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The Evolving Landscape of Immunotoxicity: Charting Mechanisms and Future Strategies for Immune Checkpoint Inhibitor Adverse Events

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ABSTRACT

The use of immune checkpoint inhibitors (ICIs) has significantly improved the efficacy of cancer therapy, but their associated immune-related adverse events (irAEs) can severely compromise treatment safety. This review systematically summarizes the core mechanisms underlying irAEs, which include multi-organ damage resulting from T-cell dysfunction, B-cell-mediated autoantibody abnormalities, cytokine network dysregulation, and monocyte-driven inflammatory cascades. Identified risk factors encompass a range of elements, including host clinical characteristics and underlying diseases, gut microbiota dysbiosis, characteristics of the treatment regimen, tumor type and its histological features, genetic factors and immunogenetic polymorphisms, pre-existing autoimmune conditions or a history of autoimmunity, and a history of previous exposures alongside various environmental factors. The grading criteria, their clinical context and incidence rates, and clinical management strategies for irAEs affecting various organ systems are detailed herein. Future research should aim to deeply analyze the shared

Abbreviations: AChR, anti-acetylcholine receptor; ACTH, adrenocorticotropic hormone; ADCC, antibody-dependent cell-mediated cytotoxicity; AEs, adverse events; ALT, alanine aminotransferase; ASCO, American Society of Clinical Oncology; AST, aspartate aminotransferase; ATG, anti-thymocyte globulin; BCR, B-cell receptor; BMI, body mass index; Bregs, regulatory B cells; CCL3, C-C motif ligand 3; CK, creatine kinase; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; CTLs, cytotoxic T lymphocytes; CXCL10, CXC chemokine ligand 10; CXCR3+, CXCR3-positive; DIHS, drug-induced hypersensitivity syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms; FAERS, FDA Adverse Event Reporting System; FDA, Food and Drug Administration; Foxp3, forkhead box P3; FT4, free thyroxine; G-CSF, granulocyte colony-stimulating factor; GBS, Guillain-Barré syndrome; GC, germinal center; GM-CSF, granulocyte-macrophage colony-stimulating factor; HLA, human leukocyte antigen; HLA-DR, human leukocyte antigen-DR; IBD, inflammatory bowel disease; ICD, implantable cardioverter-defibrillator; ICIs, immune checkpoint inhibitors; IFN- γ , interferon-gamma; IL, interleukin; IL-10, interleukin-10; IL-17, interleukin-17; IL-17A, interleukin-17A; IL-1 β , interleukin-1 beta; IL-2, interleukin-2; IL-21, interleukin-21; IL-22, interleukin-22; IL-35, interleukin-35; IL-6, interleukin-6; IL-7, interleukin-7; IL-8, interleukin-8; irAEs, immune-related adverse events; irMG, immune-related myasthenia gravis; IVIG, intravenous immunoglobulin; MART-1, melanoma antigen recognized by T cells 1; MCP-1, monocyte chemoattractant protein-1; MG, myasthenia gravis; miRNA, microRNA; MPR, maculopapular rash; MRI, magnetic resonance imaging; NB-UVB, narrowband ultraviolet B; NSAIDs, nonsteroidal anti-inflammatory drugs; NSCLC, nonsmall cell lung cancer; PaCS, protein-associated chemical switch; PCR, polymerase chain reaction; PD-1, programmed death receptor 1; PD-L1, programmed death-ligand 1; PPIs, proton pump inhibitors; RANK-L, receptor activator of nuclear factor- κ B ligand; scRNA-seq, single-cell RNA sequencing; SIADH, syndrome of inappropriate antidiuretic hormone secretion; SJS, Stevens-Johnson syndrome; SNP, single nucleotide polymorphism; T1DM, type 1 diabetes mellitus; TCR, T-cell receptor; Teff, effector T cell; TEN, toxic epidermal necrolysis; TF, tissue factor; Th, follicular helper T cell; Th, helper T cell; Th1, T helper 1 cell; Th17, T helper 17 cell; TIGIT, T-cell immunoreceptor with Ig and ITIM domains; TIM-3, T-cell immunoglobulin and mucin-domain containing-3; TLS, tertiary lymphoid structures; TMB, tumor mutational burden; TME, tumor microenvironment; TNF- α , tumor necrosis factor-alpha; TPO, thrombopoietin; Treg, regulatory T cell; TSH, thyroid-stimulating hormone; VISTA, V-domain Ig suppressor of T-cell activation.

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1 | Introduction

ICIs, representing a revolutionary breakthrough in cancer immunotherapy, restore T-cell antitumor activity by targeting and blocking inhibitory immune molecules, thereby significantly extending the survival of patients with various solid tumors [1–7]. Since the approval of the first cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor, ipilimumab, for advanced melanoma in 2011, ICIs and their combination regimens have successively become first- or second-line treatment options for various cancers, including melanoma, lung cancer, and renal cancer [7]. Currently, clinically applied ICIs primarily fall into three categories: anti-cytotoxic CTLA-4 antibodies (e.g., ipilimumab), anti-programmed death receptor 1 (PD-1) antibodies (e.g., nivolumab, pembrolizumab), and anti-programmed death-ligand 1 (PD-L1) antibodies (e.g., atezolizumab, durvalumab).

Immune-related adverse events (irAEs) are organ-specific or systemic toxic reactions arising from the overactivation of the immune system during ICI therapy; they fundamentally represent autoimmune-like pathological damage triggered by a disruption of the body's self-tolerance [8]. irAEs exhibit the following key clinical characteristics: (1) Multi-organ involvement: irAEs can affect multiple organ systems, including the skin, endocrine system, gastrointestinal tract, and lungs; although cardiac and neurological systems exhibit relatively lower involvement rates, events affecting these systems are often associated with a high risk of mortality and severe sequelae [4, 9]. (2) Heterogeneity in onset time: irAEs demonstrate distinct temporal dynamics, emerging as early as a few days after the first administration or exhibiting a delayed onset months after treatment discontinuation, and irAEs affecting different organ systems often occur within specific onset time windows [10–13]. (3) ICI regimen-specific toxicity profiles: ICIs targeting different molecules exhibit distinct toxicity profiles; anti-CTLA-4 monotherapy is more prone to induce colitis (10%–30%), rash, and hypophysitis, whereas anti-PD-1/PD-L1 agents are significantly associated with pneumonitis (3%–5%) and thyroid dysfunction (10%–20%), and combination therapy involving CTLA-4 and PD-1/PD-L1 inhibitors markedly increases the risk of severe irAEs (up to 50%–60%) [14, 15]. (4) Complexity of pathogenesis: The development of irAEs involves the dysregulation of a multilayered immunoregulatory network, including but not limited to abnormal activation of effector T cells, production of autoreactive antibodies, imbalanced release of pro-inflammatory cytokines, alterations in gut microbiota composition, and synergistic effects among various factors, such as those involving cross-reactivity to common antigens.

Although significant progress has been made in research on irAEs, several critical unresolved issues and research gaps persist in clinical practice. First, there is a lack of reliable predictive biomarkers to accurately identify patients at high risk of developing irAEs; although a series of potential biomarkers with promising applications has been identified, a dearth of

rigorously validated predictive indicators suitable for clinical practice persists [16]. Second, the molecular pathophysiology of irAEs remains incompletely elucidated, and the molecular interaction networks underlying key pathological processes—such as regulatory T-cell (Treg)/effector T-cell (Teff) imbalance, cross-reactive recognition between self-antigens and tumor antigens, and cytokine storms—require further in-depth investigation [17, 18]. Third, research on the pathogenesis of rare but potentially fatal irAEs (e.g., immune-related myocarditis, myasthenia gravis) remains notably deficient; more in-depth and systematic clinical and basic research is needed to elucidate their pathological processes. This understanding would enable the development of more effective preventive strategies, early diagnostic methods, and treatment guidelines to reduce mortality associated with these adverse reactions [19–21]. Fourth, the complex toxicity profiles induced by multi-target ICIs combination therapies and their clinical management strategies have not been systematically established; the effects of dose-dependent responses and administration timing within these combination regimens on adverse reactions warrant thorough investigation and clinical standardization. Fifth, the correlation between irAEs and antitumor efficacy remains highly controversial; some studies suggest that certain organ-specific immune-related toxicities (e.g., immune-related vitiligo) are positively associated with clinical benefits, yet excessive immunosuppressive interventions may diminish the intended antitumor immune effects [22, 23]. Sixth, the cumulative negative impact of long-term, persistent chronic irAEs (e.g., immune-related endocrine dysfunctions, rheumatic autoimmune diseases) on patients' long-term quality of life has not been fully assessed, and there is a lack of systematic analysis regarding patients with atypical symptom presentations (e.g., chronic fatigue as the primary manifestation) [2]. Lastly, safety data regarding ICI treatment in special patient populations (e.g., elderly patients, patients with a history of autoimmune diseases, or patients with significant organ dysfunction) remain markedly limited, and individualized risk-benefit assessment systems for these groups urgently require establishment and refinement.

This article systematically outlines the core mechanisms of irAEs and their respective clinical management strategies. First, this article provides an in-depth analysis of the core pathological mechanisms of irAEs, including immunopathological processes such as T-cell dysfunction, abnormal B-cell activity and autoantibody production, and cytokine network dysregulation. Second, it systematically analyzes the risk factors for irAE development across multiple dimensions, including treatment regimen characteristics (e.g., drug type, combination therapy models), genetic susceptibility factors, and host baseline immune status. Subsequently, this article comprehensively summarizes the clinical features, standardized diagnostic criteria, and severity-based tiered treatment strategies for irAEs affecting major organ systems, including the digestive, endocrine, cutaneous, and pulmonary systems. Finally, this article proposes research directions focused on areas such as further elucidating the potential shared molecular mechanisms between irAEs and antitumor effects,

developing highly specific predictive biomarkers, and optimizing precision-targeted immunomodulatory strategies, with the aim of achieving individualized toxicity management in ICI therapy. This article aims to assist clinicians in systematically understanding the pathophysiological complexity of irAEs and, by integrating the latest research evidence, to offer a foundational reference for guiding the early recognition, risk assessment, and clinical intervention strategies for irAEs. The overarching goal is to maximize the benefits of ICI therapy while effectively managing adverse reactions, ultimately improving the treatment safety and quality of life for cancer patients.

2 | Mechanism of IrAEs

Although ICIs enhance antitumor immune responses by attenuating T-cell inhibitory signals, they can also disrupt host immune homeostasis, leading to the activation of complex immunopathological mechanisms (Figure 1). Current research indicates that T-cell dysfunction (e.g., Treg exhaustion and Teff overactivation), aberrant autoantibody production mediated by B cells, cytokine network dysregulation, and monocyte/macrophage-mediated inflammatory cascades collectively form the core molecular basis of irAEs. These mechanisms are interconnected and ultimately induce organ-specific or systemic immunopathological damage through pathways including cross-antigen recognition, aberrant immune cell migration, and remodeling of the local tissue microenvironment. This section will systematically analyze the key molecular pathways implicated in the development of irAEs and their interconnected networks.

2.1 | T-Cell Dysregulation

2.1.1 | Treg Functional Exhaustion

In the pathophysiology of irAEs, the functional imbalance and exhaustion of Tregs are critical to their occurrence and development. Clinical studies have demonstrated that patients treated with CTLA-4 inhibitors exhibit significantly reduced Treg counts in peripheral blood, and the degree of Treg exhaustion is positively correlated with the clinical severity of irAEs [15]. Tregs primarily fulfill a core regulatory function in maintaining peripheral immune tolerance by expressing co-inhibitory receptors such as CTLA-4 and PD-1 and by secreting inhibitory cytokines such as interleukin-10 (IL-10) and interleukin-35 (IL-35), thereby effectively suppressing Teff responses to self-antigens and preventing the onset of autoimmune diseases [24]. However, the clinical application of ICIs may directly impair the normal immunoregulatory functions of Tregs. Specifically, anti-CTLA-4 monoclonal antibodies may selectively deplete Treg cells expressing high levels of CTLA-4 by mediating antibody-dependent cell-mediated cytotoxicity (ADCC), thereby leading to a severe imbalance in the Treg-to-Teff cell ratio in peripheral tissues and ultimately disrupting host immune homeostasis [24]. Furthermore, the blockade of the PD-1/PD-L1 signaling pathway not only potently activates Teff cell function but also significantly inhibits the differentiation of inducible Treg cells and reduces the expression levels of the key transcription factor forkhead box

P3 (Foxp3), further attenuating Treg-mediated immunosuppressive functions and collectively promoting the onset and progression of irAEs [24].

2.1.2 | Teff Cell Overactivation and Cross-Reactive Antigenicity

By alleviating inhibitory regulation of Teffs, ICIs enhance antitumor immune responses; however, this process can also disrupt host immune homeostasis, leading to Teff cell overactivation and the abnormal expansion of autoreactive T-cells, thereby inducing irAEs. Blockade of the immune checkpoint CTLA-4 and PD-1/PD-L1 pathways can significantly enhance T-cell receptor (TCR) signaling strength, promote Teff cell proliferation, and stimulate the release of various pro-inflammatory cytokines—including interferon- γ (IFN- γ), tumor necrosis factor- α (TNF- α), and interleukin-17 (IL-17)—thereby amplifying the inflammatory cascade [17]. For example, anti-PD-1 therapy can reverse T-cell functional exhaustion and restore its antitumor killing activity; however, this process may simultaneously alleviate the suppression of quiescent autoreactive T-cells, promoting their aberrant activation [17, 25]. The key molecular mechanism linking Teff cell overactivation and organ-specific immune damage—two interrelated pathophysiological processes—is cross-reactive antigenicity. Antigenic epitopes shared between tumor and normal tissues (such as melanoma antigen recognized by T cells 1 [MART-1] and tyrosinase molecules in melanoma) can be simultaneously recognized by ICI-activated specific T cells, thereby triggering immune-mediated damage to normal tissues. For instance, in patients with ICI-induced fulminant myocarditis, studies have observed significant infiltration of CD4⁺ helper T cells and CD8⁺ cytotoxic T cells into myocardial and skeletal muscle tissues; more critically, analysis using TCR sequencing technology has revealed highly similar T-cell clonal populations among tumor, myocardial, and skeletal muscle tissues. These findings suggest that Teff cells induce autoimmune tissue damage by recognizing cross-reactive antigenic epitopes shared between tumor and normal tissues [18, 22]. The dual mechanisms of Teff cell overactivation and cross-reactive antigenicity are clinically manifested as a partial statistical correlation between the occurrence of irAEs and antitumor efficacy. For example, studies have shown that the incidence of vitiligo is significantly increased in melanoma patients receiving anti-PD-1 monoclonal antibody therapy, and its appearance exhibits a positive correlation with the objective response rate; the molecular basis of this clinical phenomenon is that specific T cells simultaneously attack both melanoma cells and normal melanocytes by recognizing melanocyte differentiation antigens (such as MART-1 and gp100) [22].

2.1.3 | Helper T Cells (Th Cells)

Th cells play a central regulatory role in the initiation and development of irAEs through their differentiation into subsets with distinct functional characteristics. CD4⁺ Th cells not only directly mediate tissue inflammatory responses but also amplify the autoimmune injury cascade through synergistic regulation

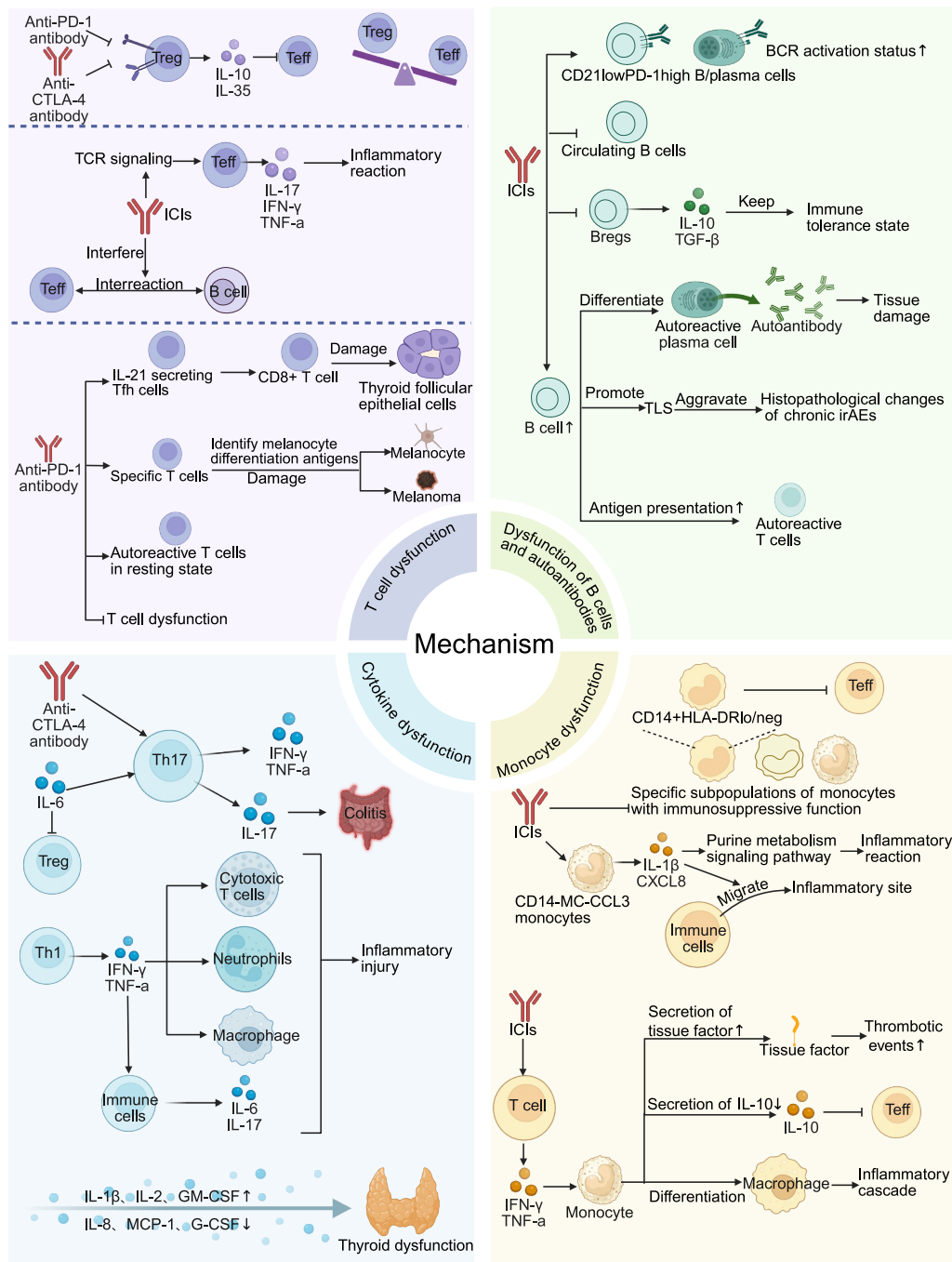


FIGURE 1 | Core immunopathological mechanisms of irAEs: dysregulation of immune cells and cytokines. Key mechanisms of irAEs include (I) T-cell dysregulation, such as Treg functional exhaustion, the overactivation and cross-reactive antigenicity of Teff cells, and dysregulated helper T (Th) cells promoting inflammatory responses and abnormal interactions with other immune cells. (II) B-cell dysfunction and abnormal autoantibody function, including plasma cells secreting autoantibodies against tissue-specific antigens, abnormally enhanced B-cell antigen presentation capacity, imbalanced proportions of different functional B-cell subsets with disrupted immune balance among these subsets, and B cells promoting the formation and maintenance of TLS. (III) Cytokine dysfunction manifests primarily as dysregulated inflammatory responses, imbalanced immune homeostasis, and tissue-specific damage. (IV) Monocyte dysregulation is primarily characterized by monocytes triggering local inflammatory cascades, abnormal interactions between monocytes and T cells, and abnormal dynamic changes in monocyte subsets. BCR, B-cell receptor; Bregs, regulatory B cells; CCL3, chemokine ligand 3; CD21^{low}PD-1^{high} B/plasma cells, B cells/plasmablasts with low expression of CD21 and high expression of PD-1; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; ICIs, immune checkpoint inhibitors; IFN- γ , interferon- γ ; IL, interleukin; IrAEs, immune-related adverse events; MCP-31, monocyte chemoattractant protein-31; PD-L1, programmed death-ligand 1; TCR, T-cell receptor; Teff, effector T cell; Tfh, follicular helper T cell; TGF- β , transforming growth factor- β ; Th, helper T cell; TLS, tertiary lymphoid structure; TNF- α , tumor necrosis factor- α ; Treg, regulatory T cell. This figure was created with [BioRender.com](https://www.biorender.com) (accessed on May 31, 2025).

of other immune cells, including CD8+ cytotoxic T cells, B cells, and macrophages. T helper 1 cells (Th1) and T helper 17 cells (Th17) are key effector T-cell subsets that drive organ-specific irAEs. Th1 cells primarily induce tissue inflammatory damage through the secretion of pro-inflammatory cytokines such as IFN- γ and TNF- α , which activate macrophages and enhance cytotoxic T lymphocyte function [17]. Th17 cells primarily mediate tissue histopathological damage through the secretion of pro-inflammatory cytokines including interleukin-17A (IL-17A), interleukin-21 (IL-21), and interleukin-22 (IL-22) [26]. Clinical research data demonstrate that melanoma patients receiving cytotoxic CTLA-4 inhibitor therapy exhibit significantly elevated proportions of Th17 cells in peripheral blood, with circulating IL-17 levels positively correlating with the clinical severity of immune-related colitis (IL-17 is primarily secreted by activated Th17 cells) [15]. Furthermore, the functional balance between Treg and Th17 cells is critically important in the pathophysiology of irAEs; ICIs may simultaneously promote Th17 cell-mediated pro-inflammatory responses (such as increased IL-17A and IL-21 secretion) while suppressing the activity of immunoregulatory Treg cells, thereby synergistically exacerbating local and systemic inflammatory responses [26]. Follicular helper T cells (Tfh cells, characterized as CXCR3 chemokine receptor 5-positive, PD-1-highly expressing CD4+ T-cell subsets) also play an important role in the pathogenesis of irAEs. For instance, in patients who develop immune-related thyroiditis following PD-1 inhibitor therapy, IL-21-secreting Tfh cells infiltrating thyroid tissue can promote the activation and proliferation of CD8+ T cells, thereby inducing thyroid follicular epithelial cell damage and structural destruction [27]. Additionally, ICIs disrupt the normal regulatory balance between Tfh cells and germinal center (GC) B cells, leading to aberrant interactions between these cell types, which may constitute another important molecular mechanism underlying irAE development [27].

2.2 | B Cell and Autoantibody Dysregulation

The aberrant activation of B cells is recognized to play a critical role in the pathogenesis of irAEs. Traditionally known for their central role in antibody production, B cells primarily contribute to the development and progression of irAEs through mechanisms of humoral immune dysregulation and autoantibody generation. Studies indicate that ICIs can disrupt B-cell immune tolerance mechanisms, thereby leading to the activation and abnormal proliferation of autoreactive B cells. For example, Das et al. found that in melanoma patients receiving anti-CTLA-4 or anti-PD-1 therapy, the total number of circulating B cells was significantly reduced, whereas the proportions of B cells with low CD21 expression and high PD-1 expression and of plasmablasts were markedly increased. Notably, these immune cell lineage changes were observed before the clinical manifestations of irAEs and positively correlated with the severity of adverse events [28]. Research has shown that B cells with low CD21 expression exhibit autoreactive B cell receptors (BCRs) on their surface and display an enhanced activation status, and this cell population displays molecular characteristics similar to B cell subsets expressing T-box transcription factors; both of these

cell types play important roles in the regulation of autoimmune responses [29].

B-cell activation may promote the development and progression of irAEs through multiple pathways. First, following their differentiation into plasma cells, autoreactive B cells can secrete autoantibodies against tissue-specific antigens; these autoantibodies can then directly induce target tissue damage via complement cascade activation or immune complex deposition mechanisms, thereby significantly increasing the risk of irAEs [30]. For example, the production of anti-acetylcholine receptor (AChR) antibodies has been closely associated with the pathogenesis of ICI-induced immune-related myasthenia gravis (irMG) [31]. However, the positive detection rate of autoantibodies in irAEs is significantly lower than that observed in spontaneous autoimmune diseases (e.g., only about 50% of patients with ICI-related diabetes test positive for pancreatic β -cell antibodies, whereas this detection rate exceeds 90% in spontaneous type 1 diabetes). This clinical observation suggests that autoantibodies may not be the sole pathogenic factor in irAEs and that their pathogenesis may be more complex. Clinical research data further indicate that the presence of baseline autoantibody levels (e.g., anti-thyroglobulin antibodies) before treatment may significantly increase the risk of specific types of irAEs and possesses predictive value [18].

Second, B cells, acting as professional antigen-presenting cells, immunologically interact with T cells. ICIs may enhance their antigen-presenting capacity, leading to the activation of autoreactive T cells, the formation of a positive feedback loop within the immune system, and, ultimately, the exacerbation of the autoimmune response cascade [17]. Furthermore, B cell-mediated local inflammatory responses can contribute to the formation and maintenance of ectopic tertiary lymphoid structures (TLS), thereby further aggravating the histopathological changes of chronic irAEs [17]. Finally, the disruption of immune balance among different functional B cell subsets represents a key molecular mechanism underlying the occurrence and progression of irAEs. Regulatory B cells (Bregs) are primarily involved in maintaining immune tolerance by secreting inhibitory cytokines such as IL-10 and transforming growth factor- β (TGF- β). ICIs may reduce the number of Bregs or inhibit their immunoregulatory functions while concurrently promoting the abnormal activation of effector B cells. These changes collectively disrupt the body's immune homeostasis, thereby inducing irAEs [32, 33].

2.3 | Cytokine Dysfunction

Cytokine dysfunction contributes to irAEs primarily through three mechanisms: promoting the dysregulation of inflammatory cascades, disrupting immune homeostasis, and inducing tissue-specific damage. By abrogating T-cell inhibitory signals, ICIs activate antitumor immune responses; however, this process can concurrently trigger the excessive release of various pro-inflammatory cytokines. For instance, IFN- γ and TNF- α secreted by Th1 cells contribute to a pro-inflammatory microenvironment by activating macrophages and recruiting neutrophils [34]. Concurrently, IL-17 produced by Th17 cells can drive

the development of colitis, and its dynamic levels demonstrate a significant correlation with colitis progression and resolution [17, 35]. Moreover, interleukin-6 (IL-6), a pleiotropic cytokine, not only enhances cutaneous inflammatory responses by promoting Th17 cell differentiation but also inhibits Treg function, thus exacerbating autoimmune reactions [17, 36]. Furthermore, an imbalance in the cytokine network can establish a positive feedback loop: immune cells activated by initial cytokines (e.g., IFN- γ) can subsequently secrete additional inflammatory mediators, such as IL-6 and IL-17, consequently amplifying the inflammatory cascade and ultimately leading to target organ damage [37]. Notably, the expression levels of specific cytokines exhibit a close correlation with the risk of developing organ-specific irAEs. Clinical studies indicate that elevated baseline levels of interleukin-1 β (IL-1 β), interleukin-2 (IL-2), and granulocyte-macrophage colony-stimulating factor (GM-CSF), coupled with an early decrease in the levels of interleukin-8 (IL-8), granulocyte colony-stimulating factor (G-CSF), and monocyte chemoattractant protein-1 (MCP-1), are significantly associated with thyroid dysfunction [38]. In ICI-related cutaneous toxicities, the expression levels of both IL-6 and IL-10 are significantly elevated, suggesting their potential involvement in the development and progression of these adverse reactions [39].

Research indicates that IL-18 and TGF- β hold promise as biomarkers for predicting the development of severe irAEs [40]. Furthermore, IL-6 serves as a potential biomarker for predicting the occurrence of irAEs, and blocking IL-6 and IL-6R may also be effective in treating moderate to severe irAEs [41–43]. The CXCL9, CXCL10, and CXCL11-IFN- γ axes have been demonstrated to possess biomarker potential [44]. In gastrointestinal-related irAEs, IL-17 not only functions as a potential biomarker, but the extent of its level reduction can also serve as an indicator of therapeutic efficacy [35, 45]. IL-72, G-CSF, IFN- γ , and CRP are also considered potential biomarkers for predicting irAEs [35, 46–48]. Notably, despite the multitude of potential biomarkers associated with irAEs, there is currently no universally acknowledged and reliable biomarker capable of predicting the risk of irAEs in the majority of patients [49].

2.4 | Monocyte Dysregulation

2.4.1 | Initiation of Local Inflammatory Cascades

Monocytes are critically involved in the onset and progression of irAEs, primarily through three key mechanisms: regulation of their differentiation, amplification of inflammatory signals, and disruption of immune homeostasis. T cells activated by ICIs have been shown to release pro-inflammatory cytokines, such as TNF- α and IFN- γ , which can drive monocyte migration to target tissues and their differentiation into macrophages, thereby initiating local inflammatory cascades. For instance, in ICI-induced Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), single-cell RNA sequencing (scRNA-seq) analysis has shown that activated monocytes can differentiate into macrophages highly expressing the chemokine CXCL10. This CXCL10, in turn, recruits CXCR3-positive (CXCR3+) cytotoxic T lymphocytes (CTLs), ultimately causing widespread

epidermal damage [50]. The TNF signaling pathway has been identified as a critical molecular regulatory axis in this pathological process. Clinical studies have demonstrated that the blockade of the TNF signaling pathway can significantly accelerate the resolution of skin lesions and effectively prevent disease recurrence [50].

2.4.2 | Interaction Between Monocytes and T Cells

The functional heterogeneity of monocytes plays a significant role in influencing the severity and clinical outcomes of irAEs. Research indicates that monocytes from patients with severe irAEs exhibit a pronounced defect in IL-10 secretion, which subsequently leads to a significant reduction in their ability to suppress T-cell proliferation *in vitro*. This, in turn, exacerbates the dysregulated expansion of autoreactive T cells and promotes the occurrence and progression of irAEs [51]. Furthermore, monocyte-derived tissue factor (TF) plays a critical regulatory role in disorders of the coagulation-fibrinolysis system associated with irAEs. Research shows that when T cells are activated by ICIs, monocytes with high expression of PD-L1 are stimulated by these activated T cells. This stimulation leads to the substantial production of TF, thereby significantly increasing the patient's risk of thrombotic events [52]. The IFN- γ signaling pathway promotes monocyte activation and functional polarization during the progression of irAEs. Notably, CD8+ cytotoxic T lymphocytes, as the primary producers of IFN- γ , play a crucial role in the activation of this signaling pathway. This finding suggests that the bidirectional regulatory mechanism between monocytes and CD8+ T cells is inextricably linked to the IFN- γ -mediated signal transduction pathway [53].

2.4.3 | Dynamic Changes in Monocyte Subsets

The dynamic changes in monocyte subsets throughout the onset, progression, and resolution phases of irAEs further underscore their functional diversity and pathophysiological significance. During the active phase of irAEs, the proportion of CD14+ monocytes in peripheral blood circulation increases significantly; concurrently, the CD14-MC-CCL3 subset, which highly expresses chemokine C-C motif ligand 3 (CCL3), exhibits marked expansion and becomes the dominant population. This specific subset is characterized by high expression levels of multiple pro-inflammatory cytokines, including IL-1 β and CXCL8, and it synergistically promotes the spread and amplification of systemic inflammatory responses by enhancing the chemotactic migration of immune cells to inflammatory sites and activating purinergic metabolic signaling pathways [53]. Notably, a significant positive correlation exists between a reduction in the abundance of specific monocyte subsets exhibiting immunosuppressive functions and the risk of developing irAEs. For example, the CD14+HLA-DR^{lo}/neg monocyte subset, characterized by low or absent expression of human leukocyte antigen-DR (HLA-DR), contributes to maintaining immune homeostasis by inhibiting effector T-cell activity; ICI therapy may disrupt this immunosuppressive balance by reducing the abundance of this inhibitory monocyte subset and upregulating HLA-DR expression on the remaining cells,

ultimately inducing the aberrant activation of autoimmune responses [54].

In summary, irAEs do not represent isolated events stemming from a singular immune cell or molecular pathway; instead, they manifest as systemic cascade reactions arising from the collective dysfunction, dysregulation, and intricate interplay of various immune components. T-cell dysfunction constitutes a central mechanism underlying irAEs, wherein the depletion of Treg cells markedly compromises critical immune tolerance barriers. Concomitantly, Teff cells and Th cells contribute to tissue inflammatory damage and release elevated levels of pro-inflammatory cytokines via diverse pathways, thereby synergistically activating downstream effector cells and remodeling the local microenvironment. B cells, functioning as crucial antigen-presenting cells, facilitate the expansion and activation of autoreactive T-cell clones. Concurrently, autoantibodies produced by aberrantly activated B cells can directly inflict tissue damage and contribute to the formation of TLS, which subsequently provide a niche conducive to chronic inflammation. Monocytes/macrophages, serving as pivotal effector cells and amplifiers of inflammation, are propelled in their activation, differentiation, migration, and functional polarization by T-cell-derived cytokines. This process consequently leads to the secretion of copious cytokines, which subsequently recruit further immune cells and can potentially induce coagulopathy, thus substantially augmenting the extent of tissue damage. The intricate interplay among T cells, B cells, monocytes, and various cytokines collectively underlies the initiation and progression of irAEs.

3 | Risk Factors for irAEs

The risk of developing irAEs is dynamically influenced by multiple factors, including host characteristics, treatment regimens, tumor biology, and the patient's genetic background (Figure 2). Clinical evidence indicates that a patient's age, sex, baseline immune status, and gut microbiota dysbiosis can significantly influence the threshold for maintaining immune homeostasis; that characteristics of the treatment regimen (such as drug type and combination strategies) can alter the toxicity spectrum via dose-dependent effects; that tumor mutational burden and the tissue-specific microenvironment can shape organ susceptibility; and that HLA polymorphisms and variations in other immune-related genes can determine an individual's genetic susceptibility to specific toxicities. Furthermore, a history of autoimmune disease or the presence of chronic inflammatory states can further elevate the risk of immune dysregulation. This section will synthesize current risk stratification models, incorporating multiple dimensions, to provide a theoretical framework for clinical prediction and preventive strategies.

3.1 | Host Clinical Characteristics and Underlying Medical Conditions

Clinical studies indicate that older age, female sex, and an increased body mass index (BMI) are significantly associated

with an elevated risk of developing irAEs. In elderly patients, physiological characteristics such as decreased renal function and hypoalbuminemia can result in elevated free drug concentrations and their subsequent renal accumulation, thereby heightening their susceptibility to ICI-related renal toxicity [55]; conversely, female patients may be more susceptible to ICI-related thyroid dysfunction attributable to differences in immune system regulation mediated by sex hormones such as estrogen [56]. Obese patients exhibit a significantly elevated risk of irAEs, which is attributed to a chronic low-grade inflammatory state mediated by adipose tissue and the increased secretion of pro-inflammatory cytokines, such as IL-6 and tumor TNF- α [57]. Additionally, a patient's underlying medical condition can further elevate the risk of developing irAEs. For example, patients with a history of cardiovascular diseases (such as myocardial infarction or heart failure) face a significantly elevated risk of developing ICI-related myocarditis following ICI therapy [19].

3.2 | Gut Microbiome Dysbiosis

ICI therapy can lead to dysbiosis of the gut microbiota in patients, and studies indicate a correlation between alterations in the abundance of specific gut microbial populations and a significantly increased risk of irAEs [58]. The phylum Bacteroidetes (exemplified by *Bacteroides fragilis*) can inhibit colitis development by promoting Treg production; furthermore, multiple studies have shown that a decreased abundance of this phylum is positively correlated with a significantly increased risk of anti-CTLA-4 therapy-induced diarrhea [59]. However, it is noteworthy that while certain gut microbiota can enhance antitumor immune responses [60–62], these same microbes may simultaneously increase the patient's risk of developing irAEs, exhibiting a dual effect. For example, clinical research data indicate that a gut abundance of *Akkermansia muciniphila* exceeding 4.8% is associated with significantly prolonged overall survival in patients with nonsmall cell lung cancer (NSCLC); this association is primarily attributed to this bacterial species' ability to promote CD8⁺ T lymphocyte activation and enhance interferon-gamma (IFN- γ) secretion, thereby augmenting the host's antitumor immune response. Importantly, an overgrowth of *A. muciniphila* may concurrently induce irAEs [63]. Furthermore, substantial research evidence indicates that the gut microbiome not only influences antitumor immune responses but is also deeply involved in the occurrence and development of irAEs by meticulously regulating the differentiation, activation status, and functional expression of distinct T-cell subsets. For example, Th17 cells play a central role in various inflammatory diseases and autoimmune pathologies, and extensive experimental studies have confirmed that the composition of the gut microbiota decisively impacts the induction, differentiation, and functional homeostasis of Th17 cells. In cancer patients receiving ICI therapy, gut dysbiosis may disrupt Th17 cell immune homeostasis, leading to their abnormal differentiation and hyperfunction, which subsequently triggers a cascade of pro-inflammatory cytokine release and the activation of inflammatory signaling pathways, significantly increasing the patient's risk of developing immune-related adverse events [64]. An experimental study

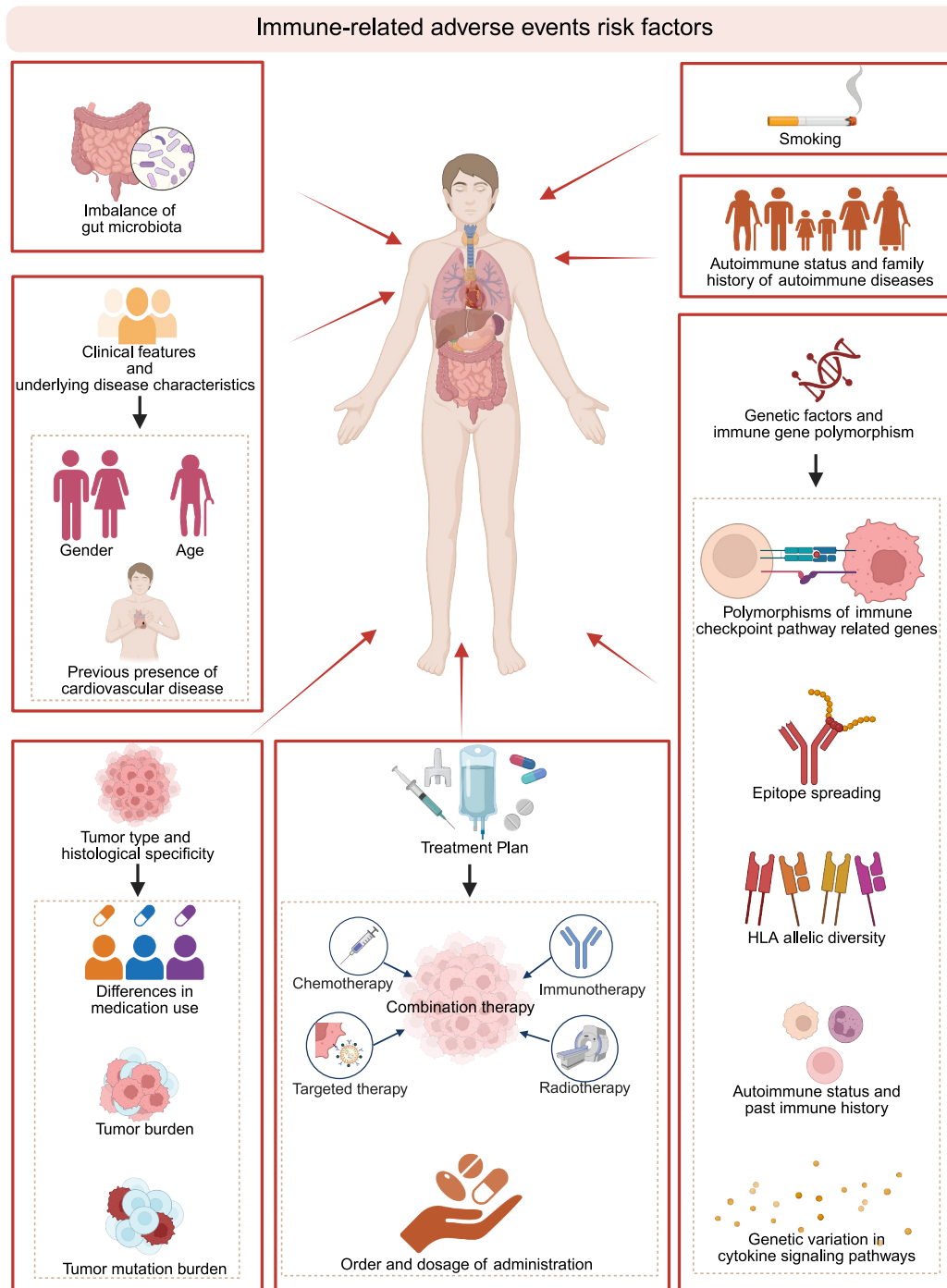


FIGURE 2 | Multidimensional factors contributing to irAEs: host, environment, treatment, tumor, genetics, and immunity. Risk factors for irAEs include (I) host clinical characteristics and baseline disease features, such as older age, female sex, and preexisting cardiovascular diseases. (II) Environmental factors, such as smoking and gut microbiome dysbiosis. (III) Treatment regimen characteristics, such as the combination of ICIs with chemotherapy, targeted therapy, or radiotherapy, and the use of high-dose ICIs. (IV) Tumor type and histological specificity, including tumors with high mutational burden, high tumor load, differences in tumor histological specificity and malignancy grade, and variations in medication use across different tumors. (V) Genetic factors and immunogenetic polymorphisms, including the diversity of HLA alleles, polymorphisms in genes related to immune checkpoint pathways, genetic variations in cytokine signaling pathways, and the phenomenon of epitope spreading. (VI) Autoimmune status, a prior history of immune diseases, and a family history of immune diseases. (HLA, human leukocyte antigen.) This figure was created with [BioRender.com](https://www.biorender.com) (accessed on May 31, 2025).

demonstrated that targeted supplementation with specific probiotic strains or prebiotics can significantly alleviate the severity of irAE symptoms; this finding provides direct experimental

evidence for the critical pathogenic role of gut dysbiosis in irAE development and also offers a theoretical basis for developing clinical intervention strategies [65].

3.3 | Characteristics of Treatment Regimens

3.3.1 | Combination Therapy Strategies and Drug Interactions

Substantial clinical evidence indicates that combining chemotherapy, targeted therapy, or radiotherapy with ICIs can significantly enhance antitumor effects; however, this synergistic action is often accompanied by an increased risk of treatment-related toxicities. Combination therapy strategies and their associated drug interaction mechanisms can markedly elevate the incidence and severity of irAEs. Research data indicate that ICI combination regimens increase the risk of myocarditis in patients by nearly five-fold ($p < 0.001$), with mortality rates related to these adverse events reaching as high as 67% [19, 66]. The mechanisms underlying these synergistic toxicities may be closely related to T-cell hyperactivation resulting from dual immune checkpoint blockade and subsequent immune-mediated tissue damage [19]. Furthermore, the concomitant use of ICIs with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), such as osimertinib, can induce interstitial pneumonitis; the potential mechanisms may involve complex interactions between sequential immune activation and drug metabolism pathways [67]. On the other hand, nonsteroidal anti-inflammatory drugs (NSAIDs) and proton pump inhibitors (PPIs) are reported to significantly increase the risk of ICI-related acute interstitial nephritis by promoting the haptenization of tubular antigens, thereby mediating tubular epithelial cell injury [67].

3.3.2 | Dosing Sequence and Dosage

In ICI therapy, the sequence and dosage of administration exhibit a significant correlation with the risk of irAEs. The sequence of osimertinib and PD-1/PD-L1 inhibitor administration significantly impacts the severity of irAEs; this phenomenon is potentially related to the long half-life and sustained immune activation properties of anti-PD-1/PD-L1 antibodies, as well as to the short half-life of osimertinib [68–72]. Regarding dosage, higher doses of ICIs are associated not only with a higher incidence of irAEs but also with their increased severity [73, 74]. Specifically, CTLA-4 inhibitor-related hypophysitis exhibits marked dose dependency [13, 74–77]; concurrently, the risk of skin and liver toxicities induced by ipilimumab also demonstrates dose dependency [64, 78, 79]. Data from two clinical trials suggest that treatment regimens employing lower doses and/or less frequent administration of ICIs may effectively reduce the risk of irAEs while maintaining antitumor efficacy [80].

3.4 | Tumor Type and Histological Specificity

Tumor type and its histological characteristics are key determinants in predicting the risk of irAEs and in stratifying their assessment. Different tumor types exhibit significant variations in tumor mutational burden (TMB) and tumor microenvironment (TME) characteristics, which directly influence the risk and clinical presentation of irAEs by modulating the degree of immune system activation. Research indicates that high-TMB tumors, through the generation of numerous neoantigens that

stimulate T-cell activation, subsequently lead to a significantly increased risk of irAEs [81]; correspondingly, a high tumor burden also significantly elevates the incidence and exacerbates the severity of irAEs by enhancing antigen exposure [82]. Furthermore, in analyzing the notable differences in the irAE spectrum among patients with various cancer types, it is crucial to consider the heterogeneity in treatment regimens and the distinct characteristics of tissue-specific immune microenvironments, as these factors collectively underlie the complex biological basis for irAE development. A systematic review and meta-analysis demonstrated that among patients receiving immunotherapy for HCC, the most common irAEs were fatigue (14%), whereas the most frequent Grade 3 or higher irAEs were anemia (6%) [83]. A study revealed that among 199 patients with malignant melanoma and advanced renal cell carcinoma receiving nivolumab and/or ipilimumab therapy, the most commonly reported irAEs were colitis/diarrhea (42.0% vs. 16.2%), skin reactions (34.0% vs. 27.0%), and hepatitis (27.2% vs. 21.6%) [84]. In a study analyzing 110 patients with head and neck squamous cell carcinoma receiving immunotherapy, the most frequently observed irAEs were hypothyroidism (30%), dermatitis (14%), and hepatitis (11%) [85]. Clinical studies indicate that the incidence of colitis in melanoma patients following ICI therapy (approximately 35%) is significantly higher than that in NSCLC patients (approximately 10%–12%) [19, 86]. However, some researchers suggest that these disparities may be partially attributable to selection bias and confounding factors in study designs, implying that the heterogeneity in irAE patterns cannot be solely ascribed to differences inherent in tumor types [86]. The histological specificity and variations in the malignancy grade of tumors are not only crucial for devising individualized treatment strategies but are also intimately linked to the patterns of occurrence, severity, and organ tropism of irAEs. For instance, CTLA-4 is highly expressed in regulatory T cells (Tregs) within the gastrointestinal mucosa; this molecule is considered a critical negative regulator in maintaining intestinal immune homeostasis and preventing autoimmune responses [59]. Anti-CTLA-4 therapy specifically blocks Treg-mediated immunosuppressive functions, leading to the overactivation of effector T cells, which subsequently disrupts the immune homeostasis and barrier function of the intestinal mucosa. Consequently, compared with PD-1 inhibitors (colitis incidence of approximately 8%–12%), CTLA-4 inhibitors are associated with a significantly increased risk of colitis, with multicenter clinical data indicating an incidence of up to 35% [19]. In contrast, the PD-1/PD-L1 signaling pathway is extensively involved in regulating immune homeostasis within endocrine organs (e.g., the thyroid) and lung tissue. Clinical studies have confirmed that anti-PD-1/PD-L1 therapy is associated with a significantly higher risk of inducing organ-specific irAEs, such as thyroid dysfunction (incidence approximately 10%–20%) and pneumonitis (incidence approximately 3%–5%), a phenomenon closely linked to the biological characteristics of PD-1/PD-L1 expression in these tissues [87].

3.5 | Genetic Factors and Immune Gene Polymorphisms

Genetic background, as a key regulatory factor of immune homeostasis, plays an important role in susceptibility to irAEs.

Polymorphisms in the HLA system and immunoregulatory genes are considered crucial genetic factors underlying the development of irAEs. The diversity of HLA alleles influences an individual's susceptibility to specific organ toxicities by modulating antigen presentation efficiency and immune response intensity. For example, studies have shown that HLA-DR4 is significantly enriched in ICI-induced autoimmune diabetes [88], whereas HLA-DRB104:05 and HLA-DRB111:01 are significantly associated with the risk of ICI-related arthritis and pruritus or colitis, respectively [89, 90]. Furthermore, HLA-DQ8 and DR53 have been reported to be significantly associated with lymphocytic hypophysitis, a finding that underscores the critical role of HLA haplotypes in the pathogenesis of organ-specific toxicities [91].

In addition to the HLA system, polymorphisms in genes related to immune checkpoint pathways also directly influence the risk of irAEs. Studies have found that the CTLA-4 single-nucleotide polymorphism (SNP) -1661A>G (rs4553808) is significantly associated with an increased incidence of endocrine toxicities [92], whereas PDCD1 804 C>T (rs2227981) may decrease the overall risk of irAEs [93]. Genetic variations in cytokine signaling pathways also contribute to the occurrence and regulation of irAEs; studies have identified the IL-7 allele rs16906115 and IL-22RA1 rs75824728 as major risk loci for irAEs [17]. Furthermore, the miR-146a rs2910164 polymorphism mediates the occurrence and progression of irAEs by reducing microRNA (miRNA) expression levels [94]. The phenomenon of epitope spreading further amplifies the impact of genetic susceptibility on the development of irAEs. Tumor antigen-specific immune responses induced by ICIs can expand to recognize other epitopes within the same antigen (intramolecular epitope spreading) or epitopes on different antigens (intermolecular epitope spreading), potentially targeting epitopes shared with normal tissues and thereby leading to multi-organ toxicities. This pathological process is more pronounced and prevalent in individuals carrying specific HLA haplotypes or immunoregulatory gene variants [17].

Multiple preclinical studies have provided direct and compelling evidence for the association between genetic susceptibility and the occurrence of irAEs. Mouse models with deficiencies in PD-1 or CTLA-4 genes exhibit distinct organ-specific autoimmune phenotypes; for example, PD-1 knockout mice on a BALB/c background develop dilated cardiomyopathy, whereas CTLA-4 deficient mice develop fatal lymphocytic infiltrative lesions [95]. Findings from dual gene knockout models (e.g., Lag3 -/-Pdc1-/-) further demonstrate that multiple gene deficiencies can synergistically enhance T-cell activation and the release of pro-inflammatory cytokines, thereby more closely simulating the severe clinical manifestations of irAEs observed in clinical practice [95].

3.6 | Autoimmune Status and History of Autoimmune Diseases

Autoimmune status and a history of autoimmune diseases represent important risk factors for irAEs. Multiple retrospective studies have confirmed that patients with a history of autoimmune diseases experience a significantly higher incidence of

recurrence or exacerbation of their preexisting conditions following ICI therapy, with rates ranging from 28% to 60% [96–98]. For example, a study involving 102 patients with a history of inflammatory bowel disease (IBD) demonstrated that 41% of these patients developed gastrointestinal-related irAEs, a rate significantly higher than that observed in patients without a history of IBD (11%, $p < 0.001$) [99]. A systematic review further indicated that irAEs can not only lead to the exacerbation of preexisting autoimmune diseases but can also affect other organ systems previously unaffected by autoimmune conditions prior to ICI treatment [100]. Furthermore, a family history of autoimmune diseases has also been demonstrated to correlate significantly with the risk of developing irAEs [101]. However, some heterogeneity exists among study findings; for instance, one study reported no significant association between underlying autoimmune diseases and the incidence or severity of irAEs [102], suggesting that interindividual variations in immune status may influence risk stratification.

From a molecular perspective, the PD-1/PD-L1 and CTLA-4 signaling pathways play crucial roles in the pathogenesis of both autoimmune diseases and irAEs. Experimental studies have demonstrated that the PD-1 signaling pathway is closely associated with the pathophysiology of IBD, rheumatoid arthritis, and various rheumatic diseases [103]. Additionally, T-cell-mediated cross-reactivity may drive the development of organ-specific toxicities. For instance, vitiligo induced in melanoma patients following CTLA-4 inhibitor therapy and the molecular mimicry observed between tumor antigens and muscle antigens in ICI-related myocarditis both suggest that autoreactive T cells may play a significant role in the pathogenesis of autoimmune diseases and irAEs [104–106]. Research has also confirmed that autoreactive antibodies and dysregulation of the IFN- γ signaling pathway are closely associated with the occurrence and progression of various endocrine irAEs, such as hypothyroidism and hypophysitis [107–111].

3.7 | Prior Exposure History and Environmental Factors

The presence of preexisting autoantibodies and exposure to certain environmental factors have been demonstrated to significantly increase the risk of developing irAEs. Evidence from multiple studies indicates a clear correlation between autoantibody positivity prior to immunotherapy and the occurrence of organ-specific irAEs; specifically, patients positive for anti-thyroid antibodies prior to treatment exhibit a higher risk of thyroid-related toxicities, whereas those positive for rheumatoid factor are more prone to developing cutaneous toxicities [108, 112]. Clinical studies have reported that smoking significantly increases the risk of irAEs in patients receiving ICI therapy; potential underlying mechanisms may involve nicotine-induced activation of inflammatory responses and dysregulation of immune system homeostasis [58, 113].

4 | irAEs in Various Organ Systems

irAEs can involve nearly all organ systems, and their clinical manifestations, severity, and management strategies vary

according to the characteristics of the target tissue. Cutaneous and gastrointestinal toxicities are the most frequently observed; cardiovascular and neurological toxicities, although less common, are associated with high mortality rates. Furthermore, rare toxicities affecting hematologic, reproductive, and sensory systems, among others, underscore the broad spectrum and diverse nature of irAEs. This section categorizes irAEs by the organ system, detailing the clinical features, grading criteria (see Table 1), and management approaches for each type.

4.1 | Skin

4.1.1 | Maculopapular Rash

Maculopapular rash (MPR) is the most common type of ICI-related cutaneous adverse reaction, typically manifesting 3–6 weeks after treatment initiation [114–116]. Studies indicate that the incidence of MPR ranges from 49% to 68% in patients treated with anti-CTLA-4 agents, compared to approximately 20% in those treated with anti-PD-1/PD-L1 agents [114–116]. Clinically, MPR often manifests as erythematous macules and papules on the trunk and limbs, which can coalesce to form plaques [104]. For patients with mild presentations, management typically includes topical corticosteroids, emollients, and oral antihistamines; however, severe cases or those accompanied by systemic symptoms necessitate systemic corticosteroid therapy [104].

4.1.2 | Pruritus

ICI-related pruritus typically manifests as mild to moderate symptoms, with an incidence rate that is second only to maculopapular rash, at approximately 13%–20% [117–119]. Epidemiological data indicate a significantly higher incidence of pruritus in patients receiving anti-CTLA-4 monotherapy (25%–36%) and combination therapy (33%–47%) [117]. Clinically, pruritus most commonly affects the trunk and scalp and can occur as an isolated symptom or coexist with other cutaneous adverse reactions [117, 120], potentially exacerbating clinical symptoms. Treatment typically involves emollients, oral antihistamines, and topical corticosteroids; for severe symptoms, discontinuation of ICI therapy may need to be considered [121, 122].

4.1.3 | Psoriasis

Among reported ICI-related psoriasis cases, 86.1% are observed in patients treated with PD-1 inhibitors, whereas 13.9% are found in those treated with PD-L1 inhibitors [123]. Typical clinical manifestations include well-demarcated, scaly erythematous plaques, primarily distributed on the trunk and limbs. First-line treatment options include topical corticosteroids, vitamin D3 analogs, and narrowband ultraviolet B (NB-UVB) therapy; for patients who exhibit an inadequate response, systemic treatments such as methotrexate, apremilast, retinoids, and biologic agents may be considered [124–127]. It should be

noted that the use of biologic agents is contraindicated in patients with active malignancies [104].

4.1.4 | Eczema

Eczema is a common cutaneous adverse reaction observed in patients treated with PD-1 inhibitors, with a reported incidence of up to 17%. Typical clinical manifestations include ill-defined, edematous macules and papules accompanied by pruritus, which may coalesce into plaques and patches, commonly affecting the trunk and limbs [124, 128]. Therapeutic approaches may involve topical corticosteroids, topical calcineurin inhibitors, systemic antihistamines, and emollients; for severe symptoms, NB-UVB therapy may additionally be considered [129, 130].

4.1.5 | Lichenoid Reactions

Lichenoid reactions are reported to occur in 0.5%–6% of patients treated with ICIs, with a relatively higher incidence observed in individuals receiving anti-PD-1/PD-L1 agents [131, 132]. Clinically, these reactions are typically characterized by erythematous to violaceous flat-topped papules or plaques on the limbs and trunk, often accompanied by significant pruritus [128, 131, 133]. Topical corticosteroids constitute the first-line treatment; for patients who do not show significant improvement, systemic therapies such as retinoids, oral corticosteroids, cyclosporine, and NB-UVB phototherapy may be considered [117, 134].

4.1.6 | Other Cutaneous Adverse Reactions

Rare yet particularly severe ICI-related cutaneous adverse reactions encompass drug-induced hypersensitivity syndrome (DIHS), drug reaction with eosinophilia and systemic symptoms (DRESS), SJS, and TEN. The occurrence of these severe adverse reactions necessitates the immediate discontinuation of ICIs and the administration of systemic corticosteroid therapy [104]. Autoimmune bullous diseases represent another category of rare ICI-related cutaneous adverse reactions, with a reported incidence of approximately 1% [135]. For patients presenting with mild symptoms, treatment may involve topical corticosteroids, potentially combined with doxycycline and niacinamide [136]; conversely, patients with more severe symptoms require systemic corticosteroids and rituximab [135–137]. Notably, ICI-related vitiligo is frequently observed in patients treated for melanoma but is less prevalent in patients with other cancers, and no definitively effective treatment measures are currently available [104].

4.2 | Digestive System

4.2.1 | Gastrointestinal Tract

4.2.1.1 | Colitis. Colitis is the most common gastrointestinal adverse reaction associated with ICI therapy, occurring in approximately 40% of patients [138, 139], and it is especially

TABLE 1 | Grading criteria for the severity of ICLs-induced diseases.

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Eczema	Clinical manifestations lack overt severity; escalation of therapeutic measures beyond standard supportive care is unnecessary	Intermediate clinical severity; topical or oral intervention indicated; with adjunctive therapeutic augmentation supplementing foundational care protocols	Clinically critical manifestations with nonimminent mortality risk necessitate intravenous therapy	—	—
Pruritus	Minor or regionally confined; surface-directed therapy is recommended	Diffuse and episodic; scratching-induced cutaneous manifestations (e.g., tissue swelling, papule formation, erosive lesions, epidermal thickening, exudative crusting); oral intervention indicated; limiting instrumental ADL	Generalized and persistent; impairing basic personal care or nocturnal rest; systemic glucocorticoid or immune-modulating treatment required	—	—
Rash maculopapular	Cutaneous eruptions involving under 10% of the body surface area, potentially asymptomatic or accompanied by pruritic manifestations, burning, or cutaneous tightness	Cutaneous lesions involving 10%–30% of the body surface area (symptomatic or asymptomatic presentations including itching, thermal discomfort, dermal tension); impairing complex daily tasks; dermatitis affecting over 30% of skin area with potential minor manifestations	Cutaneous lesions encompassing over 30% of the body surface area with significant symptom severity; compromising basic personal care ADL	—	—
Colitis	No detectable clinical manifestations; monitoring confined to clinical surveillance or diagnostic assessments; therapeutic measures deemed unnecessary	Abdominal pain; rectally expelled mucus or sanguineous stool content	Intense abdominal discomfort; peritoneal irritation manifestations	Life-threatening consequences; emergent therapeutic measures mandated	Death
Esophagitis	No symptoms present; management limited to clinical monitoring or diagnostic evaluations; therapeutic measures unnecessary	Clinical manifestations present; dysphagia or masticatory dysfunction; oral supplements required	Profound impairment of mastication and deglutition; enteral nutrition, parenteral supplementation, or acute care admission mandated	Life-threatening consequences; emergent surgical measures mandated	Death

(Continues)

TABLE 1 | (Continued)

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Gastritis	No detectable symptoms; monitoring confined to clinical assessments or diagnostic evaluations; therapeutic measures unnecessary	Clinical manifestations present; gastrointestinal dysregulation; therapeutic measures required	Critical dysfunction in mastication or gastrointestinal processing; total parenteral nutrition or inpatient management required	Mortality-risk conditions; emergency surgical intervention required	Death
Cholecystitis	—	Clinical manifestations present; therapeutic measures required	Marked clinical manifestations; invasive intervention indicated	Life-threatening consequences; emergent surgical intervention mandated	Death
Dry mouth	Clinical manifestations (e.g., xerostomia or viscous salivary consistency) with maintained nutritional intake; resting salivary secretion exceeding 0.2 mL/min	Intermediate clinical manifestations; dietary modifications (e.g., copious water, viscosity-enhancing agents, texturally modified nutrition requiring homogenized preparations, or low-mastication comestibles); basal salivary secretion 0.1–0.2 mL/min	Oral nutritional intake failure; enteral nutrition or total parenteral supplementation mandated; basal salivary secretion < 0.1 mL/min	—	—
Myocarditis	—	Clinical manifestations emerging during intermediate physical engagement or exertional tasks	Profound manifestations persisting during quiescent phases or negligible physical engagement; therapeutic measures mandated; de novo symptom emergence	Life-threatening consequences; emergent therapeutic measures mandated (e.g., sustained intravenous pharmacologic administration or mechanical circulatory support modalities)	Death
Pericardial effusion	—	Subclinical fluid accumulation with limited volumetric dimensions (minor to intermediate extent)	Pathologic fluid accumulation inducing physiologic consequences	Life-threatening consequences; emergent therapeutic measures mandated	Death
Pericarditis	Absence of clinical manifestations; electrocardiographic anomalies or auscultatory phenomena (e.g., friction rub) diagnostically concordant with pericardial inflammation	Symptomatic pericarditis with characteristic chest pain manifestations	Pericardial inflammation inducing systemic pathomechanics sequelae (exemplified by pericardial constriction)	Life-threatening consequences necessitating emergent therapeutic measures	Death
Vasculitis	Absence of clinical manifestations; no need for intervention	Mid-grade symptomatic presentation requiring medical intervention (e.g., antihistamines, NSAID regimens)	Profound symptomatic presentations necessitating medical intervention (exemplified by systemic corticosteroids)	Critical clinical sequelae with confirmed peripheral or visceral ischemia; emergency medical intervention required	Death

(Continues)

TABLE 1 | (Continued)

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Acute kidney injury	—	—	Inpatient management required	Life-threatening consequences; dialysis indicated	Death
Chronic kidney disease	eGFR or CrCl below the lower limit of normal (60 mL/min/1.73 m ²), or presence of 2+ proteinuria with urine protein-to-creatinine ratio exceeding 0.5	eGFR or CrCl ranging from 30 to 59 mL/min/1.73 m ²	eGFR or CrCl 15–29 mL/min/1.73 m ²	eGFR or CrCl below 15 mL/min/1.73 m ² ; dialysis or kidney transplantation required	Death
Hemolysis	Laboratory findings of isolated hemolysis (e.g., positive Coombs test, schistocytes, low haptoglobin)	Hemolytic process confirmed with ≥ 2 g/dL Hgb decline	Transfusion or medical treatment needed (e.g., steroid therapy)	Life-threatening consequences necessitating emergent therapeutic measures	Death
Eosinophilia	Exceeding upper reference limit and surpassing baseline measurements	—	Steroids initiated	—	—
Anemia	Hgb level is below the lower limit of normal but ≥ 10.0 g/dL (or ≥ 6.2 mmol/L, ≥ 100 g/L).	Hgb < 10.0–8.0 g/dL; < 6.2 mmol/L; < 100–80 g/L	Hgb < 8.0 g/dL; < 4.9 mmol/L; < 80 g/L; requiring blood transfusion.	Life-threatening consequences necessitating emergent therapeutic measures	Death
Hypophysitis	Asymptomatic state or minor symptomatology; diagnostic monitoring without therapeutic measures; no intervention required	Mid-grade symptomatic presentation necessitating localized/noninvasive therapeutic modalities; impairment in instrumental ADL congruent with the developmental stage	Critical clinical manifestations with defined medical gravity (nonacute mortality risk); prolonged inpatient management or extended hospitalization; compromised fundamental self-care ADL capacity	Life-threatening consequences necessitating emergent therapeutic measures	Death
Hyperthyroidism	No symptoms present; management limited to clinical monitoring or diagnostic evaluations; therapeutic measures unnecessary	Clinical manifestations requiring anti-thyroid pharmacotherapy; functional impairment in instrumental ADL	Critical symptomatic presentations; restricting fundamental self-care ADL; inpatient care mandated	Life-threatening consequences necessitating emergent therapeutic measures	Death
Hypothyroidism	No symptoms present; management limited to clinical monitoring or diagnostic evaluations; therapeutic measures unnecessary	Clinical manifestations necessitating thyroid replacement indicated; impairment in instrumental ADL	Critical symptomatic presentations; restricting fundamental self-care ADL; inpatient care mandated	Life-threatening consequences necessitating emergent therapeutic measures	Death
Glucose intolerance	No symptoms present; management limited to clinical monitoring or diagnostic evaluations; therapeutic measures unnecessary	Symptomatic; clinical manifestations necessitating nutritional intervention or oral pharmacotherapy	Severe symptoms; insulin needed	Life-threatening consequences necessitating emergent therapeutic measures	Death

(Continues)

TABLE 1 | (Continued)

	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5
Adrenal insufficiency	No symptoms present; management limited to clinical monitoring or diagnostic evaluations; therapeutic measures unnecessary		Intermediate clinical manifestations; therapeutic measures required		Severe clinical presentations; hospitalization required		Life-threatening consequences necessitating emergent therapeutic measures		Death
Hypercalcemia	Corrected serum calcium of > ULN—11.5 mg/dL; > ULN—2.9 mmol/L; ionized calcium > ULN—1.5 mmol/L		Corrected serum calcium of > 11.5–12.5 mg/dL; > 2.9–3.1 mmol/L; ionized calcium > 1.5–1.6 mmol/L; symptomatic		Corrected serum calcium of > 12.5–13.5 mg/dL; > 3.1–3.4 mmol/L; ionized calcium > 1.6–1.8 mmol/L; hospitalization indicated		Corrected serum calcium of > 13.5 mg/dL; > 3.4 mmol/L; ionized calcium > 1.8 mmol/L; life-threatening consequences		Death
Hyponatremia	< LLN—130 mol/L		125–129 mmol/L and asymptomatic		Sodium levels of 125–129 mmol/L with symptoms; 120–124 mmol/L symptomatic or asymptomatic		< 120 mmol/L; life-threatening consequences		Death
Hypocalcemia	Corrected serum calcium of < LLN—8.0 mg/dL; ionized calcium < LLN—1.0 mmol/L; < LLN—2.0 mmol/L		Corrected serum calcium of < 8.0–7.0 mg/dL; ionized calcium < 1.0–0.9 mmol/L; symptomatic; < 2.0–1.75 mmol/L		Corrected serum calcium of < 7.0–6.0 mg/dL; < 1.75–1.5 mmol/L; hospitalization indicated; ionized calcium < 0.9–0.8 mmol/L		Corrected serum calcium of < 6.0 mg/dL; ionized calcium < 0.8 mmol/L; < 1.5 mmol/L; life-threatening consequences		Death
Arthritis	Subjective discomfort with observable erythema, joint effusion, or localized pro-inflammatory states		Moderate discomfort accompanied by objective inflammatory signs (joint effusion, rubor); impaired instrumental ADL		Severe pain with signs of inflammation, erythema, or joint swelling; permanent joint damage and self-care difficulties		—		—
Meningitis	—		—		Systemic anti-infective treatment necessitated (intravenous antibacterial, antifungal, or antiviral regimens); invasive procedural measures required; localized neurological impairment		Life-threatening consequences necessitating emergent therapeutic measures		Death
Myasthenia gravis	Asymptomatic state or minor symptomatology; diagnostic monitoring without therapeutic measures; no intervention required		Mid-grade symptomatic presentation necessitating localized/noninvasive therapeutic modalities; impairment in instrumental ADL congruent with developmental stage		Critical clinical manifestations with defined medical gravity (nonacute mortality risk); prolonged inpatient management or extended hospitalization; compromised fundamental self-care ADL capacity		Life-threatening consequences necessitating emergent therapeutic measures		Death
Myelitis	Asymptomatic; mild signs (e.g., Babinski's reflex or Lhermitte's sign)		Intermediate motor deficits or sensory impairment; compromised instrumental ADL		Profound motor weakness or sensory deprivation; essential self-care capacity impaired		Life-threatening consequences necessitating emergent therapeutic measures		Death

(Continues)

TABLE 1 | (Continued)

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Myositis	Mild pain	Moderate pain with muscle weakness affecting instrumental ADL	Pain with severe weakness limiting self-care ADL	Life-threatening consequences necessitating emergent therapeutic measures	—
Other	Mild; asymptomatic state or minor symptomatology; diagnostic monitoring without therapeutic measures; no intervention required	Mid-grade symptomatic presentation necessitating localized/noninvasive therapeutic modalities; impairment in instrumental ADL congruent with the developmental stage	Severe pathology (not immediately life-threatening) requiring prolonged hospitalization; functionally disabling with fundamental ADL constraints	Life-threatening consequences necessitating emergent therapeutic measures	Death related to adverse events.

Abbreviations: ADL, activities of daily living; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; Hgb, hemoglobin; LLN, lower limit of normal; NSAID, nonsteroidal anti-inflammatory drugs; ULN, upper limit of normal.

prevalent with CTLA-4 inhibitors [140, 141]. The clinical manifestations of colitis primarily include diarrhea, abdominal distension, abdominal pain, mucus or blood in the stool, and fever; severe cases may also present with upper gastrointestinal symptoms (such as nausea and vomiting) [142]. If ICI-related colitis is suspected, treatment with glucocorticoids and antibiotics should be initiated immediately, without awaiting endoscopic or other examination results [143]. For patients with Grade 2 severity colitis, oral glucocorticoid therapy is recommended, with gradual tapering over 4–6 weeks to minimize adverse impacts on the efficacy of cancer therapy. For patients unable to tolerate oral therapy or those with severe symptoms, intravenous glucocorticoids should be administered, and the treatment course may need to be extended to 12 weeks [144, 145]. For patients refractory to glucocorticoid therapy, the combined use of infliximab or vedolizumab should be considered, as these biological agents can effectively alleviate colitis symptoms [146]. However, it should be noted that the combined use of infliximab and glucocorticoids may shorten patients' overall survival [147].

4.2.1.2 | Gastritis and Esophagitis. The incidence of ICI-related gastritis and esophagitis is low, accounting for only 3% of patients who develop upper gastrointestinal symptoms [148]. Proton pump inhibitors are the first-line treatment; if the response is inadequate, glucocorticoids, sucralfate, or H2 receptor antagonists can be selected for subsequent therapy [148]. Systematic research on treatment strategies for refractory cases is currently lacking, but published reports indicate that infliximab and vedolizumab can effectively alleviate upper gastrointestinal inflammation [149].

4.2.2 | Pancreatic Injury

The incidence of ICI-related pancreatic injury can reach up to 4% [150], with typical clinical manifestations including nausea, upper abdominal pain, fever, vomiting, diarrhea, and elevated serum lipase levels [151]. Research on treatment strategies for ICI-related pancreatic injury is relatively limited; established effective interventions primarily include discontinuing immunotherapy and providing supportive care (such as intravenous fluids). Resumption of immunotherapy may be considered only after serum lipase levels return to normal [150].

4.2.3 | Cholecystitis

A limited number of patients receiving ICI therapy may develop cholecystitis. Published data indicate that the incidence of ICI-related cholecystitis is approximately 0.6%. Its clinical presentation is similar to that of typical acute cholecystitis, with principal features including right upper quadrant pain accompanied by symptoms such as nausea, fever, vomiting, and diarrhea [151, 152]. Given that glucocorticoids may reduce patient survival rates, their routine use is not recommended for ICI-related cholecystitis. Clear treatment guidelines for this complication are currently lacking, and clinical management employing traditional treatment strategies for acute cholecystitis is advised [151, 152].

4.2.4 | Liver

The incidence of ICI-related hepatitis ranges from 1% to 17% [153]. Ipilimumab treatment is associated with the highest risk of hepatotoxicity (approximately 4%–11%) [78], whereas the incidence of hepatotoxicity related to PD-1/PD-L1 inhibitors is significantly lower than that associated with CTLA-4 inhibitors [78, 154]. Typically, patients may present with asymptomatic liver dysfunction, which is primarily characterized by elevated serum transaminase (AST and ALT) levels [155]. For patients experiencing Grade 1 hepatotoxicity, ICI therapy can be continued without special intervention; however, liver enzyme levels should be closely monitored for any changes. For patients presenting with Grade 2 hepatotoxicity, ICI therapy should be suspended, and oral glucocorticoids should be administered as an intervention. If oral glucocorticoids prove ineffective or if hepatotoxicity progresses to Grade 3 or higher, intravenous glucocorticoids should be administered, and a liver biopsy should be considered to determine the etiology [151]. For cases refractory to glucocorticoid therapy, immunosuppressants such as azathioprine, mycophenolate mofetil, or tacrolimus may be considered as second-line treatment options [153].

4.2.5 | Oral Cavity

4.2.5.1 | Oral Mucosal Lesions. Oral mucosal lesions are a common oral adverse reaction associated with ICI therapy [153], with an incidence of approximately 1.5%–5.4% [156, 157]. These lesions are primarily classified into vesiculobullous and lichenoid types, among which lichenoid lesions are more common and are characterized by symmetrical white reticular striations; some patients may also present with mucosal erythema and ulceration [158, 159]. Definitive treatment guidelines for ICI-related oral mucosal lesions have not yet been established; in clinical practice, the topical application of glucocorticoid preparations is commonly recommended. For patients with severe symptoms, suspension of ICI therapy and the administration of systemic glucocorticoids should be considered. Notably, systemic glucocorticoid therapy may compromise the efficacy of immunotherapy for the primary tumor [158, 160].

4.2.5.2 | Oral Xerostomia. Oral xerostomia is another common oral adverse reaction associated with ICI therapy [161], with an incidence of approximately 2%–11% among patients receiving ICI treatment [156, 160, 162–166]. Clinically, the affected mucosal tissue often exhibits a smooth, glazed appearance accompanied by characteristic erythematous atrophic changes, and increased local tissue sensitivity and dentin hypersensitivity frequently coexist [117, 160, 162, 163]. Patients typically report persistent oropharyngeal dryness and discomfort, often necessitating frequent water intake to alleviate difficulties in mastication and deglutition; this symptom becomes particularly pronounced when consuming foods with low moisture content [167, 168]. Accompanying symptoms may also include various clinical manifestations, including dysphonia due to laryngeal mucosal dryness, increased salivary viscosity, and dysgeusia [167]. The severity of this adverse reaction is typically Grade 1–2, and severe cases (Grade 3 or higher) are relatively rare [169]. For patients with Grade 1–2 oral xerostomia, treatment

primarily focuses on oral hygiene maintenance and dietary adjustments; additionally, supportive interventions, such as local moisturization measures including adequate hydration and stimulation of saliva secretion (e.g., chewing sugar-free gum), should be actively implemented [169]. Pharmacological interventions may include sialogogues such as pilocarpine, bethanechol, and cevimeline [169]. For patients with severe xerostomia (grade > 2) or those with difficult-to-tolerate Grade 2 symptoms, short-term oral glucocorticoid therapy may be considered on a case-by-case basis following a thorough clinical evaluation [170, 171].

4.3 | Respiratory System

4.3.1 | Lungs

Immune-related pneumonitis is a rare yet potentially fatal immune-related adverse event (irAE) [172, 173], occurring in less than 5% of patients receiving monotherapy; the incidence of pneumonitis associated with PD-1 inhibitors (3.6%) is significantly higher than that observed with PD-L1 inhibitors (1.3%), and Grade 3–4 pneumonitis induced by PD-1 inhibitors is also more common than that induced by PD-L1 inhibitors (1.1% vs. 0.4%) [140]. With ICIs' combination therapy, the incidence of pneumonitis increases to 6.88% [140]. Typical clinical manifestations of immune-related pneumonitis include dyspnea, cough, and chest pain; notably, approximately one-third of patients are asymptomatic and are identified solely through abnormal imaging findings [9, 174]. Treatment strategies for immune-related pneumonitis are guided by severity grading [175–178]. For patients with Grade 1 pneumonitis who show no disease progression, ICI therapy can be continued without requiring additional treatments, but regular chest CT scans and pulmonary function tests are necessary. For Grade 2 patients, ICI therapy should be discontinued, and oral corticosteroids should be administered, accompanied by regular symptom assessment; after symptoms alleviate, the corticosteroid dosage is gradually tapered, and resumption of immunotherapy may be considered based on assessment findings. For patients with severe Grade 3–4 pneumonitis, ICI therapy should be immediately discontinued, and intravenous corticosteroids should be administered, followed by a switch to oral therapy after symptom improvement. Resumption of ICI therapy is not recommended for Grade 3 patients and is contraindicated for Grade 4 patients. If patients have concomitant infections or if an infection is suspected, immunosuppressive therapy and empiric broad-spectrum antibiotic therapy should be administered concurrently [175, 176]. Furthermore, for patients refractory to corticosteroid therapy, salvage therapy with other immunomodulatory drugs—including infliximab, cyclophosphamide, mycophenolate mofetil, and tocilizumab—should be considered [175, 176, 178, 179].

4.4 | Cardiovascular System

4.4.1 | Myocarditis

Myocarditis is one of the most frequent and severe cardiovascular irAEs, exhibiting an incidence ranging from 0.04% to 1.14%

and a mortality rate as high as 50% [20, 180]. Clinical manifestations are typically categorized into nonspecific (mild) symptoms, such as fatigue and myalgia, and specific symptoms, including chest pain, dyspnea, sudden cardiac death, and syncope [181]. Upon diagnosis of ICI-related myocarditis, ICI therapy should be immediately and permanently discontinued, and intravenous steroid therapy should be initiated [144, 182]. For patients with steroid-refractory myocarditis, the use of second-line immunosuppressive agents, including anti-thymocyte globulin, mycophenolate mofetil, tacrolimus, intravenous immunoglobulin, infliximab, tocilizumab, abatacept, tofacitinib, and alemtuzumab, may be considered [179, 183–186].

4.4.2 | Pericardial Diseases

The exact incidence of ICIs-related pericardial diseases remains to be precisely defined; however, they are associated with high mortality rates [187, 188]. Pericardial diseases are primarily categorized into two main types: pericarditis and pericardial effusion. Among these, pericarditis clinically manifests as chest pain (characteristically relieved by sitting up and leaning forward), pericardial friction rub, and fever [189], whereas pericardial effusion can manifest as significant fluid accumulation and may progress to cardiac tamponade, the latter of which is characterized by classic signs including jugular venous distension, pulsus paradoxus, and hypotension [190]. For patients with nonsevere ICI-related pericardial disease, ICI therapy may be continued under close monitoring [191]. If patients develop asymptomatic moderate-to-severe effusion or symptomatic pericardial disease, ICI therapy should be immediately discontinued, and high-dose steroid therapy should be initiated; for patients presenting with hemodynamic instability, pericardiocentesis should be promptly performed [191]. Additionally, colchicine or nonsteroidal anti-inflammatory drugs (NSAIDs) can be utilized as adjunctive therapies for ICI-related pericardial disease. Following significant improvement in pericardial disease symptoms, clinicians may evaluate the possibility of resuming ICI therapy based on the individual patient's condition [192].

4.4.3 | Arrhythmias

The clinical manifestations of ICI-related arrhythmias are diverse and encompass atrial fibrillation, sinus tachycardia, ventricular tachycardia, bradyarrhythmias, and complete atrioventricular block [29, 181]. Notably, these arrhythmias frequently co-occur with other cardiac conditions, such as myocarditis and pericarditis [193]. Furthermore, arrhythmias associated with conduction system abnormalities are linked to a significantly increased mortality rate [194, 195]. Treatment strategies primarily involve symptomatic management with conventional antiarrhythmic drugs. For patients without concomitant myocarditis, cautious resumption of ICIs may be considered once arrhythmia control is stabilized [191]. For patients with ICI-related chronic arrhythmias, individualized assessment should guide the consideration of appropriate measures, including temporary transvenous pacemaker implantation, permanent pacemaker implantation (particularly for individuals with progressive and unresolved cardiac conduction

system fibrosis), implantable cardioverter-defibrillator (ICD) placement, or long-term antiarrhythmic drug therapy [180].

4.4.4 | Vasculitis

ICI-related vasculitis is a relatively rare immune-related adverse event that can affect blood vessels of varying calibers; its clinical manifestations are diverse, encompassing temporal arteritis (i.e., giant cell arteritis), retinal vasculitis, digital vasculitis, and aortitis [194, 196, 197]. Among ICI-related vasculitides, large-vessel vasculitis is the most common, and giant cell arteritis is the most frequently reported type [198, 199]. Currently, specific treatment protocols for ICI-related vasculitis remain unestablished; clinical practice typically involves individualized treatment guided by the therapeutic principles for conventional vasculitis [200]. In cases of diagnosed ICI-related vasculitis, treatment may necessitate suspending or permanently discontinuing ICIs, along with the administration of systemic steroids. Furthermore, for select patients, immunosuppressants such as hydroxychloroquine, rituximab, or cyclophosphamide may be judiciously used [196]. For refractory patients who respond poorly to steroid therapy, biologic agents such as abatacept or tocilizumab may be considered [201, 202]. Additionally, depending on the specific type and clinical presentation of vasculitis, antirheumatic treatment strategies should also be evaluated [198].

4.5 | Urinary System

4.5.1 | Kidneys

The incidence of renal adverse events is approximately 2% with anti-CTLA-4 or anti-PD-1 inhibitor monotherapy, rising to approximately 4%–5% with combination therapy [203, 204]. However, lower-grade renal adverse events often manifest as asymptomatic injury; thus, existing data may underestimate their actual incidence [189]. ICI therapy can induce renal allograft rejection, and studies indicate a significantly higher risk of this event with anti-PD-1/PD-L1 agents than with anti-CTLA-4 agents [205]. Clinical manifestations of ICI-related renal adverse events may include oliguria, hematuria, and peripheral edema; additionally, approximately 10% of patients may also present with systemic symptoms such as fever and rash [206]. Common laboratory abnormalities include elevated serum creatinine levels and pyuria detected on urinalysis; some patients may also exhibit microscopic hematuria, peripheral eosinophilia, or hypertension [205]. Management strategies for ICI-related renal adverse events are typically stratified by toxicity grade: for Grade 1 toxicity (mild creatinine elevation), ICI therapy may be continued with the close monitoring of creatinine levels, maintenance of adequate hydration, and avoidance of nephrotoxic drugs; for Grades 2–3 toxicity (moderate to severe creatinine elevation), ICIs should be withheld, a renal biopsy considered to determine the pathological type, and corticosteroid therapy initiated, with potential resumption of ICI therapy once creatinine levels return to Grade 1 or baseline; for Grade 4 toxicity (severe creatinine elevation), ICIs should be permanently discontinued, a renal biopsy performed, and higher-dose corticosteroid therapy administered [207].

4.5.2 | Other Urinary Organs

Reports of ICI-related adverse events involving other parts of the urinary system are currently rare [208–212]. As of 2023, only 12 cases of ICI-related cystitis have been reported; notably, all 12 patients had received PD-(L)1 inhibitors, the majority were lung cancer patients, and symptoms resolved in most patients following corticosteroid treatment [213].

4.6 | Reproductive System

Clinical reports of ICI-related reproductive system disorders are relatively rare. Male patients may present with spermatogenic dysfunction, manifesting primarily as significantly reduced sperm concentration, azoospermia, and abnormally low serum testosterone levels [214–218]. Furthermore, male patients may also experience histological damage to reproductive organs, with clinical manifestations such as benign prostatic hyperplasia, immune-related orchitis, erectile dysfunction, and prostatic hypertrophy [219]. Female patients may exhibit adverse reproductive system reactions such as genital tract fistula formation, abnormal vaginal bleeding, and persistent pelvic pain [219]. It is noteworthy that reproductive system disorders induced by ICIs are not solely limited to direct effects on reproductive organs but may also be secondary to ICI-mediated damage to organs involved in gonadal regulation. For instance, ICI-related hypophysitis can interfere with the pituitary-gonadal axis function, leading to secondary hypogonadism in patients [220]. Given the relative rarity of clinical reports on ICI-related reproductive system disorders, there are currently no specialized treatment guidelines for such adverse reactions. For patients who may face a risk of fertility impairment, fertility preservation measures, such as gamete cryopreservation techniques, are recommended [221–223]. Specifically, adult male patients may consider sperm cryopreservation [224], whereas younger male patients who have not yet developed sperm production capability may opt for preservation methods such as experimental testicular tissue banking [225, 226]. In addition, patients receiving ICI therapy are advised to undergo regular monitoring of serum sex hormone levels to assess their reproductive functional status. It is particularly emphasized that female patients should strictly avoid pregnancy during ICI treatment and for a certain period thereafter [220].

4.7 | Hematologic System

4.7.1 | Aplastic Anemia and Pure Red Cell Aplasia

ICI-related aplastic anemia and pure red cell aplasia are relatively infrequent [227]; these adverse reactions are primarily characterized by a reduction in hematopoietic cells across various lineages, leading to multisystem clinical manifestations, such as anemia, infection, and hemorrhage in affected patients [227, 228]. For patients with Grade 1 ICI-related aplastic anemia, temporary discontinuation of ICI therapy and administration of hematopoietic growth factor support are recommended; for Grade 2 patients, in addition to hematopoietic cytokines and transfusion support, prednisone should be

administered for anti-inflammatory treatment. If the therapeutic effect remains unsatisfactory after 2 weeks, early combination therapy with cyclosporine A should be initiated, and the use of thrombopoietin (TPO) and anti-thymocyte globulin (ATG) may also be considered [229].

4.7.2 | Autoimmune Hemolytic Anemia

As of early 2020, the US Food and Drug Administration (FDA) had reported a total of 68 cases of ICI-related autoimmune hemolytic anemia [230]. The clinical manifestations of this type of adverse event (AE) primarily include new-onset anemia and jaundice, with laboratory tests revealing significantly elevated levels of lactate dehydrogenase and indirect bilirubin, accompanied by an increased reticulocyte count [229]. According to the American Society of Clinical Oncology (ASCO) guidelines, corticosteroid therapy should be initiated when hemoglobin (Hb) levels fall below 100 g/L [231]. For high-risk patients with comorbid cardiovascular or cerebrovascular diseases, red blood cell transfusions should be promptly administered to maintain hemoglobin levels at or above 70 g/L [229]. For patients with Grade 3 or higher adverse events (AEs), intravenous immunoglobulin (IVIG) may be used in combination with corticosteroid therapy [232, 233]. If the aforementioned treatment regimens prove ineffective, immunosuppressants such as rituximab, cyclosporine A, and mycophenolate mofetil may be considered as second-line treatment options [231].

4.7.3 | Neutropenia

The incidence of ICI-related neutropenia is relatively low, and affected patients typically do not exhibit specific clinical manifestations. This adverse reaction is primarily observed in patients receiving ICIs for melanoma, NSCLC, and prostate cancer, with its incidence being higher among individuals treated with cytotoxic CTLA-4 inhibitors [227, 232, 234, 235]. Due to the often severe nature of ICI-related neutropenia, standard clinical management involves the immediate discontinuation of ICI therapy upon diagnosis and the concurrent initiation of combination treatment with corticosteroids and G-CSF. If the patient's response to initial treatment is inadequate, the addition of second-line immunosuppressive agents, such as mycophenolate mofetil, cyclosporine A, and anti-thymocyte globulin, should be considered [229]. Furthermore, due to significantly reduced neutrophil counts that can lead to immunodeficiency in patients, prophylactic anti-infective therapy is also crucial in clinical management [229].

4.7.4 | Eosinophilia

Published clinical reports of ICI-related eosinophilia are relatively scarce. An observational study reported that among 909 patients treated with ICIs, 26 developed ICI-related eosinophilia, and melanoma was the primary malignancy in this cohort [236]. Data from another study further indicated that among all patients receiving ICI therapy, individuals with nonsmall cell lung cancer and melanoma exhibit a higher risk of

developing eosinophilia [237]. Patients experiencing this adverse reaction typically exhibit no specific clinical symptoms [229]. Research suggests that patients with mild eosinophilia can typically be managed with close monitoring and without specific intervention; however, for those with moderate to severe eosinophilia, corticosteroid therapy is recommended for anti-inflammatory purposes [237].

4.8 | Metabolism and Endocrine System

4.8.1 | Pituitary Gland

Hypophysitis, an immune-related adverse event, is more frequently observed with CTLA-4 inhibitor therapy and exhibits a clear dose-dependent characteristic [13, 74–77], whereas its incidence with PD-1 inhibitor therapy is relatively low, at approximately 0.3%–1.1% [238, 239]. The clinical manifestations of ICI-related hypophysitis are diverse, and the most common symptoms include headache, fatigue, nausea, anorexia, hypotension, and endocrine dysfunctions such as oligomenorrhea in females and sexual dysfunction in males [239–242]. In diagnostic imaging, magnetic resonance imaging (MRI) typically reveals characteristic changes such as pituitary gland enlargement or thickening of the pituitary stalk [243]. Clinical practice guidelines recommend a baseline endocrine function assessment prior to initiating ICI therapy, including the measurement of cortisol, thyroid-stimulating hormone (TSH), and free thyroxine (FT4) levels [244]. Following the initiation of ICI therapy, adrenocorticotrophic hormone (ACTH) and cortisol levels should be monitored regularly to facilitate the timely detection of potential pituitary dysfunction [231]. When clinical symptoms of pituitary dysfunction arise, discontinuation of ICI therapy should be considered to prevent further exacerbation of these adverse reactions [178, 245]. For patients with hypopituitarism, hormone replacement therapy is the primary treatment strategy. Particularly when concomitant ACTH and TSH deficiencies occur, the sequence of treatment is crucial: hydrocortisone replacement therapy must be initiated first, and levothyroxine supplementation should only follow after the adrenal function has stabilized, to avoid precipitating an adrenal crisis [231, 245]. For patients with severe pituitary enlargement accompanied by neurological compression symptoms such as headache or visual field disturbances, pharmacological doses of glucocorticoids may be administered; these agents reduce inflammation and edema by suppressing the immune response [231, 244, 245]. Notably, high-dose steroids usually cannot reverse established pituitary damage [246], and some studies suggest that they may adversely affect overall patient survival [23]. Therefore, high-dose glucocorticoids should be used judiciously, and high-dose hydrocortisone should be considered only in life-threatening emergencies such as an adrenal crisis [178, 231, 244, 245, 247].

4.8.2 | Thyroid Gland

ICI-related thyroid toxicity primarily presents as two clinical types: thyrotoxicosis and hypothyroidism [245]. Epidemiological data indicate that the incidence rates of thyrotoxicosis induced by CTLA-4 inhibitors, PD-1 inhibitors, and combination ICI

therapies are 0.2%–1.7%, 0.6%–3.7%, and 8%–11%, respectively. Conversely, the incidence rates of hypothyroidism induced by CTLA-4 inhibitors, PD-1/PD-L1 inhibitors, and CTLA-4 inhibitors combined with PD-1 inhibitors are 2.5%–5.2%, 3.9%–8.5%, and 10.2%–16.4%, respectively, with combination therapy being associated with a higher risk [248]. Clinical management guidelines recommend systematic thyroid function monitoring throughout the entire course of ICI therapy, encompassing the pretreatment, during-treatment, and posttreatment phases. Upon the detection of thyroid-related adverse reactions, an assessment of their severity should be conducted to determine whether to suspend or discontinue ICI therapy [178, 231, 244]. For patients presenting with clinical manifestations of thyrotoxicosis, such as tachycardia, tremors, and anxiety, β -blockers (e.g., propranolol) can be used for symptomatic control [178, 231, 244, 245]. For ICI-related hypothyroidism, the standard treatment is levothyroxine replacement therapy, with dosages that are individualized based on patient age, body weight, and comorbidities [178, 231, 244, 245].

4.8.3 | Islets

ICI-related insulin-dependent diabetes mellitus is predominantly associated with PD-1 inhibitor therapy; autoimmune type 1 diabetes mellitus (T1DM) is the most common form, which typically presents clinically with diabetic ketoacidosis and severe hyperglycemia as its initial manifestations [140, 238]. Data from multiple epidemiological studies indicate that although the incidence of ICI-related T1DM is relatively low (generally < 1%), its clinical progression is rapid and potentially life-threatening [249–251]. Clinical monitoring strategies recommend establishing baseline blood glucose levels before initiating ICI therapy and dynamically monitoring blood glucose levels during treatment and at each follow-up visit. Once ICI-related T1DM is diagnosed, the necessity of discontinuing ICI therapy should be evaluated, and insulin replacement therapy should be initiated immediately; this therapy is typically required lifelong [178, 231, 244, 245]. Notably, unlike other irAEs, ICI-induced T1DM responds poorly to glucocorticoid therapy, and glucocorticoids may further exacerbate hyperglycemia. Therefore, the use of pharmacological doses of glucocorticoids is not recommended as a standard treatment strategy [245].

4.8.4 | Adrenal Glands

Among endocrine adverse events associated with ICIs, primary adrenal insufficiency is a relatively uncommon yet clinically significant complication [252]. Results from multiple meta-analyses indicate that the incidence of adrenal insufficiency induced by monotherapy with PD-1 or PD-L1 inhibitors is low, typically not exceeding 1% [249–251, 253, 254]. In contrast, CTLA-4 inhibitor monotherapy or combination therapies incorporating CTLA-4 inhibitors with PD-1/PD-L1 inhibitors exhibit a markedly higher incidence, ranging from 0.3% to 7.6% [249, 250, 253, 254]. The clinical manifestations of adrenal insufficiency are often nonspecific, including nausea, weight loss, persistent fatigue, hypotension, and characteristic skin hyperpigmentation, which can hinder early diagnosis [189]. Clinical guidelines recommend the assessment of baseline

cortisol levels prior to the initiation of ICI therapy [244]. If primary adrenal insufficiency develops during ICI treatment, suspension of ICI therapy should be considered, and hormone replacement therapy should be promptly initiated [178, 245]. The dosage of hydrocortisone replacement therapy should be individualized according to the severity of the adverse event: 10–20 mg/day for Grade 1 adverse events, 30–50 mg/day for Grade 2, and 50–100 mg every 6–8 h for life-threatening Grade 3–4 adverse events [231, 244]. For patients presenting with electrolyte disturbances such as hypotension, hyponatremia, or salt-wasting syndrome, mineralocorticoids (e.g., fludrocortisone) may be added to hydrocortisone therapy to maintain a hydro-electrolytic balance [231, 244, 245].

4.8.5 | Electrolyte Metabolism

4.8.5.1 | Hyponatremia. Common causes of severe hyponatremia encompass the syndrome of inappropriate antidiuretic hormone (SIADH), end-stage disease, hemodynamic disorders, and endocrine diseases, which respectively account for 36%, 34%, 20%, and 7% of cases [255]. In a retrospective observational study involving 2458 patients treated with ICIs, the incidence of hyponatremia reached 62% [256]. Notably, the baseline incidence of hyponatremia in cancer patients is inherently high (4%–47%), rendering it challenging to definitively determine whether hyponatremia is directly attributable to ICI therapy [256]. For hyponatremia resulting from SIADH, treatment strategies involve fluid restriction and, if necessary, the administration of oral urea or vasopressin receptor antagonists [257]. If hyponatremia originates from endocrine dysfunction, appropriate hormone replacement, such as the administration of glucocorticoids or mineralocorticoids, is required [246, 257, 258].

4.8.5.2 | Hypercalcemia. ICI-related hypercalcemia is often intimately associated with endocrine system disorders, including those secondary to thyroid dysfunction, primary adrenal insufficiency, hypophysitis, and adrenocorticotrophic hormone deficiency [259–261]. Hypercalcemia is a common metabolic abnormality in cancer patients [262], a factor that renders it clinically challenging to definitively distinguish whether the condition is specifically induced by ICI therapy. For asymptomatic patients, close monitoring is recommended, deferral of specific therapeutic interventions is advised, and the underlying cause of hypercalcemia (often an endocrine disorder) should be actively investigated. Addressing the underlying disease is the key strategy for managing ICI-related hypercalcemia [255].

4.8.5.3 | Hypocalcemia. A meta-analysis indicated that the incidence of ICI treatment-related hypocalcemia is approximately 1% [263]. In another retrospective observational study involving 2458 patients receiving ICIs, the incidence of hypocalcemia was reported at 9% [256]. Notably, the baseline incidence of hypocalcemia in cancer patients ranges from 20% to 30%, which complicates the definitive determination of whether the condition is specifically induced by ICI therapy [256]. For ICI-related hypocalcemia, treatment primarily

involves the administration of calcium and vitamin D supplements [255].

4.8.5.4 | Other Electrolyte Disturbances. Other electrolyte disturbances encompass hypokalemia, hypophosphatemia, and metabolic acidosis, which may be intimately related to ICI-associated gastrointestinal diseases, renal dysfunction, and chronic inadequate nutritional intake [255, 264–267]. In clinical practice, emphasis should be placed on the early identification of these electrolyte abnormalities and the prompt initiation of appropriate interventions.

4.9 | Bone and Rheumatic Diseases

4.9.1 | Bone

Skeletal adverse events associated with ICIs are relatively uncommon, with fractures being the most frequently reported; clinical trial data indicate a fracture incidence of less than 1% [268]. These fractures may result from ICI-induced osteoporosis, primarily affecting weight-bearing bones such as the spine, hip, and femur [269]. In terms of treatment strategies, bisphosphonates are widely used for ICI-induced osteoporosis due to their inhibitory effect on osteoclast activity; furthermore, immunosuppressants targeting TNF- α , interleukin-6 (IL-6), and receptor activator of nuclear factor- κ B ligand (RANK-L) have also demonstrated potential therapeutic values [270].

4.9.2 | Rheumatic Diseases

ICI-related rheumatic irAEs are the second most common chronic irAEs, following endocrine system adverse reactions, with research data indicating that approximately 20% of cases may progress to chronic irAEs [2]. Among these rheumatic irAEs, arthritis is the most prevalent, constituting 55% of chronic rheumatic manifestations [2]. Epidemiological data indicate that the overall incidence of ICI-related arthritis is approximately 5% [269], clinically manifesting primarily with inflammatory signs such as joint swelling, morning stiffness, tenderness, and local erythema [189]. In addition to arthritis, the incidence of other ICI-related rheumatic syndromes is relatively low (< 1%), including vasculitides (such as giant cell arteritis and polymyalgia rheumatica) and autoimmune diseases (such as Sjögren's syndrome and systemic lupus erythematosus) [173]. Treatment strategies for ICI-related arthritis vary according to severity: for Grade 1 arthritis, ICI therapy can be continued with symptomatic control using acetaminophen or nonsteroidal anti-inflammatory drugs; for Grade 2 patients, low-dose glucocorticoid therapy is recommended; and for Grade 3–4 patients, glucocorticoid therapy is necessary, and combining it with anti-rheumatic drugs should be considered to enhance efficacy [271].

4.10 | Nervous System

4.10.1 | Central Nervous System

4.10.1.1 | Encephalitis. The incidence of ICI-related neurological adverse events (nirAEs) is approximately 1%–5%,

with ICI-related encephalitis accounting for approximately 13% of these nirAEs [272]. ICI-related encephalitis primarily encompasses various types, such as meningoencephalitis, limbic encephalitis, brainstem encephalitis, and cerebellitis [273]. For patients with Grade 2 or higher ICI-related encephalitis, steroid treatment is recommended [244, 272]. Unless imaging studies show no typical features of viral encephalitis, intravenous acyclovir (10 mg/kg every 8 h) must be administered before obtaining polymerase chain reaction (PCR) results to rule out herpetic encephalitis [274]. For patients unresponsive to steroid therapy, rituximab may be considered [231, 275]; alternatively, for those with elevated IL-6 levels, tocilizumab is recommended [231, 276].

4.10.1.2 | Meningitis. ICI-related meningitis accounts for approximately 3% of nirAEs [277]. The onset of ICI-related aseptic meningitis is typically rapid, and its characteristic clinical manifestations include headache, nuchal rigidity, with or without fever, nausea, vomiting, and photophobia, though altered mental status is usually absent [278]. The preferred treatment involves corticosteroids and discontinuation of ICIs; empirical antibacterial and antiviral therapy (e.g., acyclovir, third-generation cephalosporins, or amoxicillin) may be considered pending the results of cerebrospinal fluid analysis [273].

4.10.1.3 | Neuro-Ophthalmologic Complications. The incidence of ICI-related neuro-ophthalmologic complications is low, occurring in less than 0.5% of patients [273]. ICI-related neuro-ophthalmologic complications can lead to disorders of either the afferent visual pathway (affecting the central nervous system) or the efferent visual pathway (affecting the peripheral nervous system) [279]. Afferent visual pathway diseases include optic neuritis (the most common), uveitis, neuroretinitis, retrobulbar demyelinating disease, and compressive optic neuropathy. Approximately 75% of ICI-related optic neuritis cases are bilateral and are often accompanied by decreased or lost vision and optic disc edema [273]. For patients with suspected ICI-related optic neuritis, MRI is mandatory for diagnosis, which is confirmed by optic nerve enhancement, along with cerebrospinal fluid and serological examinations to determine etiology and facilitate differential diagnosis. For ICI-related optic neuritis, discontinuation of ICIs and administration of systemic and/or local steroids are recommended; for refractory cases, combination therapy with immunosuppressants, plasma exchange, or intravenous immunoglobulin should be considered [280].

4.10.1.4 | Myelitis. ICI-related myelitis accounts for approximately 2% of nirAEs [281]. The clinical manifestations of ICI-related myelitis, which are primarily caused by spinal cord inflammation, include paraplegia, sphincter dysfunction, sensory disturbances (especially tactile and thermal, usually bilateral), and ataxia, all characterized by an acute or subacute onset [282–285]. The treatment of ICI-related myelitis is challenging, with corticosteroids typically being used as first-line therapy. However, approximately 20%–25% of patients experience a relapse upon corticosteroid tapering or discontinuation; for relapsing patients, treatment options typically include immunoglobulin therapy, plasma exchange, or readministration of corticosteroids [282, 283, 285–292]. Other

potential therapeutic agents include natalizumab, intravenous cyclophosphamide, infliximab, rituximab, tocilizumab, and ruxolitinib, although further clinical studies are needed to confirm their efficacy [285, 286, 288, 291].

4.10.2 | Peripheral Nervous System

4.10.2.1 | Myasthenia Gravis (MG). ICI-related myasthenia gravis constitutes approximately 14% of nirAEs [281, 293]. The clinical features of ICI-related MG are primarily manifested by fluctuating, activity-dependent muscle weakness, often affecting proximal muscle groups, axial neck muscles, ocular muscles, and bulbar muscles, leading to symptoms such as dysphagia, dysarthria, dyspnea, diplopia, ophthalmoplegia, and asymmetric ptosis. Notably, the proportion of respiratory muscle involvement can reach up to 50%, a rate significantly higher than that observed in spontaneous MG [21, 281, 294]. Differentiating between ICI-related MG and myositis can be challenging, particularly with respect to ocular symptoms. Key features of MG include the fluctuating nature of clinical symptoms and a decremental response on electromyography, whereas myositis is primarily distinguished by elevated creatine kinase (CK) levels and muscle pain [295, 296]. For patients with ICI-related MG, excluding those with only mild ocular muscle involvement, the vast majority require long-term immunosuppressive therapy to prevent disease recurrence [244].

4.10.2.2 | Myositis. ICI-related myositis constitutes approximately 32% of nirAEs [281, 293]. The primary clinical features of ICI-related myositis include prominent oculobulbar involvement, severe limb muscle involvement (more pronounced proximally compared to distally), and axial muscle weakness (which is especially notable in the neck). Patients often present with symptoms such as impaired ambulation, limited upper limb elevation, difficulty with neck extension and flexion, as well as ptosis, diplopia, dysphagia, dysarthria, and dyspnea [295–298]. Because ICI-related myositis frequently co-occurs with myocarditis and myasthenia gravis—complications that are associated with high mortality rates [299, 300]—routine myocarditis screening is crucial for these patients. For most patients with ICI-related myositis, corticosteroids or other immunomodulatory treatment regimens are generally effective, and the overall prognosis is typically favorable [301].

4.10.2.3 | Peripheral Neuropathy. ICI-related peripheral neuropathy represents approximately 22% of nirAEs [281, 293]. ICI-related peripheral neuropathy typically manifests as acute-onset, non-length-dependent involvement of the sensory, motor, or autonomic nervous systems, and its clinical features include diminished tendon reflexes and possible cranial nerve impairment [281, 302]. ICI-related peripheral neuropathies primarily encompass Guillain-Barré syndrome (GBS), demyelinating polyneuropathy, and cranial neuropathies (e.g., facial palsy and trigeminal neuralgia) [302–304]. For the treatment of ICI-related peripheral neuropathy, discontinuation of ICIs and/or administration of corticosteroid therapy can lead to significant symptomatic improvement in most patients [231, 244, 281, 302]. For patients with ICI-related GBS, a combination

of corticosteroids with IVIG or plasma exchange may be considered in addition to basic treatment [305].

4.11 | Sensory System

4.11.1 | Eye

The overall incidence of ICI-related ocular adverse reactions is notably low (< 1%) [306]. Among ICI-induced ocular adverse reactions, the most common are dry eye syndrome, uveitis, and ocular myasthenia gravis; other rarer ophthalmologic adverse events include retinal detachment, conjunctivitis, uveal effusion, vasculitis, vitritis, ocular myositis, episcleritis, keratitis, and choroidopathy [307–311]. For ICI-related ocular adverse reactions, topical steroid application is the preferred clinical treatment. To mitigate adverse reactions associated with systemic medication, local administration routes should be prioritized over systemic steroid applications unless there is a specific need. For patients with mild symptoms, continuation of the ICI treatment regimen under close monitoring may be considered [312–314]. Concurrently, corresponding symptomatic treatments should be implemented for specific adverse reactions (e.g., the application of artificial tears and topical cyclosporine for ICI-related dry eye syndrome). Research indicates that local treatment strategies can effectively alleviate most corneal and ocular surface diseases caused by ICIs [313].

4.11.2 | Ear

Clinical reports and systematic studies on ICI-related ototoxicity are limited, and its precise incidence remains poorly defined. Among the reported cases of ICI-related ototoxicity in the existing literature, melanoma patients constitute the highest proportion, with primary clinical manifestations that include hearing loss, tinnitus, aural fullness, and vertigo [315, 316]. Similar to the management principles for most irAEs, corticosteroids are the primary intervention for treating ICI-induced hearing loss [231]. Existing studies have demonstrated that intratympanic steroid injections can effectively alleviate ICI-related hearing impairment [317, 318].

4.11.3 | Nose

Reports in the literature and systematic studies on ICI-related nasal toxicity are also limited. A retrospective analysis of the US Food and Drug Administration Adverse Event Reporting System (FAERS) revealed that the incidence of ICI-related sinonasal adverse reactions is approximately 0.62%, with diverse clinical manifestations that include epistaxis, rhinorrhea, rhinitis, nasal obstruction, allergic rhinitis, and nasal polyp formation [319]. Previous studies suggest that clinical management for ICI-induced nasal adverse reactions may include sinus irrigation with saline or steroid solutions, or the topical application of corticosteroid nasal sprays; combining these interventions with at least one full course of antibiotic therapy is also recommended to control possible secondary infections [320].

5 | Future Perspectives

Although the clinical application of ICIs has significantly improved the efficacy of cancer treatment, the irAEs they induce remain a critical challenge necessitating further breakthroughs. Future research needs to advance across multiple dimensions (Figure 3): systematically elucidating the shared molecular mechanisms between irAEs and antitumor effects, particularly by revealing differences in T-cell activation thresholds and patterns of cross-antigen recognition, to provide a crucial theoretical basis for individualized drug dosage adjustments in clinical practice; developing targeted irAE prediction and monitoring systems based on emerging technologies such as multi-omics, biomarkers, imaging, and gene sequencing; optimizing strategies for preventing and treating irAEs by focusing on microbiome regulation and optimizing combination therapy strategies; establishing a temporal dynamic map of irAEs and antitumor immune responses to balance efficacy and safety through strategies such as dose de-escalation and intermittent dosing; and exploring novel drugs based on irAE mechanisms to minimize off-target toxicity and achieve an optimal balance between antitumor efficacy and safety. These breakthroughs will drive the establishment of individualized precision therapy paradigms, ultimately achieving the primary goal of immunotherapy: enhancing efficacy while minimizing toxicity.

5.1 | Unveiling the Shared Mechanisms Between irAEs and Anti-Tumor Effects

A profound understanding of the shared mechanisms between irAEs and antitumor effects is crucial for optimizing cancer immunotherapy strategies. In particular, by systematically analyzing the dual biological effects of T-cell activation (i.e., enhancing antitumor immune responses and inducing irAEs) [18, 22], key druggable nodes within shared molecular pathways can be further identified, potentially leading to the development of precise combination treatment regimens that can both strengthen antitumor immune responses and maintain peripheral immune tolerance. Furthermore, elucidating the threshold differences in the roles of CTLA-4/PD-1 signaling pathways in mediating antitumor effects versus inducing irAEs will provide a significant theoretical basis for individualized drug dosage adjustments in clinical practice.

5.2 | Developing Targeted irAE Prediction and Monitoring Systems

Future research should prioritize the development of biomarkers to facilitate the precise and stratified assessment of irAE risk. Specifically, systematic predictive models may be constructed utilizing integrated multi-omics analyses (encompassing genomics, microbiomics, and inflammatory factor-omics) to comprehensively evaluate circulating biomarkers (e.g., IL-6, CRP, and the neutrophil-to-lymphocyte ratio), imaging characteristics, and gut microbiota compositional features [16, 19, 321]. Concurrently, HLA gene polymorphisms (particularly HLA-DR4), microRNA expression profiles (e.g., miR-146a, miR-

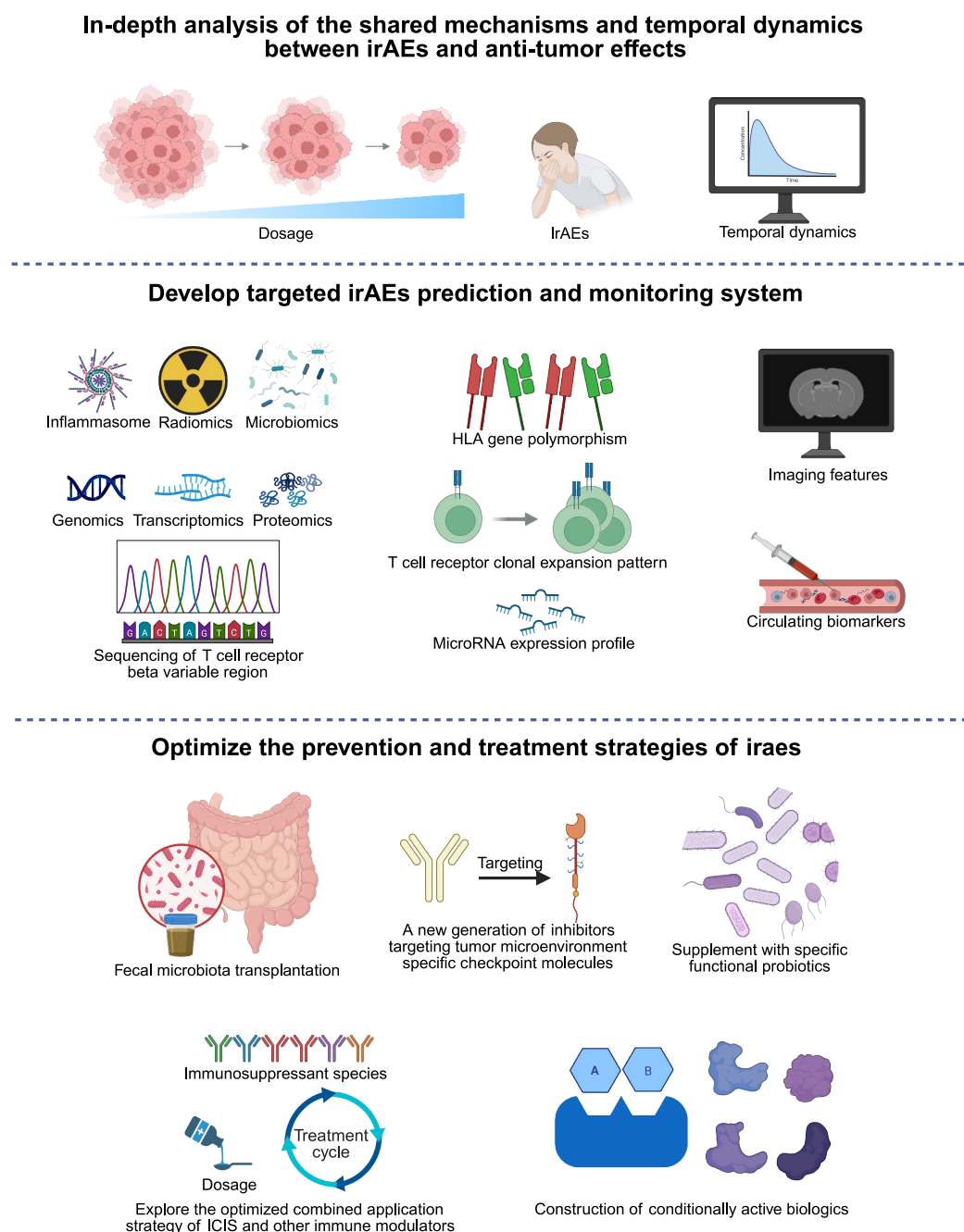


FIGURE 3 | Future research directions for irAEs: mechanistic elucidation, predictive models, and intervention strategies. Future research directions include (I) the in-depth elucidation of shared mechanisms and temporal dynamics between irAEs and antitumor effects. (II) Developing targeted irAE prediction and monitoring systems by leveraging emerging technologies such as multi-omics integrative analysis (including genomics, transcriptomics, proteomics, inflammomics, radiomics, and microbiomics) and T-cell receptor β variable region sequencing, along with comprehensively evaluating circulating biomarkers, imaging features, gut microbiota composition, HLA gene polymorphisms, microRNA expression profiles, and T-cell receptor clonal expansion patterns. (III) Optimizing irAE prevention and treatment strategies by reconstructing gut microbial ecological balance through fecal microbiota transplantation and supplementation with specific functional probiotics to enhance intestinal barrier integrity; optimizing combination strategies of ICIs with other immunomodulators, involving, for example, the precise selection of immunosuppressant types, dosages, and treatment durations; and exploring novel immunotherapy optimization strategies based on irAE mechanisms, such as developing next-generation inhibitors targeting tumor microenvironment-specific checkpoint molecules and designing conditionally active biologics to balance antitumor efficacy and autoimmune toxicity. This figure was created with [BioRender.com](https://www.biorender.com) (accessed on May 31, 2025).

34a), and T-cell receptor clonal expansion patterns should also be incorporated into the assessment framework to enable early identification and precise, stratified management of irAE risk

[19]. Moreover, the development of novel diagnostic tools based on radiomics and T-cell receptor beta variable region sequencing—utilizing routinely collected blood samples and CT

image data—can effectively predict the baseline risk of patients developing irAEs, thereby providing an objective basis for clinical treatment decisions [322–324].

5.3 | Optimizing Prevention and Treatment Strategies for irAEs

The optimization of strategies for preventing and treating irAEs can begin with microbiome modulation, such as reconstructing the gut microbiota ecological balance through fecal microbiota transplantation or supplementing with specific functional probiotics to enhance intestinal barrier integrity, thereby synergistically inhibiting overactivated pro-inflammatory signaling pathways and effectively reducing the incidence of gastrointestinal irAEs such as colitis. Furthermore, specific microbial metabolites can enhance the antitumor effects of ICIs [325–327]. For example, an experimental study demonstrated that fecal microbiota transplantation could effectively treat ICI-related colitis [65]. For cases of steroid-refractory irAEs, optimized combination strategies involving ICIs with other immunomodulatory agents should be systematically explored. This exploration should involve the precise selection of immunosuppressant types, dosages, and treatment durations to effectively control high-risk irAEs, such as myocarditis and pneumonitis, while maximally preserving antitumor immune activity [328, 329]. For example, the combination of ICIs with anti-TNF α agents has been shown to ameliorate ICI-related colitis and arthritis [330, 331], whereas the combination of ICIs with rituximab has demonstrated significant improvement in ICI-related encephalitis [107, 108, 275, 332, 333].

5.4 | Balancing Anti-Tumor Efficacy and Autoimmune Toxicity

One future research direction involves the systematic experimental exploration of optimal ICI dosing and administration frequency regimens to achieve the optimal balance between antitumor efficacy and autoimmune toxicity. Existing research data suggest that ICI regimens employing lower doses and/or reduced administration frequency may significantly lower the risk of irAEs while maintaining sufficient antitumor efficacy [80]. Furthermore, results from multiple clinical studies indicate that adopting sequential treatment strategies, as opposed to traditional combination therapy models, can effectively mitigate autoimmune toxicity while preserving antitumor effects [334–336]. Notably, significant differences in the temporal dynamics of the onset, development, and resolution of irAEs, as well as in immunomodulatory responses, are observed due to multiple factors, including the type of ICIs, combination therapy regimens, tumor types, and tissue specificity [337]. Clinical observational data indicate that enhanced antitumor effects are frequently accompanied by a higher incidence or greater severity of irAEs [17, 22, 35, 63]. Therefore, an in-depth analysis of the temporal dynamics between irAEs and antitumor immune responses is crucial for optimizing treatment strategy design, accurately predicting treatment response patterns, and providing a theoretical basis for developing personalized

precision therapy regimens, ultimately significantly improving the safety and patient tolerability of immunotherapy.

5.5 | Exploring Novel Immunotherapeutic Optimization Strategies Based on irAE Mechanisms

Future research should focus on the exploration of novel immunotherapeutic optimization strategies based on the mechanisms of irAEs. On the one hand, next-generation inhibitors targeting TME-specific checkpoint molecules, such as TIM-3, VISTA, and TIGIT, can be developed to reduce antigen cross-reactivity with normal tissues, including the myocardium and thyroid, thereby mechanistically decreasing off-target toxicity [19]. On the other hand, the unique physicochemical characteristics of the TME (e.g., high concentrations of bicarbonate or hydrogen sulfide) can be fully leveraged for the design and construction of conditionally active biologics. Through precise protein-associated chemical switch (PaCS) technology, anti-CTLA-4 antibodies can be engineered for the selective activation of their target binding exclusively within the TME, significantly reducing off-target toxicity in normal tissues and thereby achieving an optimal balance between antitumor efficacy and safety [338–340].

6 | Conclusions

This article has systematically elucidated the mechanisms, risk factors, and management strategies pertinent to irAEs. Future efforts should focus on further elucidating the underlying mechanisms of irAEs, improving predictive and monitoring systems, and optimizing individualized treatment approaches to more effectively manage the balance between irAEs and antitumor efficacy, thereby synergistically enhancing both the safety and effectiveness of immunotherapy.

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Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

Peng Luo hold the position of executive editors-in-chief for Med Research. Jian Zhang hold the position of associate editors for Med Research. Aimin Jiang hold the position of editorial board members for Med Research. They were excluded from editorial decision-making related to the acceptance of this article for publication in the journal.

Data Availability Statement

The authors have nothing to report.

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