



# Racial disparities in histological subtype, stage, tumor grade and cancer-specific survival in lung cancer

Hui Zeng<sup>1</sup>, Zhenlong Yuan<sup>1</sup>, Guochao Zhang<sup>1</sup>, Wenbin Li<sup>2</sup>, Lei Guo<sup>2</sup>, Ni Li<sup>3</sup>, Qi Xue<sup>1</sup>, Fengwei Tan<sup>1</sup>

<sup>1</sup>Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; <sup>2</sup>Department of Pathology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; <sup>3</sup>Office of Cancer Screening, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

**Contributions:** (I) Conception and design: H Zeng, N Li, Q Xue, F Tan; (II) Administrative support: N Li, Q Xue, F Tan; (III) Provision of study materials or patients: H Zeng, W Li, L Guo; (IV) Collection and assembly of data: H Zeng, Z Yuan, G Zhang; (V) Data analysis and interpretation: H Zeng, N Li, Z Yuan, G Zhang, W Li, L Guo; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

**Correspondence to:** Fengwei Tan; Qi Xue; Ni Li. Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, 17 Panjiayuan Nanli, Chaoyang District, Beijing 100021, China. Email: tanfengwei@cicams.ac.cn; xueqi@cicams.ac.cn; nli@cicams.ac.cn.

**Background:** Racial differences in lung cancer survival are well documented in the United States, but the fundamental causes are less clear. In this study we aimed to examine racial differences in lung cancer-specific survival (LCSS) and explore mediating factors.

**Methods:** We used the Surveillance, Epidemiology and End Results database to obtain data pertaining to lung cancer patients from 2004 to 2017. Outcome was LCSS and covariates included nonclinical (age at diagnosis, gender, marital status, race) and clinical factors (tumor site, year of diagnosis, tumor grading, histological subtype, tumor-node-metastasis (TNM) stage, surgery status, chemotherapy status and radiation status). Kaplan-Meier methods served for comparative LCSS disparities among patients of different racial origins. Meanwhile, univariate and multivariate survival analyses were performed to determine racial disparities in LCSS.

**Results:** Among 61,961 lung cancer patients, 75.70% were White, 12.80% were Black, 11.30% were Asian or Pacific Islander (API), and 0.20% were American Indian/Alaska Native (AIAN). In API patients, adenocarcinoma patients (54.5%) were more frequent than in White patients (43.2%), Black patients (44.1%) and American Indian/Alaska Native patients (41.2%). Black and API patients exhibited higher stage than White patients ( $P < 0.01$ ). However, our multivariate analysis identified API patients exhibited better LCSS than White patients (HR: 0.90, 95% CI: 0.88–0.93). Kaplan-Meier survival analysis confirmed that API patients exhibited best LCSS, especially in stage IV adenocarcinoma.

**Conclusions:** The novel evidence obtained from this study enrich our knowledge of racial differences among lung cancer patients and suggest that race may be associated with LCSS.

**Keywords:** Lung cancer; racial disparities; SEER database; propensity-matched survival analysis; cancer-specific survival

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## Introduction

Lung cancer is the second-most common type of cancer and the leading cause of cancer-related mortality worldwide (1,2). Non-small cell lung cancer (NSCLC) comprises about 85% of the diagnosed lung cancer cases, with more than 50% of adenocarcinoma and 30% of squamous cell carcinoma (3). Currently, the low lung cancer survival rate is attributed to more than 50% NSCLC patients diagnosed with metastatic diseases (4). Unfortunately, Blacks are more likely than Whites to develop advanced lung cancer in the United States (1,5-7). Some previous studies have shown that race can affect the survival rates of lung cancer (1,5-10), but the fundamental reasons are poorly understood. The effects of various factors, including differences in tumor characteristics, disease management and treatment, have been thought to contribute to racial survival disparities among lung cancer patients (7,9,11-14). Disparities among race in lung cancer survival exist by management and treatment, but these differences are substantially reduced (or even eliminated) in equal access health care systems, which demonstrates that access to effective care and treatments are significant causes of racial differences in cancer survival (9). Among patients with private insurance, the black-white survival disparity is greatest, while this is not the case among those without insurance, which indicates that private health insurance does not benefit all races equally (15).

Racial disparities in tumor treatment and survival must be eliminated to improve lung cancer patient outcomes. In order for this goal to be realized, multifactorial reasons for disparities must be identified and addressed. It has become possible to compare lung cancer outcomes between racial groups through the use of real-world clinical data. Cancer statistics can be found in the Surveillance, Epidemiology, and End Results (SEER) program, which provides information regarding the burden of cancer in the United States. It is hoped that using the SEER database to look for lung cancer variables will aid clinicians when dealing with patients of different racial groups suffering from lung cancer.

A systematic analysis of a defined set of prognostic factors on racial differences in lung cancer-specific survival (LCSS) is unavailable, to our knowledge. And most studies that describe the racial disparity in lung cancer have focused almost exclusively on Black *vs.* White overall survival (OS) differences. Since data from other malignancies indicated that race had an important impact on histological distribution, stage, treatment, and even cancer-specific survival (16-22), our hypothesis was that

lung cancer patients may experience the same relationship. Our study examined the racial disparities among lung cancer patients in the SEER database and analyzed the effect of sex (1,2,23), age (1,2), tumor characteristics (11,12), treatment (13,14,24,25), and married status (26) on survival. We present the following article in accordance with the STROBE reporting checklist (available at <https://tclr.amegroups.com/article/view/10.21037/tclr-21-794/rc>).

## Methods

### *Data source and study population*

The dataset in this study was obtained from SEER database and selected by SEER-stat software (SEER\*Stat 8.3.8). The case listing was based on the dataset of incidence-SEER Research Data, 18 Registers, Nov 2019 Sub (2000–2017), which covered approximately 27.8% of the United States population (27).

The study included American patients diagnosed with malignant lung cancer by positive histopathology from 2004 to 2015. The participants whose death certificates or autopsy reports indicated lung cancer were excluded. In our study, the following exclusion criteria were cited: (I) unknown race; (II) unknown survival time; (III) unknown tumor-node-metastasis (TNM) stage; (IV) unknown age at diagnosis; and (V) unknown dead causes. The TNM stage was determined by the American Joint Committee on Cancer 6th edition (28). According to the SEER mortality code, LCSS was defined as the time of the diagnosis of lung cancer to the time when lung cancer cause-specific death occurred. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences Ethics Board (No. NCC2018-064), and individual consent for this retrospective analysis was waived.

### *Data collected*

To prove our hypothesis, we extracted race, age at diagnosis, gender, marital status, tumor site, year of diagnosis, tumor grading, histological subtype, TNM stage, surgery status, chemotherapy status and radiation status. The age of the patients was divided into five subgroups based on their age, 0–49, 50–59, 60–69, 70–79, and 80+. The marital status of the participants was also classified as single, married, separated, and unknown. According to the third edition of the International Classification of Diseases for

Oncology (ICD-O-3), we divided the histological types into adenocarcinoma, squamous cell carcinoma, epithelial cell carcinoma, and others. Using the SEER race recode, we categorized race as White, Black, Asian or Pacific Islander (API), and American Indian/Alaska Native (AIAN) (29). The primary outcomes were OS and LCSS. LCSS was calculated from first day of prognosis until lung cancer death. The SEER database collects and publishes cancer incidence and survival data from 18 United States geographic areas. In addition to mortality data, this database also provides data from the National Center for Health Statistics. These areas represent the entire U.S. population, making SEER able to calculate the lung cancer survival rates of diverse populations. All variables were coded according to SEER Program criteria.

### Statistical analysis

Descriptive statistics were determined for baseline demographics and clinical characteristics by race groups. For comparing the baseline characteristics among race groups, Student's *t*-test were used for normally distributed variables, chi-square test or Fisher's exact test for categorical variables, and Mann-Whitney U-test for all other continuous variables. We compared the LCSS of patients with various variables using Kaplan-Meier survival analysis. Multivariable Cox proportional-hazards regression model was used to examine the hazard ratios (HRs) of included factors. The propensity score (PS) was used as a continuous covariate in the multivariable Cox proportional-hazards regression model, with racial groups as the dependent variable and confounders including age at diagnosis, gender, marital status, tumor site, year of diagnosis, tumor grading, histological subtype, TNM stage, surgery status, chemotherapy status and radiation status. Furthermore, a time-dependent analysis was conducted to investigate the possible influence of the external time period between diagnosis and treatment on these patients' immortal time bias (30). All tests were two-sided with a level of significance set at  $P < 0.01$ . The statistical analysis was conducted using SPSS (version 25.0) and R (version 4.0.1).

## Results

### Clinicopathological characteristics and survival analysis

As shown in *Table 1*, the study population's demographic and clinical characteristics were categorized by racial

groups. Of 61,961 eligible lung cancer patients, White accounted for 46,896 (75.7%), Black for 7,928 (12.8%), API for 6,989 (11.3%), and AIAN for 102 (0.2%), respectively. The median age at diagnosis was oldest in White (68 years) and API (68 years) compared to Black (64 years) and AIAN (65 years) (*Table 1*; *Figure S1*). The median length of follow-up was 11 months. Of all patients, 29,638 (47.8%) were female, and 32,323 (52.2%) were male. API patients had the highest rate of being married (61.8%) in four race groups ( $P < 0.01$ ). Furthermore, there were no differences in tumor site distribution ( $P = 0.26$ ). The total number of patients diagnosed was stable year to year among API and Black, however, the White group showed the opposite result ( $P < 0.01$ ). All racial patients were most likely to be diagnosed at grade III.

Histological subtype demonstrated important racial differences (*Table 1*; *Figure 1A*). First, API patients most frequently harbored adenocarcinoma (54.5%) than White patients (43.2%;  $P < 0.01$ ) or Black patients (44.1%;  $P < 0.01$ ) or AIAN patients (41.2%;  $P < 0.01$ ). Conversely, API patients exhibited the lowest rate of squamous cell carcinoma or epithelial neoplasms (17.0% and 24.7%) than White patients (21.6% and 30.8%;  $P < 0.01$ ) or Black patients (22.7% and 29.1%;  $P < 0.01$ ) or AIAN patients (27.7% and 26.4%;  $P < 0.01$ ). Among lung cancer patients with different stages, firstly, all histological subtypes were studied for the effects of race on presentation at stage (*Table 1*; *Figure 1B*). Here, in four racial groups, API and Black patients were most likely to develop lung cancer into stage III (25.0% and 24.9%, respectively). Meanwhile, Whites and Asians in four groups had the highest incidence of stage I diagnosis (23.4% and 23.6%, respectively). Our analysis then examined the effect of race on stage at presentation among the three different histological subtypes (*Figure 1C*). In adenocarcinoma, White patients exhibited the highest rates of stage I and II (28.9% and 4.7%), but the lowest rates of stage III and IV relative to other all racial groups. And Black patients carried a higher risk of being diagnosed at stage III and IV (21.9% and 51.3%, respectively) in adenocarcinoma patients. Conversely, in squamous cell carcinoma histological subtype-specific analyses, Black patients exhibited higher rate of IV stage (40.3%), and API patients exhibited higher rate of III stage (34.8%). In epithelial neoplasms histological subtype-specific analyses, a significantly highest rate of stage IV (62.8%) was recorded in the White group, relative to the other three racial groups (Black: 61.3%; API: 59.8%; AIAN: 61.5%).

**Table 1** Clinicopathological characteristics of 61,961 lung cancer patients according to race, 2004–2015

Variable	Overall, n (%)	Race				P value
		White, n (%)	Black, n (%)	API, n (%)	AIAN, n (%)	
Total	61,961	46,896 (75.70)	7,928 (12.80)	6,989 (11.30)	148 (0.20)	–
Age at diagnosis, year						<0.01
Mean (SD)	68 (11.10)	68 (10.90)	64 (10.90)	68 (11.50)	65 (10.30)	
Follow-up time, month						<0.01
Median [IQR]	11 [3, 31]	11 [3, 32]	10 [3, 27]	13 [3, 33]	8 [3, 30]	
Gender						<0.01
Female	29,638 (47.80)	22,889 (48.80)	3,754 (47.40)	2,929 (41.90)	66 (44.60)	
Male	32,323 (52.20)	24,007 (51.20)	4,174 (52.60)	4,060 (58.10)	82 (55.40)	
Marital status (at diagnosis)						<0.01
Married (including common law)	31,556 (50.90)	24,732 (52.70)	2,441 (30.80)	4,319 (61.80)	64 (43.20)	
Separated	19,485 (31.40)	15,105 (32.20)	2,610 (32.90)	1,719 (24.60)	51 (34.50)	
Single (never married)	8,512 (13.70)	5,231 (11.20)	2,497 (31.50)	756 (10.80)	28 (18.90)	
Unknown	2,408 (3.90)	1,828 (3.90)	380 (4.80)	195 (2.80)	5 (3.40)	
Site						0.26
Right	34,886 (56.30)	26,347 (56.20)	4,530 (57.10)	3,924 (56.10)	85 (57.40)	
Left	24,310 (39.20)	18,415 (39.30)	3,084 (38.90)	2,752 (39.40)	59 (39.90)	
Unknown	2,765 (4.50)	2,134 (4.60)	314 (4.00)	313 (4.50)	4 (2.70)	
Year of diagnosis						<0.01
2012–2015	18,845 (30.40)	13,559 (28.90)	2,661 (33.60)	2,568 (36.70)	57 (38.50)	
2008–2011	20,297 (32.80)	15,298 (32.60)	2,673 (33.70)	2,283 (32.70)	43 (29.10)	
2004–2007	22,819 (36.80)	18,039 (38.50)	2,594 (32.70)	2,138 (30.60)	48 (32.40)	
Median [IQR]	2009 [2006, 2012]	2009 [2006, 2012]	2009 [2007, 2012]	2010 [2007, 2013]	2010 [2007, 2013]	
Tumor grading						<0.01
Grade I	3,511 (5.70)	2,759 (5.90)	322 (4.10)	421 (6.00)	9 (6.10)	
Grade II	11,260 (18.20)	8,563 (18.30)	1,340 (16.90)	1,328 (19.00)	29 (19.60)	
Grade III	17,086 (27.60)	12,776 (27.20)	2,330 (29.40)	1,947 (27.90)	33 (22.30)	
Grade IV	2,928 (4.70)	2,486 (5.30)	250 (3.20)	187 (2.70)	5 (3.40)	
Unknown	27,176 (43.90)	20,312 (43.30)	3,686 (46.50)	3,106 (44.40)	72 (48.60)	
Histologic type						<0.01
Adenocarcinomas	27,614 (44.60)	20,249 (43.20)	3,495 (44.10)	3,809 (54.50)	61 (41.20)	
Squamous cell carcinoma	13,138 (21.20)	10,110 (21.60)	1,800 (22.70)	1,187 (17.00)	41 (27.70)	
Epithelial neoplasms	18,527 (29.90)	14,452 (30.80)	2,310 (29.10)	1,726 (24.70)	39 (26.40)	
Others	2,682 (4.30)	2,085 (4.40)	323 (4.10)	267 (3.80)	7 (4.70)	

**Table 1** (continued)

Table 1 (continued)

Variable	Overall, n (%)	Race				P value
		White, n (%)	Black, n (%)	API, n (%)	AIAN, n (%)	
TNM stage						<0.01
I	14,012 (22.60)	10,997 (23.40)	1,534 (19.30)	1,446 (20.70)	35 (23.60)	
II	3,003 (4.80)	2,307 (4.90)	355 (4.50)	332 (4.80)	9 (6.10)	
III	14,932 (24.10)	11,183 (23.80)	1,980 (25.00)	1,739 (24.90)	30 (20.30)	
IV	30,014 (48.40)	22,409 (47.80)	4,059 (51.20)	3,472 (49.70)	74 (50.00)	
Surgery						<0.01
Yes	16,345 (26.40)	12,845 (27.40)	1,702 (21.50)	1,754 (25.10)	44 (29.70)	
No	45,616 (73.60)	34,051 (72.60)	6,226 (78.50)	5,235 (74.90)	104 (70.30)	
Chemotherapy						0.12
Yes	30,951 (50.00)	23,490 (50.10)	3,863 (48.70)	3,521 (50.40)	77 (52.00)	
No	31,010 (50.00)	23,406 (49.90)	4,065 (51.30)	3,468 (49.60)	71 (48.00)	
Radiation						<0.01
Yes	27,235 (44.00)	20,474 (43.70)	3,706 (46.70)	2,995 (42.90)	60 (40.50)	
No	34,726 (56.00)	26,422 (56.30)	4,222 (53.30)	3,994 (57.10)	88 (59.50)	
Mortality status <sup>a</sup> , %						<0.01
Alive	11,839 (19.10)	8,769 (18.70)	1,386 (17.50)	1,656 (23.70)	28 (18.90)	
Dead	50,122 (80.90)	38,127 (81.30)	6,542 (82.50)	5,333 (76.30)	120 (81.10)	
Due to lung cancer	43,753 (70.60)	33,194 (70.80)	5,692 (71.80)	4,767 (68.20)	100 (67.60)	
Due to other causes	6,369 (10.30)	4,933 (10.50)	850 (10.70)	566 (8.10)	20 (13.50)	

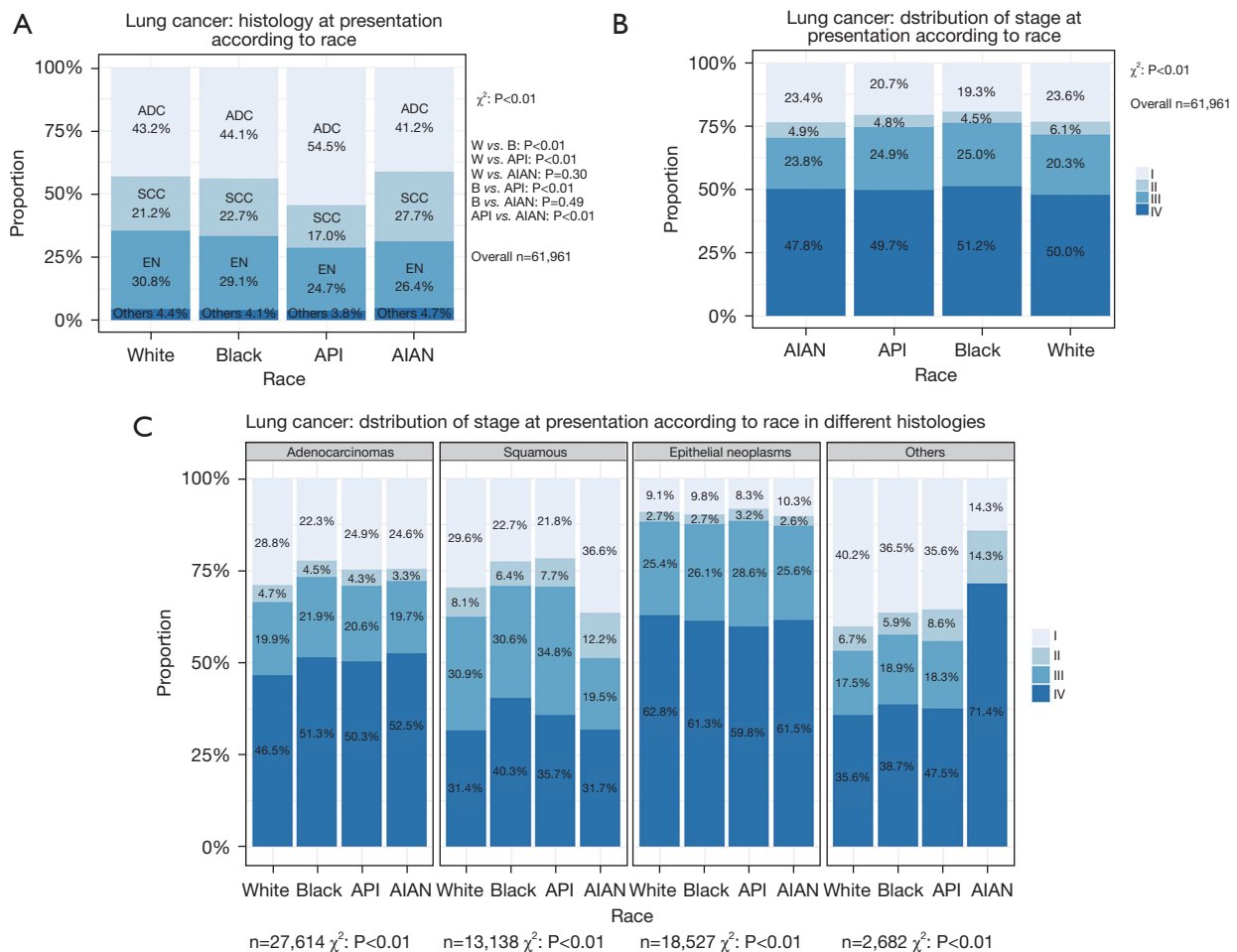
<sup>a</sup>, as of December 31, 2017. IQR, inter quartile range; TNM, tumor-node-metastasis; API, Asian or Pacific Islander; AIAN, American Indian/Alaska Native.

### Survival analysis

Baseline clinical features and treatment were evaluated in Cox proportional hazards models of OS and LCSS. A univariable analysis indicated that Black, older age, male, separated and single (never married), earlier year of diagnosis, higher histology grades, squamous and epithelial neoplasms, more advanced TNM stage, patients without surgery and an absence of chemotherapy or radiation were significantly associated with a worse OS ( $P < 0.01$ , respectively) and LCSS ( $P < 0.01$ , respectively) (Table S1). In crude survival analysis, the API group was associated with significantly better OS ( $P < 0.01$ ) and LCSS ( $P < 0.01$ ) (Figure 2). Furthermore, we included all variables mentioned earlier in the multivariable analysis. After adjustment for potential confounders, API and Black were identified as independent protective factor for both OS

(HR: 0.84, 95% CI: 0.82–0.87,  $P < 0.01$ ; HR: 0.97, 95% CI: 0.94–0.99,  $P = 0.01$ , respectively) and LCSS (HR: 0.85, 95% CI: 0.83–0.88,  $P < 0.01$ ; HR: 0.94, 95% CI: 0.92–0.97,  $P < 0.01$ , respectively) (Table S1). We used time-dependent Cox proportional hazards model for OS and LCSS in all racial patients who received treatments in different time (Table 2; Table S1). Interestingly, the significance of the married status for survival was analyzed by univariate and multivariate Cox regression analyses. We found the married group was associated with a significantly better LCSS ( $P < 0.01$ ) (Table S1). The results of multivariate analysis were similar with those of univariate analysis.

Among different racial groups, we identified statistically significant differences in LCSS with different conditions (Table S1). The multivariable Cox regression results were presented in Table 2. The adjusted HRs had the PS included in the model. The results showed a better LCSS

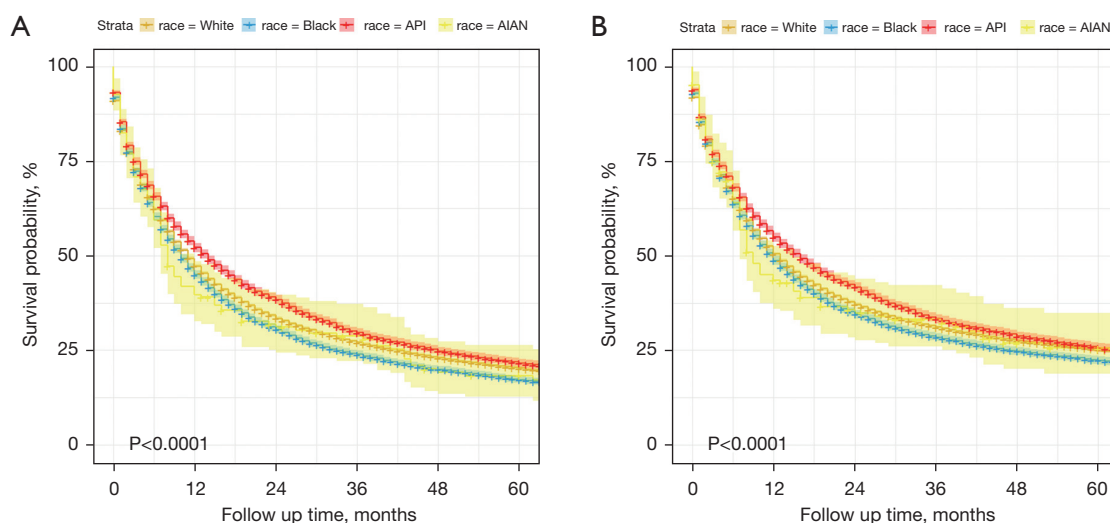


**Figure 1** Stacked bar-plots depicting the histological subtype and stage at presentation according to race in lung cancer. (A) A stack of bar plots illustrating the distribution of histological subtypes according to race in 61,961 lung cancer patients; (B) a stack of bar plots illustrating the distribution of stage at presentation according to race in the overall cohort; (C) a stack of bar plots illustrating the distribution of stage at presentation according to race in adenocarcinoma histological subtype, squamous cell carcinoma histological subtype, epithelial neoplasms histological subtype, and others. W, White; B, Black; API, Asian or Pacific Islander; AIAN, American Indian/Alaska Native; ADC, adenocarcinoma; SCC, squamous cell carcinoma; EN, epithelial neoplasms.

for API (HR: 0.85, 95% CI: 0.83–0.88; adjusted HR: 0.90, 95% CI: 0.88–0.93; Table 2). When stratifying the data by histological subtype-specific we see that, adenocarcinoma patients who were API had the best LCSS (Figure S2A). In stage I and IV, patients who were API had the best LCSS (Figure S2B). And in grade II, API patients had the best LCSS (Figure S2C). Meanwhile, in lung cancer patients treated with chemotherapy and radiation, LCSS was longer in API group (Figure S2D).

Among adenocarcinoma patients treated with chemotherapy and chemotherapy combined radiation, API group exhibited the best LCSS (Figure S3A). In stage

IV patients treated with chemotherapy, radiation, and chemotherapy combined radiation, API group demonstrated a significantly the best LCSS, respectively (Figure S3B,S3C). And API group may have the best LCSS in grade II with chemotherapy (Figure S3D). The Kaplan-Meier survival curves revealed LCSS advantage for adenocarcinoma in API group (Figure S2A), but stratifying adenocarcinoma patients by TNM stage and grade respectively, we found only in stage I, IV and grade II, LCSS in four racial groups had statistical differences (Figure S4). Further analysis, in stage I and grade II adenocarcinoma patients who underwent different treatment methods, there was no significant



**Figure 2** Kaplan-Meier curves comparing (A) OS and (B) LCSS of all racial patients with lung cancer. OS, overall survival; LCSS, lung cancer specific survival; API, Asian or Pacific Islander; AIAN, American Indian/Alaska Native.

**Table 2** Time-dependent Cox regression analyses for LCSS with PS covariate adjustment<sup>a</sup>, 2004–2015

Variable	Before PS adjusted		After PS adjusted	
	HR (95% CI)	P value	HR (95% CI)	P value
Race				
White	Reference		Reference	
Black	0.94 (0.92, 0.97)	<0.01	0.97 (0.94, 1.00)	0.06
API	0.85 (0.83, 0.88)	<0.01	0.90 (0.88, 0.93)	<0.01
AIAN	1.08 (0.88, 1.31)	0.46	0.99 (0.81, 1.20)	0.91

<sup>a</sup>, adjusted for age, sex, race, year of diagnosis, site, histology, TNM stage, marital status, grading and therapy. LCSS, lung cancer specific survival; PS, propensity score; API, Asian or Pacific Islander; AIAN, American Indian/Alaska Native; HR, hazard ratio; CI, confidential interval.

difference in LCSS among different racial patients; in stage IV adenocarcinoma patients who underwent chemotherapy, radiation and chemotherapy combined radiation, LCSS was longer in API patients, respectively (Figure S5). Interestingly, we found that married status was associated with the best LCSS (Table S1), and API group had the best LCSS in married patients (Figure S6).

## Discussion

It has been demonstrated that different racial groups of patients had differences in tumor characteristics and survival (16–22). Our findings indicated that API patients experienced the best LCSS based on the SEER population-

based data, and this survival advantage persisted in stratified analyses, especially in stage IV adenocarcinoma. Furthermore, we analyzed LCSS of four kinds of racial patients with lung cancer in different histological subtypes, TNM stages and tumor grades.

Our results differ from those of Soneji *et al.* (31), who found that early stage lung cancer patients who were Black had a worse OS than those who were White, without statistically significant differences in LCSS. It is primarily due to the fact that we included all stage lung cancer patients in our study and patients who did not receive surgery. Despite the differences, both studies found better LCSS for the API patients than for the White patients, and showed Black patients did not have worse LCSS than White

patients. In several studies (22,31-35), different comparisons were made about racial groups, without addressing their cancer-specific survival effect in a systematic and structured fashion within a large lung cancer cohort. Because tumor characteristics (11,12) including histological subtype and stage had a huge impact on the survival of lung cancer patients, to evaluate the different outcomes in different racial groups, we analyzed two important tumor features. In previous investigations, Herbst *et al.* (3) and Silva *et al.* (36) showed differences in incidence and survival rates according to histological subtypes and tumor stage. However, there are no formal tabulations or stratifications detailing the racial distribution of both tumor features. We identified important differences in the distribution of both lung cancer characteristics according to race. Although the highest proportion of all racial groups are patients with lung adenocarcinoma, the most notable difference consisted of higher proportions of adenocarcinoma in API patients. Furthermore, our observations indicated that API and Black patients were more frequently diagnosed with advanced stages at initial presentation than White patients. This pattern of more advanced stage at presentation in API and Black patients was driven by the higher incidence of adenocarcinoma and squamous cell carcinoma. However, API patients had better LCSS than White patients. The result was likely a multi-factorial problem to which many issues may contribute, including access to tumor characteristics (11,12), treatment (13,14,24,25), individual's genetics (24,25,37,38).

To provide the most unbiased illustration of the effect of race on LCSS, we relied on Cox regression analysis (including PS) and stratified Kaplan-Meier survival analysis for pathological characteristics and therapy methods, which reduced the differences in the distribution of tumor and patient characteristics in all comparisons, except for differences in race. Consistent with previous studies, our findings also showed that a best LCSS was observed for API patients in four racial groups (31,35,39,40). Furthermore, we stratified histological subtype, staging, grading, and treatment. The results indicated that API patients had a best LCSS in stage IV lung adenocarcinoma with chemotherapy, radiation, and chemotherapy combined radiation. Several studies had demonstrated that the mutation prevalence of epidermal growth factor receptor (EGFR) among Asian patients with lung adenocarcinoma was 50% to 60% compared with the 10% to 20% prevalence among White patients (41,42). And the EGFR mutation was associated with a better prognosis and better treatment response for

patients with lung adenocarcinoma (43). Moreover, married status appeared to play an important role in lung cancer patients, especially in API patients. Based on clinical studies, the survival advantage in API patients may be related to pathological characteristics and treatment methods (22,44,45).

Studies conducted in other primaries than lung cancer have shown racial differences in medical treatment, where White patients received better care than other races (5,46,47). In spite of less metastasis and active treatment, the results of our study showed that white patients with lung cancer had a significantly lower survival rate than API patients. Previous studies (14,19,22,34,44) provided a detailed analysis of racial differences in LCSS based on histological subtypes, or staging, or treatment. Moreover, Asian patients tend to have high rates of EGFR variants and may benefit from molecular-targeted therapies. Asian patients with lung cancer have significantly more EGFR variants, the most common genetic variation in NSCLC, than White patients with similar types of cancer (37,38,41,42). With the advent of EGFR inhibitors, which have demonstrated a considerable survival benefit, Asian patients with lung cancer may be able to benefit most from molecularly targeted therapy (2,24,25). Additionally, data revealed racial differences in tissue composition in normal and tumor tissue (48). Our study suggested different racial patients may have different LCSS time after treatment, and the result may be due to race's effect on cancer-initiating cells and their surrounding stromal tissue (48). Further investigation on the racial disparities reported is warranted to optimize treatment and ultimately improve the prognosis of patients with lung cancer.

Our work had limitations and should be interpreted in the context of its retrospective and population-based design. Regarding the complexity of the relationships between variables, causal relationships could not be inferred. The first limitation is that variables which may affect lung cancer such as immunotherapy, targeted therapy, smoking status, and more detailed descriptive variables such as lifestyle and environment were not included. Second, the data base was designed with the goal of providing a proportional representation of the United States population in spite of the limitations relating to all large-scale, but detailed restricted observations. And AIAN patients are relatively few, so their sample size will have little impact on the study of differences between races and tumor stages. However, few databases would be able to find a larger sample of individuals from racial groups with lung cancer. In addition,



the presence of residual differences due to unknown or unavailable confounding factors may still plague retrospective analyses, despite the best efforts to control confounding factors. This suggests that the race may become a limiting factor for LCSS although further studies are required to confirm our results.

## Conclusions

Important racial differences existed in lung cancer patients. API patients predisposed to higher rate of adenocarcinoma. Moreover, the lung cancer patients with API were older and at a higher stage when they were diagnosed. Finally, between Cox regression analysis and stratified Kaplan-Meier survival analysis, API patients exhibited significantly the best LCSS, especially in stage IV adenocarcinoma. The results indicated that race may be associated with LCSS.

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## Footnote

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*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 National

Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences Ethics Board (No. NCC2018-064), and individual consent for this retrospective analysis was waived.

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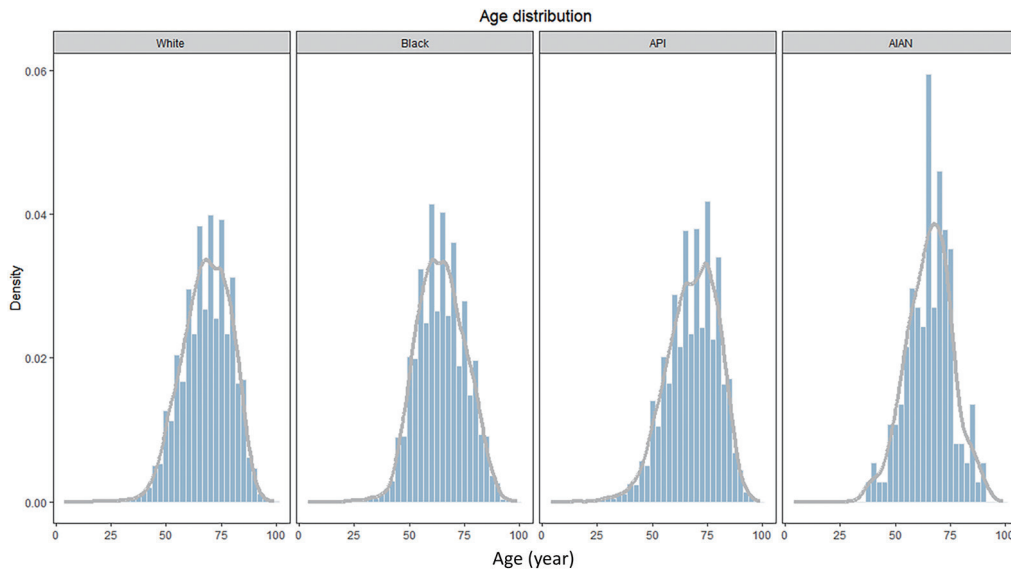
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**Figure S1** Distribution of age among lung cancer patients based on race for White (n=46,896), Black (n=7,928), API (n=6,989), AIAN (n=148). API, Asian or Pacific Islander; AIAN, American Indian/Alaska Native.

**Table S1** Univariate and time-dependent multivariate<sup>a</sup> analyses of OS and LCSS for the lung cancer patients variables included in the study

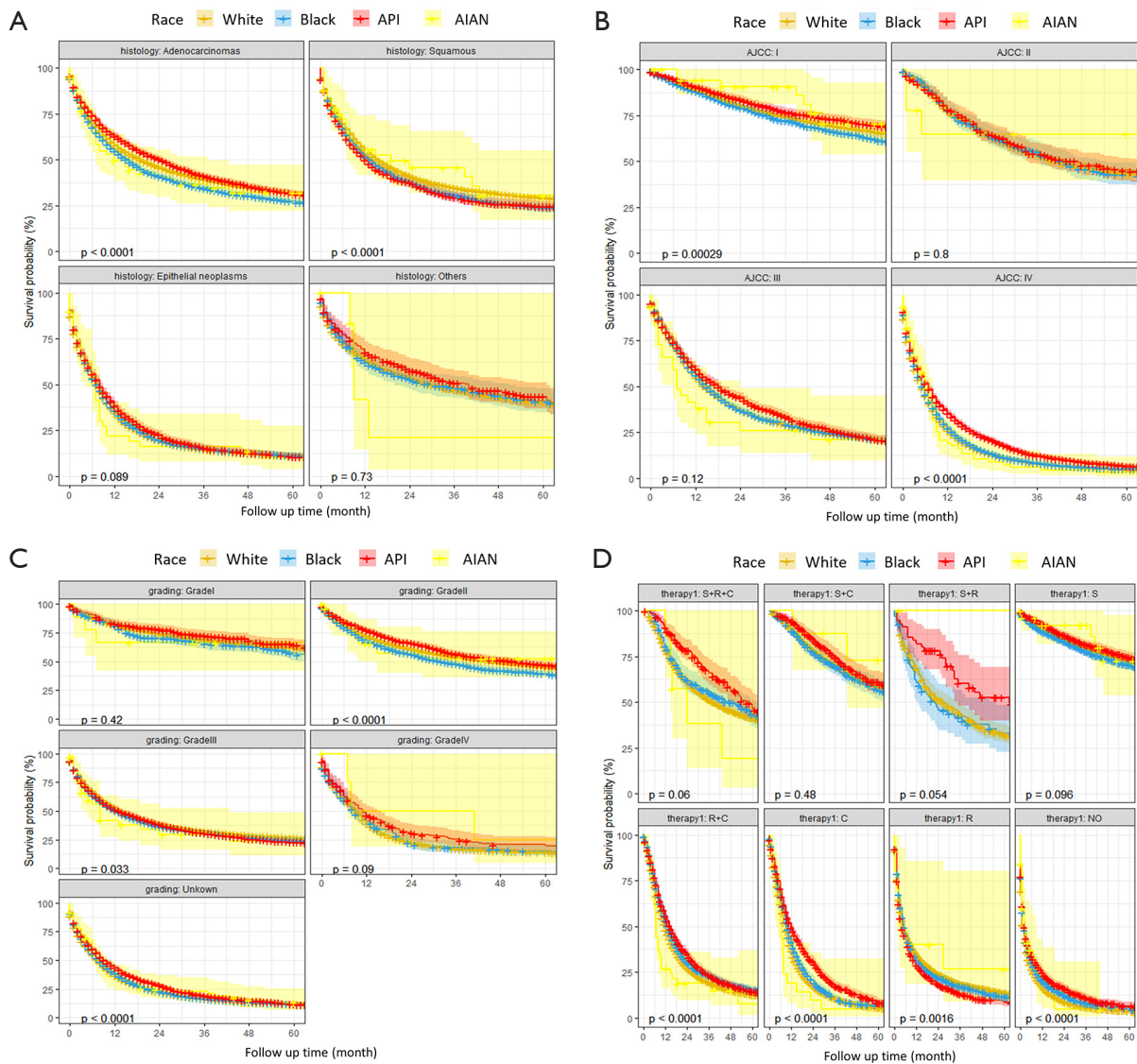
Variable	Univariate				Multivariate <sup>a</sup>			
	OS		LCSS		OS		LCSS	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
<b>Race</b>	<b>&lt;0.01</b>							
White	Reference		Reference		Reference		Reference	
Black	1.08 (1.05, 1.11)	<0.01	1.07 (1.04, 1.10)	<0.01	0.97 (0.94, 0.99)	0.01	0.94 (0.92, 0.97)	<0.01
API	0.91 (0.89, 0.94)	<0.01	0.93 (0.91, 0.96)	<0.01	0.84 (0.82, 0.87)	<0.01	0.85 (0.83, 0.88)	<0.01
AIAN	1.07 (0.89, 1.28)	0.47	1.02 (0.84, 1.24)	0.86	1.13 (0.94, 1.35)	0.18	1.08 (0.88, 1.31)	0.46
<b>Age at diagnosis, year</b>	<b>&lt;0.01</b>							
00-49	Reference		Reference		Reference		Reference	
50-59	1.05 (1.00, 1.10)	0.038	1.01 (0.97, 1.06)	0.67	1.06 (1.02, 1.11)	<0.01	1.03 (0.98, 1.08)	0.19
60-69	1.09 (1.04, 1.14)	<0.01	1.00 (0.96, 1.04)	0.99	1.20 (1.15, 1.25)	<0.01	1.12 (1.08, 1.18)	<0.01
70-79	1.26 (1.21, 1.31)	<0.01	1.10 (1.05, 1.15)	<0.01	1.36 (1.30, 1.42)	<0.01	1.22 (1.17, 1.28)	<0.01
80+	1.67 (1.60, 1.75)	<0.01	1.42 (1.36, 1.49)	<0.01	1.48 (1.41, 1.55)	<0.01	1.31 (1.25, 1.38)	<0.01
<b>Gender</b>	<b>&lt;0.01</b>							
Female	Reference		Reference		Reference		Reference	
Male	1.24 (1.21, 1.26)	<0.01	1.21 (1.19, 1.24)	<0.01	1.25 (1.23, 1.28)	<0.01	1.22 (1.20, 1.24)	<0.01
<b>Marital status (at diagnosis)</b>								
Married (including common law)	Reference		Reference		Reference		Reference	
Separated	1.23 (1.20, 1.25)	<0.01	1.20 (1.17, 1.22)	<0.01	1.13 (1.11, 1.16)	<0.01	1.11 (1.09, 1.14)	<0.01

**Table S1** (continued)

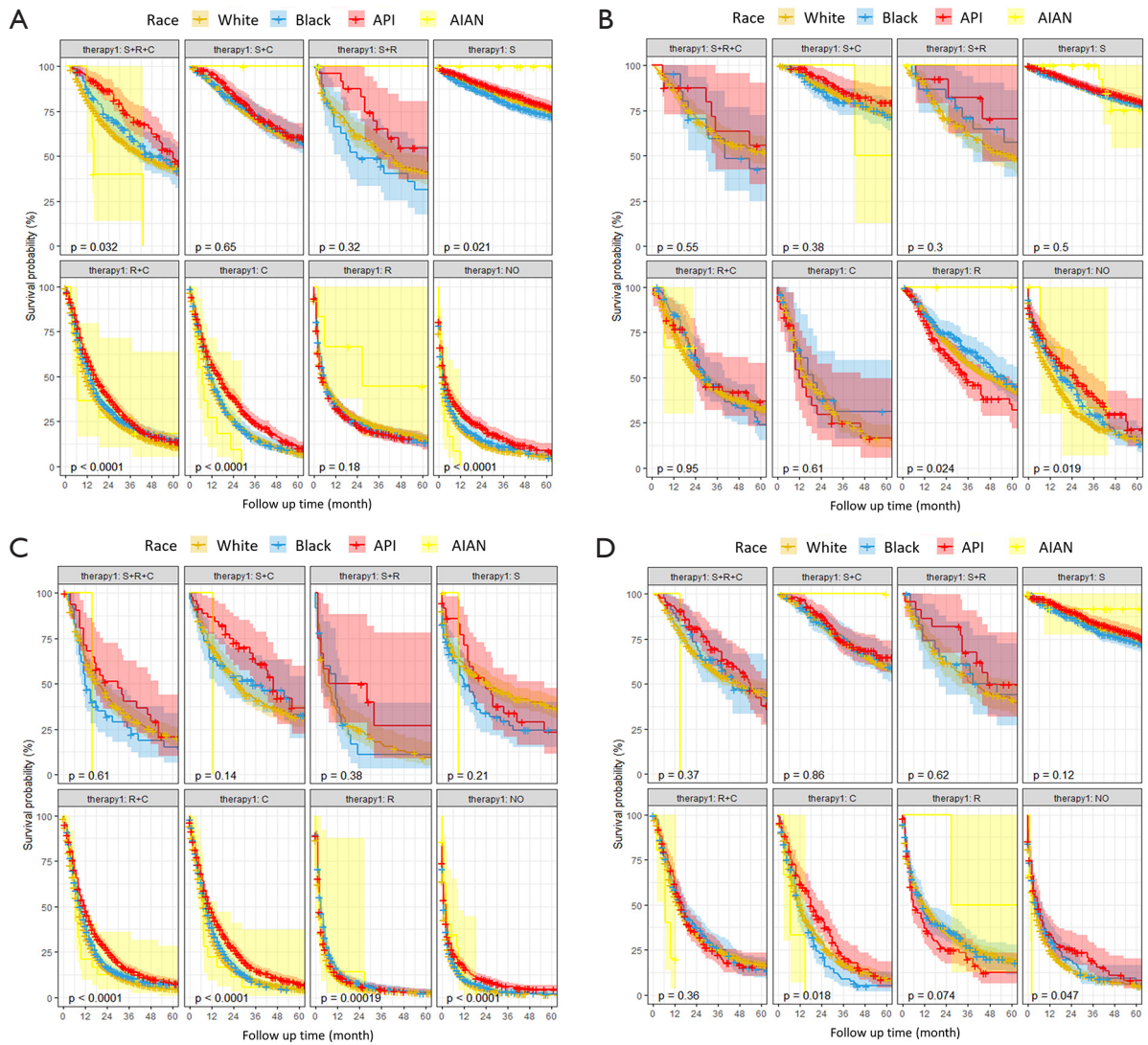
Table S1 (continued)

Variable	Univariate				Multivariate <sup>a</sup>			
	OS		LCSS		OS		LCSS	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Single (never married)	1.16 (1.13, 1.19)	<0.01	1.16 (1.13, 1.19)	<0.01	1.09 (1.06, 1.13)	<0.01	1.08 (1.04, 1.11)	<0.01
Unknown	1.04 (1.00, 1.09)	0.07	1.02 (0.97, 1.07)	0.41	0.96 (0.91, 1.00)	0.07	0.94 (0.90, 0.99)	0.02
<b>Site</b>								
Right	Reference		Reference		Reference		Reference	
Left	1.01 (0.99, 1.03)	0.43	1.01 (0.99, 1.03)	0.42	1.00 (0.98, 1.02)	0.76	1.01 (0.99, 1.03)	0.59
Unknown	2.15 (2.06, 2.23)	<0.01	2.22 (2.13, 2.32)	<0.01	1.04 (1.00, 1.09)	0.05	1.04 (0.99, 1.08)	0.10
<b>Year of diagnosis</b>								
2012–2015	Reference		Reference		Reference		Reference	
2008–2011	1.08 (1.05, 1.10)	<0.01	1.08 (1.05, 1.11)	<0.01	1.06 (1.04, 1.09)	<0.01	1.06 (1.04, 1.09)	<0.01
2004–2007	1.13 (1.11, 1.16)	<0.01	1.15 (1.12, 1.18)	<0.01	1.12 (1.09, 1.14)	<0.01	1.13 (1.10, 1.15)	<0.01
<b>Tumor grading</b>								
Grade I	Reference		Reference		Reference		Reference	
Grade II	1.50 (1.43, 1.58)	<0.01	1.62 (1.53, 1.72)	<0.01	1.30 (1.24, 1.37)	<0.01	1.36 (1.28, 1.45)	<0.01
Grade III	2.45 (2.33, 2.57)	<0.01	2.85 (2.69, 3.02)	<0.01	1.54 (1.46, 1.62)	<0.01	1.64 (1.55, 1.74)	<0.01
Grade IV	3.38 (3.18, 3.59)	<0.01	4.08 (3.82, 4.36)	<0.01	1.64 (1.54, 1.75)	<0.01	1.75 (1.63, 1.88)	<0.01
Unknown	3.70 (3.53, 3.89)	<0.01	4.41 (4.17, 4.66)	<0.01	1.49 (1.42, 1.57)	<0.01	1.58 (1.49, 1.67)	<0.01
<b>Histologic type</b>								
Adenocarcinomas	Reference		Reference		Reference		Reference	
Squamous	1.19 (1.16, 1.22)	<0.01	1.11 (1.09, 1.14)	<0.01	1.14 (1.11, 1.17)	<0.01	1.10 (1.07, 1.13)	<0.01
Epithelial neoplasms	1.87 (1.83, 1.91)	<0.01	1.91 (1.87, 1.95)	<0.01	1.24 (1.22, 1.27)	<0.01	1.24 (1.21, 1.27)	<0.01
Others	0.85 (0.81, 0.90)	<0.01	0.83 (0.78, 0.87)	<0.01	1.12 (1.07, 1.18)	<0.01	1.13 (1.07, 1.19)	<0.01
<b>AJCC stage</b>								
0-I	Reference		Reference		Reference		Reference	
II	1.54 (1.47, 1.62)	<0.01	1.88 (0.78, 1.99)	<0.01	1.73 (1.64, 1.82)	<0.01	2.04 (1.93, 2.17)	<0.01
III	2.73 (2.65, 2.81)	<0.01	3.65 (3.52, 3.78)	<0.01	2.17 (2.09, 2.24)	<0.01	2.71 (2.60, 2.82)	<0.01
IV	5.60 (5.45, 5.75)	<0.01	7.85 (7.60, 8.11)	<0.01	3.93 (3.81, 4.06)	<0.01	5.15 (4.95, 5.35)	<0.01
<b>Surgery</b>								
Yes	Reference		Reference		Reference		Reference	
No	4.74 (4.63, 4.86)	<0.01	5.70 (5.54, 5.87)	<0.01	26.59 (23.99, 29.48)	<0.01	46.62 (41.27, 52.66)	<0.01
<b>Chemotherapy</b>								
Yes	Reference		Reference		Reference		Reference	
No	1.01 (1.00, 1.03)	0.128	0.93 (0.91, 0.94)	<0.01	17.45 (15.82, 19.25)	<0.01	28.72 (25.59, 32.22)	<0.01
<b>Radiation</b>								
Yes	Reference		Reference		Reference		Reference	
No	0.78 (0.77, 0.80)	<0.01	0.75 (0.74, 0.94)	<0.01	10.30 (9.33, 11.36)	<0.01	16.96 (15.11, 19.04)	<0.01

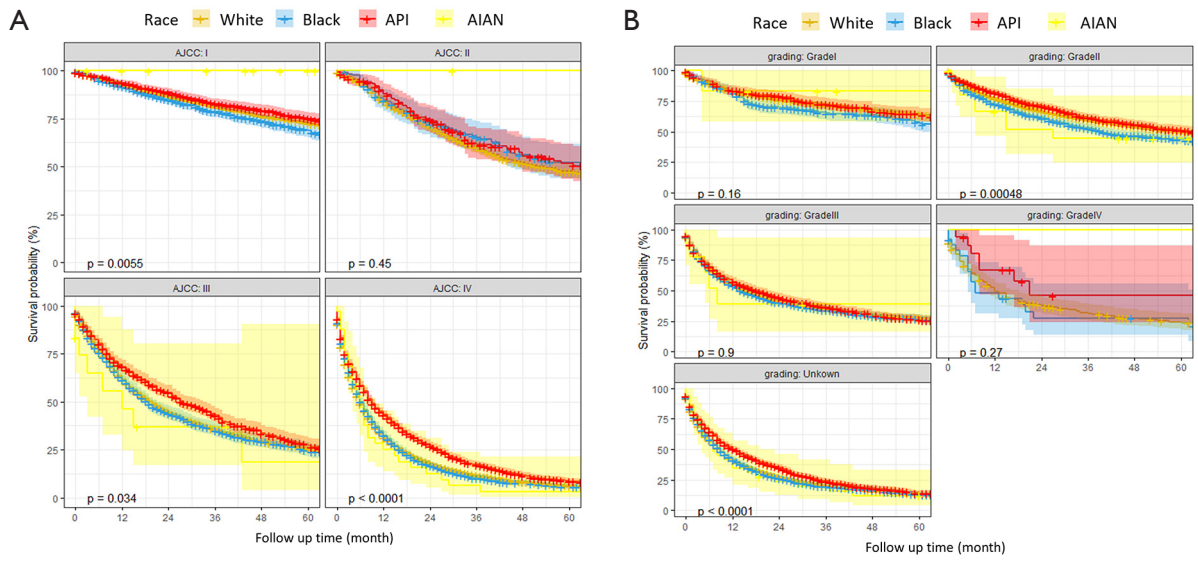
<sup>a</sup>, adjusted for age, sex, race, year of diagnosis, site, histology, AJCC, marital status, grading and therapy. OS, overall survival; LCSS, lung cancer specific survival; API, Asian or Pacific Islander; AIAN, American Indian/Alaska Native; CI, confidential interval; HR, hazard ratio.



**Figure S2** Kaplan-Meier curves comparing LCSS of all racial patients with lung cancer according to: (A) different histological subtypes; (B) different tumor stages; (C) different tumor grade; (D) different therapy. LCSS, Lung cancer specific survival; API, Asian or Pacific Islander; AIAN, American Indi-an/Alaska Native; S, surgery; R, radiation; C, chemotherapy.

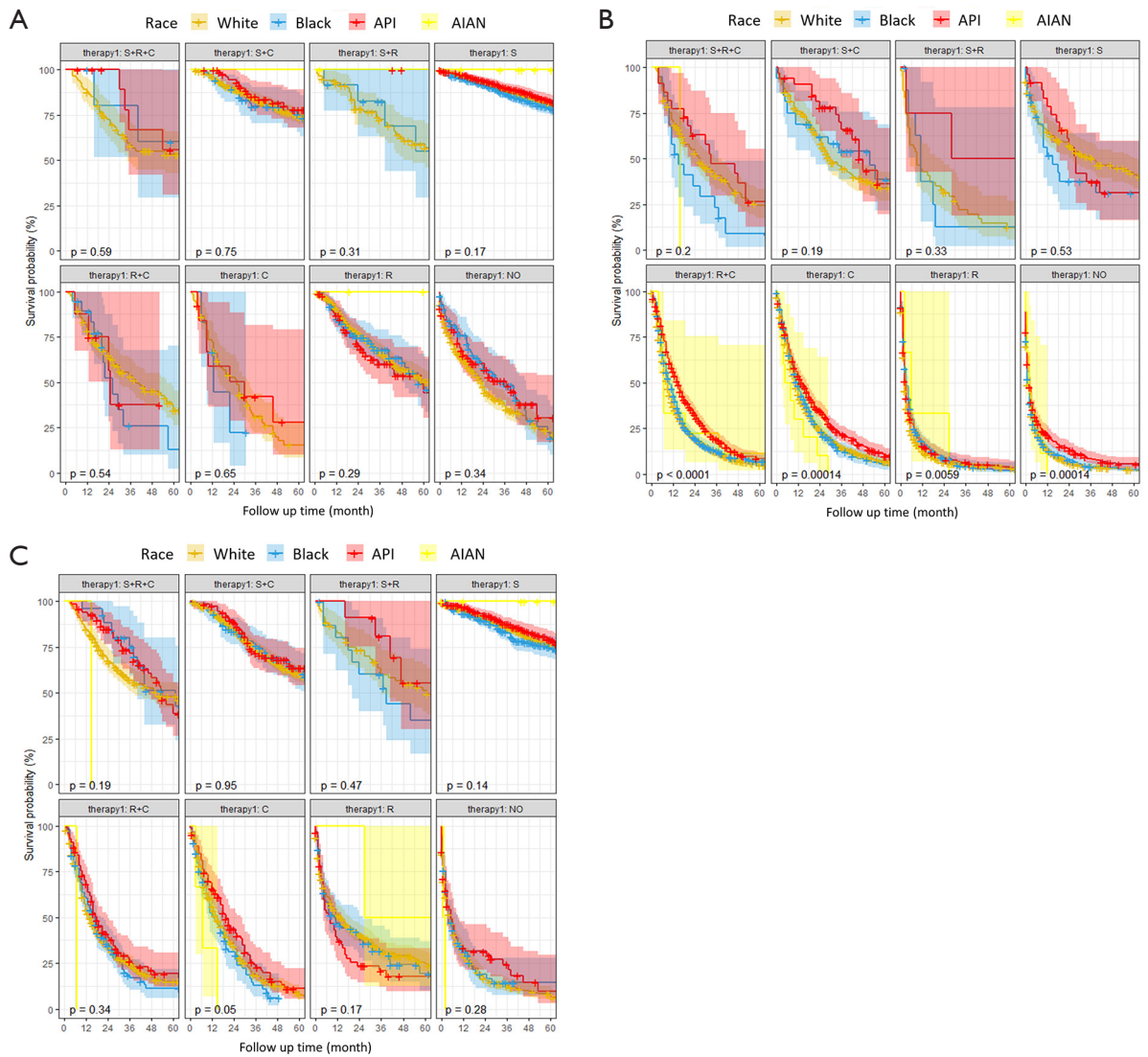


**Figure S3** Kaplan-Meier curves comparing LCSS of all racial patients with lung cancer according to different treatment methods in: (A) adenocarcinoma patients; (B) stage I patients; (C) stage IV patients; (D) grade II patients. LCSS, Lung cancer specific survival; API, Asian or Pacific Islander; AIAN, American Indian/Alaska Native; S, surgery; R, radiation; C, chemotherapy.

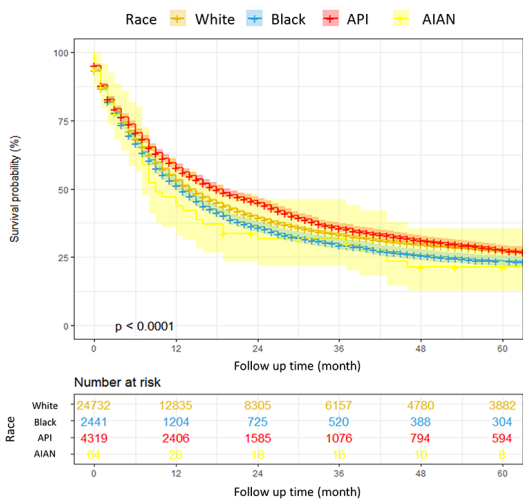


**Figure S4** Kaplan-Meier curves comparing LCSS of all racial patients with lung adenocarcinomas according to: (A) different tumor stages; (B) different tumor grade. LCSS, Lung cancer specific survival; API, Asian or Pacific Islander; AIAN, American Indian/Alaska Native.





**Figure S5** Kaplan-Meier curves comparing LCSS of all racial patients with lung adenocarcinoma patients according to different treatment methods in: (A) stage I; (B) stage IV; (C) grade II. LCSS, Lung cancer specific survival; API, Asian or Pacific Islander; AIAN, American Indian/Alaska Native; S, surgery; R, radiation; C, chemotherapy.



**Figure S6** Kaplan-Meier curves comparing LCSS of all racial groups in married lung cancer patients. LCSS, lung cancer specific survival; API, Asian or Pacific Islander; AIAN, American Indian/Alaska Native.