Prognostic impact of chronological age on efficacy of immune checkpoint inhibitors in non-small-cell lung cancer: Real-world data from 86 173 patients

Shinkichi Takamori1 | Mototsugu Shimokawa2,3 | Takefumi Komiya4

Abstract
Immune checkpoint inhibitors (ICIs) have become standard pharmacological therapies in patients with non-small-cell lung cancer (NSCLC). Because elderly patients with NSCLC are often excluded from clinical trials as a result of lower functional capacity or comorbidities, the prognostic impact of chronological age on the efficacy of ICIs is unclear. The National Cancer Database was queried for stage IV NSCLC patients between 2014 and 2015. Associations between ICI therapy and clinical characteristics were assessed using chi-squared tests. Kaplan–Meier curves were compared using the log-rank test. A Cox proportional hazards model was used to identify clinical characteristics predictive of overall survival (OS). This study included 24 136 patients with stage IV NSCLC aged ≥75 years and 62 037 patients with stage IV NSCLC aged <75 years. Patients aged ≥75 years treated with ICIs had significantly longer OS than those not treated with ICIs (hazard ratio [HR] 0.61, 95% confidence interval [CI] 0.58–0.64, p < 0.0001). The corresponding HR in patients aged <75 years was 0.67 (95% CI 0.65–0.68, p < 0.0001). Cox modeling confirmed the survival benefit of ICI therapy in patients aged ≥75 years (HR for patients not receiving ICIs 1.63 [95% CI: 1.55–1.71], p < 0.0001). The corresponding HR in patients aged <75 years was 1.47 (95% CI 1.43–1.51, p < 0.0001). Chronological age does not appear to negatively impact the survival benefit of ICI therapy in patients with stage IV NSCLC according to this large real-world database analysis.

KEYWORDS
age, immune checkpoint inhibitor, non-small-cell lung cancer, programmed cell death-1, survival

INTRODUCTION
Lung cancer has one of the highest case-fatality rates of all malignancies, and non-small-cell lung cancer (NSCLC) accounts for 85% of lung cancers. Immune checkpoint inhibitors (ICIs) targeting programmed cell death-1 (PD-1) or programmed cell death-ligand 1 (PD-L1) have been widely adopted for therapy of NSCLC. Because the small number of elderly patients with NSCLC included in the clinical trials of these drugs, the efficacy of ICIs among elderly patients with NSCLC remains unclear. The age-dependent loss of immune function is called immune senescence and is associated with decreased immune surveillance functions of both innate and adaptive immunity. Aging is associated with decreased antigen presentation by dendritic cells, decreased numbers of naïve CD8+ T cells, and reduced chemotaxis by neutrophils and macrophages. Given the potential for immune senescence, the efficacy of ICIs in elderly patients remains controversial. The aim of the current study was to clarify whether chronological age was a significant prognostic factor in patients with advanced NSCLC treated with ICIs using real-world data from the National Cancer Database (NCDB).
METHODS

NCDB

The NCDB is a joint project between the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The CoC NCDB and the participating hospitals were the sources of the de-identified data used herein. These organizations have not verified the data and are not responsible for the statistical validity of the data analysis nor the conclusions derived by the authors.

| TABLE 1 | Clinical characteristics of patients with stage IV non-small-cell lung cancer aged <75 and ≥75 years (n = 86 173) |
|---------|---------------------------------------------------------------------------------------------------|
| Factors | <75 years old (n = 62 037) | ≥75 years old (n = 24 136) |
| Immune checkpoint inhibitor | Yes (n = 8968) | No (n = 53 069) | | Yes (n = 2241) | No (n = 21 895) |
| Sex | | | | | | | p value | | | p value |
| Male | 4645 (14%) | 28 309 (86%) | 0.0067 | 1222 (10%) | 11 211 (90%) | 0.0027 |
| Female | 4323 (15%) | 24 760 (85%) | 1019 (9%) | 10 684 (91%) | 0.0272 |
| Race | | | | | | | 0.3131 | | | 0.1877 |
| Whites | 7424 (15%) | 42 528 (85%) | <0.0001 | 1973 (9%) | 18 910 (91%) | |
| Others | 1544 (13%) | 10 541 (87%) | 268 (8%) | 2985 (92%) | |
| Institution | | | | | | | | | | |
| Others | 5916 (15%) | 34 715 (85%) | 1560 (9%) | 15 535 (91%) | 0.1877 |
| Academic | 3052 (14%) | 18 354 (86%) | 681 (10%) | 6360 (90%) | |
| Charlson–Deyo score | | | | | | | | | | |
| ≥2 | 909 (12%) | 6791 (88%) | <0.0001 | 342 (8%) | 3753 (92%) | 0.0247 |
| ≤1 | 8059 (15%) | 46 278 (85%) | 1899 (9%) | 18 142 (91%) | |
| Year of diagnosis | | | | | | | | | | |
| 2014 | 3754 (12%) | 27 238 (88%) | <0.0001 | 786 (7%) | 11 155 (93%) | <0.0001 |
| 2015 | 5214 (17%) | 25 831 (83%) | 1455 (12%) | 10 740 (88%) | |
| Histology | | | | | | | | | | |
| Others | 2430 (10%) | 21 293 (90%) | <0.0001 | 694 (7%) | 12 826 (93%) | <0.0001 |
| Adenocarcinoma NOS | 6538 (17%) | 31 776 (83%) | 1547 (12%) | 9069 (88%) | |
| Nodal status | | | | | | | | | | |
| N0 | 2211 (13%) | 15 375 (87%) | <0.0001 | 719 (8%) | 8308 (92%) | <0.0001 |
| ≥N1 | 6757 (15%) | 37 694 (85%) | 1522 (10%) | 13 587 (90%) | |
| Brain metastasis | | | | | | | | | | |
| Yes | 709 (9%) | 7295 (91%) | <0.0001 | 89 (5%) | 1682 (95%) | <0.0001 |
| No | 8259 (15%) | 45 774 (85%) | 2152 (10%) | 20 213 (90%) | |
| Bone metastasis | | | | | | | | | | |
| Yes | 1403 (14%) | 8520 (86%) | 0.3343 | 303 (8%) | 3337 (92%) | 0.0301 |
| No | 7565 (15%) | 44 549 (85%) | 1938 (9%) | 18 558 (91%) | |
| Liver metastasis | | | | | | | | | | |
| Yes | 464 (11%) | 3692 (89%) | <0.0001 | 97 (6%) | 1448 (94%) | <0.0001 |
| No | 8504 (15%) | 49 377 (85%) | 2144 (9%) | 20 447 (91%) | |
| Surgery for primary lesion | | | | | | | | | | |
| Yes | 225 (11%) | 1773 (89%) | <0.0001 | 38 (8%) | 418 (92%) | 0.5155 |
| No | 8743 (15%) | 51 296 (85%) | 2203 (9%) | 21 477 (91%) | |
| Radiation | | | | | | | | | | |
| Yes | 4479 (14%) | 28 430 (86%) | <0.0001 | 865 (9%) | 8314 (91%) | 0.5680 |
| No | 4489 (15%) | 24 639 (85%) | 1376 (9%) | 13 581 (91%) | |
| Chemotherapy | | | | | | | | | | |
| Yes | 7398 (17%) | 34 928 (83%) | <0.0001 | 1444 (13%) | 9752 (87%) | <0.0001 |
| No | 1570 (8%) | 18 141 (92%) | 797 (6%) | 12 143 (94%) | |

Abbreviation: NOS, not otherwise specified.
Statistical analyses

Clinical characteristics were summarized using contingency tables. The associations between ICI (yes vs. no) and clinical demographics were compared using the chi-squared test. Survival curves were evaluated using the Kaplan–Meier method and compared between the two groups using the log-rank test. The hazard ratios (HR) for survival between groups with 95% confidence intervals (CI) were estimated using Cox proportional hazards models. A Cox proportional hazards model was used to identify the independent prognostic factor. All Cox proportional hazards analyses were performed using JMP 14.0 (SAS Institute Inc.). \( p < 0.05 \) was considered statistically significant.

RESULTS

Patient characteristics

A total of 86,173 patients with stage IV NSCLC were selected for the analysis. Among patients aged <75 years, 8,968 of 62,037 (14.5%) received ICIs, whereas 2,241 of 24,136 (9.3%) patients aged \( \geq 75 \) years received ICIs. The relationships between administration of ICIs and clinical factors, stratified by chronological age (\( \geq 75 \) vs. <75 years), are shown in Table 1.

Univariate survival analyses of patients with stage IV NSCLC treated with or without ICIs stratified by chronological age

Kaplan–Meier curves of OS among patients with stage IV NSCLC stratified by chronological age are shown in Figure 1. Among patients aged <75 years, those who received ICIs had significantly longer OS than those who did not receive ICIs (median OS 14.5 vs. 7.8 months, HR 0.67 [95% CI 0.65–0.68], \( p < 0.0001 \); Figure 1(a)). Similarly, among patients aged \( \geq 75 \) years, those who received ICIs had significantly longer OS than those who did not receive ICIs (median OS 11.9 vs. 5.4 months, HR 0.61 [95% CI 0.58–0.64], \( p < 0.000 \); Figure 1(b)).

Univariate and multivariate analyses of OS among patients with stage IV NSCLC aged <75 and \( \geq 75 \) years

The results of univariate and multivariate analyses of OS among patients with stage IV NSCLC aged <75 and \( \geq 75 \) years are shown in Table 2. Multivariate analysis of OS among patients aged <75 years demonstrated that male sex, white race, uninsured status, nonacademic institution, Charlson-Deyo score \( \geq 2 \), diagnosis in 2014, nonadenocarcinoma not otherwise specified [NOS] histology, nodal status \( \geq N1 \), bone metastasis, liver metastasis, no surgery of the primary lesion, radiation, chemotherapy, and no ICI therapy were independent predictors of shorter OS (HR for patients not receiving ICIs 1.47 [95% CI 1.43–1.51], \( p < 0.0001 \); Table 2). Among patients aged \( \geq 75 \) years, multivariate analysis of OS showed that male sex, white race, nonacademic institution, Charlson-Deyo score \( \geq 2 \), diagnosis in 2014, nonadenocarcinoma NOS histology, nodal status \( \geq N1 \), brain metastasis, bone metastasis, liver metastasis, no surgery of the primary lesion, chemotherapy, and no ICI therapy were independent predictors of shorter OS (HR for patients not receiving ICIs 1.63 [95% CI 1.55–1.71], \( p < 0.0001 \); Table 2). In multivariate analyses, both no chemotherapy and no ICI therapy were independent predictors of shorter OS in patients with stage IV NSCLC aged <75 and \( \geq 75 \) years.
### TABLE 2  Multivariate analyses of overall survival in patients with stage IV non-small-cell lung cancer aged <75 and ≥75 years

| Factors                        | <75 years old (n = 62 037) | ≥75 years old (n = 24 136) |
|-------------------------------|-----------------------------|-----------------------------|
|                               | Univariate                  | Multivariable               | Univariate                  | Multivariable               |
|                               | HR (95% CI)                 | p value                     | HR (95% CI)                 | p value                     |
|                               | HR (95% CI)                 | p value                     | HR (95% CI)                 | p value                     |
| Sex                           |                             |                             |                             |                             |
| Male                          | 1.27 (1.24–1.29)            | <0.0001                     | 1.17 (1.14–1.21)            | <0.0001                     |
| Female                        |                             |                             |                             |                             |
| Race                          |                             |                             |                             |                             |
| Whites                        | 1.13 (1.11–1.16)            | <0.0001                     | 1.16 (1.11–1.21)            | <0.0001                     |
| Others                        |                             |                             |                             |                             |
| Race                          |                             |                             |                             |                             |
| Whites                        | 1.14 (1.11–1.17)            | <0.0001                     | 1.16 (1.11–1.21)            | <0.0001                     |
| Others                        |                             |                             |                             |                             |
| Race                          |                             |                             |                             |                             |
| Whites                        | 1.14 (1.11–1.17)            | <0.0001                     | 1.16 (1.11–1.21)            | <0.0001                     |
| Others                        |                             |                             |                             |                             |
| Insurance status              |                             |                             |                             |                             |
| Uninsured                     | 1.12 (1.07–1.18)            | <0.0001                     | 1.01 (0.80–1.25)            | 1.16 (0.94–1.46)            |
| Insured                       |                             | 0.0118                      | 0.9307                      | 0.1906                      |
| Institution                   |                             |                             |                             |                             |
| Others                        | 1.20 (1.17–1.22)            | <0.0001                     | 1.18 (1.14–1.21)            | <0.0001                     |
| Academic                      |                             |                             |                             |                             |
| Charlson–Deyo score           |                             |                             |                             |                             |
| ≥2                            | 1.37 (1.33–1.40)            | <0.0001                     | 1.33 (1.28–1.38)            | <0.0001                     |
| ≤1                            | 1.26 (1.23–1.30)            | <0.0001                     | 1.22 (1.18–1.27)            | <0.0001                     |
| Year of diagnosis             |                             |                             |                             |                             |
| 2014                          | 1.05 (1.03–1.07)            | <0.0001                     | 1.04 (1.01–1.07)            | 0.91 (0.88–0.94)            |
| 2015                          |                             | 0.0088                      |                             |                             |
| Histology                     |                             |                             |                             |                             |
| Others                        | 1.23 (1.21–1.25)            | <0.0001                     | 1.14 (1.11–1.17)            | 1.05 (1.02–1.08)            |
| Adenocarcinoma not otherwise specified |                   | <0.0001                     |                             |                             |
| Nodal status                  |                             |                             |                             |                             |
| ≥N1                           | 1.22 (1.19–1.24)            | <0.0001                     | 1.17 (1.14–1.21)            | <0.0001                     |
| N0                            |                             | 0.2439                      |                             |                             |
| Brain metastasis              |                             |                             |                             |                             |
| Yes                           | 1.09 (1.06–1.12)            | <0.0001                     | 1.24 (1.18–1.31)            | 1.25 (1.18–1.32)            |
| No                            |                             | 0.2439                      |                             |                             |
| Bone metastasis               |                             |                             |                             |                             |
| Yes                           | 1.24 (1.21–1.27)            | <0.0001                     | 1.17 (1.13–1.22)            | 1.20 (1.15–1.25)            |
| No                            |                             | 0.2439                      |                             |                             |
| Liver metastasis              |                             |                             |                             |                             |
| Yes                           | 1.45 (1.40–1.50)            | <0.0001                     | 1.32 (1.25–1.39)            | 1.26 (1.19–1.33)            |
| No                            |                             | 0.2439                      |                             |                             |
| Surgery for primary lesion    |                             |                             |                             |                             |
| No                            | 2.02 (1.90–2.14)            | <0.0001                     | 1.85 (1.66–2.08)            | 1.83 (1.64–2.06)            |
| Yes                           |                             | 0.2439                      |                             |                             |
| Radiation                     |                             |                             |                             |                             |
| Yes                           | 1.10 (1.08–1.12)            | <0.0001                     | 1.06 (1.03–1.09)            | 1.00 (0.98–1.04)            |
| No                            |                             | 0.2439                      |                             |                             |
| Chemotherapy                  |                             |                             |                             |                             |
| No                            | 2.19 (2.15–2.23)            | <0.0001                     | 2.11 (2.05–2.17)            | 2.18 (2.12–2.24)            |
| Yes                           |                             | 0.2439                      |                             |                             |
(Continues)
In multivariate analyses, the HRs for patients not receiving chemotherapy were greater than those for patients not receiving ICI in patients with stage IV NSCLC aged $<75$ and $\geq 75$ years. One of the explanations of this phenomenon is that cytotoxic chemotherapy is generally not suitable for frail patients and/or those with poor performance status due to their increased incidence of adverse events, but ICI may be a potential treatment option for such population. Therefore, patients receiving ICI may have included more frail patients compared with those treated with chemotherapy. Such bias arising from patients’ selection may potentially result in the greater HR for patients not receiving chemotherapy. In addition, NCDB lacks data about names of medications, dose, and number of cycles, so detailed subset analysis cannot be conducted. These points make it difficult to compare the HRs of patients who received chemotherapy and those with ICI. Further advanced analysis is needed to determine the clinical impact of chemotherapy and that of ICI.

Our study had several limitations. First, the NCDB lacks several prognostic factors, including performance status, PD-L1 expression level, genetic mutation status, laboratory data, line of therapy, and immune-related adverse events. Analyses including these factors may further elucidate correlates of the safety and efficacy of ICIs in elderly NSCLC patients. Second, this was a retrospective study and potential biases associated with physician decisions and/or patient status cannot be ruled out. Our findings should be validated in future well-designed prospective studies.

In conclusion, the present study showed that chronological age does not appear to impact the survival benefit of ICIs in patients with stage IV NSCLC. These findings should be validated in future prospective studies.

**ACKNOWLEDGMENTS**

We thank Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript. The publication fee was supported by the Kaibara Morikazu Medical Science Promotion Foundation.

**CONFLICT OF INTEREST**

Takefumi Komiya received travel fees from Merck. All authors declare no conflicts of interest associated with this study.
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How to cite this article: Takamori S, Shimokawa M, Komiya T. Prognostic impact of chronological age on efficacy of immune checkpoint inhibitors in non-small-cell lung cancer: Real-world data from 86 173 patients. Thorac Cancer. 2021;12:2943–8. https://doi.org/10.1111/1759-7714.14178