




# Sex differences in the characteristics and survival of patients with non-small-cell lung cancer: A retrospective analytical study based on real-world clinical data of the Korean population

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## Abstract

**Purpose:** This study aimed to investigate the differences in characteristics, clinical stages, treatment modalities, and survival outcomes in patients with non-small-cell lung cancer (NSCLC) based on sex differences using Korean nationwide registry data.

**Methods:** We analyzed the data of 8650 patients diagnosed with NSCLC between 2014 and 2017, obtained from the Korean Association for Lung Cancer Registry (KALC-R). The Cox proportional hazard model was used to define the differences in survival based on sex. Propensity score matching was used to adjust for differences between men and women.

**Results:** Of a total of 10 943 patients, 8650 (79.1%) were diagnosed with NSCLC, of whom 68.7% were men and 31.3% were women. For NSCLC, the median age was higher (69.0 vs. 67.0,  $p < 0.001$ ) and the proportion of ever-smokers (84.5% vs. 10.8%,  $p < 0.001$ ) was higher in men. Adenocarcinoma (55.5% vs. 90.4%,  $p < 0.001$ ) and stage I NSCLC (26.3% vs. 41.3%,  $p < 0.001$ ) were more common in women. Survival was significantly lower in men with NSCLC (hazard ratio [HR] 1.493 [95% confidence interval, CI 1.238–1.800],  $p < 0.001$ ) even after adjusting for meaningful clinical variables, and in the matched cohort (HR 1.339 [1.075–1.667],  $p = 0.009$ ). Similarly, survival was significantly lower in men with stage IV adenocarcinoma after adjusting for other clinical variables (HR 1.493 [1.238–1.800],  $p < 0.001$ ) and in the matched cohort (HR 1.339 [1.075–1.667];  $p = 0.009$ ).

**Conclusions:** Male patients with NSCLC had poorer prognosis, not only after variable adjustments for prognostic factors, but also in the matched cohort.

## KEYWORDS

epidemiology, Korea, lung cancer, sex, survival

## INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths for both men and women worldwide.<sup>1</sup> To date, incidence rates of lung cancer are known to be higher in males.<sup>2</sup> This sex-

based difference is attributed to tobacco smoking, and genetic and biological differences.<sup>3</sup> However, the incidence of lung cancer has recently increased in women, particularly among nonsmokers.<sup>4,5</sup> In addition, non-small-cell lung cancer (NSCLC) accounts for a high proportion of lung cancer epidemiology worldwide<sup>6</sup> and the importance of NSCLC is increasing with the various types of target therapy and driver mutations.<sup>7</sup>

Da Som Jeon and Jin Woo Kim contributed equally as co-first authors.

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According to previous studies, men had poorer prognosis for lung cancer compared to women.<sup>8,9</sup> However, factors such as age, smoking, clinical staging, and genetic mutation might have influence as confounding factors.<sup>10</sup> Recently, several studies have reported that after adjustment of these confounding factors, men continued to show poor prognosis compared to women.<sup>11,12</sup> However, large-scale studies are sparse in the literature.

The goal of this study was therefore to analyze the characteristics, initial treatment modalities, and clinical stages of lung cancer according to sex, and further investigate the sex-stratified survival outcomes by adjusting the factors predicted to contribute to the prognosis in NSCLC using a large database constructed through a multicenter nationwide registry in South Korea.

## METHODS

### Study design and subjects

This study analyzed data from the Korean Association for Lung Cancer Registry (KALC-R), a multicenter cancer registry. This was set up after the second nationwide survey, and it consists about 10% of the newly diagnosed lung cancer cases in Korea each year.<sup>13</sup> From 2014 to 2017, the KALC-R registered 8650 patients who were diagnosed with incident NSCLC, of which 11 patients diagnosed with lung cancer before the study period were excluded. Thus, a total of 8650 patients were included (2047, 2098, 2237, and 2268 patients in 2014, 2015, 2016, and 2017, respectively).

The KALC-R has approximately 80 data fields comprising demographic data. Data on patient age, sex, body mass index (BMI), symptoms, smoking history, performance status, histopathologic type, clinical stage (according to the eighth edition of the TNM International Staging System), initial treatment modality, and results of molecular tests (i.e., epidermal growth factor receptor [EGFR] mutation and anaplastic lymphoma kinase [ALK] aberration) were collected using a standardized protocol. Ever-smokers were defined as patients with any history of smoking before a lung cancer diagnosis and never-smokers as those with no smoking history. Performance status was classified based on Eastern Cooperative Oncology Group (ECOG) classification.<sup>14</sup>

### Statistical analysis

Hazard ratios (HRs) and 95% confidence intervals (CIs) for death in lung cancer according to sex were estimated using Cox proportional hazard regression methods. Propensity score matching was performed to balance differences in baseline characteristics according to sex. Propensity scores were calculated via a logistic regression analysis using baseline covariates such as age, smoking status, performance status, BMI, histopathology, clinical stage, EGFR mutation, and ALK aberrant. Standardized mean differences of <0.1 for a

given covariate indicated a relatively small imbalance.<sup>15</sup> Outcomes were compared using Cox regression models with robust standard errors that accounted for the clustering of the matched pairs. On Cox-proportional hazard assumption, if  $p$  was >0.05, the assumption was satisfied, and if  $p$  was <0.05, the assumption was not satisfied. The Cox regression plot of this study is presented in Supporting Information Table S1. Adjusted HRs and 95% CIs were estimated for men in relation to women. Overall survival was defined as the time from diagnosis of lung cancer until death from any cause. Patients were followed up until December 31, 2020 or the date of death. Survival was analyzed by the Kaplan–Meier method with log-rank tests for sex differences, and subgroup analysis of patients with stage IV adenocarcinoma according to EGFR mutation and ALK aberration was also performed.

Data are expressed as the mean  $\pm$  standard deviation (SD) or median (interquartile range [IQR]). The Mann–Whitney  $U$  test was used to compare continuous variables, and the chi-square or Fisher's exact test was used to compare categorical variables. All  $p$  values <0.05 were considered statistically significant. All statistical analyses were performed using SAS software version 9.4 (SAS Institute).

### Ethical considerations

The KALC-R was approved by the Institutional Review Board (IRB) of the National Cancer Center (approval number: NCC 2018–0193). The requirement for informed consent was waived by the IRB due to the retrospective nature of the study. The study was conducted in accordance with the relevant guidelines.

## RESULTS

### Baseline characteristics

Patients diagnosed with NSCLC were analyzed according to sex (Table 1). Among the 8651 NSCLC patients, 5944 (68.7%) were men and 2706 (31.3%) were women. The median age was significantly higher (69.0 [IQR 62.0–75.0 years] vs. 67.0 [IQR 58.0–75.0 years],  $p < 0.001$ ) in men. Compared to women, the proportion of ever-smoker status (84.5% vs. 10.8%,  $p < 0.001$ ) was significantly higher in men. Respiratory symptoms except for pain were more common in men. Adenocarcinoma was more common in women (55.5% vs. 90.4%,  $p < 0.001$ ) whereas squamous cell carcinoma was more common in men (43.5% vs. 8.7%,  $p < 0.001$ ). Early-stage lung cancer was more prevalent in women (stage I 26.3% vs. 41.3%,  $p < 0.001$ ). Supporting Information Table S2 shows the baseline characteristics of NSCLC patients after propensity score matching.

### Initial treatment method

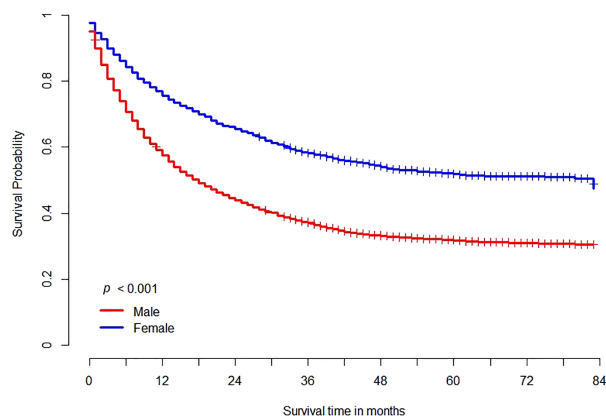
In each stage of NSCLC, most of the initial treatment modalities did not have significant differences between sex (Supporting

**TABLE 1** Baseline characteristics of non-small-cell lung cancer patients according to sex from 2014 to 2017

	Total	Male	Female	<i>p</i> value
No. of patients	8650	5944	2706	
Age (years)	69.0 (60.0–75.0)	69.0 (62.0–75.0)	67.0 (58.0–75.0)	<0.001
Ever-smoker	5316 (61.5%)	5024 (84.5%)	292 (10.8%)	<0.001
BMI (kg/m <sup>2</sup> )	23.6 (23.2–24.0)	23.4 (23.0–24.0)	23.8 (23.2–24.6)	0.388
Symptoms	8527	5861	2666	
Asymptomatic	1808 (21.2%)	1075 (18.3%)	733 (27.5%)	<0.001
Cough	2766 (32.4%)	1990 (34.0%)	776 (29.1%)	<0.001
Sputum	1676 (19.7%)	1305 (22.3%)	371 (13.9%)	<0.001
Dyspnea	1575 (18.5%)	1146 (19.6%)	429 (16.1%)	<0.001
Hoarseness	136 (1.6%)	113 (1.9%)	23 (0.9%)	<0.001
Hemoptysis	503 (5.9%)	424 (7.2%)	79 (3.0%)	<0.001
Weight loss	512 (6.0%)	389 (6.6%)	123 (4.6%)	<0.001
Pain	1504 (17.6%)	1072 (17.5%)	432 (16.2%)	0.018
Performance status	6578	4490	2087	<0.001
0–1	5796 (88.1%)	3908 (87.0%)	1887 (90.4%)	
2–4	782 (11.9%)	582 (13.0%)	200 (9.6%)	
Histopathology	8213	5564	2649	
Adenocarcinoma	5482 (66.7%)	3086 (55.5%)	2396 (90.4%)	<0.001
Squamous cell	2654 (32.3%)	2423 (43.5%)	231 (8.7%)	<0.001
Carcinoma	8524	5851	2672	<0.001
Clinical stage				
Stage I	2645 (31.0%)	1541 (26.3%)	1104 (41.3%)	
Stage II	687 (8.1%)	525 (9.0%)	162 (6.1%)	
Stage III	1528 (17.9%)	1258 (21.5%)	270 (10.1%)	
Stage IV	3663 (43.0%)	2527 (43.2%)	1136 (42.5%)	

Note: Values are presented as mean ± standard deviation, median (interquartile range), or number (%), unless otherwise indicated.

Abbreviation: BMI, body mass index.

**FIGURE 1** Overall survival in patients with non-small-cell lung cancer according to sex

Information Table S3). However, women underwent more surgery for initial treatment in stage I NSCLC (81.5% in men vs. 89.8% in women,  $p < 0.001$ ), and men received more radiation therapy (7.9% vs. 4.0%,  $p < 0.001$ ) and chemotherapy (0.9% vs. 0.3%,  $p = 0.043$ ) compared to women.

## Survival according to the sex

In the Kaplan–Meier survival curve, men showed worse survival compared to women with NSCLC (median survival 34.9 vs. 51.1 months in female,  $p < 0.001$ ) (Figure 1). In all clinical stages of NSCLC, men showed worse survival outcome (median survival 64.8 vs. 76.9 months in stage I,  $p < 0.001$ ; 48.9 vs. 59.2 months in stage II,  $p = 0.002$ ; 30.6 vs. 44.7 months in stage III,  $p < 0.001$ ; 15.5 vs. 26.2 months in stage IV,  $p < 0.001$ , respectively), compared to women. According to the Cox proportional hazard model, lung cancer survival was significantly higher for women (HR 1.827 [1.715–1.946],  $p < 0.001$ ) than for men with NSCLC. In addition, the survival of women was higher (HR 1.542 [1.335–1.781],  $p < 0.001$ ) than that of men, even after adjusting for several variables (such as age, BMI, performance status, smoking status, clinical stage, initial treatment modality, EGFR mutation, and ALK aberration) affecting prognosis. The same trend of survival was shown in the matched cohort (HR 1.225 [1.025–1.353],  $p = 0.025$ ) (Table 2 and Supporting Information Figure S1).

## Subgroup analysis among patients with stage IV adenocarcinoma

Patients diagnosed with stage IV adenocarcinoma were analyzed according to sex (Table 3). Among 2433 patients, 1469 were male. The median age was lower (67.0 [59.0–74.0 years] vs. 69.0 [IQR 58.0–77.0 years],  $p = 0.036$ ) and

**TABLE 2** Adjusted hazard ratios for death from non-small-cell lung cancer in men compared to women according to variables adjustment and matched cohort

	Hazard ratio	95% confidence interval	<i>p</i> value
Crude without adjustment	1.827	1.715–1.946	<0.001
Unmatched but adjusting for all variables <sup>a</sup>	1.542	1.335–1.781	<0.001
Propensity score matching (nearest neighbor)	1.225	1.025–1.353	0.025

<sup>a</sup>Age, BMI, performance status, smoking status, clinical stage, initial treatment methods, histopathology (adenocarcinoma, squamous cell carcinoma), EGFR mutation, ALK aberration.

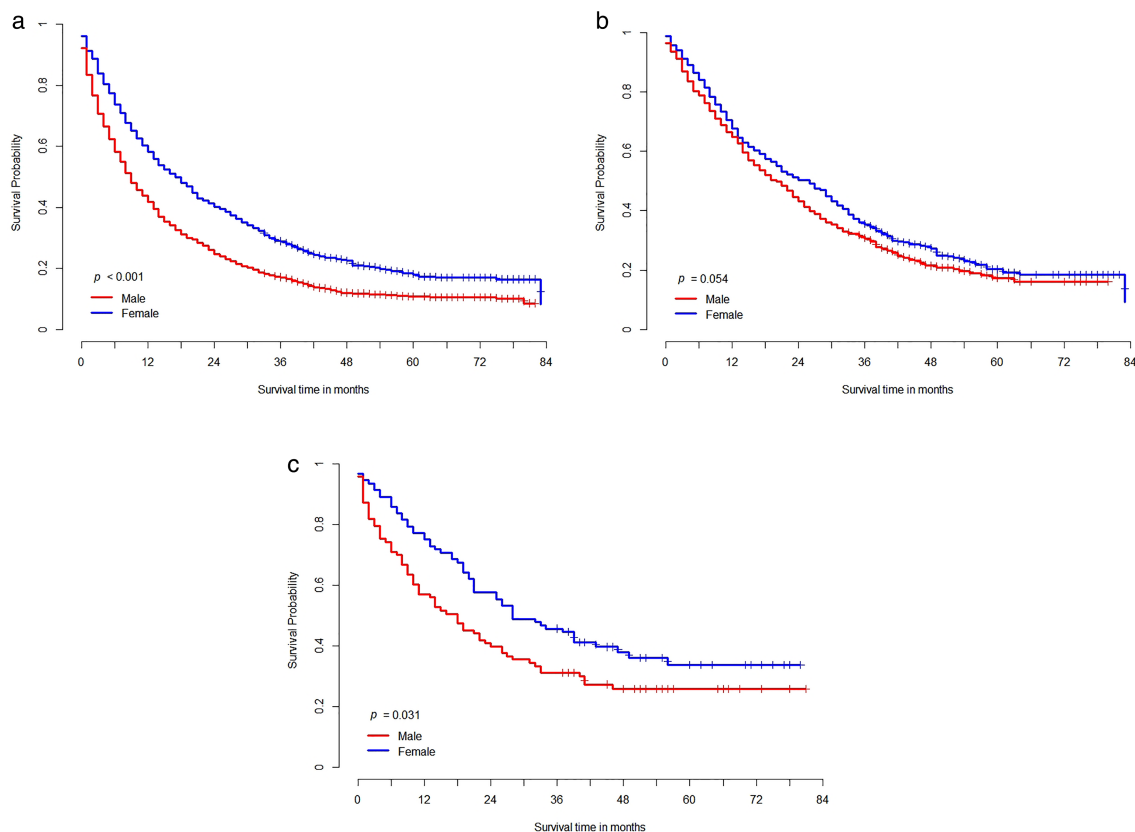
the proportion of ever-smokers was significantly higher (80.1% vs. 8.4%,  $p < 0.001$ ) among men. In women, EGFR mutation (23.8% vs. 51.1%,  $p < 0.001$ ) and ALK aberration (6.3% vs. 9.5%,  $p = 0.005$ ) were higher because EGFR (26.1% vs. 46.7%,  $p < 0.001$ ) and ALK inhibitors (2.9% vs. 4.8%,  $p = 0.007$ ) were administered more frequently in women (Supporting Information Table S4). Supporting Information Table S5 shows the baseline characteristics of stage IV adenocarcinoma patients after propensity score matching.

In the Kaplan–Meier survival curve according to sex in stage IV adenocarcinoma, men showed worse survival than women (19.3 vs. 28.6 months,  $p < 0.001$ ; Figure 2a). In addition, among individuals harboring EGFR mutation (29.2 vs. 33.3 months,  $p = 0.054$ ; Figure 2b) and ALK aberration (30.8 vs. 40.3 months,  $p = 0.031$ ; Figure 2c), men showed worse survival compared to women. In the Cox proportional hazard model, survival was significantly higher in women (HR 1.493 [1.238–1.800],  $p < 0.001$ ) after adjusting for age, BMI, performance status, smoking status, EGFR mutation, and ALK aberration. The same result was seen in the matched cohort (HR 1.339 [1.075–1.667],  $p = 0.009$ ) (Table 4 and Supporting Information Figure S2).

**TABLE 3** Baseline characteristics of stage IV adenocarcinoma patients according to sex during 2014 to 2017

	Total	Male	Female	<i>p</i> value
No. of patients	2433	1469	964	
Age (years)	67.0 (58.0–75.0)	67.0 (59.0–74.0)	69.0 (58.0–77.0)	0.036
Ever-smoker	1258 (51.7%)	1177 (80.1%)	81 (8.4%)	<0.001
BMI (kg/m <sup>2</sup> )	23.0 (22.3–23.9)	23.2 (22.2–24.3)	22.8 (21.9–24.2)	0.636
Symptoms	2392	1445	947	
Asymptomatic	221 (9.2%)	122 (8.4%)	99 (10.5%)	0.099
Cough	880 (36.8%)	517 (35.8%)	363 (38.3%)	0.216
Sputum	446 (18.6%)	287 (19.9%)	159 (16.8%)	0.058
Dyspnea	617 (25.8%)	368 (25.5%)	249 (26.3%)	0.666
Hoarseness	47 (2.0%)	35 (2.4%)	12 (1.3%)	0.046
Hemoptysis	104 (4.3%)	74 (5.1%)	30 (3.2%)	0.022
Weight loss	188 (7.9%)	116 (8.0%)	72 (7.6%)	0.699
Pain	714 (29.8%)	455 (31.5%)	259 (27.3%)	0.030
Performance status	1795	1099	696	0.341
0–1	1500 (83.6%)	916 (83.3%)	584 (83.9%)	
2–4	295 (16.4%)	183 (16.7%)	112 (16.1%)	
EGFR mutation	2433	1469	964	<0.001
Positive	842 (34.6%)	349 (23.8%)	493 (51.1%)	
Negative	1336 (54.9%)	955 (65.0%)	381 (39.5%)	
Not tested	255 (10.5%)	165 (11.2%)	90 (9.3%)	
ALK	2433	1469	964	0.005
Positive	185 (7.6%)	93 (6.3%)	92 (9.5%)	
Negative	1599 (65.7%)	963 (65.6%)	636 (66.0%)	
Not tested	649 (26.7%)	413 (28.1%)	236 (24.5%)	

Note: Values are presented as mean ± standard deviation, median (interquartile range), or number (%), unless otherwise indicated. Abbreviations: ALK, anaplastic lymphoma kinase; BMI, body mass index; EGFR, epidermal growth factor receptor.



**FIGURE 2** Overall survival in patients with stage IV adenocarcinoma (a), epidermal growth factor receptor mutated stage IV adenocarcinoma (b), and anaplastic lymphoma kinase aberrated stage IV adenocarcinoma (c) according to sex.

**TABLE 4** Adjusted hazard ratios for death from stage IV adenocarcinoma in men compared to women according to variables adjustment and matched cohort

	Hazard ratio	95% confidence interval	<i>p</i> value
Crude without adjustment	1.486	1.359–1.626	<0.001
Unmatched but adjusting for all variables <sup>a</sup>	1.493	1.238–1.800	<0.001
Propensity score matching (nearest neighbor)	1.339	1.075–1.667	0.009

<sup>a</sup>Age, body mass index, performance status, smoking status, epidermal growth factor receptor mutation, anaplastic lymphoma kinase aberration.

## DISCUSSION

In our nationwide survey, we analyzed sex differences in patients with NSCLC characteristics, treatment modalities, clinical stages, and survival outcomes. Men had a poorer prognosis than women in the total cohort and stage IV adenocarcinoma. Male lung cancer patients showed higher mortality rates, not only after adjusting for the prognostic factors such as age, smoking status, performance status, clinical stage, and treatment modalities, but also in the matched cohort after propensity score matching.

Recently, an international set of guidelines for Sex and Gender Equity in Research (SAGER) was established by the European Association of Science Editors, which encourages consideration of sex (biological attributes) and gender

(shaped by social and cultural circumstances) in research.<sup>16</sup> Conventionally, with a few exceptions, cancers are more common in men than in women, and lung cancer was also considered to be more common in men who were smokers.<sup>17,18</sup> However, the lung cancer incidence rate in never-smoker women has been rapidly increasing recently.<sup>19</sup>

Several factors have been proposed as grounds for this sex disparity. To date, biological, physiological, hormonal, and genetic factors have been suggested as the reason for the sex difference.<sup>3</sup> Although lung carcinogenesis is a complicated process, previous studies have shown that tumor-related gene mutations such as p53 and KRAS were more frequent in women.<sup>20,21</sup> Furthermore, a study showed that female sex hormones had a negative impact on smoking metabolism,<sup>22</sup> resulting in an increased risk of lung cancer.



Women who received hormone replacement treatment or were on oral contraceptives had an increased risk of lung cancer.<sup>23</sup> In addition, considering that about 80% of women with lung cancer did not meet the criteria for screening, the current system might not be effective for early lung cancer screening in women.<sup>24</sup> With the rise in incidence of lung cancer in women, it is necessary to carry out large-scale clinical and prognostic studies which may aid in early diagnosis, recognition of tumor characteristics, and appropriate management.

The sex differences in lung cancer demographics in our analysis were similar to those of other studies.<sup>9,11,12,25,26</sup> In our current study, the median age at diagnosis and the fact that the median age was lower in women was similar to that of previous studies.<sup>27,28</sup> Intrinsic factors such as sex hormones and multiple exogenous exposures might influence the difference in age at the time of diagnosis between the two sexes.<sup>8</sup> However, in our study, the difference in smoking status according to sex was larger than that in previous studies. Contrary to a previous study in which about 70% of women had experienced smoking,<sup>29</sup> our analysis showed only 12.1% of women to be ever-smokers. This may be the reason for fewer reported cases of squamous cell carcinoma among women in our study, which is closely associated with smoking, compared to that in a previous study.<sup>9</sup> Characteristically, in our study, a higher proportion of women with lung cancer were asymptomatic patients and their performance status was also better. Considering a previous study, which showed a high purchase rate of indemnity private health insurance among young women,<sup>30</sup> there might have been more active screening tests and asymptomatic visits by women with lung cancer. Thus, the proportion of stage I lung cancer was higher in women, which could be associated with better prognosis. However, as our study was not prospective or a randomized controlled trial, it could not verify the rate of screening and the type of insurance. Hence, further studies are needed in the future.

Previous research on differences in NSCLC prognosis based on sex yielded conflicting results; however, the majority of studies found that women had better prognosis than men.<sup>5,29,31,32</sup> According to the previous studies, women had a better outcome regardless of smoking status, clinical staging, histopathology, or treatment modalities.<sup>8,26,33</sup> In a Swedish nationwide cohort study, men with NSCLC had poorer prognosis even after adjusting for clinical factors such as education, marital status, performance status, comorbidity, and clinical stage.<sup>11</sup> In a United States cohort, women experienced significantly better survival for NSCLC at multiple time frames after controlling covariates like socioeconomic, clinical and comorbidity factors, compared to men.<sup>29</sup> The findings of these studies are in concordance with those of our study. In contrast, a United States-based study using data from a large single center and the Surveillance, Epidemiology, and End Results (SEER) database showed that sex was not a significant prognostic factor after adjusting for confounding factors.<sup>9</sup> Similarly, an Australian

prospective cohort study also demonstrated no significant survival difference according to sex after adjustment. However, this study used a database before tyrosine kinase inhibitors were commonly used and excluded patients under the age of 45 years; these factors might contribute in part to the sex survival rate. In our study, since more than 70% of the patients (higher than that in other studies) had advanced disease (stage III or IV), this might have affected survival according to sex.<sup>12</sup>

EGFR mutation is common in women,<sup>34</sup> especially in never-smoker Asian women.<sup>35</sup> In our study, EGFR mutation was significantly twice as common in women with stage IV adenocarcinoma. However, even after adjusting for both representative target mutations, EGFR mutation and ALK aberration, men with stage IV adenocarcinoma still showed an unfavorable outcome. This may be explained by the findings of a meta-analysis that reported that the efficacy of EGFR-tyrosine kinase inhibitor therapy for NSCLC was sex-dependent, and women had more prolonged overall survival than men.<sup>36</sup> According to a study, among EGFR mutations, EGFR 19 deletion, known to have good response to treatment and better prognosis, was more common in women.<sup>37</sup> This might have affected the difference in survival rates by sex. Our study could not analyze the survival rate according to EGFR mutation type and a response difference for each target agent, therefore further research is needed.

This study had some limitations. First, information such as smoking status and subjective symptoms in the electronic medical record and self-reported questionnaires might be incomplete. Second, disease-free survival and progression-free survival rates could not be analyzed. Third, comorbidities, familial history, socioeconomic status, education level, working status, and reasons for visiting the hospital were not included in our data, thus it was not possible to analyze the effects of these factors on the prognosis of lung cancer according to gender. In addition, the advantage of our analysis is the focus on the prognosis of lung cancer according to sex, even after adjusting for meaningful clinical factors, including EGFR mutation status in stage IV adenocarcinoma. Despite these limitations, to the best of our knowledge this is the first nationwide large-scale study representing the Korean population to analyze lung cancer mortality according to sex.

To conclude, male patients with lung cancer had a poorer prognosis not only after variable adjustments for prognostic factors but also in the matched cohort. These results suggest that it might be necessary to consider sex differences in the prediction of prognosis when performing optimal management in lung cancer.

#### AUTHOR CONTRIBUTIONS

Conceptualization: D.S.J., J.W.K., H.R.K., S.Y.S., J.C.L., W.J.J., C.M.C., H.C.K. Methodology: D.S.J., J.W.K., S.G.K., C.M.C., H.C.K. Investigation: D.S.J., J.W.K., S.G.K., H.R.K., S.Y.S., J.C.L., W.J.J., C.M.C., H.C.K. Formal analysis: D.S.J., J.W.K., S.G.K., H.C.K. Resources: H.R.K., S.Y.S., J.C.L.,

W.J.J., C.M.C., H.C.K. Writing – original draft: D.S.J., J.W.K., H.C.K. Writing – review & editing: D.S.J., J.W.K., H.R.K., S.Y.S., J.C.L., W.J.J., C.M.C., H.C.K. Visualization: D.S.J., J.W.K., S.G.K., H.C.K. Supervision: H.R.K., S.Y.S., J.C.L., W.J.J., C.M.C., H.C.K. Funding acquisition: C.M.C.

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## CONFLICTS OF INTEREST

The authors confirm that there are no conflicts of interest.

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### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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