Cardio-Oncology

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A new online dynamic nomogram based on the inflammation burden index to predict cardiac injury after antitumor therapy in lung cancer patients

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Abstract

Introduction Cardiotoxicity has become a major concern in cancer patients, especially those with lung cancer, as anti-tumor therapies can significantly affect patient survival and quality of life. This study aims to develop and validate a dynamic nomogram based on the Inflammation Burden Index (IBI) to predict the risk of cardiac injury within one year after anti-tumor treatment in lung cancer patients.

Methods This single-center, retrospective study included 1386 lung cancer patients who underwent myocardial enzyme testing between July 2018 and January 2023. The IBI was calculated as: IBI = (CRP (mg/dL) × Neutrophils (/μL)) / Lymphocytes (/μL). Statistical analysis using SPSS 22.0 and R 4.4.1, including machine learning algorithms and multivariate logistic analysis, identified independent predictors of cardiac injury. An online dynamic nomogram was developed and validated using internal validation, ROC curves, and decision curve analysis (DCA).

Results The average age of the 1386 patients was 61.98 ± 9.22 years. Significant independent predictors included age, BMI, hypertension, immunotherapy, D-dimer, LDH, NSE, CKMB, and IBI. The nomogram showed strong discriminative ability with AUC-ROC values of 0.85 for the training set and 0.86 for the validation set. Calibration curves confirmed good fit, and DCA showed high clinical utility.

Conclusion An online dynamic nomogram based on clinical and inflammatory markers was developed to predict cardiac injury in lung cancer patients following anti-tumor therapy. The model shows strong discriminative ability and potential clinical value, which can provide vital information for oncologists when designing customized clinical treatments.

Keywords Cardio-oncology, Cardiac injury, Dynamic nomogram, Lung cancer, Inflammation burden index, Antitumor therapy

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Introduction

Cardio-oncology is an emerging discipline focusing on the assessment, diagnosis and treatment of cardiovascular toxicity associated with antitumour therapy [1]. Cardiotoxicity (CTR-CVT) is one of the most common cardiovascular health issues, referring to the adverse effects on the heart caused by chemotherapy, targeted therapy, or radiotherapy during antitumor treatment [2]. These effects can impair heart function, leading to symptoms such as heart failure, arrhythmias, and cardiac injury [3]. With the advancements in antitumor therapies, cardiovascular toxicities have become more pronounced, particularly in patients with lung cancer, breast cancer, and other malignancies [4, 5].

Lung cancer is the most common cancer type in China and the leading cause of cancer-related deaths [6, 7]. In addition to traditional therapies such as radiotherapy and chemotherapy, the survival rate and quality of life of lung cancer patients have significantly improved with the advent of targeted and immunotherapy drugs [8, 9]. However, cardiovascular toxicities related to anti-tumor therapies have gradually become more apparent. A study found that over 20% of patients with locally advanced non-small cell lung cancer (NSCLC) who received chest radiotherapy experienced heart-related adverse events [10]. Another retrospective study of 1,004 lung cancer patients receiving immunotherapy found that 6.5% of them experienced varying degrees of cardiac injury [11]. Myocardial toxicity following anti-tumor therapy significantly affects patient survival outcomes [2, 12]. Therefore, monitoring cardiac injury after anti-tumor therapy is beneficial for adjusting treatment strategies and improving patient prognosis.

According to international guidelines, troponins are currently recommended as effective biomarkers for assessing cardiac damage related to anti-tumor therapies. As cardiac biomarkers, troponins can sensitively and specifically identify early cardiac injury, thus indirectly assessing cardiac toxicity. When high-sensitivity cardiac troponin T (hs-cTnT) exceeds 14 ng/L (defined as the 99th percentile concentration for the general population), cardiac injury should be considered following anti-tumor therapy [13, 14]. Additionally, cardiac biomarkers may be linked to inflammation, providing a new direction for predicting cardiac injury [15].

Cardiac injury is often associated with systemic inflammation [16, 17], and the mechanisms involved include inducing damage to cardiac muscle cells, promoting myocardial fibrosis, and exacerbating oxidative stress responses. Studies have shown that systemic inflammation can increase the permeability of cardiac vascular endothelium by releasing cytokines (such as tumor necrosis factor-alpha, interleukin-6, etc.), thereby promoting local inflammatory responses in cardiac tissue. The Inflammation Burden Index (IBI) is a newly developed biomarker used to reflect systemic inflammation, primarily for evaluating the role of systemic inflammation in cancer prognosis [18]. Studies have shown that, compared to other inflammatory markers, IBI has significant advantages in predicting survival in NSCLC patients [19]. Given that lung cancer patients often experience concurrent systemic inflammation, IBI could serve as a valuable tool for predicting cardiac injury following anti-tumor treatment in these patients.

In this era of personalized cancer therapy, nomograms are statistical tools that can consider various factors simultaneously to help patients visualize their probability of developing a disease [20]. In addition, nomograms have been several advantages in the treatment of cancer, including personalized assessment, user friendliness, and ease of understanding [21]. However, to our knowledge, no study has developed a dynamic prediction model for cardiac injury in lung cancer patients. Therefore, this study aimed to develop an online dynamic nomogram based on the Inflammation Burden Index to predict the risk of cardiac injury within one year after anti-tumor treatment in lung cancer patients.

Patients and methods

Study population and design

This single-center retrospective observational cohort study included lung cancer patients who underwent baseline myocardial enzyme testing between July 2018 to January 2023 at the Affiliated Hospital of Xuzhou Medical University. Patients older than 18 years with confirmed lung cancer and myocardial enzyme detection data were included in the analysis. On the basis of the exclusion criteria, 1386 patients were ultimately included. The inclusion and exclusion criteria are shown in Fig. 1.

The inclusion criteria were as follows:

(1) Patients with confirmed primary lung cancer (NSCLC and SCLC) across stages I-IV to ensure a representative sample.
(2) Patients with baseline hs-cTnT levels were included to assess pre-treatment cardiac function and exclude those with pre-existing heart conditions.

The exclusion criteria were as follows:

(1) had carcinoma in situ or multiple primary tumors;
(2) received only surgical treatment or perioperative patients;

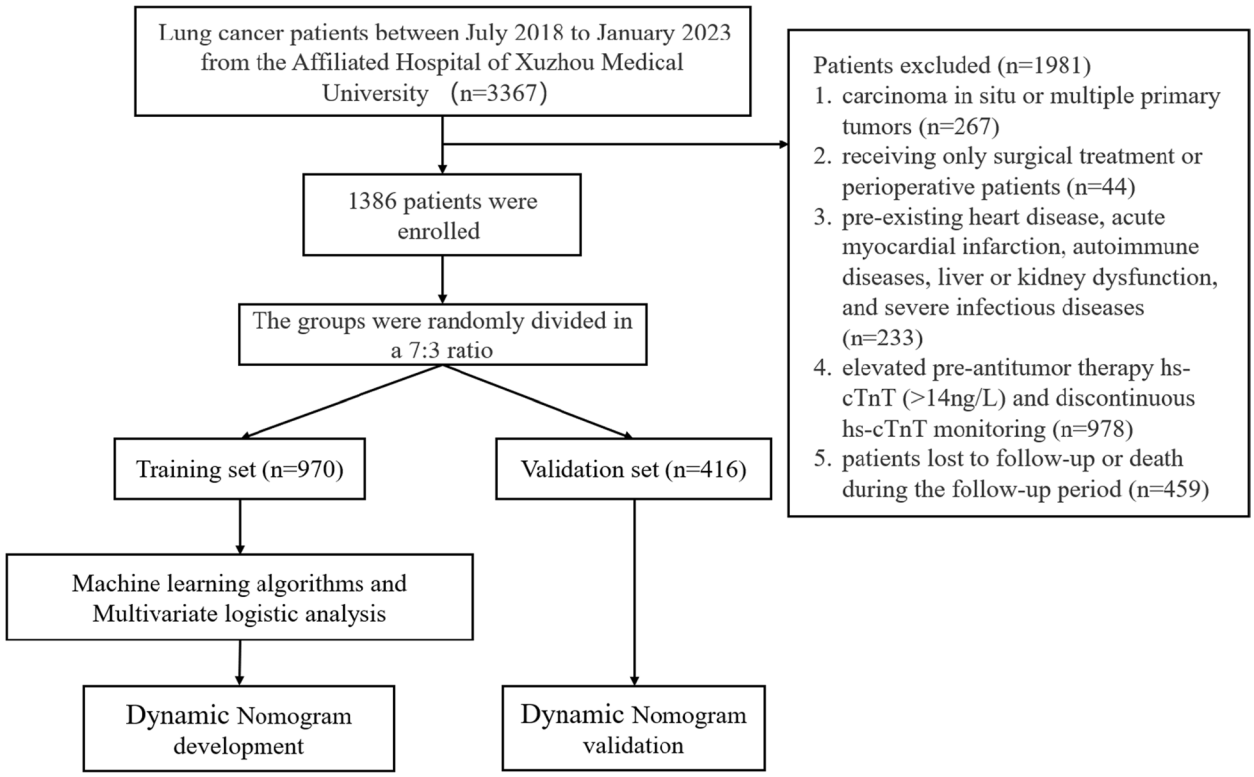

Fig. 1 Flow chart of the inclusion and exclusion process of lung cancer patients

(3) had pre-existing heart disease, acute myocardial infarction, autoimmune diseases, liver or kidney dysfunction, and or severe infectious diseases;
(4) had elevated pre-antitumour therapy hs-cTnT (> 14 ng/L) and discontinuous hs-cTnT monitoring;
(5) lost to follow-up or died during the follow-up period.

This study was approved and waived by the Research Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (approval number XYFY2024-KL156), which was carried out in accordance with the principles of the Declaration of Helsinki. Since this was a single-center retrospective study, the Investigational Review Board waived the requirement for written informed consent.

Data collection

Clinical data were collected: age, gender, smoking history, alcohol consumption history, clinical comorbidity history, and tumor-related medical history. As it is difficult to diagnose cardiac injury early with cardiac ultrasound, cardiac CT, and cardiac magnetic resonance imaging, therefore, these relevant imaging findings were not included in this study. Fasting venous blood was collected from lung cancer patients in the morning within 24 h after admission for routine blood routine and blood biochemical analysis and tumor marker detection. At the same time, troponin levels were collected within 1 year after anti-tumor treatment.

Inflammatory Burden Index (IBI) was calculated using the following formula: IBI = (CRP (mg/dL) × Neutrophils (/μL)) / Lymphocytes (/μL). This index was derived from the levels of C-reactive protein (CRP), neutrophil count, and lymphocyte count, as established by previous studies [18].

The endpoint of our study was cardiac injury within 1 year of antitumour therapy in patients with lung cancer. Diagnostic criteria for cardiac injury: According to international guidelines, when high-sensitivity cardiac troponin T (hs-cTnT) exceeds 14 ng/L (defined as the 99th percentile concentration for the general population), cardiac injury should be considered following anti-tumor therapy [14].

Statistical analysis

Statistical analysis was performed using SPSS version 22.0 and R version 4.4.1. For handling missing data, we employed multiple imputation to reduce the bias that might arise from missing values. Categorical variables

are presented as frequencies and percentages (%), and group comparisons were conducted using the chi-square test. Continuous variables were assessed for normality and homogeneity of variance using the Shapiro–Wilk test and Levene's test, respectively. If the data followed a normal distribution, they were expressed as mean ± standard deviation (x ± s), and comparisons between groups were made using the independent samples t-test. Otherwise, the data were expressed as median (M) and interquartile range [M (P25, P75)], and group comparisons were performed using non-parametric tests. A *p*-value of less than 0.05 was considered statistically significant.

In contrast to traditional methods for screening variable importance, this study utilizes a model coefficient-dependent approach to analyze the significance of variables in the training cohort. Specifically, machine learning techniques are employed to rank the features of the included variables, thereby extracting the most important ones. Two machine learning algorithms, eXtreme Gradient Boosting (XGBoost) and Random Forest (RF), were chosen for variable screening due to their ability to assess variable importance effectively. These ensemble methods are particularly suited for handling complex datasets and capturing non-linear relationships between variables. Using both XGBoost and RF allows us to reduce algorithm-specific bias by taking the intersection of the features they rank as important, ensuring a more objective and robust feature selection process.

Subsequently, Venn diagrams were performed to select the common variables filtered by both RF and XGBoost models, providing a visual demonstration of the consistency between the two models. These variables were then input into R software to create a nomogram. To facilitate their incorporation into clinical practice, an interactive web-based dynamic nomogram application was built using Shiny, version 0.13.2.26. Internal validation was conducted using the Bootstrap method. The model's discriminative ability and calibration were evaluated using the area under the receiver operating characteristic curve (AUC-ROC) and calibration curves, respectively. Finally, decision curve analysis (DCA) was employed to assess the clinical value of the model.

Results

Baseline characteristics

In total, 1386 lung cancer patients participated in the study from July 2018 to January 2023. The average age of all patients was 61.98 (± 9.22) years, and 856 (61.76%) were male. Patients were split into two groups according to whether cardiac injury occurred at the end of follow-up: the noncardiac injury group ($n = 1046$) and the cardiac injury group ($n = 340$). Table 1 list the demographic data and baseline characteristics of the lung cancer patient.

Compared with the non-cardiac injury group, patients in the cardiac injury group were older, with a higher proportion of males and a higher body mass index (BMI) level. ($P < 0{,}01$). Patients with hypertension, diabetes mellitus and a history of smoking were more common in the cardiac injury group, and the difference was statistically significant ($P < 0.01$). In addition, the cardiac injury group also had higher neutrophil, high sensitivity C-reactive protein, D-dimer, cancer antigen 125(CA125), lactate dehydrogenase (LDH), creatine kinase (CK), creatine kinase isoenzymes (CKMB) and inflammation burden index (IBI) levels ($P < 0.05$). However, the lymphocyte and neuron specific enolase (NSE) levels were lower in the cardiac injury group. Both groups received antitumor therapy, patients in the cardiac injury group were significantly more likely to have III or IV stage of tumor node metastasis classification (TMN) and non-small cell lung cancer (NSCLC). For non-surgical treatment, radiotherapy and immunotherapy were used at a higher rate in the cardiac injury group. All the above differences were statistically significant, as shown in Table 1.

Clinical features of the training set and validation set

To prevent overfitting of the nomogram in the analysis, we randomly divided lung cancer patients into the training and validation sets in the ratio of 7:3. There was little difference between the training and validation sets for any other baseline characteristics. This illustrates that the division of our dataset is reasonable and comparable, as shown in Table 2.

Feature variables selection for model development

The optimization of feature variables was conducted through the application of machine learning algorithms, namely RF (Fig. 2A) and XGBoost (Fig. 2B). Each algorithm separately identified the top 12 most important feature variables for their respective models. Subsequently, through comprehensive analysis using Venn diagrams, ten variables (Age, BMI, Hypertension, Immunotherapy, D-dimer, LDH, NSE, CK, CKMB and IBI) were identified for the construction of the prognostic model (Fig. 2C).

To clarify whether the abovementioned ten variables were independent risk factors for cardiac injury, further multivariate logistic analysis excluding other confounding factors was carried out and showed that CKMB, IBI, Hypertension, Age, D-Dimer, NSE, Immunotherapy, LDH, and BMI were significantly associated with cardiac injury. But The results showed that the variable CK had a *p*-value greater than 0.05 ($p = 0.895$) and was excluded from the final model. The odds ratios (ORs) and 95%

Table 1 Baseline characteristics of the non-cardiac injury group and cardiac injury group

Variables	Total ($n=1386$)	Noncardiac injury ($n=1046$)	cardiac injury ($n=340$)	*P*
Age	61.98 ± 9.22	60.55 ± 8.96	66.39 ± 8.59	**< .001***
Gender, n(%)				**< .001***
Female	530 (38.24)	466 (44.55)	64 (18.82)	
Male	856 (61.76)	580 (55.45)	276 (81.18)	
BMI (kg/m2)	23.55 ± 3.26	23.35 ± 3.13	24.18 ± 3.54	**< .001***
Hb (g/L)	134.53 ± 13.99	134.59 ± 13.57	134.36 ± 15.22	0.800
N ($\times 10^9$/L)	4.30 ± 1.82	4.19 ± 1.77	4.65 ± 1.91	**< .001***
L ($\times 10^9$/L)	1.60 ± 0.55	1.61 ± 0.54	1.57 ± 0.60	0.298
PLT ($\times 10^9$/L)	244.43 ± 72.07	245.23 ± 70.67	241.97 ± 76.29	0.486
CRP (mg/L)	3.10 (1.20, 7.57)	2.50 (1.10, 6.00)	5.35 (2.30, 15.33)	**< .001***
D-dimer (ug/ml)	0.28 (0.15, 0.64)	0.25 (0.13, 0.53)	0.43 (0.21, 0.85)	**< .001***
FIB (g/L)	3.87 ± 1.08	3.89 ± 1.08	3.78 ± 1.08	0.106
G (umol/L)	5.48 (5.06, 6.19)	5.50 (5.09, 6.13)	5.38 (4.93, 6.46)	0.128
TG (mmol/L)	1.26 (0.98, 1.68)	1.27 (0.98, 1.66)	1.25 (0.99, 1.74)	0.995
TC (mmol/L)	4.62 ± 0.91	4.64 ± 0.89	4.54 ± 0.96	0.087
Scr (umol/L)	60.64 ± 11.39	60.59 ± 11.34	60.79 ± 11.58	0.775
UA (mmol/L)	277.33 ± 78.29	275.00 ± 77.36	284.49 ± 80.79	0.052
CYSC (mg/L)	0.85 ± 0.17	0.84 ± 0.15	0.85 ± 0.22	0.439
ALB (U/L)	42.40 ± 4.11	42.40 ± 4.01	42.39 ± 4.42	0.970
AST (U/L)	19.00 (15.00, 23.00)	19.00 (16.00, 23.00)	18.00 (15.00, 23.00)	0.395
LDH (U/L)	198.00 (169.00, 229.75)	194.00 (167.00, 224.00)	208.00 (178.00, 259.75)	**< .001***
CK (U/L)	57.00 (41.00, 80.00)	56.00 (40.00, 77.00)	64.00 (47.00, 95.25)	**< .001***
CKMB (ng/ml)	1.06 (0.78, 1.54)	0.98 (0.72, 1.29)	1.60 (1.06, 2.03)	**< .001***
IBI	7.35 (2.63, 23.90)	6.08 (2.16, 18.80)	14.86 (5.55, 52.92)	**< .001***
CEA (ng/mL)	4.70 (2.61, 16.26)	4.42 (2.61, 16.26)	5.45 (2.71, 16.03)	0.208
NSE (ng/mL)	17.30 (14.01, 23.20)	17.47 (14.20, 23.17)	16.71 (13.04, 23.25)	**0.042***
CA125 (ng/mL)	23.31 (12.80, 58.71)	21.81 (12.40, 53.84)	26.32 (15.01, 77.73)	**< .001**
Smoking, n(%)				**< .001***
No	628 (45.31)	553 (52.87)	75 (22.06)	
Yes	758 (54.69)	493 (47.13)	265 (77.94)	
Alcohol, n(%)				0.578
No	1059 (76.41)	803 (76.77)	256 (75.29)	
Yes	327 (23.59)	243 (23.23)	84 (24.71)	
HTN, n(%)	332 (23.95)	200 (19.12)	132 (38.82)	**< .001***
DM, n(%)	166 (11.98)	82 (7.84)	84 (24.71)	**< .001***
AF, n(%)	65 (4.69)	49 (4.68)	16 (4.71)	0.987
CAD, n(%)	177 (12.77)	132 (12.62)	45 (13.24)	0.768
CVD, n(%)	436 (31.46)	328 (31.36)	108 (31.76)	0.888
NSCLC, n(%)	1186 (85.57)	908 (86.81)	278 (81.76)	**0.022***
TNM, n(%)				**< .001***
I/II	367 (26.48)	306 (29.25)	61 (17.94)	
III/IV	1019 (73.52)	740 (70.75)	279 (82.06)	
Chemotherapy, n(%)	1268 (91.49)	952 (91.01)	316 (92.94)	0.269
Radiotherapy, n(%)	355 (25.61)	249 (23.80)	106 (31.18)	**0.007***
Targeted, n(%)	608 (43.87)	457 (43.69)	151 (44.41)	0.816
Immunotherapy, n(%)	611 (44.08)	402 (38.43)	209 (61.47)	**< .001***

Abbreviation: BMI Body mass index, *Hb* Hemoglobin, *N* Neutrophils, *L* Lymphocyte, *PLT* Platelet, *FIB* Fibrin, *G* Glucose, *TG* Total cholesterol, *TC* Triglycerides, *Scr* Serum creatinine, *UA* Uric acid, *CYSC* Cystatin C, *AST* Aspartate transaminase, *ALB* Albumin, *CRP* C-reactive protein, *LDH* Lactate dehydrogenase, *CEA* Carcinoembryonic antigen, *CA125* Cancer antigen 125, *NSE* Neuron specific enolase, *CK* Creatine kinase, *CKMB* Creatine kinase isoenzymes, *HTN* Hypertension, *DM* Diabetes mellitus, *AF* Atrial fibrillation, *CAD* Coronary artery disease, *CVD* Cerebrovascular disease, Targeted: targeted therapy, *IBI* Inflammatory burden index, *TMN* Tumor node metastasis classification, *NSCLC* Non-small cell lung cancer

* $P < 0.05$ was considered a statistically significant difference

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Table 2 Baseline characteristics of training and validation sets

Variables	Total ($n=1386$)	Validation ($n=416$)	Training ($n=970$)	*P*
Cardiac Injury, n(%)				0.688
No	1046 (75.47)	311 (74.76)	735 (75.77)	
Yes	340 (24.53)	105 (25.24)	235 (24.23)	
Age	61.98 ± 9.22	62.36 ± 9.44	61.82 ± 9.12	0.323
BMI (kg/m2)	23.55 ± 3.26	23.52 ± 3.30	23.56 ± 3.24	0.822
Gender, n(%)				0.636
Female	530 (38.24)	163 (39.18)	367 (37.84)	
Male	856 (61.76)	253 (60.82)	603 (62.16)	
Smoking, n(%)				0.681
No	628 (45.31)	185 (44.47)	443 (45.67)	
Yes	758 (54.69)	231 (55.53)	527 (54.33)	
Alcohol, n(%)				0.278
No	1059 (76.41)	310 (74.52)	749 (77.22)	
Yes	327 (23.59)	106 (25.48)	221 (22.78)	
HTN, n(%)	332 (23.95)	101 (24.28)	231 (23.81)	0.853
DM, n(%)	166 (11.98)	58 (13.94)	108 (11.13)	0.140
AF, n(%)	65 (4.69)	16 (3.85)	49 (5.05)	0.331
CAD, n(%)	177 (12.77)	54 (12.98)	123 (12.68)	0.878
CVD, n(%)	436 (31.46)	129 (31.01)	307 (31.65)	0.814
Hb (g/L)	134.53 ± 13.99	133.78 ± 14.27	134.86 ± 13.86	0.190
PLT ($\times 10^9$/L)	244.43 ± 72.07	242.12 ± 75.99	245.42 ± 70.34	0.435
D-dimer (ug/ml)	0.28 (0.15, 0.64)	0.29 (0.15, 0.61)	0.28 (0.14, 0.66)	0.777
FIB (g/L)	3.87 ± 1.08	3.91 ± 1.19	3.85 ± 1.02	0.381
G (umol/L)	5.48 (5.06, 6.19)	5.47 (5.07, 6.18)	5.48 (5.06, 6.20)	0.995
TG (umol/L)	1.26 (0.98, 1.68)	1.20 (0.94, 1.63)	1.29 (1.00, 1.70)	**0.018***
TC (umol/L)	4.62 ± 0.91	4.56 ± 0.96	4.65 ± 0.89	0.105
Scr (umol/L)	60.64 ± 11.39	60.66 ± 11.61	60.63 ± 11.30	0.964
UA (umol/L)	277.33 ± 78.29	274.24 ± 79.31	278.66 ± 77.86	0.336
CYSC (mg/L)	0.85 ± 0.17	0.84 ± 0.17	0.85 ± 0.17	0.352
ALB (U/L)	42.40 ± 4.11	42.17 ± 4.16	42.50 ± 4.09	0.179
AST (U/L)	19.00 (15.00, 23.00)	18.00 (15.00, 23.00)	19.00 (16.00, 23.00)	0.137
LDH (U/L)	198.00 (169.00, 229.75)	197.50 (168.00, 226.25)	198.00 (170.00, 231.00)	0.303
CK (U/L)	57.00 (41.00, 80.00)	57.00 (41.00, 80.00)	58.00 (42.00, 79.75)	0.631
CKMB (ng/ml)	1.06 (0.78, 1.54)	1.06 (0.77, 1.52)	1.06 (0.78, 1.56)	0.814
IBI	7.35 (2.63, 23.90)	6.95 (2.28, 20.54)	7.44 (2.71, 26.24)	0.457
CEA (ng/mL)	4.70 (2.61, 16.26)	4.71 (2.62, 16.46)	4.70 (2.61, 16.10)	0.956
NSE (ng/mL)	17.30 (14.01, 23.20)	17.01 (14.10, 22.27)	17.39 (14.00, 23.59)	0.514
CA125 (ng/mL)	23.31 (12.80, 58.71)	22.24 (12.19, 63.82)	23.64 (13.10, 57.25)	0.366
NSCLC, n(%)	1186 (85.57)	363 (87.26)	823 (84.85)	0.241
TNM, n(%)				0.191
I/II	367 (26.48)	120 (28.85)	247 (25.46)	
III/IV	1019 (73.52)	296 (71.15)	723 (74.54)	
Chemotherapy, n(%)	1268 (91.49)	380 (91.35)	888 (91.55)	0.903
Radiotherapy, n(%)	355 (25.61)	102 (24.52)	253 (26.08)	0.541
Targeted, n(%)	608 (43.87)	181 (43.51)	427 (44.02)	0.861
Immunotherapy, n(%)	611 (44.08)	174 (41.83)	437 (45.05)	0.268

Abbreviation: BMI Body mass index, *Hb* Hemoglobin, *PLT* Platelet, *FIB* Fibrin, *G* Glucose, *TG* Total cholesterol, *TC* Triglycerides, *Scr* Serum creatinine, *UA* Uric acid, *CYSC* Cystatin C, *AST* Aspartate transaminase, *ALB* Albumin, *LDH* Lactate dehydrogenase, *CEA* Carcinoembryonic antigen, *CA125* Cancer antigen 125, *NSE* Neuron specific enolase, *CK* Creatine kinase, *CKMB* Creatine kinase isoenzymes, *HTN* Hypertension, *DM* Diabetes mellitus, *AF* Atrial fibrillation, *CAD* Coronary artery disease, *CVD* Cerebrovascular disease, *Targeted* Targeted therapy, *IBI* Inflammatory burden index, *TMN* Tumor node metastasis classification, *NSCLC* Non-small cell lung cancer

* $P < 0.05$ was considered a statistically significant difference

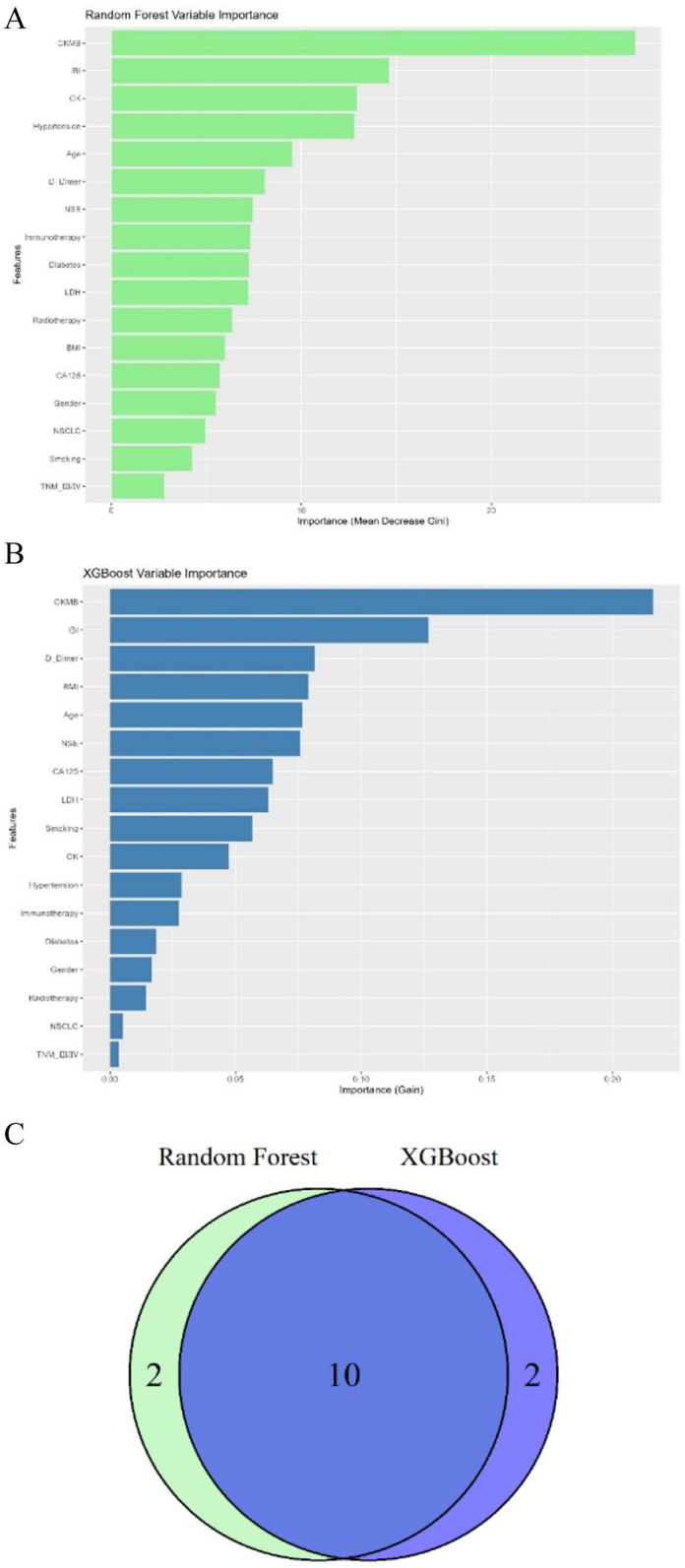

Fig. 2 **A** Importance of feature variables by random forest. **B** Importance of feature variables by XGBoost. **C** A Venn diagram analyzes the results of two machine algorithms

confidence intervals (CIs) for each variable are shown in Table 3.

Development of the nomogram

The final logistic model included nine independent predictors (Age, BMI, Hypertension, Immunotherapy, D-dimer, LDH, NSE, CKMB and IBI) and was developed as a simple-to-use nomogram, which is illustrated in Fig. 3A and available online (https://yuminwang-123.shinyapps.io/dynnomapp/) and presented in Fig. 3B.

Regarding the validation of the nomogram, we proceed through the following three steps. First, we validate the model's discriminative ability by plotting the ROC curve (Fig. 4). The AUC of the training and validation sets are 0.85 (95% CI: 0.83–0.88) and 0.86 (95% CI: 0.82–0.90), respectively. Meanwhile, the accuracy of the training and validation sets are 0.83 (95% CI: 0.81–0.85) and 0.82 (95% CI: 0.78–0.86) (Table 4). This indicates that the model has an excellent discriminative ability. Second, we used the Bootstrap self-sampling method with B = 1000 repetitions and plotted the calibration curves for the training and validation sets (Fig. 5). The results show that the predicted probability of the model output is in good agreement with the true occurrence probability, and the model calibration is good. Finally, to verify the clinical validity of the model, we plotted DCA curves (Fig. 6). The results show that the net benefit of the nomogram is significantly higher in the training and validation sets than in the two extreme cases. Therefore, the nomogram has good clinical significance.

Discussion

This study successfully developed and validated a novel online dynamic nomogram based on the Inflammation Burden Index (IBI) to predict the risk of cardiac injury in lung cancer patients undergoing antitumor therapy. The results demonstrated that age, BMI, hypertension, immunotherapy, D-dimer, lactate dehydrogenase (LDH), neuron-specific enolase (NSE), creatine kinase-MB (CKMB), and IBI were independent predictors of cardiac injury. The establishment of this model provides a robust tool for the early identification of high-risk patients in clinical settings, underscoring its significant clinical utility.

Table 3 Multivariate logistic analysis

Variables	β	S.E	Z	*P*	OR (95%CI)
CKMB	1.20	0.16	7.40	**<.001**	3.33 (2.42 ~ 4.59)
IBI	0.01	0.00	5.63	**<.001**	1.01 (1.01 ~ 1.01)
CK	−0.00	0.00	−0.13	0.895	1.00 (0.99 ~ 1.00)
Hypertension	0.84	0.20	4.21	**<.001**	2.32 (1.57 ~ 3.44)
Age	0.06	0.01	4.73	**<.001**	1.06 (1.03 ~ 1.08)
D Dimer	0.39	0.10	3.84	**<.001**	1.48 (1.21 ~ 1.81)
NSE	−0.01	0.00	−2.40	**0.016**	0.99 (0.99 ~ 0.99)
Immunotherapy	1.09	0.19	5.74	**<.001**	2.97 (2.05 ~ 4.31)
LDH	0.01	0.00	2.36	**0.018**	1.01 (1.01 ~ 1.01)
BMI	0.12	0.03	3.98	**<.001**	1.12 (1.06 ~ 1.19)

Abbreviation: BMI Body mass index, *LDH* Lactate dehydrogenase, *NSE* Neuron specific enolase, *CK* Creatine kinase, *CKMB* Creatine kinase isoenzymes, *IBI* Inflammatory burden index, *OR* Odds Ratio, *CI* Confidence Interval

Firstly, IBI, as a comprehensive tool for assessing inflammation burden, exhibits superior prognostic capabilities in cancer patients. Developed by Professor Hanping Shi's team, IBI integrates C-reactive protein (CRP), neutrophils, and lymphocytes, offering a simple yet effective method for inflammation assessment [18]. This study further validates the role of IBI in predicting cardiac injury post-antitumor therapy, supporting its potential widespread application as an inflammatory biomarker. Meanwhile , a study found that higher levels of the Inflammatory Burden Index (IBI) in cancer patients are significantly associated with increased mortality from all causes, cardiovascular disease, and cancer, suggesting its potential as a valuable prognostic biomarker [22]. Compared to traditional single inflammation markers, IBI provides a more holistic reflection of the patient's inflammatory status, thereby enhancing predictive accuracy.

Additionally, age and BMI, recognized risk factors for cardiovascular diseases [23], were confirmed as independent predictors of cardiac injury in this study. Aging is associated with a gradual decline in cardiovascular function, and antitumor therapies impose additional cardiac stress on elderly patients, elevating the risk of cardiac injury [24–26]. Elevated BMI is closely linked to metabolic syndrome and cardiovascular diseases [27], and patients with higher BMI experience increased cardiac burden during antitumor treatment, making them more susceptible to cardiac injury [28, 29].

Hypertension, a prevalent chronic condition, is closely related to the occurrence of cardiac injury [30, 31]. Hypertensive patients already exhibit structural and functional cardiac alterations, and antitumor therapies may further exacerbate cardiac stress, increasing the risk of cardiac injury [32]. Immunotherapy, a crucial modality in recent lung cancer treatments, enhances therapeutic efficacy but may also induce immune-related cardiac inflammation, thereby increasing the incidence of cardiac injury [8, 9, 28]. Studies indicate that immunotherapy increases the risk of cardiovascular events in cancer patients. A large Danish cohort study found that ICI treatment significantly raised the risk of heart events in lung cancer and melanoma patients [33]. Another study showed that a small portion of hospitalizations and costs in Asian patients receiving ICI treatment were linked to cardiovascular diseases [34]. This underscores the need to consider cardiac risks in cancer immunotherapy.

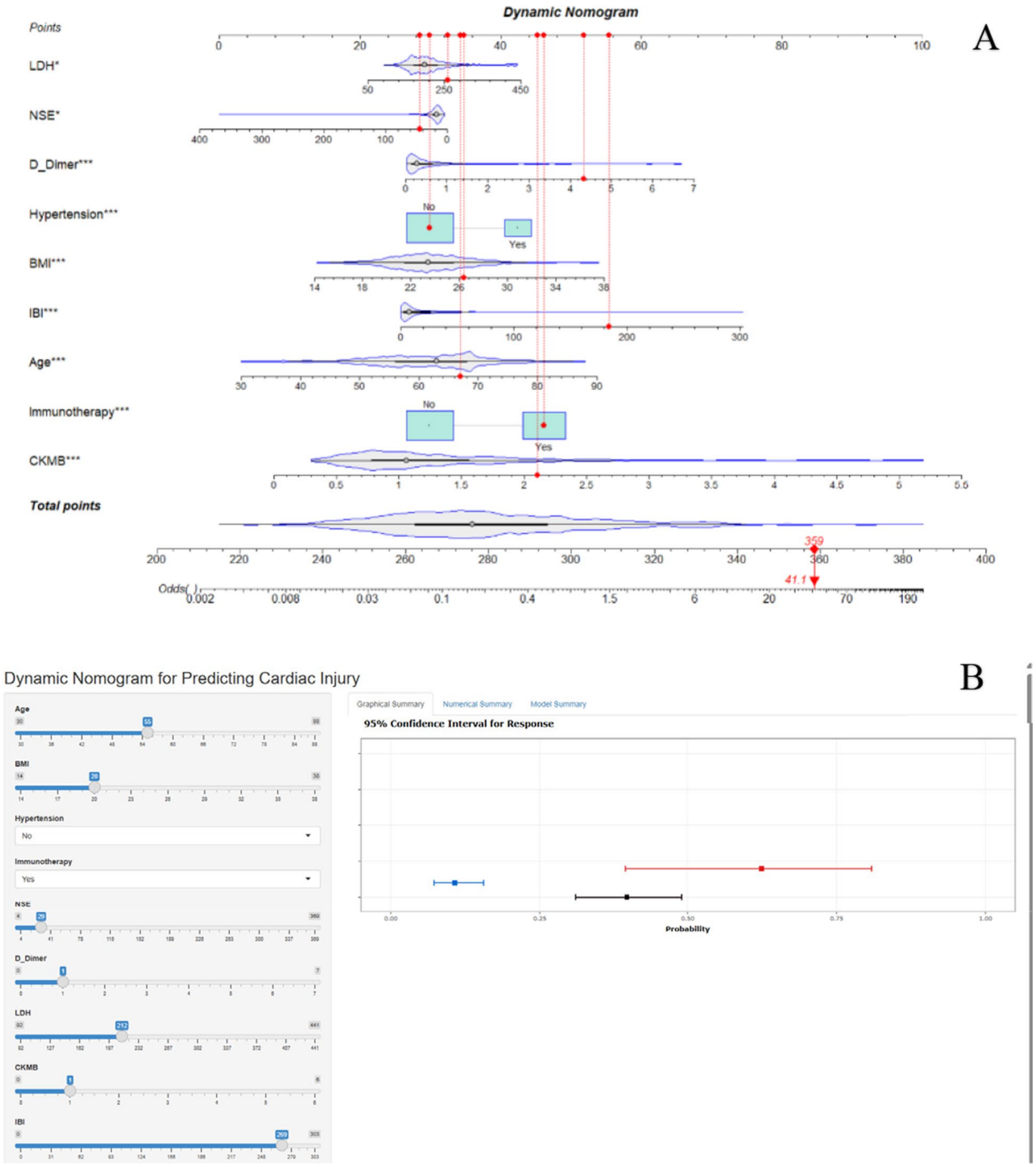

Fig. 3 Nomogram used for predicting cardiac injury after antitumor therapy in lung cancer patients. **A** Established nomogram in the training cohort by incorporating the following eleven parameters: Age, BMI, Hypertension, Immunotherapy, D-dimer, LDH, NSE, CKMB and IBI. **B** Online dynamic nomogram accessible at https://yuminwang-123.shinyapps.io/dynnomapp/. Abbreviation: BMI: body mass index, NSE: neuron specific enolase, LDH: lactate dehydrogenase, CKMB: creatine kinase isoenzymes, IBI: inflammatory burden index

Regarding laboratory indicators, D-dimer, LDH, NSE, and CKMB all demonstrated significant predictive value in this study. D-dimer, a marker of coagulation and fibrinolysis, is elevated in conditions of increased thrombosis and fibrinolytic activity [35]. Lung cancer patients with elevated D-dimer levels may be more susceptible

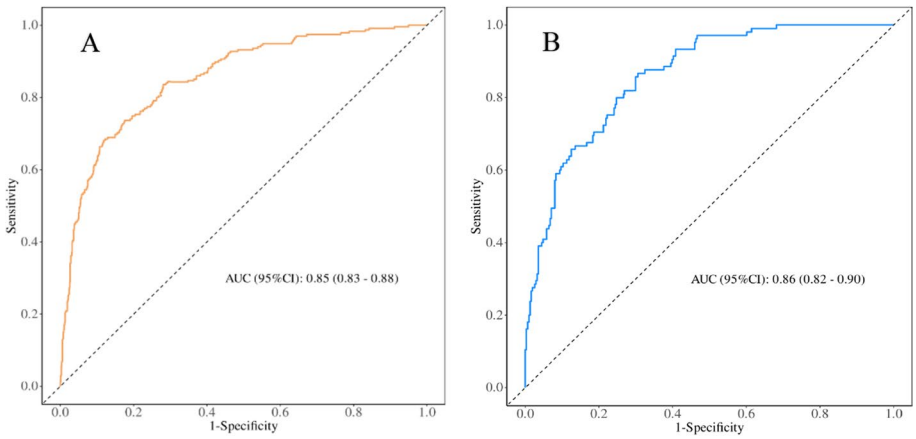

Fig. 4 ROC curves of clinical prediction models were drawn based on the data of the training set (**A**) and validation set (**B**). Abbreviation: AUC: the area under the receiver operating characteristic

Table 4 Indicators related to model prediction ability

Data	AUC (95%CI)	Accuracy (95%CI)	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	cut off
Training	0.85 (0.83–0.88)	0.83 (0.81–0.85)	0.88 (0.85—0.90)	0.69 (0.63—0.74)	0.90 (0.87—0.92)	0.64 (0.58—0.70)	0.336
Validation	0.86 (0.82–0.90)	0.82 (0.78–0.86)	0.89 (0.85—0.92)	0.63 (0.54—0.72)	0.88 (0.84—0.91)	0.65 (0.56—0.75)	0.336

Abbreviation: AUC the area under the receiver operating characteristic, *PPV* Positive predictive value, *NPV* negative predictive value

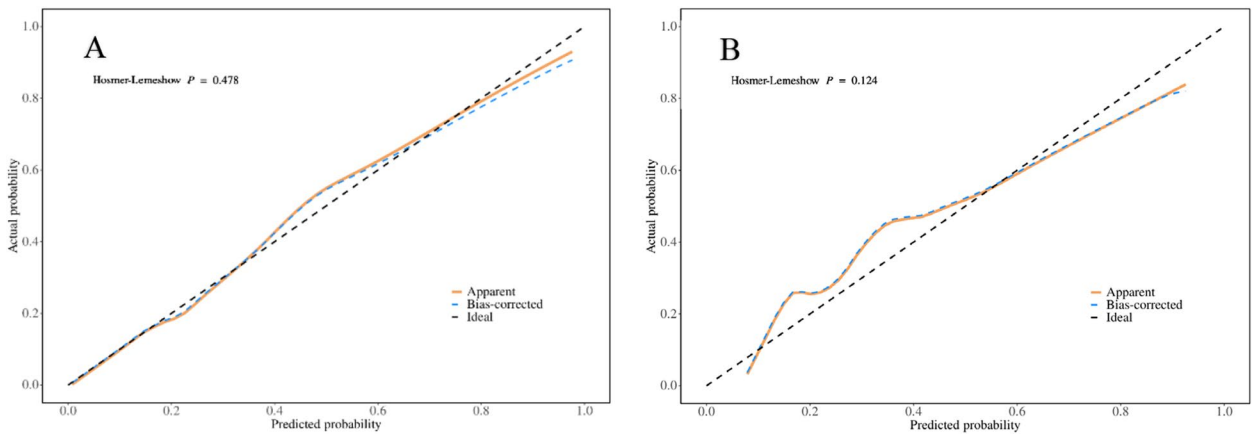

Fig. 5 Calibration curve of the nomogram on the data of the training set (**A**) and validation set (**B**)

to myocardial injury due to a chronic inflammatory state. This phenomenon was also observed by Masayoshi Oikawa's team, who found that increased baseline D-dimer levels were an independent predictor of the occurrence of chemotherapy-related cardiotoxicity (CTRCD) (OR: 3.93, 95% CI: 1.00–15.82, p=0.047) [36]. LDH is released from damaged tissues and can serve as a biomarker for injured cardiac tissue [37]. Studies have found that pre-treatment LDH levels in cancer patients are significantly elevated compared to matched healthy controls (p<0.001) [38]. Therefore, the role of LDH in cancer biology is more complex, and it may emerge as a potential therapeutic target for cancer treatment. Neuron-specific enolase (NSE) is primarily used as a biomarker for diagnosing and predicting the prognosis of lung cancer, particularly in neuroendocrine tumors [39]. However, the association between NSE levels and cardiac injury risk in lung cancer patients is not straightforward

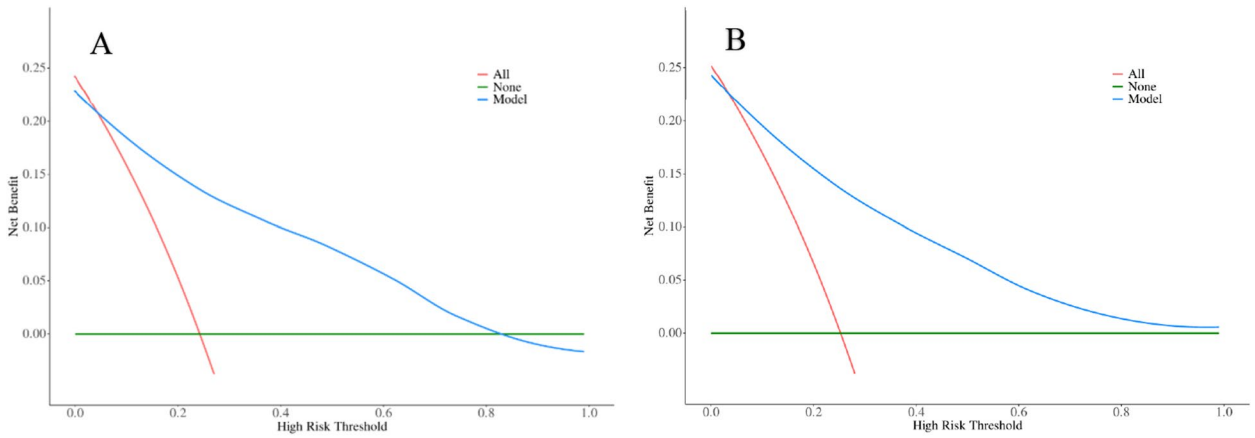

Fig. 6 Evaluation of clinical validity of predictive models on the data of the training set (**A**) and validation set (**B**)

and presents conflicting results. Initially, lower NSE levels were thought to be associated with poorer tumor differentiation or a higher tumor burden, which could indirectly influence the risk of heart damage. Lower NSE levels may also suggest neuroendocrine dysfunction, which could compromise heart adaptation during treatment and thereby increase the risk of cardiac injury [39, 40]. On the other hand, a study on advanced non-small cell lung cancer (NSCLC) found that elevated NSE levels were independently linked to poor prognosis, raising questions about its role in predicting cardiac damage [41]. High NSE levels in this context likely reflect the extent of tumor progression and metastasis rather than direct myocardial injury [42]. Therefore, while NSE is a useful prognostic marker in lung cancer, its role in predicting cardiac injury remains less clear and likely depends on the specific cancer type and stage. Further studies are needed to explore how NSE levels might contribute to the risk of myocardial injury, particularly in patients undergoing cancer treatments such as chemotherapy or immunotherapy. As for Creatine Kinase-MB (CKMB), it is widely recognized as a reliable marker for detecting myocardial injury. CKMB levels typically correlate with the extent of myocardial damage, making it a standard biomarker for evaluating heart injury in many clinical settings [43]. However, its role in predicting cardiac injury in lung cancer patients, especially those receiving immunotherapy or chemotherapy, is more complex. Some studies have supported CKMB as a marker of myocardial injury, but others have questioned its reliability, particularly in the context of immune checkpoint inhibitor (ICI)-induced myocardial injury. One small-sample study suggested that CKMB might not be as useful for predicting ICI-related cardiac toxicity, which is inconsistent with findings from other studies [44]. This discrepancy may be due to the multifactorial nature of cardiac damage in cancer patients, where CKMB levels can be influenced by factors such as skeletal muscle injury or inflammation rather than only myocardial damage [45, 46]. The challenge with CKMB as a biomarker lies in its lack of specificity, as elevated CKMB levels can also be caused by non-cardiac tissue damage, particularly in patients undergoing aggressive cancer treatments [47]. Therefore, while CKMB remains a widely used biomarker for myocardial injury, its predictive value for cardiac toxicity in lung cancer patients undergoing immunotherapy or other novel treatments requires further investigation. The variability in findings across studies suggests that a single biomarker like CKMB may not be sufficient to accurately predict heart damage in all cancer treatment contexts. A more comprehensive approach, incorporating a combination of biomarkers and clinical factors, may be necessary to better assess the risk of cardiac injury in these patients.

The findings of this study not only enrich the predictive models for cardiac injury but also provide specific intervention directions for clinical practice. In the era of precision medicine, utilizing comprehensive indicators like IBI for risk assessment enables early identification of high-risk patients and personalized treatment strategies, thereby optimizing therapeutic regimens and reducing the incidence of cardiac injury. Furthermore, dynamic monitoring of IBI levels facilitates real-time evaluation of the patient's inflammatory status and treatment response, guiding clinical decision-making.

Our article has some limitations as follows: (1) This is a single-center retrospective study with a lack of external validation. It is hoped that a multicenter, prospective study will be conducted in the future to further confirm this finding. (2) The specific anti-tumor treatment regimens were not statistically analyzed in this study. This lack of detailed information on treatment variability may have

influenced the results, and future research should account for this factor. (3) The study did not explore the different pathological types of lung cancer, which may have distinct characteristics and responses to treatment. Future studies should investigate the specific pathological subtypes of lung cancer to better understand how they influence the risk of cardiac injury following anti-tumor therapy.

Conclusion

This study was the first to develop and validate online nomograms based on the independent risk factors to dynamically predict cardiac injury after antitumor therapy in lung cancer patients. The model can provide a scientific reference for predicting the occurrence of cardiac injury and improving the prognosis of patients, which can provide vital information for oncologists when designing customized clinical treatments. To ensure generality, this model requires external validation.

Clinical trial number

Not applicable.

Authors' contributions

Yumin Wang developed the analysis plan and wrote the paper. Chunyan Huan and Huijuan Pu and Guodong Wang undertook the data analysis. Yan Liu, Xiuli Zhang, Chengyang Li, Jie Liu, Wanling Wu, collected the dataset and provided advice on its analysis. Defeng Pan guided the analysis and made substantial improvements to the paper. Yumin Wang and Chunyan Huan are co-first authors, meaning they contributed equally to the work presented in this manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Xuzhou Medical University Affiliated Hospital (Approval number XYFY2024-KL156). The requirement for signed written consent was waived owing to no risk to the patient in accordance with the relevant IRB regulatory guidelines.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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