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Review Article

Risk Factors and Biomarkers for Immune Checkpoint Inhibitor-mediated Hepatotoxicity: Emerging Insights and Future Perspectives

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Abstract

In the past decade, immune checkpoint inhibitors (ICIs) have dramatically changed cancer treatment, significantly improving outcomes for patients with various malignancies. Nonetheless, their widespread application has resulted in a rise in immune-related adverse events due to excessive immune activation, including immune-mediated hepatotoxicity (IMH). IMH can cause serious complications and even death, underscoring the need for early prediction and intervention. This review outlines the current understanding of risk factors and predictive biomarkers for IMH in cancer patients undergoing ICI therapy, with risk factors divided into patient-associated, tumor-associated, and agent-associated categories. Higher IMH risk is related to female sex, younger age, extreme BMI, Asian ethnicity, and chronic liver disease. Cancer type, prior ICI treatment, dual ICI combination therapy, and the concurrent use of chemotherapy, targeted agents, or other hepatotoxic drugs (e.g., acetaminophen, statins) also increase the risk of IMH. Potential predictive biomarkers encompass circulating blood cells, serum proteins, autoantibodies, cytokines, gene profiles, and the gut microbiome. Despite promising findings, the predictive value of these biomarkers remains inconsistent, and no definitive biomarker has been established for routine clinical use. Large-scale prospective studies are essential to verify the predictive value of these biomarkers and facilitate their integration into clinical practice, thereby providing deeper insights into the early identification and individualized management of IMH during ICI therapy.

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Introduction

Immune checkpoint inhibitors (ICIs) have revolutionized the therapeutic landscape of numerous advanced solid and haematological malignancies over the past decade, emerging as a cornerstone of modern cancer therapy.[1] ICIs are monoclonal antibodies targeting inhibitory receptors on the surface of T cells or tumor cells, primarily including cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) inhibitors (i.e., ipilimumab), programmed death protein 1 (PD-1) inhibitors (i.e., nivolumab and pembrolizumab), and programmed death protein ligand 1 (PD-L1) inhibitors (i.e., atezolizumab, durvalumab).[2] By blocking these inhibitory pathways, ICIs can activate T-cell responses and thereby amplify antitumor activity. Currently, ICIs have demonstrated remarkable efficacy in a broad spectrum of cancers, including melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma, hepatocellular carcinoma (HCC), and esophageal squamous-cell carcinoma.[3–7] Compared to traditional chemotherapy, ICIs offer superior efficacy, enhanced tolerability, and improved prognosis for patients with advanced malignancies.[8] In recent years, ICIs have garnered global attention as a revolutionary approach in cancer treatment (Table 1).

However, the widespread adoption of ICIs for advanced cancers has been accompanied by unexpected immunological and inflammatory complications, known as immune-related adverse events (irAEs), arising from an overactive immune response that targets normal tissues or organs.[9] These irAEs can influence a range of organ systems, particularly the skin, gastrointestinal tract, endocrine glands, and liver.[10] Among these, immune-mediated hepatotoxicity (IMH), a liver-related irAE, has represented a clinically significant challenge.[11] IMH typically manifests as asymptomatic elevations in aspartate aminotransferase (AST), alanine aminotransferase (ALT), and/or alkaline phosphatase (ALP), with reported incidences ranging from 1% to 15% in clinical trials.[12,13] Although most IMH cases are relatively mild, sometimes they can be life-threatening, leading to severe hepatitis, liver failure, and even fatalities, necessitating treatment discontinuation.[14,15] According to data from the World Health Organization, 20.2% (124 out of 613) of fatal ICI-related toxic events were attributed to IMH, highlighting the critical need for early detection and effective management.[16]

Currently, the precise mechanisms of IMH development

Table 1. Immune checkpoint inhibitors and their indications

Target	Drug	Indications	Time to market
CTLA-4	Ipilimumab[a,b]	Melanoma, RCC, MSI-H or dMMR CRC, HCC, NSCLC, MPM, ESCC	2011
PD-1	Nivolumab[a,b]	Melanoma, NSCLC, MPM, RCC, cHL, HNSCC, UC, MSI-H or dMMR CRC, HCC, ESCC, GC/GEJC/EAC	2014
	Pembrolizumab[a,b]	Melanoma, NSCLC, HNSCC, cHL, PMBCL, UC, MSI-H or dMMR CRC, ESCC, HCC, MCC, RCC, TNBC, BTC, CC, EC, GC/GEJC/EAC TMB-H solid tumors, cSCC	2014
	Cemiplimab[a]	cSCC, BCC, NSCLC	2018
	Toripalimab[a,b]	Melanoma, NPC, UC, NSCLC, SCLC, RCC, ESCC, TNBC	2018
	Sintilimab[a,b]	cHL, NSCLC, HCC, ESCC, GC/GEJC/EAC	2018
	Camrelizumab[a,b]	cHL, HCC, NSCLC, ESCC, NPC	2019
	Tislelizumab[a,b]	cHL, UC, NSCLC, SCLC, HCC, MSI-H or dMMR solid tumor, ESCC, NPC, GC/GEJC/EAC	2019
	Penpulimab[b]	cHL, NSCLC	2021
	Zimberelimab[b]	cHL	2021
	Serplulimab[b]	MSI-H or dMMR solid tumor, NSCLC, SCLC, ESCC	2022
	Pucotenlimab[b]	Melanoma, MSI-H or dMMR solid tumor	2022
	Enlonstobart[b]	CC	2024
PD-L1	Atezolizumab[a,b]	Melanoma, UC, NSCLC, SCLC, HCC	2017
	Avelumab[a]	MCC, UC, RCC	2017
	Durvalumab[a,b]	NSCLC, SCLC, HCC, BTC, dMRR EC	2017
	Envafolimab[b]	MSI-H or dMMR CRC	2021
	Sugemalimab[b]	NSCLC, ENKTL, ESCC, GC/GEJC/EAC	2021
	Adebrelimab[b]	SCLC	2023
	Socazolimab[b]	CC	2023
	Benmelstobart[b]	SCLC	2024
PD-L1/CTLA-4	Cadonilimab[b]	CC	2022
	Iparomlimab and tuvonralimab[b]	CC	2024
PD-1/VEGF	Ivonescimab[b]	NSCLC	2024

[a]Approved by the U.S. Food and Drug Administration (FDA). [b]Approved by the National Medical Products Administration (China). CTLA4, cytotoxic T-lymphocyte antigen 4; PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1; VEGF, vascular endothelial growth factor; RCC, renal cell carcinoma; MSI-H, microsatellite instability-high; dMMR, deficient mismatch repair; CRC, colorectal cancer; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; MPM, malignant pleural mesothelioma; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; GEJC, gastroesophageal junction cancer; EAC, esophageal adenocarcinoma; cHL, classical Hodgkin lymphoma; UC, urothelial carcinoma; HNSCC, head and neck squamous cell cancer; SCLC, small cell lung cancer; PMBCL, primary mediastinal large B-cell lymphoma; MCC, Merkel cell carcinoma; TMB-H, tumor mutational burden-high; TNBC, triple-negative breast cancer; BTC, biliary tract carcinoma; CC, cervical cancer; EC, endometrial carcinoma; cSCC, cutaneous squamous cell carcinoma; BCC, basal cell carcinoma; NPC, nasopharyngeal carcinoma; ENKTL, extranodal natural killer/T-cell lymphoma.

are not fully elucidated, with proposed roles for T-helper cell expansion, monocyte/macrophage activation, and regulatory T (Treg)-cell depletion,[17] making therapy targeting specific molecular pathways challenging. Consequently, management strategies for IMH primarily rely on expert consensus guidelines derived from clinical trial protocols, which recommend discontinuing ICIs and initiating glucocorticoids or immunosuppressants.[18,19] However, this reactive approach, which is often initiated only after toxicity manifests, fails to prevent the occurrence of severe IMH and is ineffective in patients who show a poor response or resistance to corticosteroid therapy. More critically, data on risk factors and biomarkers of IMH are limited, resulting in the lack of reliable predictive tools that can accurately identify high-risk patients before treatment initiation, which eventually complicates treatment decisions for clinicians, potentially causing treatment delays or permanent discontinuation. Therefore, identifying the risk factors and biomarkers of IMH in patients receiving ICI therapy is urgently needed. This information will allow clinicians to identify high-risk individuals early, optimize immunotherapy regimens, and initiate timely interventions, ultimately mitigating the occurrence of IMH.

Evidence suggests that several clinical risk factors, such as female sex, pre-existing non-alcoholic fatty liver disease (NAFLD), and the use of combination ICIs (e.g., anti-CTLA-4 plus anti-PD-1/PD-L1), are associated with an elevated risk of IMH, which allows for early identification of high-risk populations.[20–22] Concurrently, emerging investigations into potential biomarkers, including circulating blood cells, autoantibodies, cytokines, specific immune cell subsets (e.g., $CD8^+$ T cells), and genomic signatures, have demonstrated promise for risk stratification and early intervention of irAEs,

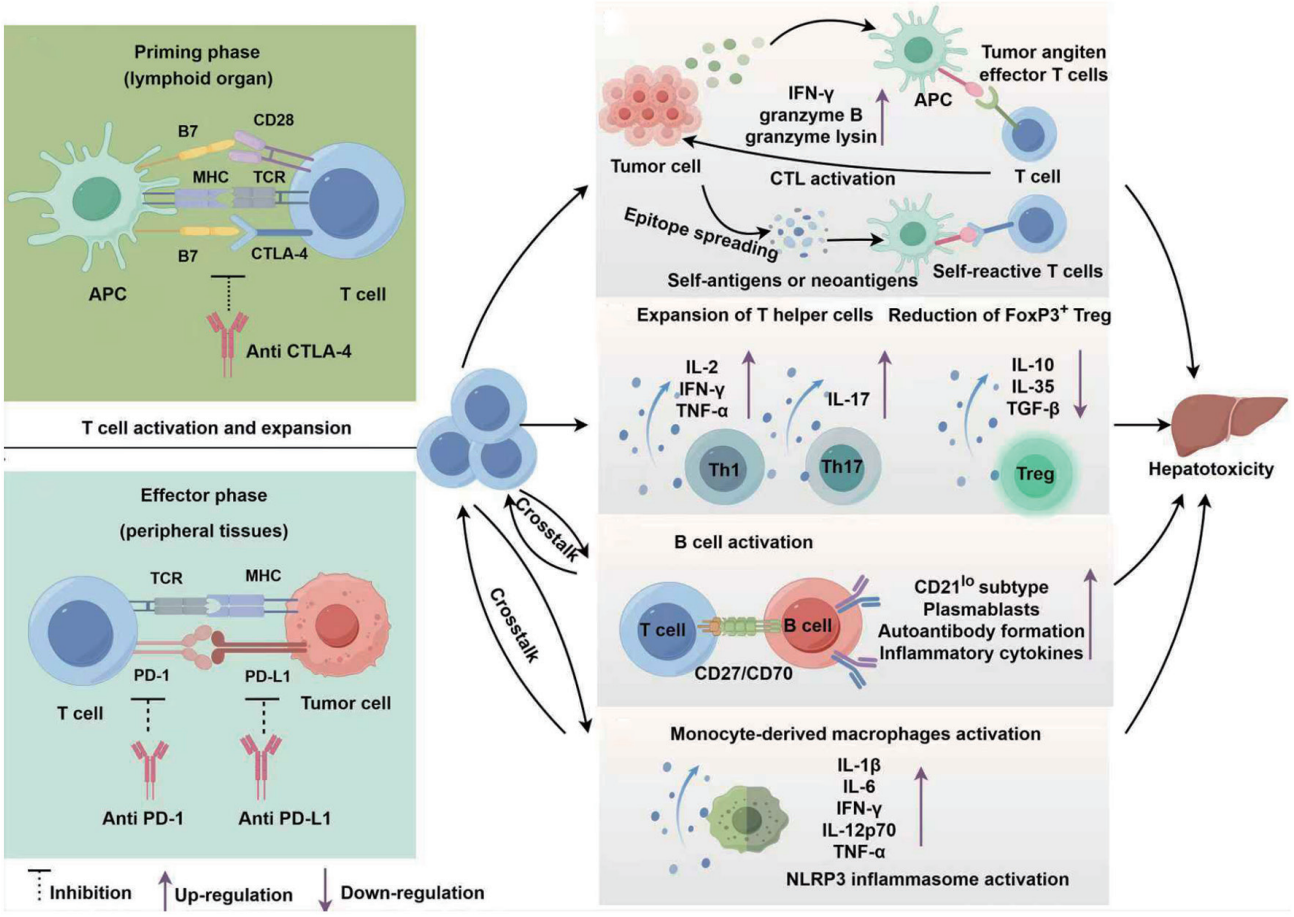

Fig. 1. Mechanisms of ICI-mediated hepatotoxicity. (A) CTLA-4 inhibitors activate T cells at the priming phase. (B) PD-(L)1 inhibitors activate T cells to exhibit an anti-tumor effect in the effector phase. ICIs can disrupt the immune-tolerant environment in the liver. (C) ICIs reactivate exhausted CTLs, which further upregulate the proliferation of IFN-γ, granzyme B, and granzyme lysin, and kill tumor cells. In this process, tumor cell lysis releases various self-antigens or neoantigens, which are recognized and cross-presented by APCs, attacking the body's own normal liver tissues. (D) Expansion of T helper cells (e.g., Th1, Th17) increases pro-inflammatory cytokines, and Treg reduction leads to a decrease in anti-inflammatory cytokines. (E) Activated B cells crosstalk with $CD8^+$ T cells through costimulatory signaling and induce an increase in $CD21^{lo}$ subtype, plasmablasts, and autoantibody formation. (F) Crosstalk between activated $CD8^+$ T cells and innate immune cells such as macrophages via inflammatory cytokines leads to NLRP3 inflammasome activation and hepatocyte apoptosis. The above processes are involved in the pathophysiologic mechanism of ICI-mediated hepatotoxicity. Created with Figdraw 2.0. CTLA4, cytotoxic T-lymphocyte antigen 4; PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1; APC, antigen-presenting cells; MHC, major histocompatibility complex; TCR, T cell receptor; IFN-γ, interferon-γ; CTL, cytotoxic T cells; IL, interleukin; TNF-α, tumor necrosis factor-α; FoxP3, Forkhead box protein P3; Treg, Treg cell; TGF-β, transforming growth factor-β; NLRP3, Nod-like receptor protein 3.

suggesting their potential as markers for IMH prediction.[23,24] However, the available evidence on the risk factors and biomarkers that predict IMH occurrence remains limited, and most studies are retrospective, not specifically focused on IMH. Therefore, this review aims to comprehensively synthesize the current landscape of the risk factors and emerging biomarkers associated with IMH during ICI therapy, which will provide promise for early identification and individualized management of IMH, thereby promoting the safety and efficacy of tumor immunotherapy.

Potential mechanism of IMH

As previously described, the central mechanism by which ICIs exert anti-tumor effects is the activation of cytotoxic T cells (CTLs) by inhibiting the CTLA-4 and PD-1/PD-L1 signaling pathways. Although these two pathways function as negative regulators of T-cell activation, they have different roles in immune regulation. CTLA-4 functions primarily during the initial priming phase of T-cell activation within secondary lymphoid organs, such as lymph nodes.[25,26] On activated T cells and Treg cells, CTLA-4 competitively binds to the co-stimulatory molecules B7-1 (CD80) and B7-2 (CD86) on antigen-presenting cells (APCs) with a higher affinity than the activating receptor CD28, thereby inhibiting the initial clonal expansion and proliferation of T cells (Fig. 1A). CTLA-4 inhibitors block this interaction, which prevents inhibitory signaling and enhances T-cell activation by promoting CD28-mediated co-stimulation. In contrast, the PD-1 pathway is primarily engaged during the effector phase within peripheral tissues and the tumor microenvironment. PD-1 is expressed on activated T cells and binds to its ligand PD-L1, which is often upregulated on tumor cells and various host cells.[26,27] This engagement suppresses downstream T-cell receptor and CD28 signaling cascades, leading to the functional impairment or exhaustion of T-cell effector functions and facilitating tumor immune evasion (Fig. 1B). PD-1/PD-L1 inhibitors also block this interaction, reinvigorating exhausted T cells and restoring their cytotoxic and proliferative potential. This fundamental mechanistic divergence underpins the differential

immune effects observed with ICI therapies: CTLA-4 blockade predominantly enhances early CD4+ T-cell clonal expansion and promotes T-cell trafficking to tumor sites, whereas PD-1/PD-L1 blockade primarily reverses the exhausted CD8+ T cells within tissues.[26] Consequently, this complementary biology provides a rationale for the use of both monotherapy and combination regimens to achieve synergistic anti-tumor immunity.

While the precise mechanisms driving IMH following ICI therapy are not yet fully understood, the liver's unique immunological properties are recognized as central to its pathophysiology. Under homeostatic conditions, the liver maintains a state of immunotolerance achieved through the anti-inflammatory functions of both parenchymal and non-parenchymal cells, as well as the constitutive expression of immune checkpoint molecules by various cell subsets.[17] Notably, a cornerstone of liver immunotolerance involves PD-L1 expressed on diverse cell types, including hepatic stellate cells, Kupffer cells, liver sinusoidal endothelial cells, hepatocytes, as well as liver-resident or infiltrating immune cells such as macrophages, along with CTLA-4 expressed on CD4+ Treg cells.[17] By suppressing CD8+ T-cell activation and function, these checkpoint molecules help protect the liver from antigen-driven autoimmune responses in various inflammatory contexts. However, due to the use of ICIs blocking these key modulatory pathways, immune tolerance of the liver can be broken, rendering it more susceptible to inflammatory damage triggered by drug exposure, underlying neoantigens, or concurrent microbial stimuli.[13]

Current evidence points to a multifactorial effect in IMH pathogenesis, involving a complex interplay between adaptive and innate immunity, which ultimately disrupts hepatic immune tolerance. The primary mechanisms include direct activation of CTLs and epitope spreading, as well as indirect effects on T-helper cells, forkhead box P3–positive Tregs, B cells, the inflammatory cytokine milieu, and activation of innate immunity (Fig. 1C–F).[28] Firstly, ICI blockades can overcome immune tolerance by stimulating the proliferation of CD8+ cytotoxic T lymphocytes, thereby inducing tumor cell death. This is accompanied by an alteration in their transcriptional profile, leading to the upregulation of proliferative and cytotoxic genes such as interferon (IFN)-γ, granzyme, and granulysin.[17,26] Concurrently, epitope spreading refers to the diversification of the initial T-cell response against novel epitopes and neoantigens that differ from the originally targeted ones.[29] In this process, lysed tumor cells release substantial amounts of self-antigens or neoantigens into the microenvironment, where APCs capture, process, and cross-present these antigens, thereby triggering a secondary immune response, leading to an immune attack toward hepatocytes that share overlapping epitopes.[17] Secondly, the expansion of T-helper cells, particularly Th1 and Th17 cells, results in an increase in pro-inflammatory cytokines, including interleukin (IL)-2, IFN-γ, tumor necrosis factor (TNF)-α, and IL-17, which can activate CTLs, natural killer cells, and monocyte-derived macrophages.[30,31] Concurrently, ICI therapy can impair the suppressive function of Treg cells, often accompanied by reduced expression of the transcription factor forkhead box P3 and decreased production of anti-inflammatory cytokines such as IL-10, IL-35, and TGF-β.[17,32] Thirdly, B cells play a crucial role in the anti-tumor immune response by engaging in crosstalk with CD8+ T cells, which involves co-stimulatory signaling through CD27/CD70 interactions, and promotes CTL survival and proliferation independently of antigen presentation.[33] CTLA-4 and PD-1 are also expressed in B cells, and their blockade by ICIs causes excessive activation and proliferation of B cells, leading to increases in CD21lo B cells, plasmablasts, and pro-inflammatory cytokines that correlate with the occurrence of irAEs and IMH.[34,35] Overactivated and dysregulated B cells may produce antibodies targeting self-antigens (i.e., autoantibodies), which can potentially mediate liver damage by antibody-dependent mechanisms and trigger inflammation and hepatocyte injury; however, the pathophysiological relevance of these antibodies and the precise role of B cells in irAEs require further investigation.[36] In addition, ICIs promote the activation of monocytes and CD8+ T lymphocytes, leading to increased secretion of pro-inflammatory cytokines (e.g., IL-1β, IL-6, IFN-γ, IL-12p70, and TNF-α) to form the inflammatory microenvironment driving hepatotoxicity.[17,30,37] These cytokines, in turn, help to activate an innate immune response by recruiting natural killer cells and macrophages, which contribute to the pathogenesis of liver injury. Liver biopsies from patients and mouse models reveal that CD8+ T cells and CCR2+ macrophages colocalize in damaged areas, with their crosstalk activating the NLRP3 inflammasome to promote hepatocyte apoptosis.[30,38] Importantly, macrophage activation and recruitment to the liver can occur independently of CD8+ T cells, highlighting the complexity and redundancy of the inflammatory networks driving IMH.

Risk factors associated with IMH

Although numerous risk factors influencing the incidence of irAEs during ICI therapy have been identified, those specifically associated with IMH remain incompletely understood. Studies have identified several risk factors for IMH onset, including patient-associated factors, tumor-associated factors, and treatment-associated factors, presented in Table 2.[20-23,39–52]

Patient-associated factors

Social demographics: Several studies have explored the association between patient demographics—such as sex, age, race, and BMI—and the risk of IMH during ICI therapy. Female sex has emerged as a significant risk factor for the development of IMH. Kitagataya *et al*. indicated that females were at a greater risk of experiencing grade 3 or higher IMH compared to males.[22] A retrospective study involving 1,096 patients treated with ICI noted a higher prevalence of IMH in females (p = 0.038), but multivariable analysis was not performed to confirm an independent association.[39] Recently, a real-world cohort study over 10 years assessed risk factors associated with IMH in 432 patients with malignant melanoma or renal cancer who received ICIs, and all IMH cases were identified using the definitions, grading, and causality assessment methods validated for drug-induced liver injury (DILI).[40] In multivariate logistic regression analysis, they identified female sex as an independent risk factor for IMH occurrence, which may be due to women being more sensitive to the toxicity of anti-tumor drugs. This enhanced risk linked to female sex has also been further found in a recent meta-analysis of 9,076 patients.[27] Nevertheless, whether this sex disparity stems from differences in tumor biology or the pharmacokinetics and pharmacodynamics of ICIs remains unclear. Further investigation is needed to elucidate the complex relationship between sex and IMH development.

Age has been considered a risk factor for IMH. A meta-analysis of 13 studies in 2022 indicated that younger age was more prone to any-grade and grade ≥3 IMH compared to older individuals.[41] This was reinforced by another recent meta-analysis of 24 studies in 2024, demonstrating that younger age was significantly associated with a higher likelihood of IMH.[42] Similarly, significant associations between

Table 2. Risk factors for IMH incidence

Risk factors	Higher risk of IMH	Significance	Reference
Patient-associated			
Social Demographics	Female sex	$p = 0.009$	Kitagaya *et al*.[22]
		$p = 0.021$	Wolffer *et al*.[23]
		$p = 0.038$	Miah *et al*.[39]
		OR = 2.54; 95% CI 1.09–6.06; $p = 0.032$	Atallah *et al*.[40]
	Young age	WMD = −5.200; 95% CI −7.481 to −2.919; $p < 0.001$	Pan *et al*.[41]
		SMD = −0.18; 95% CI −0.33 to −0.04; $p = 0.012$	Jiang *et al*.[42]
		HR = 1.527; 95% CI 1.011–2.307; $p < 0.05$	Cho *et al*.[43]
		OR = 1.757; 95% CI 1.126–2.743; $p = 0.013$	Jiang *et al*.[44]
	Asian population	China, HR = 4.25; Japan, HR = 2.98; Korea, HR = 1.38	Madjar *et al*.[45]
	Extreme BMI: Low BMI or High	WMD −2.15; 95% CI −3.92 to −0.38; $p = 0.017$	Jiang *et al*.[42]
Medical history	HBV	pooled OR = 2.46; 95% CI 1.04–5.81; $p = 0.039$	Jiang *et al*.[42]
		Seropositive HBsAg, OR = 6.30; baseline HBV DNA levels, OR = 2.39	Lin *et al*.[46]
		OR = 1.9; 95% CI 1.123–3.325; $p = 0.017$	Jiang *et al*.[47]
	NAFLD	HR = 29.34; 95% CI 3.169–271.6; $p = 0.003$	Sawada *et al*.[21]
	High baseline AST/ALT	OR = 1.03; 95% CI 1.01–1.05; $p = 0.006$	Atallah *et al*.[40]
		OR = 2.59; 95% CI 1.35–4.96; $p = 0.004$	Kaneko *et al*.[48]
	Low baseline ALP	OR = 0.99; 95% CI 0.98–1.00; $p = 0.015$	Atallah *et al*.[40]
		HR = 0.99; 95% CI 0.984–0.997; $p = 0.007$	Kawano *et al*.[49]
Tumor-associated			
Type of cancer	Melanoma	OR = 11.6; 95% CI 3.5–38.0; $p = 0.002$	Yamamoto *et al*.[20]
		HR = 1.945; 95% CI 1.029–3.677; $p = 0.041$	Kawano *et al*.[49]
	HCC	OR = 2.1; 95% CI 1.231–3.621; $p = 0.007$	Jiang *et al*.[47]
		OR = 7.866; 95% CI 3.417–18.108; $p < 0.001$	Jiang *et al*.[44]
	Biliary tract carcinoma	OR = 0.30; 95% CI 0.09–0.95; $p = 0.040$	Gao *et al*.[50]
	Gastric cancer	OR = 1.895; 95% CI 1.193–3.011; $p = 0.007$	Jiang *et al*.[44]
Drug-associated			
ICI monotherapy or combined medication	Dual ICI combination therapy	OR = 10.95; 95% CI 4.04–35.60; $p < 0.001$	Atallah *et al*.[40]
	ICI Dose: Ipilimumab at 10 mg/kg	Not reported	Wolchok *et al*.[51]
	Prior ICI history	OR = 4.491; 95% CI: 2.205–9.145; $p < 0.001$	Pan *et al*.[41]
		pooled OR = 3.09; 95% CI: 1.21–7.89; $p = 0.009$	Jiang *et al*.[42]
	ICI combined with antiangiogenic drugs or TKI	$p < 0.0001$	Ernst *et al*.[52]
	ICI combined with other hepatotoxic drugs, e.g., acetaminophen, statins	Acetaminophen, OR = 2.139; statins, OR = 4.706	Cho *et al*.[43]

IMH, immune-mediated hepatotoxicity; BMI, body mass index; HBV, hepatitis B virus; NAFLD, non-alcoholic fatty liver disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; TKI, tyrosine kinase inhibitor; OR, odds ratio; HR, hazard ratio; 95% CI, 95% confidence interval; WMD, weighted mean difference; SMD, standardized mean difference.

younger age and IMH occurrence have also been identified in two retrospective cohort studies of 194 and 744 patients.[43,44] This phenomenon may be attributed to the enhanced functional response of the innate and adaptive immune system due to increased T-cell activation in younger patients, which corresponds with the mechanism of IMH development.

Asian ethnicity has also been recognized as a potential risk factor for IMH development. The higher incidence of IMH has been seen in Asian patients, with approximately 6% in Japanese patients and up to 18% in Chinese patients, highlighting hepatotoxicity as a critical concern in these populations, especially in China.[53] A meta-analysis of 10,344 patients across 15 clinical trials with atezolizumab identified that patients from Asian countries, such as China, Japan, and Korea, have a notably higher risk of IMH compared to non-Asian patients.[45] This may be attributed to the higher proportion of hepatitis B virus infections in Asian patients, but further research is needed to obtain a definitive conclusion.

Extreme BMI levels, specifically underweight and obesity, have also been shown to be associated with a higher risk of liver damage. A pooled analysis of data from 15 clinical trials, involving 5,123 patients treated with PD-(L)1 inhibitors for various solid tumors, demonstrated that patients with BMI ≥ 30 kg/m^2 were at an increased risk of irAEs in comparison to those with normal BMI.[54] A longitudinal cohort study of 863 pan-cancer patients constructed predictive models for accurately identifying patients at high risk of acute ICI-related hepatotoxicity within one month of initiating ICI treatment, with the model indicating an enhanced likelihood of IMH in patients with BMI ≥ 30 kg/m^2, suggesting higher BMI may prolong exposure to ICIs and increase the risk of IMH occurrence.[55] Interestingly, a recent meta-analysis of 24 studies identified a significant correlation between lower BMI (<18.5 kg/m^2) and the risk of IMH in patients treated with ICIs, which may be attributed to the fact that underweight patients are often diagnosed at the advanced stage of cancer, rendering them more susceptible to adverse drug reactions.[42] However, the exact mechanism linking BMI to IMH remains unclear. It could be hypothesized that high or low BMI may alter drug pharmacokinetics, affecting absorption, distribution, metabolism, and excretion, thereby increasing susceptibility to severe liver injury.[56]

Chronic liver diseases: In patients with chronic liver disease, studies suggest a higher incidence of developing IMH compared with those without liver disease.[57] Hepatitis B virus (HBV) infection, in particular, may influence both the efficacy and liver safety of ICI therapy. For instance, a pooled analysis in 2024 indicated that the risk of IMH after ICI treatment was notably higher in cancer patients with chronic HBV (pooled OR: 2.46; 95% CI: 1.04 to 5.81; n = 7 studies).[42] In a retrospective study, Lin *et al*. further evaluated hepatotoxicity in 301 cancer patients who were hepatitis B core antibody positive (regardless of hepatitis B surface antigen status) and received PD-1 inhibitors, revealing that seropositive hepatitis B surface antigen and detectable baseline HBV DNA levels were linked to an increased risk of any-grade IMH, while prophylactic antiviral therapy reduced the incidence of grade 3/4 IMH.[46] Similarly, in a study involving 1,175 patients treated with PD-(L)1 inhibitors, Jiang *et al*. explored risk factors for ICI-related hepatotoxicity and reported that chronic HBV infection was associated with a 1.9-fold increase in the risk of IMH (95% CI, 1.123–3.325).[47] Additionally, HBV reactivation was an important risk consideration in the application of immunotherapy in patients with HBV infection. It has been observed that reactivation risk is 11–30% for patients who are positive for HBV surface antigen receiving ICI therapy without prophylaxis.[58,59] These findings indicate that cancer patients with chronic HBV infection are at higher risk for developing IMH after receiving ICI therapy, and therefore, HBV serology should be assessed before initiating ICI treatment. For individuals with chronic HBV infection, close monitoring of ALT/AST and HBV DNA levels is recommended throughout the immunotherapy course, along with appropriate consideration of preemptive antiviral medication.

Other chronic liver conditions, such as NAFLD and alcohol-related liver disease, may also elevate IMH risk. A retrospective analysis of 135 patients treated with PD-1 inhibitors revealed that patients with NAFLD were significantly associated with an increased risk of IMH compared to those without chronic liver conditions (HR = 29.34, $p = 0.003$).[21] Abnormal liver function prior to ICI treatment seems to increase the risk of IMH. Baseline elevations in serum ALT or AST levels were associated with an increased risk of IMH in two independent cohorts of 432 and 571 patients.[40,48] Meta-analyses have demonstrated a significant correlation between higher baseline AST levels and any-grade IMH.[41] Interestingly, a low baseline serum ALP level has also been shown to contribute to IMH development, although the mechanism for this is unclear.[40,49]

Although pre-existing autoimmune diseases are presumed to elevate the risk of irAEs during ICI treatment, the specific risk of IMH in this population remains inadequately investigated. Evidence from a small multicenter cohort study of 22 patients with mixed hepatic autoimmune disease who received PD-1/PD-L1 inhibitors reported no excess toxicity signal.[60] Furthermore, a recent systematic review of 699 patients with advanced HCC found that the incidence of ICI-related adverse events was comparable between those with Child-Pugh A and Child-Pugh B cirrhosis.[61] Therefore, these findings suggest that autoimmune liver disease should not be regarded as a contraindication for ICI treatment in clinical practice.

Tumor-associated factors

The type of cancer is a significant determinant of the risk of developing IMH during ICI therapy. Melanoma has been identified as a risk factor for IMH. A pooled analysis of 17 clinical trials involving over 20,000 cancer patients treated with ICIs demonstrated a higher risk of IMH in melanoma patients relative to those with other malignancies.[62] Similarly, a significant correlation between IMH and malignant melanoma has been confirmed in two independent retrospective studies of 250 and 1,086 patients.[20,49] This elevated risk in melanoma may be attributed to the frequent use of combination ICI therapy (e.g., anti-CTLA-4 plus anti-PD-1) and the disease's propensity for liver metastasis, resulting in liver injury.

HCC appears to be associated with a higher risk of IMH. Although a meta-analysis of 117 trials published in 2021 reported significantly higher rates of all-grade and ≥ grade 3 elevations in ALT, AST, bilirubin, and hepatobiliary disorders in patients with HCC versus other cancer types ($p < 0.001$), this difference was not observed for ICI-related hepatitis.[63] Recently, a two-cohort study in 2024 revealed a substantially higher exposure-adjusted incidence of any-grade IMH in patients with HCC (n = 375) than in patients with other solid organ malignancies (n = 459), with rates of 11.5% (22.1 per 100 patient-years) and 2.6% (2.1 per 100 patient-years), respectively.[64] IMH events also occurred earlier in the HCC cohort compared to the other tumor cohort, with a median time to any-grade IMH of 1.4 months (range, 0.1–25.5) versus 4.7 months (range, 0.9–12.8). This strong association has been consistently corroborated by two recent large retrospective studies of 1,175 and 744 patients, which confirmed HCC as an independent risk factor for IMH.[44,47] The discrep-

ancy arises from the fact that earlier meta-analyses evaluated hepatotoxicity in HCC patients based on liver function indicators such as AST and ALT, with significant variation or heterogeneity in the definition, type, and terms of reported hepatotoxicity across trials, which may have led to the lack of observed significant differences in IMH between HCC and other solid tumors. In contrast, subsequent real-world studies specifically focused on IMH by utilizing diagnostic grading systems for DILI and the Roussel-Uclaf causality assessment, thereby enhancing the representativeness of their findings.[44,47] Moreover, the elevated risk of IMH in HCC may be attributed to the presence of antigens shared between HCC and normal hepatocytes. These shared antigens are captured by hepatic APCs, including Kupffer cells and liver sinusoidal endothelial cells, processed, and subsequently presented to $CD8^+$ T cells. This can lead to the activation and expansion of T-cell clones that recognize self-antigens expressed on hepatocytes, thereby promoting immune attacks against normal hepatic tissue and resulting in liver injury. Hence, vigilance in monitoring liver function is strongly recommended before and during ICI treatment in patients with HCC.

Furthermore, emerging risk signals have been reported for other cancers. For instance, Gao *et al*. analyzed IMH incidence in patients during ICI therapy, finding that biliary tract cancer (BTC) had a higher IMH incidence than gastric cancer (GC), and identifying BTC as a high-risk factor for grade ≥2 IMH.[50] It was speculated that concomitant biliary obstruction and impaired baseline liver function in BTC patients may heighten their susceptibility to IMH. Meanwhile, another retrospective cohort study involving 744 individuals receiving PD-1/PD-L1 inhibitors indicated that GC was an independent risk factor for IMH, which could be driven by divergent tumor–immune interactions, thereby affecting susceptibility to IMH.[44] Therefore, enhanced liver function surveillance is warranted during immunotherapy in these populations. However, current evidence linking BTC or GC to IMH risk remains preliminary and requires validation in larger population cohorts, as well as further investigation into the underlying mechanisms.

The role of liver metastases as a risk factor for IMH remains controversial. For example, a recent meta-analysis identified liver metastases as a significant independent risk factor for IMH (OR 1.80, 95% CI 1.47–2.20; $p < 0.000$).[42] Conversely, other retrospective studies and another meta-analysis have failed to confirm this association.[39–41] This discrepancy may stem from significant heterogeneity in study populations, liver metastatic burden, ICI regimens, and the confounding effects of prior hepatotoxic treatments.

Drug-associated factors

The type, treatment regimen, and dosage of ICIs: The incidence of IMH varies depending on the type, treatment regimen (monotherapy or combination), and dosage of ICIs. The specific ICI type plays a crucial role in determining IMH risk. Clinical trial data reveal that the incidence of any-grade hepatic-related AEs ranges from 0.5–24.4% for anti-CTLA-4 monotherapy, compared to 0.3–14.1% for anti-PD-1 and 0.29–9.2% for anti-PD-L1 monotherapy.[65] Additionally, there was a higher incidence of grade 3/4 IMH in patients receiving anti-CTLA-4 therapy (0.5–12.2%) or anti-PD-L1 (0.3–10.6%) compared with anti-PD-1 (0.3–1.8%). This is further supported by a meta-analysis from Wang *et al*., which confirmed that both CTLA-4 (OR: 5.01, $p < 0.00001$) and PD-1 inhibitors (OR: 1.94, $p < 0.00001$) significantly increase IMH risk compared to control groups, with CTLA-4 inhibitors conferring a substantially higher risk.[62] Furthermore, dual ICI combination therapy, specifically anti-CTLA-4 and anti-PD-1, has been associated with a higher risk of all-grade and grade 3/4 IMH compared to monotherapy in extensive research.[11,20,39–42] For example, two meta-analyses conducted in 2022 and 2024, respectively, have consistently confirmed that the combination of dual ICIs was significantly associated with an increased risk of any-grade IMH.[41,42] Therefore, it is essential to be vigilant about liver function abnormalities and closely monitor hepatic irAEs in patients receiving CTLA-4 inhibitors or combined dual ICI treatment.

The dosage of ICIs, particularly anti-CTLA-4 agents, is a critical determinant of IMH risk. A large randomized, double-blind, multicenter study by Wolchok *et al*. established a clear dose-dependent effect for ipilimumab in patients with advanced melanoma, with severe IMH being more frequent at 10 mg/kg than at 3 mg/kg (30% vs. 0%).[51] This pattern has been consistently outlined in subsequent reviews, which demonstrated that patients receiving a higher dose of ipilimumab at 10 mg/kg had a higher risk of any-grade and severe grade 3/4 IMH compared with the standard dose of 3 mg/kg.[65] In contrast, the incidence of IMH does not appear to correlate with the dosage of anti-PD-1 or anti-PD-L1 therapies. Moreover, prior ICI treatment was also an independent risk factor for IMH in several studies, which may be due to the cumulative effects of ICIs.[41,42]

Combination with other drugs: In recent years, ICIs have been increasingly used in combination with chemotherapy or targeted therapy to enhance antitumor efficacy. However, these regimens can lead to excessive hepatocyte destruction, thereby increasing the risk of IMH. A meta-analysis of 11 clinical trials including 7,086 patients demonstrated that combining ICIs with chemotherapy had a significantly higher risk of all-grade hepatic AEs than ICI monotherapy.[66] Similarly, the concurrent use of ICIs and targeted agents also elevates hepatotoxicity risk. In the CheckMate 016 study, Amin *et al*. observed an elevated risk of all-grade and grade 3 hepatotoxicity in renal cell carcinoma patients treated with nivolumab combined with sunitinib (39.4%, 18.2%) or pazopanib (25%, 20%).[67] Schoenfeld *et al*. further identified that among 126 EGFR-mutant NSCLC patients treated with PD-(L)1 blockade and EGFR-tyrosine kinase inhibitors, osimertinib was associated with severe hepatotoxicity, particularly in those with recent prior ICI exposure.[68] Recently, a similar pattern was found with the KRAS inhibitor sotorasib, which exhibits minimal direct hepatotoxicity, leading to high rates of hepatotoxicity in patients with prior exposure to anti-PD-1 treatments.[52] The exact mechanisms underlying hepatotoxicity from combining chemotherapy or targeted drugs with ICIs remain unclear, but may involve disruptions to hepatic metabolic processes or unrecognized immunomodulatory effects.

Importantly, even concomitant use of directly hepatotoxic medications may act as cofactors for IMH. A retrospective two-center study found that acetaminophen and statins were independent risk factors in the development of IMH, with acetaminophen associated with a 2.1-fold increased risk of all-grade IMH and statins linked to a 4.7-fold increase in the risk of grade 3 or higher IMH.[43] Collectively, these findings highlight that combination strategies and sequential treatments involving ICIs can predispose patients to IMH, necessitating vigilant monitoring of liver function and careful assessment of concomitant medications throughout the treatment course.

Predictive biomarkers for IMH

While the risk factors outlined above provide a clinical foundation for identifying high-risk populations susceptible to

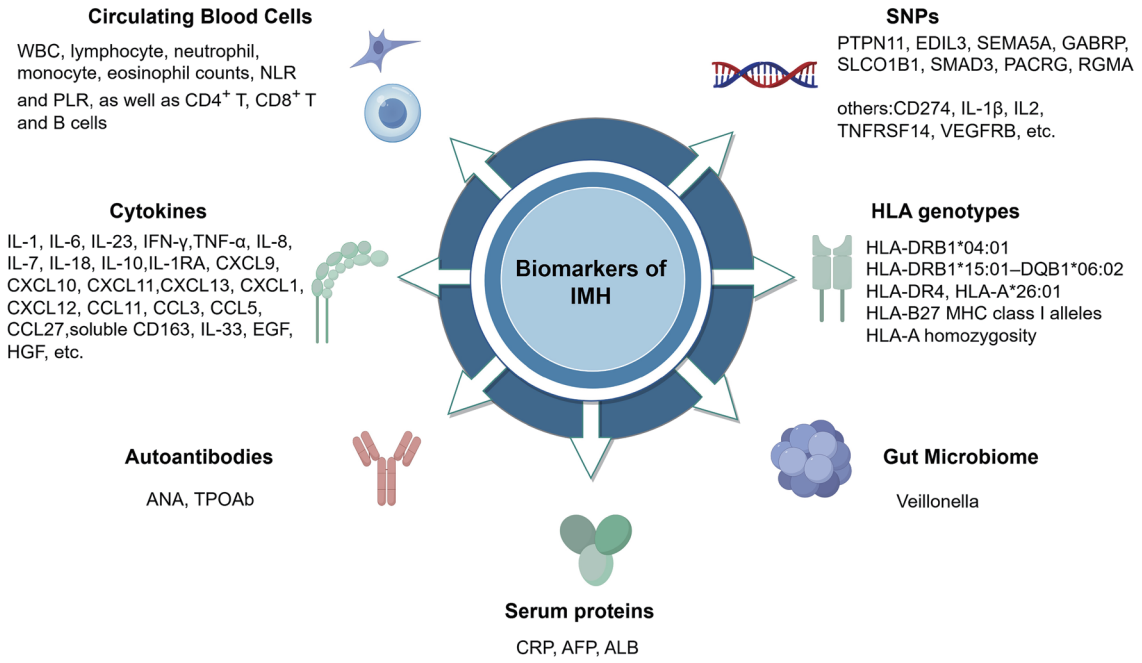

Fig. 2. The potential biomarkers of ICI-mediated hepatotoxicity. The biomarkers of IMH include blood cells, serum proteins, autoantibodies, cytokines, genetic profiles, and the gut microbiome. Created with Figdraw 2.0. WBC, white blood cell count; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; CRP, C-reactive protein; AFP, alpha-fetoprotein; ALB, albumin; ANA, antinuclear antibodies; TPOAb, thyroid peroxidase antibodies; IL, interleukin; IFN-γ, interferon-gamma; TNF-α, tumor necrosis factor-α; CXCL, C-X-C motif chemokine ligand; CCL, C-C motif chemokine ligand; EGF, epidermal growth factor; FGF, fibroblast growth factor; SNPs, single nucleotide polymorphisms; EDIL3, epidermal growth factor-like repeats and discoidin I-like domains 3; SEMA5A, semaphorin 5A; SMAD3, SMAD family member 3; GABRP, gamma-aminobutyric acid type A receptor subunit Pi; PACRG, parkin co-regulated gene protein; RGMA, repulsive guidance molecule BMP co-receptor A; SLCO1B1, solute carrier organic anion transporter family member 1B1; TNFRSF14, TNF receptor superfamily member 14; VEGFB, vascular endothelial growth factor B; HLA, human leukocyte antigen.

IMH, they often lack the sensitivity and specificity required for individualized risk prediction. To advance toward personalized immunotherapy management, there is an urgent need for reliable biomarkers capable of accurately forecasting IMH prior to its clinical onset. The development of such biomarkers would facilitate earlier detection, enable timely intervention, and ultimately enhance both the safety and efficacy of ICI therapy.

The current diagnosis of IMH primarily relies on a combination of clinical presentation, temporal association with ICI administration, abnormal liver function tests, and exclusion of other potential causes.[18,19] Liver biopsy, while considered the diagnostic gold standard, is invasive, prone to sampling variability, and unsuitable for repeated assessments. Therefore, the development of sensitive, specific, and minimally invasive biomarkers is of paramount importance. While several studies have explored potential biomarkers for predicting irAEs during ICI treatment, this section focuses on synthesizing the current evidence on promising biomarkers specifically associated with IMH, including circulating blood cell profiles, autoantibodies, cytokines, genetic and human leukocyte antigen (HLA) markers, and the gut microbiome, as illustrated in Figure 2.

Circulating blood cell-based biomarkers

Blood cell counts and ratios are attractive biomarkers due to their routine availability, low cost, and straightforward interpretation. While evidence suggests that some cellular predictors, including monocyte and eosinophil counts, lymphocytes, white blood cell (WBC) counts, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio, have emerged as potential biomarkers for IMH,[19,23,25,38,50,65] their predictive value for IMH remains inconsistent across studies, as shown in Table 3.[23,30,39,40,45,49,69–76]

Studies evaluating pre-treatment cellular counts have yielded divergent results. A prospective study in 95 melanoma patients identified a higher absolute monocyte count at ICI initiation as significantly increasing IMH risk, with no correlation found for neutrophil, lymphocyte, or eosinophil counts.[23] In contrast, a larger retrospective analysis of 533 patients treated with ICIs for various malignancies established a baseline eosinophil count ≥130/μL (HR = 3.01 for <130; p = 0.012) as an independent risk factor for grade ≥2 IMH.[69] Another study of 1,086 patients further reported a significant association between higher baseline lymphocyte counts and IMH, particularly in hepatocellular-injury-type cases.[49] These discrepancies likely arise from differences in population characteristics, study design, and methodology. Variations in cancer types, for instance, the distinct tumor immune microenvironment in melanoma compared to other solid tumors, may alter baseline immune profiles and their interaction with ICIs. Inconsistent diagnostic criteria and grading for IMH, along with variable definitions of "elevated" cell counts, hinder direct comparison of effect estimates. Furthermore, these studies relied solely on pre-treatment baseline counts, ignoring the potential predictive value of on-treatment dynamic changes in immune cells. This underscores that single baseline cell counts are unlikely to serve as reliable biomarkers for IMH prediction.

The predictive utility of baseline cell ratios, particularly the NLR, has been studied with conflicting conclusions. A meta-analysis of 1,096 patients on ICIs revealed that low NLR (<3) (OR = 2.63, 95% CI 1.63 to 4.26, p < 0.001) was significantly linked to any-grade irAEs, including IMH.[77] This association

Table 3. Potential blood cell-based biomarkers for predicting IMH

Potential biomarker	Study design	N	Cancer type	Timing of measurement	Association	Significance	References
Circulating blood cell							
Absolute monocyte counts (AMCs)	Prospective	95	Melanoma	Before ICI treatment	Elevated AMCs were associated with IMH	$p < 0.0005$	Wolffer *et al.*[23]
Absolute eosinophil count (AEC)	Retrospective	533	Solid tumors	Before ICI treatment	AEC ≥130/μL was associated with high risk of grade ≥ 2 IMH	HR = 3.01; 95% CI: 1.27–7.12; $p = 0.012$	Yoshikawa *et al.*[69]
Absolute lymphocyte count (ALC)	Retrospective	1,096	Solid tumors	Before ICI treatment	Higher ALCs were associated with risk for IMH	$p = 0.040$	Miah *et al.*[39]
	Retrospective	1,086	Solid tumors	Before ICI treatment	Higher ALCs were associated with risk for IMH	HR = 1; 95% CI: 1.000–1.001; $p = 0.013$	Kawano *et al.*[49]
Lymphocyte (%)	Retrospective	226	Solid tumors	Before ICI treatment and post-treatment	Significantly lower percentage change in lymphocyte count was associated with grade 3 IMH	$p < 0.05$	Haraguchi *et al.*[72]
Neutrophil count, Neutrophil to lymphocyte Ratio (NLR)	Retrospective	432	Melanoma Renal cancer	Before ICI treatment	Low absolute neutrophil counts and NLR were associated with high risk of IMH	$p < 0.05$	Atallah *et al.*[40]
NLR	Retrospective	1,096	Solid tumors	Before ICI treatment	Low NLR was associated with high risk of IMH	$p = 0.048$	Miah *et al.*[39]
	Meta-analysis	10,344	Solid tumors	Before ICI treatment	Higher NLR was associated with a reduced risk of IMH	HR = 0.89; 95% CI 0.82–0.96; $p = 0.002$	Madiar *et al.*[45]
	Retrospective	249	HCC	Before ICI treatment	NLR ≥3.0 was associated with high risk of any grade and grade ≥3 IMH	Any grade, $p = 0.017$; grade ≥3, $p = 0.008$	Tada *et al.*[70]
	Meta-analysis	11,491	Solid tumors	Before ICI treatment	Higher NLR was associated with an increased risk of IMH	OR = 2.44; 95% CI 1.23–4.84; $p = 0.010$	Zhang *et al.*[71]
WBC, Platelet-to-lymphocyte ratio (PLR)	Retrospective	274	NSCLC	Before ICI treatment and post-treatment	Low baseline WBC ($\leq 11.0\times10^9$/L) was an independent predictor for IMH development, and elevated WBC and PLR were associated with grade 3/4 IMH	$p < 0.05$	Yang *et al.*[73]
Cell surface markers							
$CD4^+$ T and B	Retrospective	68	HCC	Before ICI treatment and post-treatment	Patients who experienced grade3/4 IMH had a lower decrease in the levels of $CD4^+$ T lymphocytes and B lymphocytes upon irAE onset	$p < 0.05$	Yu *et al.*[74]
$CD8^+$ T cell	Cohort	20	Melanoma	Before ICI treatment and post-treatment	Increased frequency of EMRA $CD8^+$ T cells before and after dual ICI initiation, and $Ki67^+CD8^+$ T cells after starting the dual ICI treatment, was associated with severe IMH	$p < 0.05$ or $p < 0.01$	Muller *et al.*[75]
	Prospective	48	Melanoma	Before ICI treatment and post-treatment	IMH is associated with an activation of peripheral monocytes and enhanced effector phenotype of $CD8^+$ T cells	$p < 0.05$ or $p < 0.01$	Gudd *et al.*[30]
Ki-67^+ regulatory T cells	Prospective	144	Melanoma NSCLC	Before ICI treatment and post-treatment	An early expansion of Ki-67^+ regulatory T cells was associated with increased risk of IMH in melanoma patients	$p < 0.05$	Nunez *et al.*[76]

IMH, immune-mediated hepatotoxicity; AMC, absolute monocyte count; AEC, absolute eosinophil count; ALC, absolute lymphocyte count; NLR, neutrophil-to-lymphocyte ratio; WBC, white blood cell; PLR, platelet-to-lymphocyte ratio; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; HR, hazard ratio; OR, odds ratio; 95% CI, 95% confidence interval.

between lower baseline NLR and IMH development was also observed in two larger retrospective studies, though multivariable analysis was not performed or did not establish NLR as an independent predictor.[39,40] Conversely, studies focused on HCC populations consistently reported opposite findings. A multicenter study by Tada *et al*. indicated that higher baseline NLR (≥3.0) was associated with an increased risk of any-grade and grade ≥3 IMH in patients with unresectable HCC treated with atezolizumab plus bevacizumab.[70] Similarly, another large meta-analysis of 11,491 cancer patients found that high NLR (>5) was specifically correlated with a higher incidence of IMH.[71] This discrepancy may stem from constitutively elevated baseline NLR in HCC patients with chronic liver inflammation and cirrhosis, the lack of a standardized NLR cutoff value, and differences in ICI regimens, which may fundamentally alter the immunological context and subsequent irAE profiles.

Beyond baseline values, on-treatment hematological dynamics may provide crucial predictive insights. Haraguchi *et al*. compared lymphocyte counts before treatment and at the onset of irAEs, reporting a markedly lower percentage reduction in lymphocyte counts from baseline to irAE onset in patients with grade 3 IMH, coinciding with a significant rise in NLR.[72] This suggests that dynamic changes in cellular biomarkers better reflect evolving immune dysregulation. A retrospective cohort of 274 NSCLC patients receiving ICIs demonstrated that low baseline WBC (≤11.0 × 10^9/L) (p < 0.001) and high albumin (≥35 g/L) (p < 0.001) were independent predictors for IMH development, and elevated WBC (p = 0.003) and platelet-to-lymphocyte ratio (p = 0.017) were associated with grade 3/4 IMH compared to those with grade 1/2 events.[73] This indicates that although lower baseline inflammatory status may predispose to IMH, severe cases are characterized by exaggerated post-treatment immune activation. Therefore, it is imperative to observe the dynamics of these markers for IMH development in future prospective research.

T and B lymphocyte subsets have emerged as potential biomarkers for IMH severity. In a retrospective study of 67 HCC patients treated with ICIs combined with tyrosine kinase inhibitors, Yu *et al*. found that the baseline levels of lymphocyte subsets did not differ between AE and non-AE groups; however, upon irAE onset, $CD4^+$ T lymphocyte, $CD8^+$ T lymphocyte, and B lymphocyte counts decreased (p < 0.05), and the decrease in $CD4^+$ T and B lymphocyte levels was significantly greater in patients with grade 3/4 IMH compared to those with milder events (p < 0.05).[74] A small cohort study by Gudd *et al*. reported that IMH patients exhibited activated peripheral monocytes and an enhanced effector phenotype of $CD8^+$ T cells.[30] Another two-cohort study of melanoma patients receiving PD-1 blocking monotherapy or dual ICI therapy noted an increased frequency of EMRA $CD8^+$ T cells before and after dual ICI initiation, as well as a rise in $Ki67^+CD8^+$ T cells post-treatment, which could predict severe irAEs, including IMH.[75] Additionally, early expansion of Ki-67^+ Treg cells was significantly correlated with IMH risk in melanoma patients.[76]

In summary, circulating blood cells may represent accessible tools for IMH prediction, but their implementation requires consideration of tumor type, baseline liver condition, and treatment regimen. The transition from baseline to dynamic on-treatment changes of these markers offers a promising direction for IMH. Future research should focus on standardizing measurements, validating findings in large prospective cohorts, and integrating these cellular biomarkers into multi-factor prediction models to optimize their clinical utility in managing IMH.

Serum proteins

Beyond cellular biomarkers, some serum proteins have emerged as biomarkers for IMH, offering insights into the underlying inflammatory processes and tissue damage. C-reactive protein (CRP), an acute-phase protein, has been found to correlate with the risk of IMH. A retrospective study revealed that levels of CRP were significantly higher in patients experiencing grade 3/4 IMH upon irAE onset, with CRP ≥ 8.2 mg/L identified as a potential independent predictor for IMH development; when patients recovered, elevated levels of CRP returned to baseline.[74] Alpha-fetoprotein (AFP), traditionally a tumor marker, has also been utilized to evaluate liver damage associated with ICIs. A multicenter retrospective study examined the CRAFITY score, a combination of CRP and AFP, in HCC patients treated with atezolizumab and bevacizumab.[78] The scoring system assigned 0 points for AFP <100 ng/mL and CRP <10 mg/L, 1 point for either AFP ≥ 100 ng/mL or CRP ≥ 10 mg/L, and 2 points for both AFP ≥ 100 ng/mL and CRP ≥ 10 mg/L. Patients with a CRAFITY score of 2 had a significantly higher incidence of grade ≥3 IMH compared to those with scores of 0 or 1. Additionally, a recent retrospective study reported that low serum albumin, indicative of systemic inflammation, was also linked to higher IMH incidence.[79] Reduced drug binding to plasma proteins due to lower albumin levels leads to slower drug elimination and a longer half-life, consequently increasing the body's exposure to toxicity.

However, these serum proteins, particularly CRP and albumin, are susceptible to interference from non-IMH factors, reducing their specificity for IMH prediction. Future large-scale, multicenter prospective studies are warranted to validate the predictive value of these markers across various cancer types and ICI regimens. Moreover, exploring their dynamic changes in IMH and integrating them with other biomarkers could improve predictive accuracy.

Autoantibodies

Autoantibodies represent one of the most extensively investigated predictive biomarkers for irAEs. Pre-existing autoantibodies, including antinuclear antibodies (ANA), rheumatoid factor, and antithyroid antibodies, have been associated with increased incidence and severity of organ-specific irAEs following ICI treatment.[80,81] This has prompted investigation into their potential role as biomarkers for predicting or diagnosing IMH.

Several studies demonstrate correlations between baseline autoantibody profiles and subsequent IMH development. A retrospective study of 252 NSCLC patients identified ANA positivity as a significant predictor for IMH.[82] Notably, the predictive strength varied substantially between different ICI agents, with a markedly higher odds ratio observed for pembrolizumab (OR = 7.834) than for nivolumab (OR = 2.133). This suggests that the predictive value of autoantibodies may be significantly influenced by the specific ICI regimen. Similarly, Ghosh *et al*. reported differential ANA positivity rates between IMH subtypes, with 18% (15/85) in hepatitis-pattern injury and 42% (5/12) in cholangitic-pattern injury, suggesting potential phenotypic variation in autoantibody associations.[83] The spectrum of relevant autoantibodies may also extend beyond classical targets, as evidenced by Zheng *et al*., who identified thyroid peroxidase antibodies as a prognostic biomarker for liver injury in patients treated with sintilimab.[79] The underlying mechanisms linking these antibodies to IMH remain unclear. One hypothesis is that PD-1 expression is regulated through both T cell-independent and T cell-dependent pathways, resulting in high levels on

activated B cells, facilitating autoantibody production upon PD-1/PD-L1 blockade, thereby contributing to an increased incidence of IMH.

Conversely, some studies have failed to demonstrate significant associations between liver-specific autoantibodies and IMH development.[84] A prospective cohort study of 131 patients specifically found no correlation between IMH development and various autoantibodies, including ANA, anti-smooth muscle antibody, anti-mitochondrial antibody, and anti-liver-kidney microsomal antibodies, suggesting that liver autoantibodies may not serve as reliable predictors for IMH.[85] This further implies that patients with pre-existing liver autoantibodies do not exhibit an elevated risk of IMH during ICI therapy.

Overall, evidence on autoantibodies predicting IMH risk is inconsistent and limited, making them seem unreliable as predictors for IMH when used alone. Future research should prioritize the validation of defined autoantibody panels in large prospective cohorts and explore their integration with other biomarker classes to develop composite risk scores.

Cytokines

Cytokines, as central mediators of immune activation and inflammation, have emerged as promising biomarkers for predicting irAEs.[86] Given that the pathogenesis of IMH is closely related to T cell activation and inflammatory cytokines, changes in cytokine levels may serve as a valuable tool for IMH prediction.

Several pro-inflammatory cytokines have been implicated in IMH development. Among these, the IL-1 family, particularly IL-1β, acts as a central driver of liver inflammation by regulating networks of pro-inflammatory cytokine and immune-regulatory gene expression.[87] Elevated IL-1β RNA expression has been observed in patients with grade ≥3 IMH compared to those without irAEs, underscoring its potential as a susceptibility biomarker for IMH occurrence.[88] Similarly, IL-6, another pivotal cytokine, demonstrates significant associations with organ-specific irAEs, including IMH. While baseline IL-6 levels did not differ significantly between irAE and non-irAE groups, a marked rise in IL-6 was observed upon irAE onset. Specifically, HCC patients experiencing grade 3/4 IMH exhibited a more pronounced increase in IL-6 compared to those with grade 1/2 AEs, and IL-6 levels subsequently returned to baseline following resolution of hepatitis.[74] Another small cohort also found that IL-6 levels after irAEs were significantly higher compared with before.[89] This suggests that IL-6 may be a more reliable marker of active, severe inflammation than a baseline predictor, warranting further validation in large-scale cohorts. Furthermore, IL-23, a key regulator of Th17 cell differentiation, has also been linked to severe irAEs, and its blockade ameliorates liver inflammation in preclinical models, positioning it as a compelling IMH biomarker and therapeutic target.[90]

Currently, the limitations of single-cytokine measurements have prompted a shift towards combining multiple cytokine and chemokine panels, which could enhance the accuracy of irAE prediction. Lim *et al*. investigated circulating cytokines in 98 patients with melanoma using the 65-plex cytokine discovery assay, identifying that elevated baseline and early-treatment levels of 11 cytokines (G-CSF, GM-CSF, Fractalkine, FGF-2, IFN-α2, IL-12p70, IL-1α, IL-1β, IL-1RA, IL-2, and IL-13) were significantly associated with severe irAEs, including IMH.[91] The CYTOX score, which integrated these 11 cytokines, could help in the early management of severe, potentially life-threatening immune-related toxicity. In a separate report, Moi *et al*. reported high baseline levels of pro-inflammatory cytokines (e.g., IFN-γ, IL-6, CXCL9, CXCL10, CXCL11, CXCL13) and anti-inflammatory cytokines (e.g., IL-10, IL-1RA) in three consecutive patients with IMH, although these findings require validation in larger cohorts.[92] Recently, Farooqi *et al*. also noted that high baseline CXCL10 and increased TNF-α during treatment were linked to IMH risk, while elevated CCL27 levels at baseline and during treatment may reduce IMH risk, suggesting a protective role, further illustrating the complexity of the cytokine network.[93]

The timing of biomarker measurement is paramount, as cytokine levels can exhibit significant fluctuations during treatment. Zeng *et al*. analyzed plasma cytokine profiles at three key time points: baseline, IMH onset (IMH-D1), and seven days post-onset (IMH-D7).[88] They found that 12 pro-inflammatory cytokines, namely CCL11, CCL4, CXCL1, CXCL10, CXCL12, IFN-γ, IL-10RA, IL-18, IL-1α, IL-1β, IL-7, and IL-8, were significantly lower at baseline in the ≥G3 IMH group than in the non-irAE group. Interestingly, higher IL-1α levels at IMH onset were associated with resolution of grade ≥3 IMH in the subgroup, while elevated levels of nine cytokines (including CCL11, CCL3, CCL5, CXCL1, CXCL12, IL-10RA, IL-18, IL-7, and TNF-α) at IMH-D7 were linked to IMH-related mortality.[88] Recently, another prospective study of 134 solid tumor patients receiving PD-(L)1 inhibitors identified that the highest levels of CXCL9, CXCL10, CXCL11, IL-18, and IL-10 were observed at the onset of IMH, with no baseline differences between groups.[94] Notably, cytokine levels tended to be higher in severe IMH compared to mild irAEs and those without irAEs; however, this difference did not reach statistical significance due to an insufficient sample size. This underscores that cytokine profiles are not static; longitudinal monitoring is essential to capture their predictive and prognostic value. Future studies should employ standardized detection methods to evaluate dynamic changes in multiple cytokines across different time points in large-scale populations, thereby identifying which cytokines are most suitable for predicting the occurrence of IMH.

Other cytokines/chemokines may also predict IMH risk. For instance, elevated serum levels of soluble CD163 (sCD163) have been observed in IMH patients, suggesting the CD163/sCD163 axis as a potential biomarker.[30] Additionally, molecules implicated in DILI, such as IL-33, growth factors (EGF, HGF), metalloproteinases, tissue inhibitors of metalloproteinases, and damage-associated molecular patterns, may hold potential as IMH biomarkers given the pathological similarities between these conditions.[95] Large prospective cohorts will be needed to develop and validate multi-omics models that combine cytokine profiles with clinical and immunophenotypic data to improve IMH prediction and mechanistic insight.

Genetic and HLA markers

Genetic predisposition, particularly single-nucleotide polymorphisms (SNPs) in immune-associated genes and HLA profiles, is increasingly recognized as a determinant of IMH. Recent research has highlighted the role of SNPs and HLA in predicting IMH occurrence, as shown in Table 4.[23,85,96–101]

A retrospective study of 322 nivolumab-treated patients assessed the association with irAEs for seven specific SNPs in PDCD1, PTPN11, ZAP70, and IFNG genes via TaqMan allelic discrimination assays.[96] Specifically, PTPN11 333–223A>G was associated with an increased risk of IMH in the exploration cohort; however, this association was not replicated in a validation cohort, highlighting the challenges of population-specific genetic effects and the necessity for large-scale validation. The study by Fontana *et al*. selected candidate gene variants associated with IMH risk in 57 high-causality IMH cases from the Drug-Induced Liver Injury Network.[97] They

Table 4. Gene-related biomarkers for predicting IMH development

Gene-related biomarkers	Study design	N	Cancer type	Timing of measurement	Association	Significance	References
Single-nucleotide polymorphisms (SNPs)							
PTPN11 333–223A>G	Retrospective	322	NSCLC	Before ICI treatment	PTPN11 333–223A>G was associated with an increased risk of IMH in the exploration cohort	OR = 2.42; 95% CI: 1.061–5.523; $p = 0.036$	Bins *et al*.[96]
EDIL3,SEMA5A,GABRP, SLCO1B1,SMAD3	Prospective/ retrospective	57	Melanoma Lung cancer	Before ICI treatment	rs1862167 in EDIL3, rs35719165 in SEMA5A, rs73800947 in GABRP, rs34234515 in SLCO1B1 and rs12913535 in SMAD3 were strongly linked to IMH	OR = 2.08–2.4; $p < 0.01$	Fontana *et al*.[97]
GABRP, PACRG, RGMA	Retrospective	69	Melanoma	Before ICI treatment	GABRP rs11743438, GABRP rs11743735, and PACRG rs55733913 were linked to a higher risk of IMH, while RGMA rs4778080 seemed to protect against this adverse event	OR = 6.16–9.17; $p < 0.05$	Rodriguez-Pinas *et al*.[98]
CD274, SLCO1B1	Prospective	95	Melanoma	Before ICI treatment	CNVs on CD274 and SLCO1B1 were significantly linked to IMH	$p < 0.05$	Wolffer *et al*.[23]
Human leukocyte antigen (HLA) genotypes							
HLA-DRB1*04:01; HLA-DRB1*15:01-DQB1*06:02	Prospective	131	Melanoma NSCLC	Before ICI treatment	HLA-DRB1*04:01 and the haplotype DRB1*15:01–DQB1*06:02 were significantly associated with IMH	$p < 0.05$	Purde *et al*.[85]
HLA-A homozygosity	Prospective	95	Melanoma	Before ICI treatment	HLA-A homozygosity was significantly associated with IMH	$p = 0.015$	Wolffer *et al*.[23]
HLA-DR4	Retrospective	132	Melanoma	Before ICI treatment	HLA-DR4 was significantly associated with IMH	$p < 0.01$	Akturk *et al*.[99]
HLA-A*26:01	Retrospective	530	Solid tumors	Before ICI treatment	HLA-A*26:01 was significantly associated with IMH	OR = 2.67; 95% CI: 0.92–8.31; $p = 0.037$	Jiang *et al*.[100]
HLA-B*27:04	Retrospective	117	Solid tumors/ hematologic malignancies	Before ICI treatment	HLA-B27:04 was associated with grade 3 IMH	$p = 0.007$	Titmuss *et al*.[101]
HLA DR4, HLA-DRB1*15:01-DQB1*06:02	Prospective/ retrospective	57	Melanoma Lung cancer	Before ICI treatment	No association between two HLA alleles and IMH	$p > 0.05$	Fontana *et al*.[97]

IMH, immune-mediated hepatotoxicity; SNPs, single nucleotide polymorphisms; PTPN11, protein tyrosine phosphatase non-receptor type 11; EDIL3, epidermal growth factor-like repeats and discoidin I-like domains 3; SEMA5A, semaphorin 5A; SMAD3, SMAD family member 3; GABRP, gamma-aminobutyric acid type A receptor subunit Pi; PACRG, parkin co-regulated gene protein; RGMA, repulsive guidance molecule BMP co-receptor A; SLCO1B1, solute carrier organic anion transporter family member 1B1; HLA, human leukocyte antigen; NSCLC, non-small cell lung cancer; CNVs, copy number variations; OR, odds ratio; 95% CI, 95% confidence interval.

investigated 25 candidate genes and target SNPs in 5 candidate genes using an Illumina MiSeq platform, finding that rs1862167 in EDIL3, rs35719165 in SEMA5A, rs73800947 in GABRP, rs34234515 in SLCO1B1, and rs12913535 in SMAD3 were strongly linked to IMH compared to population controls. Recently, Rodríguez-Piñas *et al*. conducted a multi-center study to explore tumor SNPs associated with the risk of IMH using a MassARRAY platform.[98] Significant associations were identified between IMH risk and 4 of the 20 SNPs. Three SNPs— GABRP rs11743438, GABRP rs11743735, and PACRG rs55733913—were linked to a higher risk of IMH, whereas RGMA rs4778080 appeared to protect against this adverse event. These findings suggest that SNPs could serve as useful biomarkers to predict IMH risk, requiring confirmation in larger patient cohorts.

Beyond SNPs, other genetic alterations, such as small sequence variations and copy number variations, have been explored as potential biomarkers for IMH. A prospective study by Wolffer *et al*. identified several genes, including SMAD3, PRDM1, IL1RN, CD274, SLCO1B1, TSHR, and FAN1, as being associated with irAEs, particularly organ-specific events.[23] Notably, copy number variations in CD274 (p = 0.043) and SLCO1B1 (p = 0.010) were significantly linked to hepatitis, further underscoring the role of genetic variations in IMH risk. Additionally, specific gene expression profiling has also emerged as a valuable tool for identifying IMH. For example, Zeng *et al*. demonstrated significant upregulation of the IL-1β gene and other inflammation-related genes in tumor samples, such as HLA-C, IL-2, TNFRSF14, and VEGFRB, in patients with grade ≥3 IMH compared to those without irAEs.[88]

HLA profiles have been extensively linked to susceptibility to immune-mediated diseases and cancer.[102] Evidence suggests that specific HLA genotypes are associated with organ-specific irAEs, including IMH. In a prospective cohort study of 131 cancer patients assessing the association between HLA and IMH, Purde *et al*. observed that two HLA alleles, DRB1*04:01 and the haplotype DRB1*15:01–DQB1*06:02, were nominally significantly associated with the risk of IMH development in NSCLC patients.[85] However, this association was absent in the overall patient cohort or after correction for multiple comparisons, highlighting the need for validation in larger studies. Another prospective study by Wolffer *et al*. found that HLA-A class I homozygosity was significantly linked to the occurrence of IMH in melanoma patients.[23] Similarly, Akturk *et al*. conducted a case-control study to evaluate the association between the presence of HLA-DR alleles and irAEs in advanced melanoma patients treated with ICIs and found that HLA-DR4 was significantly associated with IMH.[99] Additionally, a large cohort study involving 530 cancer patients identified several HLA types associated with organ-specific irAEs, including a significant link between HLA-A*26:01 and elevated bilirubin levels.[100] Recently, Titmuss *et al*. analyzed 117 patients who received ICI treatment through the ongoing Personalized OncoGenomics program, reporting that MHC class I alleles in the HLA-B27 family were associated with grade 3 IMH (p = 0.007).[101] Collectively, these findings suggest that pre-treatment HLA profiling could help identify patients at risk for specific irAEs, particularly IMH, following ICI therapy.

However, not all studies have confirmed these associations. For instance, Fontana *et al*. reported no significant associations between the overall HLA DR4 or HLA-DRB1*15:01–DQB1*06:02 haplotype and the occurrence of IMH.[97] This discrepancy may be attributed to several factors, including relatively small sample sizes, heterogeneity in patient cohorts, divergent study methodologies, and lack of comprehensive genome-wide data. To clarify the role of HLA genotypes in IMH development, future studies should involve larger, well-defined cohorts of patients receiving uniform treatment regimens for the same tumor type. Direct comparisons between ICI-treated patients who develop IMH and those who do not will be essential to validate the potential of these genetic variants as predictive biomarkers.

Gut microbiome

The gut microbiome is a key regulator of immune homeostasis, and its composition has emerged as a promising predictor for both the efficacy and toxicity of ICIs.[103] For instance, patients treated with ipilimumab who exhibited a microbiome enriched with *Faecalibacterium* and *Firmicutes* at baseline were found to have a higher risk of ICI-related colitis.[104] However, this specific association between the gut microbiome and IMH has not yet been directly established.

Evidence from other organ systems may provide a rationale for a potential link. The gut-liver axis, for instance, demonstrates how intestinal microbes can influence extra-intestinal immunity. Alterations in the gut microbiome have been implicated in hepatocyte injury and immune-mediated liver dysfunction, such as in autoimmune hepatitis.[105,106] Furthermore, specific microbes, like *Veillonella* (a member of the *Firmicutes phylum*), are frequently enriched in liver diseases and cancers.[107,108] Recently, a study by Ryan *et al*. found a significant correlation between *Veillonella* abundance and the severity of ICI-related hepatotoxicity, suggesting its potential as a microbial biomarker for hepatic irAEs.[109] This mechanistic insight provides a basis for the hypothesis that gut-derived bacterial signals, known to influence systemic inflammation, could also influence the development of IMH. Therefore, future high-quality studies are urgently needed to directly determine whether specific microbial markers can reliably assess IMH risk prior to or during ICI therapy.

Future perspectives

With the increasing use of ICIs in various cancers, IMH has emerged as a significant clinical challenge due to its potential impact on treatment efficacy and patient survival. This review synthesized current evidence on risk factors and potential biomarkers for IMH prediction. While factors such as specific demographic characteristics, pre-existing conditions, particular cancer types, and combination ICI regimens have been associated with increased IMH risk, and various biomarkers, including circulating blood cell counts, autoantibodies, cytokines, and genetic profiles, demonstrate promise in predicting IMH, none of the proposed biomarkers can currently be applied in clinical practice to accurately predict its occurrence.

The current evidence base exhibits significant limitations that hinder clinical application. First, most studies are retrospective and suffer from substantial heterogeneity in patient populations, ICI regimens, and detection methods, leading to inconsistent findings. Second, the underlying mechanisms of IMH remain poorly understood, and inconsistent diagnostic and grading criteria for IMH across different studies hinder the rational selection of biomarkers. Furthermore, existing studies focus on single categories of biomarkers, with a lack of integration of multi-dimensional, cross-omics approaches, thereby limiting the development of robust prediction models. Crucially, while an ideal biomarker should enable both pre-treatment risk stratification and dynamic monitoring during therapy, most studies to date have focused on static pre-treatment assessment. The absence of longitudinal data limits the clinical translation and predictive utility of biomarkers.

It is unlikely that a single risk factor or biomarker will be

specific or sensitive enough to predict irAE development accurately. Given that several mechanisms are involved in IMH, a combination of multiple biomarkers, such as blood cell counts, autoantibodies, cytokine levels, genetic markers, and microbiome, is essential to identify risk stratification and personalize monitoring strategies to prevent the occurrence of IMH. In a retrospective study, Zheng *et al*. developed a clinical risk score to predict immune-mediated liver injury caused by sintilimab; multi-factor prediction models that integrate clinical characteristics, blood cell counts, and liver function tests to predict IMH have also been established.[79,110] Artificial intelligence and machine learning algorithms could be employed to improve the accuracy of predictive models in this setting. Advancements in multi-omics technologies, including genomics, transcriptomics, proteomics, and metabolomics, hold promise for uncovering novel biomarkers and elucidating the molecular mechanisms of irAEs.[111]

To address these gaps, well-designed prospective studies in large, multi-center cohorts are imperative. Future studies should focus on developing and validating prediction models for IMH that integrate multi-omics biomarkers and comprehensive clinical data using artificial intelligence and machine learning. It is also essential to implement longitudinal monitoring of biomarkers from baseline through treatment, onset, and resolution of IMH to capture their dynamic profiles. Standardized protocols for biospecimen collection and uniform detection methods must be established to ensure data comparability across studies. Furthermore, stratified analyses accounting for variables such as tumor type, ICI regimen, and baseline clinical characteristics are necessary to enhance model accuracy and clinical applicability. Additionally, further investigation into the immunopathological mechanisms of IMH should be pursued to identify novel therapeutic targets and strategies, which may simultaneously yield new predictive biomarkers. By leveraging multi-dimensional data through advanced technologies and validating them in large, prospective clinical cohorts, it will be possible to identify high-risk populations before treatment initiation, guide personalized monitoring strategies during therapy, and ultimately reduce the incidence and severity of IMH, thereby enhancing the safety and efficacy of cancer immunotherapy.

Conclusions

In conclusion, this review comprehensively synthesizes the current evidence on IMH risk, identifying established clinical risk factors, including female sex, young age, pre-existing liver disease, specific cancer types, dual ICI therapy, concurrent hepatotoxic drugs, as well as promising biomarkers ranging from circulating immune cells to gut microbiome profiles. However, no biomarker has yet been proven sufficiently reliable for clinical use. These findings highlight a critical translational gap and the insufficiency of current knowledge for prediction. Therefore, future research should prioritize large-scale, prospective, and longitudinal studies to develop validated, integrated multi-dimensional prediction models. This work is essential to enable pre-emptive risk stratification and improve the safety of cancer immunotherapy.

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Conflict of interest

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Author contributions

Study concept and design (ZY, YH, CZ), literature review (ZY, YX, WL), drafting of the manuscript (ZY, YX), critical review, and manuscript revisions (ZY, YX, WL, YH, CZ). All authors have approved the final version and publication of the manuscript.

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