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Myocarditis prediction in locally advanced or metastatic lung cancer patients with cardiac parameters abnormalities undergoing immunotherapy: development and validation of a risk assessment model

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Abstract

Background Immune checkpoint inhibitors (ICIs) have revolutionized treatment for advanced lung cancer, yet their cardiotoxicity, particularly immune checkpoint inhibitor-related myocarditis, poses significant clinical challenges. This study aims to create a predictive model using cardiac biomarkers to identify patients prone to myocarditis during treatment, thereby enhancing clinical decision-making and patient outcomes.

Methods In this retrospective cohort study, 1,838 patients with locally advanced and metastatic lung cancer and abnormal baseline cardiac parameters receiving immunotherapy from June 2018 to August 2024 were analyzed, with a follow-up date cutoff of September 20, 2024. Patients were randomly divided into training (70%) and validation (30%) cohorts. Logistic regression analysis was conducted on demographic information, clinical characteristics, treatments, and cardiac parameters of these patients prior to immunotherapy. A nomogram was constructed via multivariable logistic regression, and AUC and Hosmer-Lemeshow tests were performed to verify the accuracy of the model.

Results Among 1,838 patients, 89 (4.84%) developed myocarditis. Independent predictors included α-HBDH > 910 U/L (OR = 10.57, 95%CI: 2.47–45.22, $P = 0.001$), CK-MB > 15 ng/mL (OR = 3.87, 95%CI: 1.06–14.11, $P = 0.040$), hs-cTnT elevation (14–28 pg/mL: OR = 4.19; 28–42 pg/mL: OR = 13.10; >42 pg/mL: OR = 25.43, $P < 0.001$), NT-proBNP > 3× age-adjusted upper limit (OR = 9.72, 95%CI: 1.09–86.73, $P = 0.042$), and Caprini score ≥ 4 (OR = 4.49, 95%CI: 2.26–8.90, $P < 0.001$). The nomogram demonstrated strong discrimination ability, with an AUC of 0.831 in the training cohort (sensitivity: 0.842, specificity: 0.717) and an AUC of 0.844 in the validation cohort.

Conclusions This study establishes a validated risk assessment model integrating cardiac biomarkers (α-HBDH, CK-MB, hs-cTnT, NT-proBNP) and Caprini risk score to predict ICI-related myocarditis in lung cancer patients with cardiac abnormalities. The tool facilitates early identification of high-risk patients, enabling tailored monitoring and

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preemptive management. These findings underscore the critical role of baseline cardiac profiling in optimizing immunotherapy safety.

Keywords Immune checkpoint inhibitors, Myocarditis, Lung cancer, Risk Model for Myocarditis, Cardiac biomarkers

Introduction

Lung cancer remains one of the foremost contributors to cancer-related mortality globally [1], underscoring the pressing necessity for continued investigation into effective therapeutic strategies. Conventional treatments, including surgical intervention, chemotherapy and radiotherapy, have progressed to incorporate immune checkpoint inhibitors (ICIs), which have shown promise in enhancing patient survival rates and improving overall quality of life. Nevertheless, the introduction of immunotherapy has raised significant concerns regarding its potential cardiotoxic implications, particularly since a substantial number of lung cancer patients present with pre-existing cardiovascular conditions, often attributable to advancing age or other underlying health complications [2, 3]. The cardiovascular status of these individuals is a vital consideration, as existing literature indicates that myocarditis may significantly influence treatment efficacy and overall survival outcomes [4, 5].

Myocarditis is a complex issue that can arise from various cancer treatments, with immunotherapy being a significant factor [6, 7]. Although the incidence of immune checkpoint inhibitor-related myocarditis is relatively low, the associated risk of mortality is significantly elevated, and once it occurs, the prognosis for patients is often poor [8, 9]. Thus, the risk of myocarditis associated with immunotherapy poses significant clinical challenges. Previous studies have suggested that such pre-existing cardiac biomarker abnormalities may be associated with an increased susceptibility to the cardiotoxic effects of immunotherapy [10]. Currently, there is a lack of research specifically targeting the potential risk of ICI-related myocarditis in patients with pre-existing abnormal cardiac parameters. Therefore, it is necessary to conduct in-depth exploration of cardiac biomarkers and their predictive capabilities for myocarditis in cancer patients.

Methods

Data collection

Data collection was performed retrospectively from electronic medical records and hospitalization records at Shandong Cancer Hospital and Institute, Shandong First Medical University including patients with advanced or metastatic lung cancer received Programmed Cell Death Protein 1 (PD-1) or Programmed Cell Death 1 Ligand 1 (PD-L1) inhibitors as monotherapy or combination therapy between June 2018 and August 2024. The study received approval from the hospital's ethics committee (approval number: SDTHEC202401022). Eligible patients were identified based on specific inclusion and exclusion criteria.

Inclusion Criteria

(1) age ≥ 18 years; (2) received at least one dose of immune checkpoint inhibitor therapy; (3) had at least one follow-up appointment; (4) had abnormal baseline cardiac parameters; (5) patients with multiple occurrences of immune checkpoint inhibitor-related myocarditis were only counted once.

Subjects were excluded if they had any of the following

(1) diagnosis of myocarditis prior to the administration of ICIs; (2) with other malignancies; (3) complicated autoimmune disease; (4) suspected or confirmed pulmonary embolism (PE), defined as clinical signs of acute PE and radiological confirmation.

Abnormal cardiac parameters are defined as follows

(1) α-hydroxybutyrate dehydrogenase (α-HBDH) level > 182 U/L (normal range 72 U/L to 182 U/L); (2) creatine kinase-M/B (CK-MB) level > 5 ng/ml (normal range 0 to 5 ng/ml); (3) high-sensitivity cardiac troponin T (hs-cTnT) level > 14 pg/ml (normal range 0 to 14 pg/ml); (4) abnormal level of N-terminal pro-brain natriuretic peptide (NT-proBNP), NT-proBNP levels outside the normal range based on age [11]: ≤450 pg/ml for individuals under 50 years of age, ≤ 900 pg/ml for those between 50 and 75 years of age, and ≤ 1800 pg/ml for those over 75 years of age; (5) presence of concomitant coronary artery disease (CAD). Patients meeting any of the aforementioned criteria were considered to have abnormal cardiac parameters.

The patient datasets encompass a wide range of dimensions, including characteristics (age and gender), tumor pathological types and staging, and essential clinical comorbidities-particularly cardiovascular background (CAD, atrial fibrillation), hypertension, diabetes, and cerebral infarction. Additionally, we documented whether patients received combined radiotherapy to the left chest and mediastinum, concomitant medications (including paclitaxel, docetaxel, vascular endothelial growth factor inhibitors and tyrosine kinase inhibitors) and the number of times ICIs.

Laboratory tests were performed to assess various indicators, including α-HBDH, CK-MB, hs-cTnT, NT-proBNP prior to the initiation of immunotherapy (all references to NT-proBNP subsequently denote the multiple of the measured value in relation to the upper limit

of the normal range based on age). We also documented the Caprini risk scores of patients prior to the initiation of immunotherapy.

Furthermore, we investigated whether patients experienced myocarditis. The assessment of myocarditis was based on the guidelines established by the European Society of Cardiology (ESC) in the 《2022 ESC Guidelines for Cardio-Oncology》. To distinguish ICI-related myocarditis from other types of cardiomyopathies, we also paid particular attention to the temporal pattern of biomarker changes: (1) new-onset and complex ventricular arrhythmias, such as non-sustained ventricular tachycardia, in the context of recent initiation of ICI treatment were weighted more heavily in the diagnosis; (2) a rapid and significant increase in hs-cTnT, NT-proBNP and inflammatory markers (c-reactive protein, erythrocyte sedimentation rate), especially when accompanied by new-onset or aggravated heart failure symptoms such as dyspnea at rest or reduced exercise tolerance, was regarded as a strong indication of ICI-related myocarditis; (3) temporal association with ICIs: symptom onset within 12 weeks of immunotherapy initiation; (4) a sudden and substantial decrease in LVEF, rather than the gradual decline typical of progressive cardiomyopathy, was considered a key diagnostic clue (5). acute coronary syndrome, infectious myocarditis, other drug toxicities need to be excluded. This comprehensive diagnosis integrated clinical presentation, laboratory results, and other relevant auxiliary examinations.

Statistical Analysis

The final follow-up date was September 20, 2024. All statistical analyses were conducted using SPSS version 26.0, and the nomogram prediction model was constructed using R language version 4.4.0. Categorical data are presented as n (%), while non-normally distributed continuous data, results are presented as M (Q1, Q3), with the Wilcoxon rank-sum test or Kruskal-Wallis H test employed for analysis. Inter-group comparisons were conducted using Z-tests or χ^2 tests. A logistic regression model was utilized to further identify independent risk factors associated with myocarditis and to establish a risk prediction model along with the calculation of risk scores. $P<0.05$ was considered statistically significant.

We ensured the reproducibility of the results by setting a random seed. Subsequently, we utilized the `sample()` function in R to randomly extract 70% of the data to construct the training set, with the remaining data automatically allocated to the validation set. This method ensured the randomness of the datasets and the fairness of model evaluation.

Result

Analysis of General Information for Patients in the Non-myocarditis Group and the Myocarditis Group

In this study, a total of 1,838 patients were enrolled, with 89 cases experiencing cardiotoxicity, resulting in an incidence rate of 4.84%. To better understand the patient population, we further analyzed the underlying cardiovascular backgrounds of these patients. Among the patients with abnormal cardiac parameters, 22.58% had a history of CAD and 2.45% had a history of atrial fibrillation (Table 1). No statistically significant differences were observed between the training and test cohorts in baseline characteristics, including age, gender, pathological type, staging, the number of times ICIs, α-HBDH, CK-MB, hs-cTnT, the multiple of NT-proBNP levels, cardiovascular backgrounds, hypertension, diabetes, cerebral infarction, concomitant medications, radiotherapy or Caprini scores (all $P>0.05$, Table 1).

The training cohort comprised 1,286 cases, with 53 cases in the myocarditis group. In the non-myocarditis group, the median age was 67.00, while in the myocarditis group, the median age was 69.00. No significant differences were observed between the two patient cohorts with respect to median age, gender, tumor pathology, staging, cardiovascular background (CAD, atrial fibrillation), diabetes, cerebral infarction, whether concurrent left chest and mediastinal radiotherapy and concomitant medications (all $P>0.05$, Table 2). However, the number of times ICIs ($P=0.005$, Table 2), the baseline α-HBDH ($P=0.026$, Table 2), CK-MB ($P=0.003$, Table 2), hs-cTnT ($P<0.001$, Table 2), the multiple of NT-proBNP ($P=0.003$, Table 2) based on the upper limit of the normal range for age, prevalence of hypertension($P=0.041$, Table 2) and the Caprini risk score($P<0.001$, Table 2) demonstrated statistically significant differences.

Multivariate Logistic Regression between the Non-myocarditis Group and the Myocarditis Group

All variables in Table 2 were included in univariate logistic regression analysis, and variables with $P<0.05$ were included in multivariate regression analysis. The analysis was conducted using a stepwise forward approach. Results showed that α-HBDH > 910 U/L (OR = 10.57, 95%CI: 2.47–45.22, $P=0.001$, Table 3), CK-MB > 15 ng/ml (OR = 3.87, 95%CI: 1.06–14.11, $P=0.040$, Table 3), hs-cTnT = 14–28 pg/ml (OR = 4.19, 95%CI: 2.02–8.65, $P<0.001$, Table 3), hs-cTnT = 28–42 pg/ml (OR = 13.10, 95%CI: 4.18–40.47 $P<0.001$, Table 3), hs-cTnT > 42 pg/ml (OR = 25.43, 95%CI: 9.33–69.35, $P<0.001$, Table 3), the multiple of NT-proBNP ≥ 3 (OR = 9.72, 95%CI: 1.09–86.73, $P=0.042$, Table 3) based on the upper limit of the normal range for age and Caprini risk score ≥ 4 (OR = 4.49, 95%CI: 2.26–8.90, $P<0.001$, Table 3) are independent risk factors for immune-mediated cardiotoxicity.

Table 1 The baseline characteristics of the training and test cohort

Variables	Total ($n=1838$)	train ($n=1286$)	test ($n=552$)	Statistic	*P*
Age, M (Q_1, Q_3)	67.00 (60.00, 72.00)	67.00 (60.00, 72.00)	67.00 (61.00, 73.00)	Z=-1.66	0.097
gender, n (%)				χ^2=0.03	0.870
male	1434 (78.02)	1002 (77.92)	432 (78.26)		
female	404 (21.98)	284 (22.08)	120 (21.74)		
Pathological type, n (%)				χ^2=0.00	0.945
NSCLC	1427 (77.64)	999 (77.68)	428 (77.54)		
SCLC	411 (22.36)	287 (22.32)	124 (22.46)		
Staging, n (%)				χ^2=0.71	0.400
III	324 (17.63)	233 (18.12)	91 (16.49)		
IV	1514 (82.37)	1053 (81.88)	461 (83.51)		
The number of times ICIs, M (Q_1, Q_3)	4.00 (2.00, 6.00)	4.00 (2.00, 6.00)	4.00 (2.00, 6.00)	Z=-1.27	0.204
α-HBDH, n (%)				χ^2=4.24	0.237
≤182	470 (25.57)	327 (25.43)	143 (25.91)		
182–546	1248 (67.90)	877 (68.20)	371 (67.21)		
546–910	84 (4.57)	62 (4.82)	22 (3.99)		
>910	36 (1.96)	20 (1.56)	16 (2.90)		
CK-MB, n (%)				χ^2=2.10	0.551
≤5	1651 (89.83)	1151 (89.50)	500 (90.58)		
5–10	118 (6.42)	88 (6.84)	30 (5.43)		
10–15	27 (1.47)	20 (1.56)	7 (1.27)		
>15	42 (2.29)	27 (2.10)	15 (2.72)		
hs-cTnT, n (%)				χ^2=6.55	0.088
≤14	1284 (69.86)	913 (71.00)	371 (67.21)		
14–28	467 (25.41)	308 (23.95)	159 (28.80)		
28–42	50 (2.72)	35 (2.72)	15 (2.72)		
>42	37 (2.01)	30 (2.33)	7 (1.27)		
The multiple of NT-proBNP, n (%)				-	0.642
normal	1760 (95.76)	1233 (95.88)	527 (95.47)		
1–2	59 (3.21)	42 (3.27)	17 (3.08)		
2–3	12 (0.65)	7 (0.54)	5 (0.91)		
>3	7 (0.38)	4 (0.31)	3 (0.54)		
CAD, n (%)				χ^2=0.43	0.514
yes	415 (22.58)	285 (22.16)	130 (23.55)		
no	1423 (77.42)	1001 (77.84)	422 (76.45)		
Atrial fibrillation, n (%)				χ^2=2.21	0.137
yes	45 (2.45)	36 (2.80)	9 (1.63)		
no	1793 (97.55)	1250 (97.20)	543 (98.37)		
Hypertension, n (%)				χ^2=0.02	0.889
yes	657 (35.75)	461 (35.85)	196 (35.51)		
no	1181 (64.25)	825 (64.15)	356 (64.49)		
Diabetes, n (%)				χ^2=3.34	0.068
yes	255 (13.87)	166 (12.91)	89 (16.12)		
no	1583 (86.13)	1120 (87.09)	463 (83.88)		
Cerebral infarction, n (%)				χ^2=0.45	0.500
yes	119 (6.47)	80 (6.22)	39 (7.07)		
no	1719 (93.53)	1206 (93.78)	513 (92.93)		
Concomitant medications, n (%)				χ^2=0.43	0.510
yes	61 (3.32)	45 (3.50)	16 (2.90)		
no	1777 (96.68)	1241(96.50)	536 (97.10)		
Radiotherapy, n (%)				χ^2=2.73	0.099
yes	52 (2.83)	31 (2.41)	21 (3.80)		
no	1786 (97.17)	1255 (97.59)	531 (96.20)		
Caprini risk score, n (%)				χ^2=0.34	0.559

Table 1 (continued)

Variables	Total ($n=1838$)	train ($n=1286$)	test ($n=552$)	Statistic	P
≤3	1090 (59.30)	757 (58.86)	333 (60.33)		
≥4	748 (40.70)	529 (41.14)	219 (39.67)		

NSCLC: Non-Small Cell Lung Cancer; SCLC: Small Cell Lung Cancer; ICIs: immune checkpoint inhibitors; α-HBDH: α-hydroxybutyrate dehydrogenase; CK-MB: creatine kinase-M/B; hs-cTnT: high-sensitivity cardiac troponin T; NT-proBNP: N-terminal pro-brain natriuretic peptide, the multiple of the measured value in relation to the upper limit of the normal range based on age: 450 pg/ml for individuals under 50 years of age, 900 pg/ml for those between 50 to 75 years of age and 1800 pg/ml for those over 75 years of age; CAD: coronary artery disease.

Z: Mann-Whitney test, χ^2: Chi-square test, -: Fisher exact

M: Median, Q_1: 1st Quartile, Q_3: 3st Quartile

Nomogram for Predictive Modeling and Validation

All factors with $P<0.05$ in Table 3 were set as independent variables and myocarditis occurrence as the dependent variable, assignment details are presented in Table 4 and a nomogram prediction model was constructed (Fig. 1).

The predictive accuracy of the model was ascertained utilizing the pROC package in R software for the generation of the Receiver Operating Characteristic (ROC) curve. The model demonstrated an area under the curve (AUC) of 0.831(95%CI: 0.772–0.890) (Fig. 2), with a sensitivity of 0.842 and a specificity of 0.717 (Table 5), suggesting a robust diagnostic efficacy.

For external validation, the remaining 30% of the patient dataset was employed as a validation cohort. This validation exercise revealed an AUC of 0.844 (95%CI: 0.786–0.903) (Fig. 2), further substantiating the model's predictive power. The Calibration plot indicated a close alignment between the predicted and standard curves, indicative of the model's reliability. The Hosmer-Lemeshow goodness-of-fit test yielded a chi-square (χ^2) statistic of 6.412 ($P=0.093>0.05$), thereby confirming the model's excellent calibration (Fig. 3).

Discussion

Lung cancer remains a leading cause of cancer-related mortality globally, with an increasing incidence attributed to factors such as smoking, environmental exposures, and genetic predispositions [12–15]. The management of advanced lung cancer has evolved significantly, particularly with the advent of targeted therapies and immunotherapy, which aim to enhance patient outcomes by utilizing the body's immune system to combat tumors. Despite these advancements, the risk of treatment-related adverse effects, including cardiotoxicity, remains a critical concern. ICI-related myocarditis has the highest fatality rate, reported as high as 50%, although the number of reported cases is low compared to other toxicities [16, 17]. It is worth noting that the true incidence of immunological myocarditis may be underestimated. The occurrence of myocarditis can severely impact the treatment and overall survival rate of cancer patients, making it urgent to identify the risk status of individual patients as early as possible to adopt prudent monitoring and management strategies. Our study focused on advanced lung cancer patients with abnormal cardiac biomarkers or pre-existing cardiovascular diseases, as these individuals represent a high-risk population for immunotherapy-related myocarditis [18]. Elevated cardiac biomarkers often reflect subclinical myocardial injury or hemodynamic stress, which may amplify the inflammatory response triggered by ICIs [19]. By restricting enrollment to this cohort, we aimed to identify predictors of cardiotoxicity in patients most vulnerable to adverse cardiac events.

In this study, among 1,838 patients, 89 cases of myocarditis were observed, resulting in an incidence rate of 4.84%. This proportion is slightly higher compared to previously reported myocarditis rates in lung cancer patients treated with immunotherapy [20–24]. However, the patients included in this study were lung cancer patients with abnormal cardiac parameters, suggesting that abnormal cardiac parameters may play a promotional role in the development of cardiotoxicity. In the multivariate analysis, baseline α-HBDH, CK-MB, hs-cTnT, the multiple of NT-proBNP based on the upper limit of the normal range for age and Caprini risk score were identified as independent risk factors for the development of myocarditis in advanced or metastatic lung cancer patients undergoing immunotherapy.

Hs-cTnT is specifically expressed in cardiomyocytes and is released into the peripheral blood in various forms, such as monomers and complexes, during myocardial injury or necrosis, serving as a biomarker for myocardial damage, with studies indicating that elevated levels of cardiac troponin can be observed in 94% of patients with clinically confirmed myocarditis [25–28]. Prior research has likewise shown that individuals with ICIs treatment and cardiac troponin T (cTnT) levels ≥ 1.5 ng/ml exhibit a four times higher risk of experiencing cardiac adverse events [29]. Additionally, a retrospective cohort study has demonstrated that patients on immunotherapy with baseline troponin levels above 0.01 ng/mL have a risk of cardiac adverse events that is seven times greater compared to those with normal baseline troponin levels (HR: 7.27, 95%CI: 2.72–19.43, $P<0.001$) [30]. Research has demonstrated that pretreatment troponin T levels, detected using the enhanced fourth-generation

Table 2 Analysis of general information for patients in the non-myocarditis group and the myocarditis group in training cohort

Variables	Total ($n=1286$)	Non-myocarditis Group ($n=1233$)	Myocarditis Group ($n=53$)	Statistic	*P*
Age, M (Q_1, Q_3)	67.00 (60.00, 72.00)	67.00 (60.00, 72.00)	69.00 (61.00, 73.00)	Z=-0.96	0.336
gender, n (%)				χ^2=2.53	0.112
male	1002 (77.92)	956 (77.53)	46 (86.79)		
female	284 (22.08)	277 (22.47)	7 (13.21)		
Pathological type, n (%)				χ^2=1.98	0.160
NSCLC	999 (77.68)	962 (78.02)	37 (69.81)		
SCLC	287 (22.32)	271 (21.98)	16 (30.19)		
Staging, n (%)				χ^2=2.56	0.109
III	233 (18.12)	219 (17.76)	14 (26.42)		
IV	1053 (81.88)	1014 (82.24)	39 (73.58)		
The number of times ICIs, M (Q_1, Q_3)	4.00 (2.00, 6.00)	4.00 (2.00, 6.00)	2.00 (2.00, 6.00)	Z=-2.81	**0.005**
α-HBDH, n (%)				-	**0.026**[1]
≤182	327 (25.43)	315 (25.55)	12 (22.64)		
182–546	877 (68.20)	843 (68.37)	34 (64.15)		
546–910	62 (4.82)	59 (4.79)	3 (5.66)		
>910	20 (1.56)	16 (1.30)	4 (7.55)		
CK-MB, n (%)				-	**0.003**[1]
≤5	1151 (89.50)	1110 (90.02)	41 (77.36)		
5–10	88 (6.84)	83 (6.73)	5 (9.43)		
10–15	20 (1.56)	18 (1.46)	2 (3.77)		
>15	27 (2.10)	22 (1.78)	5 (9.43)		
hs-cTnT, n (%)				-	**<0.001**[1]
≤14	913 (71.00)	897 (72.75)	16 (30.19)		
14–28	308 (23.95)	287 (23.28)	21 (39.62)		
28–42	35 (2.72)	29 (2.35)	6 (11.32)		
>42	30 (2.33)	20 (1.62)	10 (18.87)		
The multiple of NT-proBNP, n (%)				-	**0.003**[1]
normal	1233 (95.88)	1186 (96.19)	47 (88.68)		
1–2	42 (3.27)	39 (3.16)	3 (5.66)		
2–3	7 (0.54)	6 (0.49)	1 (1.89)		
>3	4 (0.31)	2 (0.16)	2 (3.77)		
CAD, n (%)					
yes	285 (22.16)	270 (21.90)	15 (28.30)	χ^2=1.21	0.272
no	1001 (77.84)	963 (78.10)	38 (71.70)		
Atrial fibrillation, n (%)				χ^2=2.94	0.086
yes	36 (2.80)	32 (2.60)	4 (7.55)		
no	1250 (97.20)	1201 (97.40)	49 (92.45)		
Hypertension, n (%)				χ^2=4.19	**0.041**[1]
yes	461 (35.85)	435 (35.28)	26 (49.06)		
no	825 (64.15)	798 (64.72)	27 (50.94)		
Diabetes, n (%)				χ^2=0.23	0.628
yes	166 (12.91)	158 (12.81)	8 (15.09)		
no	1120 (87.09)	1075 (87.19)	45 (84.91)		
Cerebral infarction, n (%)				χ^2=0.49	0.485
yes	80 (6.22)	75 (6.08)	5 (9.43)		
no	1206 (93.78)	1158 (93.92)	48 (90.57)		
Concomitant medications, n (%)				χ^2=1.58	0.209
yes	45 (3.50)	41 (3.33)	4 (7.55)		
no	1241 (96.50)	1192 (96.67)	49 (92.45)		
Radiotherapy, n (%)				χ^2=1.25	0.264
yes	31 (2.41)	28 (2.27)	3 (5.66)		
no	1255 (97.59)	1205 (97.73)	50 (94.34)		

Table 2 (continued)

Variables	Total ($n=1286$)	Non-myocarditis Group ($n=1233$)	Myocarditis Group ($n=53$)	Statistic	*P*
Caprini risk score, n (%)				χ^2=26.91	**<0.001**[1]
≤3	757 (58.86)	744 (60.34)	13 (24.53)		
≥4	529 (41.14)	489 (39.66)	40 (75.47)		

NSCLC: Non-Small Cell Lung Cancer; SCLC: Small Cell Lung Cancer; CAD: coronary artery disease; α-HBDH: α-hydroxybutyrate dehydrogenase; CK-MB: creatine kinase-M/B; hs-cTnT: high-sensitivity cardiac troponin T; NT-proBNP: N-terminal pro-brain natriuretic peptide, the multiple of the measured value in relation to the upper limit of the normal range based on age: 450 pg/ml for individuals under 50 years of age, 900 pg/ml for those between 50 to 75 years of age and 1800 pg/ml for those over 75 years of age.

1: Univariate logistic regression, $P<0.05$.

Z: Mann-Whitney test, χ^2: Chi-square test, -: Fisher exact

M: Median, Q_1: 1st Quartile, Q_3: 3st Quartile

Table 3 Multivariate logistic regression between the non-myocarditis group and the myocarditis group

Variables	β	Z	*P*	OR (95%CI)
α-HBDH U/L				
≤182				1.00 (Reference)
182–546	0.38	1.01	0.312	1.46 (0.70–3.07)
546–910	1.18	1.66	0.096	3.26 (0.81–13.08)
>910	2.36	3.18	**0.001**	10.57 (2.47–45.22)
CK-MB ng/ml				
≤5				1.00 (Reference)
5–10	0.43	0.79	0.428	1.53 (0.53–4.37)
10–15	1.19	1.32	0.186	3.30 (0.56–19.40)
>15	1.35	2.05	**0.040**	3.87 (1.06–14.11)
hs-cTnT pg/ml				
≤14				1.00 (Reference)
14–28	1.43	3.86	**<0.001**	4.19 (2.02–8.65)
28–42	2.57	4.43	**<0.001**	13.10 (4.18–40.47)
>42	3.24	6.32	**<0.001**	25.43 (9.33–69.35)
The multiple of NT-proBNP				
normal				1.00 (Reference)
1–2	0.22	0.32	0.752	1.25 (0.32–4.85)
2–3	0.47	0.40	0.686	1.60 (0.16–15.62)
>3	2.27	2.04	**0.042**	9.72 (1.09–86.73)
Atrial fibrillation				
no				1.00 (Reference)
yes	0.78	1.23	0.217	2.18 (0.63–7.51)
Hypertension				
no				1.00 (Reference)
yes	0.30	0.96	0.335	1.36 (0.73–2.52)
Caprini risk score				
≤3				1.00 (Reference)
≥4	1.50	4.30	**<0.001**	4.49 (2.26–8.90)

α-HBDH: α-hydroxybutyrate dehydrogenase; CK-MB: creatine kinase-M/B; hs-cTnT: high-sensitivity cardiac troponin T; NT-proBNP: N-terminal pro-brain natriuretic peptide, the multiple of the measured value in relation to the upper limit of the normal range based on age: 450 pg/ml for individuals under 50 years of age, 900 pg/ml for those between 50 to 75 years of age and 1800 pg/ml for those over 75 years of age

Table 4 Description of variable assignment in the multivariate analysis of myocarditis in lung cancer patients with Aaseline cardiac parameters abnormalities

Factor	Variable Name	Assignment Description
Myocarditis Occurrence	Y	occurred = 1; did not occur = 0
α-HBDH	X1	≤ 910 = 0; >910 = 2
CK-MB	X2	≤ 15 = 0; >15 = 1
hs-cTnT	X3	≤ 14 = 0; 14–28 = 1; 28–42 = 2; >42 = 3
The multiple of NT-proBNP	X4	≤ 3 = 0; >3 = 2
Caprini risk score	X5	≤ 3 = 0; ≥4 = 1

α-HBDH: α-hydroxybutyrate dehydrogenase; CK-MB: creatine kinase-M/B; hs-cTnT: high-sensitivity cardiac troponin T; NT-proBNP: N-terminal pro-brain natriuretic peptide, the multiple of the measured value in relation to the upper limit of the normal range based on age: 450 pg/ml for individuals under 50 years of age, 900 pg/ml for those between 50 to 75 years of age and 1800 pg/ml for those over 75 years of age.

cTnT assay at a critical value of 14 ng/L, are capable of forecasting cardiovascular outcomes and the advancement of cardiac involvement in individuals undergoing immunotherapy [31]. α-HBDH, is highly expressed in myocardial tissue and red blood cells. Previous studies have suggested its potential value in assessing myocardial damage during cancer therapy [32]. CK-MB, an enzyme mainly present in myocardial cells, is rapidly released into the bloodstream after myocardial injury, making it suitable for early detection of acute damage [33]. Hs-cTnT is a highly specific marker of cardiomyocyte necrosis, with sustained elevation in chronic or severe injury [34]. Incorporating these biomarkers into a nomogram allows for a comprehensive capture of various aspects of myocardial injury, thereby enhancing the accuracy of predicting ICI-related myocarditis.

NT-proBNP is a pivotal biomarker for the detection of stress-induced overload, myocardial stretch and cardiotoxicity. It is instrumental in screening for heart failure associated during cancer therapy [35, 36]. Our study findings are consistent with the notion that a history of heart failure is a potential risk factor for immune-mediated cardiotoxicity, as highlighted in previous literature [37]. A report suggests that baseline assessments, including cardiac troponin and NT-proBNP or BNP, should be considered for all patients, with monitoring protocols provided for those at risk, focusing particularly on the first 12 weeks, which appear to be the highest-risk time

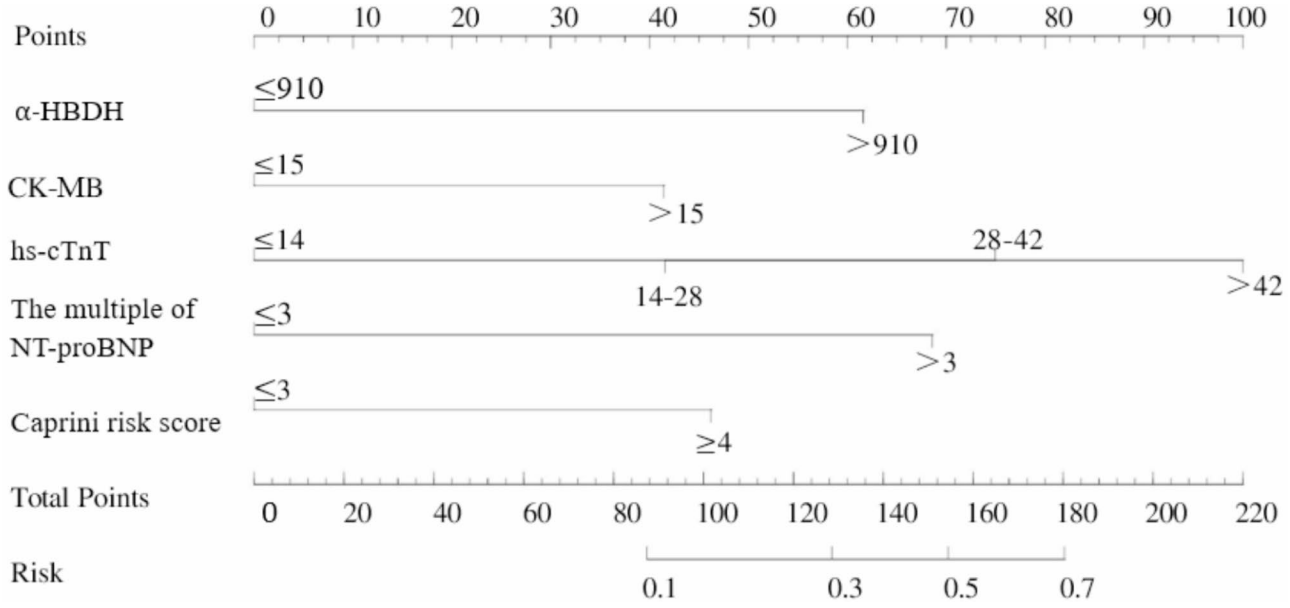

Fig. 1 nomogram prediction model of lung cancer patients treated with immunotherapy

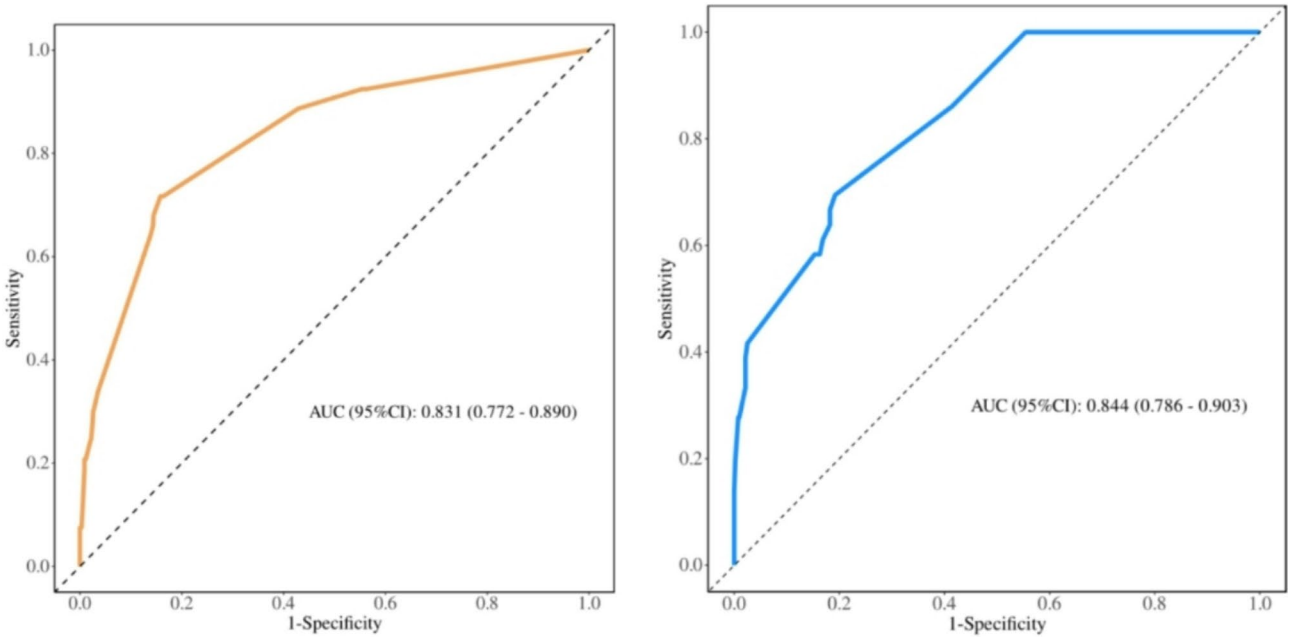

Fig. 2 ROC curve for the myocarditis prediction model in patients in training cohort (left) and test cohort (right)

Table 5 The area under the curve for the risk prediction model of the training cohort

	AUC (95% CI)	Accuracy (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	*P*	Youden Index
Prediction model	0.831 (0.772–0.890)	0.837 (0.815–0.857)	0.842 (0.821–0.862)	0.717 (0.596–0.838)	<0.001	0.559

window [37]. In addition, studies have demonstrated elevated levels of NT-proBNP are correlated with adverse outcomes, with a hazard ratio for death of 1.54 (95%CI: 1.24–1.90, $P<0.001$) [38]. Another study has demonstrated that elevated baseline levels of NT-proBNP are associated with an 11-fold increased risk of cardiovascular adverse events during treatment [39]. Therefore, elevated NT-proBNP levels in patients receiving ICIs may portend an elevated risk of cardiotoxicity, particularly immune checkpoint inhibitor-related myocarditis,

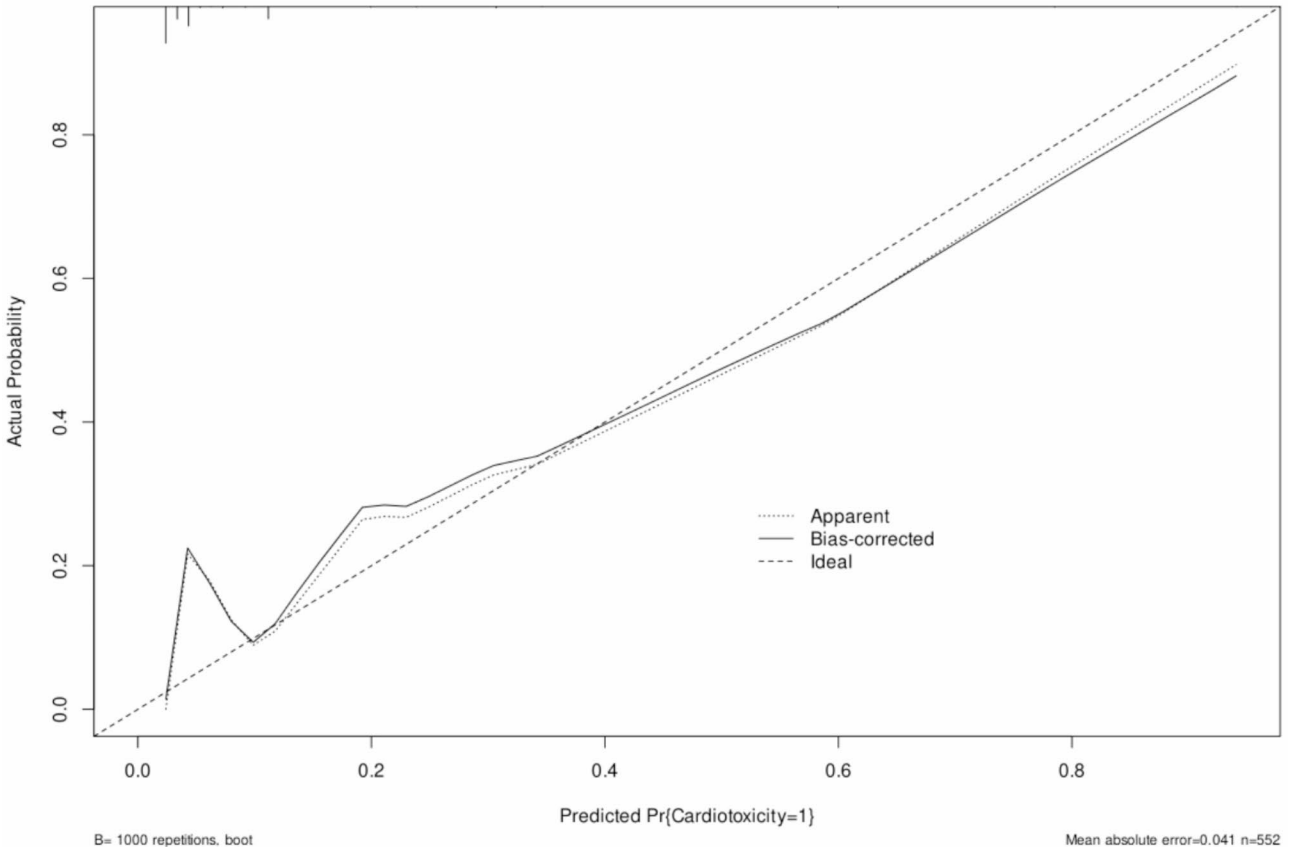

Fig. 3 Risk prediction model calibration curve validation

necessitating rigorous cardiac surveillance and early risk stratification to optimize clinical outcomes.

Our research has demonstrated that the baseline Caprini score before immunotherapy is associated with the risk of ICI-related cardiotoxicity. Caprini risk score is primarily designed for the risk assessment of VTE, and its application in the context of ICI-related myocarditis is novel. While the Caprini score was originally designed for venous thromboembolism risk stratification, emerging evidence suggests that hypercoagulability and systemic inflammation (captured by Caprini items) may synergistically contribute to immune checkpoint inhibitor-related cardiovascular toxicity [37]. The mechanism by which elevated Caprini risk scores increase the risk of ICI-associated myocarditis remains to be further explored.

Although patients with elevated biomarkers shared common inclusion criteria, their cardiovascular backgrounds were heterogeneous. Analyses revealed that heart failure was independently associated with myocarditis risk, consistent with prior studies suggesting that pre-existing ventricular dysfunction exacerbates ICI-induced myocardial inflammation [40]. However, the lack of significant differences in CAD or atrial fibrillation prevalence between groups may indicate that structural heart disease alone is insufficient to predict myocarditis, whereas biomarker-driven myocardial stress plays a more direct role in pathogenesis. In this study, we developed a predictive model for assessing the risk of myocarditis in lung cancer patients undergoing immunotherapy. The model's predictive capabilities were substantiated through rigorous validation processes, demonstrating its potential to enhance clinical decision-making by identifying patients at heightened risk for cardiac complications. Previous studies have underscored that myocarditis remains a significant risk for cancer patients undergoing immunotherapy, with a mortality rate that is relatively high among all immune-related adverse reactions [41], thus highlighting the indispensable importance of predictive tools. This is crucial for devising personalized treatment plans targeting cardiovascular risks in patients with abnormal baseline cardiac parameters.

The limitations of this study mainly arise from the retrospective approach to data collection, which can introduce bias and restrict the broader applicability of our findings. While we documented major cardiovascular comorbidities, the retrospective design limited our ability to capture nuanced cardiovascular phenotypes (e.g., diastolic dysfunction, cardiomyopathy). Moreover, our focus on specific cardiac biomarkers might oversimplify the intricate relationship between immunotherapy and

cardiac health, as various confounding factors could affect the observed connections. Additionally, the performance of the model may differ in various clinical environments, highlighting the need for validation in larger, prospective cohorts and consideration of incorporating more biomarkers to enhance the model's accuracy and applicability. Lastly, our analysis did not consider the long-term impacts of immunotherapy on cardiac function, which is an important area for future research.

Conclusion

In summary, as the number of cancer survivors increases, cardiac health has become a focal point for both oncologists and cardiologists. It is imperative for physicians to minimize the risk of adverse cardiac outcomes while providing the best possible cancer treatment. Currently, assessment models for immune checkpoint inhibitor-related myocarditis are continuously evolving. Biomarkers such as α-HBDH > 910 U/L, CK-MB > 15 ng/ml, hs-cTnT > 14 pg/ml, the multiple of NT-proBNP > 3 based on the upper limit of the normal range for age and Caprini risk score ≥ 4 are identified as risk factors for immune checkpoint inhibitor-related myocarditis in advanced and metastatic lung cancer patients with abnormal cardiac parameters. A Nomogram prediction model based on these risk factors has been developed, which demonstrates good discrimination, accuracy, clinical practicability and can effectively guide clinical practice. This underscores the importance of predictive tools in managing the cardiovascular risks of patients with abnormal baseline cardiac parameters.

Abbreviations

ICIs	immune checkpoint inhibitors
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Cell Death 1 Ligand 1
PE	pulmonary embolism
α-HBDH	α-hydroxybutyrate dehydrogenase
CK-MB	creatine kinase-M/B
hs-cTnT	high-sensitivity cardiac troponin T
NT-proBNP	N-terminal pro-brain natriuretic peptide
CAD	coronary artery disease
ESC	European Society of Cardiology
OR	odds ratios
ROC	Receiver Operating Characteristic
CI	confidence intervals; A
AUC	area under the curve
cTnT	cardiac troponin T

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Author contributions

Author Contributions Xiangjiao Meng designed the study, edited and approved final manuscript. Feng Du, Yan Zhang, Qiang Wang and Jianjian Dou collected the materials. Shanshan Li analyzed the materials and drafted the article. All authors read and approved the final manuscript.

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Data availability

Data availabilityThe datasets generated and analyzed during the current study are available from the corresponding author on request.

Declarations

Ethics approval and consent to participate

The study was approved by the Shandong Cancer Hospital and Institute ethics committee (approval number: SDTHEC202401022), and due to the retrospective design of the study, the ethics committee of Shandong Cancer Hospital and Institute waived the necessity for informed consent. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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