BMC Cancer

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Immune checkpoint inhibitor-related myocarditis in patients with lung cancer

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Abstract

Background The clinical characteristics of immune checkpoint inhibitors (ICIs)-related myocarditis in lung cancer remains uncertain. The purpose of this study was to evaluate the incidence, clinical characteristics, risk factors, and prognosis of myocarditis in lung cancer patients treated with ICIs. Therefore, this study would enhance the understanding of immune related myocarditis in lung cancer population.

Methods A total of 1004 patients were analyzed, among those who developed elevated serum creatine kinase isoenzyme, MB form (CK-MB) and/or high-sensitivity troponin I (hs-cTnI) with electrocardiographic or clinical symptoms after immunotherapy were enrolled in the myocarditis group. The same number of patients who had received immunotherapy but didn't develop myocarditis was randomly selected as the control group. Clinicopathologic features, risk factors, and prognostic factors were evaluated in this study.

Results 66 patients (6.6%) developed ICIs-related myocarditis. In these patients, there were 60 case of possible myocarditis (90.9%), 5 probable myocarditis (7.6%), and 1 definite myocarditis (1.5%). The median time to the occurrence of myocarditis was 3.8 months. The median progression-free survival (PFS) for NSCLC and SCLC patients were 24.4 months and 13.0 months, while the median overall survival (OS) for NSCLC and SCLC patients were 43.3 months and 44.6 months. The grade of myocarditis (OR: 5.79; 95%CI: 1.14–29.41, $P=0.034$), immunotherapy cycle (OR: 0.38; 95% CI: 0.16–0.92, $P=0.032$), and combination of immune-related adverse events (irAEs) (OR: 3.63; 95% CI: 1.55–8.48, $P=0.003$) were the influencing factors of PFS in NSCLC patients. In SCLC patients, the immunotherapy cycle was the influential factor for PFS (OR: 0.16; 95%CI: 0.04–0.61, $P=0.007$) and OS (OS: 0.12; 95% CI: 0.03–0.48, $P=0.002$). Anti-PD1 therapy (OR: 0.4, 95% CI: 0.13–0.97, $P=0.043$) and age (OR: 0.36, 95% CI: 0.16–0.84, $P=0.018$)might be the protective factors of myocarditis patients compared with the control group.

Conclusions The presentations of ICIs-related myocarditis in lung cancer are mainly possible myocarditis and probable myocarditis, which have a mild impact on the prognosis. More cycles of ICI treatment accompany the longer the PFS and OS, as a protective factor. Anti-PD1 therapy and older age may be protective factors for ICI-related myocarditis.

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Keywords Lung cancer, Immunotherapy, Myocarditis, Onco-cardiology, Prognosis

Introduction

In recent years, immune checkpoint inhibitors (ICIs) have been paid much attention as an emerging anti-tumor therapy. Several clinical trials have confirmed that the combination of chemotherapy and immunotherapy has become the standard first-line treatment for advanced lung cancer [1–3]. Commonly used immune checkpoints in the field of tumor therapy include PD-1, PD-L1, and CTLA-4 (cytotoxic lymphocyte antigen 4) [4, 5]. ICIs activate the patient's immune system by blocking the negative regulatory mechanism of T-lymphocytes to better identify and attack cancer cells [6–8]. They improve the survival of cancer patients, meanwhile, some adverse reactions, especially irAEs are accompanied [9]. In all types of irAEs, cardiotoxicity has become a great concern. The clinical manifestations include arrhythmia, myocarditis, and heart failure. Among them, ICI-related myocarditis has the highest incidence, and the worst prognosis, with the most clinical studies [10–12]. However, the mechanisms of ICI-related myocarditis are not fully understood. The gold standard for the diagnosis of ICIs-related myocarditis is an endomyocardial biopsy(EMB) [13], therefore definitive myocarditis is less common. Most studies about ICI-related myocarditis are performed in an all-included population of cancer patients, rather than a single tumor type. A systematic analysis of ICI-related myocarditis in patients with lung cancer is still lacking. Our study focused on ICI-related myocarditis in patients with lung cancer, including NSCLC and SCLC.

Methods

Study design

This is a retrospective study from the Department of Thoracic Oncology, Peking University Cancer Hospital. From January 2016 to December 2023, lung cancer patients admitted into the hospital for immune therapy were included. They were divided into two groups, namely the myocarditis group and the others. The main inclusive criteria of the myocarditis group were the elevation of CK-MB and/or hs-cTnI accompanied by electrocardiogram (ECG) evidence of myopericarditis or clinical symptoms after immunotherapy and those who had an elevation of the CK-MB and/or hs-cTnI due to other cardiovascular diseases were excluded. We employed block sampling to ensure comparability between the control and myocarditis groups while preserving randomization. Among the 938 eligible patients, we stratified by age, sex, cardiovascular history, and immunotherapy type, and randomly selected 66 controls from each stratum. (Fig. 1).

Basic personal information, time of lung cancer diagnosis, pathological type and tumor stage, underlying disease, immunotherapy regimens, occurrence time of myocarditis, concomitant symptoms, electrocardiographic changes, cardiac biomarkers, echocardiographic results, concomitant irAEs, treatment for myocarditis, and the prognosis of the patients were collected. For biomarker assessment, total cholesterol (TC), triglycerides (TG), Neutrophil-to-lymphocyte ratio (NLR), CK-MB, and hs-cTnI were measured at baseline before immunotherapy and at maximum levels after myocarditis.

All procedures complied with the requirements of medical ethics and the Declaration of Helsinki. This study was approved by the institutional review board of Peking University Cancer Hospital (IRB number: 2023KT40). Each patient signed an informed consent form before treatment.

Diagnosis of ICIs-related myocarditis

Cardiotoxicity includes different categories such as myocarditis, cardiac insufficiency, hypertension, coronary artery disease, and arrhythmia, in which myocarditis has the highest incidence. This study focused on ICI-related myocarditis. The 2022 European Society of Cardiology (ESC) guidelines on myocarditis diagnosis are referenced for context [14]; however, one of the primary objectives of this study is to identify myocarditis patients at an early stage for prompt intervention. Therefore, we adopted the diagnostic criteria proposed by Bonaca et al. [15], which classifies myocarditis into three categories: "definite myocarditis," "probable myocarditis," and "possible myocarditis." The severity of myocarditis was graded according to the American National Comprehensive Cancer Network [16].

Evaluation of efficacy

In this study, efficacy was evaluated after every two cycles of treatment and was divided into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Progression-free Survival (PFS) was the time from the patient's first immunotherapy to tumor progression. Overall survival (OS) was defined as the time from the date the patient received the first immunotherapy to death from any cause. Patients who did not progress,

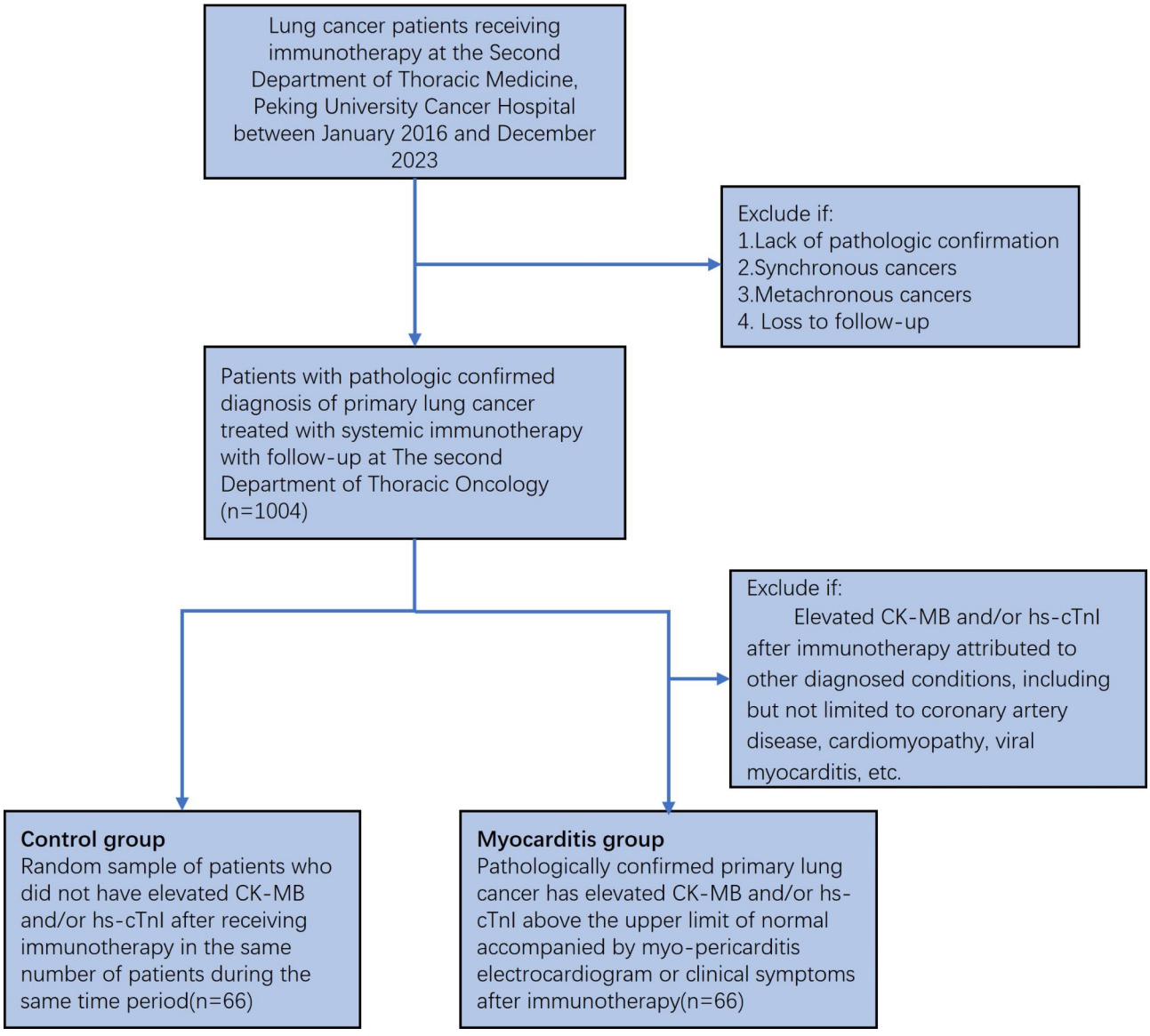


Fig. 1 Patient Cohort Selection

died, or were lost to follow-up should be dated at their last follow-up visit.

Statistics

Quantitative data were presented as the median with interquartile range (IQR) and compared using the Mann-Whitney U test. Categorical variables were expressed as percentages and compared using chi-square tests. Univariate and multivariate logistic regression analyses were employed to identify risk factors associated with the onset of ICIs-related myocarditis in patients, while COX regression analysis was utilized to assess factors impacting the prognosis of patients with ICIs-related myocarditis. Kaplan-Meier curves were used in survival analysis. A significance threshold of $P<0.05$ was applied to determine statistical significance. Statistical analyses were conducted by SPSS version 27.

Results

Patient characteristics

A total of 1,004 lung cancer patients received immunotherapy from January 2016 to December 2023, among which 66 (6.6%) developed ICI-related myocarditis. A total of 10 patients were identified with mutations, including one with BRAF, four with EGFR, two with HER2, and three with KRAS mutations. The clinical characteristics of the myocarditis group are shown in Table 1.

Table 1 Baseline clinical characteristics of patients with myocarditis ($n=66$)

Characteristics	Patients (*n*), No. (%)
Sex	
Male	50(75.8)
Female	16(24.2)
Age (year)	
≤ 70	54(81.8)
> 70	12(18.2)
Body mass index (kg/m2)	
≤ 24	35(53.0)
> 24	31(47.0)
ECOG score	
0	42(63.6)
1	24(36.4)
Smoking history	
No	17(25.8)
Yes	49(74.2)
Drinking history	
No	36(54.5)
Yes	30(45.5)
Pathological type	
Squamous cell carcinoma	19(28.8)
Non-squamous NSCLC	24(36.4)
Small-cell lung cancer	23(34.8)
NSCLC stage	
I-II	3(4.5)
III-IV	40(60.6)
SCLC stage	
Limited- stage	1(1.5)
Extensive- stage	22(33.4)
PD-L1 express	
No	46(69.7)
Yes	20(30.3)
Driver gene mutations	
No	56(84.8)
Yes	10(15.2)
Immunotherapy lines	
1	16(24.2)
≥ 2	50(75.8)
History of radiotherapy	
No	46(69.7)
Yes	20(30.3)
Number of cycles of immunotherapy	
≤ 2	23(34.8)
> 2	43(65.2)
Types of ICI	
PD-1	49(74.2)
PD-L1	17(25.8)
ICI combination	
No	10(15.2)
Yes	56(84.8)
Cardiovascular history	
No	32(45.5)
Yes	36(54.5)
History of diabetes	
No	57(86.4)
Yes	9 (13.6)

ECOG, eastern cooperative oncology group performance status; NSCLC stage, non-small cell lung cancer stage; SCLC stage, small cell lung cancer stage; PD-L1 express, anti-programmed death-ligand 1 express; ICI, immune checkpoint inhibitors; PD-1, anti-programmed death-1

Clinical manifestations and laboratory tests

Symptoms such as pain, chest tightness, fatigue, pain, and even syncope were observed in 30 patients (45.5%). 41 patients (62.1%) had marked myo-pericarditis electrocardiogram, mainly tachycardia (10/41). The elevation of TG, TC, CKMB, and hs-cTnI is significant compared to baseline values, with TG (4.8 VS 5.3 mmol/L, $P<0.001$), TC (1.6 VS 2.1 mmol/L, $P=0.041$), CK-MB (1.2 vs. 29.6 ng/mL, $P<0.001$), hs-cTnI (0.03 vs. 0.8 ng/mL, $P<0.001$). While the elevation level of NLR is not significant (3.3 VS 3.9, $P=0.135$) (Table 2).

30 patients (45.5%) had a combination of other irAEs, with immune thyroid dysfunction in 8 (12.1%) accounting for the largest number of cases (Table 2). The median time to occurrence of myocarditis was 3.8 months. The median number of cycles of myocarditis was 3, of which myocarditis occurred in the first 2 cycles of immunotherapy in 32 patients (48.4%). The more severe myocarditis is, the earlier it occurs, with G1 (165.0 ± 156.2 days), G2 (120.2 ± 68.8 days), G3 (22.0 ± 26.9 days), and G4 (2.0 ± 1.4 days).

Treatment and follow-up

16 patients (24.2%) received therapy of glucocorticosteroids, with 2 patients (3.0%) receiving concomitant gammaglobulin and other immunosuppressive agents. 41 patients (62.1%) restarted immunotherapy, while 18 patients (27.3%) permanently stopped immunotherapy.

As of the follow-up date of April 15, 2024, 25 patients (37.9%) had died, including 4 patients (6.1%) who died of myocarditis.

Risk factors of ICIs-related myocarditis

To find the risk factors of ICIs-related myocarditis, 66 patients who had received immunotherapy but didn't develop myocarditis were randomly selected as the control group (Table 3).

Comparative analyses between the control and myocarditis groups revealed significant differences in the demographic and treatment-related factors. Specifically, the control group had a higher proportion of NSCLC patients ($P=0.017$), males ($P=0.039$), a history of alcohol consumption ($P=0.008$), and a higher proportion of patients receiving anti-PD1 therapy ($P=0.024$). Multiple

Table 2 Clinical manifestations of patients with myocarditis

Clinical manifestation	Patients (*n*), No. (%)
Accompanied by symptoms	
No	36(54.5)
Yes	30(45.5)
Electrocardiogram change	
No	25(37.)
Yes	41(62.1)
Elevated biomarkers	
Only CK-MB	10(15.2)
Only hs-cTnI	10(15.2)
Both	45(68.1)
Other elevated biomarkers	
TC	45 (68.2)
TG	44 (66.7)
NLR	21 (31.8)
Types of myocarditis	
Definite myocarditis	1(1.5)
Probable myocarditis	5(7.6)
Possible myocarditis	60(90.9)
Grade of myocarditis	
G1	57(86.4)
G2	5(7.6)
G3	2(3.0)
G4	2(3.0)
Echocardiography changes	
No	57(86.4)
Left ventricular diastolic hypoplasia	7(10.)
Ventricular wall segmental motion abnormalities	2(3.0)
cMRI change	
No	65(98.5)
Oedema and delayed enhancement	1 (1.5)
Concurrent other irAEs	
No	36(54.5)
Thyroiditis	8(12.1)
Pneumonia	7(10.6)
Liver dysfunction	7(10.6)
Rash	6(9.1)
Myositis	3(4.5)
Renal injury	3(4.5)
Heart failure	2(3.0)
Pancreatitis	2(3.0)
Venous thromboembolism	2(3.0)
Neuritis	1(1.5)
Adrenal insufficiency	1(1.5)

CK-MB, serum creatine kinase isoenzyme, MB; hs-cTnI, high-sensitivity troponin I; TC, total cholesterol; TG, triglycerides; NLR, Neutrophil-to-lymphocyte ratio; G1-4, grade 1–4; cMRI, cardiovascular magnetic resonance imaging; irAEs, immune-related adverse events

logistic regression analysis confirmed that anti-PD1 treatment (OR: 0.4, 95% CI: 0.13–0.97, $P = 0.043$) and age (OR: 0.4, 95% CI: 0.16–0.84, $P = 0.018$) are strongly associated with the development of myocarditis(Table 4).

Table 3 Baseline characteristics of two groups

Characteristics	Control group(*n*) No. (%)	Myocarditis group No. (%)	*P*Value
Age (year)	65.92 ± 8.52	64.55 ± 8.02	0.341
Body mass index (kg/m2)	23.68 ± 3.64	23.82 ± 2.73	0.811
Sex			0.039
Male	59 (89.4)	50(75.8)	
Female	7(10.6)	16(24.2)	
Smoking history			0.201
No	11(16.7)	17(25.8)	
Yes	55(83.3)	49(74.2)	
Drinking history			0.008
No	21(31.8)	36(54.5)	
Yes	45(68.2)	30(45.5)	
Pathological type			0.017
NSCLC	55(83.3)	43(65.2)	
SCLC	11(16.7)	23(34.8)	
Types of ICI			0.024
PD-1	59(89.4)	49(74.2)	
PD-L1	7(10.6)	17(25.8)	
ICI combination			0.367
No	14(21.2)	10(15.2)	
Yes	52(78.8)	56(84.8)	
Cardiovascular history			0.601
No	33(50.0)	30(45.5)	
Yes	33(50.0)	36(54.5)	
History of diabetes			0.627
No	54(81.8)	57(86.4)	
Yes	11(18.2)	9(13.6)	

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; ICI, immune checkpoint inhibitors; PD-1, anti-programmed death-1; PD-L1, anti-programmed death-ligand 1

Table 4 Logistic regression analysis of risk factors affecting the incidence of ICIs-related myocarditis

Factors	Univariable		Multivariable	
	Hazard Ratio (95% CI)	*P*Value	Hazard Ratio (95% CI)	*P*Value
Age ≥ 70	0.4(0.19–0.89)	0.025	0.4(0.16–0.84)	0.018
BMI ≥ 24	1.0(0.48–1.86)	0.808		
Male	0.4(0.14–0.97)	0.044	0.5(0.16–1.53)	0.225
Smoke	0.6(0.25–1.35)	0.204		
NSCLC	0.4(0.16–0.85)	0.019		
IV stage	1.3(0.57–3.10)	0.518		
PD1	0.3(0.13–0.89)	0.028	0.4(0.13–0.97)	0.043
Combined ICI	1.5(0.68–4.27)	0.369		
Cardiovascular history	1.2(0.64–2.53)	0.601		
Diabetes Mellitus	0.8(0.33–2.34)	0.628		

BMI, body mass index; NSCLC, non-small cell lung cancer; PD-1, anti-programmed death-1; ICI, immune checkpoint inhibitors

Survival analysis

Among myocarditis patients, different pathology types have different prognoses. No significant difference in PFS (Fig. 2A) and OS (Fig. 2B) between NSCLC patients and SCLC patients (PFS: 24.4 months vs. 13.0 months, $P = 0.895$; OS: 43.3 months vs. 44.6 months, $P = 0.651$).

There was no significant difference in PFS (Fig. 3A) and OS (Fig. 3B) in patients with or without myocarditis (PFS: 16.7 months vs. 14.3 months, $P = 0.491$; OS: 43.3 months vs. 30.3 months, $P = 0.986$).

Prognostic factors of myocarditis in NSCLC

In the 43 cases of myocarditis with NSCLC, the grade of myocarditis (OR: 5.8; 95%CI: 1.14–29.41, $P = 0.034$), immunotherapy cycle (OR: 0.4; 95% CI: 0.16–0.92, $P = 0.032$), and combination of other irAE (OR: 3.6; 95% CI: 1.55–8.48, $P = 0.003$) were the independent influence factors of PFS. The immunotherapy cycle (OR: 0.3; 95%CI: 0.12–0.79, $P = 0.014$) was the influencing factor of OS (Tables 5 and 6).

Prognostic factors of myocarditis in SCLC

In the 23 cases of myocarditis with SCLC, the immunotherapy cycle was the independent influencing factor of PFS (OR: 0.2; 95%, CI: 0.04–0.61, $P = 0.007$) and OS (OR: 0.1; 95%, CI: 0.03–0.48, $P = 0.002$) as well. (Tables 7 and 8)

Discussions

This cohort study provided a summary of the clinical features and prognostic influences associated with ICI-related myocarditis in lung cancer patients. Previous studies have found the prevalence of ICI-related myocarditis to be approximately 1% [17]. In our study, 66 cases of myocarditis were found out of 1004 lung cancer patients, so the prevalence of ICI-related myocarditis was 6.6% (66/1004), which was slightly higher than the previous studies. Notably, only one of the 66 patients was diagnosed with definite myocarditis, with the others diagnosed with probable or possible myocarditis. This could potentially explain the high incidence.

Patients with myocarditis have a wide variety of symptoms, ranging from asymptomatic to lethal myocarditis [15]. In this study, only 45.5% (30/66) of patients exhibited symptoms, which suggests that a considerable number of myocarditis patients were not recognized promptly due to the absence of symptoms. Consequently, ECG examinations and cardiac biomarker assessments are vital for the identification of cases. Bonaca et al. [15] recommended cTnI and CK-MB as the main cardiac biomarkers for the diagnosis of myocarditis, which is the main inclusive criteria in our study. Other commonly used cardiac biomarkers include cTnT, NT-proBNP, BNP, CK, and NLR etc [18]. One study found that elevated levels of CK-MB following immunotherapy were identified as an independent risk factor for myocarditis, while elevated cTnI and NLR were regarded as risk factors for severe myocarditis [19]. Mahmood et al. [13] concluded that cTnI is the preferred indicator of myocarditis because cTnT and CK are also elevated in myositis patients, but Lehman et al. [20] came to the opposite conclusion. Therefore, more studies are needed to explore the possible differences between cTnT and cTnI in diagnosing myocarditis.

An understanding of the occurrence time of ICI-related myocarditis is crucial for the identification and timely addressing of this issue. In this study, we found that myocarditis typically occurred 3.8 months after the first dose of immunotherapy, which means most cases of myocarditis occurred after three ICI cycles. Some studies have reported shorter median times. A study found that 11.7% (23/196) of lung cancer patients developed myocarditis 46 days after the first immunotherapy [18], while another study found the median time was 71 days [19]. Besides, Mahmood et al. [13] found a median time of 34 days, while Mosleh et al. [11] found a median time of 27 days. These studies include different types of tumors, and interestingly, compared to other malignant tumors, the occurrence of myocarditis in lung cancer patients seems to be later. Nevertheless, given the widespread use of ICI in lung cancer patients and the notable mortality rate of myocarditis, it remains crucial to pay attention to this adverse reaction in the initial stages of immunotherapy. Therefore, the cardiac indicators should be monitored during the baseline period and after the second and fourth ICI cycles.

A meta-analysis in 2023 showed that in lung cancer patients, those receiving PD1 monotherapy were more likely to develop myocarditis than those receiving PD-L1 monotherapy. Besides, immune combinations were more likely to induce myocarditis than immune monotherapies, with the highest incidence observed in patients who received PD-1 plus CTLA-4 [21]. This finding is contrary to the results of our study. In our cohort, we found that receiving PD1 therapy may be a protective factor for myocarditis and that immune-mono and immune-combination therapy had no significantly different effect on the occurrence of myocarditis. Besides, we found that age more than 70 years might serve as protective factor as well. This may be due to a weakened immune response in older patients, which is associated with a reduced incidence of myocarditis.

Among NSCLC patients, the median PFS (mPFS) and OS (mOS)were 24.4 and 43.3 months, which appear to be longer than those observed in previous large clinical trials. For example, pembrolizumab combined with chemotherapy in advanced squamous lung cancer has a mPFS of only 6.4 months and a mOS of 15.9 months [3], while in non-squamous lung cancer, the mPFS is 9 months and

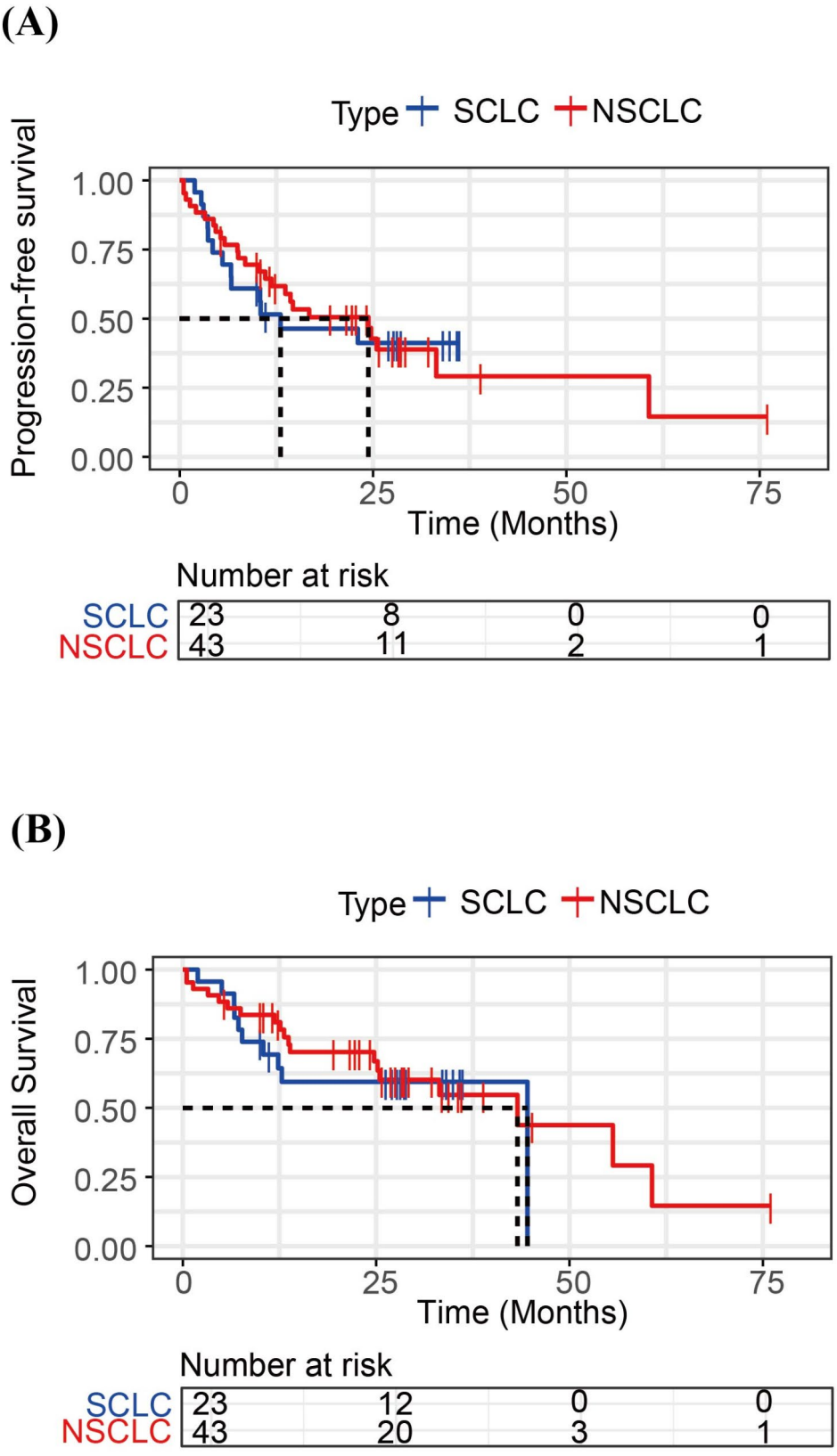
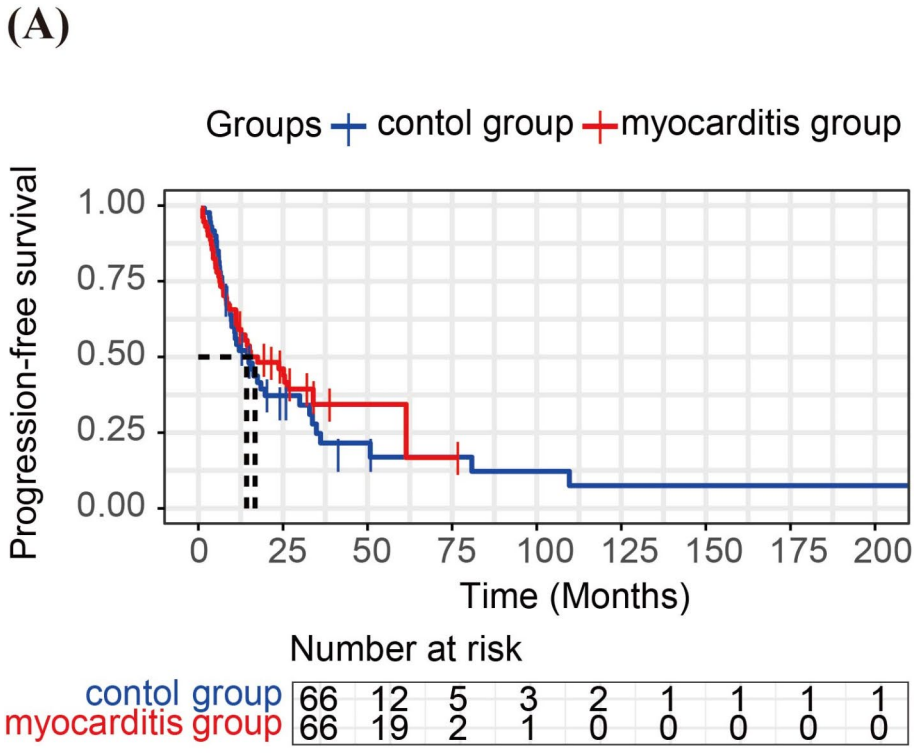


Fig. 2 Progression-free survival (PFS) and overall survival (OS) in patients with myocarditis. (**A**) PFS; (**B**) OS



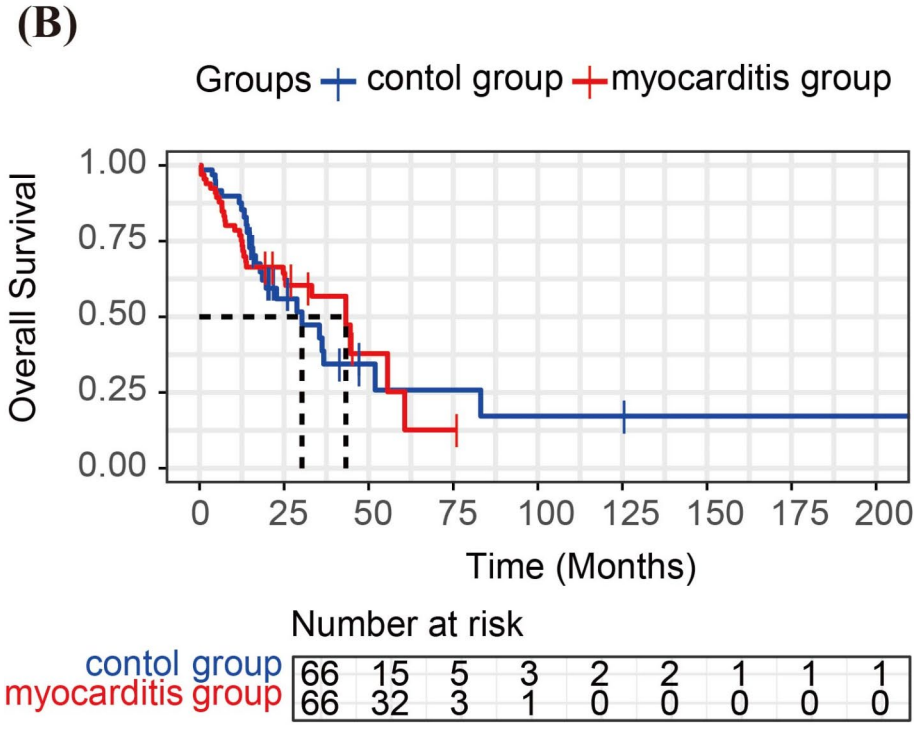


Fig. 3 Progression-free survival (PFS) and overall survival (OS) of two groups of patients. (**A**) PFS; (**B**) OS

Table 5 COX regression analysis of prognostic factors affecting PFS in NSCLC ICIs-related myocarditis

Factors	Univariable		Multivariable	
	Hazard Ratio (95% CI)	*P*Value	Hazard Ratio (95% CI)	*P*Value
Age ≥ 70	1.4(0.53–0.90)	0.447		
BMI ≥ 24	1.3(0.55–2.85)	0.588		
Male	1.6(0.60–4.35)	0.337		
Smoke	1.4(0.60–4.35)	0.496		
Drink	1.5(0.53–0.90)	0.293		
IV stage	1.6(0.55–2.85)	0.356		
PD1	0.8(0.55–3.47)	0.645		
Combined ICI	0.8(0.69–3.45)	0.697		
Cardiovascular history	0.9(0.59–4.34)	0.777		
Diabetes Mellitus	0.7(0.26–2.30)	0.647		
PD-L1 express	1.2(0.32–2.13)	0.714		
Driving gene mutations	0.8(0.39–2.03)	0.728		
History of radiotherapy	1.1(0.17–3.05)	0.841		
Immunotherapy lines ≥ 2	1.6(0.52–2.60)	0.284		
Concurrent other irAEs	2.69(0.28–2.43)	0.015	3.6(1.55–8.48)	0.003
Glucocorticoids therapy	1.89(0.45–2.65)	0.131		
immunotherapy cycles ≥ 2	0.44(0.68–3.73)	0.048	0.4(0.16–0.92)	0.032
Grade of myocarditis>2	6.31(1.21–5.96)	0.018	5.8(1.14–29.41)	0.034

BMI, body mass index; NSCLC, non-small cell lung cancer; PD-1, anti-programmed death-1; ICI, immune checkpoint inhibitors; irAEs, immune-related adverse events; PD-L1 express, anti-programmed death-ligand 1 express

Table 6 COX regression analysis of prognostic factors affecting OS in NSCLC ICIs-related myocarditis patients

Factors	Univariable	
	Hazard Ratio (95% CI)	*P*Value
Age ≥ 70	1.9(0.62–6.07)	0.255
BMI ≥ 24	0.7(0.29–1.81)	0.487
Male	1.3(0.44–4.09)	0.609
Smoke	1.6(0.53–4.85)	0.410
Drink	1.7(0.68–4.36)	0.254
IV stage	2.6(0.59–11.48)	0.207
PD1	0.6(0.17–2.14)	0.433
Combined ICI	0.7(0.25–2.03)	0.527
Cardiovascular history	1.0(0.38–2.57)	0.985
Diabetes Mellitus	1.3(0.30–5.87)	0.705
PD-L1 express	1.3(0.49–3.49)	0.595
Driving gene mutations	1.8(0.56–5.52)	0.338
History of radiotherapy	0.8(0.26–2.13)	0.584
Immunotherapy lines ≥ 2	1.3(0.47–3.38)	0.641
Concurrent other irAEs	2.2(0.89–5.55)	0.089
Glucocorticoids therapy	2.2(0.86–5.51)	0.103
Immunotherapy cycles ≥ 2	0.3(0.12–0.79)	0.014
Grade of myocarditis > 2	1.9(0.40–9.35)	0.410

BMI, body mass index; NSCLC, non-small cell lung cancer; PD-1, anti-programmed death-1; ICI, immune checkpoint inhibitors; irAEs, immune-related adverse events; PD-L1 express, anti-programmed death-ligand 1 express

the mOS is 22 months [22]. In SCLC patients, this study showed that mPFS and mOS were approximately 13 months and 44 months, which is also better than previous trial data. For example, Serpluliumab combined with chemotherapy as first-line treatment for extensive SCLC had an mPFS of 5.7 months and an mOS of 15.4 months [1]. Interestingly, the mOS of SCLC patients in our study was slightly longer than that of NSCLC patients, which may be related to the limitations of the small sample size and inpatient selection bias.

Our study found that more ICI cycles may serve as a protective factor, indicating that longer immunotherapy exposure during the occurrence of myocarditis is associated with milder myocarditis, longer PFS, and OS. Besides, in NSCLC patients, the more severe the myocarditis and combined irAEs, the shorter the PFS. It appears that the emergence of irAEs can potentially enhance efficacy in certain instances. A study including 70 cases showed that NSCLC patients treated with Nivolumab had better objective response rates, disease control rates, and longer PFS compared with patients who did not have any irAEs. This would seem to shed some light on this, suggesting that the occurrence of irAEs can enhance the efficacy of immunotherapy and improve patient prognosis. However, the limitation of this study is that the irAEs did not include myocarditis [23]. Similarly, it has been found that the presence of immune-related thyroid dysfunction has a longer OS [24], while the presence of cutaneous irAEs is associated with a better response to immunotherapy [25]. This phenomenon may be attributed to the stimulation of the immune system by irAEs, which may result in enhanced efficacy. Most cases in our study were mild myocarditis, which did not result in abnormalities in cardiac structure or function. The elevated cardiac biomarker might accompany the further stimulation of the patient's immune response, which has the potential to extend both PFS and OS. We can therefore speculate that despite the poor prognosis of myocarditis, once a patient has passed the initial 'dangerous period', the subsequent impact on PFS and OS may be mild, and may even enhance the efficacy of immunotherapy and indicate a better prognosis.

In our cohort, only 24.2% (16/66) of the patients received glucocorticoid therapy, while 62.1% (41/66) restarted immunotherapy. This may be because most of the patients in our study were G1 myocarditis. The 2020 NCCN guidelines recommend that immunotherapy should be discontinued for G3 or G4 myocarditis and that high-dose glucocorticoids should be administered intravenously for 3–5 days, followed by a gradual reduction

Table 7 COX regression analysis of prognostic factors affecting PFS in SCLC ICIs-related myocarditis patients

Factors	Univariable		Multivariable	
	Hazard Ratio (95% CI)	*P*Value	Hazard Ratio (95% CI)	*P*Value
Age ≥ 70	0.8(0.21–2.8)	0.703		
BMI ≥ 24	1.5(0.47–4.95)	0.489		
Male	1.4(0.31–6.25)	0.675		
Smoke	1.2(0.32–4.22)	0.824		
Drink	0.8(0.26–2.29)	0.635		
Extensive stage	22.5(0.001-376273.39)	0.530		
PD1	1.5(0.49–4.71)	0.465		
Cardiovascular history	1.5(0.47–4.48)	0.512		
Diabetes Mellitus	0.3(0.04–2.49)	0.276		
PD-L1 express	0.04(0-742.42)	0.530		
Driving gene mutations	1.9(0.24–14.87)	0.551		
History of radiotherapy	0.8(0.25–2.38)	0.660		
Immunotherapy lines ≥ 2	2.0(0.62–6.57)	0.244		
Concurrent other irAEs	1.1(0.35–3.28)	0.910		
Glucocorticoids therapy	0.8(0.18–3.67)	0.787		
immunotherapy cycles ≥ 2	0.1(0.04–0.50)	0.002	0.2(0.04–0.61)	0.007
Grade of myocarditis > 2	21.5(1.34–343.70)	0.030	6.4(0.37-109.32)	0.201

BMI, body mass index; NSCLC, non-small cell lung cancer; PD-1, anti-programmed death-1; ICI, immune checkpoint inhibitors; irAEs, immune-related adverse events; PD-L1 express, anti-programmed death-ligand 1 express

Table 8 COX regression analysis of prognostic factors affecting OS in SCLC ICIs-related myocarditis patients

Factors	Univariable	
	Hazard Ratio (95% CI)	*P*Value
Age ≥ 70	0.9(0.18–4.17)	0.854
BMI ≥ 24	1.4(0.34–5.50)	0.656
Male gender	0.6(0.13–2.94)	0.535
Smoke	0.9(0.19–4.34)	0.890
Drink	1.7(0.42–6.75)	0.464
IV stage	22.0(0-6406832.19)	0.630
PD1	0.8(0.21–2.96)	0.730
Cardiovascular history	1.4(0.38–5.29)	0.603
Diabetes Mellitus	0.5(0.06–4.12)	0.532
PD-L1 express	0.1(0-0-13232.32)	0.630
Driving gene mutations	3.1(0.37–25.83)	0.295
History of radiotherapy	0.7(0.17–2.85)	0.630
Immunotherapy lines ≥ 2	2.2(0.54–8.68)	0.277
Concurrent other irAEs	0.8(0.20–2.83)	0.671
Glucocorticoids therapy	1.2(0.52–5.91)	0.801
immunotherapy cycles ≥ 2	0.1(0.03–0.48)	0.002
Grade of myocarditis > 2	5.0(0.56–44.6)	0.151

BMI, body mass index; NSCLC, non-small cell lung cancer; PD-1, anti-programmed death-1; ICI, immune checkpoint inhibitors; irAEs, immune-related adverse events; PD-L1 express, anti-programmed death-ligand 1 express

in glucocorticoid dose over 4–6 weeks [16]. Despite the prevailing view that immunotherapy should be permanently discontinued in myocarditis patients, there are some re-challenges of immunotherapy. A study found that re-treatment with immunotherapy did not result in the recurrence or worsening of myocarditis in four (4/30) patients with a history of myocarditis [16]. However, the safety of restarting immunotherapy needs to be validated with larger sample sizes, and great care must be taken in deciding to restart immunotherapy in clinical practice.

There are several limitations in this study. Firstly, this is a single-center, retrospective study. The sample size is not large and there is bias in the patients' selection. Secondly, in clinical practice, the lack of routine monitoring of cardiac biomarkers and echocardiography before and after immunotherapy may lead to delayed diagnosis of myocarditis. Thirdly, tumor treatment is usually combined with other drugs such as chemotherapy and targeted therapy. Therefore, myocarditis cannot be attributed to immunotherapy alone, but also by the interaction of several complex factors, and further prospective studies are required to in-depth exploration.

Conclusions

ICI-related myocarditis is not rare in lung cancer patients treated with immunotherapy. The presentations of ICIs-related myocarditis in lung cancer are mainly possible myocarditis and probable myocarditis, which have a mild impact on the overall prognosis of the patient. More cycles of ICI treatment accompany the longer the PFS and OS, as a protective factor. In NSCLC patients, the more severe the myocarditis and the combination of other irAEs may indicate the shorter PFS. Anti-PD1 therapy and older age may be protective factors for ICI-related myocarditis.

Abbreviations

ICIs	Immune checkpoint inhibitors
NSCLC	Non-small cell lung cancer
SCLC	Small cell lung cancer
PD-1	Programmed cell death protein-1
PD-L1	Programmed cell death ligand-1
CK-MB	Serum creatine kinase isoenzyme MB form
Hs-cTnI	High-sensitivity troponin I
irAEs	Immune-related adverse events
PFS	Progression-free survival
OS	Median overall survival
CTLA-4	Cytotoxic lymphocyte antigen 4

EMB	Endomyocardial biopsy
ECG	Electrocardiogram
TC	Total cholesterol
TG	Triglycerides
NLR	Neutrophil-to-lymphocyte ratio

Acknowledgements
This work was supported by the National Natural Science Foundation of China (Project No. 82103497), Beijing Municipal Administration of Hospitals Incubating Program (PX2023040) and Science Foundation of Peking University Cancer Hospital (No. JC202508).

Author contributions
Jian Fang and Sen Han conceived and designed the study. Wenli Cao drafted the manuscript. Lan Mi and Wenli Cao performed the data analysis. The other authors followed up the patients. Sen Han and Kai Wang revised and finalized the paper. All authors have critically reviewed and approved the final version of the manuscript.

Funding
This work was supported by the National Natural Science Foundation of China (Project No. 82103497), Beijing Municipal Administration of Hospitals Incubating Program (PX2023040) and Science Foundation of Peking University Cancer Hospital (No. JC202508).

Data availability
All data and material relevant to the study are available from the corresponding authors upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the institutional review board of Peking University Cancer Hospital (IRB number: 2023KT40). Each patient signed an informed consent form before treatment.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 16 December 2024 / Accepted: 24 March 2025
Published online: 14 April 2025

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