



OPEN ACCESS

EDITED BY

Bo Tu,
University of Nebraska Medical Center,
United States

REVIEWED BY

Carlos Vera,
Stanford University, United States
Zhanwen Xu,
Affiliated Hospital of Hebei University, China

*CORRESPONDENCE

Beibei Du

✉ beibeidu2012@jlu.edu.cn

Yuquan He

✉ heyq@jlu.edu.cn

[†]These authors have contributed
equally to this work

RECEIVED 16 April 2025

ACCEPTED 02 June 2025

PUBLISHED 18 June 2025

CITATION

Pan Y, Peng K, Jiang Y, Yang P, Du B and
He Y (2025) Electrocardiographic changes
in QTc interval and other parameters
associated with osimertinib therapy.
Front. Oncol. 15:1612758.
doi: 10.3389/fonc.2025.1612758

COPYRIGHT

© 2025 Pan, Peng, Jiang, Yang, Du and He.
This is an open-access article distributed under
the terms of the [Creative Commons Attribution
License \(CC BY\)](https://creativecommons.org/licenses/by/4.0/). The use, distribution or
reproduction in other forums is permitted,
provided the original author(s) and the
copyright owner(s) are credited and that the
original publication in this journal is cited, in
accordance with accepted academic
practice. No use, distribution or reproduction
is permitted which does not comply with
these terms.

Electrocardiographic changes in QTc interval and other parameters associated with osimertinib therapy

Yilin Pan^{1,2}, Kexin Peng¹, Yichuan Jiang³, Ping Yang¹,
Beibei Du^{1*†} and Yuquan He^{1*†}

¹Department of Cardiology, China-Japan Union Hospital of Jilin University, Jilin Provincial Cardiovascular Research Institute, Changchun, China, ²Department of Critical Care Medicine, Beijing Anzhen Hospital, Capital Medical University, Beijing, China, ³Department of Pharmacy, China-Japan Union Hospital of Jilin University, Jilin Provincial Cardiovascular Research Institute, Changchun, China

Introduction: Osimertinib, a third-generation EGFR-TKI, is approved for the first-line treatment of EGFR-mutated advanced NSCLC and for T790M-positive NSCLC after progression on previous EGFR-TKI therapy. Osimertinib is associated with cardiotoxicity, including severe QT interval prolongation, which necessitates detailed evaluation due to its increasing use.

Methods: This retrospective, single-center study conducted at Jilin University China-Japan Union Hospital evaluated electrocardiographic changes with EGFR-mutated NSCLC treated with osimertinib. The study consecutively included 102 patients diagnosed with NSCLC at the China-Japan Union Hospital of Jilin University from August 1, 2019, to December 31, 2022. Among them, 41 patients who had both pre- and post-treatment ECG records while receiving osimertinib (80 mg daily) were analyzed. ECG parameters such as heart rate, PR interval, QRS duration, QRS axis, and QT intervals were manually calculated and analyzed.

Results: The study population had a mean age of 68.56 ± 8.73 years, comprising 46.34% males. Significant changes were observed in the QTc Bazett interval ($P < 0.0001$), QTc Fridericia interval ($P = 0.0002$) and QRS axis ($P = 0.0387$) post-treatment. QT interval prolongation was significant (McNemar test $P = 0.0039$), with both QTc Bazett and QTc Fridericia intervals showing notable prolongation. However, the changes in heart rate, PR interval, and QRS duration were not statistically significant.

Conclusion: This study comprehensively investigates the electrocardiographic changes before and after osimertinib treatment in patients with EGFR-mutated NSCLC. The significant prolongation of QTc intervals underscores the need for rigorous ECG monitoring to mitigate potential cardiotoxicity.

KEYWORDS

osimertinib, QTc interval, electrocardiographic changes, cardiotoxicity, cardio-oncology

1 Introduction

Osimertinib is a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) (1). Osimertinib has been approved globally for the first-line treatment of patients with EGFR-mutated (EGFRm) advanced non-small cell lung cancer (NSCLC) and for those with NSCLC who have progressed after EGFR-TKI treatment and are T790M-positive. In the FLAURA and AURA studies, osimertinib exhibited manageable and consistent tolerability characteristics (2–5).

Similar to many antitumor drugs, osimertinib also causes several adverse reactions. Common adverse events include diarrhea, rash, dry skin, and paronychia (2). Cardiotoxicity, though less common, is a significant adverse effect (6–8). With the increasing use of osimertinib in postoperative adjuvant chemotherapy and combination therapy, its cardiotoxicity has become a significant concern (9, 10). In a previously published case report by our team, a patient treated with experienced severe QT interval prolongation, ventricular arrhythmias, and syncope, indicating its potential to cause serious cardiac adverse reactions (11).

Compared to gefitinib and erlotinib, osimertinib appears to have a higher incidence of cardiac-related adverse events. Anand K et al. (12) found through analysis of the FDA Adverse Event Reporting System that among the 315 cardiac adverse events related to EGFR-TKIs, osimertinib accounted for more than half (158 cases, 50.1%). The most common cardiac adverse event was heart failure, followed by QT interval prolongation. However, the Adverse Event Reporting System has limitations, such as the lack of baseline cardiac characteristics of patients. Ewer et al. (13), based on analyses of three large databases including FLAURA and AURA3, concluded that there is no correlation between osimertinib and the development of heart failure. However, the relationship between osimertinib and QT interval prolongation remains unclear, as no prior studies have systematically evaluated ECG changes before and after treatment in patients. These findings prompted a detailed single-center retrospective analysis to better understand osimertinib-related cardiac adverse events in EGFR-mutant NSCLC patients.

2 Method

2.1 Patients selection

This retrospective, single-center, observational study was conducted at the China-Japan Union Hospital of Jilin University, approved by the Ethics Committee of China-Japan Union Hospital of Jilin University (Approval No: 20220118014), and conducted in accordance with the Declaration of Helsinki. Throughout the study, patient data were kept strictly confidential. The study included patients diagnosed with NSCLC at the China-Japan Union Hospital of Jilin University from August 1, 2019, to December 31, 2022, whose gene testing showed EGFR T790M mutation positivity and who regularly used osimertinib mesylate (80 mg daily) for at least one cycle. Patients without electrocardiogram records before and

after medication, those unwilling to follow up, or those who did not agree to participate in the study were excluded, resulting in a total of 41 patients being included.

2.2 Data acquisition

First, detailed inquiries were made through telephone follow-ups regarding the patient's medical history, smoking history, long-term medication history, and the duration of osimertinib use. Second, the basic information of enrolled patients, such as gender, age, and BMI, was recorded. Electrocardiograms from the electronic medical records before osimertinib use, during use, or within 28 days after discontinuation were extracted, recording heart rate, heart rhythm, PR interval, QRS duration, QRS axis, QT interval, and QT interval corrected by Bazett and Fridericia. The Bazett and Fridericia formulas use the square root and cube root of heart rate, respectively, to correct the impact of heart rate on the QT interval, more accurately reflecting the drug's effect under constant heart rate conditions. These electrocardiogram parameters were then manually calculated by a doctor with more than 10 years of experience in cardiology. If there was a greater than 20% difference between automatic and manual measurements, the result was adjudicated by a doctor with more than 15 years of experience in cardiology. Osimertinib-related adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

2.3 Statistical analysis

All data were analyzed using IBM SPSS Statistics version 25.0 software. Measurement data were tested for normal distribution using the Kolmogorov-Smirnov test. Measurement data conforming to a normal distribution are expressed as mean $\pm$ standard deviation ($\bar{x} \pm s$), and comparisons of parameters before and after medication were performed using paired t-tests. Measurement data not conforming to a normal distribution are expressed as median [M (P_{25} , P_{75})], and comparisons between two groups were performed using the Wilcoxon signed-rank test. Count data were expressed as rates and composition ratios and analyzed using the chi-square test. For paired binary data, the McNemar test was used to analyze the significance of differences in prolongation before and after medication. $P < 0.05$ was considered statistically significant.

3 Result

3.1 Patient characteristics

Of the 102 patients included in the study, 41 had both pre- and post-treatment ECG records. The average age of these 41 patients was 68.56 ± 8.73 years, with 46.34% being male, and an average body mass index of 23.47 ± 3.38 kg/m². Regarding medical history, 31.70% were

smokers, 14.63% had hypertension, 2.44% had diabetes, 36.59% had hyperlipidemia, and 9.76% had coronary artery disease. In terms of baseline medication, 2.44% of patients used ACEI/ARB/ARNI, 4.88% used β -blockers, 4.88% used calcium channel blockers, 7.32% used antiplatelet drugs, 2.44% used anticoagulants, 7.32% used statins, and 2.44% used antiarrhythmic drugs. No other QT interval-prolonging drugs were used. The baseline characteristics of these patients are shown in Table 1.

3.2 Changes in ECG parameters with osimertinib

In this study, we compared the changes in electrocardiogram parameters before and after osimertinib use. The baseline data included 41 patients; however, due to one patient having a sinus rhythm before medication and atrial fibrillation after medication, the PR interval analysis for this patient could not be performed. Consequently, the PR interval analysis included only 40 patients. The analysis of other electrocardiogram parameters still included 41 patients. The results showed no statistically significant changes in the following parameters: heart rate ($P = 0.1466$), PR interval ($P = 0.1368$), QRS duration ($P = 0.4713$), and QT interval ($P = 0.3945$). However, some parameter changes were statistically significant, including QRS axis ($P = 0.0387$), QTc Bazett interval ($P < 0.0001$),

and QTc Fridericia interval ($P = 0.0002$). The median prolongation for QTc Bazett was 18.64 ms, and for QTc Fridericia, it was 12.59 ms. Detailed results are shown in Table 2, Figure 1.

According to the CTCAE 5.0 standard, the QT interval corrected using Bazett's formula (QTcB) intervals before and after medication were classified as prolonged or non-prolonged and analyzed using the McNemar test. In three patients, the QTcB prolongation reached grade 3 after medication (an increase of 64 ms, 68 ms, and 108 ms compared to baseline QTcB,

TABLE 2 Changes in electrocardiography parameters associated With osimertinib exposure.

Electrocardio graphy parameters	Pre-treatment	Post-treatment	<i>P</i> value
Heart rate (per minute)	75.00 (67.00, 91.00)	80.00 (72.00, 96.00)	0.1466
PR interval(ms)	157.43 $\pm$ 17.33	152.18 $\pm$ 21.62	0.1368
QRS duration(ms)	90.00 (84.00, 98.00)	94.00 (80.00, 102.00)	0.4713
QRS axis(degree)	46.00 (6.00, 60.00)	20.00 (-3.00, 45.00)	0.0387
QT interval(ms)	373.61 $\pm$ 32.90	378.27 $\pm$ 28.70	0.3945
QTc Bazett(ms)	422.49 $\pm$ 21.29	442.74 $\pm$ 29.32	<0.0001
QTc Fridericia(ms)	405.05 $\pm$ 17.62	419.68 $\pm$ 22.13	0.0002

Data are presented as mean $\pm$ standard deviation for normally distributed variables and median (interquartile range) for non-normally distributed variables. QTc Bazett, QT interval corrected using Bazett's formula; QTc Fridericia, QT interval corrected using Fridericia's formula. Bold *P* values indicate statistical significance ($P < 0.05$).

TABLE 1 Baseline patient demographics.

Baseline Patient Demographics	Value
Male sex	19 (46.34%)
Age, mean years	68.56 $\pm$ 8.73
Body mass index, kg/m ²	23.47 $\pm$ 3.38
Ever smokers	13 (31.70%)
Past Cardiac History	
Hypertension	6 (14.63%)
Diabetes Mellitus	1 (2.44%)
Hyperlipidemia	15 (36.59%)
Coronary Artery Disease	4 (9.76%)
Baseline medications	
Angiotensin converting enzyme inhibitors/angiotensin II receptor blockers/angiotensin receptor-neprilysin inhibitors	1 (2.44%)
Beta blockers	2 (4.88%)
Calcium channel blockers	2 (4.88%)
Antiplatelet Drugs	3 (7.32%)
Anticoagulants	1 (2.44%)
Statins	3 (7.32%)
Antiarrhythmics	1 (2.44%)
Other QT-prolonging drugs	0 (0%)

Data are presented as n (%) for categorical variables and mean $\pm$ standard deviation for continuous variables. Body mass index was calculated as weight in kilograms divided by height in meters squared.

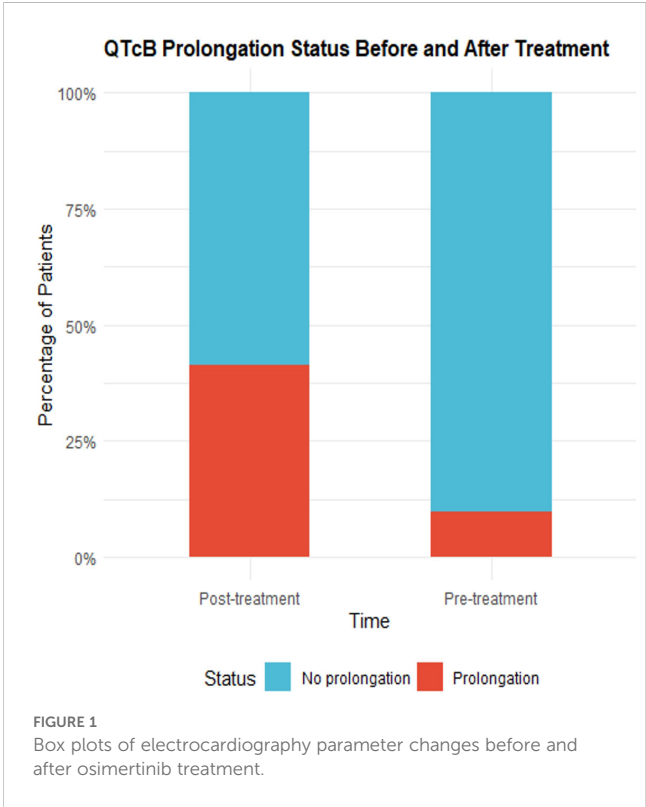


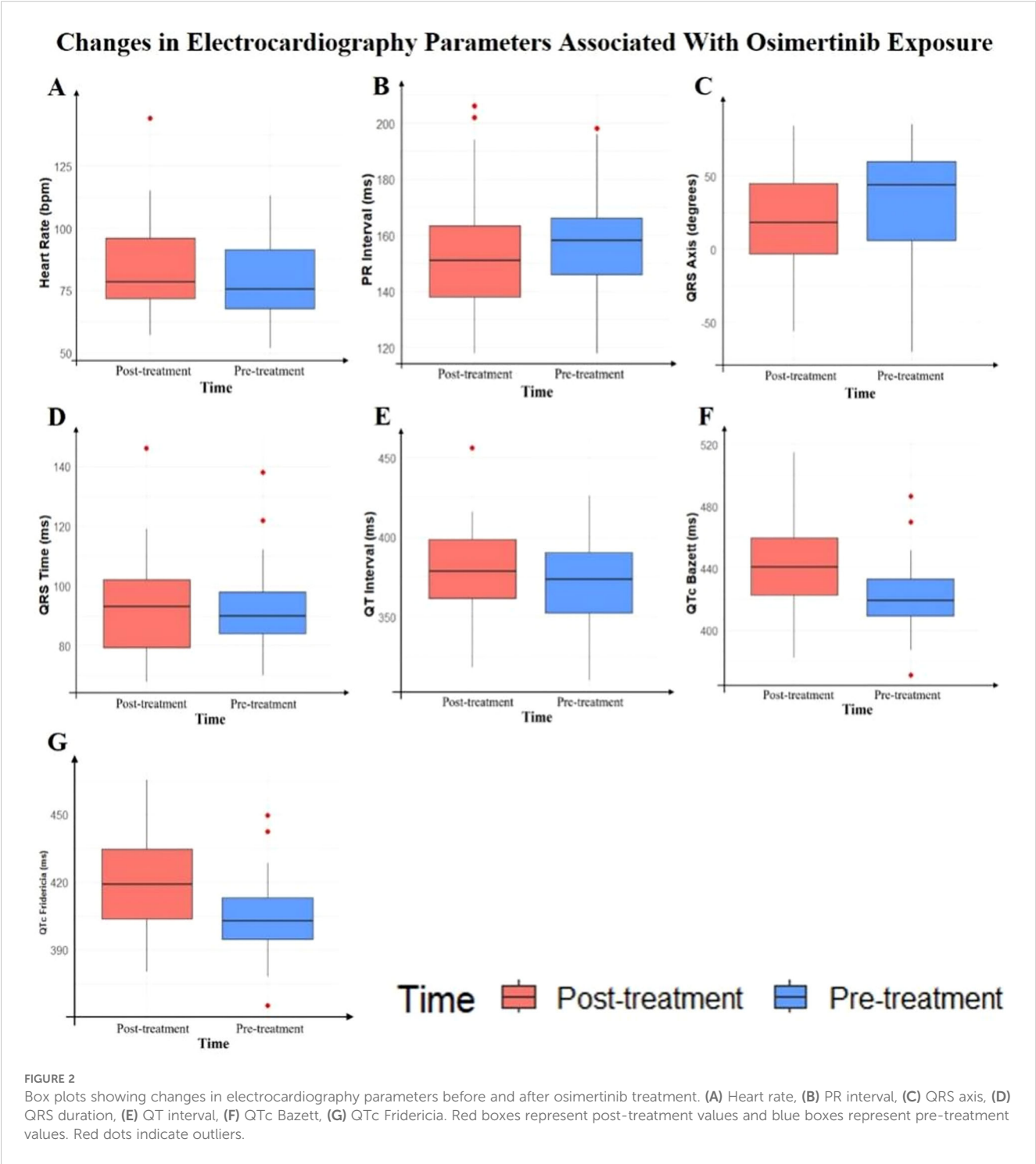
FIGURE 1 Box plots of electrocardiography parameter changes before and after osimertinib treatment.

respectively). Additionally, there were 37 patients (90.24%) without QTcB prolongation before medication, which decreased to 24 patients (58.54%) after medication. Correspondingly, there were 4 patients (9.76%) with QTcB prolongation before medication, which increased to 17 patients (41.46%) after medication. The P-value of the McNemar test was 0.0039, indicating that the change in QTcB prolongation before and after medication was statistically significant. Detailed results are shown in Table 3 and Figure 2.

TABLE 3 QTcB Prolongation status before and after treatment.

Category	Pre-treatment	Post-treatment	P value
No prolongation	37 (90.24%)	24 (58.54%)	0.0039
Prolongation	4 (9.76%)	17 (41.46%)	

Data are presented as n (%). QTcB = QT interval corrected using Bazett’s formula. Prolongation was defined according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. P value was calculated using McNemar test for paired nominal data. Bold P value indicates statistical significance ($P < 0.05$).



4 Discussion

This study comprehensively investigates the electrocardiographic changes before and after osimertinib treatment in patients with EGFR-mutated NSCLC. Our study shows that the corrected QTc Bazett and QTc Fridericia intervals exhibited statistically significant changes.

In the AURA3 study, 1.8% of patients (n=5) had an increase in QTc of more than 60 ms from baseline, and 1.4% of patients (n=4) had QTc exceeding 500 ms after medication; whereas, in our study, these rates were 7.3% and 2.4%, respectively, indicating higher incidence rates (2). Additionally, although the AURA3 study and our retrospective study did not find malignant arrhythmias related to QT interval prolongation, previous case reports have repeatedly recorded instances of ventricular tachycardia and even torsades de pointes in NSCLC patients treated with osimertinib (11, 14–17). These findings suggest that the risk of fatal arrhythmias induced by osimertinib may be underestimated. Physicians should be vigilant about the possibility of such rare malignant arrhythmias in patients using osimertinib and conduct electrocardiogram monitoring for these patients.

The mechanism of QTc prolongation caused by osimertinib is not yet fully understood. Pharmacological and toxicological studies have confirmed that osimertinib affects the cardiac repolarization process by inhibiting the cardiac potassium ion channel Kv11.1 (18). Additionally, animal model studies have shown that downregulating the PI3K signaling pathway through tyrosine kinase inhibition can affect multiple ion channels, including delayed rectifier potassium currents, L-type calcium currents, and sodium currents. This may also be one of the mechanisms by which osimertinib causes QTc prolongation (19).

This study has several limitations that need to be considered. First, this is a small-scale retrospective study conducted at a single center with a small sample size. This patient population does not routinely obtain baseline electrocardiograms, and there is currently no standardized protocol for ECG monitoring and follow-up, which may lead to selection bias. Second, the QT interval is greatly influenced by activity and circadian rhythm changes, which may cause confounding bias. However, all enrolled electrocardiograms were obtained during waking hours, and standardized heart rate correction formulas were used, which should minimize these potential confounding biases. Additionally, as a retrospective study, we were unable to directly correlate ECG changes with the patients' clinical symptoms at the time, which is a limitation. Future prospective studies are needed to further evaluate the clinical implications of QT prolongation.

QTc prolongation, particularly when exceeding 500 ms, requires careful clinical management. The 2022 ESC guidelines recommend close monitoring for patients with QTc >500 ms, and suggest the use of magnesium agents and beta-blockers to manage the risk of torsades de pointes; for cancer therapy-induced QTc prolongation, normalizing electrolytes and minimizing QT-prolonging drug use are critical strategies; these guidelines also recommend considering beta-blockers if cancer therapy is associated with cardiac toxicity (20).

This study comprehensively examines electrocardiographic changes before and after osimertinib treatment in patients with EGFR-mutated NSCLC. Our findings demonstrate that osimertinib

significantly prolongs QTc intervals in these patients. These results emphasize the importance of ECG monitoring to prevent arrhythmic events in patients receiving osimertinib therapy.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of China-Japan Union Hospital of Jilin University (Approval No: 20220118014). The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because Written informed consent was waived because this study was conducted as a retrospective analysis of existing clinical and electrocardiographic data, with no additional interventions or patient contact. The study posed minimal risk to participants, and all data were anonymized to ensure confidentiality and privacy, in accordance with institutional ethical guidelines.

Author contributions

YP: Data curation, Investigation, Methodology, Formal Analysis, Writing – original draft, Conceptualization. KP: Writing – original draft, Data curation. YJ: Data curation, Writing – original draft. PY: Supervision, Writing – original draft. BD: Validation, Funding acquisition, Resources, Writing – original draft, Visualization, Conceptualization, Supervision. YH: Validation, Supervision, Writing – original draft.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This study was supported by National Natural Science Foundation of China (No. 82470327, 82100337), Jilin Provincial Natural Science Foundation (No. YDZJ202201ZYT097) and the Project of Jilin Provincial Department of Finance (No. 2022SCZ40).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated

organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

- Ramalingam SS, Vansteenkiste J, Planchard D, Cho BC, Gray JE, Ohe Y, et al. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. *N Engl J Med.* (2020) 382:41–50. doi: 10.1056/NEJMoa1913662
- Mok TS, Wu YL, Ahn MJ, Garassino MC, Kim HR, Ramalingam SS, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med.* (2017) 376:629–40. doi: 10.1056/NEJMoa1612674
- Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med.* (2018) 378:113–25. doi: 10.1056/NEJMoa1713137
- Goss G, Tsai CM, Shepherd FA, Bazhenova L, Lee JS, Chang GC, et al. Osimertinib for pretreated EGFR Thr790Met-positive advanced non-small-cell lung cancer (AURA2): a multicentre, open-label, single-arm, phase 2 study. *Lancet Oncol.* (2016) 17:1643–52. doi: 10.1016/s1470-2045(16)30508-3
- Jänne PA, Yang JC, Kim DW, Bazhenova L, Lee JS, Chang GC, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N Engl J Med.* (2015) 372:1689–99. doi: 10.1056/NEJMoa1411817
- Li Y, Peng X, Lin R, Wang X, Liu X, Meng F, et al. Tyrosine kinase inhibitor antitumor therapy and atrial fibrillation: potential off-target effects on mitochondrial function and cardiac substrate utilization. *Cardiovasc Innov Appl.* (2023) 8. doi: 10.15212/cvia.2023.0070
- Wang X, Guo X. A rare case of a primary cardiac tumor presenting as fatal ventricular tachycardia. *Cardiovasc Innov Appl.* (2022) 7. doi: 10.15212/cvia.2022.0014
- Dumani S, Dibra L, Likaj E, Ikonomi M, Kuci S, Baboci A, et al. Calcified amorphous tumor of the mitral valve causing stroke: A rare case of heart tumor. *Heart Mind.* (2025). doi: 10.4103/hm.HM-D-24-00053
- Wu YL, Tsuboi M, He J, John T, Grohe C, Majem M, et al. Osimertinib in resected EGFR-mutated non-small-cell lung cancer. *N Engl J Med.* (2020) 383:1711–23. doi: 10.1056/NEJMoa2027071
- Akamatsu H, Toi Y, Hayashi H, Fujimoto D, Tachihara M, Furuya N, et al. Efficacy of osimertinib plus bevacizumab vs osimertinib in patients with EGFR T790M-mutated non-small cell lung cancer previously treated with epidermal growth factor receptor-tyrosine kinase inhibitor: west Japan oncology group 8715L phase 2 randomized clinical trial. *JAMA Oncol.* (2021) 7:386–94. doi: 10.1001/jamaoncol.2020.6758
- Zhang Y, Wang X, Pan Y, Du B, Nanthakumar K, Yang P. Overdrive pacing in the acute management of osimertinib-induced ventricular arrhythmias: A case report and literature review. *Front Cardiovasc Med.* (2022) 9:934214. doi: 10.3389/fcvm.2022.934214
- Anand K, Ensor J, Trachtenberg B, Bernicker EH. Osimertinib-induced cardiotoxicity: A retrospective review of the FDA adverse events reporting system (FAERS). *JACC CardioOncol.* (2019) 1:172–8. doi: 10.1016/j.jacc.2019.10.006
- Ewer MS, Tekumalla SH, Walding A, Atuah KN. Cardiac safety of osimertinib: A review of data. *J Clin Oncol.* (2021) 39:328–37. doi: 10.1200/jco.20.01171
- Matsuura C, Kato T, Koyama K. Successful management of refractory torsades de pointes due to drug-induced long QT syndrome guided by point-of-care monitoring of ionized magnesium. *Cureus.* (2021) 13:e13939. doi: 10.7759/cureus.13939
- Ikebe S, Amiya R, Minami S, Ihara S, Higuchi Y, Komuta K. Osimertinib-induced cardiac failure with QT prolongation and torsade de pointes in a patient with advanced pulmonary adenocarcinoma. *Int Cancer Conf J.* (2021) 10:68–71. doi: 10.1007/s13691-020-00450-2
- Bian S, Tang X, Lei W. A case of torsades de pointes induced by the third-generation EGFR-TKI, osimertinib combined with moxifloxacin. *BMC Pulm Med.* (2020) 20:181. doi: 10.1186/s12890-020-01217-4
- Kaira K, Ogiwara Y, Naruse I. Occurrence of ventricular fibrillation in a patient with lung cancer receiving osimertinib. *J Thorac Oncol.* (2020) 15:e54–5. doi: 10.1016/j.jtho.2019.11.029
- Jin T, Hu B, Chen S, Wang Q, Dong X, Zhang Y, et al. An *in vitro* assay of hERG K (+) channel potency for a new EGFR inhibitor FHND004. *Front Pharmacol.* (2018) 9:577. doi: 10.3389/fphar.2018.00577
- Lu Z, Wu CY, Jiang YP, Ballou LM, Clausen C, Cohen IS, et al. Suppression of phosphoinositide 3-kinase signaling and alteration of multiple ion currents in drug-induced long QT syndrome. *Sci Transl Med.* (2012) 4:131ra150. doi: 10.1126/scitranslmed.3003623
- Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J.* (2022) 43:4229–361. doi: 10.1093/eurheartj/ehac244