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The inflammation burden index can predict the cardiac injury following antitumour therapy in lung cancer patients with diabetes

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Lung cancer is a leading cause of cancer-related morbidity and mortality worldwide. Diabetes, as a common metabolic disorder, further increases the risk of cardiovascular damage. Studies have shown that myocardial cells in diabetic patients are more vulnerable to the toxic effects of cancer treatments, thereby raising the risk of heart failure. Therefore, cardiovascular risk assessment in lung cancer patients with diabetes is particularly important. The Inflammatory Burden Index (IBI) is a biomarker that reflects systemic inflammation, combining the levels of C-reactive protein (CRP), neutrophils, and lymphocytes. It has been shown to be a significant prognostic indicator in various cancer populations. This study aims to investigate the predictive ability of IBI and the triglyceride-glucose (TyG) index for cardiac injury in lung cancer patients with diabetes undergoing antitumor therapy. A single-center retrospective case-control study was conducted, including clinical data of 192 lung cancer patients with diabetes who received anti-tumor therapy from July 2018 to January 2023.Cardiac injury was assessed by measuring high-sensitivity cardiac troponin T (hs-cTnT) levels. The Inflammatory Burden Index (IBI) was calculated using the formula: IBI = (C-reactive protein [CRP] × Neutrophils)/Lymphocytes. Univariate and multivariate logistic regression analyses were performed to assess the relationship between clinical factors, IBI, TyG index, and cardiac injury. The clinical predictive value of these factors was further evaluated using receiver operating characteristic (ROC) curves, and the relationship between IBI and cardiac injury was explored using the Restricted Cubic Spline (RCS) model. In the 192 patients, 101 (52.6%) developed cardiac injury during follow-up. Univariate analysis showed that age, male, hypertension, smoking, D-dimer, CKMB, IBI, TNM stage: III/IV, and Immunotherapy were significantly associated with cardiac injury ($P < 0.001$). Multivariate analysis identified IBI ($P = 0.007$), age ($P = 0.01$), smoking ($P < 0.001$), CKMB ($P < 0.001$), TNM stage ($P = 0.014$), and hypertension ($P = 0.007$) as independent predictors of cardiac injury. ROC analysis revealed an area under curve (AUC) of 0.722 for IBI (cut-off: 8.408), indicating good predictive value. RCS analysis showed a significant nonlinear positive correlation between IBI and cardiac injury ($P = 0.0079$), with the risk of cardiac injury increasing significantly as IBI levels rose. The TyG index was not significantly associated with cardiac injury. IBI, as a simple and accessible biomarker, can effectively predict cardiac injury in lung cancer patients with diabetes undergoing antitumor therapy. Although the TyG index did not show a significant association with cardiac injury in this study, IBI demonstrated strong predictive ability in this patient group. Future studies should further validate the use of IBI across different cancer types and evaluate its prognostic role in long-term follow-up.

Cardio-oncology is an emerging discipline focusing on the assessment, diagnosis and treatment of cardiovascular toxicity associated with antitumour therapy[1,2]. Cancer therapy-related cardiovascular toxicity (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. These effects can impair heart function, leading to symptoms such as heart failure, arrhythmias, and cardiac injury[2,3]. With the advancements

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in antitumor therapies, cardiovascular toxicities have become more pronounced, particularly in patients with lung cancer, breast cancer, and other malignancies[4,5].

Lung cancer remains one of the leading causes of cancer-related morbidity and mortality worldwide, with patients undergoing treatment often experiencing significant cardiotoxicity[6]. Studies show that more than 20% of patients with locally advanced non-small cell lung cancer (NSCLC) receiving chest radiotherapy experience radiation-induced cardiac adverse events, and 6.5% of 1,004 lung cancer patients treated with immunotherapy suffer from cardiac injury[7,8]. Diabetes mellitus, a common metabolic disorder, further complicates this issue[9]. In the context of cancer treatment, antitumor drugs themselves may provoke additional inflammatory responses, which, when combined with diabetes, exacerbate the degree of inflammation and increase the risk of cardiac toxicity. Research has shown that cardiac cells in diabetic patients are more vulnerable to the damaging effects of cancer treatment, significantly increasing the likelihood of heart dysfunction[10]. Therefore, cardiovascular risk assessment in lung cancer patients with diabetes is particularly important. Comprehensive cardiovascular risk assessments, including medical history evaluation, electrocardiograms (ECG), echocardiography, and biomarker testing, can help develop personalized treatment strategies[2,11].

According to international guidelines, troponins, as cardiac biomarkers, can sensitively and specifically identify early cardiac injury in cancer patients, thus indirectly assessing cardiac toxicity[12]. When high-sensitivity cardiac troponin T (hs-cTnT) exceeds 14 ng/L, defined as the 99th percentile concentration for the general population, the patient should be considered to have cardiac injury following antitumor treatment[2]. Furthermore, cardiac biomarkers may be related to inflammatory responses, providing a new direction for predicting cardiac injury.

Cardiac injury is often accompanied by systemic inflammation[9,12]. The inflammatory burden index (IBI) is a newly developed biomarker used to reflect systemic inflammation. It is calculated by integrating multiple inflammation-related markers and is primarily used to assess the role of systemic inflammation in cancer prognosis[13]. Studies have shown that, compared to other inflammatory markers, the IBI has significant advantages in predicting survival in NSCLC patients[14]. Given that lung cancer patients with diabetes often have concomitant systemic inflammation, the IBI may serve as a valuable tool for predicting cardiac injury following antitumor treatment in this patient group. However, there is still a gap in research regarding the predictive role of the IBI in cardiac injury. While the IBI has shown promise in certain contexts, insulin resistance in diabetic patients may also impact the overall evaluation of cardiac injury risk. Insulin resistance has been shown to be associated with cardiovascular risk, and the TyG index (Triglyceride-Glucose) is considered an effective marker of insulin resistance[15]. The TyG index may have potential value in assessing cardiac toxicity in lung cancer patients with diabetes. Although research in this field is still limited, the association between the TyG index, insulin resistance, inflammation, and cardiac health suggests that its application in cardiac injury risk assessment warrants further exploration.

In summary, this study aims to explore the predictive ability of the IBI and TyG index for cardiac injury following antitumor treatment in lung cancer patients with diabetes, through the retrospective collection of clinical baseline data from the patients. The findings may provide a more precise risk assessment for clinical treatment in these patients, helping clinicians design personalized treatment plans in advance, ultimately improving treatment outcomes and reducing the incidence of adverse events such as cardiac injury during the treatment process.

Patients and methods

Study population and design

This study is a single-center, retrospective, observational case-control study conducted at the Affiliated Hospital of Xuzhou Medical University, located in Xuzhou, China. It included patients diagnosed with lung cancer and type 2 diabetes mellitus who underwent baseline cardiac enzyme testing between July 2018 and January 2023. The study population consisted of adult patients (aged ≥ 18 years) with confirmed lung cancer and documented cardiac enzyme levels.

Inclusion criteria

- Primary lung cancer, confirmed by pathological diagnosis.
- History of type 2 diabetes mellitus, which was diagnosed according to the *World Health Organization's Guidelines for the Prevention and Treatment of Type 2 Diabetes*[16]. The criteria include: (1) fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL), (2) 2-h plasma glucose ≥ 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test, (3) HbA1c ≥ 6.5%, or (4) random plasma glucose ≥ 11.1 mmol/L (200 mg/dL) with typical diabetes symptoms. A diagnosis was also made if the patient had a prior diagnosis of diabetes and was receiving anti-diabetic treatment.
- Patients received at least one anti-tumor therapy, including chemotherapy, radiotherapy, targeted therapy, and immunotherapy.
- Baseline cardiac enzyme testing conducted before starting antitumor therapy.

Exclusion criteria

- Carcinoma in situ or multiple primary tumors.
- Surgical treatment only or perioperative patients.
- Pre-existing heart disease, acute cardiac infarction, autoimmune diseases, liver or kidney dysfunction, or severe infectious diseases.
- Elevated pre-antitumor therapy hs-cTnT (> 14 ng/L) or discontinuous hs-cTnT monitoring.
- Loss to follow-up or death during the follow-up period.

A total of 192 patients were ultimately included in the study, after applying the inclusion and exclusion criteria. The flowchart depicting patient inclusion and exclusion is shown in Fig. 1.

Due to the retrospective nature of the study, the Investigational Review Board of the Affiliated Hospital of Xuzhou Medical University waived the need of obtaining informed consent. (approval number XYFY2024-KL156)

Data collection methods

As a retrospective study, most of the baseline data were obtained from the hospital's case system, including patient laboratory results and past medical history. This includes the study's primary endpoint—whether myocardial injury is present, which is defined based on high-sensitivity cardiac troponin levels from laboratory tests. Baseline data were collected before antitumor therapy and finally troponin data were collected 1 year after antitumor therapy. All laboratory data were sourced from the Affiliated Hospital of Xuzhou Medical University, ensuring the reliability of the data. In cases where baseline information was missing, such as smoking, alcohol consumption, and past medical history, we collected this information through telephone interviews and face-to-face consultations. All data were collected and recorded by well-trained researchers following a standardized protocol to ensure both reliability and validity.

High-sensitivity cardiac troponin testing

Regarding the measurement of high-sensitivity cardiac troponin T (hs-cTnT) and high-sensitivity cardiac troponin I (hs-cTnI), both biomarkers were considered in this study to evaluate cardiac injury. The use of hs-cTnT and hs-cTnI was based on their well-established roles in detecting cardiac injury, with hs-cTnT being the primary marker. Regular monitoring of these markers prior to initiating antitumor therapy was conducted for all patients. This approach was chosen because both hs-cTnT and hs-cTnI are sensitive and specific biomarkers for cardiac injury, and their inclusion helped to strengthen the validity of the study findings. These markers were regularly measured as part of routine clinical practice at our institution to monitor for early signs of cardiac damage, especially given the potentially cardiotoxic nature of the antitumor therapies used.

Diagnostic criteria for cardiac injury

Cardiac injury was defined as an elevation of high-sensitivity cardiac troponin T (hs-cTnT) levels greater than 14 ng/L, which corresponds to the 99th percentile upper reference limit (URL) of hs-cTnT in the general population[2]. This diagnostic criterion was applied to identify cardiac injury in patients who had undergone antitumor therapy.

Baseline evaluation

At baseline, a comprehensive evaluation of the patients was conducted, including demographic data, laboratory test results, and clinical data related to the tumor and comorbid conditions. The demographic variables included age, sex, and BMI. Laboratory data assessed included blood glucose, lipid profiles, and inflammatory markers such as C-reactive protein (CRP) and white blood cell count. Serological tests were conducted using an automated diagnostic system, which ensured consistency and precision in measurements. Clinical data related to the tumor included cancer stage, treatment history, and the presence of any other underlying diseases such as hypertension, coronary artery disease, and diabetes mellitus. Baseline clinicopathological variables were

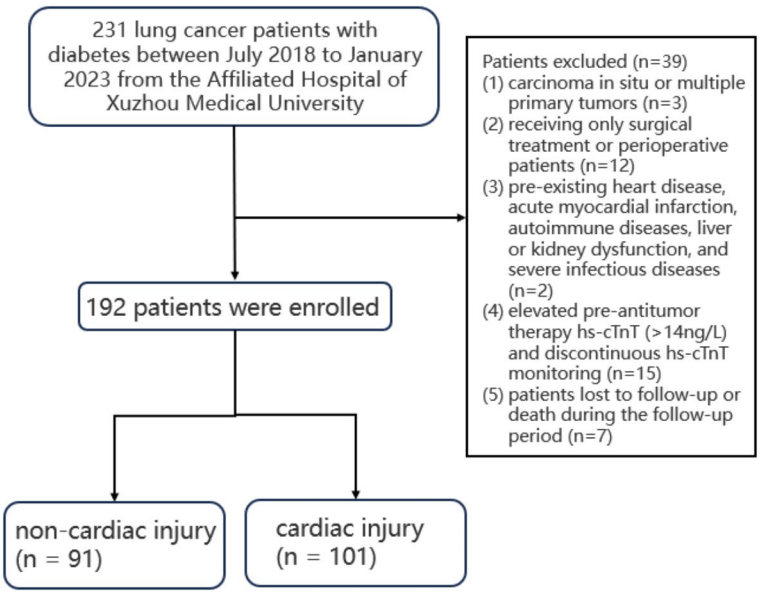

Fig. 1. Flow chart of the study population.

obtained through patient interviews and clinical records, and the pathological diagnoses were validated by experienced pathologists.

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[13].

Additionally, the Triglyceride-Glucose (TyG) index, which reflects combined glucose and lipid metabolism, was calculated using the following formula: TyG index = ln [(Fasting Triglycerides (mg/dL) × Fasting Glucose (mg/dL))/2]. This formula is widely used to evaluate insulin resistance and has been linked to cardiovascular and metabolic health[17].

Statistical analysis

Statistical analysis was performed using SPSS version 22.0 and R version 4.4.1. 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. Univariate logistic regression analyses were initially performed for each variable. The significant predictors identified from the univariate analyses were then subjected to a stepwise multivariate logistic regression analysis. The diagnostic accuracy of each variable was also evaluated using the area under the curve (AUC) from receiver operating characteristic (ROC) curves. Additionally, the relationships between selected variables and cardiac injury were explored using Restricted Cubic Spline (RCS) models to assess potential non-linear associations. All tests were two-tailed, with a significance level set at $P < 0.05$.

Power analysis

To ensure the sample size was sufficient to detect statistically significant differences, a power analysis was conducted prior to data collection. Using an expected effect size based on prior studies, we determined that a minimum of 192 patients was required to achieve 80% power at a significance level of $P < 0.05$. This sample size calculation was based on assumptions regarding the prevalence of cardiac injury and the expected differences in cardiac enzyme levels between groups.

Ethical considerations

This study was approved by the Investigational Review Board of the Affiliated Hospital of Xuzhou Medical University (approval number XYFY2024-KL156) and adhered to the ethical principles outlined in the Declaration of Helsinki. The confidentiality of patient data was maintained throughout the study. All personally identifiable information was anonymized, and data were stored in secure, password-protected files. Due to the retrospective nature of the study, written informed consent was exempted by the Investigational Review Board, but all patients' clinical data were collected and analyzed in accordance with standard ethical guidelines.

Result

Baseline characteristics of patients

In total, 192 lung cancer patients with diabetes participated in the study from July 2018 to January 2023. The average age of all patients was 64.03 ± 8.15 years, and 126 (65.62%) were male. Patients were split into two groups according to whether cardiac injury occurred at the end of follow-up: the cardiac injury group ($n = 101$) and the noncardiac injury group ($n = 91$). Table 1 list the demographic data and baseline characteristics of the lung cancer patients with diabetes.

Compared with noncardiac injury patients, patients with cardiac injury were significantly more likely to be older and male ($P < 0.01$). Patients with hypertension and a history of smoking were more common in the cardiac injury group, and the difference was statistically significant ($P < 0.01$). The Hs-cTnT(post-antitumor), neutrophil, CRP, CA125, D-dimer, Serum creatinine, LDH, CKMB and IBI levels were significantly lower in the noncardiac injury group than in the cardiac injury group ($P < 0.05$). Both groups received antitumour therapy; patients in the cardiac injury group were significantly more likely to have stage III/IV TMN, and most were treated with immunotherapy ($P < 0.05$).

Univariate and multivariate logistic regression analyses

Univariate logistic regression analysis (Table 2) revealed that age, male sex, HBP, smoking, D-dimer, FIB, Scr, ALB, LDH, CKMB, IBI, TNM, and Immunotherapy were associated with cardiac injury ($P < 0.05$), which was included in the multiple factors logistic stepwise regression analysis shown in Table 3.The results indicate that age, smoking, CKMB, IBI, TMN (III/IV), and HTN were predictors of cardiac injury in lung cancer patients with diabetes within 1 year following antitumour therapy.

ROC curve analysis

ROC curve analysis was performed on the above five related factors identified in the multivariate regression analysis (Fig. 2; Table 4). The results revealed that hypertension (AUC = 0.618, 95% 0.539 ~ 0.698, $p < 0.001$), TNM (III/IV) (AUC = 0.608, 95% 0.528 ~ 0.689, $p < 0.001$), smoking (AUC = 0.723, 95% 0.649 ~ 0.797, $p < 0.001$), age (AUC = 0.688, cut-off: 63.50, 95% 0.614 ~ 0.763, $p < 0.001$), CKMB (AUC = 0.712, cut-off: 1.385, 95% 0.638 ~ 0.785, $p < 0.001$), and the IBI (AUC = 0.722, cut-off: 8.408, 95% 0.651 ~ 0.793, $p < 0.001$) all had predictive value for cardiac injury.

Variables	Total ($n=192$)	Noncardiac injury ($n=91$)	Cardiac injury ($n=101$)	*P*
Age	64.03 ± 8.15	61.33 ± 7.13	66.46 ± 8.28	< **0.001**
Gender, n(%)				< **0.001**
Female	66 (34.38)	53 (58.24)	13 (12.87)	
Male	126 (65.62)	38 (41.76)	88 (87.13)	
Hs-cTnT(Pre, ng/L)	7.22 ± 2.93	7.32 ± 2.98	7.13 ± 2.89	0.644
Hs-cTnT(Post, ng/L)	14.45 (6.61, 19.90)	6.37 (4.80, 9.09)	19.66 (15.90, 28.49)	< **0.001**
BMI (kg/m2)	24.47 ± 3.12	24.45 ± 3.21	24.50 ± 3.05	0.904
SBP(mmHg)	129.27 ± 15.05	127.13 ± 14.39	131.19 ± 15.44	0.062
DBP (mmHg)	78.53 ± 9.85	78.73 ± 9.22	78.36 ± 10.43	0.796
Smoking, n(%)	121 (63.02)	36 (39.56)	85 (84.16)	< **0.001**
Alcohol, n(%)	39 (20.31)	18 (19.78)	21 (20.79)	0.862
HTN, n(%)	83 (43.23)	28 (30.77)	55 (54.46)	< **0.001**
AF, n(%)	17 (8.85)	8 (8.79)	9 (8.91)	0.977
CAD, n(%)	28 (14.58)	12 (13.19)	16 (15.84)	0.603
CVD, n(%)	71 (36.98)	39 (42.86)	32 (31.68)	0.109
Hb (g/L)	133.56 ± 14.53	135.31 ± 13.29	131.99 ± 15.46	0.114
N ($\times10^9$/L)	4.87 ± 2.21	4.03 ± 1.48	5.63 ± 2.47	< **0.001**
L ($\times10^9$/L)	1.58 ± 0.63	1.66 ± 0.59	1.51 ± 0.66	0.106
PLT ($\times10^9$/L)	249.22 ± 82.50	240.76 ± 78.36	256.84 ± 85.73	0.178
CRP (mg/L)	15.20 ± 26.81	6.92 ± 12.48	22.65 ± 33.39	< **0.001**
D-Dimer (μg/ml)	0.71 ± 1.00	0.42 ± 0.63	0.97 ± 1.19	< **0.001**
FIB (g/L)	4.10 ± 1.34	3.87 ± 1.00	4.30 ± 1.56	**0.023**
G (μmol/L)	8.54 ± 3.08	9.11 ± 3.85	8.03 ± 2.04	**0.018**
TG (mmol/L)	1.69 ± 1.19	1.64 ± 0.83	1.75 ± 1.44	0.522
TC (mmol/L)	4.67 ± 0.99	4.77 ± 0.95	4.57 ± 1.01	0.178
Scr (μmol/L)	58.06 ± 11.88	55.53 ± 11.18	60.35 ± 12.08	**0.005**
UA (mmol/L)	256.05 ± 75.91	249.78 ± 73.38	261.70 ± 78.06	0.278
CYSC (mg/L)	0.83 ± 0.18	0.81 ± 0.16	0.85 ± 0.19	0.152
ALB (U/L)	42.70 ± 4.50	43.44 ± 3.86	42.03 ± 4.94	**0.029**
AST (U/L)	19.64 ± 9.73	19.74 ± 9.77	19.55 ± 9.75	0.898
LDH (U/L)	212.28 ± 66.33	197.37 ± 53.18	225.71 ± 73.98	**0.002**
CK (U/L)	67.10 ± 43.04	62.49 ± 36.51	71.25 ± 47.98	0.160
CKMB (ng/ml)	1.38 ± 0.78	1.11 ± 0.60	1.62 ± 0.84	< **0.001**
IBI	97.09 ± 265.33	25.10 ± 63.42	161.95 ± 349.11	< **0.001**
TyG Index	9.10 (8.76, 9.49)	9.17 (8.83, 9.48)	9.03 (8.70, 9.48)	0.181
CEA (ng/mL)	62.85 ± 190.11	69.35 ± 201.97	57.00 ± 179.56	0.654
CA125 (ng/mL)	100.90 ± 372.57	55.62 ± 101.14	141.69 ± 502.37	0.110
NSE (ng/mL)	16.13 (13.04, 21.41)	16.09 (13.29, 21.04)	16.67 (12.96, 21.45)	0.778
Pathological Type, n(%)				0.997
NSCLC	154 (80.21)	73 (80.22)	81 (80.20)	
SCLC	38 (19.79)	18 (19.78)	20 (19.80)	
TNM, n(%)				< **0.001**
I/II	52 (27.08)	35 (38.46)	17 (16.83)	
III/IV	140 (72.92)	56 (61.54)	84 (83.17)	
Chemotherapy, n(%)				0.256
No	15 (7.81)	5 (5.49)	10 (9.90)	
Yes	177 (92.19)	86 (94.51)	91 (90.10)	
Radiotherapy, n(%)				0.991
No	133 (69.27)	63 (69.23)	70 (69.31)	
Yes	59 (30.73)	28 (30.77)	31 (30.69)	
Targeted, n(%)				0.750
Continued				

Variables	Total ($n=192$)	Noncardiac injury ($n=91$)	Cardiac injury ($n=101$)	*P*
No	118 (61.46)	57 (62.64)	61 (60.40)	
Yes	74 (38.54)	34 (37.36)	40 (39.60)	
Immunotherapy, n(%)				**0.003**
No	90 (46.88)	53 (58.24)	37 (36.63)	
Yes	102 (53.12)	38 (41.76)	64 (63.37)	

Table 1. Baseline Characteristics of the Two Groups. *Hs-cTnT(Pre)* high-sensitivity cardiac troponin T before antitumor therapy, *Hs-cTnT(Post)* high-sensitivity cardiac troponin T after antitumor therapy, *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, *TyG index* the triglyceride-glucose index, *TMN* tumor node metastasis classification, *NSCLC* non-small cell lung cancer, *SCLC* small cell lung cancer, *CEA* carcinoembryonic antigen, *NSE* neuron-specific enolase, *CA125* cancer antigen 125. Significant values are in bold.

Nonlinear relationships: RCS model analysis

Furthermore, the RCS model revealed a nonlinear relationship between the inflammatory burden index (IBI) and the incidence of cardiac injury in all the subjects (nonlinear $P=0.0079$) (Fig. 3). As the inflammatory burden index increased, the OR for cardiac injury gradually increased. These results suggest that when the inflammatory burden index increases, the incidence of cardiac injury increases significantly. The dose–response relationships between the inflammatory burden index (IBI) and cardiac injury were consistent with a logistic model.

Discussion

Interpretation of results

This study represents the first investigation into the relationship between the inflammatory burden index (IBI) and cardiac injury in lung cancer patients with diabetes following antitumor therapy. Our findings demonstrate a significant association between elevated IBI levels and an increased incidence of cardiac injury in this patient population. Specifically, we observed that patients in the cardiac injury group had higher IBI levels compared to those without cardiac injury, even after adjusting for confounding factors like age and smoking. This suggests that IBI can be a valuable, easily accessible biomarker for predicting the risk of cardiac injury in lung cancer patients with diabetes who undergo antitumor therapy.

Additionally, we found that the TyG index, another inflammatory marker and indicator of insulin resistance in diabetic patients[15], did not show significant differences between the cardiac injury and noncardiac injury groups in our study. This finding indicates that the TyG index may not be as relevant as IBI for predicting cardiac injury in this cohort, potentially due to the effects of nutritional status or other metabolic factors in these patients.

The elevated IBI appears to be an independent risk factor for cardiac injury following antitumor therapy in lung cancer patients with diabetes. This is consistent with the role of chronic inflammation in the pathophysiology of both cancer and cardiovascular diseases, where inflammatory markers like CRP, neutrophils, and lymphocytes play a significant role in promoting cardiac injury[18,19].

While chronic inflammation is indeed a shared characteristic of diabetes and cancer, our findings demonstrate that the inflammatory burden index (IBI) provides unique predictive value beyond routine inflammatory markers. Notably, after adjusting for baseline neutrophil levels (cardiac injury group:5.63 ± 2.47 vs. non-cardiac injury group:4.03 ± 1.48, $p<0.001$) and CRP (22.65 vs. 6.92 mg/L, $p<0.001$) in multivariate analysis, IBI remained an independent predictor (OR = 1.01, 95%1.01–1.01, $p=0.003$). This suggests that IBI captures inflammatory dysregulation distinct from the background inflammation inherent in these diseases. The specificity of this relationship is further supported by the differential predictive performance of other metabolic indicators like TyG index (OR = 0.71, $p=0.171$), which showed no significant association. Importantly, even in subgroups with comparable treatments (e.g., immunotherapy recipients: $p=0.003$), the predictive accuracy of IBI persisted, indicating its value transcends therapeutic contexts that may modulate inflammation.

Comparison with existing literature

Our results align with previous studies showing the critical role of systemic inflammation in cancer prognosis[18]. The IBI, as an integrative measure of inflammation, has been shown to predict cancer outcomes in various malignancies, including non-small cell lung cancer (NSCLC). For example, in a cohort of 1,843 NSCLC patients, the IBI was identified as one of the most reliable systemic inflammatory biomarkers for predicting patient prognosis[14]. Our findings build upon this by showing that the IBI can also serve as an important marker for predicting cardiac injury in lung cancer patients undergoing treatment, particularly those with diabetes, a known risk factor for both cancer and cardiovascular disease.

The TyG index has also been associated with cardiovascular risk and cancer prognosis[20,21]. However, our study did not find a significant association between the TyG index and cardiac injury following antitumor therapy.

Variables	β	S.E	Z	*P*	OR (95%CI)
Age	0.08	0.02	4.18	< **0.001**	1.09 (1.05 ~ 1.13)
Male	2.25	0.37	6.15	< **0.001**	9.44 (4.61 ~ 19.32)
BMI	0.01	0.05	0.12	0.903	1.01 (0.92 ~ 1.10)
SBP	0.02	0.01	1.85	0.064	1.02 (1.00 ~ 1.04)
DBP	− 0.00	0.01	− 0.26	0.795	1.00 (0.97 ~ 1.03)
Smoking	2.09	0.35	6.04	< **0.001**	8.12 (4.11 ~ 16.01)
Drinking	0.06	0.36	0.17	0.862	1.06 (0.53 ~ 2.15)
HTN	0.99	0.30	3.27	**0.001**	2.69 (1.49 ~ 4.87)
AF	0.01	0.51	0.03	0.977	1.01 (0.37 ~ 2.75)
CAD	0.21	0.41	0.52	0.603	1.24 (0.55 ~ 2.78)
CVD	− 0.48	0.30	− 1.60	0.110	0.62 (0.34 ~ 1.12)
Hb	− 0.02	0.01	− 1.57	0.116	0.98 (0.96 ~ 1.00)
PLT	0.00	0.00	1.35	0.179	1.00 (1.00 ~ 1.01)
D-Dimer	0.96	0.29	3.26	**0.001**	2.60 (1.46 ~ 4.62)
FIB	0.26	0.12	2.18	**0.029**	1.29 (1.03 ~ 1.63)
TC	− 0.20	0.15	− 1.34	0.180	0.82 (0.61 ~ 1.10)
Scr	0.04	0.01	2.76	**0.006**	1.04 (1.01 ~ 1.06)
UA	0.00	0.00	1.09	0.278	1.00 (1.00 ~ 1.01)
CYSC	1.17	0.82	1.42	0.157	3.21 (0.64 ~ 16.15)
ALB	− 0.07	0.03	− 2.13	**0.033**	0.93 (0.87 ~ 0.99)
AST	− 0.00	0.01	− 0.13	0.897	1.00 (0.97 ~ 1.03)
LDH	0.01	0.00	2.83	**0.005**	1.01 (1.01 ~ 1.01)
CK	0.01	0.00	1.38	0.167	1.01 (1.00 ~ 1.01)
CKMB	1.11	0.26	4.30	< **0.001**	3.04 (1.83 ~ 5.06)
IBI	0.01	0.00	3.00	**0.003**	1.01 (1.01 ~ 1.01)
TyG	− 0.34	0.25	− 1.37	0.171	0.71 (0.44 ~ 1.16)
SCLC	0.00	0.36	0.00	0.997	1.00 (0.49 ~ 2.04)
TNM(III/IV)	1.13	0.34	3.29	< **0.001**	3.09 (1.58 ~ 6.04)
Chemotherapy	− 0.64	0.57	− 1.12	0.262	0.53 (0.17 ~ 1.61)
Radiotherapy	− 0.00	0.31	− 0.01	0.991	1.00 (0.54 ~ 1.84)
Targeted	0.09	0.30	0.32	0.750	1.10 (0.61 ~ 1.97)
Immunotherapy	0.88	0.30	2.97	**0.003**	2.41 (1.35 ~ 4.31)
CEA	− 0.00	0.00	− 0.45	0.654	1.00 (1.00 ~ 1.00)
NSE	− 0.00	0.00	− 0.12	0.906	1.00 (0.99 ~ 1.01)
CA125	0.00	0.00	1.90	0.057	1.00 (1.00 ~ 1.01)

Table 2. Univariate logistic regression analysis for the occurrence of cardiac injury. *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *Hb* haemoglobin, *Neu* neutrophi, *Lym* lymphocyte, *PLT* platelet, *CRP* C-reactive protein, *FIB* fibrinogen, *G* glucose, *TC* total cholesterol, *TG* triglyceride, *Scr* serum creatinine, *UA* uric acid, *CYSC* Cystatin C, *ALB* albumin, *AST* glutamic oxaloacetic transaminase, *LDH* lactate dehydrogenase, *CK* creatine kinase, *CKMB* creatine kinase isoenzymes, *IBI* inflammatory burden index, *TyG* triglyceride glucose index, *HTN* hypertension, *AF* atrial fibrillation, *CAD* coronary artery disease, *CVD* cerebral vascular disease, *COPD* chronic obstructive pulmonary disease, *CEA* carcinoembryonic antigen, *NSE* neuron-specific enolase, *CA125* Cancer Antigen 125, *SCLC* small cell lung cancer, *TNM(III/IV)* III or IV stage of tumor node metastasis classification. Significant values are in bold.

This is in contrast to previous studies that have demonstrated the TyG index as a predictor for atherosclerosis, thrombosis, and inflammation[8,22,23]. One possible explanation for this discrepancy is the nutritional status of the patients, which could influence the TyG index but not necessarily the inflammatory burden reflected by the IBI. In addition, as we did not find significant differences in BMI between the groups, the influence of obesity, which is often associated with high TyG index levels, may not have played a major role in this cohort[24].

Furthermore, inflammatory markers such as CRP, neutrophils, and lymphocytes have been implicated in both diabetes and cardiovascular disease[9,25]. The chronic inflammation observed in diabetes exacerbates insulin resistance, promotes atherosclerosis, and contributes to cardiac injury[26,27]. This aligns with our finding that higher IBI levels were associated with an increased risk of cardiac injury in this patient population.

Clinical significance

Our study provides valuable insights into the clinical relevance of the IBI as a predictive tool for cardiac injury in lung cancer patients with diabetes. Given the high incidence of cardiovascular complications in cancer patients,

Variables	β	S.E	Z	*P*	OR (95%CI)
Age	0.07	0.03	2.57	**0.010**	1.07 (1.02 ~ 1.13)
Smoking	1.90	0.43	4.40	< **0.001**	6.65 (2.86 ~ 15.48)
HTN	1.09	0.41	2.68	**0.007**	2.99 (1.34 ~ 6.65)
CKMB	1.19	0.32	3.76	< **0.001**	3.29 (1.77 ~ 6.13)
IBI	0.01	0.00	2.70	**0.007**	1.01 (1.01 ~ 1.01)
TNM(III/IV)	1.15	0.47	2.46	**0.014**	3.17 (1.26 ~ 7.95)

Table 3. Logistic regression analysis of multiple factors for the occurrence of cardiac injury. *CKMB* creatine kinase isoenzymes, *IBI* inflammatory burden index, *TNM(III/IV)* III or IV stage of tumor node metastasis classification. Significant values are in bold.

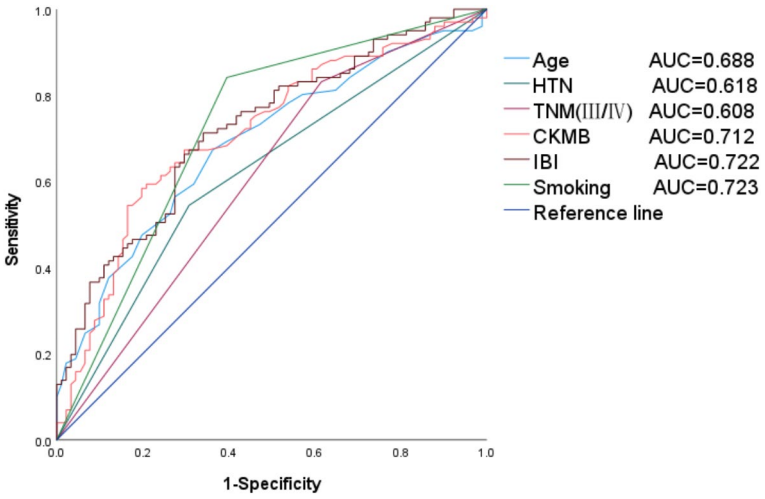

Fig. 2. ROC curve analysis for age, smoking status, HTN, TNM (III/IV), IBI, and CKMB in the prediction of cardiac injury.

	AUC	95% CI	*P*	Cut-off	Sensitivity	Specificity
Age	0.688	0.614 ~ 0.763	$p < 0.001$	63.50	0.673	0.637
Smoking	0.723	0.649 ~ 0.797	$p < 0.001$	–	0.842	0.604
HTN	0.618	0.539 ~ 0.698	$p < 0.001$	–	0.545	0.692
TNM (III/IV)	0.608	0.528 ~ 0.689	$p < 0.001$	–	0.832	0.385
IBI	0.722	0.651 ~ 0.793	$p < 0.001$	8.408	0.713	0.659
CKMB	0.712	0.638 ~ 0.785	$p < 0.001$	1.385	0.584	0.802

Table 4. Predictive performance of predictors. *CKMB* creatine kinase isoenzymes, *IBI* inflammatory burden index, *TNM(III/IV)* III or IV stage of tumor node metastasis classification.

particularly those receiving antitumor therapies, the ability to predict cardiac injury early in the treatment course is critical[5,28]. The IBI, which integrates readily available clinical markers such as CRP, neutrophils, and lymphocytes, can be easily assessed in clinical practice and could serve as a simple, cost-effective tool for identifying patients at high risk for cardiac complications.

The clinical implications of our findings suggest that early interventions targeting inflammation might help reduce the risk of cardiac injury in this vulnerable population. For example, the use of anti-inflammatory agents or strategies to optimize glucose control in diabetic patients could mitigate the harmful effects of systemic inflammation[29,30]. Moreover, these findings support the need for closer monitoring of cardiac function in lung cancer patients with high IBI levels, especially those receiving aggressive therapies such as immune checkpoint inhibitors (ICIs), which have been associated with increased cardiovascular events[31].

Limitations and future research

Despite the promising results, this study has several limitations. First, the single-center, retrospective design and small sample size limit the generalizability of the findings. Future studies should employ multicenter, large-scale randomized controlled trials (RCTs) to validate the effectiveness of the IBI as a predictive tool for cardiac injury

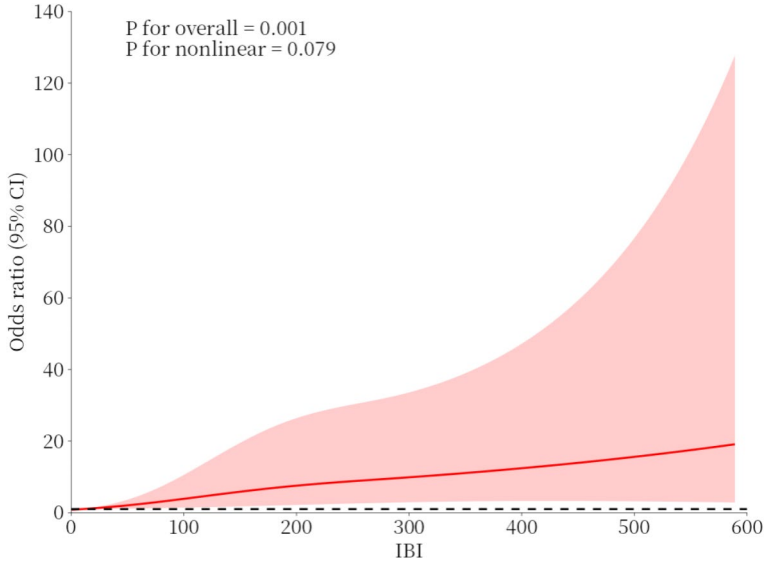

Fig. 3. Restricted cubic spline models showing the associations between the inflammatory burden index and the incidence of cardiac injury in all participants.

in lung cancer patients with diabetes. Second, our cohort consisted only of lung cancer patients, which restricts the ability to extrapolate these results to other cancer types. To enhance generalizability, future research should investigate the relationship between IBI and cardiac injury in other cancer populations, including those with lymphoma, melanoma, and breast cancer.

Third, the cross-sectional nature of our study, where systemic inflammatory biomarkers were measured only at a single time point, limits our understanding of how changes in inflammation over time might correlate with cardiac injury. Longitudinal studies that track inflammatory biomarkers throughout the course of treatment could provide a clearer picture of how inflammation evolves and impacts cardiac function in cancer patients. Additionally, our study did not assess the mechanistic pathways underlying the relationship between inflammation and cardiac injury, which warrants further exploration.

A fourth limitation relates to potential treatment heterogeneity. Although we performed multivariate regression adjustments for chemotherapy ($p = 0.256$), radiotherapy ($p = 0.991$), and targeted therapy ($p = 0.750$)1, these variables were treated as categorical rather than continuous dosing parameters. Immunotherapy remained an independent predictor ($p = 0.003$) despite our adjustments. As explicitly noted in the limitations section:" The lack of statistical adjustment for therapeutic heterogeneity may impact results interpretation, warranting regimen-specific analysis in future studies". However, current studies and guidelines have not standardized the exact dose adjustment and combination regimen. This reflects real-world clinical practice but may introduce residual confounding. Importantly, the IBI maintained predictive accuracy (HR 1.18, 95% 1.07–1.30) across all therapeutic subgroups, demonstrating robustness despite treatment variation.

Lastly, although the IBI emerged as a robust predictor of cardiac injury, its potential dose-response relationship and cut-off values need further validation in independent cohorts. Establishing standardized cut-off points for the IBI could help clinicians stratify patients based on risk and guide treatment decisions more effectively.

Conclusion and future directions

In conclusion, our study provides strong evidence that the IBI is a useful and accessible tool for predicting cardiac injury in lung cancer patients with diabetes receiving antitumor therapy. Given the growing number of cancer survivors at risk for cardiovascular complications, early identification of those at high risk for cardiac injury is essential for improving patient outcomes. Future research should focus on validating the IBI across different cancer types, assessing its ability to predict long-term cardiovascular events, and exploring the potential benefits of early intervention in patients with elevated IBI levels.

Furthermore, expanding research on the interaction between lung cancer, inflammation, and diabetes will enhance our understanding of the pathophysiological mechanisms underlying these diseases and help develop targeted therapies that address both cancer and cardiovascular risk.

Data availability

Statement All data generated or analysed during this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding author.

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Author contributions

Y. W developed the analysis plan and wrote the paper. C.H and G. W undertook the data analysis. H.P., Y.L., X.Z.,C.L., J.L. and W. W.collected the dataset and provided advice on its analysis. D.P.guided the analysis and made substantial improvements to the paper. Y. W.and C.H.contributed equally to this work, They are the first co-authors.

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Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and consent to participate
This study was approved by the Investigational Review Board 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 regulatory guidelines of the Investigational Review Board of the Affiliated Hospital of Xuzhou Medical University.

Additional information
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