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Time-varying effect of sex on prognosis of lung adenocarcinoma surgical patients in China

Zezhou Wang[1,2] | Miao Mo[1,2] | Changming Zhou[1,2] | Xiaoshuang Feng[1,2] | Jie Shen[1,2] | Ting Ye[2,3,4,5] | Yang Zhang[2,3,4,5] | Hong Hu[2,3,4,5] | Haiquan Chen[2,3,4,5] | Ying Zheng[1,2,6]

[1]Department of Cancer Prevention, Fudan University Shanghai Cancer Center, Shanghai, China
[2]Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China
[3]Department of Thoracic Surgery, Fudan University Shanghai Cancer Center, Shanghai, China
[4]Institute of Thoracic Oncology, Fudan University, Shanghai, China
[5]State Key Laboratory of Genetic Engineering, School of Life Sciences, Fudan University, Shanghai, China
[6]Shanghai Engineering Research Center of Artificial Intelligence Technology for Tumor Diseases, Shanghai, China

Correspondence
Department of Cancer Prevention, Shanghai Cancer Center, Fudan University, China, 270 Dongan Road, 200032, Shanghai, China.
Email: zhengying@fudan.edu.cn

Abstract

Background: Little is known about the prognostic advantage of sex for pulmonary adenocarcinoma among Chinese patients. In this study, we aimed to investigate the true sex differences in prognosis by adjusting for confounders and to explore whether the differences were time-varying.
Methods: We identified 4438 lung adenocarcinoma patients who underwent surgery at a regional Cancer Center of China from 2008 to 2016, retrospectively. Sex, age group, smoking history, year of diagnosis and pathological stage were collected. Time-dependent Cox regression models with inverse probability of treatment weighting (IPTW) based on propensity score were used to assess the effect of sex and account for confounders. Landmark analyses were conducted to assess survival before, and after, five years.
Results: Of these patients, 1761 (39.7%) were men and 2677 (60.3%) were women. Median follow-up time was 52.6 months. After IPTW adjustment, women were found to have significantly better survival than men varying with time in both crude and IPTW models (hazard ratio [HR] [t] = $0.453 * 1.015^{t}$, where t is the length of time from treatment and its unit is month, $p < 0.001$). Women had significantly better survival than men within 0–5 years after surgery (HR = 0.763, 95% CI: 0.649–0.897, p = 0.001), whereas there was no difference after five years (HR = 1.135, 95% CI: 0.803–1.605, p = 0.472). In subgroup analysis, women in the 61–71+ age group, in the more than 20 year packs group, pathological stage 0–IB group, and 2013–2016 diagnosis period group revealed the same prognostic pattern.
Conclusions: Compared with men, women had better survival after surgical resection of lung adenocarcinoma, especially those who were older and nonsmokers or heavy-smokers and were pathological stage 0–IB in early years, while the advantage for women diminished with time.

KEYWORDS
adenocarcinoma, inverse probability of treatment weighting, prognosis, sex, time-dependent effect

INTRODUCTION

Lung cancer is the most common malignant tumor both in China and worldwide.[1] Previous studies have suggested that there may be huge differences in lung cancer between men and women.[2–12] Compared to men, a lower proportion of women with lung cancer smoke, but some cancer suppressor gene mutations and genetic susceptibility gene expression related to smoking are more common in women. Female lung cancer patients are more likely to have histologically diagnosed adenocarcinoma and are younger in age of onset than males.[13–16]

Most studies have reported that female sex is an independent favorable prognostic factor for lung cancer, yet there are also varying opinions.[17–21] Among the latter, some studies have found no sex-specific survival difference after surgical resection for early stage non-small cell lung cancer (NSCLC) patients;[19,21] others have found that when follow-up time exceeds five years, although there is a separation in the survival curves between sexes within early years, long-term survival rates are similar, especially after five years.[20] As the survival time of lung cancer patients becomes progressively longer, it is doubtful whether the effect of sex on prognosis is still consistent. It is therefore necessary to further explore exactly what patient characteristics will have sex prognostic differences and whether they change over time.[22]

According to World Health Organization statistics, adenocarcinoma has been the most common histological type of lung cancer in the world since 2004, with a significant increase in incidence worldwide in recent years.[23,24] China has one of the largest burdens of lung cancer disease worldwide, with adenocarcinoma accounting for 53.9% of all lung cancers according to a recent National Cancer Registry data report. However, the majority of current conclusions regarding whether female sex is a positive prognostic factor of lung adenocarcinoma have been acquired from United States, Europe or Japan,[4–7,12] and there is currently a lack of evidence in Chinese patients with lung adenocarcinoma. Compared with Europe and the United States, Chinese lung cancer patients have a unique disease incidence pattern, for example, the smoking ratio of female lung adenocarcinoma patients is very low.

The aim of the present study was to compare the epidemiological and clinical characteristics and the overall survival of surgical patients with lung adenocarcinoma by sex and to test whether the prognosis difference is time-varying, using a stabilized inverse probability of treatment weighting method to control related factors, from a single cancer center database in China with long-term follow-up.

METHODS

Study population

This study retrospectively reviewed the data of 4438 lung adenocarcinoma patients who underwent surgery at Fudan University Shanghai Cancer Center (FUSCC) from January 2008 to December 2016. The following exclusion criteria were applied:

TABLE 1 Unadjusted and inverse probability of treatment weighting (IPTW)-adjusted characteristics of pulmonary adenocarcinoma patients undergoing surgery

Characteristics		Before IPTW Men (*n* = 1761) n (%)	Before IPTW Women (*n* = 2677) n (%)	Test SMD	After IPTW Men (*n* = 1766.0) n (%)	After IPTW Women (*n* = 2654.2) n (%)	Test SMD
Age group (years)				0.195			0.039
	≤40	89 (5.1)	190 (7.1)		113.6 (6.4)	185.5 (7.0)	
	41–50	245 (13.9)	488 (18.2)		299.2 (16.9)	457.8 (17.2)	
	51–60	580 (32.9)	934 (34.9)		600.5 (34.0)	912.4 (34.4)	
	61–70	606 (34.4)	798 (29.8)		548.1 (31.0)	781.2 (29.4)	
	71+	241 (13.7)	267 (10.0)		204.6 (11.6)	317.2 (12.0)	
Smoking history				1.704			0.016
	Nonsmoker	563 (32.0)	2527 (94.4)		1231.2 (69.7)	1864.1 (70.2)	
	< 20 year packs	326 (18.5)	74 (2.8)		158.8 (9.0)	242.4 (9.1)	
	≥20 year packs	872 (49.5)	76 (2.8)		376.1 (21.3)	547.6 (20.6)	
Pathological stage				0.281			0.049
	0–IA	1042 (59.2)	1926 (71.9)		1196.3 (67.7)	1838.6 (69.3)	
	IB	197 (11.2)	228 (8.5)		170.6 (9.7)	246.4 (9.3)	
	IIA	24 (1.4)	29 (1.1)		18.2 (1.0)	23.7 (0.9)	
	IIB	139 (7.9)	136 (5.1)		105.1 (6.0)	139.0 (5.2)	
	IIIA	300 (17.0)	317 (11.8)		237.9 (13.5)	359.1 (13.5)	
	IIIB	48 (2.7)	33 (1.2)		30.9 (1.7)	39.8 (1.5)	
	IVA	11 (0.6)	8 (0.3)		7.0 (0.4)	7.6 (0.3)	
Diagnosis period				0.121			0.018
	2008–2012	512 (29.1)	636 (23.8)		457.1 (25.9)	708.1 (26.7)	
	2013–2016	1249 (70.9)	2041 (76.2)		1308.9 (74.1)	1946.1 (73.3)	

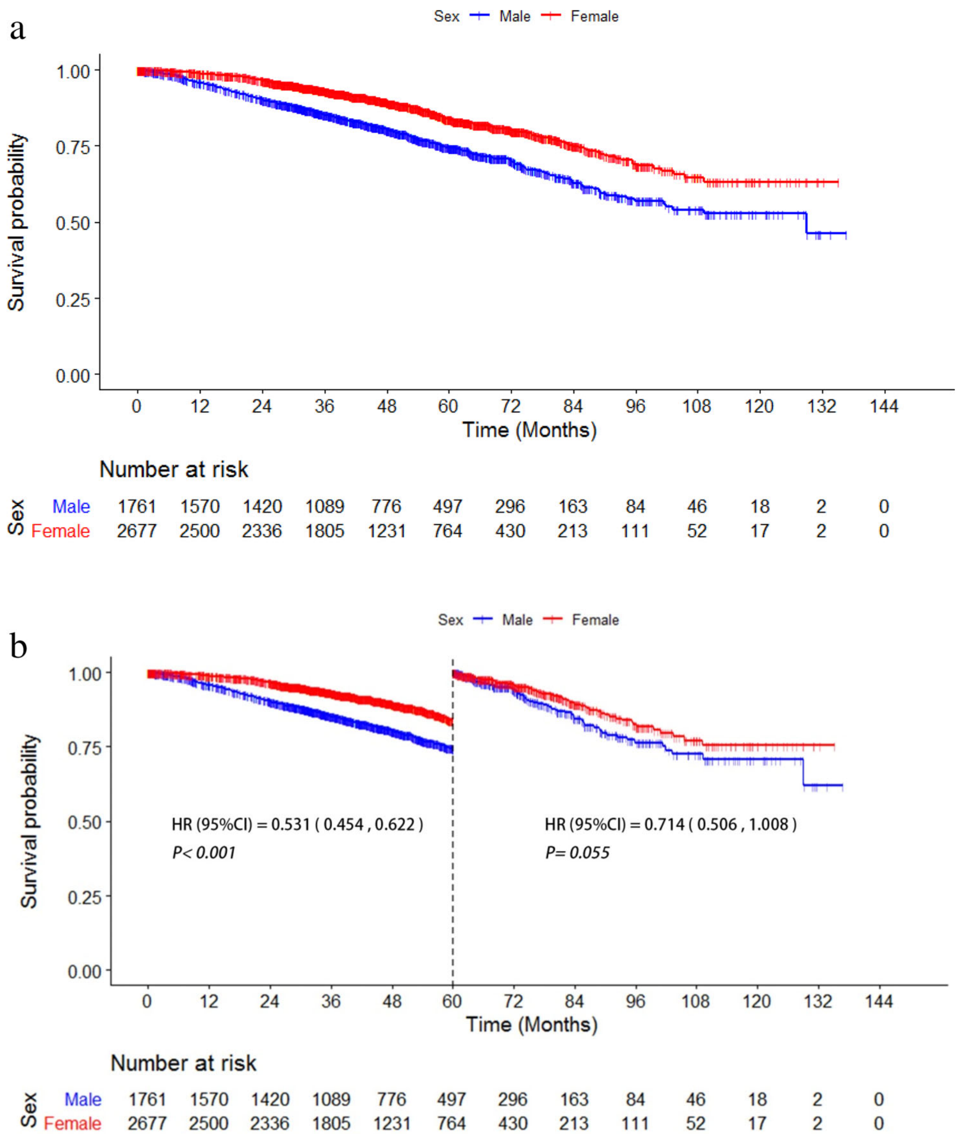

FIGURE 1 (a) Overall survival curves stratified by sex before inverse probability of treatment weighting (IPTW). (b) Landmark analysis discriminating survival before and after five year of follow-up, before IPTW. HR, hazard ratio; CI, confidence interval

(i) patients with lung cancer who had previously undergone surgery in other hospitals, (ii) patients who had only undergone lymph node biopsy and not radical resection, (iii) patients with malignant tumors whose primary tumor was not in the lungs (such as lung metastases from the breast, bone, digestive tract and genitourinary system), (iv) precancerous lesions such as squamous epithelial dysplasia and atypical adenomatous hyperplasia, and (v) benign lesions such as granulation hyperplasia or nonlung cancer lesions. This study was approved by the Fudan University Shanghai Cancer Center Institutional Review Board (Registration number: 2018 L02009/LC2019-12).

Characteristics collected for this analysis included: sex, age (≤40, 41–50, 51–60, 61–70, 71–80, and ≥81), smoking history (nonsmoker, <20 pack years, and ≥20 pack years), year of diagnosis and treatment (2008–2012 vs. 2013–2016). In addition, Patient stage data was defined according to the Eighth Edition of Union for the International Cancer Control (UICC)/ the American Joint Committee on Cancer (AJCC) TNM staging criteria for lung cancer.[25]

Outcome measures

The outcome was overall survival (OS), measured from the date of operation to the date of death due to any cause for patients who had died or the last follow-up date before December 2019 for surviving patients. Patients with no endpoint event, or the endpoint event status was unknown, were treated as censored at the date of last contact. Mortality information was derived from medical visit records, telephone visits, and death certificate data linkage. Death date and cause of death were collected by linking with the cancer registry system or death certificate system run by the provincial centers for disease control and prevention (CDC).

Statistical analysis

Stabilized inverse probability of treatment weighting (IPTW) based on propensity score was performed to

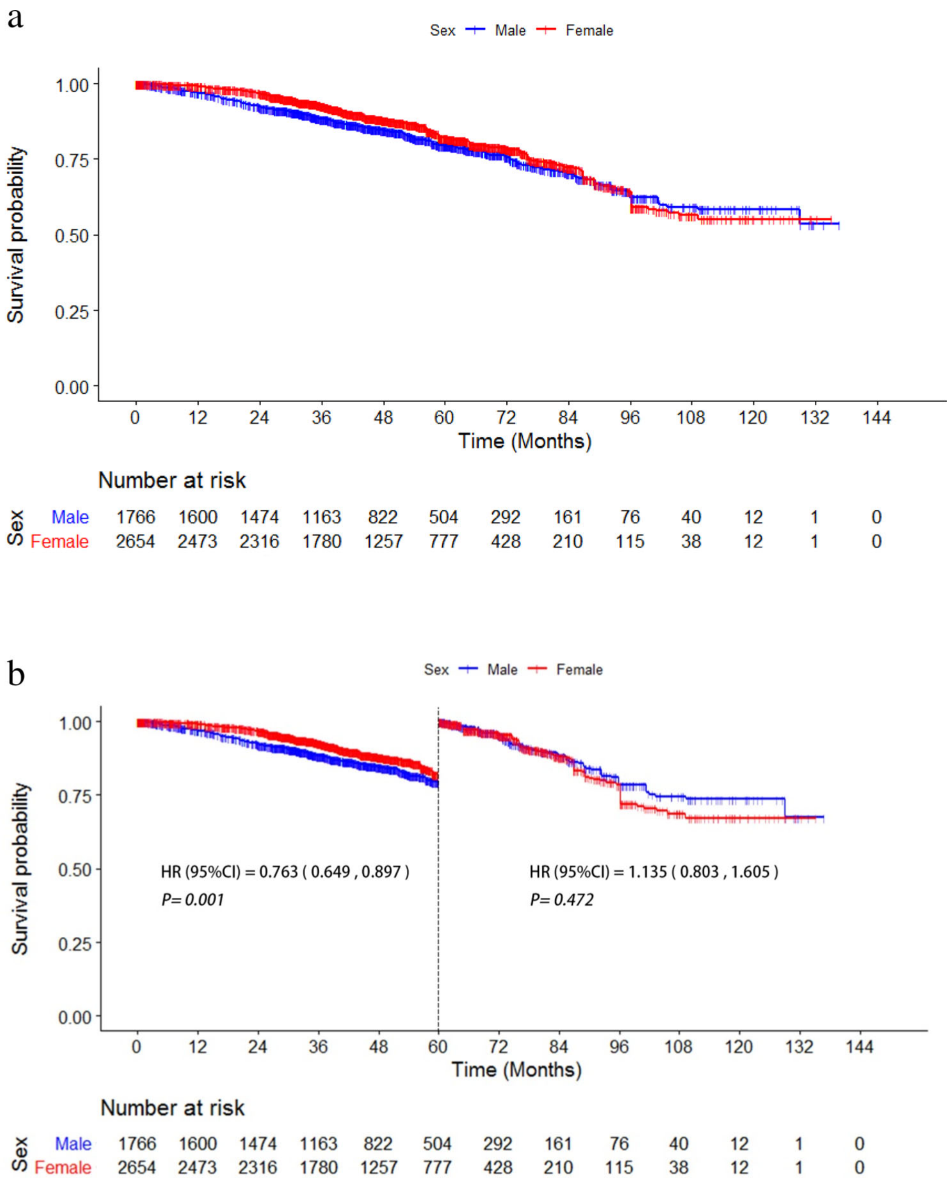

FIGURE 2 (a) Overall survival curves stratified by sex after inverse probability of treatment weighting (IPTW). (b) Landmark analysis discriminating survival before and after five year of follow-up, after IPTW. HR, hazard ratio; CI, confidence interval

control selection bias and potential confounding factors between groups in comparisons of outcome. The propensity score model included all the characteristics listed above. The χ^2 tests were used to evaluate the differences in categorical variables between male and female. The standardized mean differences (SMD) were used to measure the balance of individual covariates before and after IPTW. IPTW-adjusted Kaplan–Meier survival curves compared OS between sex groups. Time-dependent Cox regression analysis estimated both unadjusted and IPTW-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). Additionally, landmark analyses were conducted to assess survival before and after five years. Hypothesis testing was performed on two-sided 5% significance levels. Multivariable cox regression was used to conduct sensitivity analysis. Statistical analyses were implemented in R version 3.6.0 (R Foundation for Statistical Computing).

RESULTS

Unweighted and weighted baseline characteristics

This analysis included 4438 lung adenocarcinoma cases between 2008 and 2016. Of these, 1761 (39.7%) were men and 2677 (60.3%) were women. Patient characteristics before and after IPTW adjustment are summarized in Table 1. Before propensity adjustment, compared with the male group, female surgical patients with lung adenocarcinoma were younger (mean age, 57.1 vs. 59.4 years; $p < 0.001$). Individuals in the 51- to 60-year-old age group in female and 61- to 70-year-old age group in male were predominant, respectively. Women smoked less than men ($p < 0.001$). Within the female group, 94.4% were nonsmokers and 2.8% smoked less than 20 pack years, compared with 32.0% and 18.5% of patients in the male group. A statistically

TABLE 2 Unadjusted and inverse probability of treatment weighting (IPTW)-adjusted time-dependent hazard ratios

Characteristics		Before IPTW				After IPTW			
		HR/HR (0) (95% CI)	*p*	HR(*t*)	*p* for interaction	HR/HR (0) (95% CI)	*p*	HR(t)a	*p* for interaction
All		0.351 (0.267,0.462)	<0.001	$0.351*1.012^t$	<0.001	0.453 (0.339,0.604)	<0.001	$0.453*1.015^t$	<0.001
Age group (years)									
	≤40	1.075 (0.436,2.650)	0.875		0.089	1.671 (0.644,4.332)	0.291		0.061
	41–50	0.971 (0.628,1.499)	0.893		0.426	1.376 (0.872,2.173)	0.170		0.119
	51–60	0.640 (0.494,0.831)	0.001		0.178	1.092 (0.846,1.411)	0.499		0.462
	61–70	0.269 (0.164,0.443)	<0.001	$0.269*1.015^t$	0.008	0.255 (0.150,0.434)	<0.001	$0.255*1.025^t$	<0.001
	71+	0.483 (0.345,0.677)	<0.001		0.098	0.444 (0.314,0.629)	<0.001		0.146
Smoking history									
	nonsmoker	0.449 (0.294,0.688)	<0.001	$0.449*1.012^t$	0.026	0.609 (0.424,0.874)	0.007	$0.609*1.009^t$	0.028
	< 20 year packs	0.691 (0.341,1.403)	0.306		0.288	0.870 (0.521,1.453)	0.595		0.124
	≥20 year packs	0.205 (0.066,0.634)	0.006	$0.205*1.029^t$	0.006	0.216 (0.122,0.383)	<0.001	$0.216*1.031^t$	<0.001
Pathological stage									
	0–IA	0.300 (0.172,0.525)	<0.001	$0.300*1.013^t$	0.018	0.340 (0.185,0.624)	0.001	$0.340*1.016^t$	0.009
	IB	0.614 (0.404,0.932)	0.022		0.199	0.178 (0.057,0.551)	0.003	$0.178*1.030^t$	0.009
	IIA	0.717 (0.269,1.913)	0.506		0.240	0.855 (0.257,2.846)	0.798		0.628
	IIB	0.707 (0.482,1.039)	0.077		0.821	0.615 (0.406,0.933)	0.022		0.233
	IIIA	0.460 (0.294,0.722)	0.001	$0.460*1.016^t$	0.005	0.470 (0.290,0.760)	0.002	$0.470*1.018^t$	0.004
	IIIB	0.714 (0.390,1.305)	0.274		0.784	1.080 (0.580,2.011)	0.807		0.510
	IVA	0.645 (0.208,1.997)	0.447		0.240	0.669 (0.191,2.34)	0.529		0.180
Diagnosis period									
	2008–2012	0.735 (0.601,0.899)	0.003		0.089	0.613 (0.399,0.943)	0.026	$0.613*1.012^t$	0.004
	2013–2016	0.279 (0.181,0.429)	<0.001	$0.279*1.015^t$	0.017	0.595 (0.480,0.738)	<0.001		0.063

Note: t is the length of time from treatment, unit: month(s).

TABLE 3 Unadjusted and inverse probability of treatment weighting (IPTW)-adjusted hazard ratios before and after five years

		Before IPTW				After IPTW			
Characteristics		**HR before 5 years (95%CI)**	***p***	**HR after 5 years (95%ci)**	***p***	**HR before 5 years (95%ci)**	***p***	**HR after 5 years (95%CI)**	***p***
All		0.531 (0.454,0.622)	<0.001	0.714 (0.506,1.008)	0.055	0.763 (0.649,0.897)	0.001	1.135 (0.803,1.605)	0.472
Age group (years)									
	≤40	0.728 (0.282,1.882)	0.513	—	—	1.182 (0.443,3.153)	0.738	—	—
	41–50	1.011 (0.626,1.634)	0.964	0.799 (0.284,2.245)	0.670	1.344 (0.814,2.219)	0.248	1.542 (0.510,4.665)	0.443
	51–60	0.625 (0.467,0.838)	0.002	0.702 (0.396,1.245)	0.227	1.096 (0.820,1.465)	0.536	1.080 (0.626,1.863)	0.782
	61–70	0.435 (0.332,0.569)	<0.001	0.776 (0.426,1.412)	0.406	0.552 (0.416,0.732)	<0.001	1.698 (0.863,3.340)	0.125
	71+	0.486 (0.338,0.700)	<0.001	0.464 (0.187,1.153)	0.098	0.458 (0.315,0.666)	<0.001	0.362 (0.135,0.973)	0.044
Smoking history									
	nonsmoker	0.667 (0.525,0.848)	0.001	0.834 (0.480,1.449)	0.519	0.840 (0.684,1.031)	0.096	0.988 (0.622,1.570)	0.960
	< 20 year packs	0.645 (0.289,1.441)	0.285	0.900 (0.206,3.936)	0.889	0.788 (0.438,1.419)	0.428	1.162 (0.423,3.196)	0.771
	≥20 year packs	0.556 (0.303,1.020)	0.058	1.526 (0.537,4.335)	0.428	0.610 (0.453,0.822)	0.001	1.607 (0.839,3.076)	0.152
Pathological stage									
	0–IA	0.472 (0.339,0.655)	<0.001	0.774 (0.443,1.351)	0.367	0.614 (0.440,0.856)	0.004	1.010 (0.565,1.809)	0.972
	IB	0.624 (0.384,1.013)	0.057	0.585 (0.257,1.330)	0.201	0.561 (0.329,0.957)	0.034	1.223 (0.541,2.767)	0.629
	IIA	0.510 (0.162,1.608)	0.250	2.183 (0.227,21.022)	0.499	0.614 (0.154,2.443)	0.488	2.928 (0.132,64.787)	0.497
	IIB	0.728 (0.487,1.088)	0.122	0.517 (0.133,2.010)	0.341	0.637 (0.413,0.985)	0.042	0.406 (0.088,1.882)	0.250
	IIIA	0.766 (0.597,0.981)	0.035	1.032 (0.535,1.988)	0.926	0.880 (0.687,1.127)	0.310	0.937 (0.476,1.847)	0.851
	IIIB	0.788 (0.418,1.484)	0.461	0.277 (0.031,2.513)	0.254	1.190 (0.596,2.376)	0.622	0.698 (0.166,2.937)	0.624
	IVA	0.787 (0.249,2.480)	0.682	—	—	0.766 (0.217,2.704)	0.678	—	—
Diagnosis period									
	2008–2012	0.733 (0.576,0.931)	0.011	0.740 (0.510,1.074)	0.113	1.031 (0.806,1.317)	0.810	1.224 (0.848,1.765)	0.280
	2013–2016	0.438 (0.355,0.540)	<0.001	0.501 (0.198,1.269)	0.145	0.597 (0.479,0.743)	<0.001	0.555 (0.184,1.673)	0.296

significant difference also existed in tumor stage, with more female patients at early stage than male ($p < 0.001$). Additionally, the proportion of female patients diagnosed and treated from 2013 to 2016 was higher than those in 2008–2012 ($p < 0.001$). After IPTW adjustment, an excellent balance of baseline characteristics between groups resulted. All SMD values of weighted characteristics were less than 0.1 (Table 1).

Overall survival and hazard ratios

Median follow-up time was 52.6 months (interquartile range [IQR] 38.3–71.6 months). The survival curves are shown in Figures 1 and 2. The survival advantage for women undergoing lung adenocarcinoma surgery versus men declined over time in both unadjusted (hazard ratio [t] [HR(t)] = $0.351^{*}1.012^{t}$, where t is the length of time from treatment, and its unit is month, $p < 0.001$) and IPTW-adjusted models (HR [t] = $0.453^{*}1.015^{t}$, $p < 0.001$). Landmark analysis with five years as the cutoff point also showed that women had significantly better survival than men within 0–5 years after surgery (unadjusted HR [unadjHR] = 0.531, 95% CI: 0.454–0.622, $p < 0.001$; IPTW-adjusted HR [adjHR] = 0.763, 95% CI: 0.649–0.897, p = 0.001). However, hazard rates did not differ significantly between sexes after five years (unadjHR = 0.714, 95% CI: 0.506–1.008, p = 0.055; adjHR = 1.135, 95% CI: 0.803–1.605, p = 0.472).

Stratified analyses were performed in subsets of patients according to age group, smoking history, pathological stage and diagnosis period. Patients in 61–71+ age group, with more than 20 year packs smoking history group, pathological stage 0–IB group, and 2013–2016 diagnosis period group revealed the same pattern after IPTW adjustment. The results of the time-dependent coefficient method and landmark analysis were approximately consistent (Tables 2 and 3).

Sensitivity analysis

In the sensitivity analysis, multivariable Cox regression yielded consistent results (HR [t] = $0.536^{*}1.011^{t}$, $p < 0.001$). A total of 9.8% of patients were lost to follow-up in this study whose characteristics were similar to patients overall (Table S1). The exclusion of patients who were lost to follow-up did not substantially alter the findings in our study (HR[t] =$0.462^{*}1.015^{t}$, $p < 0.001$].

DISCUSSION

In our study, lung adenocarcinoma surgical patients who were female showed significantly better survival than men at a specific time period, and this finding remained, even after adjusting for various confounding factors. The study shown that female sex was one of the statistically positive independent predictors of survival among Chinese lung adenocarcinoma surgical patients. This result was consistent with many other studies that have evaluated the effect of sex on lung cancer prognosis in the United States, Europe or Japan.[4–7,12]

Women with lung adenocarcinoma were found to be younger, had earlier stage tumors, and smoked less than men in this study. Since computed tomography (CT) was introduced to diagnose cancer, and low-dose CT has been used more and more in general lung cancer screening in China, these tools have provided vital opportunities in the resection of small-size lung cancers. Most of the lung cancers detected by CT screening are likely to be small-size and slow-growing adenocarcinomas. In addition, women account for a large proportion of people with lung cancer detected by CT screening. This is one of the reasons for the increased incidence of early-stage lung cancers among women.[26,27] In fact, it has been reported that early-stage lung cancers such as bronchioloalveolar carcinoma or adenocarcinoma mixed bronchioloalveolar subtype tend to occur more frequently in nonsmoking women. These data indicate that the difference in the pathobiological characteristics of adenocarcinoma between sexes should be addressed. However, there is still a concern that whether the higher average age of onset and later tumor stages in men is due to their slow response to health condition and illness. In our study, we controlled these confounding factors that may affect the survival prognosis difference as much as possible by using the inverse probability weighting method. When the analysis of sex differences in prognosis was performed, age, smoking history, pathological stage, and diagnosis period were balanced between the two sex groups, therefore making the results more credible.

The novelty we found in this study was that the survival advantage of women over men was not consistently. In most cases, women survived better than men within five years, but the advantage tended to decrease over time, with no significant difference between male and female in survival after five years, or even in some cases that survival in women was inferior to that in men. One possible reason for this is that the treatment difference is mainly manifested in the early period. As the survival time is longer, the homogeneity of male and female survivors is higher. For patients with early stage or less severe disease, they are likely to be in a completely cured state without tumor burden if they survive more than five years after surgery. For patients with advanced stage and severe disease, the early survival advantage is usually due to the use of targeted drugs; however, patients may develop resistance after about one year to most of the targeted drugs, or new mutations occur that may lead to treatment failure. After that, the treatment modalities converge between the sexes. Another reason could be that the effect of smoking cessation in men is evident after being diagnosed with cancer. Similar smoking patterns between the sexes cause similar long-term mortality risks.[28] On the other hand, some studies also suggest that the prognostic gap between men and women is diminishing.[19]

With further analysis, we found that the survival advantage of women was manifested in older patients, nonsmokers, heavy smokers and stage 0–IB and IIB–IIIA cases.

These findings were consistent with former population-based samples.[29] A prospective trial studied 981 patients newly diagnosed with stage I, II or III NSCLC also suggested that women with NSCLC live longer, even when researchers control for every factor that might influence survival in NSCLC, including tobacco and other exposures, lifestyle factors, disease stage, treatment, tumor biology, and hormonal factors.[30]

We also found women treated from 2013 to 2016 in Shanghai had significantly better OS than men at the same period. One possible reason for this is the development of specific treatment techniques. Initially the treatment of lung cancer is guided by the disease, the tumor found on imaging, and then subsequent surgery, radiotherapy, or chemotherapy treatment selection. Subsequently, treatment enters the pathology-guided treatment stage, squamous cell carcinoma or adenocarcinoma of lung cancer is divided by pathological type, and the corresponding therapeutic drugs are selected according to different pathological types.[31] In the last decade, the treatment of lung cancer has advanced and entered the molecular oncology stage.[32] Compared with male lung adenocarcinoma cancer patients, female patients have been found to have a higher proportion caused by specific types of gene mutations (such as *EGFR*), especially in East Asia.[16] At present, there are precise targeted therapy drugs for some lung cancers with specific types of gene mutations and patient prognosis is also good. Therefore, having early screening and genetic testing as soon as possible after diagnosis are important. Tyrosine kinase inhibitors such as gefitinib contribute to improvements in the prognosis of adenocarcinoma patients with *EGFR* mutations.[33,34] Since gefitinib was approved in China, it is likely that this drug has partly contributed to the increasing sex differences in lung cancer survival since the 2000s. It is worth noting that some patients will develop drug resistance or new mutations after targeted drug therapy, therefore regular follow-up and secondary genetic testing are important.[35]

The strength of this study is that a propensity score based on IPTW adjustment was taken to significantly reduce confounding bias and imbalance in covariates and thus potentially offers an estimation of treatment effect similar to randomized trials. We also made efforts in data verification and in adherence to follow-up information accuracy. By using the entire database of 4438 patients, the IPTW approach increased the study power compared with matched-pairs analysis. To obtain the most accurate estimation of the effect of sex, we selected variables associated with survival in surgical lung adenocarcinoma patients. After IPTW adjustment, all characteristics in this study were well balanced between sex groups. Furthermore, our results remained consistent with previous unadjusted data and showed significantly better survival in female patients. Another strength is that our database data collection is complete, with an overall visit rate of more than 90%, making the results reliable.

One of the limitations of this study is that it is a retrospective rather than a prospective study. Only all-cause mortality data were collected. Although there was no lung cancer-specific mortality data in this study, it is generally believed that the vast majority of deaths in patients with lung cancer are due to primary tumors. Another disadvantage is that *EGFR* mutation and ALK rearrangement or other genetic factors were not tested during the time period included in our study. We used an IPTW adjustment analysis; however, there are still some important confounding factors, such as unmeasured socioeconomics, not included in our database or available during chart review. A slight disadvantage may be that our study was a single center study in which treatment approaches did not vary, and patients with similar treatment protocols and certain reference values for laboratory data were included.

Our study found that survival duration was longer in women after surgical resection of lung adenocarcinoma who were older, heavy-smokers and in pathological stages 0–IB only in early years. The results of this study indicate that lung adenocarcinoma present as a different disease in women and men. A different natural history and tumor biology exist between men and women. Studies exploring mechanisms mediating these differences in prognosis are further required to validate our findings, which may lead to improved, patient-specific treatment in the future.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Haiquan Chen https://orcid.org/0000-0001-7846-257X
Ying Zheng https://orcid.org/0000-0002-6408-8510

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