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Biomarkers and Risk Stratification in the Prognostication of Immune Checkpoint Inhibitors-associated Myocarditis

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Abstract: The advent of immune checkpoint inhibitors (ICIs) has fundamentally reshaped oncology, yet their success is overshadowed by a spectrum of immune-related adverse events (irAEs), among which immune checkpoint inhibitors-associated myocarditis (ICIs-M) stands out as a rare but potentially fatal complication. Characterized by a high case fatality rate, ICIs-M presents a formidable clinical challenge that urgently demands early diagnosis, accurate risk stratification, and timely intervention. Peripheral biomarkers, particularly cardiac troponins (cTn), have become central to its management, but their application is fraught with complexities and controversies. This review adopts a problem-solution-future framework, moving beyond a traditional chronological summary to critically appraise the role of clinical characteristics and peripheral biomarkers at key clinical decision points. We deconstruct the "troponin paradox"—the observed discrepancy in diagnostic sensitivity and prognostic accuracy between cardiac troponin T (cTnT) and I (cTnI) assays—and delve into its potential mechanistic underpinnings, including the confounding role of concomitant myositis. We scrutinize the evidence for emerging inflammatory and systemic biomarkers, highlighting limitations regarding their specificity and clinical readiness. Furthermore, we offer a critical perspective on the prevailing consensus on therapeutic strategies, such as the timing of corticosteroid initiation, by exposing potential confounding biases in the existing literature. By structuring the analysis around the diagnostic-prognostic-therapeutic continuum, this review aims to address potential misconceptions, identify critical knowledge gaps, and propose a new paradigm for future research. We advocate for a shift from a reactive, troponin-centric approach to a proactive, multi-parameter, and dynamic risk assessment model. Ultimately, this work contributes to the advancement toward where ICIs-M is a predictable, preventable, and precisely treatable condition, moving the field from describing the problem to solving it.

Keywords: Immune checkpoint inhibitors; Myocarditis; Biomarkers; Cardiac troponins; Prognostication.

Introduction

The advent of immune checkpoint inhibitors (ICIs) represents one of the most significant therapeutic breakthroughs in modern oncology, fundamentally altering the prognosis for patients with a wide array of malignancies, including melanoma, non-small-cell lung cancer, renal cell carcinoma, among others[1–3]. By targeting inhibitory pathways that regulate T-cell function, such as the programmed cell death protein 1/programmed cell death-ligand 1 (PD-1/PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) pathways, ICIs unleash the host's immune system to eradicate tumor cells with unprecedented efficacy[4]. However, this potent immune activation is a double-edged sword. The same mechanisms that mediate anti-tumor immunity can also lead to a breakdown in self-tolerance, giving rise to a unique constellation of immune-related adverse events (irAEs) that can affect virtually any organ system[5].

Among these toxicities, immune checkpoint inhibitors-associated myocarditis (ICIs-M) has emerged as a paramount concern. While its reported incidence is relatively low, estimated between 0.04% and 1.14%, it carries the highest mortality rate of all irAEs, with case fatality rates reaching up to 17–50%[6–8]. This stark contrast between low frequency and high lethality creates a high-stakes clinical scenario where early recognition and intervention are critical determinants of survival. Moreover, as the indications for ICIs expand into earlier stages of cancer, including adjuvant and neoadjuvant settings, the absolute number of patients at risk for this complication is projected to rise substantially, amplifying the urgency for improved management strategies. The clinical presentation of ICIs-M is notoriously heterogeneous, ranging from asymptomatic elevations in cardiac biomarkers to fulminant myocarditis characterized by cardiogenic shock, life-threatening arrhythmias, and sudden death[6,7,9]. This variability, coupled with the absence of pathognomonic clinical features, renders diagnosis a significant challenge, often requiring a multi-modality approach that integrates clinical suspicion, electrocardiography, cardiac imaging, and, in some cases, endomyocardial biopsy (EMB)[10–12].

In this complex landscape, peripheral biomarkers have be-

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come the cornerstone of diagnosis, risk stratification, and therapeutic monitoring. Cardiac troponins (cTn), in particular, are integral to virtually all diagnostic algorithms[10,13]. However, the burgeoning body of literature has revealed significant complexities and knowledge gaps that challenge their routine application. Key unmet needs include: (1) a lack of consensus on the optimal biomarker panel and surveillance frequency; (2) uncertainty regarding the prognostic significance of different biomarker trajectories; and (3) an inability to reliably predict which patients will develop major adverse cardiovascular events (MACE) and who will prove refractory to standard high-dose corticosteroid therapy. The central challenge lies in moving beyond simple biomarker elevations to an integrated framework that combines clinical phenotypes with a dynamic, multi-parameter biomarker signature to guide real-time clinical decisions.

This review aims to provide a comprehensive and critical analysis of the current state of knowledge regarding the clinical characteristics and prognostic value of peripheral biomarkers in ICIs-M. Departing from a traditional chronological or descriptive structure, we adopt a problem-oriented framework that is organized around critical clinical decision points. We will critically evaluate the evidence, re-examine established paradigms, and highlight the most pressing controversies and knowledge gaps. Our focus will be on the practical application of peripheral biomarkers—both cardiac and systemic—as tools for diagnosis, prognostication, and therapeutic guidance, with the ultimate goal of charting a clear path forward for future research and improved clinical management.

Pathophysiological foundation from mechanism to biomarker

A rational approach to biomarker utilization in ICIs-M must be grounded in an understanding of its underlying pathophysiology. While the precise mechanisms remain incompletely elucidated, a coherent picture is emerging that links the disruption of immune homeostasis to specific patterns of myocardial injury and subsequent biomarker release. The core event is the iatrogenic disruption of self-tolerance, primarily mediated by the blockade of PD-1/PD-L1 and CTLA-4 pathways, which are crucial for maintaining T-cell exhaustion and preventing autoimmunity in peripheral tissues, including the heart[14]. The susceptibility starts in the thymus, where central tolerance fails to eliminate T cells recognizing cardiac antigens like alpha-myosin heavy chain (MYHCA) because the encoding gene (myosin heavy chain 6, MYH6) is absent in thymic epithelial cells[15,16]. The subsequent ICI therapy removes the peripheral restraints, leading to the clonal expansion and activation of autoreactive $CD8^+$ T cells, and infiltration of inflammatory macrophages, leading to myocyte necrosis[17,18]. This direct T-cell-mediated cytotoxicity is the primary driver of cardiac troponin release, the hallmark biomarker of ICIs-M. The intensity and location of this infiltration likely dictate the magnitude and kinetics of troponin elevation. The observation that combination therapy with anti-CTLA-4 and anti-PD-1 agents confers a significantly higher risk of myocarditis, nearly doubling the incidence and mortality, underscores the synergistic effect of blocking multiple non-redundant checkpoints that restrain autoreactive T-cells[6,8].

One of the leading hypotheses to explain the cardiac-specific targeting is the "shared antigen" theory. This posits that T-cells activated to recognize tumor antigens may cross-react with structurally similar self-antigens expressed by cardiomyocytes[19]. Damage is exacerbated by an interferon-gamma (IFN-γ) driven T-cell/macrophage crosstalk and potentially by molecular mimicry between tumor and cardiac antigens, culminating in myocyte necrosis and release of cTn[20,21]. This represents a critical knowledge gap; identifying the specific target antigens and the genetic basis of susceptibility is a crucial next step for developing predictive screening tools.

The specific patterns of biomarker release are a direct consequence of these underlying mechanisms (Fig. 1). The T-cell-mediated myocyte necrosis is the primary driver of cTn release. However, the frequent overlap with myositis (30–35% of cases)

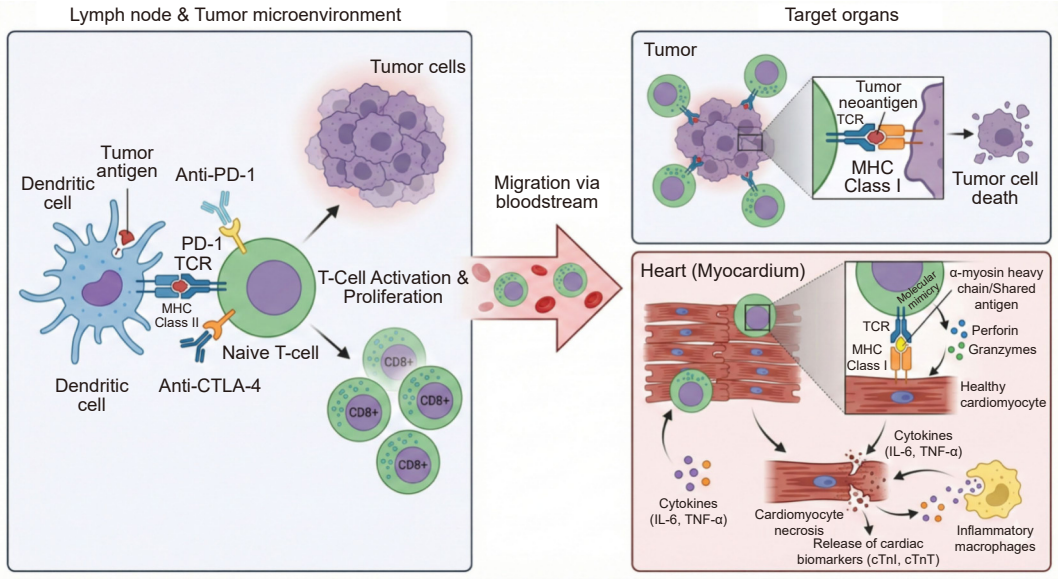

Fig. 1. Pathophysiological Mechanisms of ICIs-M and Biomarker Release.

introduces a significant confounder[7]. Evidence derived primarily from non-ICI neuromuscular disorders (e.g., Duchenne muscular dystrophy, polymyositis) demonstrates that regenerating skeletal muscle can re-express fetal isoforms of cardiac troponins, particularly cTnT, which are typically undetectable in healthy skeletal muscle[22,23]. While direct proteomic confirmation in ICI-associated myositis remains limited, this biological phenomenon offers a strong plausible mechanism—rather than a proven causality in every case—for the observed "troponin paradox". Furthermore, this discordance may be amplified by analytical variations, specifically the susceptibility of current high-sensitivity cTnT assays to cross-react with these re-expressed skeletal isoforms, a limitation that is significantly less pronounced in cTnI assays due to the lack of fetal skeletal isoform re-expression. Consequently, the superior sensitivity of cTnT assays may, in part, reflect their detection of troponin originating from concomitant skeletal muscle injury, rather than purely from the heart. This does not necessarily invalidate its prognostic utility, as severe myositis is itself a marker of poor prognosis, but it complicates the interpretation of cTnT as a specific marker of cardiac injury[24]. In contrast, cTnI is considered more cardio-specific[25], which may explain its lower sensitivity but potentially higher specificity in cases without myositis overlap. This intricate relationship between the underlying pathology and biomarker expression is central to the clinical challenges discussed later in this review.

Immune checkpoint blockade disrupts self-tolerance, leading to activation of T-cells. Through molecular mimicry, these T-cells recognize antigens shared between tumor cells and cardiomyocytes (e.g., α-myosin). Activated T-cells and macrophages infiltrate the myocardium, causing myocyte necrosis and release of cardiac-specific biomarkers like cTnI and cTnT. In a substantial subset of patients, a similar process occurs in skeletal muscle (myositis), leading to the release of Creatine kinase (CK) and, importantly, re-expressed cTnT from regenerating muscle fibers, which can be detected by cTnT assays and contribute to its elevated levels.

Clinical phenotypes and risk

The clinical manifestation of ICIs-M is a wide and treacherous spectrum, posing a significant diagnostic challenge. The classic presentation often involves acute heart failure symptoms, such as dyspnea, chest pain, and fatigue, but the disease can also manifest more insidiously or, conversely, as a catastrophic fulminant event[7]. A substantial portion of patients (31%) present with arrhythmias, including varying degrees of atrioventricular block, which can rapidly progress to complete heart block and hemodynamic collapse[12,26]. This heterogeneity necessitates a high index of suspicion in any ICI-treated patient presenting with new cardiopulmonary symptoms or electrocardiogram (ECG) abnormalities.

The concept of clinical phenotypes is crucial for risk stratification. While not formally defined, presentations can be broadly categorized. Fulminant myocarditis, characterized by rapid hemodynamic deterioration and cardiogenic shock, represents the most feared phenotype and is associated with the worst outcomes. At the other end of the spectrum lies asymptomatic or subclinical myocarditis, identified only through routine biomarker surveillance showing elevated troponin levels without overt symptoms. The natural history and optimal management of this latter group remain a major clinical and research question. Between these extremes are patients with mild to moderate symptoms of heart failure or arrhythmias. Furthermore, the frequent co-occurrence of skeletal myositis and/or myasthenia gravis constitutes a distinct overlap syndrome phenotype, which may carry unique prognostic implications and require more aggressive or broader-acting immunosuppressive therapy[7].

Several risk factors for developing ICIs-M have been identified, though their predictive power for individual patients is limited. The most robustly established risk factor is the use of combination ICI therapy (e.g., anti-PD-1 plus anti-CTLA-4), which is associated with a more than twofold increased risk compared to monotherapy[6,8]. The onset of ICIs-M is most common after the first or second cycle of treatment, with a median time from ICI initiation to admission of approximately 30 days, although the range is exceptionally wide, from a few days to over a year, highlighting the need for sustained vigilance[26,27]. Other potential but less consistently proven risk factors include pre-existing diabetes and, possibly, underlying cardiovascular disease.

Beyond clinical presentation, diagnostic modalities offer further phenotypic characterization. The ECG is abnormal in the majority of cases, but findings are often non-specific, including sinus tachycardia, new conduction abnormalities, or ST-T wave changes[28]. Echocardiography (Echo) may reveal regional wall motion abnormalities or a reduced left ventricular ejection fraction (LVEF), but it is insensitive in early or less severe cases, with many patients presenting with preserved LVEF. In this context, speckle-tracking Echo to assess global longitudinal strain (GLS) has emerged as a more sensitive tool. A reduction in GLS often precedes a decline in LVEF and can be an early sign of subclinical myocardial dysfunction, making it a valuable imaging biomarker for surveillance and early detection[29]. In this context, cardiac magnetic resonance (CMR) has emerged as a powerful non-invasive tool. While findings can be variable, a characteristic pattern of late gadolinium enhancement (LGE), typically with a non-coronary distribution that is patchy, multifocal, and often involves the mid-myocardium or subepicardial layers of the basal to mid-ventricular wall, particularly the septum, appears to be a distinguishing feature of ICIs-M[30]. A major distinction between ICIs-M and viral myocarditis lies in the diagnostic sensitivity of CMR. While LGE is present in over 90% of patients with typical acute viral myocarditis. Zhang et al.[31] reported that LGE was observed in only 48% of ICIs-M cases. Similarly, the prevalence of myocardial edema on T2-weighted imaging was significantly lower in ICIs-M (28%) compared to non-ICI myocarditis (approximately 94%). They demonstrated that even in patients with biopsy-proven lymphocytic infiltration and diffuse inflammation, LGE was present in only 39%, suggesting that ICIs-M may present as diffuse myocardial involvement that eludes detection by traditional LGE sequences. Critically, the presence of septal LGE has been identified as an independent predictor of MACE, even after adjusting for peak troponin levels, making it a vital component of risk stratification[30]. There are currently multiple established guidelines for the diagnosis and grading of ICIs-M[6,10,13,32–35].

Cardiac biomarkers: deconstructing the troponin paradox

cTn are the undisputed cornerstone for the diagnosis and management of ICIs-M. However, the field's uncritical reliance on the general concept of "troponin elevation" masks a crucial and clinically significant controversy: the profound heterogeneity between cTnT and cTnI assays, a phenomenon we term the "troponin paradox."

A nuanced and cautious interpretation is warranted for the "troponin paradox", which is specifically defined by the superior diagnostic sensitivity of cardiac troponin T (cTnT, 98%) over cardiac troponin I (cTnI, 88%) as documented in the study by Lehmann et al[24]. Crucially, the methodological heterogeneity in their definition of MACE, which included respiratory muscle failure requiring mechanical ventilation, complicates direct cross-study comparisons. Unlike traditional cardiovascular trials where MACE is strictly limited to primary cardiac events (e.g., cardiogenic shock, heart failure), this nonstandard composite endpoint captures the broader spectrum of systemic ICI-myotoxicity. Given that respiratory failure in this population is frequently driven by concomitant diaphragmatic myositis or myasthenia gravis rather than primary pump failure[7], the enhanced sensitivity of cTnT may partially reflect its role as a surrogate for skeletal muscle involvement. This distinction is vital when comparing these findings to other ICIs-M cohorts that utilize more conventional MACE definitions. Furthermore, while the analytical specificity of high-sensitivity cTnT remains a concern due to the expression of cTnT isoforms in regenerating skeletal muscle, a phenomenon less pronounced in cTnI assays, it remains unclear whether cTnT's superior performance in the Lehmann cohort is a result of improved myocarditis detection or a more sensitive tracking of the lethal 'overlap syndrome' involving systemic myotoxicity.

While the re-expression of fetal cTnT isoforms in regenerating skeletal muscle provides a compelling explanation for this discordance, the current evidence remains largely inferential and requires critical appraisal. (a) In terms of evidence quality, while transcriptomic and immunohistochemical data have confirmed the presence of TNNT2 mRNA and cTnT protein in ICI-myositis biopsies[24], (b) a clear distinction must be made between this biological plausibility and a proven clinical mechanism. The precise quantitative contribution of non-cardiac cTnT to total serum levels, and whether it is sufficient to independently trigger clinical 'positivity', has not been definitively established in vivo. (c) Notably, this diagnostic discordance is unlikely to be a purely analytical artifact. Because cTnT assays are highly standardized (single-vendor), the observed discrepancy persists across diverse clinical cohorts even when compared against various cTnI platforms, further supporting a biological rather than an assay-specific basis for the troponin differential performance.

This raises a pivotal mechanistic question: is the superior prognostic power of cTnT simply a reflection of its ability to detect severe, overlapping myositis, which is itself a potent predictor of mortality? The answer is likely complex. Rather than viewing this as a flaw, it may be more clinically relevant to interpret an elevated cTnT as a highly sensitive marker for a severe striated muscle inflammatory syndrome**,** encompassing both cardiac and skeletal muscle. In this paradigm, cTnT's value lies not in its absolute cardio-specificity, but in its capacity to identify a systemic and aggressive autoimmune process targeting striated muscle, which portends a poor prognosis. In contrast, cTnI acts as a more specific marker of *myocardial* injury. Therefore, the discordance between the two markers is clinically informative: a patient with elevated cTnT but normal or minimally elevated cTnI may have a predominant myositis with subclinical cardiac involvement, whereas a patient with markedly elevated cTnI unequivocally has significant myocardial necrosis. The key distinctions and clinical implications of these two biomarkers are summarized in Table 1.

Table 1. Comparative Analysis of cTnT and cTnI in ICIs-M.

Feature	cTnT	cTnI
Diagnostic Sensitivity	Higher (~ 98%)[24]	Lower (~ 88%)[24]
Cardio-specificity	Lower; potential cross-reactivity with regenerating skeletal muscle[21]	Higher; more specific to myocardial tissue
Prognostic Value (MACE)	Excellent; peak level is a strong predictor (AUC 0.84)[24]	Good, but may be normal in a subset of MACE cases (~ 11%)[24]
Influence of Myositis	Significant; levels may reflect both cardiac and skeletal muscle injury	Minimal; primarily reflects cardiac injury
Release/Clearance	Slower clearance; remains elevated longer	Faster clearance; normalizes earlier in the course[24]
Clinical Interpretation	Sensitive marker of striated muscle injury; high prognostic value for overall severity	Specific marker of myocardial injury; confirms cardiac involvement

Despite the specificity debate, the prognostic value of cTnT elevation is undeniable. The Franco-German cohort study found that the peak cTnT value (normalized to the upper reference limit) was the single best predictor of 90-day MACE (Area Under Curve, AUC 0.84)[24]. This indicates that regardless of its precise origin, a large-magnitude troponin release signals a process severe enough to confer high risk. Based on these observations, we hypothesize that clinical utility might be improved by shifting focus from a binary positive/negative interpretation to a quantitative and kinetic one. Future studies are needed to confirm whether the trajectory of troponin elevation, its rate of rise and peak level, contains more prognostic information than a single static measurement. A rapidly rising troponin, for example, may reflect a more aggressive inflammatory process than a slowly smoldering one, even if the peak values are similar. This area remains a critical knowledge gap requiring further investigation.

Biomarkers play a central role in the 'diagnostic-prognostic-therapeutic continuum' of ICIs-M. While cardiac-specific troponins remain the gold standard, other markers provide critical

complementary information. B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are frequently elevated, reflecting myocardial wall stress and hemodynamic compromise; these are valuable for identifying concomitant heart failure and are associated with long-term prognosis[36]. Crucially, foundational work by Vasbinder et al. has redefined our understanding of early disease detection. Their prospective cohort study demonstrated that elevations in non-cardiac biomarkers—specifically Creatine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH)—can precede the clinical presentation of ICIs-M by a median of 20 days with a remarkable diagnostic sensitivity of 99%[37]. Building on these findings, a subsequent screening algorithm was proposed, emphasizing the integration of these systemic markers to facilitate early immunosuppressive intervention before the onset of fulminant heart failure[38].

While this high sensitivity is clinically invaluable for early surveillance, the clinical challenge evolves toward cardiac-specificity as the diagnostic process moves from screening to confirmation. The utility of total CK and its isoenzyme (CK-MB) can be tempered by the frequent context of concomitant myositis[39]. In cases of extensive skeletal muscle damage, massively elevated CK levels may complicate the interpretation of the CK-MB fraction, necessitating a careful distinction between systemic myotoxicity and primary myocardial injury to guide targeted management[24].

Inflammatory and systemic biomarkers: emerging frontiers

While cardiac-specific biomarkers confirm myocardial injury, they do not fully capture the systemic inflammatory storm that drives ICIs-M. This has led to a search for peripheral inflammatory and systemic biomarkers that could offer additional prognostic value and reflect the underlying immunological process. These markers are often readily available from routine blood tests, making them highly attractive for clinical implementation.

In the quest for accessible biomarkers, recent studies have highlighted the potential of composite inflammatory and metabolic indices for risk stratification in ICIs-M. Parameters such as the Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and Lymphocyte-to-Monocyte Ratio (LMR) have been identified as baseline indicators of general irAEs risk and overall survival[40]. More specifically, in the context of ICIs-M, the Systemic Immune-Inflammation Index (SII) and the Neutrophil-to-Eosinophil Ratio (NER) at onset have been significantly associated with severe disease conditions and poorer clinical outcomes[36]. Notably, biochemical ratios integrating organ damage and nutritional status, such as the Lactate Dehydrogenase-to-Albumin Ratio (LAR) and the Aspartate Aminotransferase-to-Albumin Ratio (AAR), have demonstrated robust performance in predicting 30-day mortality and MACE, with AUC values often exceeding 0.80[41,42]. However, while these indices offer a cost-effective diagnostic-prognostic continuum, it must be emphasized that the current evidence is derived primarily from retrospective cohorts and remains preliminary. These markers can be influenced by systemic confounders such as tumor burden or concurrent infections; thus, their routine clinical implementation for therapeutic guidance remains aspirational until further validated by large-scale prospective studies.

This non-specificity renders them largely powerless in the critical task of differential diagnosis. For a clinician faced with a cancer patient on ICIs presenting with non-specific symptoms, the key question is often distinguishing ICIs-M from tumor progression, sepsis, or other treatment-related toxicities. In this context, an elevated SII or LAR has virtually no diagnostic value, as all these conditions can produce a similar inflammatory signature. Therefore, while these markers may hold some value as prognostic indicators—reflecting a patient's overall inflammatory state, nutritional status, and physiological reserve—their role in the specific diagnosis of ICIs-M is likely minimal. Their true utility may lie in identifying patients with a generalized hyper-inflammatory phenotype who are at high risk for poor outcomes from any cause, rather than in pinpointing cardiac-specific immune pathology. Rigorous prospective studies are required to dissect the prognostic contribution of these markers beyond their role as indicators of general patient frailty.

Beyond these composite indices, specific cytokines—including Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha(TNF-α), and IFN-γ—are mechanistically implicated in the pathogenesis of ICIs-M[43,44]. Elevated levels of IL-6 and TNF-α have been consistently linked to severe ICIs-M, and this association provides a strong mechanistic rationale for targeted second-line therapies in steroid-refractory cases. Specifically, agents such as tocilizumab (an IL-6 receptor antagonist) and infliximab (a TNF-α antagonist) are supported by this mechanistic link[45,46]. This suggests that the measurement of specific cytokines could evolve from a purely prognostic role to one that directly guides the selection of targeted second-line therapeutic strategies.

Integrated prognostic models: from biomarkers to clinical decisions

The goal of biomarker research is not to identify individual markers in isolation but to integrate them into robust prognostic models that can guide clinical decision-making. The complexity of ICIs-M, which sits at the nexus of immunology, cardiology, and oncology, demands a multi-parameter approach. Early attempts to create such models have emerged, but the field is still in its infancy.

Several groups have developed risk scores or nomograms, typically based on retrospective data, that incorporate a combination of clinical variables (e.g., LVEF, ECG abnormalities), and biomarker levels (e.g., peak troponin, CK)[47]. While these models represent a crucial first step, their performance has been modest, and they suffer from the limitations of the small, single-center datasets from which they were derived. A major challenge is that they often rely on static, admission-time variables and fail to incorporate the dynamic evolution of the patient's clinical or biomarker status. The true clinical course of ICIs-M is a rapidly evolving process, and a risk score calculated at admission may be obsolete within 24 hours.

A promising avenue for future investigation lies in the development of dynamic, multi-parameter risk stratification tools. To operationalize such a model, we propose defining a 'minimal viable dataset' comprising universally accessible parameters: quant-

itative cTn trajectory (delta change), ECG stability, and hemodynamic status (NT-proBNP)[24,48,49]. While advanced imaging like CMR provides depth, a dynamic risk model must rely on high-frequency data available at the bedside. Critically, we advocate for assessment at three physiological inflection points:

(1) Baseline (Day 0): To establish risk magnitude and identify high-risk phenotypes based on initial biomarker clusters[24,33].

(2) Early Response Phase (Hours 48–72): This interval aligns with the pharmacokinetic peak of high-dose corticosteroids. A failure of cTn to plateau or decline by this window could serve as a specific 'futility signal,' prompting the immediate addition of second-line agents (e.g., abatacept or ruxolitinib) rather than continuing ineffective steroid monotherapy[24,50].

(3) Subacute Phase (Day 7): To guide de-escalation. A sustained reduction in biomarkers (e.g., >50% drop in cTn) combined with stable conduction could validate the decision to taper intravenous steroids to oral formulations, whereas persistent elevation would mandate prolonged observation[26].

By structuring data collection around these actionable windows, the field can move from retrospective scoring to real-time precision management.

Recently, artificial intelligence (AI) and machine learning have been applied to this problem with promising results. A multimodal fusion AI model that integrated clinical data, ECGs, and biomarkers demonstrated good performance in predicting the development of myocarditis and subsequent MACE in patients starting ICI therapy. By integrating baseline electronic health record (EHR) tabular data with one-dimensional (1D) ECG signals through an end-to-end deep learning framework, the model achieved a superior AUC of 0.72. Most notably, the model demonstrated an exceptional negative predictive value (NPV) of 0.98, positioning it as a powerful screening tool[48]. The power of AI lies in its ability to identify complex, non-linear relationships within high-dimensional data that may be invisible to traditional statistical methods. However, the widespread adoption of these models faces significant hurdles. External validation in large, diverse cohorts is paramount to ensure generalizability. Furthermore, the "black box" nature of some AI models also presents a barrier to clinical adoption, as clinicians are often hesitant to trust predictions without a clear, understandable rationale. The challenge, therefore, is not only to build more accurate models but also to ensure they are validated, interpretable, and seamlessly integrated into clinical workflows.

Biomarkers to guide therapy: A precision medicine approach

Beyond diagnosis and prognosis, the holy grail for biomarker research is to guide therapy, enabling a precision medicine approach where treatment is tailored to the individual patient's risk profile and underlying biology. In ICIs-M, this concept is most critical in the context of corticosteroid therapy and the management of steroid-refractory disease.

High-dose intravenous corticosteroids followed by long-term oral corticosteroids are the primary standard therapy for ICIs-M. The influential multicenter registry study by Zhang et al. has established a strong association between early corticosteroid initiation and improved outcomes in ICIs-M[26]. Patients receiving treatment within 24 hours of admission experienced a MACE rate of only 7%, compared to 34.3% for those treated between 24–72 hours and 85.1% for those treated after 72 hours ($P < 0.001$)[26]. We acknowledge that the significant difference in MACE rates between early (<24 h) and late (>72 h) corticosteroid initiation (7.0% vs. 85.7%; adjusted HR 0.03) could be influenced by confounding by indication, as patients with delayed treatment may have had greater baseline complexity. However, to quantitatively assess the robustness of this finding against unmeasured confounding, we calculated an Expectation value (E-value)[51]. For the observed HR of 0.03, the E-value is approximately 66.1, indicating that an unmeasured confounder would need a risk ratio of at least 66.1 with both treatment timing and MACE to nullify the effect. Given this exceptionally high threshold, it is highly improbable that confounding alone could explain such a profound clinical benefit, suggesting that the early therapeutic window is of paramount importance in ICIs-M management. Similarly, high-dose corticosteroids ($\geq$ 500 mg/day methylprednisolone equivalent) were associated with significantly lower MACE rates (22.0%) compared to intermediate (54.6%) or low doses (61.9%, $P < 0.001$)[26]. These findings have profoundly influenced clinical practice and guideline recommendations.

Patients presenting with fulminant, classic manifestations are more readily recognized and treated immediately, whereas those with atypical or insidious presentations, potentially reflecting more complex underlying pathophysiology, experience diagnostic delays that manifest as delayed treatment initiation. In this scenario, the observed association between late treatment and poor outcomes may reflect the severity and complexity of the underlying disease rather than a missed therapeutic window. The inability of high-dose corticosteroids to overcome the adverse effect of delayed initiation further supports this interpretation, as one would expect a sufficiently potent intervention to partially compensate for timing if the relationship were purely causal[26].

This analysis does not diminish the importance of prompt treatment. It must be emphasized that in the absence of definitive randomized controlled trial (RCT) evidence, early and high-dose corticosteroid administration remains the undisputed standard of care for suspected ICIs-M. The critique of confounding by indication serves not to question this practice, but to highlight that our greatest challenge may be "diagnostic delay" rather than "treatment delay." It calls for the development of more sensitive surveillance strategies and lower thresholds for empiric treatment to capture atypical cases, rather than promoting any deviation from the current emergency management principles.

The practical application of biomarkers in guiding corticosteroid therapy represents an opportunity to move toward precision medicine. We propose a theoretical framework where a rapidly rising cTnT trajectory, for instance, could be evaluated in prospective trials as a potential trigger for empiric high-dose steroid initiation, potentially capturing atypical cases earlier. Conversely, biomarkers might theoretically help identify a subgroup of low-risk patients (e.g., those with minimal cTnT elevation, normal inflammatory markers, and absence of septal LGE on CMR)who could be candidates for de-escalation trials to determine if they can be safely managed with lower doses of steroids, thus minimizing the risks of high-dose immunosuppression, which may include potential negative impacts on cancer outcomes[52].

A significant proportion of patients, estimated at up to 50%, do

not respond adequately to high-dose corticosteroids alone, leading to steroid-refractory myocarditis[53]. This is a pivotal and often fatal juncture in the patient's course. Currently, the decision to add a second-line immunosuppressive agent is made empirically after a perceived failure of steroids, but there are no validated tools to predict who will be refractory from the outset. This is a critical gap where biomarkers could have a major impact. Conceptually, a baseline biomarker profile of extreme risk—for example, a massively elevated cTnT (>100x URL), a profoundly elevated SII or LAR, and specific cytokine signatures (e.g., very high IL-6)—might identify high-risk patients. It is biologically plausible to hypothesize that these patients may benefit from upfront combination immunosuppression, a strategy that warrants rigorous testing in randomized controlled trials. Validating such a predictive profile is a high-priority research area. Furthermore, biomarkers could guide the choice of second-line agent. The current armamentarium includes tocilizumab, infliximab, and abatacept (a CTLA-4 agonist), among others[54]. Selection of second-line agents should be tailored to the patient's clinical phenotype and cytokine profile (cytokine-guided therapy) rather than an empirical approach. For instance, while Abatacept is favored for isolated cardiac involvement, Infliximab has shown a superior response rate in systemic inflammatory presentations (Table 2).

Table 2. Second-line Therapeutic Options for Steroid-Refractory ICIs-M.

Target Cytokine/Pathway	Therapeutic Agent	Mechanism of Action	Clinical Utility and Reported Efficacy
CD80/CD86 - CD28 Axis (T-cell Costimulation)	Abatacept	CTLA-4 agonist: Binds to CD80/86 on APCs to block CD28-mediated T-cell activation.	Indicated for isolated myocarditis and severe cases. Latest data show that combination with Ruxolitinib can reduce mortality to <5%. Rapidly lowers troponin levels and stabilizes cardiac electrical activity[50].
JAK-STAT Pathway (Cytokine Storm)	Ruxolitinib / Tofacitinib (JAK Inhibitors)	JAK Inhibitor: Blocks signaling of multiple pro-inflammatory cytokines (IFN-γ, IL-2, etc.).	Previous guidelines primarily listed Tofacitinib; Ruxolitinib now has stronger evidence. High salvage success rate for steroid-refractory cases and promotes rapid recovery of LVEF. Convenient oral administration; becoming a standard second-line regimen[50,55].
T-cell Depletion	Anti-thymocyte globulin (ATG)	Polyclonal antibody: Causes rapid T-cell depletion via complement/cell-mediated cytotoxicity.	Indicated for fulminant cases with hemodynamic instability. It is a critical life-saving agent particularly for patients with concomitant Myasthenia Gravis (MG)[6,56].
CD52 (Lymphocytes)	Alemtuzumab	Anti-CD52 mAb: Causes profound and rapid lymphocyte depletion (pan-lymphocyte).	Reserved for near-terminal cases where other therapies (Steroids/Abatacept/ATG) have failed. Can achieve biochemical reversal but requires high vigilance for infection risks[57].
TNF-α	Infliximab	Anti-TNF-α mAb: Inhibits Tumor Necrosis Factor-alpha.	Important Update: Although effective for myocarditis, it increases the risk of cardiovascular death (OR 12.0) in myocarditis patients with heart failure. Use is limited to patients with normal LVEF and primary myocarditis[56].
Immune Regulation	Intravenous immunoglobulins (IVIG)	Immunomodulator: Neutralizes autoantibodies; modulates Fc receptors.	Generally, not used alone as a potent second-line agent for myocarditis, but rather as an adjuvant. Highly valuable for patients with concomitant Myositis or Guillain-Barré Syndrome (GBS)[33].
IL-6 Signaling	Tocilizumab	IL-6 receptor antagonist: Blocks IL-6 mediated inflammation.	Considered if the patient exhibits significant Cytokine Release Syndrome (CRS)-like features (e.g., very high fever, extremely high CRP). Evidence is weaker than Abatacept for isolated cardiac-specific inflammation[33,58,59].
Lymphocyte Proliferation	Mycophenolate (MMF)	IMPDH inhibitor: Blocks de novo purine synthesis in T/B cells.	Slow onset of action. Preferred for non-fulminant subacute cases or as a long-term steroid-sparing maintenance agent during corticosteroid tapering[34].

While the literature on ICIs-M is expanding rapidly, its methodological rigor remains frequently inadequate. Most studies rely on retrospective, single-center case series with inherently small sample sizes. This overreliance on retrospective data introduces substantial biases, including confounding, selection bias, and publication bias. Furthermore, the field is critically hindered by a lack of standardization: heterogeneity in key definitions, such as those for MACE, the use of disparate biomarker assays, and variable diagnostic criteria, renders cross-study comparisons and meta-analyses exceedingly challenging. The current literature is invaluable for hypothesis generation but must be interpreted with extreme caution. Most of the existing "evidence" reflects strong associations rather than proven causation, underscoring the urgent need for confirmation through well-designed prospective, controlled studies.

Conclusion

ICIs-M remains a critical, high-mortality challenge, rapidly moving from case reports to partial mechanistic understanding. Peripheral biomarkers, especially cTn, are currently indispensable but

imperfect tools for diagnosis and risk stratification. The future demands a fundamental shift from a reactive "diagnose-and-treat" model to a proactive "predict-and-prevent" paradigm. Key research priorities to achieve this vision include:

Solidifying Foundational Tools: Resolving the "troponin paradox" through head-to-head assay comparisons and standardizing the MACE definition. Integrating Risk Assessment: Developing and validating multi-parameter risk models that incorporate biomarkers, imaging (e.g., septal LGE), and clinical features to replace static, single-biomarker reliance. Targeting Prevention: Leveraging advancements like "liquid biopsy" (TCR sequencing) to detect autoreactive T-cell clones before injury and moving toward biomarker-guided precision therapy. Achieving zero preventable deaths from ICIs-M requires rigorous prospective studies and unprecedented collaboration across cardio-oncology, immunology, and basic science.

Abbreviations

AAR, Aspartate Aminotransferase-to-Albumin Ratio; AI, artificial intelligence; ALT, alanine aminotransferase; APC, Antigen-Presenting Cells; AST, aspartate aminotransferase; ATG, Antithymocyte globulin; AUC, Area Under Curve; BNP, B-type natriuretic peptide; CK, Creatine kinase; CK-MB, creatine kinase isoenzymes-MB; CMR, cardiac magnetic resonance; CRP, C-reactive protein; CRS, Cytokine Release Syndrome; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; cTn, cardiac troponins; cTnI, cardiac troponin I; cTnT, cardiac troponin T; ECG, electrocardiogram; Echo, Echocardiography; EHR, electronic health record; EMB, endomyocardial biopsy; E-value, Expectation value; GBS, Guillain-Barre Syndrome; GLS, global longitudinal strain; ICIs, immune checkpoint inhibitors; ICIs-M, immune checkpoint inhibitors-associated myocarditis; IFN-γ, interferon-gamma; IL-6, Interleukin-6; IMPDH, Inosine Monophosphate Dehydrogenase; irAEs, immune-related adverse events; IVIG, Intravenous immunoglobulins; JAK, Janus Kinase; LAR, Lactate Dehydrogenase-to-Albumin Ratio; LDH, lactate dehydrogenase; LGE, late gadolinium enhancement; LMR, Lymphocyte-to-Monocyte Ratio; LVEF, left ventricular ejection fraction; mAb, monoclonal Antibody; MACE, major adverse cardiovascular events; MG, Myasthenia Gravis; MYHCA, alpha-myosin heavy chain; MYH6, myosin heavy chain 6; NER, Neutrophil-to-Eosinophil Ratio; NLR, Neutrophil-to-Lymphocyte Ratio; NPV, negative predictive value; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PD-1/PD-L1, programmed cell death protein 1/programmed cell death-ligand 1; PLR, Platelet-to-Lymphocyte Ratio; RCT, randomized controlled trial; SII, Systemic Immune-Inflammation Index; STAT, Signal Transducer and Activator of Transcription; TNF-α, Tumor Necrosis Factor-alpha; URL, Upper Reference Limit.

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Conflicts of interest

The author declares no conflicts of interest.

Authors' contributions

QY, YTZ and WWC: Literature Reading and Recording Summary. QY and YTZ: Writing original draft. YHK and LYZ: Review and editing.

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