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Cardio- immunotoxicity of Immune Checkpoint Inhibitors: A Focus on Myocarditis

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Abstract:

Immune checkpoint inhibitors (ICIs) have changed modern oncology by considerably improving survival outcomes across a wide range of cancers by boosting antitumor immune responses. In cancers like melanoma, lung cancer, renal cell carcinoma, and Hodgkin lymphoma, agents that target cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), programmed cell death protein-1 (PD-1), and programmed death-ligand 1 (PD-L1) have shown impressive efficiency. However, immune-related adverse events (irAEs), among which myocarditis is one of the rarest but deadliest toxicities, can be brought on by the immune system's nonspecific activation. Immune-mediated myocardial inflammation brought on by loss of self-tolerance, excessive T-cell activation, cytokine dysregulation, and cross-reactivity between tumor and cardiac antigens are the hallmarks of ICI-associated myocarditis. Due to the condition's quick progression to arrhythmias, cardiogenic shock, and fulminant heart failure, it has a high death rate despite its low incidence. The risk of cardiotoxicity is further increased by concurrent autoimmune disorders, pre-existing cardiovascular disease, and combination immunotherapy. With a focus on immunopathogenesis, molecular mechanisms, inflammatory signaling pathways, histopathological findings, biomarkers, and diagnostic modalities, this review investigates the toxicological foundation of ICI-associated myocarditis. Additionally, new developments in translational cardio-oncology are emphasized to enhance early detection and lower mortality. In order to balance therapeutic efficacy with cardiovascular safety in cancer patients receiving immunotherapy, it is crucial to comprehend the cardioimmunotoxic processes underpinning checkpoint blockade therapy.

Keywords: myocarditis, cardio-oncology, immune checkpoint inhibitors, immune-related adverse events

1. Introduction

In recent decades, immunotherapy has been at the leading-edge of groundbreaking advancements and breakthroughs in cancer treatment. Compared to traditional therapies, new and promising treatments for cancers with historically poor prognoses have been approved more quickly, and the field of cancer care is continuously and quickly changing. Immunotherapy for cancer treatment has been developing for centuries, with numerous important figures and discoveries. Attempts to inject different pathogens to trigger an immune response against neoplasia have been documented since 1777 [1]. One of the most significant discoveries in medicine, checkpoint inhibition, was made possible by the understanding of innate tumor suppression by a functional immune system. Selective antibodies can deliver anticancer activity with more manageable toxicities by suppressing the immune system's regulatory checks and balances through intricate mechanisms [2]. Checkpoint inhibitors gained prominence in cancer research shortly after IL-2 was approved. All subsequent checkpoint inhibitors were made possible by the identification of cytotoxic

T lymphocyte-associated antigen 4, or CTLA-4. T cells express CTLA-4, which helps regulate immunological hyperactivation and host harm [3]. Immune checkpoint inhibitors (ICIs) have increased cancer survival rates. They can, however, result in a variety of immune-related adverse events (irAEs). Cardiovascular toxicity can be linked to high rates of morbidity and mortality, but the majority of irAEs are treatable with brief ICI and immunosuppressive discontinuation. The incidence and significance of ICI-associated cardiotoxicity may increase as ICIs expand to encompass high-risk individuals with preexisting cardiovascular risk factors and disease [4]. Immune-mediated toxicities can impact any organ or tissue, including the skin, gastrointestinal system, endocrine system, lung, or liver, and can be largely controlled with glucocorticoids. Cardiotoxicity, a potentially fatal irAE, was rarely observed in early clinical studies of ICI treatment due to its low prevalence and uncertain symptomatology.

Immune checkpoint inhibitor (ICI)-associated myocarditis is estimated to occur in approximately 0.3–1.4% of patients receiving ICI therapy. However, determining the exact incidence remains challenging because of differences in diagnostic criteria, screening practices, and reporting methods across studies. Most current data are derived from post-marketing surveillance studies and clinical registries that emerged after the first reported cases of ICI-associated myocarditis. Recent studies have also identified subacute and smoldering forms of myocarditis, suggesting that the condition may be underdiagnosed. Mild cases are often mistaken for other cardiac conditions, such as demand ischemia, particularly when patients present with low-level troponin elevations. In cancer patients, these elevations may also result from comorbid conditions including anemia, atrial fibrillation, hypotension, sepsis, or underlying coronary artery disease, making diagnosis more complex. Epidemiological findings indicate that ICI-associated myocarditis appears to occur more frequently in males, with most large cohort studies reporting a male predominance. The condition is also more commonly observed in older individuals, typically around 65–67 years of age. However, this trend may partly reflect the general demographics of the cancer population, which itself is skewed toward older male patients [5, 6]. In this review, we go into further detail about the prevalence, clinical signs, diagnosis, mechanisms, and consequences of cardiotoxicity linked to ICIs in order to improve knowledge of this condition and lower mortality rates. Based on pertinent research and current understanding, we will also go over preventative measures, possible therapies, and management of ICI-associated cardiotoxicity [7].

2. Immunopathogenesis of ICI-Associated Myocarditis

ICI-induced myocarditis is one of the most dangerous immune-related side effects of cancer immunotherapy. The first severe cases were reported in 2016, and since then, many similar cases have been identified worldwide. Although it is rare, myocarditis caused by immune checkpoint inhibitors can be life-threatening and may leave lasting heart complications in survivors. The reported incidence is around 0.27–1.14%, but the actual number may be higher due to missed diagnoses and inconsistent reporting. Studies also show that patients receiving ICIs have a much higher risk of developing myocarditis, especially those treated with combination immunotherapy. These findings highlight the importance of early detection and close cardiac monitoring during ICI treatment [8].

It is still unclear exactly how immune-related adverse events (irAEs), especially ICI-associated myocarditis, occur. According to available data, certain tumor cells and cardiac muscle cells may have identical antigens, which could lead activated T-cells to unintentionally target the heart instead of the tumor. One of the main theories explaining immune-mediated heart damage is the "shared antigen" theory. Additionally, the early onset of myocarditis following the initiation of immune checkpoint inhibitor medication suggests that certain patients may already have immunological susceptibilities or underlying diseases that raise their risk. The protective function of immune checkpoint pathways like CTLA-4 and PD-1 in preserving cardiac immunological tolerance is further supported by research conducted on experimental animals [9].

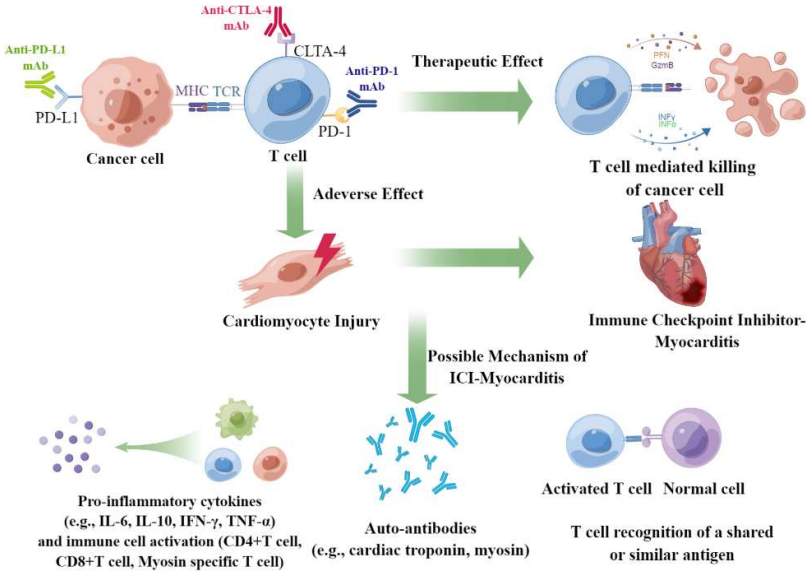

figure-1 [11]

Excessive T-cell activation against cardiac tissue is the primary cause of ICI-associated myocarditis. The major involvement of immunological dysregulation is highlighted by the presence of cardiac-specific autoantibodies in myocarditis patients as well as infiltration of CD4+ and CD8+ T-cells and macrophages into the myocardium. Immunological checkpoints like CTLA-4 and PD-1 typically protect the heart by preserving immunological tolerance, according to experimental research. Uncontrolled inflammation, cardiac damage, and autoimmune myocarditis can result from disruption of these mechanisms. By reducing T-cell-mediated damage, PD-L1 expression in the heart seems to function as a protective mechanism under cardiac stress; immune checkpoint drugs, however, hinder this protective pathway [10].

3. Clinical Presentation of ICI-Associated Myocarditis

The symptoms of ICI-associated myocarditis can vary from mild to potentially fatal. While severe cases may develop to arrhythmias, hemodynamic instability, multiorgan failure, or sudden cardiac death, common symptoms include palpitations, exhaustion, shortness of breath, and chest pain. Myositis and myasthenia gravis are frequently linked to fulminant myocarditis, which typically develops soon after beginning ICI therapy. Myocarditis, sometimes known as "smoldering myocarditis," might be asymptomatic in many people and only manifest as increased cardiac biomarkers [12].

The severity of ICI-associated myocarditis can vary widely, from mild, asymptomatic illness to potentially fatal cardiac problems. While severe "fulminant" cases can quickly escalate to cardiogenic shock, severe arrhythmias, multiorgan dysfunction, and death, some individuals may just exhibit increased cardiac biomarkers. Acute coronary syndrome-like symptoms, new-onset heart failure, and persistent heart failure are examples of moderate forms of myocarditis that can resemble viral myocarditis. Chest pain, shortness of breath, exhaustion, palpitations, orthopnea, and paroxysmal nocturnal dyspnea are typical symptoms. The frequent reporting of severe cases over milder or subclinical forms contributes to the high mortality rate linked to ICI myocarditis [13].

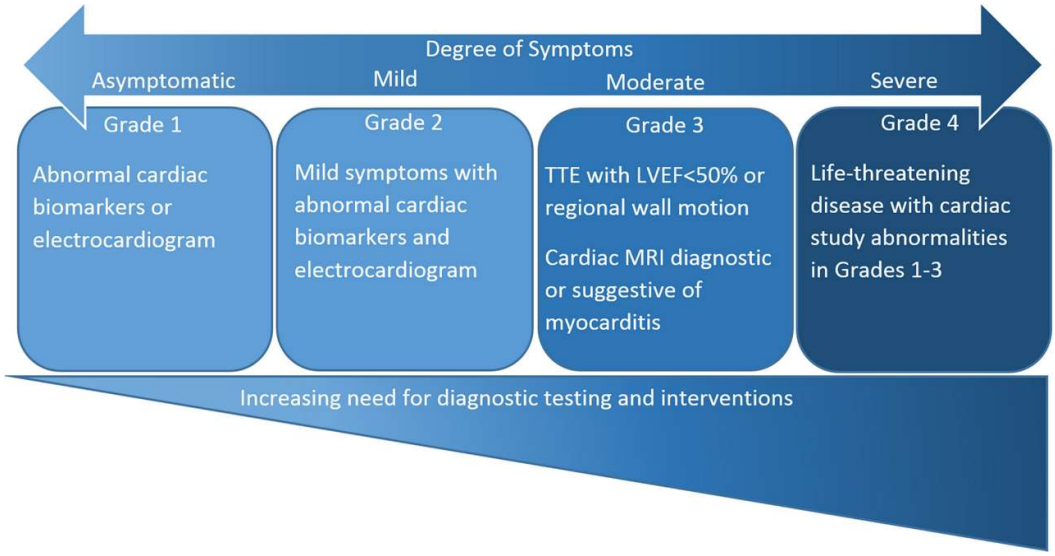

figure-2 [15]

Pericardial effusion may occur in patients with ICI-associated myocarditis, either with or without concomitant pericarditis. Immune checkpoint inhibitors have occasionally been connected to recurrent pleural and pericardial effusions. Pericardial effusion may indicate underlying myopericarditis because it is regarded as a supporting characteristic of myocarditis. Pericardial effusions, however, can be independently caused by a variety of malignancies, especially lung cancer. Thus, in patients on ICIs, a new or worsening pericardial effusion should raise the possibility of ICI-related myocarditis; nevertheless, it should always be interpreted in conjunction with other clinical and diagnostic findings [14].

4. Diagnosis

Because the symptoms of ICI-associated myocarditis can vary greatly and mimic those of other cardiac or pulmonary disorders such acute coronary syndrome, viral myocarditis, Takotsubo cardiomyopathy, or pneumonitis, diagnosing it can be challenging. Early suspicion and prompt evaluation are crucial because the disease can advance quickly and prove lethal. Endomyocardial biopsy is still the gold standard for diagnosis, but it is invasive and can occasionally yield false-negative results because of sampling errors. As a result, a combination of ECG, cardiac biomarkers, imaging tests such cardiac MRI, and biopsy when required are typically used to make the diagnosis. Recent guidelines for cardio-oncology state that ICI myocarditis can be diagnosed clinically or pathologically. After ruling out other potential causes, the clinical diagnosis is mostly based on high troponin levels combined with supporting evidence such as abnormal cardiac MRI, arrhythmias, conduction abnormalities, impaired left ventricular function, or the presence of other immune-related adverse events [16, 10].

Among the most significant laboratory results indicating ICI-associated myocarditis are elevated blood troponin and natriuretic peptide levels. Since troponin T may also rise in patients with concomitant myositis, which frequently coexists with ICI myocarditis, troponin I is typically recommended over troponin T. According to studies, increased troponin levels are observed in the majority of patients with clinically confirmed ICI myocarditis. Severe consequences include cardiogenic shock, cardiac arrest, total heart block, and cardiovascular mortality are closely linked to higher troponin concentrations. A worse prognosis and an increased risk of significant adverse cardiovascular events have also been associated with persistent elevation of troponin levels. As a result, troponin is a significant predictor of clinical outcome and disease severity in addition to being a diagnostic biomarker [6, 17].

Although ECG results in ICI-associated myocarditis are frequently ambiguous, they can offer crucial early indicators. PR interval lengthening, atrioventricular block, ventricular arrhythmias, frequent premature ventricular complexes, ST-segment depression, and diffuse T-wave inversions are common abnormalities. But initially, it's important to rule

out other causes like acute coronary syndrome. Because it can identify intermittent arrhythmias such ventricular tachycardia and developing ventricular ectopy, continuous telemetry monitoring is helpful in suspected instances. Atrial fibrillation has been recorded in a considerable percentage of patients, indicating the possibility of atrial arrhythmias. In general, cardiac rhythm monitoring and ECG are crucial for the early identification and evaluation of myocarditis linked to ICI [18].

For the diagnosis of myocarditis, endomyocardial biopsy is regarded as the gold standard. The presence of both cardiac

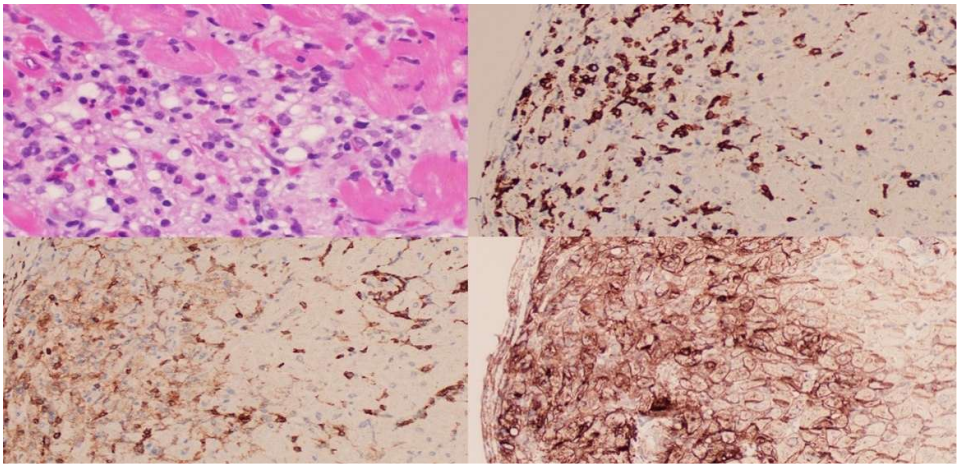

figure-3 [20, 15]. Pathological findings in ICI-associated myocarditis typically demonstrate dense lymphocytic infiltration within the myocardium on hematoxylin and eosin staining. Immunohistochemical analysis commonly reveals prominent infiltration of CD8+ cytotoxic T-cells, along with CD4+ helper T-cells, indicating strong immune activation within cardiac tissue. Increased PD-L1 expression is also observed in myocardial cells, possibly representing a protective response aimed at limiting excessive immune-mediated cardiac damage [20, 15].

necrosis and inflammatory cell infiltration is used to make the diagnosis. The inflammation frequently mirrors the rejection pattern observed in transplanted hearts and might appear patchy or diffuse. Histological investigations of ICI-associated myocarditis frequently reveal CD8+ T-cell infiltration in addition to CD4+ T-cells and macrophages, underscoring the disease's immune-mediated character. Similar T-cell clones have also been found in cardiac muscle, skeletal muscle, and tumor tissue, which lends credence to the idea that the heart and malignancies share antigens. Furthermore, elevated PD-L1 expression has been noted in myocardial tissue that is impacted, indicating a potential defense against excessive immune-mediated cardiac damage [19].

5. Treatment

Due to the paucity of randomized clinical trials, the management of ICI-associated myocarditis is primarily based on case reports and professional suggestions. The first and most crucial approach is to stop immune checkpoint inhibitor medication right away. Because they inhibit the excessive T-cell activation that causes cardiac inflammation, high-dose corticosteroids are regarded as the cornerstone of treatment. High-dose intravenous methylprednisolone is typically administered at the start of treatment, and oral corticosteroids are then gradually tapered off over a few weeks. While postponing treatment raises the risk of serious adverse cardiovascular events, early commencement of steroid medication is closely linked to improved outcomes. Additional immunosuppressive treatments, such as intravenous immunoglobulin, mycophenolate mofetil, anti-thymocyte globulin, or abatacept, may be necessary for patients who do not respond well to corticosteroids. Depending on the severity of the condition, normal cardiovascular management, such as beta-blockers, renin-angiotensin system inhibitors, diuretics, antiarrhythmic therapy, and sophisticated mechanical assistance, may be required in addition to immunosuppression. Continuous cardiac monitoring is advised, particularly for individuals with hemodynamic instability, decreased ventricular function, or increased biomarkers [21].

Immunosuppressive medication, supportive cardiovascular care, and the prompt cessation of immune checkpoint inhibitors are the main treatments for immune checkpoint inhibitor-associated myocarditis (ICI-M). Early diagnosis and timely treatment are essential for improving survival results since ICI-M can quickly proceed to fulminant myocarditis, cardiogenic shock, deadly arrhythmias, and multiorgan failure. Because they effectively reduce excessive T-cell-mediated immunological activation, glucocorticoids continue to be the mainstay of first-line therapy. According to available data, early high-dose corticosteroid administration—especially within the first 24 hours of symptom onset—is linked to a markedly better prognosis and a lower risk of major adverse cardiac events (MACE). Intravenous methylprednisolone is usually started as soon as fulminant or non-fulminant ICI-M is diagnosed [22,23]. Mycophenolate mofetil, anti-thymocyte globulin, intravenous immunoglobulin (IVIG), abatacept, alemtuzumab, tocilizumab, and Janus kinase (JAK) inhibitors like tofacitinib and ruxolitinib have all been used as immunomodulatory treatments for refractory ICI-M. Because abatacept can restore immune checkpoint signaling by modulating the CTLA-4 pathway, it has garnered significant attention among new treatments. In critically ill patients, combination therapy with abatacept and ruxolitinib has shown encouraging results, especially when immune surveillance techniques like CD86 receptor occupancy measurement are used [24]. Throughout the course of treatment, supportive cardiovascular control is still crucial. Individuals with reduced left ventricular ejection fraction, increased biomarkers, or arrhythmias ought to be treated in critical care or monitored cardiac settings. When clinically indicated, standard heart failure treatments such as beta-blockers, diuretics, and renin-angiotensin system inhibitors should be given. Advanced mechanical circulatory assistance, such as intra-aortic balloon pumps, extracorporeal membrane oxygenation (ECMO), or micro-axial flow pumps, may be necessary in situations of hemodynamic instability or cardiogenic shock. Optimizing outcomes for patients with severe ICI-associated myocarditis requires early ICU admission and interdisciplinary collaboration between oncologists, cardiologists, intensivists, and immunologists [25, 26].

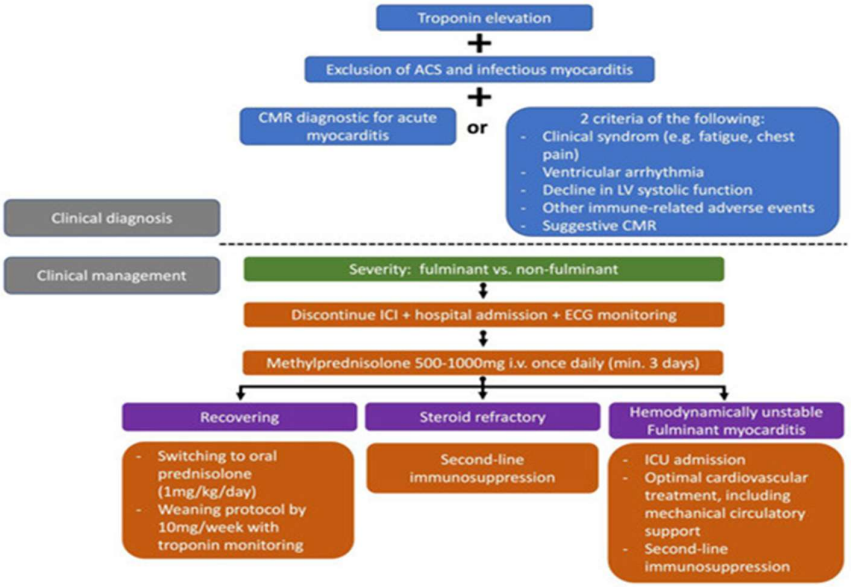

figure-4

6. Future Perspective

A key therapeutic challenge in ICI-associated myocarditis is evaluating whether immune checkpoint inhibitor therapy can be safely resumed following recovery. Despite being among the most serious IRAEs, myocarditis and neurological immune-related adverse events may not always have greater recurrence rates upon rechallenge than other IRAEs, according to current pharmacovigilance studies. According to current guidelines, patients who have cardiac toxicity should stop ICI medication immediately and permanently. But in moderate or silent situations, such as isolated elevation of cardiac biomarkers without clinically apparent myocarditis, the choice becomes more difficult, especially in patients with advanced malignancies who might have few therapy options [27, 28].

Therefore, the choice to rechallenge should be personalized and founded on a thorough risk-benefit analysis. A number of factors should be taken into account, such as the prognosis of cancer, the severity of earlier myocarditis, the response to immunosuppressive medication, the recovery of cardiac function, the previous response to immunotherapy, and patient preference. Because anti-PD-1 monotherapy may have a reduced cardiotoxic risk than combination immunotherapy, some expert guidelines support reintroduction with anti-PD-1 monotherapy when rechallenge is required. Prevention and early identification of ICI-associated myocarditis is another important area of investigation. ICI cessation may improve myocarditis outcomes, but it may have a detrimental effect on cancer control. As a result, current research is investigating preventative measures and supplemental treatments that could aid in the management of immune-related side effects without necessitating the permanent discontinuation of immunotherapy. Future research will also concentrate on finding predictive biomarkers, such as granulocyte colony-stimulating factor (G-CSF), IL-6, and IL-17, which may help with early diagnosis, risk assessment, and IRAE monitoring. By detecting mild myocardial failure before traditional metrics like ejection fraction become abnormal, advances in cardiac imaging techniques, such as speckle-tracking echocardiography, may further enhance early detection [29, 30].

7. Conclusion

ICI-associated myocarditis is an uncommon but dangerous complication that can be difficult to diagnose and treat since it can mimic many other acute heart diseases. Clinical evaluation is made more difficult by its recent discovery and our incomplete knowledge of the underlying mechanisms. Standardized diagnosis and treatment methods are still developing because the majority of the evidence that is now available comes from case reports and short studies. Timely diagnosis requires early suspicion on the part of cardiologists and oncologists. Future developments in endomyocardial biopsies and multimodal imaging may contribute to increased diagnostic precision. Currently, glucocorticoids are the mainstay of treatment; however, in severe or resistant instances, specific immunomodulatory treatments may be necessary. Additional immunosuppressive medications such abatacept, mycophenolate mofetil, intravenous immunoglobulin, or targeted biologics may be necessary in addition to rigorous cardiovascular support in severe or steroid-refractory cases. More knowledge of the cardiotoxic effects of immune checkpoint inhibitors is crucial as their clinical use in treating various cancers continues to grow. To lower mortality and improve patient outcomes, further research is required to better understand the molecular underpinnings, find predictive biomarkers, enhance early diagnostic techniques, and create evidence-based treatment protocols [15].

Disclosure Statement

This is to acknowledge any financial interest or benefit that has arisen from the direct applications of your research.

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