Original Article

Impact of gender on response to immune checkpoint inhibitors in patients with non-small cell lung cancer undergoing second- or later-line treatment

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Background: Several previous clinical trials have reported that male patients with non-small cell lung cancer (NSCLC) respond better to immunotherapy than females. However, the impact of gender on prognosis remains uncertain because no real-world study considering various factors that affect patients' response to immunotherapy with gender exists. Therefore, we evaluated the effect of gender on immunotherapy response adjusted by multiple factors in actual clinical practice.

Methods: This study was a single-center real-world retrospective cohort study, comprising 387 patients with NSCLC who received pembrolizumab, nivolumab, or atezolizumab alone as second- or later-line treatments. Subsequently, we compared their progression free survival (PFS) and overall survival (OS) scores based on gender, then analyzed prognostic factors accounting for immunotherapy response.

Results: The mean age of the understudied patients was 64.0 years old, comprising 68.7% males, with non-squamous cell carcinoma accounting for 70.3% of these patients. Male patients also showed higher smoking rates, programmed death-ligand 1 (PD-L1) expression, and expression of wild type epidermal growth factor receptor (EGFR), known as favorable prognostic factors. However, no difference in PFS and OS according to gender was observed [PFS 2.2 (male) *vs.* 2.1 (female) months, P=0.144; OS 7.6 (male) *vs.* 8.8 (female) months, P=0.383]. Furthermore, an Eastern Cooperative Oncology Group (ECOG) performance status ≥2, high expression of PD-L1, and EGFR mutations were proposed as prognostic factors in multivariate analysis for PFS. Besides, ECOG performance status ≥2 and squamous cell carcinoma were poor prognostic factors accounting for OS. Yet, gender was not an independent prognostic factor in PFS and OS.

Conclusions: Gender was not an independent prognostic factor for immunotherapy in real-world data although various factors affected immunotherapy response, such as wild type EGFR and high expression of PD-L1, which frequently occur in males.

Keywords: Immunotherapy; gender; non-small cell lung cancer (NSCLC)

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Introduction

Depending on gender, the immune response and immune system function for both foreign and self-antigens are different (1,2). Therefore, the prevalence of autoimmune diseases related to immunity is higher in females (3-5). Likewise, differences in immune response have consistently been suggested to be based on gender, with outcomes of males being better in patients with malignancies who received immunotherapy (6-8). Although the mechanism accounting for this difference is unclear, several hypotheses have been raised. The first proposition was the difference in immunity between genders. It is hypothesized that malignancies in females with relatively strong immunities have a high ability to escape immune surveillance, leading to the observed increased incidence of lessened immunogenic malignancies (9,10). The second hypothesis was the difference in cancer biology, such as the increased tumor mutational burden in males (11,12), and the third one was differences in behavior, such as smoking status and environmental factors (13,14).

Studies have shown that males with non-small cell lung cancer (NSCLC) responded better to pivotal clinical immunotherapy trials (15-17). A recent study also reported that the efficacy of immunotherapy in males was better than in females, based on a meta-analysis (18). However, these studies were either clinical trials or meta-analyses analyzing clinical trials, which did not adjust for various factors affecting immunotherapy responses. Therefore, a real-world study in actual clinical practice is necessary because various factors account for the observed differences in immunotherapy response, including gender. Unfortunately, no real-world study exists to date. Hence, we investigated whether gender would affect immunotherapy response even in actual clinical practice, comprehensively considering various factors that can affect this response. We present the following article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-146/rc).

Methods

Study design and population

This study was a single-center real-world retrospective cohort study. Patients with NSCLC who received pembrolizumab, nivolumab, or atezolizumab alone from January 2020 to June 2021 were analyzed. Patients with malignancies other than NSCLC, those undergoing combination therapies with cytotoxic chemotherapy, those with a previous history of immunotherapy, and those with incomplete data were excluded. Furthermore, patients undergoing first-line treatment, which was mostly conducted as clinical trials, were also excluded.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of the Asan Medical Center (IRB No. 2021-1167) and individual consent for this retrospective analysis was waived.

Data collection

Patients' baseline clinical, demographic, and survival data were obtained from medical or National Health Insurance of Korea records during immunotherapy. Furthermore, epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and programmed death-ligand 1 (PD-L1) from the most recent biopsy examination results were collected before immunotherapy. Then, NSCLC staging was conducted according to the 8th edition of the TNM staging classification (19). We performed progression free survival (PFS) analysis based on the Response Evaluation Criteria in Solid Tumors guideline (version 1.1) (20).

Prognostic outcomes

This study's primary endpoint was to compare PFS and overall survival (OS) according to gender in patients with NSCLC who received immunotherapy as second- or later-line treatment. The secondary outcome was the prognostic factor for PFS and OS in NSCLC patients undergoing immunotherapy, after which comparison of prognosis according to gender during subgroup analyses was conducted.

Statistical analyses

Continuous variables were denoted as mean ± standard deviation and were compared using a *t*-test. Categorical variables presented as numbers (percentages) were compared using Chi-squared tests. Furthermore, Kaplan-Meier's curve and the log-rank test were used to compare survival. Then, Cox regression analysis was used to obtain immunotherapy-based prognostic factors for PFS and OS and its hazard ratio (HR). For multivariate analysis, variables with a P value <0.2 in the univariate analysis were included. Besides,

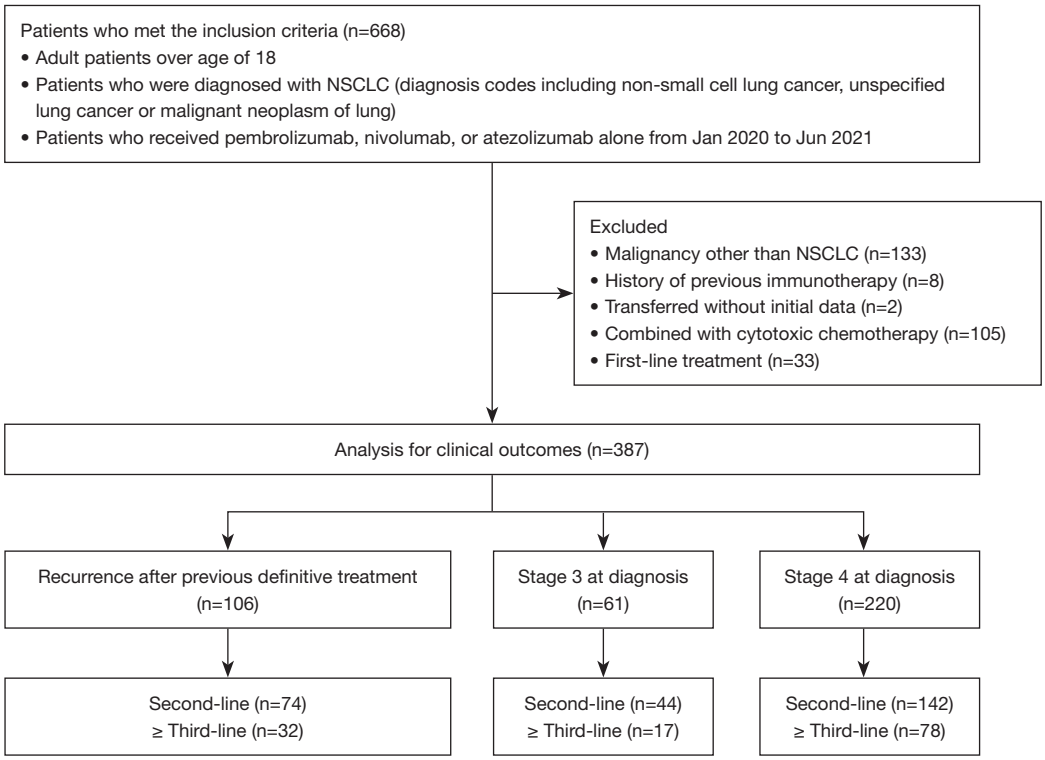

Figure 1 Flowchart of the study population. NSCLC, non-small cell lung cancer.

a P value of <0.05 was considered statistically significant. Finally, statistical analyses were performed using IBM SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics

A total of 668 patients met the inclusion criteria during the analysis period. Finally, data from 387 patients with NSCLC who received immunotherapy as second- or later-line treatment were retrospectively analyzed after excluding 281 patients who met the exclusion criteria (*Figure 1*).

The mean age of the understudied patients was 64.0 years old, of which 68.7% were male (*Table 1*). Results also showed that while 15.0% of these patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or higher, 70.3% had the non-squamous cell carcinoma pathology type. Before initiating the first systemic treatment, records showed that 27.4% of patients experienced recurrence after the previous definitive treatment, whereas 72.6% had advanced-stage cancers. Furthermore, while PD-L1 positivity was confirmed in 65.6% of patients, 22.2% and 2.6% had EGFR and ALK mutations, respectively. Notably, male patients were older age, had higher smoking rates, previously underwent ≥ third-line treatment, experienced high PD-L1 expression (tumor proportion score of ≥50%), and had a lower rate of non-squamous cell carcinoma and EGFR mutations.

Prognostic differences based on gender

The median PFS in all patients was 2.1 months [interquartile range (IQR), 1.4–5.7 months]. It was 2.2 months (IQR, 1.4–6.1 months) in males and 2.1 months (IQR, 1.4–4.5 months) in females. Meanwhile, the median OS in these patients was 8.1 months (IQR, 2.9–not reached) and 7.6 months (IQR, 2.2–not reached) for males, then 8.8 months (IQR, 3.9–not attained) for females. However, no statistical difference based on gender was observed in PFS and OS (*Figure 2*).

Prognostic factors for PFS and OS

In the Cox regression analysis for PFS, while an ECOG performance status ≥2 was a poor prognostic factor [HR 2.200, 95% confidence interval (CI): 1.621–2.985, P<0.001],

Table 1 Baseline characteristics of patients with NSCLC who received immunotherapy as ≥ second-line treatment

Variables	Total patients (n=387)	Male (n=266)	Female (n=121)	P value
Age (years), mean ± SD	64.0±9.6	65.3±9.5	61.1±9.1	<0.001
Smoking status, n (%)				<0.001
Ever smoker	256 (66.1)	243 (91.4)	13 (10.7)	
Never smoker	123 (31.8)	20 (7.5)	103 (85.1)	
Unknown	8 (2.1)	3 (1.1)	5 (4.1)	
ECOG PS, n (%)				0.567
0–1	329 (85.0)	228 (85.7)	101 (83.5)	
≥2	58 (15.0)	38 (14.3)	20 (16.5)	
Pathology, n (%)				<0.001
Non-squamous cell carcinoma	272 (70.3)	163 (61.3)	109 (90.1)	
Squamous cell carcinoma	99 (25.6)	90 (33.8)	9 (7.4)	
Others	16 (4.1)	13 (4.9)	3 (2.5)	
Stage at the time of initiation of systemic treatment, n (%)				0.241
Stage III	61 (15.8)	43 (16.2)	18 (14.9)	
Stage IV	220 (56.8)	144 (54.1)	76 (62.8)	
Recurrence	106 (27.4)	79 (29.7)	27 (22.3)	
Treatment line of immunotherapy, n (%)				<0.001
Second-line	260 (67.2)	201 (75.6)	59 (48.8)	
≥ Third-line	127 (32.8)	65 (24.4)	62 (51.2)	
Immunotherapy, n (%)				0.010
Pembrolizumab	99 (25.6)	79 (29.7)	20 (16.5)	
Nivolumab	68 (17.6)	40 (15.0)	28 (23.1)	
Atezolizumab	220 (56.8)	147 (55.3)	73 (60.3)	
PD-L1 status, n (%)				0.006
<1%	92 (23.8)	55 (20.7)	37 (30.6)	
1–49%	130 (33.6)	93 (34.9)	37 (30.6)	
≥50%	124 (32.0)	96 (36.1)	28 (23.1)	
Unknown	41 (10.6)	22 (8.3)	19 (15.7)	
EGFR, n (%)				<0.001
Wild type	235 (60.7)	171 (64.3)	64 (52.9)	
Mutation	86 (22.2)	36 (13.5)	50 (41.3)	
Unknown	66 (17.1)	59 (22.2)	7 (5.8)	
ALK, n (%)				0.001
Wild type	300 (77.5)	193 (72.6)	107 (88.4)	
Mutation	10 (2.6)	6 (2.3)	4 (3.3)	
Unknown	77 (19.9)	67 (25.1)	10 (8.3)	

NSCLC, non-small cell lung cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed cell death-ligand 1; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; SD, standard deviation.

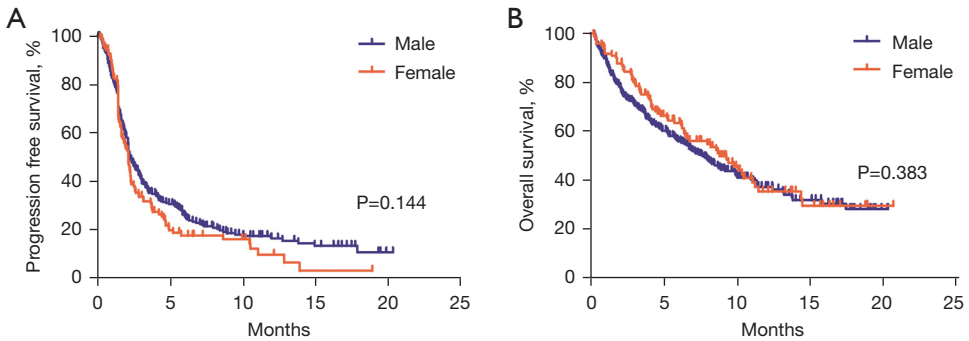

Figure 2 Comparison of Kaplan-Meier curves among understudied patients who received immunotherapy. (A) PFS [median PFS: 2.2 (male) *vs.* 2.1 (female) months, P=0.144]. (B) OS [median OS: 7.6 (male) *vs.* 8.8 (female) months, P=0.383]. PFS, progression free survival; OS, overall survival.

the high expression of PD-L1 (≥50%) was a favorable prognostic factor (HR 0.551, 95% CI: 0.402–0.754, P<0.001) (*Table 2*). Additionally, EGFR mutations was proposed as a poor prognostic factor for PFS (HR 1.304, 95% CI: 0.987–1.722, P=0.062). Furthermore, in the Cox regression analysis for OS, an ECOG performance status ≥2 and squamous cell carcinoma were independent poor prognostic factors (HR 3.200, 95% CI: 2.314–4.426, P<0.001; HR 1.584, 95% CI: 1.188–2.113, P=0.002, respectively) (*Table 3*). However, gender was not an independent prognostic factor in PFS and OS.

We also investigated prognostic factors accounting for immunotherapy response in each subgroup. As observed, PFS in patients with a high PD-L1 expression (≥50%) and wild type EGFR was significantly higher than patients with <50% expression of PD-L1 and EGFR mutations (*Figures 3,4*). By subsequently analyzing gender differences through stratified subgroups using PD-L1 expression and EGFR mutation, although statistical differences were only observed, depending on the presence of high PD-L1 expression and EGFR mutations, no prognostic difference according to gender exists. Therefore, no difference in OS according to gender in these subgroups was observed.

Similarly, no difference was observed in prognosis according to gender in the subgroups stratified by ECOG performance status and pathology type, which were prognostic factors for PFS or OS (Figures S1,S2).

Discussion

When we compared immunotherapy response and demographic characteristics based on gender using real-world data, we observed that gender was not an independent prognostic factor accounting for immunotherapy in patients with NSCLC. Furthermore, although ECOG performance status ≤1 and high PD-L1 expression (≥50%) were favorable prognostic factors, EGFR mutation was a poor prognostic factor for PFS in these patients who received immunotherapy as second- or later-line treatment. Therefore, even though gender was not a prognostic factor, high expression of PD-L1 and wild type EGFR, which are favorable prognostic factors for PFS, were significantly more common in males.

Based on our extensive literature search, the largest study on response differences based on gender was the systematic review and meta-analysis conducted by Conforti *et al.* (18). In that study, 20 randomized controlled trials (RCTs) for immune checkpoint inhibitors were used (11,351 subjects with advanced and metastatic cancers). Their results showed that the pooled OS's HR for males and females was 0.72 (95% CI: 0.65–0.79) and 0.86 (95% CI: 0.79–0.93), compared with patients treated in the control group. Furthermore, the efficacy in males was better than in females in a comparative analysis (P=0.0019). However, most of the RCTs included in the previous meta-analysis did not provide any information on differences in PD-L1 expression and EGFR mutation according to gender (16,21,22). Additionally, these variables in the meta-analysis did not adjust gender (18). Therefore, since gender was adjusted using various factors in this real-world study, we assumed that gender was not an independent prognostic factor. Moreover, in previous real-world studies, the incidence of immune-related adverse events—which could be a predictor of better response to immunotherapy (23,24)—or oligoprogression was not different between genders (25-27). One previous

Table 2 Cox regression analysis for progression free survival

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age	0.999	0.987–1.011	0.918	–	–	–
Male *vs.* female	0.843	0.665–1.070	0.161	0.920	0.716–1.181	0.513
Ever smoker *vs.* never smoker	0.840	0.662–1.065	0.150	0.871	0.673–1.129	0.297
ECOG PS						
0–1	1.000			1.000		
≥2	2.204	1.633–2.974	<0.001	2.200	1.621–2.985	<0.001
Pathology						
Non-squamous NSCLC	1.000					
Squamous cell carcinoma	1.178	0.915–1.516	0.205	–	–	–
Stage						
Stage 3	1.000			–		
Stage 4	0.971	0.712–1.325	0.854	–	–	–
Recurrence	1.007	0.713–1.420	0.970	–	–	–
Treatment line						
Second-line	1.000					
≥ Third-line	1.188	0.939–1.504	0.151	0.937	0.676–1.300	0.698
PD-L1 status						
<1%	1.000			1.000		
1–49%	0.900	0.679–1.192	0.463	1.010	0.758–1.346	0.947
≥50%	0.503	0.369–0.686	<0.001	0.551	0.402–0.754	< 0.001
EGFR						
Wild type	1.000			1.000		
Mutation	1.329	1.014–1.742	0.039	1.304	0.987–1.722	0.062
ALK						
Wild type	1.000			–		
Mutation	0.871	0.387–1.959	0.738	–	–	–

HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death-ligand 1; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

study showed that gender played no role in the occurrence of severe immune-related adverse events in multivariate analysis (OR 1.07, P=0.45) (26). Our findings supported this evidence.

Notably, no difference in PFS and OS between males and females was observed, unlike previous studies. This difference is proposed to be the differing proportion in pathology type. Also, in the previous meta-analysis (18), the proportion of non-squamous cell carcinoma among patients included in clinical trials for PD-L1 inhibitor was 77.3% (15,16,21,22), and higher than the proportion of non-squamous cell carcinoma in this study (70.3%). Additionally, in one previous clinical trial, HR in females was lower than in males with squamous cell carcinoma who received pembrolizumab plus a combination (females: HR 0.42, 95% CI: 0.22–0.81 *vs.* males: HR 0.69, 95% CI: 0.51–0.94) (28).

Table 3 Cox regression analysis for overall survival

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age	1.016	1.001–1.031	0.038	1.008	0.994–1.023	0.269
Male gender	1.137	0.852–1.518	0.384	–	–	–
Ever smoker *vs.* never smoker	1.125	0.842–1.502	0.426	–	–	–
ECOG PS						
0–1	1.000			1.000		
≥2	3.254	2.355–4.496	<0.001	3.200	2.314–4.426	<0.001
Pathology						
Non-squamous NSCLC	1.000			1.000		
Squamous cell carcinoma	1.634	1.226–2.179	0.001	1.584	1.188–2.113	0.002
Stage						
Stage 3	1.000			1.000		
Stage 4	0.942	0.650–1.364	0.751	0.946	0.652–1.373	0.771
Recurrence	1.331	0.895–1.979	0.158	1.246	0.834–1.862	0.282
Treatment line						
Second-line	1.000			–		
≥ Third-line	0.953	0.719–1.264	0.740	–	–	–
PD-L1 status						
<1%	1.000			–		
1–49%	1.069	0.754–1.517	0.707	–	–	–
≥50%	0.893	0.619–1.288	0.545	–	–	–
EGFR						
Wild type	1.000			–		
Mutation	1.098	0.792–1.521	0.575	–	–	–
ALK						
Wild type	1.000			–		
Mutation	1.043	0.428–2.541	0.927	–	–	–

HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death-ligand 1; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

Interestingly, a difference in PFS between males and females in the subgroup with non-squamous cell carcinoma was observed in this study (median PFS: 2.3 months, 95% CI: 1.4–7.3 *vs.* 2.1 months, 95% CI: 1.4–4.4, P=0.033) (Figure S3). However, gender was also not an independent prognostic factor in the Cox multivariate analysis adjusted using these variables (PFS: HR 0.946, 95% CI: 0.607–1.475, P=0.808; OS: unadjusted HR 0.949, 95% CI: 0.678–1.327, P=0.758) (Tables S1,S2).

Additionally, studies have reported that while EGFR mutation is a poor prognostic factor (16,22,29), the high expression of PD-L1 is a favorable prognostic factor in patients with NSCLC who are receiving immunotherapy (30). Comparing the prevalence of EGFR mutations according to

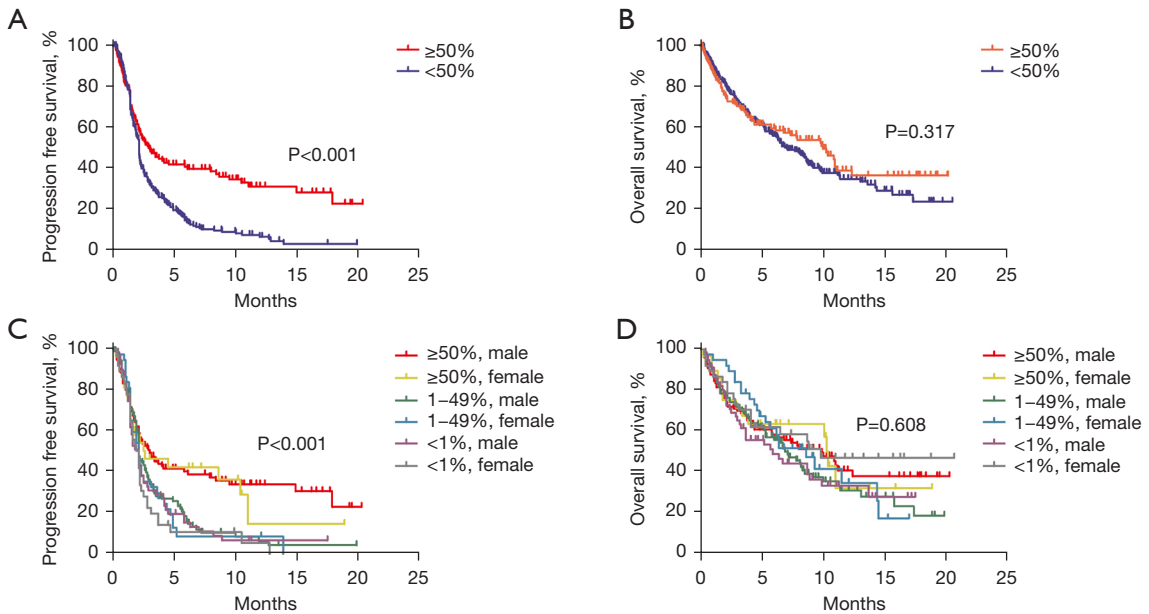

Figure 3 Progression free survival and overall survival based on patient PD-L1 status. (A,B) High expression of PD-L1 (≥50%) *vs.* lower expression or negative for PD-L1 (<50%): (A) progression free survival; (B) overall survival. (C,D) Kaplan-Meier curves subdivided according to PD-L1 status and gender: (C) progression free survival; (D) overall survival.

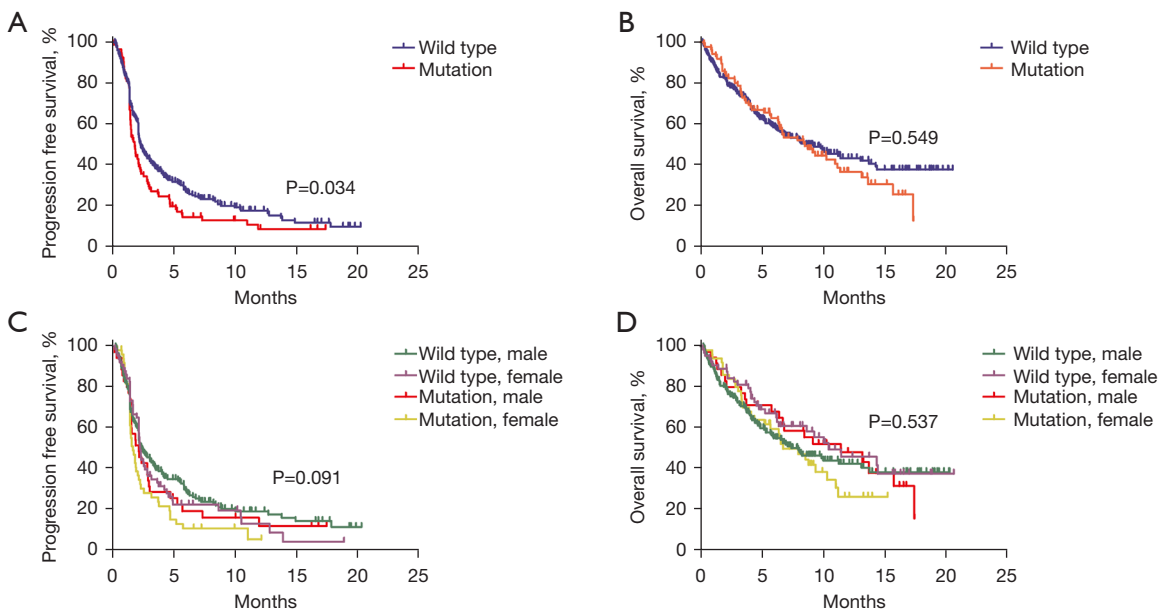

Figure 4 Progression free survival and overall survival based on EGFR mutations. (A,B) Mutation *vs.* wild type: (A) progression free survival; (B) overall survival. (C,D) Kaplan-Meier curves subdivided according to EGFR mutation and gender: (C) progression free survival; (D) overall survival.

gender, although the prevalence of EGFR mutations varied by ethnicity, the overall ratio of EGFR mutations was high in females (31,32). Several studies have also reported the higher expression of PD-L1 in males (33,34). Nevertheless, although the mechanism accounting for this difference is uncertain, a hypothesis has been proposed that the effect of estrogen or environmental causes, such as smoking history, can affect the incidence of EGFR mutations (35,36). The prevalence of PD-L1 expression is also hypothesized to be affected by patient's smoking history (34). Therefore, the difference in the prevalence of EGFR mutations and PD-L1 positivity according to gender could seem to make a difference in prognosis between male and female patients with NSCLC undergoing immunotherapy in previous studies.

In addition to EGFR and PD-L1, while an ECOG performance status of ≥2 was a poor prognostic factor for PFS and OS, the pathology type of squamous cell carcinoma was also a poor prognostic factor for OS in patients with NSCLC undergoing immunotherapy. So far, most immunotherapy-based clinical trials have excluded patients with an ECOG performance status of ≥2. In agreement, one recent real-world meta-analysis study showed that an ECOG performance status of ≥2 was a poor prognostic factor for PFS (HR 2.39, 95% CI: 1.81–3.15, P<0.0001) and OS (HR 2.72, 95% CI: 2.03–3.63, P<0.001) in patients with NSCLC undergoing immunotherapy (37). Moreover, median OS in patients with non-squamous cell carcinoma (16) were proposed to be higher than in patients with squamous cell carcinoma (17) who received nivolumab as a second- or later-line treatment (median OS 9.5 *vs.* 9.2 months, respectively). Similarly, our findings supported the results of these previous studies.

In spite of our insightful findings, several limitations were faced in this study. The first limitation was that this study was a single-center retrospective study. The cohort in this study comprised only Asian patients. Therefore, the proportion of characteristics, including driver mutations, could differ from other races. However, we confirmed prognostic factors accounting for immunotherapy response during multivariate analysis adjusted by various factors, including molecular testing. Second, median PFS and OS were shorter than in previous clinical trials. The reason was that patients with an ECOG performance status of ≥2 were also included. Therefore, we made the immunotherapy indications more comprehensive than those in clinical trials. A real-world study recently reported similar PFS and OS results with our current study (38). Third, no difference in OS based on PD-L1 expression, which has been proposed as a prognostic factor for immunotherapy response, was observed. This result is considered to be due to the heterogeneous pathology type, ECOG performance status, or treatment line, which can affect survival. Finally, at a time of the recent increase in the use of immunotherapy as the first-line treatment worldwide, first-line immunotherapy—which were mainly conducted as clinical trials because of its inapplicable insurance coverage in Korea during the study period—was excluded from this study. Nevertheless, there was no difference in response to immunotherapy according to gender between the first-line and the subsequent-line treatment in the previous study (18). Moreover, gender played no role in response to immunotherapy by different treatment line in this study. Therefore, the impact of gender would not depend on the line of therapy, and the results of this study could be applicable in clinical practice regardless of the line of therapy.

In conclusion, gender was not an independent prognostic factor for immunotherapy in real-world data although various factors affected immunotherapy response, such as wild type EGFR and high expression of PD-L1, which frequently occur in males. Therefore, we propose that when predicting treatment responses and selecting patients to be treated with immunotherapy, various factors that affect prognosis should be considered comprehensively.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-146/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-146/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.

com/article/view/10.21037/tlcr-22-146/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of the Asan Medical Center (IRB No. 2021-1167) and individual consent for this retrospective analysis was waived.

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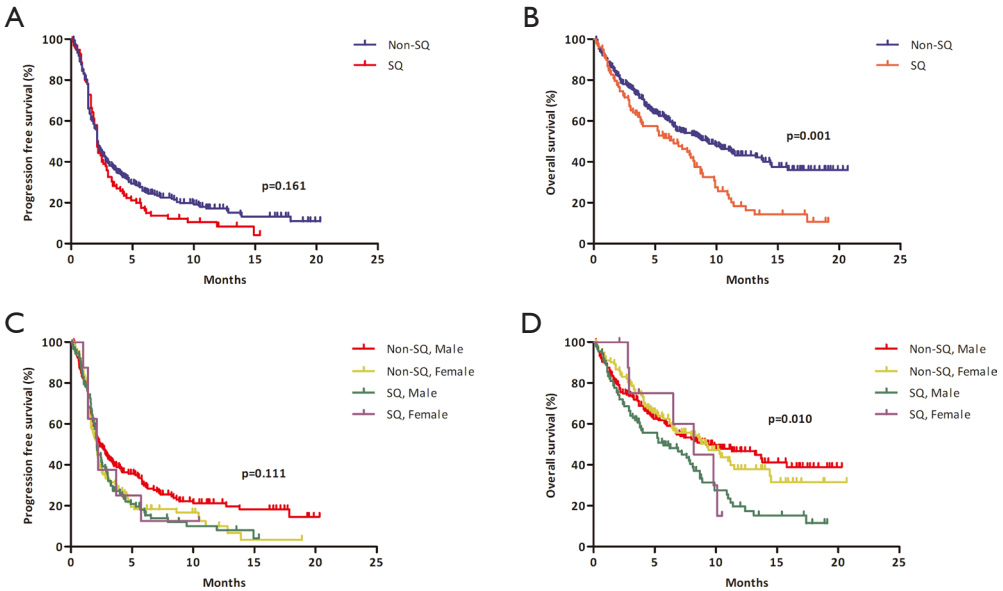

Figure S1 Progression free survival and overall survival based on pathology. (A,B) Non-squamous *vs.* squamous cell carcinoma (A, progression free survival; B, overall survival). (C,D) Kaplan-Meier curves subdivided according to pathology and sex (C, progression free survival; D, overall survival).

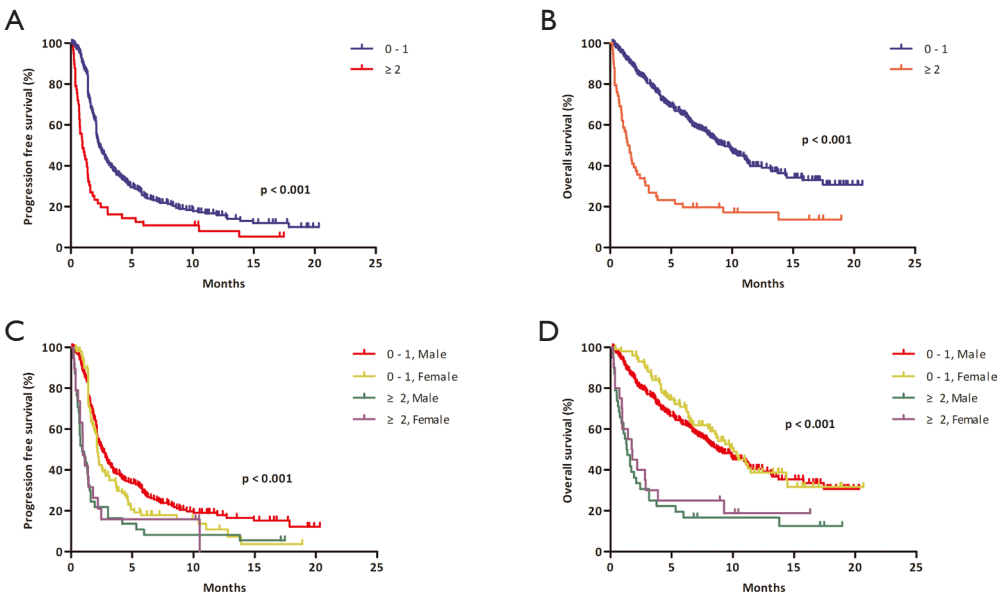

Figure S2 Progression free survival and overall survival based on ECOG PS. (A,B) ECOG PS 0–1 *vs.* ECOG PS ≥2 (A, progression free survival; B, overall survival). (C,D) Kaplan-Meier curves subdivided according to ECOG PS and sex (C, progression free survival; D, overall survival). ECOG PS, Eastern Cooperative Oncology Group performance status.

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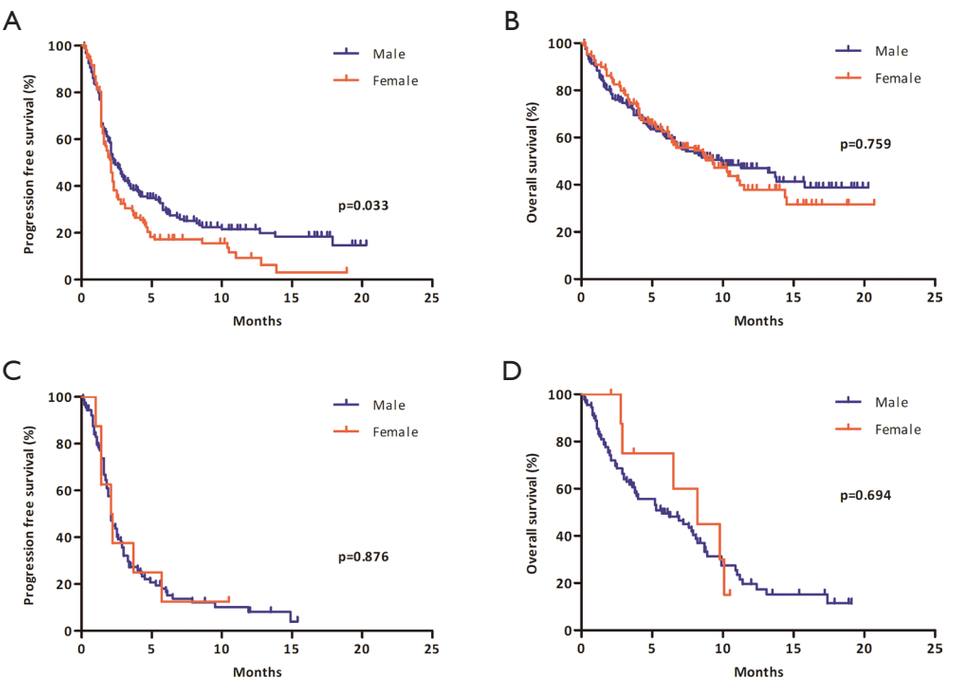

Figure S3 Comparison of Kaplan-Meier curves based on gender in subgroups classified by pathology type. (A) Progression free survival in patients with non-squamous cell carcinoma. (B) Overall survival in patients with non-squamous cell carcinoma. (C) Progression free survival in patients with squamous cell carcinoma. (D) Overall survival in patients with non-squamous cell carcinoma.

Table S1 Cox regression analysis for progression free survival in patients with non-squamous NSCLC

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age	0.993	0.980–1.008	0.360	-	-	-
Male *vs.* female	0.754	0.575–0.988	0.041	0.946	0.607–1.475	0.808
Ever smoker *vs.* never smoker	0.762	0.581–0.999	0.049	0.841	0.633–1.119	0.235
ECOG PS						
0–1	1.000			1.000		
≥2	2.185	1.530–3.120	<0.001	2.074	1.440–2.987	<0.001
Stage						
Stage 3	1.000			-		
Stage 4	1.055	0.737–1.511	0.768	-	-	-
Recurrence	1.041	0.680–1.593	0.854	-	-	-
Treatment line						
Second-line	1.000			1.000		
≥ Third-line	1.314	1.003–1.723	0.048	0.961	0.644–1.435	0.847
PD-L1 status						
<1%	1.000			1.000		
1–49%	0.886	0.635–1.237	0.478	0.988	0.703–1.389	0.945
≥50%	0.461	0.320–0.665	<0.001	0.504	0.349–0.729	<0.001
EGFR						
Wild type	1.000			1.000		
Mutation	1.427	1.069–1.905	0.016	1.370	1.017–1.844	0.038
ALK						
Wild type	1.000			-		
Mutation	0.879	0.390–1.982	0.757	-	-	-

NSCLC, non-small cell lung cancer; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed cell death-ligand 1; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

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Table S2 Cox regression analysis for overall survival in patients with non-squamous NSCLC

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age	1.005	0.987–1.024	0.563	-	-	-
Male sex	0.949	0.678–1.327	0.758	-	-	-
Ever smoker *vs.* never smoker	0.953	0.681–1.335	0.781	-	-	-
ECOG PS						
0–1	1.000			1.000		
≥2	3.503	2.353–5.216	<0.001	3.535	2.368–5.275	<0.001
Stage						
Stage 3	1.000			1.000		
Stage 4	0.756	0.495–1.156	0.196	0.699	0.456–1.070	0.099
Recurrence	1.186	0.734–1.916	0.487	1.066	0.659–1.726	0.794
Treatment line						
Second-line	1.000			-		
≥Third-line	1.071	0.766–1.498	0.687	-	-	-
PD-L1 status						
<1%	1.000			-		
1–49%	1.149	0.750–1.762	0.523	-	-	-
≥50%	0.845	0.537–1.329	0.466	-	-	-
EGFR						
Wild type	1.000			-		
Mutation	1.126	0.789–1.606	0.513	-	-	-
ALK						
Wild type	1.000			-		
Mutation	1.104	0.451–2.699	0.829	-	-	-

NSCLC, non-small cell lung cancer; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed cell death-ligand 1; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

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