

High-Sensitivity Troponin I and NT-proBNP as Early Indicators of Disease Severity and Prognostic Markers in Immune Checkpoint Inhibitor-Associated Fulminant Myocarditis

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Background: The study aims to investigate the utility of high-sensitivity cardiac troponin I (hs-cTnI) and N-terminal pro-brain natriuretic peptide (NT-proBNP) measured at initial presentation as indicators of disease severity and prognostic markers in patients with immune checkpoint inhibitor (ICI)-associated myocarditis. While these biomarkers reflect myocardial injury and ventricular dysfunction—consequences of the underlying pathology—their levels at diagnosis may aid in early risk stratification and identification of patients likely to follow a fulminant course.

Methods: This study implemented a retrospective cohort design, involving 341 patients identified with myocarditis associated with immune checkpoint inhibitors (ICIs). The participants were divided into two categories: those with fulminant myocarditis (62 subjects) and those with non-fulminant myocarditis (279 subjects). An in-depth examination was conducted on their clinical features, biomarker concentrations, and health outcomes. To ascertain the predictive capability of these biomarkers, multivariable logistic regression analyses and survival assessments were utilized. Additionally, a subgroup analysis was carried out by classifying patients into high and low biomarker groups according to the optimal cutoff points determined through receiver operating characteristic (ROC) curve evaluations. The subgroups were then compared regarding treatment modalities (including immunosuppressive therapy and mechanical circulatory support) and clinical outcomes (including ICU admission, complications, and survival).

Results: Patients with fulminant myocarditis had significantly higher hs-cTnI (1.38 ± 0.56 vs. 0.22 ± 0.10 ng/mL) and NT-proBNP (2384.43 ± 912.67 vs. 528.72 ± 192.33 pg/mL) levels (both $P < 0.001$). Both biomarkers were independent predictors of fulminant disease, with areas under the ROC curve of 0.984 and 0.981, respectively. Optimal cutoffs were 0.435 ng/mL for hs-cTnI and 970.07 pg/mL for NT-proBNP. Patients above these thresholds received more intensive therapy and had worse outcomes, including lower 3-month survival (75.86% vs. 97.64%, $P < 0.001$).

Conclusion: Hs-cTnI and NT-proBNP levels at presentation are strong indicators of myocardial injury severity and ventricular dysfunction in ICI-associated myocarditis. Their measurement facilitates early risk stratification, identifying patients at highest risk for fulminant disease who may benefit from intensive monitoring and timely intervention. Additionally, pre-existing cardiovascular comorbidities remain crucial for identifying vulnerable populations prior to ICI initiation.

Keywords: tumor treatment-related fulminant myocarditis, high-sensitivity cardiac troponin I, N-terminal pro-brain natriuretic peptide, immune checkpoint inhibitors, risk stratification, prognostic biomarkers

Introduction

The advent of immune checkpoint inhibitors (ICIs) has revolutionized the treatment paradigm for numerous types of cancer. These therapies function by obstructing inhibitory pathways, including PD-1/PD-L1 and CTLA-4, thereby boosting the body's immune response against tumors. This enhancement results in substantial and lasting clinical

advantages.¹⁻³ As a result, the use of ICIs is expected to continue expanding substantially. However, this potent immune activation is a double-edged sword, as it may inadvertently target healthy tissues, resulting in a spectrum of immune-related adverse events (irAEs).^{1,4} These toxicities can involve almost any organ system, with the skin, intestinal mucosa, endocrine glands, and lungs being the most commonly affected sites.⁴

Among irAEs, cardiovascular complications, particularly ICI-associated myocarditis, present a significant clinical concern. This is largely attributed to their propensity for swift progression and elevated risk of mortality.^{5,6} Although the reported incidence is relatively low, ranging from approximately 0.27% to 1.14% with monotherapy and increasing significantly with combination regimens,^{5,7,8} the associated fatality rate remains alarmingly high, estimated between 30% and 50%.^{5,6,9} This discrepancy between rarity and severity underscores a critical gap in modern oncology practice. The clinical presentation of ICI-myocarditis is highly heterogeneous, typically emerging within the first few months of treatment.^{7,10} It may range from non-specific symptoms such as fatigue and chest pain to fulminant presentations characterized by acute hemodynamic compromise, severe arrhythmias, and cardiogenic shock, which represent the most devastating form of the disease.^{10,11}

Diagnosing ICI-associated myocarditis, particularly its fulminant variant, remains challenging. Symptoms are often non-specific, and the clinical course can deteriorate rapidly, narrowing the window for effective intervention.^{12,13} This diagnostic difficulty underscores the urgent need for reliable biomarkers to facilitate early detection and risk stratification. Cardiac troponin (cTn), serving as a highly specific indicator for myocardial damage, plays a pivotal role in the assessment and diagnosis.^{10,14} The development of high-sensitivity assays (hs-cTn) represents a major advancement, enabling the detection of minor myocardial necrosis with up to 100-fold greater precision than conventional tests.¹⁵ Despite this improved sensitivity, a key limitation remains: elevated hs-cTn indicates myocardial injury but does not elucidate the underlying mechanism or reliably predict progression to fulminant deterioration.^{16,17} Furthermore, the optimal troponin subtype for risk stratification in this context is under investigation. A recent study by Lehmann et al suggested that high-sensitivity troponin T (hs-cTnT) may have a stronger association with major adverse cardiac events than high-sensitivity cardiac troponin I (hs-cTnI) in ICI-myocarditis.¹⁸ However, the widespread clinical availability of hs-cTnI, supports its pragmatic use as a readily accessible biomarker for early risk assessment, which is the focus of this study.

Current diagnostic strategies integrate clinical symptoms, cardiac biomarkers, and imaging findings. However, conventional biomarkers such as troponin and natriuretic peptides, while essential for diagnosis, are not fully optimized for identifying patients at highest risk of developing severe or fulminant disease.¹⁹ It should be emphasized that N-terminal pro-brain natriuretic peptide (NT-proBNP) elevation is a consequence of increased ventricular wall stress secondary to myocardial dysfunction, manifesting as part of the heart failure spectrum in these patients. Similarly, hs-cTnI release reflects ongoing myocardial necrosis.^{20,21} Thus, while these biomarkers are invaluable for diagnosis and severity assessment, they represent downstream effects of the pathological process rather than pre-treatment predictive factors. Their clinical utility lies in early identification of patients with more severe myocardial involvement who require intensified monitoring and therapeutic intervention.

This deficiency in risk assessment underscores the necessity for dependable and easily-administered predictive instruments that can be implemented early in the diagnostic process. Recognizing individuals with ICI-myocarditis who are likely to progress to a fulminant course could facilitate preemptive escalation of care and more aggressive immunosuppressive strategies, potentially improving clinical outcomes. Consequently, this study seeks to methodically examine and validate the prognostic utility of hs-cTnI and NT-proBNP levels measured at the initial presentation. We aimed to determine their independent and combined value for specifically forecasting the development of fulminant myocarditis and subsequent clinical outcomes in this high-risk population, and to establish clinically applicable cutoff values to facilitate early risk stratification.

Materials and Methods

Study Design

This retrospective cohort study was carried out at a single tertiary medical center and encompassed 341 cancer patients who underwent immune checkpoint inhibitor (ICI) therapy from January 2023 to June 2024. The primary aim was to

investigate prognostic markers in patients with diagnosed ICI-associated myocarditis, not to determine the incidence of myocarditis among all ICI recipients. Therefore, a systematic screening of the total ICI-treated population to identify all potential myocarditis cases was not performed; instead, we identified patients with an established diagnosis. Potentially eligible cases were initially identified from the hospital's electronic health record (EHR) system by a research coordinator using a broad search strategy. This search employed International Classification of Diseases, Tenth Revision (ICD-10) codes for myocarditis (I40, I41, I51.4) and cardiomyopathy (I42), combined with keywords for immune checkpoint inhibitors ("anti-PD-1", "anti-PD-L1", "pembrolizumab", "nivolumab", "atezolizumab", "durvalumab", etc). The resulting patient list and clinical charts were then independently reviewed by two investigators to adjudicate eligibility and confirm the diagnosis of ICI-associated myocarditis based on the predefined 2022 ESC/IC-OS criteria²² (see section 1.2). Information regarding demographic details, clinical symptoms, laboratory results, imaging reports, treatment strategies, and clinical outcomes was gathered and analyzed.

This study is reported following the RECORD (REporting of studies Conducted using Observational Routinely-collected Data) guidelines. The study protocol received approval from the Institutional Review Board and Ethics Committee of Henan Provincial People's Hospital (Approval No. 2024-1-112), adhering to the guidelines set forth in the Declaration of Helsinki. Given the retrospective nature of the study, informed consent was waived by the Institutional Review Board and Ethics Committee of Henan Provincial People's Hospital.

Case Selection

Participants were eligible if they were 18 years of age or older, had a histologically confirmed cancer diagnosis, and had undergone at least one cycle of treatment with an ICI. For this study, we only included patients who received monotherapy with either an anti-PD-1 or an anti-PD-L1 agent. Patients who had received anti-CTLA-4 therapy (eg, ipilimumab), either as monotherapy or in combination with a PD-1/PD-L1 inhibitor, were not included in this cohort to maintain treatment regimen homogeneity. The diagnosis of ICI-associated myocarditis for all included patients was rigorously adjudicated based on the 2022 ESC/IC-OS criteria,²² requiring a combination of: (1) clinical manifestations suggestive of cardiac involvement; (2) elevated cardiac biomarkers (hs-cTnI and/or NT-proBNP) above the 99th percentile upper reference limit; and (3) corroborative evidence from cardiac imaging (echocardiography or cardiac magnetic resonance) or endomyocardial biopsy. All cases were reviewed and confirmed by a cardio-oncology multi-disciplinary team. Patients were excluded if they had a pre-existing diagnosis of myocarditis prior to ICI initiation, other active malignancies, severe autoimmune diseases requiring ongoing immunosuppressive therapy, suspected or confirmed acute coronary syndrome or pulmonary embolism at the time of myocarditis diagnosis, end-stage heart failure (NYHA Class IV) prior to ICI, severe hepatic impairment (Child-Pugh C), or incomplete laboratory, imaging, or clinical outcome data necessary for analysis.

Diagnostic and Grouping Criteria

Patients were stratified based on the development of fulminant myocarditis, which was defined according to the 2022 ESC Guidelines for Cardio-Oncology.²³ Fulminant myocarditis was diagnosed if a patient met at least one of the following major clinical criteria: acute hemodynamic compromise (cardiogenic shock), severe ventricular arrhythmias, or conduction disturbances requiring intensive care unit (ICU) admission and either mechanical circulatory support or vasoactive drug support. This clinical diagnosis required concomitant support from elevated cardiac biomarkers and confirmatory imaging (Figure 1), or histopathological confirmation. Thus, fulfillment of any one of these major clinical criteria, alongside the requisite laboratory/imaging evidence, was sufficient for classification as fulminant myocarditis. Using these criteria, 62 patients were assigned to the fulminant myocarditis group, while the remaining 279 patients were placed in the non-fulminant myocarditis group.

Data Collection

Demographic and Clinical Characteristics

Comprehensive demographic, clinical, laboratory, and outcome data were systematically retrieved from the hospital's electronic health record system. Cancer-related information, including primary cancer type and stage, as well as the

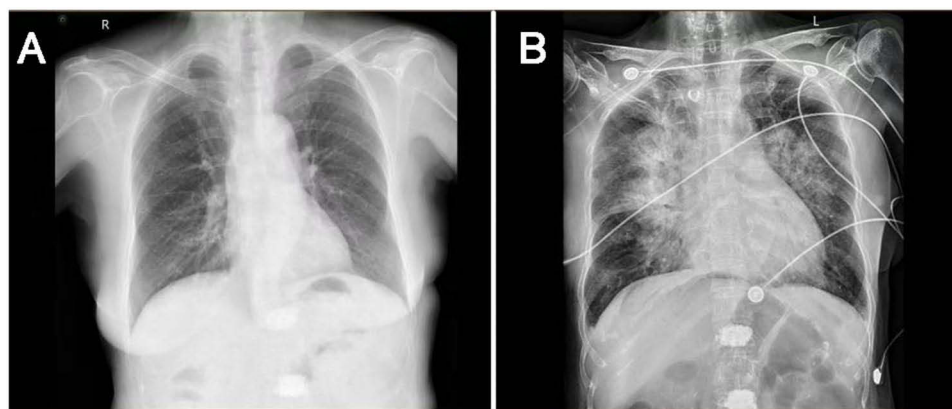


Figure 1 Representative chest radiographs of a patient with fulminant myocarditis. **(A)** Chest X-ray at admission (day 13) showing clear lung fields. **(B)** Chest X-ray at the onset of fulminant myocarditis (day 17) revealing decreased lung permeability and pulmonary edema.

specific ICI agent administered, was also documented. Clinical symptoms present at or within one week prior to the diagnosis of myocarditis were carefully assessed, including fever (body temperature $\geq 38.0^{\circ}\text{C}$), chest pain, consciousness disorder (eg, confusion, syncope), respiratory symptoms (dyspnea, cough), gastrointestinal symptoms (nausea, vomiting), fatigue, and palpitations.

Clinical Symptom Assessment

The presence of early clinical symptoms preceding or accompanying the diagnosis of myocarditis was carefully evaluated. Symptoms of interest included fever (body temperature $\geq 38.0^{\circ}\text{C}$), chest pain, consciousness disorder (eg, confusion, syncope), respiratory symptoms (eg, dyspnea, cough), gastrointestinal symptoms (eg, nausea, vomiting), fatigue, and palpitations. These symptoms were identified and recorded based on physician notes, nursing records, and patient-reported outcomes documented in the clinical charts.

Laboratory Biomarker Measurements

Venous blood samples for laboratory biomarker analysis were collected at the time of initial clinical presentation leading to the diagnosis of myocarditis, following an overnight fast where feasible in stable patients. Samples were processed within 2 hours of collection. Complete blood count (CBC) was assessed utilizing a standard automated hematology analyzer (Sysmex series automated line). C-reactive protein (CRP) levels were determined on a specific protein analyzer (PA-990). Cardiac biomarkers, including hs-cTnI, NT-proBNP, and creatine kinase-MB (CK-MB), were quantified using chemiluminescence immunoassays on a single, unified platform (Ortho VITROS 5600 analyzer).

Electrocardiographic (ECG) and Echocardiographic Evaluation

A standard 12-lead electrocardiogram (ECG) was obtained for all patients at the time of initial presentation using a MAC 5500 HD ECG machine (GE Healthcare). Parameters assessed included QRS complex duration (>120 ms defined as abnormal), ST-segment elevation (≥ 1 mm in two contiguous leads), T-wave inversion, and the presence of conduction blocks. Transthoracic echocardiography was performed using a Vivid E95 system (GE Healthcare) within 48 hours of myocarditis diagnosis. Experienced echocardiographers measured left ventricular ejection fraction (LVEF) using the biplane Simpson's method, left ventricular end-diastolic dimension (LVD), left ventricular end-systolic dimension (LVS), left atrial (LA) diameter, and interventricular septal thickness at end-diastole, following American Society of Echocardiography guidelines.

Treatment Modalities and Clinical Outcome Measures

Detailed information regarding the treatment for myocarditis was collected. Immunosuppressive therapy was categorized as: 1) High-dose corticosteroids (eg, methylprednisolone ≥ 500 mg/day intravenously for 3 days); 2) Second-line immunosuppressants (eg, mycophenolate mofetil, infliximab, antithymocyte globulin); and 3) Intravenous immunoglobulin (IVIG). Treatment decisions were individualized by a multidisciplinary cardio-oncology team based on clinical severity, guided by

contemporary guidelines.^{22,23} In general, high-dose corticosteroids were initiated for patients with moderate to severe myocarditis. Escalation to second-line immunosuppressants or IVIG was considered in cases of fulminant myocarditis or in patients with a poor clinical response to initial high-dose steroid therapy. The utilization of mechanical circulatory support (MCS) was documented, encompassing the use of intra-aortic balloon pumps (IABP) and veno-arterial extracorporeal membrane oxygenation (VA-ECMO). The clinical outcomes evaluated included: admission to the intensive care unit (ICU), peak serum lactate levels during hospitalization, incidence of acute kidney injury, in-hospital mortality, cardiovascular death, and the 3-month survival rate. Furthermore, we collected data on specific life-threatening complications, including the occurrence of severe bradyarrhythmias, severe ventricular tachyarrhythmias, and cardiogenic shock.

Statistical Analysis

Statistical evaluations were conducted utilizing SPSS software (version 29.0, SPSS Inc.) alongside R programming (version 4.2.1). For categorical data, frequencies and percentages were calculated and comparisons were made through the chi-square test or Fisher's exact test, depending on the suitability of the dataset. Continuous variables underwent normality testing via the Shapiro–Wilk test. Data following a normal distribution were reported as means $\pm$ standard deviations and analyzed using independent samples *t*-tests. Conversely, non-normally distributed data were depicted as medians with interquartile ranges and examined using the Mann–Whitney *U*-test. To refine the variable selection process and prevent overfitting, the least absolute shrinkage and selection operator (LASSO) regression method was applied for initial feature selection, facilitated by the “glmnet” package in R. Variables selected by the LASSO model (with non-zero coefficients at the optimal lambda value) were then entered into a traditional multivariate logistic regression model to pinpoint independent risk factors for fulminant myocarditis and to obtain the final odds ratios (ORs) along with 95% confidence intervals (CIs). The efficacy of hs-cTnI and NT-proBNP in prediction was assessed through receiver operating characteristic (ROC) curve analysis, where optimal cutoff points were identified by maximizing Youden's index. A two-sided *P*-value below 0.05 was deemed indicative of statistical significance.

Results

Baseline Characteristics and Clinical Profiles

Table 1 encapsulates the foundational demographic and clinical features of the study cohort. It was observed that individuals diagnosed with fulminant myocarditis (*n*=62) were notably older and exhibited a greater incidence of

Table 1 Baseline Demographic and Clinical Characteristics of Patients with and without Fulminant Myocarditis

Parameters	Non-Fulminant Myocarditis (n=279)	Fulminant Myocarditis (n=62)	<i>t</i> / χ^2	<i>P</i> value
Age (years)	42.83 $\pm$ 11.24	53.67 $\pm$ 9.86	7.017	< 0.001
Body Mass Index (kg/m ²)	23.51 $\pm$ 3.08	24.39 $\pm$ 3.72	1.74	0.086
Gender (Male/Female)	162/117	38/24	0.218	0.641
Comorbidities [n (%)]				
Hypertension	59 (21.15%)	28 (45.16%)	15.394	< 0.001
Diabetes	32 (11.47%)	15 (24.19%)	6.911	0.009
Coronary Artery Disease	26 (9.32%)	12 (19.35%)	5.16	0.023
Chronic Kidney Disease	21 (7.53%)	10 (16.13%)	4.542	0.033
Atrial Fibrillation	18 (6.45%)	7 (11.29%)	1.108	0.292
Dyslipidemia	47 (16.85%)	15 (24.19%)	1.841	0.175
Prior Stroke	14 (5.02%)	4 (6.45%)	0.02	0.887
Neuromuscular irAEs [n (%)]				
Myositis	26 (9.32%)	22 (35.48%)	28.713	< 0.001
Myasthenia Gravis	9 (3.23%)	12 (19.35%)	20.129	< 0.001

(Continued)

Table 1 (Continued).

Parameters	Non-Fulminant Myocarditis (n=279)	Fulminant Myocarditis (n=62)	t/ χ^2	P value
Thymoma (active or prior) [n (%)]	4 (1.43%)	5 (8.06%)	6.291	0.012
Cancer Type [n (%)]			0.925	0.819
Lung Cancer	124 (44.44%)	26 (41.94%)		
Renal Cell Carcinoma	58 (20.79%)	15 (24.19%)		
Melanoma	42 (15.05%)	11 (17.74%)		
Others	55 (19.71%)	10 (16.13%)		
ICI Type [n (%)]			0.064	0.800
Anti-PD-I	198 (70.97%)	45 (72.58%)		
Anti-PD-LI	81 (29.03%)	17 (27.42%)		

Note: Thymoma: a neoplasm originating from the thymic epithelial cells, which may be associated with paraneoplastic autoimmune disorders including myasthenia gravis and myocarditis.

Abbreviations: BMI, Body Mass Index; ICI, Immune Checkpoint Inhibitor; PD-I, Programmed Cell Death Protein I; irAEs, immune-related adverse events; PD-LI, Programmed Death-Ligand I.

hypertension, diabetes, coronary artery disease, chronic kidney disease, neuromuscular irAEs and active or previous history of thymoma, cancer type in contrast to those with non-fulminant myocarditis (n=279) (all $P < 0.05$). Nevertheless, there were no marked distinctions in terms of body mass index, gender distribution, atrial fibrillation, dyslipidemia, history of stroke, or ICI type between the two groups under comparison.

Early Symptoms

Clinical manifestations either preceding or at the time of myocarditis diagnosis were compared amongst the groups, as detailed in Table 2. It was found that symptoms such as chest pain and disturbances of consciousness (including confusion or syncope) occurred significantly more often in patients suffering from fulminant myocarditis (with P-values of 0.004 and less than 0.001, respectively). In contrast, the prevalence of fever, respiratory symptoms, gastrointestinal symptoms, fatigue, and palpitations was not significantly different. This suggests that chest pain and neurological manifestations are key early clinical indicators of a more severe, fulminant course.

Laboratory Markers

As illustrated in Figure 2, patients with fulminant myocarditis exhibited significantly elevated levels of all measured inflammatory and cardiac biomarkers compared to the non-fulminant group (all $P < 0.001$). Marked differences were observed in white blood cell count (12.84 ± 4.12 vs. $8.63 \pm 2.41 \times 10^9/L$), C-reactive protein (16.38 ± 6.82 vs. 5.47 ± 2.23 mg/L), high-sensitivity troponin I (1.38 ± 0.56 vs. 0.22 ± 0.10 ng/mL), NT-proBNP (2384.43 ± 912.67 vs. 528.72 ± 192.33 pg/mL), and creatine kinase-MB (29.76 ± 11.34 vs. 8.28 ± 3.52 ng/mL). These results demonstrate a pronounced systemic inflammatory response and severe myocardial injury in patients with fulminant myocarditis.

Table 2 Early Symptoms and Laboratory Markers Between the Two Groups [n (%)]

Parameters	Non-Fulminant Myocarditis (n=279)	Fulminant Myocarditis (n=62)	χ^2	P value
Fever	73 (26.16%)	20 (32.26%)	0.950	0.330
Chest Pain	42 (15.05%)	19 (30.65%)	8.395	0.004
Consciousness Disorder	8 (2.87%)	14 (22.58%)	29.478	< 0.001
Respiratory Symptoms	96 (34.41%)	22 (35.48%)	0.026	0.872
Gastrointestinal Symptoms	58 (20.79%)	19 (30.65%)	2.819	0.093
Fatigue	134 (48.03%)	32 (51.61%)	0.261	0.610
Palpitations	67 (24.01%)	16 (25.81%)	0.088	0.766

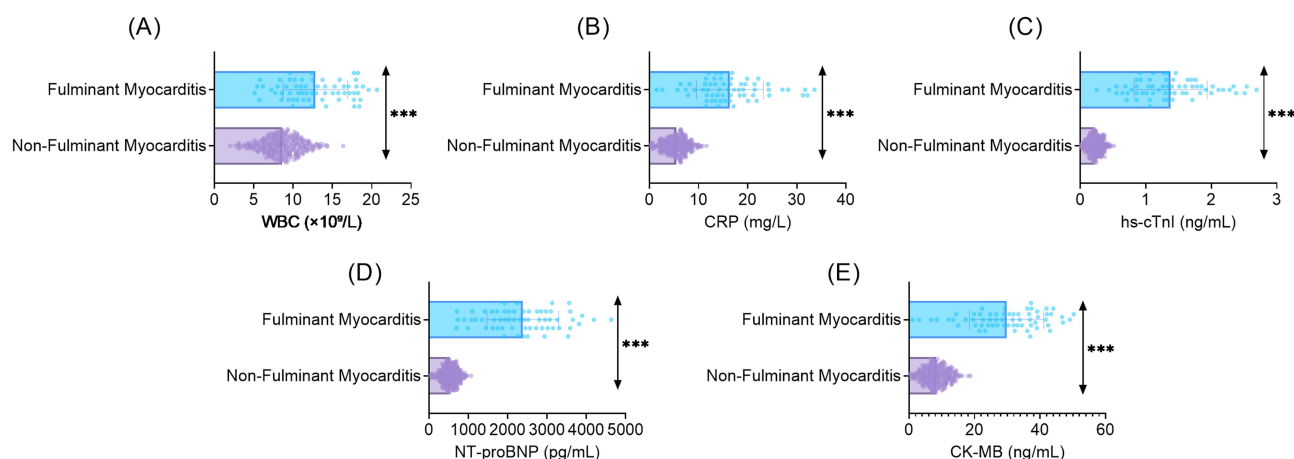


Figure 2 Comparative Analysis of Baseline Inflammatory Markers Between Patient Groups. (A) WBC; (B) CRP; (C) hs-cTnI; (D) NT-proBNP; (E) CK-MB.

Note: *** $p < 0.001$.

Abbreviations: WBC, White Blood Cell; CRP, C-Reactive Protein; hs-cTnI, high-sensitivity Cardiac Troponin I; NT-proBNP, N-terminal pro-Brain Natriuretic Peptide; CK-MB, Creatine Kinase-MB.

Imaging Data

Notable distinctions in electrocardiographic and echocardiographic parameters were identified between the groups, as summarized in Table 3. The fulminant myocarditis group had a higher prevalence of QRS duration >120 ms, ST-segment elevation, and conduction blocks (all $P < 0.05$). These electrical abnormalities, particularly conduction blocks, are clinical correlates of the extensive myocardial injury and inflammation affecting the cardiac conduction system. Echocardiography revealed significantly impaired left ventricular function, evidenced by a lower left ventricular ejection fraction, evidenced by a lower left ventricular ejection fraction ($34.92 \pm 11.89\%$ vs. $56.18 \pm 8.61\%$, $P < 0.001$) and a larger left ventricular end-systolic dimension (40.89 ± 6.12 mm vs. 32.67 ± 4.48 mm, $P < 0.001$) in the fulminant group. This confirms that fulminant myocarditis is associated with more severe electrical instability and profound systolic dysfunction.

LASSO-Based Logistic Regression Analysis for Fulminant Myocarditis Risk

Feature selection via LASSO regression identified key variables for the prediction model (Supplementary Figure 1). Subsequent multivariable logistic regression analysis established high-sensitivity troponin I (OR= 18.427), NT-proBNP (OR= 14.565), left ventricular ejection fraction (OR= 6.788), and QRS duration >120 ms (OR= 3.129) as independent

Table 3 Comparison of Imaging Data Between the Two Groups

Parameters	Non-Fulminant Myocarditis (n=279)	Fulminant Myocarditis (n=62)	χ^2/t	P
ECG Findings [n (%)]				
QRS duration >120 ms	38 (13.62%)	32 (51.61%)	44.883	< 0.001
ST elevation	24 (8.60%)	11 (17.74%)	4.601	0.032
T wave inversion	51 (18.28%)	15 (24.19%)	1.137	0.286
Conduction block	31 (11.11%)	15 (24.19%)	7.44	0.006
Echocardiography				
LVEF (%)	56.18 ± 8.61	34.92 ± 11.89	13.325	< 0.001
LVD (mm)	48.34 ± 5.72	49.87 ± 6.93	1.622	0.109
LVS (mm)	32.67 ± 4.48	40.89 ± 6.12	9.994	< 0.001
LA (mm)	35.41 ± 4.28	37.12 ± 5.34	2.366	0.020
Septal thickness (mm)	9.18 ± 1.31	9.56 ± 1.64	1.707	0.092

Abbreviations: ECG, Electrocardiogram; LVEF, Left Ventricular Ejection Fraction; LVD, Left Ventricular end-Diastolic dimension; LVS, Left Ventricular end-Systolic dimension; LA, Left Atrial.

Table 4 Multivariable Logistic Regression Analysis of Independent Risk Factors for Fulminant Myocarditis (Using LASSO-Selected Variables)

Variables	Univariable Analysis		Multivariable Analysis	
	OR (95% CI)	P	OR (95% CI)	P
Age	1.083 (1.057–1.122)	<0.001	1.041 (1.006–1.068)	0.048
Hypertension	2.814 (1.567–5.068)	<0.001	1.921 (0.940–3.892)	0.073
hs-cTnI	24.611 (11.343–53.475)	<0.001	18.427 (7.854–43.282)	<0.001
NT-proBNP	20.894 (9.718–44.620)	<0.001	14.565 (6.241–374.157)	<0.001
LVEF	12.314 (6.12–24.859)	<0.001	6.788 (2.890–15.911)	<0.001
QRS	8.45 (4.324–16.526)	<0.001	3.129 (1.381–7.017)	0.006

Abbreviations: OR, Odds Ratio; CI, Confidence Interval; hs-cTnI, high-sensitivity Cardiac Troponin I; NT-proBNP, N-terminal pro-Brain Natriuretic Peptide; LVEF, Left Ventricular Ejection Fraction.

risk factors for fulminant myocarditis (Table 4). This identifies a core set of biomarkers and imaging parameters that independently predict the development of fulminant disease.

Predictive Performance of Hs-cTnI and NT-proBNP

The robust predictive capacity of the key biomarkers identified in the regression analysis was quantitatively assessed using ROC analysis (Figure 3). High-sensitivity troponin I demonstrated an optimal cutoff of 0.435 ng/mL, with an AUC of 0.984, sensitivity of 97.4%, and specificity of 97.6%. NT-proBNP showed a cutoff of 970.07 pg/mL, with an AUC of 0.981, sensitivity of 92.5%, and specificity of 98.6% (Figure 3). Both hs-cTnI and NT-proBNP exhibit outstanding discriminative ability for identifying fulminant myocarditis, providing validated thresholds for clinical use.

Treatment and Clinical Outcomes Stratified by Biomarker Levels

Patients with hs-cTnI >0.435 ng/mL received significantly more intensive immunosuppressive therapy and mechanical circulatory support compared to those with lower levels (all *P*<0.001, Table 5). Consequently, this high-biomarker group experienced markedly worse outcomes, including higher rates of ICU admission (89.66% vs. 12.60%), cardiogenic shock (59.77% vs. 3.94%), severe ventricular tachyarrhythmias (39.08% vs. 3.15%), and acute kidney injury (50.57% vs.

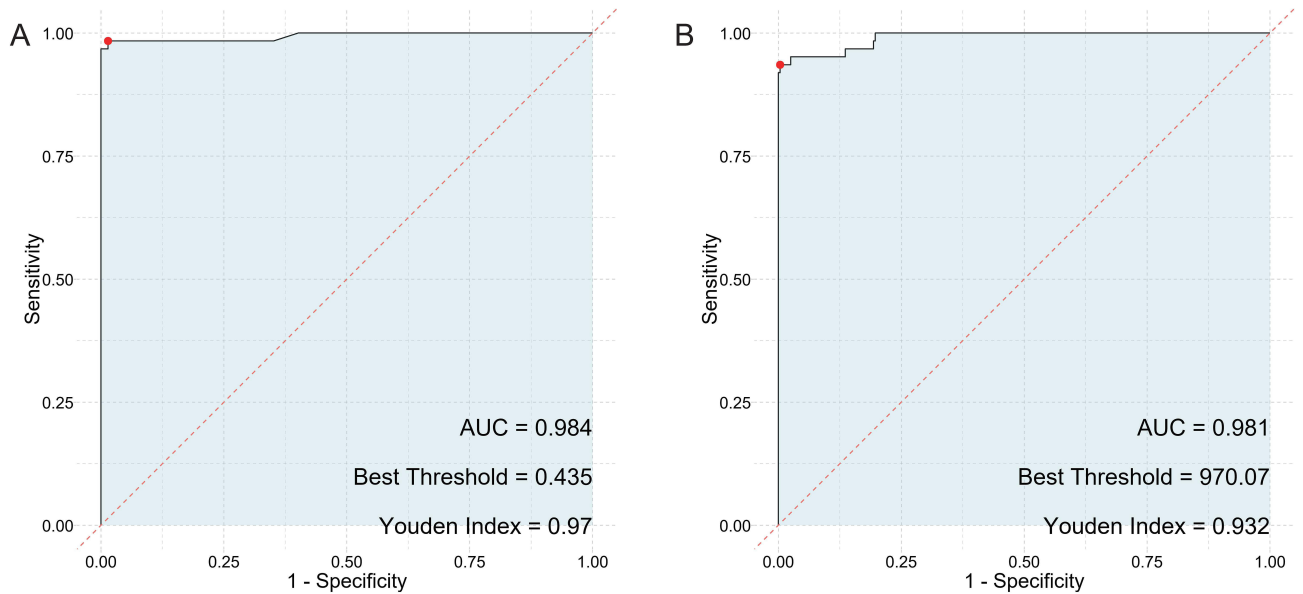


Figure 3 ROC Analysis for Prediction of Fulminant Myocarditis. (A) hs-cTnI; (B) NT-proBNP. **Abbreviations:** AUC, Area Under The Curve; hs-cTnI, high-sensitivity Cardiac Troponin; NT-proBNP, N-terminal pro-Brain Natriuretic Peptide.

Table 5 Treatment Modalities and Clinical Outcomes Stratified by Hs-cTnI Levels

Parameters	Low hs-cTnI (n=254)	High hs-cTnI (n=87)	t/χ^2	P value
Immunosuppressive Therapy [n (%)]				
High-dose Corticosteroids	72 (28.35%)	81 (93.10%)	109.858	< 0.001
Second-line Immunosuppressants	32 (12.60%)	48 (55.17%)	65.413	< 0.001
IVIg	20 (7.87%)	32 (36.78%)	41.902	< 0.001
Mechanical Circulatory Support [n (%)]				
Any MCS	18 (7.09%)	52 (59.77%)	110.253	< 0.001
IABP	18 (7.09%)	32 (36.78%)	45.668	< 0.001
ECMO	14 (5.51%)	38 (43.68%)	73.041	< 0.001
Clinical Outcomes				
ICU Admission [n (%)]	32 (12.60%)	78 (89.66%)	176.086	< 0.001
Peak Lactate (mmol/L)	1.89 ± 0.76	5.64 ± 2.34	14.605	< 0.001
Cardiogenic Shock [n (%)]	10 (3.94%)	52 (59.77%)	135.799	< 0.001
Severe Ventricular Tachyarrhythmias [n (%)]	8 (3.15%)	34 (39.08%)	77.468	< 0.001
Severe Bradyarrhythmias [n (%)]	6 (2.36%)	22 (25.29%)	45.189	< 0.001
Acute Kidney Injury [n (%)]	36 (14.17%)	44 (50.57%)	47.821	< 0.001
In-Hospital Mortality [n (%)]	5 (1.97%)	19 (21.84%)	39.107	< 0.001
Cardiovascular Death [n (%)]	4 (1.57%)	17 (19.54%)	36.192	< 0.001
3-Month Survival Rate [n (%)]	248 (97.64%)	66 (75.86%)	42.146	< 0.001

Abbreviations: hs-cTnI, high-sensitivity Cardiac Troponin I; IVIG, Intravenous Immunoglobulin; MCS, Mechanical Circulatory Support; IABP, Intra-Aortic Balloon Pump; ECMO, Extracorporeal Membrane Oxygenation; ICU, Intensive Care Unit.

14.17%) (all $P < 0.001$). In-hospital mortality (21.84% vs. 1.97%) and cardiovascular death (19.54% vs. 1.57%) were dramatically higher, resulting in significantly lower 3-month survival (75.86% vs. 97.64%, $P < 0.001$). Stratification by NT-proBNP (> 970.07 pg/mL) revealed nearly identical trends across all treatment and outcome measures (all $P < 0.001$, Table 6). Patients with elevated NT-proBNP similarly demonstrated higher rates of ICU admission (96.20% vs. 12.98%), cardiogenic shock (63.29% vs. 4.58%), in-hospital mortality (22.78% vs. 2.29%), and poorer 3-month survival (70.89% vs. 98.47%). These findings demonstrate that the identified biomarker cutoffs effectively identify patients with the most

Table 6 Treatment Modalities and Clinical Outcomes Stratified by NT-proBNP Levels

Parameters	Low NT-proBNP (n=262)	High NT-proBNP (n=79)	t/χ^2	P value
Immunosuppressive Therapy [n (%)]				
High-dose Corticosteroids	78 (29.77%)	75 (94.94%)	104.201	< 0.001
Second-line Immunosuppressants	28 (10.69%)	52 (65.82%)	102.759	< 0.001
IVIg	18 (6.87%)	34 (43.04%)	61.436	< 0.001
Mechanical Circulatory Support [n (%)]				
Any MCS	16 (6.11%)	54 (68.35%)	144.165	< 0.001
IABP	16 (6.11%)	34 (43.04%)	66.161	< 0.001
ECMO	12 (4.58%)	40 (50.63%)	99.608	< 0.001
Clinical Outcomes				
ICU Admission [n (%)]	34 (12.98%)	76 (96.20%)	192.393	< 0.001
Peak Lactate (mmol/L)	1.92 ± 0.81	5.83 ± 2.26	15.051	< 0.001
Cardiogenic Shock [n (%)]	12 (4.58%)	50 (63.29%)	140.645	< 0.001
Severe Ventricular Tachyarrhythmias [n (%)]	10 (3.82%)	32 (40.51%)	75.657	< 0.001
Severe Bradyarrhythmias [n (%)]	8 (3.05%)	20 (25.32%)	39.916	< 0.001
Acute Kidney Injury [n (%)]	34 (12.98%)	46 (58.23%)	69.216	< 0.001
In-Hospital Mortality [n (%)]	6 (2.29%)	18 (22.78%)	38.967	< 0.001
Cardiovascular Death [n (%)]	5 (1.91%)	16 (20.25%)	32.243	< 0.001
3-Month Survival Rate [n (%)]	258 (98.47%)	56 (70.89%)	63.358	< 0.001

severe myocardial injury and ventricular dysfunction, who are consequently at highest risk for a fulminant clinical course. This patient subset, characterized by high hs-cTnI and NT-proBNP, predictably required more intensive life-supporting therapies and experienced poorer clinical outcomes, underscoring that the biomarker levels are a direct reflection of the extent of cardiac damage.

Discussion

This research offers vital understanding of the predictive significance of hs-cTnI and NT-proBNP in recognizing cancer patients undergoing ICI treatment who are at risk for severe myocarditis. The results indicate that, when assessed upon first presentation, the magnitude of elevation of these biomarkers reflects the extent of ongoing myocardial necrosis and ventricular wall stress. This quantification of acute cardiac damage allows them to serve as powerful indicators for the likelihood of progression to a fulminant disease trajectory, effectively acting as a gauge of disease severity at the point of diagnosis.

In our cohort, individuals who developed fulminant myocarditis tended to be older and carried a greater prevalence of cardiovascular and metabolic disorders, such as hypertension, diabetes, coronary artery disease, and chronic kidney disease. This aligns with previous reports by Pirozzi et al⁷ and Cozma et al,¹⁰ which suggested that pre-existing cardiovascular risk factors may exacerbate the severity of ICI-related cardiac complications. The presence of these comorbidities may reflect a diminished cardiac reserve or a more vulnerable myocardial substrate, potentially facilitating a more aggressive inflammatory response upon immune activation.^{24–26} The significantly higher proportion of patients with a history of thymoma in the fulminant group further reinforces the concept that specific patient populations are at an exceptionally high risk for severe ICI cardiotoxicity, a finding consistent with prior reports.²⁷

Clinically, patients with fulminant myocarditis more frequently presented with chest pain and consciousness disorders such as confusion or syncope. While fatigue, respiratory, and gastrointestinal symptoms were common across both groups, the presence of chest pain and neurological manifestations emerged as distinctive early warning signs of a fulminant trajectory. Furthermore, our analysis revealed that concurrent myositis and myasthenia gravis were significantly more common in the fulminant group, corroborating the work of Pathak et al²⁸ which identified these neuromuscular conditions as key risk factors for poorer outcomes in ICI-myocarditis. This finding aligns with the research conducted by Johnson et al,²⁹ who highlighted the atypical and often rapidly progressive nature of ICI-myocarditis, where non-specific symptoms can swiftly evolve into life-threatening hemodynamic instability.

Laboratory profiling revealed markedly elevated levels of inflammatory and cardiac biomarkers in the fulminant group. Both hs-cTnI and NT-proBNP were substantially higher in these individuals reflecting extensive myocardial injury and significant ventricular stress.^{30,31} Similar patterns have been noted by He et al,²⁰ who reported that NT-proBNP elevation was closely associated with adverse outcomes in severe ICI-myocarditis. The pronounced systemic inflammatory response, evidenced by elevated white blood cell counts and C-reactive protein, further supports the concept of an overwhelming immune-mediated injury in fulminant cases. This is in line with mechanisms proposed by Gergely et al,⁶ where unchecked T-cell activation and inflammatory cytokine release play central roles in driving myocardial damage.

Electrocardiographic and echocardiographic assessments further differentiated the fulminant group. A higher prevalence of prolonged QRS duration, ST-segment elevation, and conduction blocks indicated greater electrical instability. Echocardiography demonstrated severely impaired left ventricular systolic function, characterized by reduced ejection fraction and enlarged end-systolic dimensions. These imaging findings corroborate the clinical and biomarker evidence of profound myocardial dysfunction and are consistent with the ESC Guidelines on cardio-oncology which highlight the necessity of thorough cardiac assessment in patients receiving ICI treatment.^{23,32,33}

Multivariable logistic regression analysis identified hs-cTnI, NT-proBNP, left ventricular ejection fraction, and prolonged QRS duration as independent predictors of fulminant myocarditis. This combination of biomarkers and functional parameters provides a more holistic risk assessment than any single metric alone. The strong independent association of hs-cTnI and NT-proBNP with fulminant disease underscores their dual role as indicators of both myocardial necrosis and hemodynamic stress, a concept also supported by McGrath et al,¹⁷ who emphasized the complementary value of multi-marker strategies in inflammatory cardiomyopathies.

The excellent discriminative performance of hs-cTnI and NT-proBNP, as demonstrated by ROC analysis, supports their utility in early risk stratification. The derived cutoff values effectively identified patients at high risk, who

subsequently received more intensive immunosuppressive therapy and mechanical circulatory support. The expanded analysis now demonstrates that these biomarkers also powerfully predict the risk of specific life-threatening events, including cardiogenic shock and severe arrhythmias, which are the primary drivers of the high in-hospital and cardiovascular mortality observed in the high-biomarker groups. This biomarker-based stratification also correlated strongly with poorer clinical outcomes, such as increased rates of ICU admissions, acute kidney injury, and diminished short-term survival. These findings are consistent with those reported by He et al,²⁰ who similarly found that NT-proBNP levels could predict the need for advanced cardiac support and were associated with higher mortality.

From a clinical perspective, the integration of hs-cTnI and NT-proBNP levels at presentation, using the specific cutoffs identified in this study, offers a practical and accessible tool for early risk assessment. This moves beyond a qualitative assessment of risk to a quantitative one, enabling clinicians to identify patients who are likely to develop fulminant myocarditis before overt clinical deterioration occurs. Such early identification could prompt timely escalation of care, including initiation of high-dose corticosteroids, second-line immunosuppressants, or preparedness for mechanical support, potentially mitigating the risk of catastrophic outcomes. Furthermore, these biomarkers may aid in monitoring treatment response and guiding the intensity and duration of immunosuppressive therapy.^{31,34}

While our findings are promising, several limitations must be acknowledged. As a single-center retrospective study, our results may not be generalizable to all clinical settings. The relatively small number of fulminant cases limits the robustness of our multivariate models. Additionally, our analysis relied on biomarker levels measured at initial presentation, which were selected to assess early risk stratification. However, peak biomarker values during hospitalization may offer additional prognostic insight, and future studies should compare the predictive utility of initial versus peak measurements. Furthermore, while the distribution of anti-PD-1 and anti-PD-L1 agents was similar between groups, our study did not perform a detailed analysis comparing monotherapy versus combination ICI regimens. Given that combination therapy is known to carry a higher risk of severe irAEs, including myocarditis, future studies with larger cohorts should investigate differential biomarker patterns and prognosis based on specific ICI regimens. Future prospective, multi-center studies with serial biomarker assessments are needed to validate our findings and to develop dynamic prediction models. Notably, the ROC-derived cutoffs in this study were not validated in an independent cohort, which may limit their generalizability. While single-dataset ROC analyses without split-sample validation are common in exploratory biomarker research (eg, He et al;²⁰ Yang et al³⁴), we acknowledge this as a limitation. Future studies should incorporate internal validation techniques, such as bootstrapping or split-sample approaches, or ideally, external validation in independent populations, to confirm the robustness of these cutoffs. Further research should also explore the underlying molecular mechanisms linking these biomarkers to fulminant disease progression and investigate the utility of combining them with other novel biomarkers or imaging modalities. In particular, future studies with larger cohorts should examine discordant patterns of hs-cTnI and NT-proBNP elevation (eg, high hs-cTnI with low NT-proBNP, or vice versa) to determine whether such profiles identify distinct pathophysiological subtypes—such as predominant myocardial necrosis versus ventricular wall stress—and whether they are associated with differential clinical outcomes and treatment responses.

Conclusion

In conclusion, hs-cTnI and NT-proBNP levels at presentation demonstrate strong predictive value for identifying cancer patients at risk of developing fulminant myocarditis during ICI therapy. These biomarkers, when integrated with clinical and imaging parameters, offer a promising approach for early risk stratification and personalized treatment planning in this high-risk population. Their implementation could potentially lead to more timely interventions and improved outcomes in patients with ICI-associated myocarditis.

Data Sharing Statement

The datasets used during the present study are available from the corresponding author upon reasonable request.

Author Contributions

Chongmei Zhou: Conceptualization, Formal analysis, Writing - Original Draft. Qiong Ma: Data Curation, Methodology, Investigation, Writing-Review & Editing. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

The authors have no conflicts of interest to declare.

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