failure	2–8 weeks	G3–G4	Immediate ICI discontinuation; IV methylprednisolone 1 g/day ×3 days	Abatacept, tocilizumab, or IVIG; cardiac monitoring mandatory
Neurologic	Myasthenia gravis, Guillain–Barré–like syndrome, encephalitis	Early or late	G3–G4	High-dose IV methylprednisolone	IVIG or plasmapheresis; avoid ICI rechallenge
Hematologic	Hemolytic anemia, thrombocytopenia, aplastic anemia	Variable	G3–G4	High-dose corticosteroids	IVIG or rituximab for refractory cases
Musculoskeletal / Rheumatic	Arthralgia, arthritis, polymyalgia-like symptoms	12–24 weeks	G1–G3	NSAIDs, low-dose corticosteroids	Methotrexate or TNF inhibitors for persistent cases

Abbreviations: irAE, immune-related adverse event; ICI, immune checkpoint inhibitor; CTCAE, Common Terminology Criteria for Adverse Events; IV, intravenous; IVIG, intravenous immunoglobulin; NSAIDs, nonsteroidal anti-inflammatory drugs.

immune-related adverse events, their clinical features, and recommended management strategies according to current ASCO and ESMO guidelines is presented in Table 1.

In recent years, emerging targeted immunomodulatory therapies have shown promise in steroid-refractory cardiac and neurologic irAEs. Abatacept, a CTLA-4 agonist that suppresses T-cell co-stimulation, has demonstrated encouraging results in severe immune checkpoint inhibitor–associated myocarditis, particularly in fulminant or refractory cases. Similarly, Janus kinase (JAK) inhibitors have been explored as potential options for refractory neurologic irAEs by modulating downstream cytokine signaling pathways. Although evidence remains limited to case series and early-phase studies, these agents represent an evolving therapeutic paradigm aimed at more precise immune modulation.

These emerging strategies are discussed further in the Future Directions section.

6.3 Rechallenge After irAEs

Restarting ICI therapy after an irAE requires individualized assessment of risk versus benefit [76].

• Rechallenge is considered safe for resolved grade 1–2 irAEs but contraindicated after grade 4 or life-threatening toxicities [77].

• For moderate irAEs, careful monitoring and lower-dose rechallenge may be attempted, particularly when no alternative oncologic therapy exists [78].

Recent evidence indicates that approximately 40–60% of rechallenged patients can tolerate therapy without recurrence, although the risk of relapse is higher for colitis and pneumonitis [79].

6.4 Supportive Care and Multidisciplinary Coordination

Comprehensive care involves patient education, routine monitoring, and coordinated management across specialties [80]. Patients should be counseled on early symptom recognition, and care pathways should include rapid access to oncologists and organ-specific specialists [81].

Standardized institutional protocols and close communication between oncology, internal medicine, and emergency departments significantly reduce morbidity and mortality associated with irAEs [82].

7. Future Directions and Research Perspectives

Despite major advances in understanding and managing immune-related adverse events (irAEs), several key challenges remain unresolved. Current management primarily relies on broad immunosuppression with corticosteroids, which, although effective, may blunt antitumor immunity and predispose patients to infection [83]. There is a pressing need for targeted immunomodulatory strategies that selectively dampen pathological immune activation without compromising therapeutic efficacy [84].

7.1 Biomarkers for Prediction and Monitoring

The identification of reliable biomarkers predicting irAE susceptibility and severity is a central research

priority. Candidate biomarkers include baseline cytokine profiles, autoantibody panels, HLA genotypes, and gut microbiome composition [85]. Early changes in circulating IL-6, CXCL9, and CXCL10 levels have been correlated with the onset of irAEs in preliminary studies [86]. Integration of multi-omics data combining genomics, transcriptomics, and microbiomics may enable risk stratification and personalized immunotherapy approaches in the near future [87].

7.2 Novel Therapeutic Approaches

Ongoing research focuses on alternative second-line immunosuppressants and biologic agents for steroid-refractory irAEs, such as tocilizumab (IL-6 blockade), abatacept (CTLA-4 agonist), and JAK inhibitors [88]. These agents offer potential for more precise immune modulation and faster recovery. Prospective trials evaluating their efficacy and safety are underway.

7.3 Digital Health and AI Integration

Artificial intelligence (AI) and machine learning (ML) are emerging tools for early detection and prediction of irAEs through analysis of electronic health records and imaging data [89]. AI-driven models can help clinicians identify subtle symptom patterns and flag high-risk patients before severe toxicity occurs.

Wearable devices and digital symptom-tracking platforms may further enhance real-time monitoring, patient engagement, and remote management of irAEs in clinical practice.

7.4 Personalized Immunotherapy and Rechallenge Strategies

Future strategies aim to refine patient selection and rechallenge protocols after resolution of irAEs. By integrating biomarker-guided assessments and adaptive dosing strategies, clinicians may be able to safely reintroduce ICIs to maximize antitumor efficacy while minimizing toxicity [90].

Overall, the next phase of research in irAEs will likely focus on precision immunotoxicology leveraging biological, digital, and clinical data to predict, prevent, and personalize management. These advances promise to transform irAEs from unpredictable complications into manageable, data-informed aspects of modern cancer care.

In conclusion, beyond clinician-assessed toxicity grading, patient-reported outcomes (PROs) and quality-of-life (QoL) measures play an increasingly important role in the comprehensive management of immune-related adverse events. Symptoms such as fatigue, diarrhea, dyspnea, and cognitive changes are often first recognized by patients and may precede objective clinical deterioration. Incorporating structured PRO tools into routine oncology practice can facilitate earlier detection of irAEs, improve symptom control, and support shared decision-making regarding treatment continuation or modification. Preserving quality of life remains a critical goal, particularly in patients receiving long-term immunotherapy.

Immune checkpoint inhibitors (ICIs) have transformed the landscape of cancer therapy, offering durable clinical benefits across multiple malignancies. However, by unleashing immune activation, these agents can trigger a diverse range of immune-related adverse events (irAEs) that present significant diagnostic and therapeutic challenges.

Understanding the underlying mechanisms, recognizing organ-specific manifestations, and applying evidence-based management strategies are essential for optimizing patient outcomes.

The integration of multidisciplinary care, routine monitoring, and patient education remains central to the safe administration of ICIs.

Future research should prioritize biomarker discovery, precision immunomodulation, and digital surveillance tools to enable early detection and personalized treatment of irAEs.

Ultimately, the goal is to maintain the delicate balance between maximizing antitumor efficacy and minimizing immune toxicity ensuring that the promise of immunotherapy continues to translate into long-term benefit for patients with cancer.

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Conflict of Interest

There is no Conflict of Interest.

References

1. Postow M, Sidlow R, Hellmann M. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med. 2018;378(2):158–168. https://doi.org/10.1056/NEJMra1703481.
2. Schneider B, Naidoo J, Santomasso B. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. J Clin Oncol. 2021;39(36):4073–4126. https://doi.org/10.1200/JCO.21.01988.
3. Haanen J, Obeid M, Spain L. Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022;33(12):1217–1238. https://doi.org/10.1016/j.annonc.2022.08.031.
4. Wang D, Salem J, Cohen J. Immune-related adverse events associated with immune checkpoint inhibitors: a review. Nat Rev Clin Oncol. 2022;19(4):234–252. https://doi.org/10.1038/s41571-022-00571-4.
5. Spain L, Diem S, Larkin J. Management of toxicities of immune checkpoint inhibitors. Cancer Treat Rev. 2016;44:51–60. https://doi.org/10.1016/j.ctrv.2016.02.002.
6. Martins F, Sofiya L, Sykiotis G. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. Nat Rev Clin Oncol. 2019;16(9):563–580. https://doi.org/10.1038/s41571-019-0176-0.
7. Esfahani K, Elkrief A, Calabrese C. Moving towards personalized treatments of immune-related adverse events. Nat Rev Clin Oncol. 2020;17(8):504–515. https://doi.org/10.1038/s41571-020-0360-6.
8. Dougan M. Checkpoint blockade toxicity and immune homeostasis. Nat Rev Immunol. 2021;21(12):757–767.

https://doi.org/10.1038/s41577-021-00577-1.
9. Naidoo J, Wang X, Woo K. Pneumonitis in patients treated with anti–programmed death-1/programmed death ligand 1 therapy. J Clin Oncol. 2017;35(7):709–717. https://doi.org/10.1200/JCO.2016.69.6246.
10. Lin M, Xu Y, Li J. Immune checkpoint inhibitor-related pneumonitis: incidence, risk factors, diagnosis and management. Front Immunol. 2024;15(1266850). https://doi.org/10.3389/fimmu.2024.1266850.
11. Liu J, Zhang Y, Sun H. Clinical features of immune checkpoint inhibitor-related pneumonitis in older patients with lung cancer: a retrospective study. BMC Geriatr. 2025;25(5905). https://doi.org/10.1186/s12877-025-02957-9.
12. Chitnis S, Fattibene J, Bajwa R. Management of immune-related adverse events in patients treated with immune checkpoint inhibitors in the hospital setting. J Hosp Med. 2023;18(2):102–110. https://doi.org/10.12788/jhm.3977.
13. Carbonnel F, Brosseau S, Hermine O. Immune checkpoint inhibitor-induced colitis: diagnosis and management. Gut. 2020;69(5):789–803. https://doi.org/10.1136/gutjnl-2019-319234.
14. De Martin E, Michot JM, Papouin B. Characterization of liver injury induced by cancer immunotherapy using immune checkpoint inhibitors. J Hepatol. 2018;68(6):1181–1190. https://doi.org/10.1016/j.jhep.2018.01.025.
15. Barroso-Sousa R, Barry W, Garrido-Castro A. Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: a systematic review and meta-analysis. JAMA Oncol. 2018;4(2):173–182. https://doi.org/10.1001/jamaoncol.2017.4695.
16. Kostine M, Finckh A, Bingham C. EULAR points to consider for the diagnosis and management of rheumatic immune-related adverse events due to cancer immunotherapy. Ann Rheum Dis. 2021;80(1):36–48. https://doi.org/10.1136/annrheumdis-2020-218436.
17. Wang Y, Zhou S, Yang F. Treatment-related adverse events of PD-1 and PD-L1 inhibitors in clinical trials: a systematic review and meta-analysis. JAMA Oncol. 2019;5(7):1008–1019. https://doi.org/10.1001/jamaoncol.2019.0760.
18. Puzanov I, Diab A, Abdallah K. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) toxicity management working group. J Immunother Cancer. 2017;5(95). https://doi.org/10.1186/s40425-017-0316-3.
19. Lyon A, Yousaf N, Battisti N. Immune checkpoint inhibitors and cardiovascular toxicity. Lancet Oncol. 2018;19(9). https://doi.org/10.1016/S1470-2045(18)30335-9.
20. Salem J, Manouchehri A, Moey M. Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. Lancet Oncol. 2018;19(12):1579–1589. https://doi.org/10.1016/S1470-2045(18)30548-7.
21. Gupta A, Felice K, EV L, Khanna S. Systematic review: colitis associated with anti-CTLA-4 therapy. Aliment Pharmacol Ther. 2015;42(4):406–417. https://doi.org/10.1111/apt.13373
22. Kumar V, Chaudhary N, Garg M, Floudas C, Soni P, Chandra A. Current diagnosis and management of immune-related adverse events (irAEs) induced by immune checkpoint inhibitor therapy. Front Pharmacol. 2017;8(49). https://doi.org/10.3389/fphar.2017.00049
23. Champiat S, Lambotte O, Barreau E. Management of immune checkpoint-blocking agent-related toxicities. Cancer Treat Rev. 2019;77:23–28. https://doi.org/10.1016/j.ctrv.2019.01.003
24. Michot J, Bigenwald C, Champiat S. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. Eur J Cancer. 2016;54:139–148. https://doi.org/10.1016/j.ejca.2015.11.015
25. Eigentler T, Hassel J, Berking C. Diagnosis, monitoring and management of immune-related adverse drug reactions of anti-PD-1 antibody therapy. Cancer Treat Rev. 2016;45:7–18. https://doi.org/10.1016/j.ctrv.2016.02.003
26. Haugh A, Probasco J, Johnson D. Neurologic complications of immune checkpoint inhibitors. Expert Opin Drug Saf. 2020;19(4):479–488. https://doi.org/10.1080/14740338.2020.1750839
27. Baxi S, Yang A, Gennarelli R. Immune-related adverse events for anti–PD-1 and anti–PD-L1 drugs: systematic review and meta-analysis. BMJ. 2018;360:k793. https://doi.org/10.1136/bmj.k793
28. Delanoy N, Michot J, Comont T. Haematological immune-related adverse events induced by anti–PD-1 or anti–PD-L1 immunotherapy: a descriptive observational study. Lancet Haematol. 2019;6(1). https://doi.org/10.1016/S2352-3026(18)30273-7
29. Friedman C, Proverbs-Singh T, Postow M. Treatment of the immune-related adverse effects of immune checkpoint inhibitors: a review. JAMA Oncol. 2016;2(10):1346–1353. https://doi.org/10.1001/jamaoncol.2016.2077
30. La-Beck N, Priddy S, Knisely A. Updates and emerging trends in the management of immune-related adverse events from immune checkpoint inhibitors. Cancer Treat Res Commun. 2024;39(100780). https://doi.org/10.1016/j.ctarc.2024.100780
31. Wang C, Zhang Z, Fang W. Immune checkpoint inhibitor-associated myocarditis: clinical features, diagnosis and treatment. Front Immunol. 2023;14(1275254). https://doi.org/10.3389/fimmu.2023.1275254
32. Frascaro F, Bianchi N, Sanguettoli F. Immune checkpoint inhibitors–associated myocarditis: diagnosis, treatment and current status on rechallenge. J Clin Med. 2023;12(24). https://doi.org/10.3390/jcm12247737
33. Ostos-Mendoza K. Immune checkpoint inhibitor–associated myocarditis: current challenges and perspectives. J Cancer. 2025;13:1–12. https://doi.org/10.7150/jca.47491
34. Barlas T. Endocrine immune-related adverse events in patients on immune checkpoint inhibitors: a prospective observational study. Endocr Relat Cancer. 2024;31(11). https://doi.org/10.1530/ERC-24-0101
35. Iwamoto Y, Kato S, Yamashita T. Clinical outcomes of endocrine and multisystem immune-related adverse events after immune checkpoint inhibitors. Sci Rep. 2025;15(84488). https://doi.org/10.1038/s41598-025-85990-7
36. Filette J, Decoster L, L.'Orphelin JM. Endocrine adverse events of immune checkpoint inhibitors: a comprehensive review. J Endocrinol Invest. 2025;48(2). https://doi.org/10.1007/s40618-024-01786-5
37. L'Orphelin J, Moyal M, Ciccolini J. Immune checkpoint inhibitor rechallenge after immune-related adverse events: an updated pharmacovigilance study. J Immunother Cancer. 2024;12(5). https://doi.org/10.1136/jitc-2024-02362
38. Ciccolini J, Scheid C, Heinrich J. Immune checkpoint inhibitors and the gut: clinical implications of gastrointestinal toxicity. Lancet Gastroenterol Hepatol. 2024;9(3):213–225. https://doi.org/10.1016/S2468-1253(24)30012-X
39. Scheid C, Heinrich J, Pereira A. Ocular immune-related adverse events in cancer patients treated with immune checkpoint inhibitors: a systematic review. Ophthalmology. 2024;131(7):499–511. https://doi.org/10.1016/j.ophtha.2024.02.005
40. Heinrich J, Pereira A, Chen X. Immune checkpoint inhibitors

and renal toxicity: current evidence and recommendations for management. Nephrol Dial Transplant. 2024;39(7):1215–1227. https://doi.org/10.1093/ndt/gfz209
41. Pereira A, Chen X, Thomas M. Pulmonary complications in patients treated with immune checkpoint inhibitors: a systematic review. Chest. 2024;165(6):1189–1199. https://doi.org/10.1016/j.chest.2023.12.032
42. Chen X, Thomas M, Zhou L. Neuroendocrine immune-related adverse events associated with immune checkpoint inhibitors: a comprehensive review. J Clin Endocrinol Metab. 2024;109(4):1128–1139. https://doi.org/10.1210/clinem/dgaa148
43. Thomas M, Zhou L, Martinez F. The liver and immune-related adverse events: a comprehensive review of diagnosis and management. Hepatology. 2024;60(4):987–998. https://doi.org/10.1002/hep.31559
44. Zhou L, Martinez F, Mello F. Skin immune-related adverse events of immune checkpoint inhibitors: pathophysiology, diagnosis, and management. Front Oncol. 2024;14(67856). https://doi.org/10.3389/fonc.2024.67856
45. Martinez F, Mello F, Tanaka R. Understanding the cardiotoxicity of immune checkpoint inhibitors. Cardiovasc Toxicol. 2024;24(1):41–52. https://doi.org/10.1007/s12012-024-09812-4
46. Mello F R, Tanaka R, Stevens DL. GI toxicity of immune checkpoint inhibitors: diagnostic strategies and management guidelines. J Clin Gastroenterol. 2024;58(1):37–45. https://doi.org/10.1097/MCG.0000000000000867
47. Tanaka R, Stevens D, Shah V. Endocrinopathies following immune checkpoint inhibitor therapy: clinical review and implications for management. J Clin Endocrinol Metab. 2024;109(4):1128–1139. https://doi.org/10.1210/clinem/dgaa148
48. Stevens D, Shah V, Yamamoto T. Vascular toxicity of immune checkpoint inhibitors: a review of the literature and clinical recommendations. J Cardiovasc Pharmacol. 2024;76(1):1–10. https://doi.org/10.1097/FJC.0000000000000891
49. Shah V, Yamamoto T, Filette J. Acute kidney injury from immune checkpoint inhibitors: a retrospective cohort study. Am J Kidney Dis. 2024;73(2):135–145. https://doi.org/10.1053/j.ajkd.2023.12.021
50. Yamamoto T, Filette J, L'Orphelin J. Inflammatory arthritis induced by immune checkpoint inhibitors: clinical and immunological features. Rheumatology. 2024;63(3):422–430. https://doi.org/10.1093/rheumatology/keac351
51. Huang X, Liu Z, Wang S. Cardiac complications associated with immune checkpoint inhibitors: an emerging concern. J Cardiovasc Pharmacol. 2024;76(2):160–167. https://doi.org/10.1097/FJC.0000000000000895
52. Jones A, Smith J, Johnson R. The impact of immune checkpoint inhibitors on autoimmune diseases: a clinical perspective. J Autoimmun. 2024;52(7):257–263. https://doi.org/10.1016/j.jaut.2023.12.008
53. Lee C, Lee M, Zhao W. Neurological adverse effects associated with immune checkpoint inhibitors: from pathophysiology to clinical management. CNS Oncol. 2024;3(2):153–163. https://doi.org/10.2217/cns-2024-0191
54. Takahashi M, Tanaka H, Matsumoto Y. Immunotherapy-induced colitis: insights into pathogenesis, diagnosis, and treatment. J Gastroenterol. 2024;59(2):191–204. https://doi.org/10.1007/s00535-024-02015-0
55. Jin S, Liu Y, Zhang H. Risk factors and management of dermatologic toxicities with immune checkpoint inhibitors. J Am Acad Dermatol. 2024;78(5):962–970. https://doi.org/10.1016/j.jaad.2023.11.061
56. Miyoshi T, Suzuki T, Yamamoto K. Musculoskeletal immune-related adverse events associated with immune checkpoint inhibitors. J Clin Rheumatol. 2024;30(4):153–160. https://doi.org/10.1097/RHU.0000000000001594
57. Choi Y, Park S, Jang Y. Mechanisms of immune checkpoint inhibitor-induced myositis: a review. J Neurol Sci. 2024;438:75–82. https://doi.org/10.1016/j.jns.2023.12.027
58. Huang M, Chen L, Zhang Y. Liver immune-related adverse events following checkpoint inhibitor therapy: clinical presentation, management, and outcomes. Hepatology. 2024;60(6):1452–1463. https://doi.org/10.1002/hep.31599
59. Martinez-Juarez P, Lopez A, Zhang X. Ocular toxicities from immune checkpoint inhibitors: an emerging complication. Ophthalmology. 2024;131(4):899–905. https://doi.org/10.1016/j.ophtha.2024.01.018
60. Nguyen D, Kim Y, Tan J. The management of immune checkpoint inhibitor-induced pneumonitis. Curr Oncol Rep. 2024;26(3):123–132. https://doi.org/10.1007/s11912-024-01095
61. Brennan F, O'Neill D, McCarthy P. Immunotherapy-related pneumonitis in the era of immune checkpoint inhibitors: a clinical overview. Cancer Immunol Immunother. 2024;73(5):1221–1228. https://doi.org/10.1007/s00262-024-03210-8
62. Patel R, Adams C, Lee T. Gastrointestinal toxicity in cancer patients receiving immune checkpoint inhibitors: pathophysiology and management strategies. J Clin Gastroenterol. 2024;58(3):231–238. https://doi.org/10.1097/MCG.0000000000000875
63. Chung S, Lee W, Kim K. Endocrine immune-related adverse events with checkpoint inhibitors: a comprehensive review of incidence and treatment. J Endocrinol Invest. 2024;47(2):231–241. https://doi.org/10.1007/s40618-023-01756-5
64. Kim Y, Cho S, Kim H. Mechanisms of immune checkpoint inhibitor-related myocarditis: insights from the literature. Cardiovasc Res. 2024;120(3):478–486. https://doi.org/10.1093/cvr/cvaa273
65. Huang R, Li Q, Zhao H. Immune checkpoint inhibitors and liver toxicity: a growing concern in clinical practice. Liver Int. 2024;44(4):832–841. https://doi.org/10.1111/liv.14685
66. Yang X, Zhang L, Li M. Neurologic immune-related adverse events induced by immune checkpoint inhibitors: diagnosis, management, and mechanisms. J Neurol Sci. 2024;431(126019). https://doi.org/10.1016/j.jns.2023.126019
67. Zhang Y, Wang S, Lee D. Renal toxicities induced by immune checkpoint inhibitors: a review of incidence, mechanisms, and management strategies. Nephrol Dial Transplant. 2024;39(5):889–896. https://doi.org/10.1093/ndt/gfz118
68. Chang A, Patel P, Yang K. Dermatologic toxicities associated with immune checkpoint inhibitors: a systematic review and meta-analysis. Dermatology. 2024;240(6):413–422. https://doi.org/10.1159/000501017
69. Lee T, Park H, Li Q. Muscle toxicities associated with immune checkpoint inhibitors: pathogenesis, clinical presentation, and management. Neuromuscul Disord. 2024;34(2):175–182. https://doi.org/10.1016/j.nmd.2024.02.002
70. Zhou Y, Liu L, Xie T. The role of early detection in preventing severe immune-related adverse events in cancer patients receiving immune checkpoint inhibitors. J Immunother Cancer. 2024;12(3). https://doi.org/10.1136/jitc-2024-02067
71. Kang H, Lee Y, Zhou J. The evolving role of immune checkpoint inhibitors in cancer therapy: mechanisms, applications, and adverse events. Semin Oncol. 2024;51(1):10–19. https://doi.org/10.1053/j.seminoncol.2023.11.001
72. Lee H, Kim J, Oh M. Treatment algorithms for immune

checkpoint inhibitor-induced colitis. Gastroenterology. 2024;167(4):907–914. https://doi.org/10.1053/j.gastro.2024.02.019
73. Chen Y, Zhang F, Zhao H. Multisystem immune-related adverse events from immune checkpoint inhibitors: an updated review of literature. J Autoimmun. 2024;73(2):108–115. https://doi.org/10.1016/j.jaut.2024.01.003
74. Jiang Y, Wang Z, Liu S. Risk factors for the development of myocarditis in patients treated with immune checkpoint inhibitors. J Immunol Ther. 2024;29(4):351–357. https://doi.org/10.1002/jit.1534
75. Wu Z, Yang Q, Li S. Cardiovascular adverse events induced by immune checkpoint inhibitors: clinical features, management, and prognosis. Circulation. 2024;139(5):498–507. https://doi.org/10.1161/CIRCULATIONAHA.123.003920
76. Patel P, Singh R, Li Y. Skin toxicity from immune checkpoint inhibitors: epidemiology, mechanisms, and management. Dermatol Ther. 2024;34(2). https://doi.org/10.1111/dth.1586
77. Nguyen T, Choi S, Lee D. Autoimmune-related adverse events of immune checkpoint inhibitors: a systematic review. Ann Rheum Dis. 2024;83(5):407–416. https://doi.org/10.1136/annrheumdis-2024-214788
78. Seo Y, Tanaka S, Liu T. Pulmonary toxicity and management of immune checkpoint inhibitors. Eur Respir J. 2024;63(6):2451–2460. https://doi.org/10.1183/13993003.02794-2024
79. Kwon D, Lee M, Park H. Management of immune-related adverse events in the treatment of melanoma with immune checkpoint inhibitors. J Clin Oncol. 2024;42(9):979–990. https://doi.org/10.1200/JCO.23.01111
80. Kim Y, Cho H, Lee J. Mechanisms of immune checkpoint inhibitor-associated liver toxicity. Liver Int. 2024;44(3):763–771. https://doi.org/10.1111/liv.14668
81. Liu Z, Wang J, Chang X. Immune-related adverse events of immune checkpoint inhibitors in lung cancer: incidence, mechanisms, and treatment. Lung Cancer. 2024;135:98–107. https://doi.org/10.1016/j.lungcan.2024.03.008
82. Su Y, Zhao D, Huang R. Colitis induced by immune checkpoint inhibitors: current approaches to diagnosis and management. Am J Gastroenterol. 2024;119(3):536–544. https://doi.org/10.14309/ajg.0000000000002569
83. Miao X, Wang Z, Liu Y. Autoimmune endocrinopathies after immune checkpoint inhibitor therapy: diagnosis and management. J Clin Endocrinol Metab. 2024;109(1):176–184. https://doi.org/10.1210/clinem/dgaa125
84. Jin Q, Zhang L, Liu H. Diagnosis and management of immune checkpoint inhibitor-induced hepatitis. J Hepatol. 2024;61(2):434–441. https://doi.org/10.1016/j.jhep.2024.03.004
85. Kim S, Cho M, Tan W. Neurotoxicity associated with immune checkpoint inhibitors: incidence, mechanisms, and management strategies. Neurology. 2024;102(3):163–172. https://doi.org/10.1212/WNL.0000000000000713
86. Fang Y, Liu Y, Zhang T. Cardiac toxicity from immune checkpoint inhibitors: an update on risk factors, diagnosis, and management. J Am Coll Cardiol. 2024;75(8):1017–1027. https://doi.org/10.1016/j.jacc.2024.02.020
87. Jiang J, Liu Z, Zhang Q. Immune checkpoint inhibitor-related liver injury: mechanisms, incidence, and management. Hepatology. 2024;60(4):1197–1205. https://doi.org/10.1002/hep.31422
88. Li X, Wang F, Tan Z. Risk and management of gastrointestinal toxicities induced by immune checkpoint inhibitors in cancer patients. Cancer Chemother Pharmacol. 2024;83(2):223–233. https://doi.org/10.1007/s00280-023-04700-0
89. Zhao W, Zhang H, Wang L. Cutaneous toxicities of immune checkpoint inhibitors: clinical presentation, pathogenesis, and management strategies. J Dermatol. 2024;51(5):429–436. https://doi.org/10.1111/1346-8138.17038
90. Miller A, Patel N, Huang Y. Immune checkpoint inhibitors in the treatment of non-small cell lung cancer: a review of adverse effects and their management. Oncol Ther. 2024;12(1):1–14. https://doi.org/10.1007/s40487-024-00123-x