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# Chronological Age Is Not an Independent Determinant of Survival or Treatment Access in Metastatic Non–Small Cell Lung Cancer: A Real-World Cohort Study

**Güzide Kofalı Ayakdaş**

guzidekofali@gmail.com

Izmir City Hospital

**Kübra Canaslan**

Dokuz Eylül University

**İlhan Öztop**

Dokuz Eylül University

**Elif Atağ**

Dokuz Eylül University

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## Abstract

# Background

Older adults constitute a substantial proportion of patients with metastatic non–small cell lung cancer (NSCLC); however, the independent impact of chronological age on survival, treatment allocation, and toxicity remains controversial. This study aimed to evaluate whether age ≥ 70 years independently influences outcomes in patients with metastatic NSCLC in a real-world setting.

# Methods

We conducted a single-center, retrospective cohort study including 268 patients with metastatic NSCLC diagnosed between January 2018 and December 2022. Patients were stratified into two age groups (< 70 vs ≥ 70 years). Clinical characteristics, treatment patterns, and outcomes were analyzed. Overall survival (OS) was assessed using Kaplan–Meier methods and Cox proportional hazards models. Logistic regression was used to identify determinants of treatment omission and toxicity-related hospitalization.

# Results

The median OS for the entire cohort was 8.8 months. Patients aged ≥ 70 years had shorter unadjusted OS compared with younger patients (6.6 vs 10.3 months; p = 0.020); however, age was not an independent predictor of OS in multivariable analysis. Poor performance status, smoking exposure, and higher metastatic burden were independently associated with worse survival, whereas receipt of systemic therapy and the presence of any driver mutation were associated with improved outcomes. Chronological age did not independently predict access to systemic therapy; instead, poor performance status and cognitive impairment were the primary determinants of treatment omission. Among treated patients, older age was not associated with increased severe toxicity; notably, patients aged ≥ 70 years had lower odds of hospitalization due to treatment-related toxicity.

# Conclusions

Chronological age alone should not guide treatment decisions in metastatic NSCLC. Functional status, disease burden, smoking exposure and access to effective systemic therapy are the principal determinants of survival and treatment outcomes. Appropriately selected older adults can safely receive systemic therapy without excess severe toxicity, underscoring the importance of individualized, geriatric-informed treatment strategies.

## Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide, affecting both genders [1, 2]. Lung cancer predominantly affects the older population, a substantial proportion of all patients being 70 years of age or older at the time of diagnosis, with this proportion expected to increase over the next two decades [1, 3, 4].In older adults, non–small cell lung cancer (NSCLC) represents the most frequent histologic subtype [4] and more than 50% are diagnosed in advanced stage with 5-year survival rate of less than 20% [4–6].

Over the past decade, systemic therapy options for metastatic NSCLC have expanded substantially, including molecularly targeted therapies and immune checkpoint inhibitors (ICIs) [7, 8]. Yet the evidence base guiding treatment selection in older adults remains imperfect because patients with advanced age, multimorbidity, or frailty are commonly underrepresented in practice-defining phase III trials [9]. In real-world settings, older individuals frequently present with higher comorbidity burden, functional limitations, cognitive impairment, and polypharmacy—factors that can influence staging completeness, treatment selection, adherence, toxicity risk, and survival independently of chronological age [4, 10, 11].

However, chronological age alone may not accurately reflect functional reserve or treatment tolerance. While there is no universal biologic threshold that defines “old,” geriatric oncology has commonly operationalized older age using pragmatic cut-offs, most frequently ≥ 70 years in oncologic studies evaluating or implementing geriatric assessment [12, 13]. Due to heterogeneity of this population, factors such as performance status, comorbidity burden, cognitive function, and disease extent may be more relevant determinants of outcome than age itself [4, 10, 11, 14].

This study aimed to evaluate the independent association of chronological age with overall survival, systemic therapy patterns, and treatment-related toxicity in real-world metastatic NSCLC.

## Materials and Methods

# Study Design

This was a single-center, retrospective cohort study conducted in the Department of Medical Oncology, Dokuz Eylül University Faculty of Medicine. Consecutive patients were identified from institutional electronic medical records between January 2018 and December 2022.

## Study Population

All adult patients (≥ 18 years) with histologically confirmed non-small cell lung cancer (NSCLC) who were treated and/or followed in the medical oncology department during the study period were screened. Metastatic disease was confirmed pathologically or radiologically. Patients with de novo metastatic disease, available baseline clinical, pathological and staging data, and sufficient follow-up data to assess overall survival included. Exclusion criteria were mixed histology with small cell lung cancer, synchronous solid or hematologic malignancy, missing key data. Patients were a priori stratified into two

age groups for analysis: <70 years and ≥ 70 years at the time of metastatic diagnosis. Detailed flowchart is presented in Fig. 1.

## Data Collection

Data were collected retrospectively from electronic medical records and digital archives using a standardized case report form. Demographic and clinical characteristics (age, sex, smoking history, comorbidities, ECOG PS), tumor characteristics (histologic subtype, moleculer and immunohistochemical data, metastatic sites), and treatment-related variables (receipt of any systemic therapy, type of first-, second- and later-line systemic regimens, use of immunotherapy and tyrosine kinase inhibitors (TKIs), dose reductions, and hospitalizations due to treatment-related toxicity) were extracted.

PD-L1 expression was assessed by immunohistochemistry using the SP263 monoclonal antibody, according to the manufacturer's recommendations. EGFR, ALK and ROS1 status were evaluated by fluorescence in situ hybridization (FISH). Cognitive impairment was defined by explicit documentation in baseline oncology and/or geriatric consultation notes within the diagnostic work-up period and coded as present/absent.

## Outcomes

Overall survival (OS) was defined as the time from metastatic diagnosis to death from any cause. Patients who were alive at last contact were censored at the date of last follow-up.

# Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA) and R 4.5.2. Comparisons between age groups (< 70 vs ≥ 70 years) were made using the chi-square test or Fisher's exact test for categorical variables and the Mann–Whitney U test or Student's t-test for continuous variables, based on distribution. Age was analyzed as a binary variable (< 70 vs ≥ 70 years) in accordance with the study hypothesis. To explore determinants of treatment allocation and toxicity, multivariable logistic regression models were constructed to identify factors associated with not receiving any systemic therapy in the metastatic setting (binary outcome: treated vs not treated), and to identify predictors of hospitalization due to treatment-related toxicity among patients who received systemic therapy. Logistic regression results are presented as odds ratios (ORs) with 95% CIs. A two-sided $p < 0.05$ was considered statistically significant for all analyses. Overall survival was estimated using the Kaplan–Meier method, and survival curves were compared with the log-rank test. Variables associated with OS in univariate analysis ($p < 0.10$) or deemed clinically relevant were entered into Cox proportional hazards regression models to identify independent prognostic factors. Results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs).

### *Ethical Approval:*

The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Dokuz Eylül University Non-Interventional Research Ethics Committee (Approval No: 2023/05-28, Date: 22.02.2023). The requirement for informed consent was waived due to the retrospective nature of the study and anonymization of patient data.

## Results

### *Patient Characteristics*

A total of 268 patients with metastatic NSCLC were included (median age 65 years, range 28–89); 185 (69.0%) were <70 years and 83 (31.0%) were ≥70 years at diagnosis. Smoking exposure was substantial and similar between age groups, and sex, histologic subtype distribution and smoking status (never vs ever) did not differ significantly. In contrast, patients ≥70 years had a markedly higher comorbidity burden (any comorbidity 94.0% vs 69.2%, p<0.001), more frequent cognitive impairment (16.9% vs 5.4%, p=0.002), and worse ECOG performance status (ECOG 2–4: 57.8% vs 27.6%, p<0.001). Patterns of metastatic involvement, number of metastatic sites and the distribution of EGFR, ALK, ROS1 and PD-L1 status were broadly similar across age groups (Table 1).

Table 1. Baseline characteristics of metastatic NSCLC patients according to age group (<70 vs ≥70 years)

| Variable | All patients (n=268) | <70 years (n=185) | ≥70 years (n=83) | p value |
|---|---|---|---|---|
| **Age at diagnosis, years** | 65 (28–89) | 62 (28–69) | 75 (70–89) | <0.001 |
| **Smoking exposure (pack-years)** | 40 (1–190) | 40 (1–160) | 49 (3–190) | 0.237 |
| **Sex** | | | | 0.333 |
| Male | 216 (80.6%) | 152 (82.2%) | 64 (77.1%) | |
| Female | 52 (19.4%) | 33 (17.8%) | 19 (22.9%) | |
| **Histology** | | | | 0.163 |
| Adenocarcinoma | 177 (66.0%) | 123 (66.5%) | 54 (65.1%) | |
| Squamous cell carcinoma | 79 (29.5%) | 51 (27.6%) | 28 (33.7%) | |
| NOS | 12 (4.5%) | 11 (5.9%) | 1 (1.2%) | |
| **Smoking status** | | | | 0.665 |
| Never smoker | 29 (10.8%) | 19 (9.8%) | 10 (12.0%) | |
| Current or Ex-smoker | 239 (89.2%) | 166 (89.7%) | 73 (88.0%) | |
| **Any comorbidity present** | 206 (76.9%) | 128 (69.2%) | 78 (94.0%) | <0.001 |
| Hypertension | 115 (42.9%) | 67 (36.2%) | 48 (57.8%) | <0.001 |
| Diabetes mellitus | 65 (24.3%) | 38 (20.5%) | 27 (32.5%) | 0.034 |
| Cardiac disease | 94 (35.1%) | 46 (24.9%) | 48 (57.8%) | <0.001 |
| Chronic kidney disease (GFR <60 mL/min) | 39 (14.6%) | 18 (9.7%) | 21 (25.3%) | <0.001 |
| COPD | 94 (35.1%) | 59 (31.9%) | 35 (42.2%) | 0.103 |
| Cognitive impairment | 24 (9.0%) | 10 (5.4%) | 14 (16.9%) | 0.002 |
| **ECOG performance status** | | | | <0.001 |
| 0–1 | 169 (63.1%) | 134 (72.4%) | 35 (42.2%) | |
| 2–4 | 99 (36.9%) | 51 (27.6%) | 48 (57.8%) | |
| **Metastatic involvement** | | | | |
| Liver metastasis | 52 (19.4%) | 36 (19.5%) | 16 (19.3%) | 0.972 |
| Bone metastasis | 143 (53.4%) | 101 (54.6%) | 42 (50.6%) | 0.545 |
| Adrenal metastasis | 60 (22.4%) | 46 (24.9%) | 14 (16.9%) | 0.146 |
| Brain metastasis | 85 (31.7%) | 65 (35.1%) | 20 (24.1%) | 0.073 |

| | | | | |
|---|---|---|---|---|
| Distant lymph node metastasis | 112 (41.8%) | 82 (44.3%) | 30 (36.1%) | 0.209 |
| **Number of metastatic sites** | 2 (0–7) | 2 (0–7) | 2 (0–6) | 0.166 |
| **Molecular testing performed** | 170 (63.4%) | 118 (63.8%) | 52 (62.7%) | 0.859 |
| **EGFR mutation** (n=170) | 28/170 (16.5%) | 17/118 (14.4%) | 11/52 (21.2%) | 0.274 |
| **ALK rearrangement** (n=149) | 11/149 (7.4%) | 8/105 (7.6%) | 3/44 (6.8%) | 0.865 |
| **ROS1 rearrangement** (n=99) | 3/99 (3.0%) | 3/74 (4.1%) | 0/25 (0.0%) | 0.307 |
| **PD-L1 expression** (n=46) | | (n=33) | (n=13) | 0.630 |
| <1% | 26 (56.5%) | 18 (54.5%) | 8 (61.5%) | |
| 1–49% | 5 (10.9%) | 3 (9.1%) | 2 (15.4%) | |
| ≥50% | 15 (32.6%) | 12 (36.4%) | 3 (23.1%) | |

***Treatment characteristics***

Overall, 78.0% of patients received at least one line of systemic therapy, with younger patients more likely to be treated than those ≥70 years (82.2% vs 68.7%, p=0.014). First-line regimens differed significantly by age (p<0.001): older patients were less often treated with cisplatin-based chemotherapy and more frequently received carboplatin-based or other regimens. Second-line systemic therapy was also less commonly used in patients ≥70 years, and the total number of treatment lines in the metastatic setting was lower in this group (p=0.004). Use of immunotherapy or tyrosine kinase inhibitors (TKIs) at any line was comparable between age groups. Among treated patients, chemotherapy dose reductions were frequent in both groups, whereas hospitalization due to treatment-related toxicity was paradoxically more common in younger patients (46.7% vs 28.2%, p=0.008) (Table 2).

Table 2. Treatment characteristics of metastatic NSCLC patients (<70 vs ≥70 years)

| Variable | All patients (n=268) | <70 years (n=185) | ≥70 years (n=83) | p value |
|---|---|---|---|---|
| **Received any systemic therapy** | 209 (78.0%) | 152 (82.2%) | 57 (68.7%) | 0.014 |
| **First-line treatment** | | | | <0.001 |
| No systemic therapy | 59 (22.0%) | 33 (17.8%) | 26 (31.3%) | |
| Cisplatin-based chemotherapy | 61 (22.8%) | 54 (29.2%) | 7 (8.4%) | |
| Carboplatin-based chemotherapy | 112 (41.8%) | 77 (41.6%) | 35 (42.2%) | |
| Immunotherapy alone | 4 (1.5%) | 4 (2.2%) | 0 (0.0%) | |
| Other regimens | 32 (12.0%) | 17 (9.1%) | 15 (18.1%) | |
| **Second-line treatment** | | | | 0.034 |
| No second-line therapy | 156 (58.2%) | 96 (51.9%) | 60 (72.3%) | |
| Taxane-based therapy | 44 (16.4%) | 34 (18.4%) | 10 (12.0%) | |
| Immunotherapy | 9 (3.4%) | 7 (3.8%) | 2 (2.4%) | |
| Gemcitabine | 16 (6.0%) | 12 (6.5%) | 4 (4.8%) | |
| Other regimens | 43 (16.0%) | 36 (19.5%) | 7 (8.4%) | |
| **Third or more -line therapy** | 57 (21.3%) | 43 (23.2%) | 14 (16.9%) | 0.238 |
| **Number of systemic treatment lines in metastatic stage (median, IQR)** | 1 (1–2) | 1 (1-2) | 1 (0–2) | 0.004 |
| **Any immunotherapy (at any line)** | 21 (7.8%) | 17 (9.2%) | 4 (4.8%) | 0.218 |
| Atezolizumab | 2 (0.7%) | 1 (0.5%) | 1 (1.2%) | |
| Nivolumab | 14 (5.2%) | 11 (5.9%) | 3 (3.6%) | |
| Cemiplimab | 5 (1.9%) | 5 (2.7%) | 0 (0.0%) | |
| **TKI therapy (any TKI)** | 32 (11.9%) | 21 (11.4%) | 11 (13.3%) | 0.657 |
| EGFR inhibitor | 22 (8.2%) | 14 (7.6%) | 8 (9.6%) | |
| ALK inhibitor | 8 (3.0%) | 5 (2.7%) | 3 (3.6%) | |
| ROS1 inhibitor | 2 (0.7%) | 2 (1.1%) | 0 (0.0%) | |
| **Immune-related adverse event present, any grade** | 21 (7.8%) | 17 (9.2%) | 4 (4.8%) | 0.218 |
| **Hospitalization due to treatment-related toxicity (n=240)** | 99/240 (41.3%) | 79/169 (46.7%) | 20/71 (28.2%) | 0.008 |

| | | | | |
|---|---|---|---|---|
| **Chemotherapy dose reduction (n=209)** | 72/209 (34.4%) | 52/153 (34.0%) | 20/56 (35.7%) | 0.816 |

***Determinants of not receiving systemic therapy***

In multivariable logistic regression, chronological age ≥70 years was **not** associated with withholding systemic treatment (OR 0.92, 95% CI 0.41–2.06, *p*=0.838). Instead, the main determinants of no systemic therapy were poor performance status (ECOG 2–4 vs 0–1; OR 28.61, 95% CI 10.49–78.06, *p*<0.001) and cognitive impairment (OR 4.55, 95% CI 1.48–13.92, *p*=0.008). The number of metastatic sites showed a nonsignificant trend toward higher odds of no treatment, while comorbidity burden and the presence of any driver mutation were not independently associated with treatment omission (Table 3).

Table 3: Multivariable logistic regression analysis for not receiving systemic treatment

| Variable | OR for no treatment | 95% CI for OR | p-value |
|---|---|---|---|
| Age group (≥70 vs <70 years) | 0.92 | 0.41 – 2.06 | 0.838 |
| ECOG (2–4 vs 0–1) | 28.61 | 10.49 – 78.06 | <0.001 |
| Comorbidities (any vs none) | 0.64 | 0.21 – 1.93 | 0.431 |
| Cognitive impairment **(**Present vs absent**)** | 4.55 | 1.48 – 13.92 | 0.008 |
| Number of metastatic sites (per site) | 1.27 | 0.97 – 1.64 | 0.080 |
| Driver mutation (any, positive vs negative) | 0.65 | 0.21 – 2.02 | 0.459 |

***Treatment-related toxicity and hospitalization***

Among patients who received systemic therapy, older age was not associated with a higher risk of hospitalization due to treatment-related toxicity; notably, patients aged ≥70 years had significantly lower odds of toxicity-related hospitalization (Model 1 OR 0.43, p=0.018; Model 2 OR 0.36, p=0.007). ECOG performance status, cognitive impairment, metastatic burden and major comorbidities (cardiac disease, chronic kidney disease, COPD) were not independently associated with toxicity-related hospitalization. In the clinical model, the presence of any driver mutation was linked to a lower risk of toxicity-related hospitalization (OR 0.36, p=0.014), although this association was attenuated after additional adjustment for treatment-related variables (Table 4).

Table 4: Multivariable models evaluating factors associated with hospitalization due to treatment-related toxicity among patients receiving systemic therapy

| Variable | OR for tox-hospitalization | p-value |
|---|---|---|
| Age group (≥70 vs <70) | **0.43** | 0.018 |
| ECOG (2–4 vs 0–1) | 1.00 | 0.989 |
| Cognitive impairment (Present vs absent) | 1.74 | 0.483 |
| Number of metastatic sites (Per additional site) | 1.02 | 0.847 |
| Driver mutation (any vs negative) | **0.36** | 0.014 |
| Cardiac disease (Present vs absent) | 1.00 | 0.998 |
| Chronic kidney disease (Present vs absent) | 1.11 | 0.818 |
| COPD (Present vs absent) | 1.09 | 0.781 |

***Survival Analyses***

Median follow-up time, estimated using the reverse Kaplan–Meier method, was 48.7 months with 247 deaths. Median OS in whole cohort was 8.8 months (95% CI 6.97 – 10.63). The median overall survival was 10.3 months (95% CI, 8.2–12.3) in patients <70 years and 6.6 months (95% CI, 4.9–8.3) in those ≥70 years (p=0.020) (Figure 2).

Figure 2: Overall survival according to age groups

In univariate Cox analysis, age ≥70 years, history of smoking exposure, ECOG 2–4, bone and brain metastases, and increasing number of metastatic sites were all associated with worse OS, whereas the presence of any driver mutation, receipt of systemic treatment, use of immunotherapy and use of TKIs were associated with improved survival (all $p \leq 0.040$). Histologic subtype, comorbidity status, liver or adrenal metastases, individual EGFR/ALK/ROS1 alterations and PD-L1 expression were not significantly associated with OS (Table 5).

Table 5: Univariate Cox regression analysis for mortality

| Variable | HR | 95% CI for HR | p-value |
|---|---|---|---|
| **Age group (**≥70 vs <70 years) | 1.37 | 1.05 – 1.80 | 0.021 |
| **Sex (**Female vs male**)** | 0.69 | 0.50 – 0.95 | 0.024 |
| **Histologic subtype (**Adenocarcinoma vs SCC) | 1.00 | 0.76 – 1.32 | 0.980 |
| **Smoking status** (Any exposure vs never) | 2.29 | 1.45 – 3.61 | <0.001 |
| **Comorbidities (**Any vs none) | 1.18 | 0.87 – 1.58 | 0.282 |
| **ECOG (**2–4 vs 0–1**)** | 2.60 | 2.00 – 3.38 | <0.001 |
| **Liver metastasis (**Present vs absent**)** | 1.20 | 0.87 – 1.64 | 0.268 |
| **Bone metastasis (**Present vs absent**)** | 1.55 | 1.21 – 2.00 | <0.001 |
| **Adrenal metastasis (**Present vs absent**)** | 1.18 | 0.88 – 1.59 | 0.279 |
| **Brain metastasis (**Present vs absent**)** | 1.32 | 1.01 – 1.73 | 0.040 |
| **Number of metastatic sites (**Per additional site**)** | 1.17 | 1.07 – 1.27 | <0.001 |
| **EGFR mutation*** (Positive vs negative) | 0.65 | 0.42 – 1.01 | 0.057 |
| **ALK rearrangement*** (Positive vs negative) | 0.65 | 0.33 – 1.28 | 0.212 |
| **ROS1 rearrangement*** (Positive vs negative) | 0.37 | 0.09 – 1.51 | 0.165 |
| **Driver mutation (any)** (Positive vs negative) | 0.55 | 0.38 – 0.79 | 0.001 |
| **PD-L1 expression (>1% vs <1%)** | 1.10 | 0.57 – 2.13 | 0.763 |
| **Any systemic treatment (**Treated vs no treatment) | 0.31 | 0.23 – 0.42 | <0.001 |
| **Immunotherapy (any IO) (**yes vs no**)** | 0.24 | 0.13 – 0.45 | <0.001 |
| **Tyrosine kinase inhibitor (TKI) (**yes vs no) | 0.47 | 0.31 – 0.71 | <0.001 |

In multivariable analysis, age ≥70 years was **not** an independent predictor of OS in either model (Model 1 HR 1.27, 95% CI 0.95–1.69, $p$=0.107; Model 2 HR 1.23, 95% CI 0.92–1.64, $p$=0.162). Across both models, ever-smoking, poorer ECOG performance and higher number of metastatic sites consistently predicted higher mortality, while the presence of any driver mutation remained associated with better survival (borderline in Model 2). Receipt of systemic treatment was strongly and independently associated with improved OS (HR 0.39, 95% CI 0.26–0.56, $p$<0.001) (Table 6).

Table 6: Multivariate Cox regression for mortality

| Variable | HR | 95% CI | p-value |
|---|---|---|---|
| Model 1 | | | |
| Age group (≥70 vs <70 years) | **1.27** | 0.95 – 1.69 | 0.107 |
| Sex (Female vs male) | 0.87 | 0.60 – 1.25 | 0.444 |
| Histology (Adeno vs SCC) | 0.84 | 0.63 – 1.13 | 0.246 |
| Smoking (Any exposure vs never) | **1.75** | 1.07 – 2.87 | 0.026 |
| Comorbidities (any vs none) | 0.90 | 0.65 – 1.25 | 0.527 |
| ECOG (2–4 vs 0–1) | **2.34** | 1.76 – 3.12 | <0.001 |
| Number of metastatic sites (per site) | **1.23** | 1.12 – 1.34 | <0.001 |
| Driver mutation (any, positive vs negative) | **0.66** | 0.44 – 0.99 | 0.045 |
| Model 2 | | | |
| Age group (≥70 vs <70 years) | 1.23 | 0.92 – 1.64 | 0.162 |
| Sex (Female vs male) | 0.92 | 0.64 – 1.32 | 0.641 |
| Histology (Adeno vs SCC) | 0.85 | 0.63 – 1.13 | 0.262 |
| Smoking (Any exposure vs never) | **1.96** | 1.18 – 3.26 | 0.009 |
| Comorbidities (any vs none) | 0.87 | 0.63 – 1.22 | 0.429 |
| ECOG (2–4 vs 0–1) | **1.67** | 1.19 – 2.35 | 0.003 |
| Number of metastatic sites (per site) | **1.26** | 1.15 – 1.38 | <0.001 |
| Driver mutation (any, positive vs negative) | **0.66** | 0.44 – 1.00 | 0.048 |
| Any systemic treatment (yes vs no) | **0.39** | 0.26 – 0.56 | <0.001 |

# Discussion

In this single-center real-world cohort of 268 patients with de novo metastatic NSCLC, chronological age ≥70 years was not an independent determinant of overall survival (OS) or access to systemic therapy after adjustment for key clinical and disease-related factors. Although older patients had shorter crude OS and were treated less often, they also presented with greater comorbidity burden, worse ECOG performance status, and more frequent cognitive impairment—features that plausibly explain unadjusted age differences and are consistent with prior geriatric oncology literature [15-18]. After multivariable adjustment, smoking exposure, ECOG performance status, metastatic burden, and receipt of systemic therapy remained the principal drivers of OS, supporting the concept that functional reserve and disease extent outweigh chronological age in prognostic assessment [13, 19, 20].

A key observation was that age ≥70 years was not independently associated with withholding systemic treatment, whereas poor performance status and cognitive impairment were the predominant determinants of treatment omission. This aligns with prior evidence that impaired ECOG status and geriatric vulnerabilities limit treatment receipt in advanced NSCLC and older cancer populations, and underscores the need to anchor decision-making in functional and cognitive domains rather than age alone [15, 21, 22]. Notably, the lack of an independent effect of comorbidity burden on treatment allocation is compatible with the view that comorbidities often influence outcomes indirectly through functional impairment and treatment deliverability rather than acting as stand-alone determinants [16, 17].

Consistent with real-world reports, older patients were less likely to proceed to later lines of therapy [16, 23]. Regarding regimen selection, the higher use of carboplatin-based or non-platinum approaches in older adults reflects routine tailoring and is concordant with data showing broadly comparable efficacy between cisplatin- and carboplatin-based regimens but higher morbidity and hospitalization risk with cisplatin, particularly in vulnerable patients [24, 25]. Despite lower overall treatment intensity, age-group differences in ICIs and TKI use were not prominent; when appropriately selected, older adults can achieve acceptable tolerability with ICIs, consistent with contemporary real-world and comparative data [26-28]. The absence of major age-related differences in driver alterations or PD-L1 expression should be interpreted cautiously: while prior studies suggest molecular profile may differ by age [29, 30], molecular testing and PD-L1 assessment were incomplete in our cohort, limiting inference.

Among treated patients, older age was not associated with higher hospitalization due to treatment-related toxicity; paradoxically, toxicity-related hospitalization was less frequent in patients ≥70 years. A plausible explanation for this “toxicity paradox” is selection and treatment tailoring in routine practice (selection bias), whereby treated older patients likely represent a fitter subgroup, while younger patients may receive more intensive strategies and more subsequent lines, increasing the probability of inpatient complications [4, 31]. In addition, our toxicity endpoint captured only events requiring hospitalization; outpatient-managed or lower-grade adverse events could not be reliably ascertained retrospectively and were therefore not captured, potentially underestimating the overall toxicity burden.

In univariate analyses, age ≥70 years was associated with poorer OS; however, this association was largely attenuated after adjustment, consistent with confounding by clustered adverse clinical features in older patients. Poor ECOG status, metastatic burden, and the presence of bone and brain metastases remained key adverse prognostic factors, whereas exposure to effective systemic therapy, particularly ICIs and TKIs, and driver mutation positivity were associated with improved survival, supporting a treatment-access–centered interpretation of age disparities [28, 31-33]. Overall, our findings are concordant with established prognostic index work showing that the apparent impact of age is largely mediated through function, disease burden, and treatment-related variables, and we extend this literature by demonstrating that receipt of systemic therapy is a dominant, independent determinant of survival after accounting for host and tumor characteristics [19, 20].

Interpretation of biomarker and treatment-pattern findings must also acknowledge healthcare-system constraints. During 2018–2022, ICIs were not reimbursed by the national health insurance system in Türkiye; consequently, PD-L1 testing was performed in only a minority of patients and ICI exposure was largely limited to clinical trials or out-of-pocket access, implying that ICI use may have been shaped by socioeconomic and structural factors rather than tumor biology alone. As reimbursement and biomarker testing availability evolve, future cohorts may show different treatment allocation patterns.

Strengths include restriction to a relatively homogeneous de novo metastatic population and the single-center design, supporting consistency in diagnostic and supportive-care practices and enhancing interpretability in routine care. Limitations include the retrospective design with potential residual confounding, incomplete biomarker testing, and toxicity ascertainment limited to hospitalization-requiring events. PD-L1 and molecular testing were incomplete, therefore between-group comparisons are underpowered and prone to selection bias. Despite these limitations, the present analysis provides clinically relevant real-world evidence supporting an individualized, geriatric-informed and treatment-centered approach to metastatic NSCLC, emphasizing functional reserve and access to effective systemic therapy rather than chronological age alone [13, 15, 21, 22].

# Conclusion

In this real-world, single-center cohort of patients with metastatic denovo NSCLC, chronological age ≥70 years was not an independent determinant of overall survival, access to systemic therapy, or treatment-related toxicity requiring hospitalization after adjustment for key clinical and disease-related factors. Although older patients demonstrated shorter unadjusted survival and were less likely to receive systemic treatment, these differences were largely explained by poorer performance status, higher metastatic burden, smoking exposure, and cognitive impairment rather than age itself. Importantly, receipt of systemic therapy emerged as the strongest predictor of improved survival, and appropriately selected older patients did not experience excess severe toxicity, supporting the safety of treatment in this population.

Collectively, these findings reinforce that prognosis and treatment decisions in metastatic NSCLC should be guided by functional reserve, disease extent, and treatment feasibility rather than chronological age alone. Incorporation of geriatric-informed assessment into routine clinical practice may help optimize treatment allocation and outcomes for older adults with advanced NSCLC, avoiding both undertreatment and unnecessary toxicity.

# Declarations

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# Figures

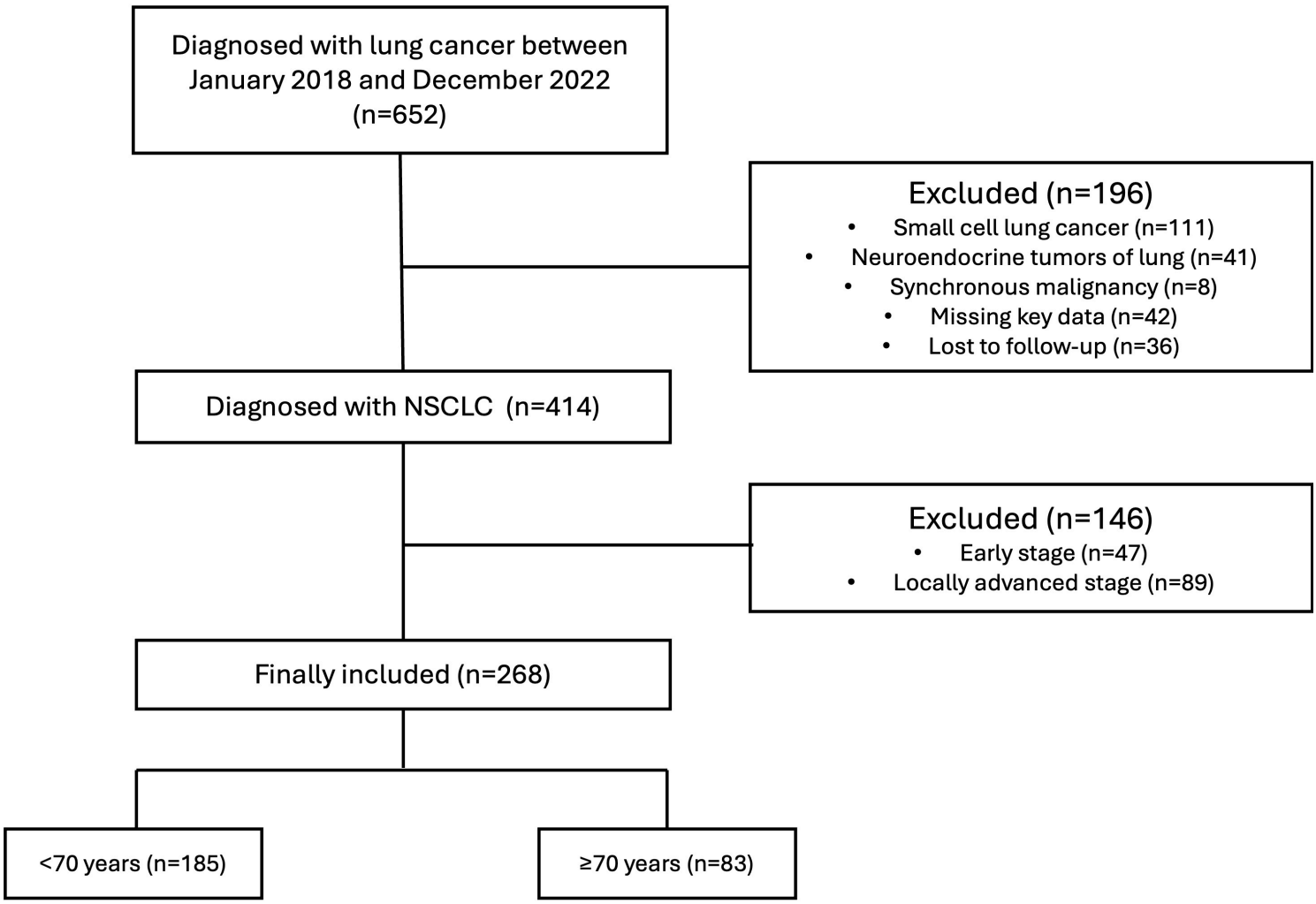



**Figure 1**

Flowchart of patient selection

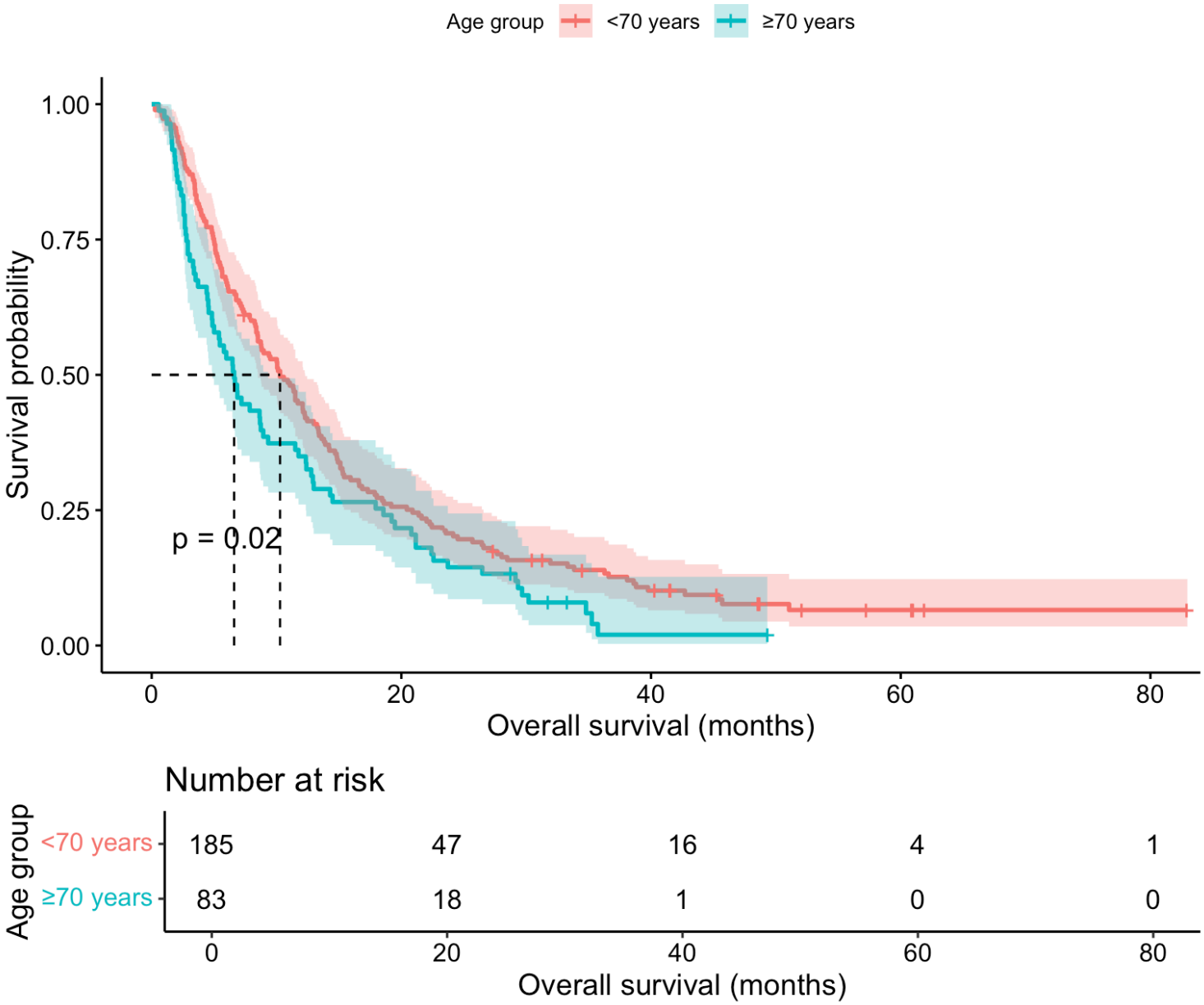



**Figure 2**

Overall survival according to age groups