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Review Article

Future Prospects for Pharmacogenomics of Immune Checkpoint Inhibitors Cardiotoxicity

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Abstract
Immune checkpoint inhibitors (ICIs), including PD-1, PD-L1, and CTLA-4 inhibitors, have revolutionized cancer therapy but are associated with immune-related adverse events (IRAEs). Among these, ICI-associated cardiotoxicity is an uncommon yet serious complication, often resistant to glucocorticoid therapy, which effectively manages most IRAEs. A pharmacogenomic approach might be useful in prescribing ICIs and screening for relevant clinically measurable phenotypes such as the history of autoimmune diseases and cardiovascular disorders. This review explores the impact of genetic variations on ICI-associated cardiotoxicity, the mechanistic basis behind it, potential clinical applications, and directions of the future on how pharmacogenomics can assist oncologists in reducing the risk of cardiotoxicity. Evidence-based hypotheses on how ICI-associated cardiotoxicity occurs suggest that genetic differences might play a role in ICI response, especially regarding cardiotoxic IRAEs. Pharmacogenomic studies and multi-omics profiling might provide valuable insight regarding ICI-induced cardiotoxicity. They could be implemented to make fine-tuned clinical decisions for individual patients in the future.

Keywords: cardiotoxic agents, immunotherapy, immune checkpoint inhibitors, myocarditis, pharmacogenomics

Prospek Masa Depan untuk Farmakogenomik Terkait Kardiotoksisitas *Immune Checkpoint Inhibitors*

Abstrak
Inhibitor checkpoint imun (*immune checkpoint inhibitors*/ICIs), termasuk inhibitor PD-1, PD-L1, dan CTLA-4, telah merevolusi terapi kanker, namun diasosiasikan dengan kejadian efek samping terkait imun (*immune-related adverse events*/IRAEs). Salah satu efek samping tersebut adalah kardiotoksisitas terkait ICI. Meskipun jarang terjadi, kardiotoksisitas merupakan komplikasi serius dan sering kali resisten terhadap terapi glukokortikoid, yang umumnya efektif untuk sebagian besar IRAEs. Pendekatan farmakogenomik dapat berguna untuk mengoptimalkan pemberian ICIs selain upaya skrining fenotipe klinis yang relevan seperti riwayat penyakit autoimun dan gangguan kardiovaskular. *Review* ini membahas dampak variasi genetik terhadap kardiotoksisitas terkait ICI, mekanisme yang mendasarinya, potensi aplikasi klinis, serta arah penelitian masa depan tentang bagaimana farmakogenomik dapat membantu ahli onkologi mengurangi risiko kardiotoksisitas. Hipotesis berbasis bukti menunjukkan bahwa variasi genetik dapat memengaruhi respons terhadap ICI, khususnya terkait kardiotoksiksitas. Studi farmakogenomik dan profil multiomik dapat memberikan wawasan penting terkait kardiotoksisitas yang diinduksi oleh ICI, yang nantinya dapat digunakan untuk pengambilan keputusan klinis yang lebih presisi bagi pasien secara individual.

Kata Kunci: agen kardiotoksik, imunoterapi, *immune checkpoint inhibitors*, miokarditis, farmakogenomik

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Introduction

To this day, cancer presents a major global health problem. The World Health Organization (WHO) states that cancer is a leading cause of death worldwide, with a death toll of about 9.6 million deaths in 2018. This accounts for 13% of all deaths worldwide, rendering cancer the second leading cause of death globally, behind cardiovascular diseases.[1] Furthermore, the incidence of cancer is increasing worldwide, particularly in low- and middle-income countries. According to the WHO, the number of new cases of cancer is expected to rise from an estimated 18.[1] million in 2018 to 29.5 million by 2040. In addition to that, cancer treatment can pose a significant financial burden and is therefore inaccessible to certain demographics of people.

The data mentioned above has partly made research on cancer management one of the top priorities in the healthcare sector, particularly in the discovery and development of better cancer therapeutics. Indeed, significant gaps in currently existing cancer therapeutics still exist. Many cancer treatments are associated with significant side effects owing to their lack of specificity in targeting cancer cells. In addition, despite the array of treatment choices currently present, many types of cancer are still challenging to treat effectively. For example, pancreatic cancer and glioblastoma—a type of brain cancer—have five-year survival rates of just 11% and 5%, respectively.[2,3]

Cancer is a notorious group of diseases characterized by uncontrollable cell growth and division. In cancer patients, abnormal cells defy the rules governing cell biology and proliferate excessively. These abnormal cells are capable of invading nearby tissues, even migrating to sites far away via the circulatory and lymphatic systems in a process known as metastasis. At its core, cancerous cells strive to survive selfishly on their own, at the cost of the individual who hosts them.[4] These characteristics of cancer are summarized in a well-known concept among oncologists termed the "Hallmarks of Cancer," which includes sustained proliferative signaling, evasion of growth suppressors, resistance towards cell death, replicative immortality, access towards vasculature, invasion and metastasis, reprogrammed cellular metabolism, and immune evasion.[5]

To continuously improve existing cancer therapies and discover novel ones, researchers and clinicians have begun looking into harnessing the immune system's power in battling cancer. This approach is known as cancer immunotherapy. One of the most straightforward strategies in immunotherapy involves the administration of monoclonal antibodies—protein molecules that aid the immune system in recognizing specific antigens. The term monoclonal refers to its specificity in targeting only one epitope or one site within an antigen to which the antibody binds. These monoclonal antibodies are manufactured to target specific proteins that play a role in the signaling pathway that drives cancer progression in hopes of halting cancerous growth.[6]

Generally, monoclonal antibodies can be administered naked—without any enhancements—or conjugated to a particular drug. Naked monoclonal antibodies exert their anticancer mechanisms by employing four basic strategies: 1) stimulating the immune system's response to cancer cells by binding to cancer-associated antigens, or antigens found on the cancer cell's surface; 2) enhancing the anticancer immune response by binding to, and therefore blocking, specific immune-checkpoint proteins which negatively regulate the activity of cytotoxic immune cells; and 3) binding to growth factor receptors on the surface of cancer cells, thereby blocking the signaling pathway

orchestrated by them.[6]

The second approach mentioned above involves using monoclonal antibodies known as immune checkpoint inhibitors (ICIs), such as PD-1 inhibitors, PD-L1 inhibitors, and CTLA-4 inhibitors. PD-1 (programmed cell death protein-1), PD-L1 (programmed death-ligand 1), and CTLA-4 (cytotoxic T-lymphocyte-associated antigen 4) are proteins present on the surface of cytotoxic T cells, which act like brake switches. When bound to their respective ligands, CTLA-4 (ipilimumab), PD-L1 (atezolizumab, avelumab, durvalumab), and PD-1 (nivolumab, pembrolizumab) pull the brakes on the cytotoxic immune response exerted by these T cells, enabling immunosuppression.[7,8] The mechanisms by which these proteins mediate immunosuppression are distinct, yet they both result in the same outcome.

The approach involving the blockade of these two proteins delivered the 2018 Nobel Prize in Physiology and Medicine to its pioneers, James P. Allison and Tasuku Honjo, and has since been deemed a promising strategy in cancer treatment.[9] Indeed, ipilimumab, a CTLA-4 inhibitor, has been documented to double rates of 10-year survival in metastatic melanoma.10 In addition, PD-1 and PDL-1 inhibitors have shown significant clinical impact in several types of cancers, including melanoma, non-small cell lung cancer, bladder cancer, ovarian cancer, and colorectal cancer.[9]

Despite having revolutionized cancer therapy, ICIs have been associated with a range of side effects known as immune-related adverse events (IRAEs), which occur when the immune system becomes overactive and attacks normal cells in the recipient's body involving the gastrointestinal system, skin, endocrine system, liver, and lung.[11] These autoimmune toxicities are more common when a single or dual ICI is administered along with another chemotherapy, especially cardiotoxic cancer medication.[8,12] ICI-associated cardiotoxicity has emerged as an uncommon but serious adverse event that may be resistant to glucocorticoids, in contrast to the majority of IRAEs, which are reversible and can be adequately treated with glucocorticoid therapy.[13]

This review explores the ICI-associated with cardiotoxicity, impact of genetic variations on ICI-associated cardiotoxicity, potential clinical applications, and future directions on how pharmacogenomics can assist oncologists in reducing the risk of cardiotoxicity.

Methods

The article search focused on studies on the pharmacogenomics of drugs belonging to ICI. The inclusion criteria included any type of article that matched the keywords and was published in English. The exclusion criteria were articles whose full text could not be accessed. The initial search was conducted on PubMed and Scopus using the following combination of keywords: ((pharmacogenomics[MeSH Terms]) OR (pharmacogenetics[MeSH Terms])) AND (((((immunotherapies[MeSH Terms]) OR (immune checkpoint inhibitors)) OR (PD-1 inhibitors)) OR (PD-L1 inhibitors)) OR (CTLA-4 inhibitors)). The initial search yielded 87 articles. Each manuscript was then reviewed to assess its relevance to ICI-associated cardiotoxicity. An additional search was performed using the following combination of keywords: pharmacogenomics, pharmacogenetics, toxicity, cardiotoxicity, cardiomyopathy, myocarditis ICI, immune checkpoint inhibitors, PD-1 inhibitors, PD-L1 inhibitors, CTLA-4 inhibitors, ipilimumab, atezolizumab, avelumab, durvalumab, nivolumab, and pembrolizumab. Ultimately, 27 articles were identified for further

discussion.

Immune Checkpoint Inhibitors (ICI) Associated with Cardiotoxicity

Immune checkpoint inhibitors (ICI) associated with cardiotoxicity encompass several conditions, including pericarditis, myocarditis, and arrhythmias.[9] According to a large case series, the manifestations can vary, including heart failure, cardiomyopathy, heart block, myocardial fibrosis, and myocarditis.[14] Amongst these cardiac conditions, myocarditis appears to be the most common case, accounting for 14.1% of all documented cardiac IRAE individual cases.[15]

Granted, these adverse effects are quite rare. Studies looking into databases for individual cases of IRAEs found that only 0.09% of patients who received ICIs developed reported cases of myocarditis.[15] A recent pharmacovigilance study using the World Health Organization's VigiAccess database found 4.2% of cardiac disorders, including myocarditis, for anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapies.[16] Nevertheless, these rare cases present a high mortality burden in those afflicted—ranging from 25% to 50% of patients presented with cardiac IRAEs.[16,17]

Distinguishing ICI-related cardiotoxicity from other IRAEs or unrelated cardiac conditions necessitates a comprehensive diagnostic approach that combines clinical evaluation, specialized testing, and occasionally tissue biopsy.[18] ICI-associated cardiotoxicity often manifests as myocarditis, heart failure, arrhythmias, or acute coronary syndromes, which can overlap with symptoms of other cardiac events. In contrast, general IRAEs frequently affect other organ systems, such as the skin, gastrointestinal tract, or endocrine glands, and are typically reversible with glucocorticoid therapy. Diagnostic workup for suspected ICI-induced cardiotoxicity includes cardiac biomarkers like troponin and brain natriuretic peptides (BNP or NT-proBNP), electrocardiography (ECG) to assess electrical activity, and echocardiography to evaluate cardiac structure and function. This multidimensional approach ensures accurate differentiation and guides timely intervention, reducing the risk of severe outcomes.

The latest population-based study reported that the incidence of cardiotoxicity among patients treated with ipilimumab, nivolumab, pembrolizumab, cemiplimab, avelumab, atezolizumab, or durvalumab is 12.5% within one year after initiation of ICIs, where 9.3% of adverse events manifested as arrhythmia and 2.1% manifested as myocarditis. This study also added that ipilimumab and pembrolizumab pose a higher risk of cardiotoxicity toward recipients compared to other agents.[19] A systematic review from 50 trials also revealed that PD-1/PD-L1 inhibitors combined with chemotherapy increased the risk of all-grade and grade 3-5 cardiotoxicity, while single-agent PD-1/PD-L1 inhibitors increased the risk of all-grade cardiotoxicity, particularly in patients treated with PD-1 inhibitor-containing therapy and those with non-small cell lung cancer.[12] Though when comparing singular ICI therapy to multiple ICI therapy, there was no significant increase in the risk of cardiotoxicity, compared to singular ICI therapy to ICI therapy, with an additional chemotherapy.[20]

In general, reduced peripheral tolerance to the heart and/or potentiation of T lymphocytes targeting an antigen shared by both the heart and the tumor are two proposed pathways for ICI cardiotoxicity.[13] Narrowing down the path, ICI-associated cardiotoxicity can be explained by three hypotheses. The first hypothesis states that the T cell receptor (TCR) is able to recognize the same antigen present in cancer cells and the heart. This hypothesis implies that cardiomyocytes naturally

express antigens that would elicit an immune response—however, they rely on immune-escape mechanisms that the administration of ICIs could abrogate. The second hypothesis states that antigens in cancer cells and cardiomyocytes possess significant sequence overlap, which would lead to them being recognized by the same TCR. The third hypothesis states that one T-cell might have a chimeric TCR, which enables it to recognize two antigens simultaneously. Essentially, these three hypotheses suggest the presence of TCR signaling overlap between cancer cells and cardiomyocytes.[9] More lymphocytes were found in the heart and other organs when PD-1 and CTLA-4 were blocked.21 Histological analysis from patients with ICI-induced myocarditis also showed elevated levels of CD4+ and CD8+ T cells, as well as macrophages.[22,23]

The clinical and pathological findings of ICI-associated myocarditis were confirmed through a mouse model of ICI-associated myocarditis with Ctla4+/- and Pdcd1-/-, which led to premature death in approximately half of the subjects due to myocardial infiltration by T cells and macrophages as well as severe ECG abnormalities.[24] Another study using a novel melanoma mouse model reported that anti-PD1 therapy promoted myocardial infiltration with CD4+ T cells and activation of CD8+ T cells. Additionally, left ventricular function was impaired during pharmacological stress.[25] Another in vivo study incubated by ipilimumab, pembrolizumab and avelumab had shown that pembrolizumab had been the only one that had shown toxicity, with 2 weeks of use with coronary endothelial and diastolic dysfunction, and cardiac inflammation at 5 weeks.[26]

The increasing number of prescriptions for ICIs in various cancer cases,[27] and a mortality rate of up to 50% in cases of IRAE-associated myocarditis—despite those cases being rare—warrant attention on assessing the pharmacovigilance of this particular group of drugs from various perspectives, including pharmacogenomics.

Genetic Variations Associated with Immune Checkpoint Inhibitors

As is the case for most drugs, no two individuals exhibit the same response to the same drug administered with the same dosage—and this holds true for ICIs. This concept is emphasized in pharmacogenomics—the study of how an individual's genome impacts drug response. Cumulative studies have suggested that there might be differences in patient responses toward ICIs, particularly regarding ICI-induced cardiotoxicity, associated with variations in specific genes.[9] Hence, a pharmacogenomic approach might serve as a useful tool in prescribing ICIs and screening for relevant clinically measurable phenotypes such as a history of autoimmune diseases and cardiovascular disorders. This concept correlates with the three main hypotheses of how cardiotoxicity is induced following the administration of ICIs.

Considering these three hypotheses, it is plausible to think that genetic differences—both somatic and germline—could contribute to TCR signaling overlap, ultimately resulting in cardiotoxicity following ICIs. However, genetic variants that predispose certain individuals to cardiotoxicity associated with ICIs have not been comprehensively mapped, owing to the fact that pharmacogenomic-based studies on immunotherapy-related cardiotoxicity are still in their infancy.[9] Nevertheless, according to studies in mouse models, the pathogenicity of cardiac antigen-specific effector T cells and the likelihood of autoimmune T cell-mediated myocarditis are both increased by genetic abnormalities of checkpoint molecules, such as PD-1, PD-L1, and CTLA-4.[28]

Single nucleotide polymorphisms (SNPs)—variations in the genome by a single nucleotide—with significant associations to IRAEs in general have been mapped (Table 1). Specifically, three SNPs in the gene encoding CTLA-4 with the accession numbers rs4553808, rs11571317, and rs231775 have been shown to associate with IRAEs in patients administered with ipilimumab.[6] However, limited information is available to elucidate the potential mechanism of action of CTLA4 in cardiotoxicity, as gene expression data is only available for rs231775. Based on GTEx database of this SNP, single-tissue eQTL analysis revealed that the expression of CTLA4 in the artery aorta is significantly lower in individuals with variant alleles (AG and GG) compared to those with the wildtype (AA).[29] In general, genetic variations can alter the expression or function of *CTLA-4*, potentially leading to heightened immune activity that predisposes individuals to myocarditis and other cardiac complications. Genetic variations in this gene may contribute to cardiotoxicity through the following mechanisms: 1) Altering *CTLA-4* expression, affecting its ability to regulate T-cell activation[30,31], 2) Hyperactivation of T cells can lead to autoimmune myocarditis. Variants in CTLA4 are linked to excessive cytokine release, which can damage cardiac tissue. 3) Altered signaling pathways due to SNPs facilitate immune cell infiltration into cardiac tissues, compounding cardiotoxicity.[32] This imbalance, exacerbated by ICIs like ipilimumab, can increase the risk of autoimmune responses targeting cardiac tissues.

A study regarding ICI-related IRAEs conducted on patients with autoimmune disease suggested the presence of biomarkers in several loci of the MHC-encoding gene that are strongly associated with ICI-induced myocarditis such as *HLA-DR4, HLA-DR12*, *HLA-DR15*, and *HLA-DPB*06:01*.[33] Genetic variations in HLA-related genes may affect the binding affinity for peptides, influencing the immune system's ability to distinguish self from non-self. This can trigger autoimmune myocarditis.[34,35] Variants in HLA genes may also predispose patients to a hyperinflammatory state, exacerbating cytokine release and immune cell infiltration into cardiac tissues.[36,37] HLA gene variations may also contribute to aberrant activation of CD4+ and CD8+ T-cells, which can lead to cardiac tissue damage.[9,34] These polymorphisms also potentially amplify inflammation through pathways involving interferon-gamma and other cytokines, leading to direct myocardial injury.[35,36]

A recently published article attempted to find the association between genetic variants and nivolumab-induced immune-related adverse events through a genome-wide approach among 622 Japanese patients.[38] Although a significant genome-wide association remained unidentified throughout this study, 90 SNPs were highlighted as possible genetic susceptibility factors for the risk of nivolumab-induced IRAEs. Of 90 SNPs, 27 were consistently associated with a combined p-value of $< 1.00 \times 10^{-4}$. Although no cardiotoxicity was detected among the patients, the findings from this study warrant further investigations in different populations. To further clarify, among the 27 SNPs analyzed, no relevant mechanistic explanations were identified, as we could not find any association between the variants in these genes and their expression in relevant tissues, such as atrial heart tissue, ventricular heart tissue, and coronary artery tissue.

Another genome-wide analysis conducted on 1,751 American patients on ICIs found significant associations between three germline variants located near *IL7* and IRAEs in which one SNP rs16906115 was replicated in 3 independent studies.[39] The SNP was also successfully replicated in

Table 1 Genetic Variants that Warrant Further Study in ICI-Associated Cardiotoxicity

Gene	rsid	ICI Studied	Genotyping Method	References
CTLA-4	rs4553808; rs11571317; rs231775	Ipilimumab	bidirectional re-sequencing	6,49
*HLA-DR4, HLA-DR12, HLA-DR15, HLA-DPB*06:01*	(not reported)	Various	PCR-SBT; PCR-SSO; PCR-RFLP	33,50–52
Intergenic	rs469490; rs971030; rs1929254; rs344569; rs1029674; rs10511373; rs7212872; rs13067334; rs1188390; rs884802; rs4896251; rs13154524; rs12683872	Nivolumab	Microarray (Infinium OmniExpressExome-8 v1.4 DNA Analysis Kit)	38
PCCA, LOC107984575	rs16957301			
LOC107986022	rs6805565			
CSGALNACT1	rs4472533			
BASP1-AS1	rs11952802			
TNRC6B	rs4821942			
CFAP57, LOC105378685	rs1760668			
LINC01572	rs212175			
CD300LB	rs10512596			
CD300C, LOC107985074	rs11652446; rs4789073; rs4789074			
AKAIN1	rs11081175			
ADAMTS19	rs30642			
GRIK4	rs12295498			
IL-7	rs16906115	Nivolumab; pembrolizumab; ipilimumab; tremelimumab; Combination (durvalumab/ tremelimumab; ipilimumab/ nivolumab; ipilimumab/ pembrolizumab); atezolizumab; durvalumab	Combination of WGS and microarray analysis (varies by cohort)	39,40

PCR-SBT: polymerase chain reaction-sequencing based typing; PCR-SSO: polymerase chain reaction-sequence specific oligonucleotides; PCR-RLFP: polymerase chain reaction-restriction fragment length polymorphism; WGS: whole-genome sequencing

another independent study on 214 melanoma patients.[40] Interestingly, IL7 plays an essential role in lymphocyte regulation, and rs16906115 was reported to form a B cell-specific expression quantitative trait locus (eQTL) for IL7. In patients carrying the risk allele, an increase in the expression of pre-treatment B cell IL7, immunoglobulin, and B cell receptor mutations was observed. However, further analysis of TCGA data has seen improved melanoma survival.[40] Based on GTEx database analysis of rs231775, no relevant tissues associated with cardiotoxicity were identified. The only significant finding from single-tissue eQTL analysis revealed that the expression of IL7 in the testis was significantly lower in individuals with the variant alleles (GA and AA) compared to those with the wildtype (GG).[41] Further subgroup analysis among patients with cardiotoxicity or a candidate gene study focusing on these SNPs would provide further insight.

Potential Clinical Application

As for now, the gold standard pharmacological treatment for ICI-associated cardiotoxicity is the following three approaches: 1) consideration of ICI termination with regards to the severity of the cardiotoxicity, 2) conventional cardiac treatments for the complications, and 3) immunosuppression with intravenous glucocorticoids.[8] Prevention by determining baseline cardiac status is also advised for all patients scheduled to receive ICIs, followed by surveillance strategies for individuals at higher risk based on their ICI treatment strategy and past medical history (cardiovascular and autoimmune).[8]

Due to limited pharmacogenomic evidence, personalized selection of ICIs through patient stratification strategy to avoid ICI-associated cardiotoxicity is not yet possible. This is evident in the PharmGKB database, which currently lacks prescribing information, drug label annotations, clinical annotations, and pathways describing the correlation between genetic variations and ICI-associated cardiotoxicity for ipilimumab,[42] nivolumab,[43] pembrolizumab,[44] tremelimumab,[45] durvalumab,[46] and atezolizumab.[47] The only recorded variant annotations for ICIs pertain to hepatotoxicity associated with genetic variations in *GABRP*, *EDIL3*, and *SMAD3*. This highlights the absence of strong clinical evidence supporting the role of genetic variations in developing clinical guidelines to mitigate the risk of cardiotoxicity associated with ICI use.

To strengthen the body of clinical evidence, more international collaborative studies such as GWAS through The Clinical Pharmacogenetics Implementation Consortium (CPIC) and PharmGKB would be essential, owing to the rarity of cardiotoxicity cases. Further translational in vitro screens to evaluate drug responses and adverse effects can be conducted to compile cellular validation evidence in order to accelerate the adoption of pharmacogenomics into a clinical setting.

Directions for the Future

Despite still being in its infancy, pharmacogenomics and its supporting technologies that have risen in the genomics era could provide valuable insights into managing ICI-related cardiotoxicity. In the near future, more functional molecular studies could be conducted to grasp further how specific genetic variants could lead to severe cardiotoxic side effects. Future prospects regarding the clinical implementation of pharmacogenomic testing should consider a holistic viewpoint, which incorporates concepts such as epigenetics—the concept that variations in phenotypes can be influenced by how specific genes

are expressed. Indeed, treatments involving epigenetic modulators such as DNMT inhibitors and HDAC inhibitors in tandem with ICI administration have been tested in clinical trials in hopes of gaining a more precise and fine-tuned method of prescribing ICIs.[9] Single-cell multi-omics analysis, such as time-of-flight mass cytometry (CyTOF), single-cell RNA sequencing (scRNA-seq), single-cell T-cell receptor sequencing (scTCR-seq), and cellular indexing of transcriptomes and epitopes by sequencing (CITE-seq) could also be used in elucidating disease mechanisms involved in ICI-induced myocarditis, as these multi-omics technologies are useful in understanding cell subsets or phenotypes. These approaches may further guide precision therapy to minimize risks as well as present a better treatment plan for managing ICI-associated cardiotoxicity.[48]

Conclusion

This review outlines how cancer immunotherapy, specifically ICIs, comes with a significant drawback: IRAEs, especially cardiotoxic IRAEs. Evidence-based hypotheses on how ICI-associated cardiotoxicity occurs suggest that genetic differences might play a role in ICI response, especially regarding cardiotoxic IRAEs. Pharmacogenomic studies and multi-omics profiling might provide valuable insight regarding ICI-induced cardiotoxicity. Unfortunately, the lack of evidence from clinical trials currently limits its impact on clinical practice. However, once a robust body of clinical evidence is established, it could pave the way for implementing fine-tuned clinical decisions tailored to individual patients in the future.

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Conflict of Interest

The authors have no conflicts of interest to declare.

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