Targeted therapy-associated cardiotoxicity in patients with stage-IV lung cancer with or without cardiac comorbidities

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Abstract. Targeted drugs have revolutionized the treatment of advanced non-small cell lung cancer (NSCLC). However, the understanding of how cardiac comorbidity and toxicity affect the clinical outcomes of patients following targeted therapy remains limited. In a 14-year cohort, cardiac comorbidities and toxicities among patients with stage-IV NSCLC treated with targeted therapy were identified. The cardiotoxicities were compared in three patient groups: Cardiac, other and no comorbidities. Survival analysis employed Cox Proportional Hazard Models. In the prospectively followed 3,767 patients with stage-IV NSCLC, 701 received targeted therapy; of which 133 (19.0%) had cardiac comorbidity, 504 (71.9%) had other comorbidities and 64 (9.1%) had none. In total, 15 patients (2.1%) developed cardiotoxicity after taking drugs targeting epidermal growth factor receptor, anaplastic lymphoma kinase (*ALK*), c-ros oncogene 1 (*ROS1*) or vascular endothelial growth factor/receptor (*VEGF)/VEGFR*, and all 15 had comorbidities: 10 cardiac and 5 other comorbidities. Cardiac comorbidity was associated with a 7.5-fold higher risk of targeted therapy-related cardiotoxicity than other comorbidities (7.5 vs. 1.0%; P<0.001). Patients with or without cardiotoxicity had a median survival time of 4.7 or 1.9 years, respectively, and patients with cardiotoxicity had a lower risk of death (hazard ratio, 0.45; 95% confidence interval, 0.25-0.81) than those without (P=0.003), when adjusting for comorbidities. In the 164 patients that received osimertinib, 32 (19.5%) had cardiac comorbidity and a 1.7-fold higher risk of death than the 121 (73.8%) patients with other comorbidities. In the 74 patients treated with *ALK/ROS1* inhibitors, cardiotoxicity was 14 times more common in patients with heart disease (30.0%) than those without (2.1%) (P=0.001). Cardiotoxicity was uncommon in patients with targeted drug-treated stage-IV NSCLC but was more prevalent in those with cardiac comorbidity and appeared to be a protector for longer survival. However, in osimertinib-treated patients, cardiac comorbidity increased mortality.

Introduction

Advances in targeted therapies have improved the survival rates of patients with non-small cell lung cancer (NSCLC), with a 36-month overall survival (OS) time observed among 84% of patients treated with osimertinib (1). Heart disease is the second leading cause of morbidity and mortality following cancerous progression and recurrence among cancer survivors (2). A number of patients with lung cancer are diagnosed with coexisting heart disease, and some may experience adverse cardiac events due to anticancer treatment, including targeted therapies, or from exacerbation of preexisting cardiac comorbidities. The incidence, presentation and impact of cardiotoxicity vary depending on the anticancer therapies and underlying comorbidities (3). A retrospective, population-based study of 20,689 patients with lung cancer revealed that 47.4% had heart disease, including myocardial infarction, congestive heart failure and chronic arrhythmias (4). In a cohort of 345 consecutive patients with NSCLC, 32% were diagnosed with

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heart disease, presenting a higher risk of mortality and distant metastasis (5). Data from the Surveillance, Epidemiology, and End Results (SEER) registry linked to U.S. Medicare administrative claim files (SEER-Medicare) showed that the impact of coexisting heart disease on NSCLC survival varies by cancer stage and treatment. For instance, cardiac comorbidities significantly increase the risk of death for patients with stage I and II disease treated with surgery and patients with stage I-IIIB disease treated with chemotherapy and chemoradiation, but not for patients with stage-IV (6). The present study aimed to fully characterize the effects of cardiac comorbidity on the occurrence of cardiotoxicity in patients with stage-IV NSCLC.

Cardiotoxicity from anticancer agents can affect the drug tolerance, quality of life and survival of patients, causing issues such as arrhythmias, cardiac arrest, coronary artery disease, heart failure, ischemia, left ventricular dysfunction, myocardial infarction and tachycardia (7). In recent decades, targeted therapy has rapidly evolved, improving the management of advanced NSCLC by targeting mutated driver genes and angiogenesis (8,9). The National Comprehensive Cancer Network guidelines recommend appropriate targeted therapy for patients with NSCLC harboring oncogenic driver mutations (10). However, different targeted therapies are associated with varying cardiotoxic effects: Epidermal growth factor receptor (*EGFR*) inhibitors can cause coronary artery events, heart failure and prolonged QT corrected (QTc) interval and anaplastic lymphoma kinase (*ALK*) inhibitors most commonly cause atrial fibrillation and electrocardiogram changes. By contrast, anti-vascular endothelial growth factor *(VEGF)* therapy is more related to vascular complications, including arterial hypertension, which can lead to cardiac disorders (11).

Studies exploring the relationship between cardiotoxicity and clinical outcomes in patients with or without cardiac comorbidities remain limited, particularly advanced disease studies based on real-world patients. Therefore, the present study aims to address a critical gap in this knowledge using a 14-year clinical cohort of patients with stage-IV NSCLC.

Patients and methods

Study population. All patients in the present study were previously enrolled in an ongoing Mayo Clinic (USA) lung cancer cohort study, which included ~20,000 patients with newly diagnosed primary lung cancer from 1997 to 2016 (12-15) and 144 consecutive cases of stage-IV NSCLC from 2017 to 2019 in Rochester (USA) (16). The enrollment and follow-up of patients were conducted with the approval of the Mayo Clinic Institutional Review Board (Rochester, USA). The detailed procedures for patient enrollment, diagnosis, data collection and follow-up have been described in previous publications (12,17). All patients were staged at the time of their primary diagnosis according to either the 5th (18) or 7th (19) edition of the TNM staging system. The enrolled patients met the following inclusion criteria: i) Newly diagnosed with stage-IV NSCLC from January 1, 2006 to December 31, 2019; and ii) treated with targeted therapies. The exclusion criteria were as follows: i) Those with unknown toxicity information; and ii) those lost to follow-up within 1 month after taking the targeted drugs. All the patients were followed until April 30, 2022. The targeted therapy mainly consisted of inhibitors for *EGFR*, *ALK*, c-ros oncogene 1 (*ROS1*), Kirsten rat sarcoma virus, V-raf murine sarcoma oncogene homolog B1 (*BRAF*), human epidermal growth factor receptor, mitogen-activated protein kinase, mesenchymal-epithelial transition (MET), rearranged during transfection, neurotrophic tyrosine receptor kinase, mammalian target of rapamycin and *VEGF*/*VEGFR* [including the anti-*VEGF* antibody, bevacizumab, and tyrosine kinase inhibitors (TKIs) of the *VEGF* receptors].

Data collection. Comprehensive data on each patient were collected from medical records in two steps: i) At the time of diagnosis including demographic information, smoking status, cell type, lung tumor site and prior and concurrent disease; and ii) after treatment including treatment type, treatment line, targeted drug-induced toxicity, severity and onset time of cardiotoxicity, response to drug therapy, recurrence, disease progression and vital status (20). Patients were categorized into three groups: Those with cardiac comorbidity, those with other comorbidities (excluding heart disease) and those with no comorbidity.

Toxicity, comorbidity and clinical outcome evaluation. The data were sourced from the electronic health records at Mayo Clinic. Cardiotoxicity, as well as other targeted drug-induced toxicities, were identified and graded by the attending physicians using the Common Terminology Criteria for Adverse Events version 5.0 (21) and recorded in the medical records for the patient. Cardiotoxicity encompassed various cardiac disorders with the terms of ejection fraction (EF) decreased, tachycardia, heart failure, electrocardiogram QTc interval prolonged, bradycardia, pericarditis, atrioventricular block complete, atrial fibrillation, myocardial infarction and mitral valve disease. Patients who took >1 targeted drug were analyzed as a whole and separately in sub-group analysis.

The duration between the initiation of targeted therapy and the development of cardiotoxicity was defined as the onset time and identified within 1.5 years. For patients experiencing cardiotoxicity, detailed information was retrieved and analyzed, including details on the demographics, gene mutation status, responsible drugs, symptoms associated with cardiotoxicity, laboratory values, cardiac investigations, cardiotoxicity consequences, concurrent with other toxicities, prior therapies, type of comorbid heart disease, cardiovascular risk factors (such as hypertension, high cholesterol, stroke, diabetes, obesity and family history). Electrocardiograms (ECGs) were used for routine monitoring of heart conditions in patients receiving targeted drugs (22).

Cardiac comorbidity (such as coronary artery disease, myocardial infarction, cardiomyopathy, arrhythmia, heart valve disease and heart failure) and other comorbidities (comorbid disease beyond heart disease) was defined based on the World Health Organization (WHO) International Classification of Disease 10th Revision classifications (23). The Charlson Comorbidity Index (CCI) score (24,25) was employed to assess comorbidity. The assigned weights for scoring were as follows: i) Myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease and diabetes received a score of 1; ii) hemiplegia, moderate or severe renal disease, diabetes with end organ damage, any tumor, leukemia and lymphoma were

scored as 2; iii) moderate or severe liver disease was assigned a score of 3; and iv) metastatic solid tumor and acquired immunodeficiency syndrome had a score of 6. Additionally, the diseases in CCI score list, excluding myocardial infarction and congestive heart failure, were also evaluated.

Recurrence and progression were assessed during the targeted therapy. Responses were defined as the best response to targeted therapy and evaluated by Response Evaluation Criteria in Solid Tumors version 1.1 (26). The responses were divided into complete response (CR), partial response (PR), stable disease and progressive disease. CR was defined as disappearance of all targeted lesions, and any pathological lymph nodes (whether target or non-target) must have a reduction in the short axis to <10 mm; PR was defined as at least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. CR and PR were collectively recognized as an objective response and abbreviated as 'response'.

Statistical analysis. The characteristics and distributions of the patients are presented as the mean (± standard deviation; SD) or median for continuous variables, and the count (n) and frequency (%) for categorical variables. The distribution of the demographics, smoking status (never vs. ever), cell type (adenocarcinoma vs. other), tumor site (left vs. right), recurrence, progression, treatment (drug vs. surgery, drug vs. surgery with drug, and radiation vs. radiation and drug), treatment line (palliative first line vs. other), drug-induced toxicity (yes vs. no) and response to drug therapy (response vs. no response) within the comorbidity subgroups (cardiac, other or no comorbidities) were compared using χ^2 tests and Fisher's exact test. Detailed information regarding cardiotoxicity was descriptively analyzed. The CCI was compared using a two-sample unpaired t-test. OS was defined from the date of treatment initiation to the last follow-up date or patient death; notably, for patients who experienced cardiotoxicity, OS was defined from the median onset date of all cardiotoxicities to the last follow-up date or patient death. Patients who were alive or lost to follow-up were censored in the analysis. Survival analyses of subgroups was performed using Cox Proportional Hazard models [measured as hazard ratios (HR) with 95% confidence intervals (95% CI)] and the log-rank test and graphically illustrated by Kaplan-Meier curves. Univariable Cox Proportional Hazard models were utilized to analyze the relationship between known prognostic factors (such as comorbid diseases, treatment toxicity including cardiotoxicity and any toxicity, sex, ethnicity, smoking status, side of tumor, cell type, treatment type, treatment line, treatment response, toxicity severity, CCI score and age at diagnosis) and to estimate the 5-year survival. Multivariable Cox models were developed using significant variables (defined as P<0.1) from the univariable analysis, and the HR with 95% CI was calculated. Two-sided P<0.05 was considered to indicate a statistically significant difference. All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc.).

Results

Distribution differences of patients in the three comorbidity groups. A total of 3,767 patients with newly diagnosed stage-IV NSCLC were identified. Among them, 1,856 (49.3%) received systemic therapy. Of the remaining 1,911 (50.7%) patients who did not receive systemic therapy, 185 underwent surgery and 625 received radiotherapy. All other patients did not receive standard anticancer therapies at Mayo Clinic. Out of the 1,856 patients receiving systemic therapy, 1,002 (54.0%) received chemotherapy and immunotherapy and 854 (46.0%) received targeted therapy. After excluding 153 patients without information on the targeted drug-related toxicity, 701 evaluable patients were included in the analyses (Fig. 1).

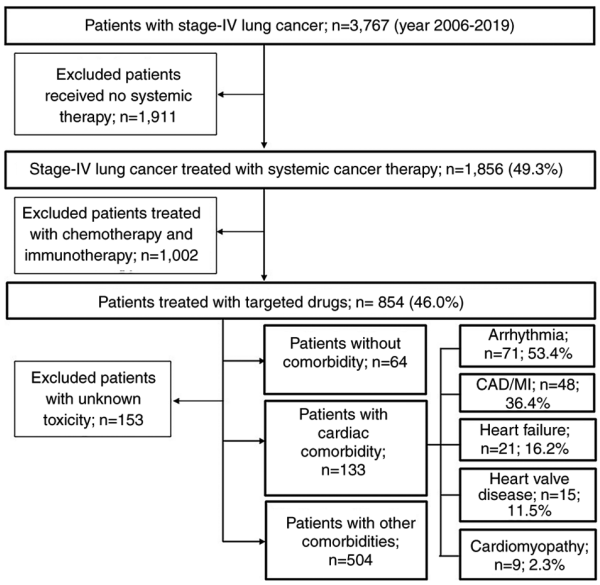

Figure 1. Flow chart of the study population with patient inclusion and exclusion criteria. CAD, coronary artery disease; MI, myocardial infarction.

Among the included patients, 133 (19.0%) had cardiac comorbidities, 504 (71.9%) had other comorbidities and 64 (9.1%) had no comorbidity. Among the 701 patients, the mean (±SD) age at lung cancer diagnosis was 62 (±12) years with 57.6% being women, 88.6% Caucasian and 42.5% never-smokers (Table I). Patients with heart disease were older (67±12 years) than those with other comorbidities (62±12 years) and no comorbidity (52±13 years) (P<0.001). There was a higher frequency of men than women (24.9 vs. 14.6%; P=0.002), more Caucasian patients than patients of other ethnicities (20.6 vs. 7.6%; P=0.003) and more smokers than never-smokers (22.5 vs. 15.8%; P=0.020) with heart disease (data not shown). However, no differences were observed in the treatment type, treatment line or response to therapy among the three comorbidity groups.

Characteristics of comorbid disease. In the three comorbidity groups, the comorbid disease and CCI burden showed some differences. Among the 133 patients with cardiac comorbidity, 71 (53.4%) had arrhythmia (predominately 48 with atrial fibrillation, 10 with tachycardia and 3 with bradycardia), 48 (36.4%) had coronary artery disease or myocardial infarction, 21 (16.2%) had heart failure, 15 (11.5%) had heart valve disease and 9 (2.3%) had cardiomyopathies (Fig. 1). Some patients had >1 cardiac comorbidity. Additionally, these patients exhibited conditions such as hypertension (58.6%), hyperlipidemia (43.2%), stroke (15.8%), diabetes (18.9%) and obesity (3.0%).

Table I. Comorbidities of patients treated with targeted therapies.

Variable	Comorbidity of targeted drug				P-value
	None, n=64	Cardiac, n=133	Other, n=504	Total, n=701	
Age at diagnosis, years					<0.001
Mean (SD)	52.1 (12.62)	66.9 (11.55)	61.6 (11.65)	61.7 (12.27)	
Median	50.5	66	63	63	
Range	30.0, 79.0	38.0, 94.0	25.0, 86.0	25.0, 94.0	
Sex, n (%)					0.002
Female	35 (54.7)	59 (44.4)	310 (61.5)	404 (57.6)	
Male	29 (45.3)	74 (55.6)	194 (38.5)	297 (42.4)	
Ethnicity, n (%)					0.003
Caucasian	50 (79.4)	127 (95.5)	439 (88.0)	616 (88.6)	
Other[a]	13 (20.6)	6 (4.5)	60 (12.0)	79 (11.4)	
NA	1	0	5	6	
Smoking status, n (%)					0.020
Never	41 (64.1)	58 (43.6)	269 (53.4)	368 (52.5)	
Ever	23 (35.9)	75 (56.4)	235 (46.6)	333 (47.5)	
Cell type, n (%)					0.321
Adenocarcinoma	53 (82.8)	115 (86.5)	448 (88.9)	616 (87.9)	
Other	11 (17.2)	18 (13.5)	56 (11.1)	85 (12.1)	
Side of tumor, n (%)					0.757
Left	30 (46.9)	60 (45.8)	215 (43.1)	305 (43.9)	
Right	34 (53.1)	71 (54.2)	284 (56.9)	389 (56.1)	
NA	0	2	5	7	
Treatment, n (%)					0.485
Drug therapy	50 (78.1)	103 (77.4)	369 (73.2)	522 (74.5)	
Surgery + drug	2 (3.1)	5 (3.8)	25 (5.0)	32 (4.6)	
Surgery + radiation + drug	3 (4.7)	3 (2.3)	8 (1.6)	14 (2.0)	
Radiation + drug	9 (14.1)	22 (16.5)	102 (20.2)	133 (19.0)	
Reason for drug therapy, n (%)					0.520
Palliative first-line	59 (95.2)	122 (93.8)	472 (96.1)	653 (95.6)	
Other	3 (4.8)	8 (6.2)	19 (3.9)	30 (4.4)	
NA	2	3	13	18	
Treatment response, n (%)					0.554
Response	35 (55.6)	63 (47.7)	259 (51.8)	357 (51.4)	
No response	28 (44.4)	69 (52.3)	241 (48.2)	338 (48.6)	
NA	1	1	4	6	
Toxicity, n (%)					<0.001
Cardiotoxicity	0 (0.0)	10 (7.5)	5 (1.0)	15 (2.1)	
Other	58 (90.6)	116 (87.2)	460 (91.3)	634 (90.5)	
None	6 (9.4)	7 (5.3)	39 (7.7)	52 (7.4)	

[a]Other ethnicity: Hispanic (n=15), Asian/Pacific islander (n=38), Alaskan/Native American (n=11), black (n=9) and other (n=6). NA, not available. χ^2 tests were used for statistical analysis.

In comparison, 504 patients with other comorbidities showed lower frequencies of hypertension (33.3%), hyperlipidemia (20.4%), stroke (4%), diabetes (8.1%) and obesity (0.6%) (P<0.02; data not shown). Furthermore, the cardiac comorbidity group had a much higher CCI score compared with the other comorbidity group (2.29 vs. 1.14; P<0.001), as shown in Table II. A similar difference in CCI score was observed in the two comorbidity groups when excluding heart disease (myocardial infarction and congestive heart failure) (2.02 vs. 1.14; P<0.001; Table II). When focusing on osimertinib-treated patients, those with cardiac or other comorbidities showed a significant difference in CCI scores even when excluding heart

Table II. Comparison of CCI scores between two comorbidity groups of targeted drug-treated patients.

A, CCI scores in the cardiac and other comorbidity groups

CCI score	Cardiac comorbidity, n=133	Other comorbidity, n=504	P-value
Mean (± SD)	2.29 (±2.38)	1.14 (±1.68)	<0.001
Score distribution, n (%)			<0.001
0	29 (21.8)	218 (43.3)	
1	32 (24.1)	158 (31.3)	
2	31 (23.3)	70 (13.9)	
3+	41 (30.8)	58 (11.5)	

B, CCI scores when excluding for heart disease[a] in the cardiac and other comorbidity groups

CCI score	Cardiac comorbidity, n=133	Other comorbidity, n=504	P-value
Mean (± SD)	2.02 (±2.23)	1.14 (±1.68)	<0.001
Score distribution, n (%)			<0.001
0	35 (26.3)	218 (43.3)	
1	33 (24.8)	158 (31.3)	
2	28 (21.1)	70 (13.9)	
3+	37 (27.8)	58 (11.5)	

[a]The CCI excluded myocardial infarction and congestive heart failure. Two-sample unpaired t-test was used for mean score and χ^2 test for the score distribution analysis. CCI, Charlson Comorbidity Index.

diseases (2.16 vs. 0.86; P<0.001), as shown in Table III. These results suggested that patients with cardiac comorbidity had a higher risk of heart-related diseases and a heavier comorbid disease burden.

Cardiotoxicity occurs more frequently among patients in the cardiac comorbidity group. Out of the 701 included patients, 15 (2.1%) developed cardiotoxicity, all of which occurred in patients with comorbidities. Among these, 10 (7.5%) were in the cardiac comorbidity group and 5 (1.0%) were in the other comorbidities group. Patients with cardiac comorbidity had a 7.5-fold higher risk of targeted therapy-related cardiotoxicity compared to those with other comorbidities (P<0.001; Table I). Of the 15 patients who experienced cardiotoxicities, the mean (± SD) age at diagnosis was 64 (±14) years and included 73.3% men, 93.3% Caucasian individuals and 53.3% smokers. Additionally, 6 of the 15 patients (40%) were diagnosed with left-side lung cancer, one of whom received a total of 2,000 cGy chest radiation with good tolerance and response. Small molecule TKIs targeting *EGFR* and *ALK*/*ROS1* appeared to cause cardiotoxicities following 6 months of treatment while anti-*VEGF* therapy led to cardiotoxicity following 1.5 months. The most common cardiac comorbidity was arrhythmia and the predominant cardiovascular risk factor was hypertension (Table IV-VI).

Frequency of cardiotoxicities varies by inhibitor (EGFR, ALK/ROS1 and VEGF/VEGFR). The targeted drugs responsible for cardiotoxicity involved inhibitors of *EGFR*, *ALK*/*ROS1* and *VEGF*/*VEGFR* (Fig. 2). The frequency of cardiotoxicity (n, %) from the lowest to highest were bevacizumab (2, 0.9%), osimertinib (4, 2.4%), crizotinib (4, 5.9%), alectinib/ceritinib (1, 5.0-5.6%), lorlatinib/brigatinib (1, 20-25%) and amivantamab/vatalanib (1, 100%).

As shown in Table SI, the 233 patients who received monoclonal antibodies (bevacizumab; 233/701, 33.3%) had a similar distribution in terms of the three comorbidity groups to those patients treated with small molecule inhibitors, mainly *EGFR* inhibitors (474/701, 67.6%) and *ALK*/*ROS1* inhibitors (74/701, 10.6%), and no significant difference was detected between patients treated with the monoclonal antibody and the small molecule inhibitor treatment groups (P=0.310). Of the 474 patients treated with *EGFR* inhibitors, patients with heart disease had a higher rate of cardiotoxicities (3.4%) than those with other comorbidities (0.6%), although the differences did not reach statistical significance (P=0.054). Notably, within the group treated with *EGFR* inhibitors, cardiac comorbidity was significantly associated with a higher risk of osimertinib-related cardiotoxicity (9.4 vs. 0.8%; P=0.018). Of the 74 patients treated with *ALK*/*ROS1* inhibitors, *ALK*/*ROS1* inhibitor-associated cardiotoxicities were more frequent in patients with heart disease (30.0%) than in those with other comorbidities (2.1%) (P=0.001). Of the 251 patients treated with anti-*VEGF* therapy, bevacizumab was the most frequent anti-*VEGF* therapy used (233 patients), causing cardiac disorders in 2/233 (0.9%) patients. Additionally, 2 of 3 patients with anti-*VEGF* therapy-associated cardiotoxicity continued chemotherapy (bevacizumab plus paclitaxel/carboplatin or vatalanib plus pemetrexed) and tolerated treatment well when anti-*VEGF* therapy was stopped. This suggested that

Table III. Comparison of CCI scores between two comorbidity groups of osimertinib-treated patients.

A, CCI scores in the cardiac and other comorbidity groups

CCI score	Cardiac comorbidity, n=32	Other comorbidity, n=132	P-value
Mean (± SD)	2.41 (±2.96)	0.86 (±1.08)	<0.001
Score distribution, n (%)			
0	8 (25.0)	69 (52.3)	0.005
1	8 (25.0)	27 (20.5)	
2	7 (21.9)	25 (18.9)	
3+	9 (28.1)	11 (8.3)	

B, CCI scores when excluding for heart disease[a] in the cardiac and other comorbidity groups

CCI	Cardiac comorbidity, n=32	Other comorbidity, n=132	P-value
Mean (± SD)	2.16 (±2.83)	0.86 (±1.08)	<0.001
Score distribution, n (%)			0.032
0	10 (31.3)	69 (52.3)	
1	8 (25.0)	27 (20.5)	
2	6 (18.7)	25 (18.9)	
3+	8 (25.0)	11 (8.3)	

[a]The CCI excluded myocardial infarction and congestive heart failure. Two-sample unpaired t-test was used for Mean score and χ^2 test for the score distribution analysis. CCI, Charlson Comorbidity Index.

cardiotoxicity was less related to chemotherapy. Another patient discontinued bevacizumab plus paclitaxel/carboplatin treatment due to cardiotoxicity, with bevacizumab considered the primary cause. This patient subsequently switched to *EGFR* inhibitors after the detection of a sensitive mutation and did not report any cardiac problems.

Patient characteristics and the management of targeted drug-associated cardiotoxicity. In total, 16 cardiac disorders among the 15 patients with cardiotoxicity were identified, including 5 with bradycardia, 2 tachycardia, 2 QTc interval prolonged, 1 decreased EF, 1 heart failure, 1 atrial fibrillation, 1 pericarditis with pericardial effusion, 1 complete heart block, 1 non-ST-evaluation myocardial infarction (NSTEMI) and 1 marantic endocarditis of the mitral valve leading to cardioembolic strokes possibly due to malignancy and clinical study agent. Additionally, 8 cardiac events presented with mild symptoms and most could be tolerated well, while grade ≥2 cardiotoxicity frequently led to discontinuation or interruption of the targeted drugs (Fig. 3). An asymptomatic patient who had prior bradycardia had a pacemaker implanted due to lorlatinib-related complete heart block and restarted treatment with a good tolerance after a 7-day interruption. Other cardiotoxicities were tolerable under monitoring and no further intervention was necessary at the time of detection, including discontinuation or interruption of the targeted therapy. Furthermore, 10 of the 16 (62.5%) cardiotoxicities were symptomatic and were identified through periodic cardiac monitoring. ECGs detected 12 cardiac events, including prolonged QTc interval (480-501 ms), bradycardia (45-54 bpm), tachycardia (108-134 bpm), atrial fibrillation and heart block. Echocardiograms were performed to identify 4 cardiac events of heart failure (EF 28%), decreased EF (48%), pericarditis and marantic endocarditis. Significantly increased N-terminal pro b-type natriuretic peptide levels and increasing trends of troponin were tested for the diagnoses of heart failure and NSTEMI, respectively.

Survival. The median survival time of patients who displayed cardiotoxicity was 4.7 years, which was much longer than the 1.9 years observed for those who did not. The 4-year survival curves showing the survival rate trends following univariable analysis are shown in Fig. 4A-B. Multivariable analyses demonstrated cardiac comorbidity was not an independent prognostic factor among patients with targeted therapy. However, patients with cardiotoxicities were at a lower risk of death (HR, 0.56; 95% CI, 0.32-0.99) than those without (P=0.003). Smokers (HR, 1.45; 95% CI, 1.23-1.72), non-adenocarcinoma (HR, 1.51; 95% CI, 1.18-1.92), only drug therapy (HR, 1.79; 95% CI, 1.46-2.19), targeted therapy not used at the first line (HR, 1.21; 95% CI, 1.02-1.44), no response to therapy (HR, 1.61; 95% CI, 1.36-1.91) and older age (HR, 1.01; 95% CI, 1.00-1.02) predicted a worse survival (Table VII).

When focusing on *EGFR* inhibitors, osimertinib-treated patients with comorbid heart disease had a median survival time of 1.4 years, much shorter than those without comorbidities (4.2 years) and with other comorbidities (2.5 years). The survival curves showing the survival rate trends following univariable analysis are shown in Fig. 4C-H. Compared with other comorbidities, the multivariable analyses showed that

Table IV. Demographics of patients with cardiotoxicity (n=15).

Demographic	Value
Mean age, years (SD)	64.2 (13.5)
Sex, n (%)	
Female	4 (26.7)
Male	11 (73.3)
Ethnicity, n (%)	
Caucasian	14 (93.3)
Other	1 (6.7)
Smoking status, n (%)	
Never	7 (46.7)
Former	6 (40.0)
Current	2 (13.3)
Tumor site, n (%)	
Left	6 (40.0)
Right	9 (60.0)
Gene mutation, n (%)	
EGFR	6 (40.0)
ALK	4 (26.7)
ROS1	3 (20.0)
Unknown	2 (13.3)

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; ROS1, c-ros oncogene 1.

Table V. Cardiotoxicity characteristics and outcome of patients with cardiotoxicity (n=15),

Characteristic	Value
Mean onset time of cardiotoxicity, months (SD)	
EGFR inhibitors (including osimertinib)	8.1 (7.2)
ALK/*ROS1* inhibitors	4.3 (3.2)
Osimertinib	11.0 (6.1)
Anti-*VEGF* therapy	1 or 2 cycles
Median onset time of cardiotoxicity, months	
Overall	3
Osimertinib	12
EGFR inhibitors (including osimertinib)	8
ALK/*ROS1* inhibitors	3
Anti-*VEGF* therapy	1.5
Diagnostic method of cardiotoxicity, n	
Symptoms	6
Electrocardiogram	11
Echocardiogram	4
N-terminal pro b-type natriuretic peptide	1
Troponin	1
Median follow-up time, months (range)	52 (3-128)

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; ROS1, c-ros oncogene 1; VEGFR, vascular endothelial growth factor receptor.

cardiac comorbidities predicted a ~1.7-fold risk of death when adjusted for age, treatment type, response and cardiotoxicity status; however, the no comorbidity group did not demonstrate significant preponderance (P=0.069) in multivariable analysis. Patients treated with *ALK*/*ROS1* inhibitors who experienced cardiotoxicity had a significantly longer median survival time (10.8 years) than those who did not experience cardiotoxicity (2 years), although this was not an independent prognostic factor in the multivariable analysis (P=0.058). For patients treated with anti-*VEGF* therapy, comorbid heart disease (P=0.737) and cardiotoxicity (P=0.466) showed no associations with the survival length in the multivariable analysis.

Discussion

The employment of targeted therapies has led to paradigm advances in the management of NSCLC and new spectrums in toxicities. Cardiotoxicity has emerged as a challenge with the administration of targeted drugs. Data from the WHO Pharmacovigilance database, VigiBase (https://who-umc.org/vigibase/vigibase-who-s-global-database/), reported that 1.8% of all arrhythmias and 1.2% of all heart failures are attributed to targeted drugs among all adverse reactions for metastatic NSCLC. Additionally, *ALK*/*ROS1* inhibitors were associated with increased odds of conduction disorders, while *BRAF* and *EGFR* inhibitors were related to a prolonged QTc interval (27). However, due to the lack of exposure data of comorbidities in VigiBase, the incidence of cardiotoxicity and the prevalence of comorbid heart disease could not be identified. The present study focused on the associations between comorbid heart disease and targeted therapy-related cardiotoxicity, along with their influence in clinical outcomes, with long-term follow-ups among patients with advanced-stage NSCLC.

In the present study, it was found that 19.0% of patients with stage-IV lung cancer had heart disease, which was lower than the 32% reported for all-stage patients from a previous study (5). The correlation between cardiac disorders and the survival of patients with NSCLC were investigated through the SEER-Medicare database, which showed comorbid cardiac arrhythmias (28.6%), heart failure (17.5%) and myocardial infarction (8.7%) were predictors of a worse survival (6). In the present study, a greater comorbidity burden in patients with cardiac disease (2.02) at a higher CCI score than those with other comorbidities (1.14) was found even when excluding comorbid conditions. Although it was not surprising to find that targeted therapy-induced cardiotoxicity had a greater association with cardiac comorbidity, the results further validated that baseline cardiovascular disease may contribute to anticancer agent-associated cardiotoxicity (28). However, the cardiotoxic occurrences and consequences varied by the type of drugs used under different comorbidity conditions, and it was noted that cardiotoxicity was reported with targeted drugs that inhibited *EGFR*, *ALK*, *ROS1* and *VEGF*/*VEGFR*.

EGFR inhibitors have been the standard of care to treat NSCLC with *EGFR*-sensitive mutations in 10-16% Western populations and 40-50% Asian populations who harbor EGFR-sensitive mutations (29). Osimertinib, the

Table VI. Comorbid disease, toxicity and treatment of patients with cardiotoxicity (n=15).

Characteristic	No. of patients
Cardiac comorbidity[a]	
Arrhythmia	7
Heart failure	5
Myocardial infarction	3
Coronary artery calcifications	1
Heart valve disease	1
None	6
Cardiovascular risk factors[a]	
Hypertension	9
High cholesterol	5
Family history	3
Stroke	2
Diabetes	1
None	3
Other toxicities (>5 observation)[a]	
Nausea	8
Fatigue	7
Skin toxicity	5
Diarrhea	5
Hypertension	5
Prior antitherapy[a]	
Chest radiation	1
Chemotherapy	6
Targeted therapy	7
Immunotherapy	1
None	7

[a]The total was >15 as some patients had multiple observations.

third-generation irreversible *EGFR*-TKI, has been approved for the first-line treatment of advanced-stage NSCLC based on the improved OS time observed compared with the comparator in a clinical trial (38.6 vs. 31.8 months; P=0.046) (30), but is also the most related to the cardiotoxicity risk (4.7-21.6%) profile of *EGFR* inhibitors (31,32). Therefore, a subgroup analysis of patients treated with osimertinib was performed in the present study and a lower cardiotoxicity frequency (2.4%) was found, reported as heart failure, prolonged QTc interval, decreased EF and tachycardia (33). Severe cardiotoxicity (grade ≥3) was found in 4.9% of (6/123) patients after osimertinib administration. However, 1 of the 6 patients with cardiac events had prior heart disease and 4 had cardiovascular risk factors (hypertension and obesity) (34). These results validated coexisting heart disease as an independent prognostic factor among patients treated with osimertinib, predicting a higher risk of death. Amivantamab, a novel *EGFR-MET* bispecific antibody approved for *EGFR* exon 20 insertion mutations (35), was identified as the cause of tachycardia in the single patient treated with this drug in the present study, but this has not been reported in clinical trials (36). The underlying mechanism of EGFR-TKI-induced cardiotoxicity might be involved in PI3K signaling pathway inhibition, ion channel blockade, oxidative stress, inflammatory response and apoptosis (37).

ALK/ROS1 inhibitors are approved for NSCLC with *ALK* and *ROS1* fusions observed in 1-10% and 0.9-2.6% of patients, respectively (29). Data on cardiac disorders associated with *ALK* inhibitors based on the Food and Drug Administration Adverse Event Reporting System (FAERS) showed a median onset time of 33 days and bradycardia as a common associated event (38). The present study found potential new cardiotoxicities of ceritinib-initiated myocarditis and lorlatinib-initiated cardiomyopathy; however, comorbidity data could not be mined from FAERS. In the present study, cardiotoxicity was identified at an average of 4.3 months and validated bradycardia comprised 71% of patients with *ALK/ROS1* inhibitor-induced cardiotoxicity. Prolonged QTc interval and bradycardia occurred in the clinical setting with crizotinib (39). There were 2 patients with crizotinib-related bradycardia, which has previously been found to be related to an impaired autophagy process, causing cardiomyocyte death and cardiac injury (40). Follow-up of 51 patients with alectinib showed an incidence of 42% for bradycardia, but no relationship between bradycardia and prior history of >1 cardiovascular risk factor (including hypertension, diabetes mellitus, dyslipidemia, familial history and prior cardiovascular events) was found (P=0.69) (41). In the present study, 1 patient treated with alectinib experienced bradycardia at an occurrence rate of 5% and had prior comorbid sinus bradycardia and hypertension, which were identified as independent risk factors of alectinib-induced bradycardia (42). Brigatinib-related cardiotoxicity has scarcely been reported, with only bradycardia reported at 5-8% in clinical trials (9,43). In the present study, a prolonged QTc interval was observed in 1 patient treated with brigatinib (25%) who had previously experienced crizotinib-associated bradycardia.

Anti-*VEGF* therapies perform anticancer efficacy by inhibiting angiogenesis in tumor development and metastases, among which bevacizumab is the frequently used anti-*VEGF* drug for NSCLC (44). Based on the role of *VEGF* in the development and functional integrity of the vasculature and the importance of the coronary artery, it is not surprisingly that the *VEGF* antibody universally results in hypertension, contributing to heart failure in 2-4% of patients receiving bevacizumab and 3-8% patients receiving all anti-*VEGF* therapies; additionally, cardiac ischemia is mechanistically related to the use of anti-*VEGF* therapies (45). However, a much lower incidence (0.9%) of cardiotoxicity among patients treated with bevacizumab was found in the present study. All 3 patients with anti-*VEGF* therapy-associated cardiotoxicity had concurrent hypertension, supporting that hypertension is a risk factor of cardiotoxicity (46). Unlike other studies on cardiovascular toxicities, only cardiotoxicity was analyzed in the present study and vascular disorders such as hypertension and venous thrombus were not included, which might lead to a lower observed incidence of bevacizumab-induced cardiotoxicity.

Regarding the potential relationship between cardiotoxicity occurrence and longer survival, in the present study, the OS time of patients with cardiotoxicity was calculated from the median cardiotoxicity onset date and compared with those without cardiotoxicity from the treatment initiation date. Under this conservative estimated survival, it was delineated that the presence of cardiotoxicity predicted a longer 5-year survival

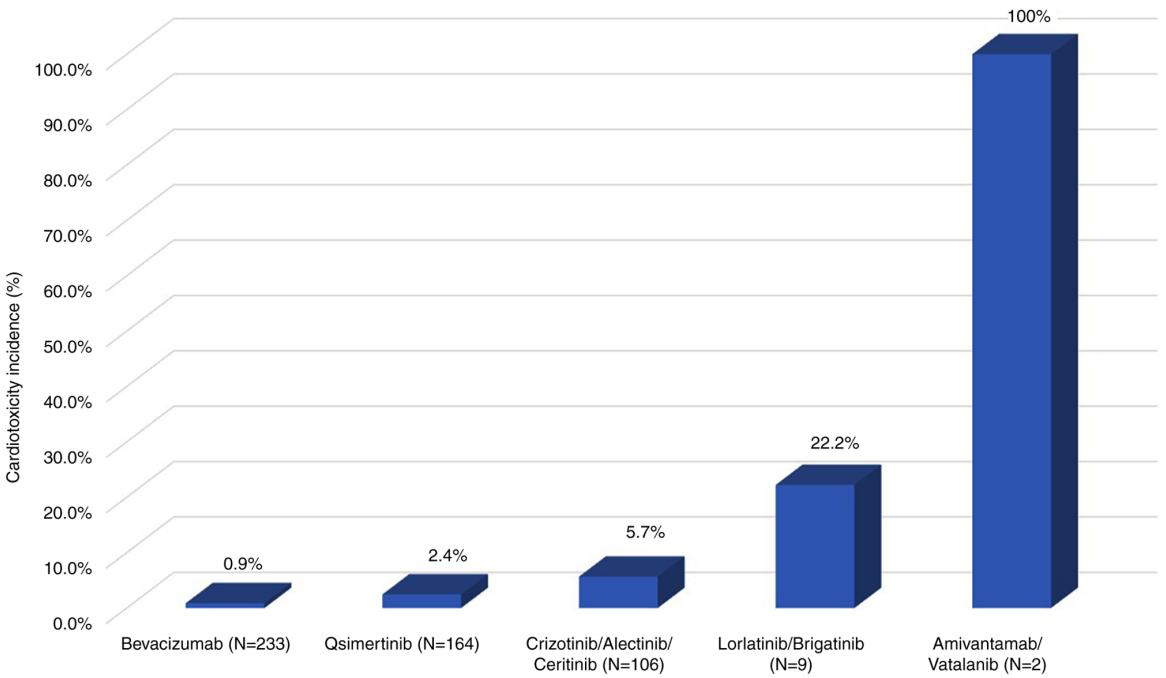

Figure 2. Incidence of cardiotoxicity for different targeted drugs in total related patients.

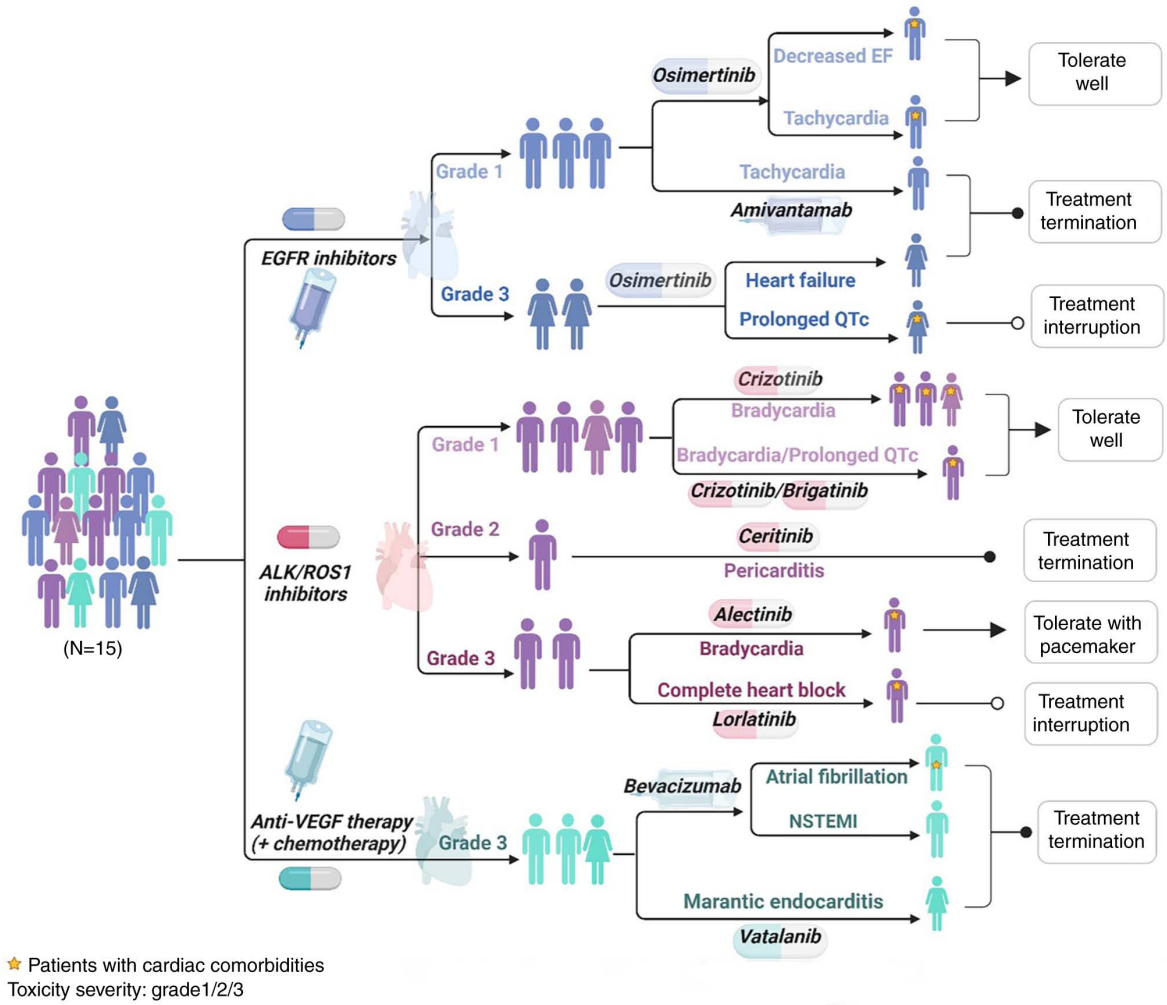

Figure 3. Patients with targeted therapy-associated cardiotoxicity. ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; ROS1, c-ros oncogene 1; VEGFR, vascular endothelial growth factor receptor; QTc, corrected QT interval; EF, ejection fraction; NSTEMI, non-ST-evaluation myocardial infarction.

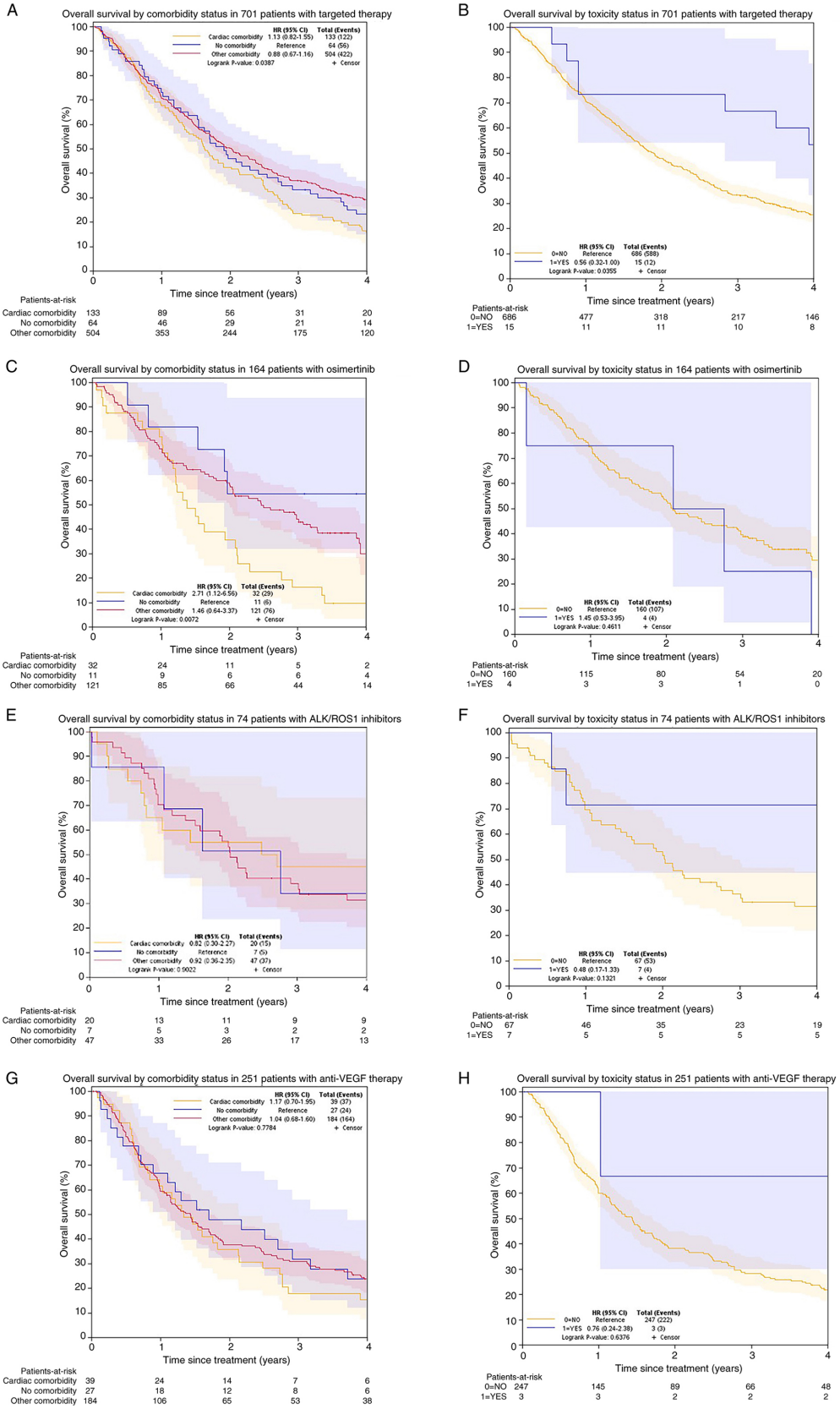

Figure 4. Kaplan-Meier curves of overall survival by comorbidity and toxicity status. (A) In 701 patients receiving targeted therapy, no survival differences were observed among the three comorbidity groups. (B) In 701 patients receiving targeted therapy, patients with cardiotoxicity had an improved survival compared with those without. (C) In 164 patients receiving osimertinib, patients with cardiac comorbidity had a worse survival than those with other comorbidities. (D) In 164 patients receiving osimertinib, no survival difference was observed in patients with or without cardiotoxicity. (E) In 74 patients with *ALK/ROS1* inhibitors, no survival differences were observed among three comorbidity groups. (F) In 74 patients with *ALK/ROS1* inhibitors, no survival differences were observed in patients with or without cardiotoxicity. (G) In 251 patients with anti-*VEGF* therapy, no survival differences were observed among the three comorbidity groups. (H) In 251 patients with anti-*VEGF* therapy, no survival differences were observed in patients with or without cardiotoxicity. ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; ROS1, c-ros oncogene 1; VEGFR, vascular endothelial growth factor receptor; HR, hazard ratio; CI, confidence interval.

Table VII. Univariable and multivariable survival analysis for 701 patients receiving targeted therapy.

Variable	n	Events, n (%)	Median, years	5-year survival % (95% CI)	Cox univariable		Cox multivariable	
					HR (95% CI)	P-value	HR (95% CI)	Likelihood Ratio P-value (n=633)
Comorbidity						0.0548		0.1463
No comorbidity	64	56 (88)	1.9	14.1 (5.5-22.8)	-		-	
Cardiac comorbidity	133	122 (92)	1.6	13.6 (7.8-19.5)	1.14 (0.83-1.57)		0.96 (0.68-1.36)	
Other comorbidity	504	422 (84)	2	23.5 (19.7-27.3)	0.89 (0.68-1.18)		0.81 (0.60-1.09)	
Sex						0.2432		
Female	404	344 (85)	2	21.3 (17.2-25.5)	-			
Male	297	256 (86)	1.7	19.7 (15.1-24.3)	1.10 (0.94-1.29)			
Ethnicity						0.3592		
Caucasian	616	535 (87)	1.9	20.7 (17.5-24.0)	-			
Other	79	59 (75)	2.3	21.5 (11.5-31.5)	0.88 (0.67-1.15)			
Smoking status						<0.0001		<0.0001
Never	368	296 (80)	2.4	27.5 (22.8-32.2)	-		-	
Ever	333	304 (91)	1.3	13.2 (9.5-17.0)	1.60 (1.36-1.88)		1.45 (1.23-1.72)	
Side of tumor						0.7769		
Left	305	262 (86)	1.9	20.6 (15.9-25.2)	-			
Right	389	331 (85)	1.9	21.2 (17.0-25.4)	1.02 (0.87-1.20)			
Cell type						<0.0001		0.0016
Adenocarcinoma	616	519 (84)	2.1	21.8 (18.4-25.1)	-		-	
Other	85	81 (95)	1.1	12.7 (5.6-19.9)	1.65 (1.30-2.09)		1.51 (1.18-1.92)	
Treatment type						<0.0001		<0.0001
Drug therapy	522	471 (90)	1.7	15.6 (12.4-18.8)	1.81 (1.49-2.21)		1.79 (1.46-2.19)	
Drug combined with other therapies	179	129 (72)	3.3	35.5 (28.3-42.7)	-		-	
Treatment line						0.0026		0.0266
Palliative first-line	425	353 (83)	2.1	22.9 (18.8-27.1)	-		-	
Other	258	232 (90)	1.6	16.5 (11.9-21.1)	1.29 (1.09-1.52)		1.21 (1.02-1.44)	
Treatment response						<0.0001		<0.0001
Response	357	285 (80)	2.5	26.8 (22.1-31.6)	-		-	
No response	338	315 (93)	1.4	13.7 (9.9-17.4)	1.78 (1.52-2.09)		1.61 (1.36-1.91)	
Any toxicity						0.0481		
No	52	46 (88)	1.4	19.2 (8.2-30.3)	-			
Yes	649	554 (85)	1.9	20.8 (17.6-24.0)	0.74 (0.55-1.00)			

Table VII. Continued.

Variable	n	Events, n (%)	Median, years	5-year survival % (95% CI)	Cox univariable		Cox multivariable	
					HR (95% CI)	P-value	HR (95% CI)	Likelihood Ratio P-value (n=633)
Cardiotoxicity						0.0452		0.0027
No	686	588 (86)	1.9	20.2 (17.1-23.3)	-		-	
Yes	15	12 (80)	4.7	40.0 (15.2-64.8)	0.56 (0.32-0.99)		0.45 (0.25-0.81)	
Toxicity severity						0.2952	0.5331	
None	30	28 (93)	1.6	10.0 (0.0-20.7)	-			
Grade 1	407	347 (85)	1.9	21.9 (17.8-26.0)	0.76 (0.52-1.12)			
Grade ≥2	212	178 (84)	2.4	21.1 (15.3-26.8)	0.73 (0.49-1.08)			
CCI							0.2031	
0	312	261 (84)	2	22.4 (17.6-27.2)	-			
1	190	166 (87)	1.9	22.0 (16.0-28.0)	1.10 (0.91-1.34)			
2+	199	173 (87)	1.6	16.8 (11.4-22.2)	1.19 (0.98-1.44)			
Age at diagnosis	701	600 (86)	1.9	20.7 (17.6-23.8)	1.02 (1.01-1.02)	0.0001	1.01 (1.00-1.02)	0.0039

CCI, Charlson Comorbidity Index; HR, hazard ratio; CI, confidence interval. Cox Proportional Hazard models was used for survival analysis.

in patients treated with targeted drugs. Patients treated with *ALK*/*ROS1* inhibitors who experienced cardiotoxicity had a longer median survival time (10.8 years) than those who did not experience cardiotoxicity (2.0 years) in the multivariable analysis, although the differences did not reach the threshold for statistical significance due to limitations in the sample size. Data from the PROFILE 1001 and PROFILE 1005 clinical trials was previously analyzed to determine the association between decreased heart rate and the clinical response to crizotinib. The results indicated that patients with sinus bradycardia had a significantly greater overall response rate (62.1 vs. 23.1%; P=0.02) and the maximum tumor shrinkage (53.0 vs. 21%; P=0.021) compared with those without (47). In another study, follow-up of patients with crizotinib-induced asymptomatic sinus bradycardia also showed excellent tolerance and potential positivity for clinical response to treatment (48). These results implied cardiotoxicity, specifically in the form of sinus bradycardia, may be associated with a more favorable response to therapy and potentially a longer survival time. However, in a previous study of alectinib, based on administrative source of data, the results showed no significant association between bradycardia and clinical efficacy (P=0.687) (42). Unfortunately, the survival analyses to evaluate cardiac comorbidity and cardiotoxicity were unmet synthetically due to the lack of detailed information. The results of the present study demonstrated that cardiotoxicity may be a predictor of longer survival in patients treated with targeted drugs, partly driven by a favorable survival in patients treated with *ALK*/*ROS1* inhibitors, which necessitates further studies to validate our hypothesis and elucidate the underlying mechanism. Additionally, the present study showed that patients with heart disease were older than those with other comorbidities or no comorbidity, and age was indeed an independent prognostic factor in the multivariable analysis. However, age-stratified analysis could not be performed due to the relatively small number of events of interest. For instance, all the 15 patients with cardiotoxicity were in the cardiac and other comorbidity groups, and their age was relatively concentrated at the mean age of 64.2±13.5 years old. This is another important point for the future effort.

The present study highlighted the importance of considering the comorbid disease and risk factors that may facilitate cardiotoxicity when patients with lung cancer are administered targeted therapy. Furthermore, the benefit-risk balance for cardiotoxicity should be individually recognized by the type of targeted drugs and the severity of toxicity. However, the findings of the present study remain in their infancy and future research, including larger, prospective studies are required for validation.

Although the present study provided a clinical implication of cardiotoxicity among patients with advanced lung cancer, limitations should be acknowledged. First, a limitation of the study stems from its retrospective nature, which may produce bias with toxicity identification and evaluation. For instance, cardiotoxicity was identified through the monitoring of heart condition during treatment and not via a protocol driven assessment. Second, in a few patients who had no history of cardiac disease or new cardiac symptoms and did not receive QTc interval prolongation-related drugs, the risk of cardiotoxicity was likely underestimated, which have may have produced potential selection bias. Furthermore, the stratified analysis of cardiotoxicity in different types of heart diseases was limited by the small sample size of patients with cardiotoxicity in this single-institution study. Prospective studies, combined with cardiac evaluation and surveillance (such as blood pressure, ECG, left ventricular function, biomarkers and heart medications), are required to address cardiotoxic susceptibility prior to treatment and for the appropriate management of cardiotoxicity.

In conclusion, cardiotoxicity was significantly more prevalent in patients with comorbid heart diseases and was shown to be a promising predictor of longer survival in patients with stage-IV NSCLC treated with targeted drugs, indicating an underlying implication of cardiotoxicity for clinicians. However, the results were limited by the retrospective nature of the study and sample size. Future preclinical and clinical studies are needed to validate the findings, to identify and rank modifiable risk factors and to investigate the biological and pharmacological mechanisms of the observed cardiac effects of the targeted drugs.

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Availability of data and materials

The data generated in the present study are not publicly available due to patient confidentiality but deidentified or aggregated data may be requested from the corresponding author.

Authors' contributions

PY, JAW and YP confirm the authenticity of all the raw data. PY and YP contributed to conceptualization, design, methodology and the original draft preparation. DL and JAW contributed to data collection, visualization, investigation and analysis using SAS software. YP and YHL contributed to supervision, data interpretation and validation. AVK, ZG, NK, NYY and ZW contributed to data collection and assembly. KL and VE contributed to data interpretation, reviewing and editing. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

All participants in the present study consented to the Mayo Clinic Institutional Review Board approved protocol (approval no. IRB-225-99) and signed the consent form.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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