Lung Cancer and Prognosis in Taiwan
A Population-Based Cancer Registry

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Introduction: Lung cancer is the leading cause of cancer death in Taiwan. This study investigated the prognostic factors affecting survival of patients with lung cancer in Taiwan.

Methods: Data were obtained from the National Health Insurance Research Database published in Taiwan. Clinicopathologic profiles and prognostic factors of 33,919 lung cancer patients were analyzed between 2002 and 2008 in this retrospective review. The impact of the clinicopathologic factors on overall survival was assessed.

Results: Nearly two thirds of the patients were men. The 5-year survival rate was 15.9%, with a median survival of 13.2 months. The clinical staging of the patients included stage I (n = 4254; 12.5%), stage II (n = 1140; 3.4%), stage III (n = 10,161; 30.0%), and stage IV (n = 18,364; 54.1%). In the multivariate analysis, age more than 65 years, sex, cell type, histologic grade, and primary tumor location were identified as independent prognostic factors.

Conclusion: In additional to tumor-nodes-metastasis (TNM) staging system, patient sex and age, tumor location, cell type, and differentiation were independent prognostic factors. We recommend incorporation of these factors to subclassify lung cancer patients.

Key Words: Lung cancer, Age, Sex, Cell type, Differentiation.

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Lung cancer is identified as the leading cause of tumor-related deaths in the world[1] and also represents the most common cancer death in Taiwan. Survival of patients with lung cancer remains poor, and the 5-year survival rates vary from 6% to 18% (2–4). Most patients are diagnosed at an advanced stage, and the opportunity for complete surgical resection with improved long-term survival is lost.

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The biology and pathogenesis of lung cancer is complex, and the treatment strategy depends on accurate staging. The 6th edition of tumor, node, metastasis (TNM) classification for lung cancer was published in 1997 (5)and the 7th edition was updated in 2007. The two staging systems only included tumor size, presence of nodal invasion, and presence of metastasis to distant organs as staging factors. Many prognostic factors influence survival with lung cancer; however, the impact of factors such as tumor location, cell type, and histologic grading were still undetermined.

The purpose of the staging system is to group cancer patients with similar prognoses and provide treatment guidelines to physicians. The identification of prognostic factors is important for patients and physicians to choose adequate treatment modalities. The Taiwan National Health Insurance Research Database records detailed clinical information about individuals diagnosed with lung cancer in Taiwan. For this study, we obtained data from Taiwan National Health Insurance Research Database over a 7-year period to examine the prognostic factors influencing survival for lung cancer patients and also described characteristics of lung cancer patients in Taiwan.

PATIENTS AND METHODS

Database

The population data were obtained from National Health Insurance Research Database (NHIRD), which included approximately 98% of the 23 million total population in Taiwan. The NHIRD is one of the largest such data sets, and hundreds of researchers have used it in published studies. The database provides principal diagnostic and demographic information for each patient, along with one principal diagnosis code and up to four secondary diagnosis codes obtained from the International Classification of Disease, Tenth Revision code. Comprehensive health care data include the enrollment files, claims data, catastrophic illness files, registry for treatments, and Taiwan death certificates. All the patients were confirmed by tissue diagnosis. Because the information was released strictly for research purposes, the study was exempt from full review by the Internal Review Board in our hospital. The following items were included in the study: age, sex, tumor location, cell type, histologic grading, surgical resection methods, clinical T, clinical N, clinical stage, treatment modality, survival time, and cause

of death. The histologic diagnosis was described according to the World Health Organization classification. All the patients were staged according to the 6th edition of the TNM staging system published in 1997.[2] The initial treatment was defined as the therapy administered to the patient within 3 months of diagnosis.

Study Sample

This study uses generalized data from NHIRD between 2002 and 2008. The clinical sample was identified from the pooled database by the diagnostic codes C34.0, C34.1, C34.2, C34.3, C34.8, and C34.9. We identified a total of 43,986 patients with malignant bronchial and lung neoplasms. A total of 10,067 patients were excluded from the study because of incomplete data. Therefore, a total of 33,919 patients were enrolled into the study.

Statistical Analysis

The SAS software (SAS System for Windows, version 9.2; SAS Institute, Cary, NC) was used to perform the statistical analysis for this study. The overall survival (OS) was defined from the date of tissue confirmation of malignancy to the death or December 2010. Date and cause of death were confirmed with Taiwan death certificates. The Taiwan death certificates updated data in December 2010. An observation was censored in December 2010 when the patients were alive, or had died from other causes. OS was calculated by the Kaplan–Meier method, and the difference in survival was determined by the log-rank test. Univariate and multivariate analyses were performed with the Cox proportional hazards model using SAS software.

To investigate the impact on OS, the following clinicopathologic factors were included in the univariate analyses: age, sex, tumor location, cell type, surgical method, "T," "N," histologic grade, tumor location, and all therapeutic methods within 3 months after diagnosis.

The prognostic predictors in the 6th edition of the American Joint Committee on Cancer TNM staging system ("T" and "N"), age, sex, tumor location, histologic grade, surgery (yes and no), chemotherapy (yes and no), and radiotherapy (yes and no) were entered in the multivariate analyses to identify independent predictors of survival. Statistical analysis was considered to be significant with a p value less than 0.05.

RESULTS

During the study period, data from 33,919 lung cancer patients were analyzed. Nearly two thirds of the patients were men (n = 22,217). Among these 33,919 patients, 5,657 patients (16.7%) were still alive in December 2010; 25,957 patients (76.5%) had died from lung cancer; and, 2,305 patients (6.8%) had died from other causes.

The 5-year OS rate was 15.9%, with a median survival of 13.2 months (Fig. 1*A*). The clinicopathologic characteristics are shown in Table 1. The 5-year OS rate was assessed and stratified according to each clinical parameter (age, sex, tumor location, cell type, surgical methods, clinical T, clinical N, clinical stage, histologic grading, and treatment method).

Patients were distributed according to the clinical stage: stage I (n = 4254; 12.5%); stage II (n = 1140; 3.4%); stage III (n = 10,161; 30.0%); and stage IV (n = 18,364; 54.1%). The survival curves according to clinical stage are shown in Figure 1*B*. The 5-year survival rates by clinical stage were 60.7% for stage I, 36.3% for stage II, 13.3% for stage III, and 4.9% for stage IV. The difference in survival was significant between neighboring stages.

The 5-year OS rates according to patient age were 20.8% (<45 years), 21.2%, (46–64 years), and 12.6% (>65 years). Patients over 65 years of age at the time of diagnosis (n = 21,375) had a significantly inferior 5-year OS (Fig. 2*A*). Similar 5-year survival and median survival rates were demonstrated for patients less than or equal to 45 years of age and patients 45 to 64 years of age.

Men diagnosed with lung cancer (n = 22,217) had a worse prognosis than women (Fig. 2*B*). Women with lung cancer (n = 11,702) had a longer median survival (19.6 months) and better 5-year survival rate (20.7%) than men (median

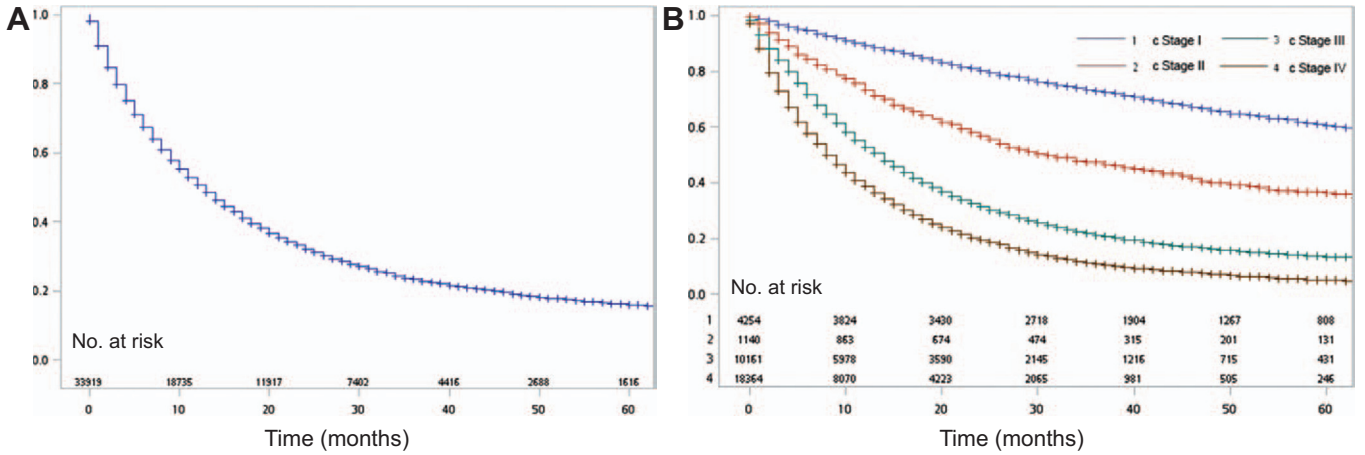

FIGURE 1. *A*, Kaplan–Meier survival curves for 33,919 patients with lung cancer, and (*B*) Kaplan–Meier survival curves for 33,919 patients stratified by clinical stage. The survival difference was significant ($p < 0.0001$).

TABLE 1. Patient Demographic Data and Univariate Survival Analysis

Variables	Numbers	5-Year Survival (%;95% CI)	Median Survival Time (month; 95% CI)	*p*
All	33,919	15.88 (15.39–16.37)	13.20 (12.95–13.46)	
Age (yr)				<0.0001
<45	1,728	20.83 (18.5–23.16)	20.81 (19.7–21.92)	
45–64	10,816	21.29 (20.33–22.25)	19.31 (18.74–19.89)	
≥65	21,375	12.64 (12.08–13.2)	10.19 (9.95–10.42)	
Sex				<0.0001
Male	22,217	13.28 (12.73–13.83)	10.80 (10.58–11.02)	
Female	11,702	20.67 (19.74–21.6)	19.57 (19.03–20.11)	
Tumor location				<0.0001
Main bronchus	770	6.74 (4.49–8.99)	8.08 (7.35–8.8)	
Upper lobe	17,068	17.46 (16.75–18.17)	14.17 (13.8–14.54)	
Middle lobe	2,233	20.3 (18.26–22.34)	16.98 (15.88–18.08)	
Lower lobe	10,960	15.92 (15.05–16.79)	13.40 (12.96–13.84)	
Multiple lobes	448	9.95 (6.68–13.22)	9.13 (7.74–10.53)	
Unspecific	2,440	4.41 (3.36–5.46)	7.19 (6.62–7.76)	
Cell type				<0.0001
Adenocarcinoma	17,875	18.66 (17.93–19.39)	17.6 (17.19–18.02)	
SQCC	7,321	14.73 (13.77–15.69)	11.2 (10.78–11.62)	
Others	8,723	10.69 (9.9–11.48)	8.63 (8.34–8.92)	
Surgical methods				<0.0001
No surgery	28,372	7.46 (7.06–7.86)	10.37 (10.18–10.55)	
Pneumonectomy	188	35.16 (27.52–42.8)	24.31 (18.13–30.48)	
Bilobectomy	123	44.59 (34.44–54.74)	49.49 (43.48–55.5)	
Lobectomy	3,557	64.48 (62.52–66.44)	>108	
Segmentectomy	161	46.38 (36.83–55.93)	50.74 (44.14–57.35)	
Wedge resection	1,518	44.6 (41.35–47.85)	49.54 (47.53–51.55)	
T				<0.0001
1	3,651	51.13 (49.09–53.17)	64.23 (61.57–66.90)	
2	9,202	23.2 (22.14–24.26)	19.37 (18.7–20.05)	
3	3,974	10.59 (9.4–11.78)	10.76 (10.25–11.26)	
4	17,092	5.34 (4.89–5.79)	9.16 (8.94–9.38)	
N				<0.0001
0	9,557	34.4 (33.24–35.56)	29.39 (28.24–30.55)	
1	2,632	17.12 (15.26–18.98)	16.11 (14.96–17.26)	
2	11,870	9.59 (8.91–10.27)	11.34 (11.01–11.66)	
3	9,860	4.98 (4.4–5.56)	8.68 (8.43–8.93)	
Stage				<0.0001
1	4,254	60.65 (58.83–62.47)	102.10 (101.16–103.04)	
2	1,140	36.29 (32.9–39.68)	31.33 (22.68–39.97)	
3	10,161	13.34 (12.51–14.17)	14.17 (13.78–14.56)	
4	18,364	4.91 (4.47–5.35)	8.98 (8.78–9.17)	
Grade				<.0001
Well differentiated	1,329	51.49 (48.14–54.84)	65.25 (62.12–68.39)	
Moderately differentiated	5,422	35 (33.47–36.53)	29.15 (27.02–31.29)	
Poorly differentiated	5,131	15.77 (14.54–17)	11.95 (11.38–12.52)	
Undifferentiated	22,037	8.94 (8.46–9.42)	10.79 (10.58–11)	
Treatment				
Surgery				<0.0001
Yes	5,547	57.19 (55.57–58.81)	81.47 (75.89–87.06)	
No	28,372	7.46 (7.06–7.86)	10.37 (10.18–10.55)	
Chemotherapy				0.0006
Yes	18,163	10.99 (10.39–11.59)	14.2 (13.92–14.48)	
No	15,756	21.57 (20.8–22.34)	11.14 (10.64–11.63)	
Radiotherapy				<0.0001
Yes	10,122	7.91 (7.23–8.59)	9.88 (9.64–10.13)	
No	23,797	19.23 (18.61–19.85)	15.38 (15.04–15.71)	

CI, confidence interval; M, metastasis; N, node; T, tumor; SD, standard deviation; SQCC, squamous-cell carcinoma.

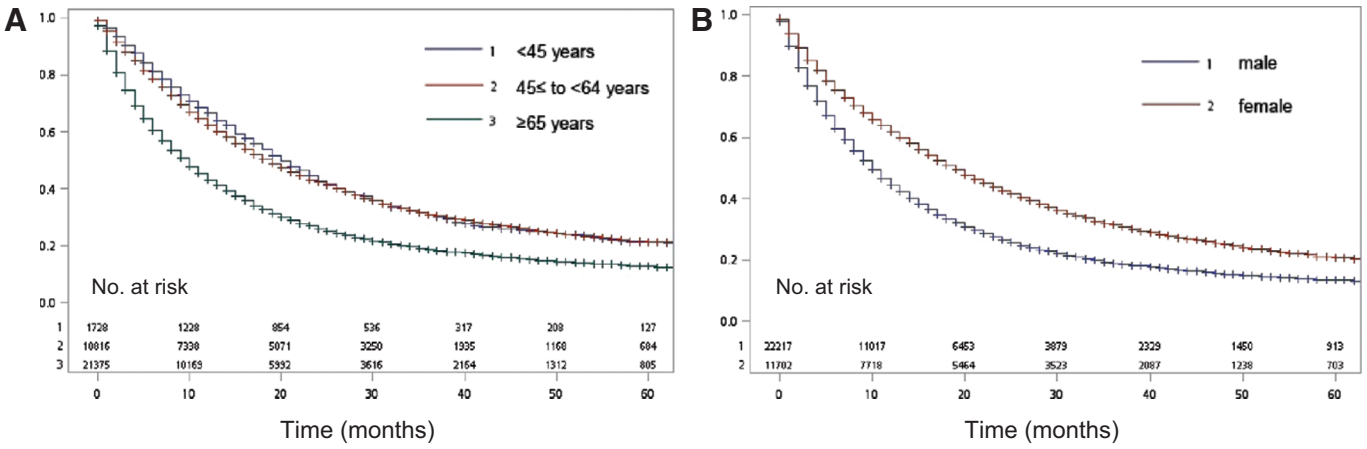

FIGURE 2. *A,* Kaplan–Meier survival curves for lung cancer patients according to age. Groups were defined as age less than 45 years ($n = 1728$), age 45 to 64 years ($n = 10,816$), and age more than or equal to 65 years ($n = 21,375$). An age of 65 years or more was associated with a significantly worse prognosis than the other two age groups ($p < 0.0001$). *B,* Kaplan–Meier survival curves for lung cancers patients stratified by sex. The survival difference is significant ($p < 0.0001$).

survival, 10.8 months; 5-year survival rate, 13.3%; both, $p < 0.001$).

As shown in Figure 3*A*, the median survival in patients with squamous-cell carcinoma (SQCC) ($n = 7321$; median survival, 11.2 months) was worse than that of patients with adenocarcinoma (AC) ($n = 17,875$; median survival, 17.6 months). The histologic grading significantly influenced the OS ($p < 0.001$). The 5-year OS rates according to histology were well-differentiated (51.5%), moderately differentiated (35.0%), poorly differentiated(15.8%), and undifferentiated (8.9%). The difference in survival was significant between classes of differentiation (Fig. 3*B*).

The survival curve was stratified by tumor location (Fig 4*A*). The survival time for patients with middle- and upper-lobe involvement was similar ($p = 0.3201$). Patients with lower-lobe tumors or main bronchial tumors had inferior survival rates. Furthermore, multiple lung tumors demonstrated the worst survival.

The population database also contained the information about the initial treatment each patient received (generally within 3 months of diagnosis). However, there were no comprehensive data for all treatments recorded in the database. Chemotherapy was administrated to 18,163 patients (53.6%), and radiotherapy was performed in 10,122 patients (29.8%). Only 5547 patients (16.4%) received surgical resection according to the database analysis.

Of the 5547 patients who underwent pulmonary resection for lung or bronchial tumors, 161 (2.9%) underwent segmental resection; 1518 (27.4%) underwent wedge resection; 3557 (64.1%) underwent lobectomy; 123 (2.2%) underwent bilobectomy; and, 188 (3.4%) underwent pneumonectomy. The overall surgical resection rate was 16.4% (based on

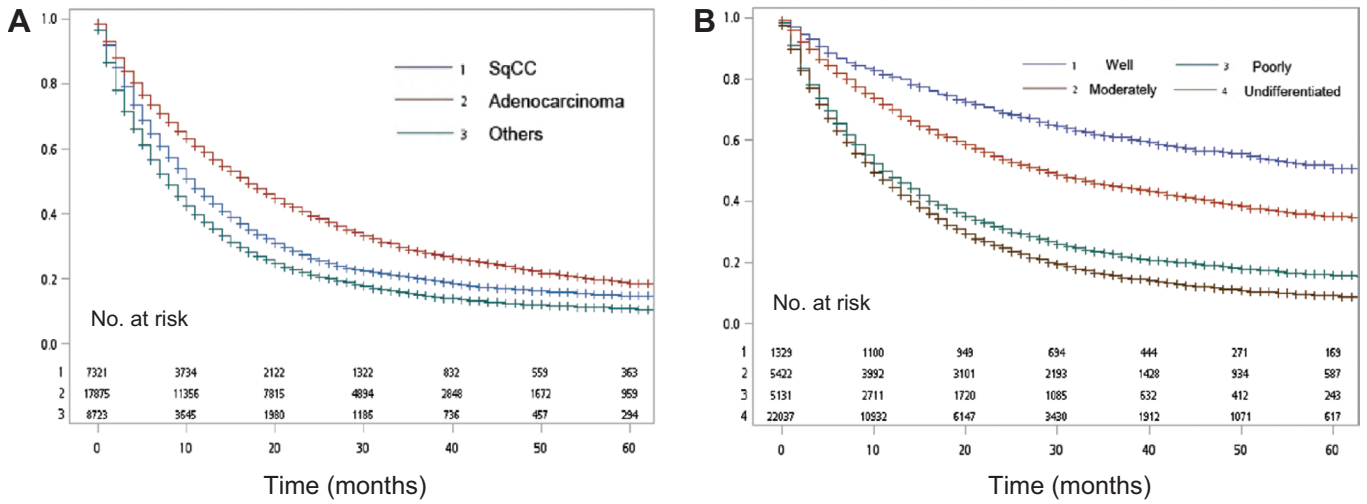

FIGURE 3. *A,* Kaplan–Meier survival curves stratified by histologic cell type. Adenocarcinoma has a significantly better prognosis than squamous-cell carcinoma ($p < 0.0001$). *B,* Kaplan–Meier survival curves stratified by cell differentiation. The difference was significant ($p < 0.0001$). SQCC, squamous-cell carcinoma.

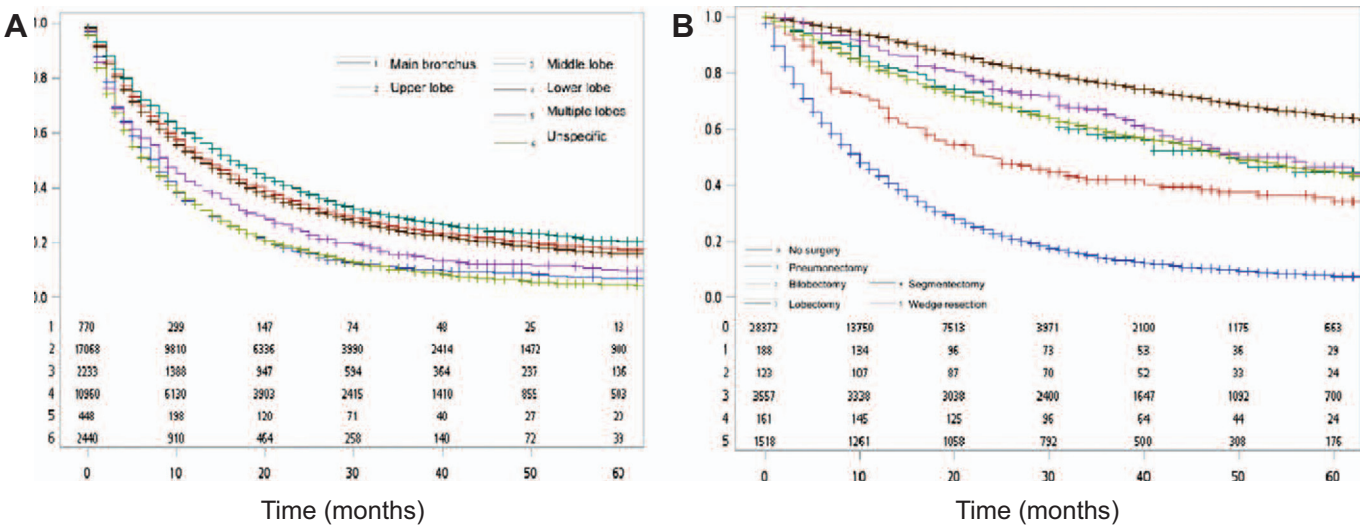

FIGURE 4. *A,* Kaplan–Meier survival curves stratified by tumor location. Patients with lower-lobe cancers have worse survival rates than upper-/middle-lobe cancers (*B*) Kaplan–Meier survival curves stratified by surgical method. Patients without surgical resection have the worst survival, and patients undergoing lobectomy have the best survival in the surgical group.

33,919 patients). During the study period, the 5-year survival rate for patients who underwent surgical resection was 57.2%. The 5-year OS rate for patients who did not have surgery was only 7.5%. Patients who underwent lobectomy had the best 5-year survival rate compared with patients who underwent other surgical procedures (Fig. 4*B*).

In univariate analysis, age, sex, tumor location, cell type, surgical method, T, N, degree of differentiation, and surgical resection were found to be statistically associated with OS (Table 1). A multivariate Cox regression model was constructed incorporating patient age, sex, "T," "N," tumor location, histologic grade, and treatment methods. Age, sex, tumor location, "T," "N," histologic grade, and surgical resection remained independent prognostic factors (Table 2).

DISCUSSION

This study investigated the clinicopathologic features of patients with lung cancer in Taiwan, based on the 6th TNM system, which included an assessment of tumor size, nodal invasion, and presence of metastasis as staging factors. Our study indicated that age, sex, cell type, histologic grading, and tumor location were independent prognostic factors in multivariate analysis.

Of the 33,919 patients diagnosed with lung cancer, 5547 patients (16.4%) underwent surgical resection. Other studies reported resection rates between 8.2% and 27%.[3–7] The surgical rate in Taiwan was similar with previous reports. Complete surgical resection provided the highest probability of long-term survival. Anatomic resection with radical lymph node dissection was a curative treatment for lung cancer. The difference in the 5-year survival rates for patients who underwent surgery (57.2%) and patients who did not receive surgical intervention (7.5%) was significant ($p < 0.0001$). Those patients who did not undergo surgery had a median survival of 7.46 months. Sawabata et al.[8] collected the first prospective data of surgical and nonsurgical lung cancer patients in Japan. The database contained a high percentage (57.4%) of surgical cases. Of the patients who underwent surgery, the 5-year survival rate was 66%. Otherwise, 5-year survival rate of patients who did not receive surgery was 8.5%. The 5-year survival rate was 44.3% for all patients. Survival difference existed in different population lung cancer database, because different database included various cancer stages and treatment modalities.

Most patients were diagnosed at an advanced stage (stage IV; $n = 18{,}364$; 54.1%) in Taiwan. Among the surgical methods, lobectomy and wedge resection were performed most often in this Taiwanese population. This finding was also consistent with an English study.[9]

The impact of age on the outcomes of lung cancer patients has been inconclusive.[10–14] Gradgeel et al.[11] found that younger patients with lung cancer have similar OS when compared with older patients. Subramanian et al.[14] conducted an analysis of Surveillance, Epidemiology, and End Results data to assess the presentation and outcomes of lung cancer in younger patients (≤45 years of age) and older patients (>45 years of age) and concluded there was better OS in the younger cohort. Our data suggested similar survival between patients less than 45 years of age and patients 46 to 64 years of age. Age more than 65 years at the time of diagnosis was an unfavorable prognostic factor in the multivariate analysis. The clinicopathologic features varied between the younger and older patients in previous studies.[10–14] Young patients who develop lung cancer may have inherited risk factors, making them more sensitive to the carcinogenic effects. Further studies are required to understand the influence of age on survival.

Lung cancer seems to be more prevalent in men than women.[1,3,15] In this study, the male/female lung cancer incidence ratio was 1.90. In the survival analysis, female sex is an independent prognostic factor for better survival in the multivariate analysis ($p < 0.0001$). However, the influence of sex on

TABLE 2. Multivariate Analysis of Overall Survival

Variables	Hazard Ratio	95% Confidence Interval	*p*
Age			
<45 (reference)	1	—	
45–64	1.049	(0.987–1.114)	0.1221
≥65	1.474	(1.390–1.563)	<0.0001
Sex			
Male	1.314	(1.278–1.35)	<0.0001
Female (reference)	1	—	
T classification			
T1 (reference)	1	—	
T2	1.56	(1.473–1.652)	<0.0001
T3	1.976	(1.855–2.106)	<0.0001
T4	2.309	(2.183–2.442)	<0.0001
N classification			
N0 (reference)	1	—	
N1	1.223	(1.161–1.288)	<0.0001
N2	1.428	(1.379–1.478)	<0.0001
N3	1.69	(1.63–1.752)	<0.0001
Tumor location			
Main bronchus	1.195	(1.091–1.309)	0.0001
Upper lobe	1.027	(0.975–1.081)	0.3201
Middle lobe (reference)	1	—	
Lower lobe	1.112	(1.055–1.173)	<0.0001
Multiple lobes	1.338	(1.195–1.497)	<0.0001
Unspecific	1.368	(1.282–1.46)	<0.0001
Cell type			
Adenocarcinoma (reference)	1	—	
SQCC	1.073	(1.038–1.109)	<0.0001
Others	1.217	(1.181–1.254)	<0.0001
Differentiation			
Well (reference)	1	—	
Moderate	1.319	(1.205–1.444)	<0.0001
Poor	1.582	(1.446–1.731)	<0.0001
Undifferentiated	1.545	(1.418–1.684)	<0.0001
Surgery			
No (reference)	1	—	
Yes	0.35	(0.333–0.369)	<0.0001
Chemotherapy			
No (reference)	1	—	
Yes	0.722	(0.703–0.741)	<0.0001
Radiotherapy			
No (reference)	1	—	
Yes	1.283	(1.249–1.318)	<0.0001

SQCC, squamous-cell carcinoma; T, tumor; N, node.

survival is still controversial. Two studies indicated there was no survival difference between men and women.[16,17] Several other studies indicated women with lung cancer have a better prognosis than men; however, these studies only included patients who underwent surgical resection.[18–22] Surgical resection was not indicated for advanced lung cancer (i.e., stages III and IV). These studies only concluded sex was a prognostic factor for resected lung cancer. Radzikowska et al.[23] studied the Poland population database, which reported 14.8% of lung cancer patients were classified as stage IV. This study also indicated women with lung cancer had a better prognosis than men. In our study, most patients were diagnosed with stage IV lung cancer (54.1%), and female sex was still an independent prognostic factor. The pathogenesis of lung cancer in women may be different from men and requires further investigation.

In the 6th and 7th TNM systems, the location of the primary tumor does not affect the prognosis. Whether or not the tumor location is associated with survival is controversial. Some studies indicated that lower-lobe tumors have a worse survival than upper-lobe tumors.[24–27] However, other reports showed no association between tumor location and survival.[26,28] Our study was the largest population database to address this issue. We identified a poorer survival in patients with lower lobe tumors compared with upper and middle tumors. Additionally, tumors located in main bronchus were also identified as an independent prognostic factor in the multivariate analysis. Tumors located in multiple lobes represented multiple lung metastasis and carried the worst prognosis.

Cellular differentiation was also an independent prognostic factor in our study. Most studies also showed cellular differentiation was associated with OS in lung cancer patients.[28–32] Moderately to poorly differentiated lung cancers are associated with significantly shorter survival than well-differentiated cancers, and our results also validated this finding. Tumors with moderate to poor differentiation may have a greater ability for invasion and hence correlate with poor prognosis. In future revisions of the TNM classification system for lung cancer, histologic grading should be incorporated as a prognostic factor in the staging system.

The most common subtypes of lung cancer worldwide are SQCC and AC.[3,15] The influence of tumor cell type on lung cancer survival was still controversial. Alexiou et al.[33] showed that the squamous-cell type was an independent favorable prognostic factor. Chansky et al.[34] published a prognostic analysis of a cohort of 9137 lung cancer patients[37] and also suggested that the SQCC may have a better prognosis than non–squamous-cell carcinoma. However, some studies[38–40] found no significant difference in survival between SQCC and non-SQCC. Asamura et al.[21] analyzed the clinicopathologic characteristics of lung cancers in Japan and found that the AC histology had significantly better survival than other histologic types ($p = 0.0000$ each). Guerra et al. studied 1402 consecutive stages I to III (N0–N1) non–small-cell lung cancer patients who underwent complete resection, and indicated there was a significantly increased risk of mortality for those patients with SQCC.[37] In our study, patients with SQCC had an increased risk of death from AC on multivariate analysis (hazard ratio = 1.073; 95% confidence interval, 1.038–.1.109, $p < 0.0001$). The pathologies of SQCC and AC are different, and their influence on survival needs further investigation. Similar to esophageal cancer, AC and SQCC have distinctly different prognostic factors and separate staging systems. We may assume that AC and SQCC involving the lung are different clinical diseases with different disease courses.

The strength of this study is its large national population size, which resulted in ample power to detect even small differences in outcomes. In addition, the study included all lung cancer patients with tissue diagnoses, and therefore, reflected the entire lung cancer population. Some studies only recognized surgically resected lung cancer patients for analysis, and therefore, only represented the features of early-stage lung cancer. However, this study had limitations. Data were conducted on a retrospective cohort, based on diagnostic codes and prescription histories. Information about possible prognostic factors, such as performance status, visceral pleural invasion, and lymphovascular invasion, was lacking in the database, and these factors could affect the data analysis. In addition, 10,067 patients (22.9%) were excluded because of incomplete data. The percentage was relative high compared with that in other population database. We identified the parameters: age, sex, tumor location, cell type, surgical method, "T," "N," clinical stage, histologic grade, tumor location, and all therapeutic methods within 3 months after diagnosis. If any one value was lost, we excluded the patient. Some data were difficult to obtain. For example, it is difficult to establish the histologic differentiation diagnosis for every patient. Patients will be excluded if histology grade was not available.

In conclusion, the OS of lung cancer remains poor. In addition to the TNM stages, age, sex, tumor location, cell type, and differentiation were independent prognostic factors. Prognostic factor analysis confers a better evaluation of this subgroup of patients. The influence of these prognostic factors on survival may result in the use of different treatment strategies for lung cancer patients.

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