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Sex Differences in Cardiovascular Outcomes Among Patients With Lung Cancer Treated With ALK Inhibitors: A Propensity Score-Matched Analysis

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Introduction

ALK inhibitors are a cornerstone of therapy for **ALK-positive** non-small cell lung cancer (NSCLC). Cardiovascular toxicities have been reported with these agents, yet potential sex based differences in risk remain poorly defined. We evaluated sex-specific cardiovascular outcomes among patients with lung cancer treated with **ALK inhibitors**.

Methods

- **Study Design:** Retrospective cohort study using the TriNetX Global Collaborative Network.
- **Patient Population:** Adult lung cancer patients treated with ALK inhibitors (alectinib, crizotinib, ceritinib, brigatinib, or lorlatinib), stratified by sex (male vs. female).
- **Follow-up Period:** Outcomes were systematically assessed over 1 year following therapy initiation.
- **Statistical Analysis:** Propensity score matching (1:1) was performed for demographics, comorbidities, cancer characteristics, treatment exposures, and laboratory variables. Time-to-event analyses were conducted using Kaplan-Meier methods and Cox proportional hazards models.

Results

Table 1. Baseline Characteristics After Propensity Score Matching

Characteristic	Male (N=1,616)	Female (N=1,616)	SMD
Age, mean $\pm$ SD (years)	60.8 $\pm$ 13.5	60.3 $\pm$ 13.4	0.033
BMI, mean $\pm$ SD	26.7 $\pm$ 5.7	26.5 $\pm$ 6.0	0.032
White race	49.3%	47.9%	0.028
Black race	6.5%	6.5%	<0.001
Asian race	16.8%	17.4%	0.016
Metastatic disease	43.4%	43.5%	0.002
Platinum chemotherapy	14.4%	14.6%	0.005
Pemetrexed	11.8%	11.5%	0.008
Hypertension	31.4%	30.9%	0.009
Hyperlipidemia	24.8%	24.3%	0.012
Diabetes mellitus	13.1%	12.9%	0.007
Atrial fibrillation	7.4%	6.8%	0.022
Heart failure	5.4%	5.1%	0.014

Note: SMD, standardized mean difference. SMD of less than 0.10 indicates that the covariate is well matched.

Table 2. Cardiovascular Outcomes Within 1 Year

Outcome	Male Events	At Risk (Male)	Female Events	At Risk (Female)	HR (95% CI)	P-value
Mortality	322	1,616	277	1,616	1.19 (1.02–1.40)	0.031
VTE	106	1,383	106	1,378	1.02 (0.78–1.34)	0.866
ATE	42	1,480	51	1,483	0.84 (0.56–1.27)	0.411
Myocardial infarction	19	1,567	18	1,576	1.00 (0.57–2.07)	0.804
Stroke	34	1,515	40	1,514	1.13 (0.88–1.44)	0.331
Atrial fibrillation	138	1,616	106	1,616	1.33 (1.03–1.71)	0.029
Conduction abnormalities	38	1,540	23	1,539	1.70 (1.01–2.85)	0.043
Heart failure	45	1,501	54	1,519	0.85 (0.58–1.26)	0.449
Pericardial disease	51	1,500	78	1,494	0.65 (0.46–0.93)	0.017

Note: VTE, venous thromboembolism (includes pulmonary embolism and deep vein thrombosis); ATE, arterial thromboembolism (includes myocardial infarction and ischemic stroke).

Study Population

After matching, 1,616 patients were included in each cohort. Baseline characteristics were well balanced, including age (~60 years), metastatic disease (~43%), and prior chemotherapy, including platinum chemotherapy (~14%) and pemetrexed (~11%).

Results

Male patients had a higher risk of all-cause mortality compared with female patients (**HR 1.19**, 95% CI 1.02–1.40). There were no significant differences in VTE (HR 1.02, 95% CI 0.78–1.34) or ATE (HR 0.84, 95% CI 0.56–1.27). Male patients also had higher risks of atrial fibrillation (**HR 1.33**, 95% CI 1.03–1.71) and conduction abnormalities (**HR 1.70**, 95% CI 1.01–2.85), but a lower risk of pericardial disease (**HR 0.65**, 95% CI 0.46–0.93). There were no significant differences in heart failure, myocardial infarction, or stroke.

Conclusion

In this large propensity score-matched real-world analysis, male patients receiving ALK inhibitors had higher risks of **arrhythmias and mortality**, but a lower risk of **pericardial disease** compared with female patients, with no significant differences in **thromboembolic outcomes**. These findings suggest sex-specific differences in cardiovascular toxicity associated with ALK-targeted therapy and support tailored risk stratification in patients with NSCLC.