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BRIEF REPORT

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

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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.[1] 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.[2–7] Because of 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.[8,9] 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.[10] Aging is associated with decreased antigen presentation by dendric cells, decreased numbers of naïve $CD8^+$ T cells, and reduced chemotaxis by neutrophils and macrophages.[10,11] 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 ($n = 86\,173$)

	<75 years old ($n = 62\,037$)			≥75 years old ($n = 24\,136$)		
	Immune checkpoint inhibitor			Immune checkpoint inhibitor		
Factors	**Yes ($n = 8968$)**	**No ($n = 53\,069$)**	***p* value**	**Yes ($n = 2241$)**	**No ($n = 21\,895$)**	***p* value**
Sex						
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%)	
Race						
Whites	7424 (15%)	42 528 (85%)	<0.0001	1973 (9%)	18 910 (91%)	0.0272
Others	1544 (13%)	10 541 (87%)		268 (8%)	2985 (92%)	
Institution						
Others	5916 (15%)	34 715 (85%)	0.3131	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

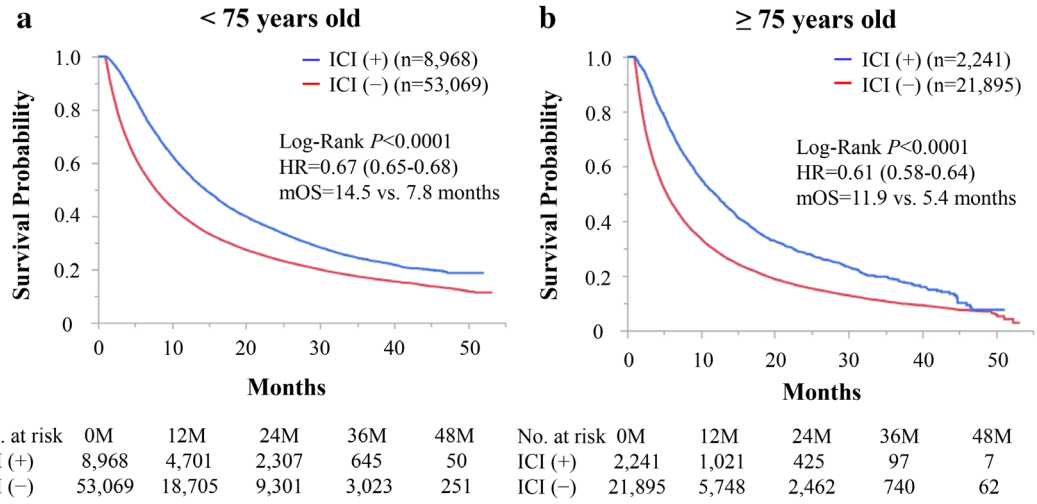
A total of 86 173 patients with stage IV NSCLC were selected for the analysis. Among patients aged <75 years, 8968 of 62 037 (14.5%) received ICIs, whereas 2241 of 24 136 (9.3%) patients aged ≥75 years received ICIs. The relationships between administration of ICIs and clinical factors, stratified by chronological age (≥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 ≥75 years, those who received ICIs had significantly longer OS than the 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 ≥75 years

The results of univariate and multivariate analyses of OS among patients with stage IV NSCLC aged <75 and ≥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 ≥ 2, diagnosis in 2014, nonadenocarcinoma not otherwise specified [NOS] histology, nodal status ≥ 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 ≥75 years, multivariate analysis of OS showed that male sex, white race, nonacademic institution, Charlson-Deyo score ≥ 2, diagnosis in 2014, nonadenocarcinoma NOS histology, nodal status ≥ 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



No. at risk	0M	12M	24M	36M	48M
ICI (+)	8,968	4,701	2,307	645	50
ICI (−)	53,069	18,705	9,301	3,023	251

No. at risk	0M	12M	24M	36M	48M
ICI (+)	2,241	1,021	425	97	7
ICI (−)	21,895	5,748	2,462	740	62

FIGURE 1 Kaplan–Meier curves of overall survival (OS) among patients with stage IV non-small-cell lung cancer treated with immune checkpoint inhibitors (ICIs) stratified by chronological age. (a) Among patients aged <75 years, those receiving ICIs had significantly longer OS than those who did not receive ICIs. (b) Among patients aged ≥75 years, those receiving ICIs had significantly longer OS those who did not receive ICIs. Hr, hazard ratio; mOS, median overall survival

TABLE 2 Multivariate analyses of overall survival in patients with stage IV non-small-cell lung cancer aged <75 and ≥75 years

	<75 years old ($n = 62\,037$)		≥75 years old ($n = 24\,136$)	
	Univariate	Multivariable	Univariate	Multivariable
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Factors	***p* value**	***p* value**	***p* value**	***p* value**
Sex				
Male	1.27 (1.24–1.29)	1.22 (1.20–1.24)	1.17 (1.14–1.21)	1.19 (1.16–1.23)
Female	<0.0001	<0.0001	<0.0001	<0.0001
Race				
Whites	1.13 (1.11–1.16)	1.14 (1.11–1.17)	1.16 (1.11–1.21)	1.16 (1.11–1.21)
Others	<0.0001	<0.0001	<0.0001	<0.0001
Insurance status				
Uninsured	1.12 (1.07–1.18)	1.06 (1.01–1.12)	1.01 (0.80–1.25)	1.16 (0.94–1.46)
Insured	<0.0001	0.0118	0.9307	0.1906
Institution				
Others	1.20 (1.17–1.22)	1.19 (1.16–1.21)	1.18 (1.14–1.21)	1.14 (1.11–1.18)
Academic	<0.0001	<0.0001	<0.0001	<0.0001
Charlson–Deyo score				
≥2	1.37 (1.33–1.40)	1.26 (1.23–1.30)	1.33 (1.28–1.38)	1.22 (1.18–1.27)
≤1	<0.0001	<0.0001	<0.0001	<0.0001
Year of diagnosis				
2014	1.05 (1.03–1.07)	1.05 (1.02–1.07)	1.04 (1.01–1.07)	0.91 (0.88–0.94)
2015	<0.0001	<0.0001	0.0088	<0.0001
Histology				
Others	1.23 (1.21–1.25)	1.13 (1.11–1.15)	1.14 (1.11–1.17)	1.05 (1.02–1.08)
Adenocarcinoma not otherwise specified	<0.0001	<0.0001	<0.0001	0.0014
Nodal status				
≥N1	1.22 (1.19–1.24)	1.33 (1.30–1.36)	1.17 (1.14–1.21)	1.31 (1.27–1.35)
N0	<0.0001	<0.0001	<0.0001	<0.0001
Brain metastasis				
Yes	1.09 (1.06–1.12)	1.02 (0.99–1.05)	1.24 (1.18–1.31)	1.25 (1.18–1.32)
No	<0.0001	0.2439	<0.0001	<0.0001
Bone metastasis				
Yes	1.24 (1.21–1.27)	1.13 (1.11–1.15)	1.17 (1.13–1.22)	1.20 (1.15–1.25)
No	<0.0001	<0.0001	<0.0001	<0.0001
Liver metastasis				
Yes	1.45 (1.40–1.50)	1.32 (1.27–1.36)	1.32 (1.25–1.39)	1.26 (1.19–1.33)
No	<0.0001	<0.0001	<0.0001	<0.0001
Surgery for primary lesion				
No	2.02 (1.90–2.14)	2.04 (1.92–2.16)	1.85 (1.66–2.08)	1.83 (1.64–2.06)
Yes	<0.0001	<0.0001	<0.0001	<0.0001
Radiation				
Yes	1.10 (1.08–1.12)	1.12 (1.10–1.14)	1.06 (1.03–1.09)	1.00 (0.98–1.04)
No	<0.0001	<0.0001	<0.0001	0.7468
Chemotherapy				
No	2.19 (2.15–2.23)	2.30 (2.25–2.34)	2.11 (2.05–2.17)	2.18 (2.12–2.24)
Yes	<0.0001	<0.0001	<0.0001	<0.0001

(Continues)

TABLE 2 (Continued)

	<75 years old ($n = 62\,037$)		≥75 years old ($n = 24\,136$)	
	Univariate	Multivariable	Univariate	Multivariable
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Factors	*p* value	*p* value	*p* value	*p* value
Immune checkpoint inhibitor				
No	1.50 (1.46–1.54)	1.47 (1.43–1.51)	1.65 (1.57–1.73)	1.63 (1.55–1.71)
Yes	<0.0001	<0.0001	<0.0001	<0.0001

Abbreviations: CI, confidence interval; HR, hazard ratio; NOS, not otherwise specified.

≥75 years. In each group, the HR for patients not receiving chemotherapy was greater than that for patients not receiving ICI.

DISCUSSION

The efficacy of ICIs among elderly patients is controversial given the potential for immune senescence. Aging may reduce the potency of the effector phase of the cancer immunity cycle because of decreased antigen presentation by dendritic cells and decreased numbers of naïve $CD8^+$ T cells.[10,11] However, patients with melanoma aged ≥60 years old receiving ICIs responded more efficiently to anti-PD-1 inhibitors than younger patients.[12] One potential explanation of this phenomenon is that in younger patients, regulatory T cells are more abundant in the tumor microenvironment[12] and negatively impact the efficacy of ICIs.[13] In addition, frequencies of $CD8^+$ T cells, which play significant roles in the cancer immunity cycle, were decreased in melanoma tumors from younger patients.[12] Thus, despite immune senescence, elderly patients with cancer can still potentially benefit from ICI therapy.

An Italian multicenter retrospective study investigated the efficacy and safety of anti-PD-1 immunotherapy among patients with advanced NSCLC aged ≥75 years and found that the efficacy and toxicity of ICIs in elderly patients were comparable with the profiles observed in younger patients.[14] A meta-analysis showed that ICI therapy and non-ICI therapy of NSCLC had comparable efficacy in patients aged ≥65 years and those aged <65 years.[15] Another meta-analysis of a large clinical dataset suggested that NSCLC patients aged ≥65 years can benefit even more from ICI therapy than younger patients.[16] In the current study, we found that the HR for death among patients with stage IV NSCLC aged ≥75 years who did not receive ICIs was greater than among those aged <75 years (1.63 vs. 1.48). A survival benefit of ICI therapy was observed in both age strata. Consistently, the HR for death among patients with stage IV NSCLC aged ≥75 years who received ICIs was smaller than that among those who did not receive ICIs (1.23 vs. 1.32). These results suggest that aging does not negatively impact ICI efficacy in patients with stage IV NSCLC, in line with these previous reports.[8,12,14–17]

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 ≥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.[18] 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.

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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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