UDC 616.24-006.6:575.224.2]-079:577.2](479.24)
DOI: 10.14739/2310-1210.2026.1.326859

Clinical and molecular characteristics of MET gene mutations in Azerbaijani patients with non-small cell lung cancer: a retrospective analysis

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Lung cancer is the leading cause of cancer-related mortality globally, with non-small cell lung cancer (NSCLC) accounting for approximately 85 % of all cases. The *MET* proto-oncogene has emerged as a critical molecular target due to its involvement in cellular proliferation, motility, and metastasis. Among *MET* alterations, exon 14 skipping mutations have gained significant clinical relevance as actionable biomarkers in NSCLC.

Aim: to determine the frequency and clinical characteristics of *MET* gene mutations in Azerbaijani patients diagnosed with NSCLC, and to provide a detailed descriptive analysis of mutation-positive cases.

Materials and methods. This retrospective study included 187 patients with histologically confirmed NSCLC treated at the National Oncology Center (Baku, Azerbaijan) between 2014 and 2024. *MET* mutation analysis was performed on formalin-fixed paraffin-embedded (FFPE) tumor samples using real-time polymerase chain reaction (PCR) with Qiagen and EntroGen reagents. All detected mutations were subsequently validated using next-generation sequencing (NGS). Descriptive statistics were used due to the limited number of mutation-positive cases (n = 16).

Results. *MET* gene mutations were identified in 16 out of 187 patients, representing a prevalence of 8.6 %. The mean age of *MET*-positive patients was 66.5 years (range: 53–84), with a male predominance (81 %). Most patients presented with advanced-stage disease (stage III–IV: 93.7 %), and adenocarcinoma was the predominant histological subtype (93.7 %). The median overall survival was 598 days. Tobacco use was reported in 56 % of cases, and alcohol consumption in 19 %. Patients originated from diverse regions of Azerbaijan, with the majority residing in the Baku metropolitan area.

Conclusions. Despite the relatively low prevalence, the presence of *MET* mutations in Azerbaijani NSCLC patients underscores the clinical necessity of routine molecular profiling. Real-time PCR proved to be an efficient screening tool, supported by NGS validation. These findings highlight the feasibility and importance of integrating *MET* mutation testing into national oncology protocols. Larger prospective studies are required to further investigate the prognostic and therapeutic implications of *MET*-altered NSCLC in the South Caucasus population.

Keywords: MET mutation, non-small cell lung cancer, real-time PCR, NGS confirmation, molecular diagnostics, Azerbaijan.

Zaporozhye Medical Journal. 2026;28(1):25-29

Клінічне та молекулярне значення мутацій гена MET у пацієнтів із недрібноклітинним раком легень в Азербайджані: ретроспективний аналіз

Сабіна Ганбар Мехдізаде

Недрібноклітинний рак легень (НДРЛ) є провідною причиною онкологічної смертності у світі. Протоонкоген *MET*, який кодує рецептор тирозинкінази, відіграє ключову роль у клітинній проліферації, міграції та метастазуванні. Мутації з пропуском 14 екзона (exon 14 skipping) набувають клінічного значення як мішені для таргетної терапії.

Мета роботи – оцінити частоту та клінічні характеристики мутацій гена *MET* у пацієнтів із НДРЛ в Азербайджані та надати описовий аналіз виявлених випадків.

Матеріали і методи. Проаналізовано 187 парафінових зразків пухлинної тканини пацієнтів із гістологічно підтвердженим НДРЛ, які перебували на лікуванні в Національному онкологічному центрі (м. Баку, Азербайджан) у період 2014–2024 років. Молекулярний аналіз здійснили методом ПЛР у реальному часі з використанням реагентів Qiagen і EntroGen. Усі позитивні зразки додатково підтверджено за допомогою секвенування нового покоління (NGS). Через обмежену кількість позитивних випадків (n = 16) застосовано лише описову статистику.

Результати. Мутації гена *MET* виявлено у 16 із 187 пацієнтів (8,6 %). Медіана віку обстежених становила 66,5 року (діапазон – від 53 до 84 років), 81 % пацієнтів – чоловіки. У 93,7 % випадків діагностовано аденокарциному, більшість пацієнтів мали пізню стадію захворювання (III–IV). Середня загальна виживаність становила 598 днів. Куріння в анамнезі зафіксовано у 56 % пацієнтів, вживання алкоголю – у 19 %. Найбільшу кількість випадків зафіксовано в м. Баку та прилеглих регіонах.

Висновки. Незважаючи на невисоку поширеність, мутації гена *MET* у пацієнтів із НДРЛ в Азербайджані підтверджують необхідність рутинного молекулярного тестування. Метод ПЛР у реальному часі – надійний скринінговий інструмент, що підтверджено NGS. Доцільно здійснити проспективні дослідження для поглиблення знань щодо прогностичного та терапевтичного значення цих змін у популяції Південного Кавказу.

Ключові слова: мутації MET, недрібноклітинний рак легень, ПЛР у реальному часі, секвенування нового покоління, молекулярна діагностика, Азербайджан.

Запорізький медичний журнал. 2026. Т. 28, № 1(154). С. 25-29

Lung cancer (LC) continues to be the leading cause of cancer-related mortality globally, with an estimated 2.0 million new diagnoses and 1.8 million deaths annually [1]. Non-small cell lung cancer (NSCLC) accounts for approximately 85 % of all LC cases and is frequently diagnosed at advanced stages, contributing to its poor prognosis. In Azerbaijan, LC constitutes a significant portion of the national oncological burden, particularly affecting men over the age of 55 [2]. Established risk factors include active and passive tobacco exposure, occupational and environmental contact with asbestos, urban air pollution, excessive alcohol intake, and elevated indoor radon concentrations. Notably, several regions of Azerbaijan report radon levels that exceed European thresholds, potentially contributing to the increasing incidence of LC in the region [3].

In recent years, molecular profiling has become integral to NSCLC diagnostics and therapeutic decision-making. The identification of targetable genomic alterations has enabled the development of personalized treatments that improve clinical outcomes and reduce unnecessary toxicity. One of the emerging molecular targets is the *MET* (mesenchymal-epithelial transition) proto-oncogene, located on chromosome 7q31, which encodes a receptor tyrosine kinase (RTK) activated by hepatocyte growth factor (HGF). Aberrant *MET* signaling, mediated through exon 14 skipping mutations, gene amplification, or protein overexpression, promotes uncontrolled cell proliferation, resistance to apoptosis, enhanced invasiveness, and metastasis [4,5].

Among these alterations, *MET* exon 14 skipping mutations have garnered significant attention as oncogenic drivers, specifically in lung adenocarcinoma. These mutations impair normal ubiquitination and degradation of the *MET* receptor, resulting in sustained oncogenic signaling [6]. Importantly, *MET* exon 14 mutations are known to confer resistance to epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitors (TKIs), necessitating the use of alternative therapeutic strategies for affected patients [7].

The clinical relevance of *MET* amplification in NSCLC is supported by evidence that targeted *MET* inhibition, including treatment with crizotinib, results in significant antitumor activity in selected patient populations [8,9]. Moreover, interactions between *MET* alterations and immune response markers, such as *PD-L1* expression and tumor mutational burden (TMB), are being actively investigated to better understand their potential influence on immunotherapy outcomes [10].

Despite these advancements, data on *MET* gene mutations in geographically underrepresented populations, including countries in the South Caucasus, remain scarce. To date, no large-scale, population-specific study has evaluated the prevalence and clinicopathological features of *MET*-positive NSCLC in Azerbaijan. Therefore, investigating the molecular landscape of *MET* mutations in this regional context is critical for closing existing data gaps and enhancing the implementation of precision oncology in Azerbaijan.

Aim

To determine the frequency and clinical characteristics of *MET* gene mutations in Azerbaijani patients diagnosed with NSCLC, and to provide a detailed descriptive analysis of mutation-positive cases

Materials and methods

This was a retrospective observational study conducted at the National Oncology Center in Baku, Azerbaijan. The study assessed *MET* gene mutations in patients with histologically confirmed NSCLC who were diagnosed and treated between 2014 and 2024.

Tumor specimens from 187 patients with NSCLC were analyzed. All samples were formalin-fixed, paraffin-embedded (FFPE) blocks obtained during diagnostic biopsy or surgical procedures. *MET* mutation testing was performed on all 187 samples; *MET* gene alterations were detected in 16 cases (8.6 %).

Genomic DNA was extracted from FFPE samples using standard protocols. *MET* mutation analysis was initially performed using real-time PCR with commercially available kits from Qiagen and EntroGen following the manufacturers' instructions. Real-time PCR was selected due to its high specificity, cost-effectiveness, rapid turnaround time, and clinical applicability, especially to FFPE-derived nucleic acids, where DNA degradation may occur. All *MET*-positive results were subsequently validated by next-generation sequencing (NGS) platforms providing orthogonal confirmation and confirming the detected mutations to ensure methodological robustness.

Relevant demographic and clinical data were retrieved from institutional electronic medical records, including patient age, sex, tumor histology, and stage (TNM classification and overall clinical stage), as well as lifestyle factors such as tobacco smoking and alcohol consumption, coded as binary variables (1 = user, 0 = non-user).

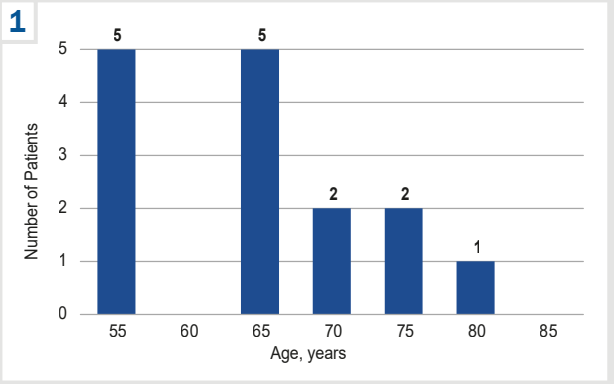
Due to the small number of cases harboring *MET* mutations, the statistical analysis was restricted to descriptive approaches. Continuous variables, including age and survival time, were summarized using means, medians, and minimum/maximum values. Categorical variables, such as sex, disease stage, and smoking status, were reported as frequencies and percentages. Consistent with the study design, no inferential statistical analyses or hypothesis testing were conducted.

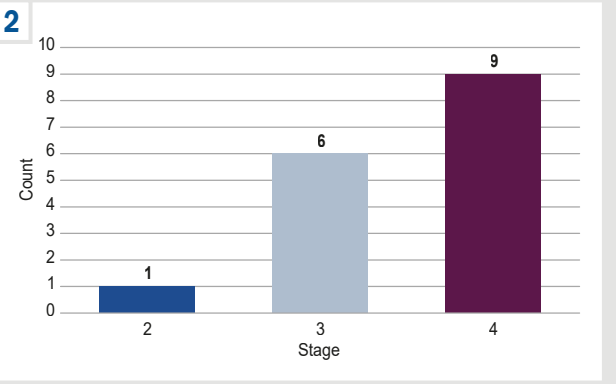
Results

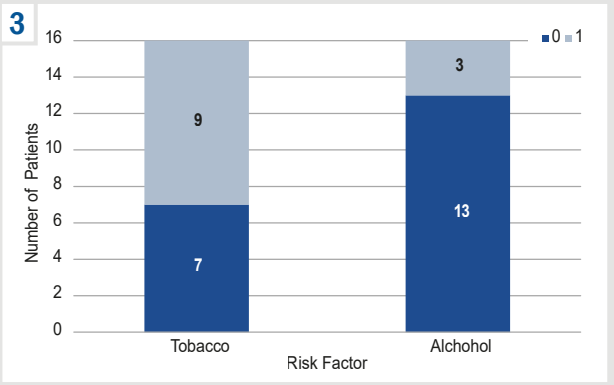
Among 187 patients with histologically confirmed NSCLC analyzed using real-time PCR, *MET* gene mutations were identified in 16 individuals, corresponding to a prevalence rate of 8.6 %. Histopathological analysis revealed a strong predominance of adenocarcinoma, which accounted for 93.7 % of *MET*-positive cases (n = 15), while squamous cell carcinoma was identified in only one patient (6.3 %). In terms of sex distribution, a significant male predominance was observed (81.2 %; 13/16), with only 3 patients (18.8 %) being female. These findings are consistent with prior epidemiological reports suggesting that *MET* alterations occur more frequently in elderly male patients with adenocarcinoma histology.

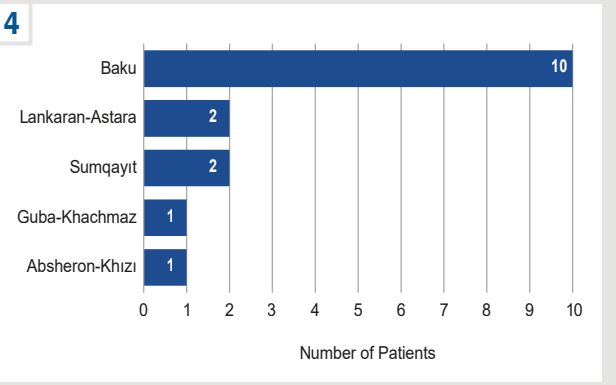
The median age of *MET*-positive patients was 66.5 years (range 53–84 years), with a mean age of 66.0 years. The majority of patients (75 %) were between 60 and 80 years of age. *Fig. 1* illustrates the age distribution, demonstrating that *MET* alterations predominantly occurred in older adults.

Clinical staging at the time of diagnosis revealed that the vast majority of *MET* mutation-positive patients presented









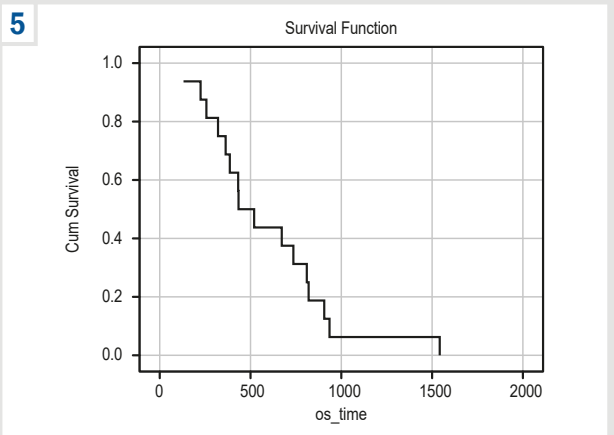


Fig. 1. Age distribution of *MET* mutation-positive NSCLC patients.

Fig. 2. Clinical stage distribution of *MET* mutation-positive NSCLC patients.

Fig. 3. Tobacco and alcohol use among *MET* mutation-positive patients.

Fig. 4. Geographic distribution of *MET*-positive cases across the economic regions of Azerbaijan.

Fig. 5. Kaplan–Meier survival estimates for *MET* mutation-positive NSCLC patients.

with advanced disease. Specifically, 15 out of 16 patients (93.7 %) were diagnosed with Stage III or IV NSCLC, with Stage IV being the most prevalent (n = 9, 56.2 %), followed by Stage III (n = 6, 37.5 %). Only one patient (6.3 %) was diagnosed at Stage II, and no cases were identified at early stages (Stage 0 or I). *Fig. 2* depicts the clinical stage distribution.

TNM classification further highlighted the advanced nature of the disease at presentation. T4 tumors were identified in 50 % of patients (n = 8), while T3 and T2 stages were each observed in 4 (25.0 %) patients. With respect to nodal involvement, N2 status was the most common (n = 9, 56.2 %), followed by N1 (n = 4, 25.0 %) and N0 (n = 3, 18.8 %). Regarding distant metastases, M1 disease was present in 9 (56.2 %) patients, and M0 in 7 (43.8 %) patients, indicating no metastatic involvement in the latter. These data underscore the characteristic late-stage presentation of *MET*-mutant NSCLC, with a high proportion of patients demonstrating both lymphatic and distant dissemination.

Tobacco use was reported by 9 out of 16 patients (56.2 %), while alcohol consumption was documented in 3 patients (18.8 %). *Fig. 3* shows the proportions of tobacco and alcohol use among *MET*-positive individuals.

The majority of patients resided within or in the proximity of the Baku metropolitan area. The regional distribution across the economic zones of Azerbaijan is illustrated in *Fig. 4*. The highest prevalence of *MET*-positive cases was observed in Baku, followed by the Lankaran–Astara and Sumgayit regions.

The estimated Kaplan–Meier survival curve for the cohort of *MET* mutation-positive NSCLC patients is presented in *Fig. 5*. This analysis was based on the interval from the date of initial diagnosis to the known date of death.

The curve demonstrates a progressive decline in survival probability over the follow-up period. The median overall survival (mOS) was 434 days, while the mean survival was 598 days. Observed survival times ranged from a minimum of 131 days to a maximum of 1542 days (approximately 4.2 years). Although the limited sample size precluded formal inferential survival modeling, this visualization provides critical descriptive insight into the clinical trajectory of this genetically defined patient population.

Discussion

In this retrospective cohort of 187 Azerbaijani patients with histologically confirmed NSCLC, *MET* gene mutations were detected in 16 individuals (8.6 %), primarily identified through real-time PCR. These findings are consistent with previously reported global prevalence estimates of 3–5 % for *MET* exon 14 skipping mutations, particularly among adenocarcinoma subtypes [4,5]. The slightly higher frequency observed in this cohort may reflect regional genetic specificities, methodological differences, or potential underreporting in neighboring countries due to limited molecular testing infrastructure.

All *MET*-positive tumors in this study were classified as either adenocarcinoma (93.7 %) or squamous cell carcinoma (6.3 %), supporting prior reports that suggest a strong predominance of *MET* alterations in non-squamous NSCLC histology. Additionally, the median age of affected individuals was 66.5 years, with the majority of patients aged between 60 and 80 years, consistent with prior studies describing *MET* mutations primarily in elderly populations [5,10]. Most mutation-positive cases were diagnosed at advanced clinical stages (stages III and IV, 93.7 %), indicating a strong association between *MET* alterations and late-stage disease presentation.

Regarding lifestyle factors, tobacco use was reported by 56.2 % of *MET*-positive patients and alcohol consumption in 18.8 %, suggesting a potential environmental component. However, given the small sample size, no definitive associations can be inferred regarding risk. Similarly, the male predominance (81.2 %) observed in our study aligns with global epidemiological patterns, though larger regional cohorts are required to confirm this finding.

The clinical significance of *MET* mutations has been reinforced by recent approvals of selective *MET* inhibitors such as capmatinib and tepotinib, both demonstrating significant clinical efficacy in patients with *MET* exon 14 skipping mutations. Nevertheless, challenges such as therapeutic resistance caused by secondary alterations (*MET* D1228V) or concurrent mutations in *EGFR* or *KRAS* continue to limit durable responses [5,6]. Consequently, routine molecular screening for *MET* alterations has become a vital component of NSCLC management algorithms, particularly for patients who are ineligible for *EGFR*-targeted therapies.

Importantly, this study presents one of the initial molecular epidemiological assessments of *MET* mutations in NSCLC within the Azerbaijani population. Given that most available data originate from Western and East Asian countries, our results provide valuable insights into the underrepresented South Caucasus region, thereby contributing to the diversification of the global oncogenomic landscape.

However, this study has several limitations. The relatively small number of *MET*-positive patients (n = 16) restricted our ability to perform robust statistical comparisons or survival modeling. Additionally, only *MET*-specific testing was performed; alterations in other clinically actionable genes (*ALK*, *EGFR*, *KRAS*, *PD-L1*) were not assessed, thereby limiting the molecular scope of the cohort. While all *MET* mutations were validated using NGS, a broader panel-based genomic profiling would provide a more comprehensive understanding of co-mutation patterns and their clinical impact.

To address these limitations, future prospective studies with larger sample sizes and expanded NGS panels are warranted. Furthermore, integrating immunologic markers such as *PD-L1* expression and TMB could help refine patient selection for immunotherapy or combination strategies. Such multi-dimensional profiling will be essential to advancing precision oncology in Azerbaijan and comparable healthcare systems in the region.

Conclusions

1. This study provides a pioneering molecular characterization of *MET* gene alterations in Azerbaijani patients with non-small cell lung cancer. A mutation prevalence of 8.6 % was identified, consisting with global data, and underscoring the role of *MET* as a clinically actionable biomarker. The higher prevalence of *MET* mutations in patients with adenocarcinoma histological subtypes and in older age groups reinforces the necessity of molecular stratification, particularly in geographically underrepresented populations.

2. Despite the limitations associated with a limited sample size, our findings support the integration of routine *MET* testing into national lung cancer diagnostic protocols. The successful application of real-time PCR in this study demonstrates its value as a cost-effective and accessible diagnostic tool, particularly in resource-constrained settings.

3. With the increasing availability of *MET*-targeted therapies, such as capmatinib and tepotinib, early identification of eligible patients through molecular testing is critical for optimizing treatment outcomes. Furthermore, by addressing the current oncogenomic data gap in the South Caucasus region, this study contributes to a more comprehensive understanding of global lung cancer genomics.

Prospects for further research. Future research should focus on larger, multicenter prospective studies incorporating broad-panel NGS and comprehensive outcome data. Such efforts will be pivotal in advancing precision oncology and improving the clinical management of lung cancer in Azerbaijan and other similarly underserved regions.

Ethical approval

The study protocol was approved by the Local Ethics Committee of Azerbaijan Medical University (Protocol No. 36, dated October 18, 2024). The study was conducted in accordance with the principles of the Declaration of Helsinki and relevant national regulations. The research involved a retrospective analysis of archived human tissue samples. All samples were fully anonymized prior to analysis, and no identifiable patient information was accessed. Due to the retrospective nature of the study and the use of anonymized archival material, the requirement for written informed consent was waived by the Ethics Committee.

Funding
This study did not receive any external or commercial funding.
All molecular analyses were performed as part of routine diagnostics within a state-funded institutional laboratory framework.

Conflicts of interest: author has no conflict of interest to declare.
Конфлікт інтересів: відсутній.

Надійшла до редакції / Received: 14.04.2025
Після доопрацювання / Revised: 26.06.2025
Схвалено до друку / Accepted: 11.07.2025

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