Original Article

The utility of histological subtype for predicting survival of lung cancer patients with rheumatoid arthritis

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Background: This study determined whether the survival of lung cancer (LC) patients with rheumatoid arthritis (RA) is differed by histological subtype.

Materials: This observational, retrospective study compared the LC survival rate of 34 RA patients with that of 132 age- and sex-matched patients without RA who received medical care from 2011 to 2016. Survival curves were generated using the Kaplan-Meier method. Cox proportional hazards regression analyses were used to estimate hazard ratios and determine risk factors predicting mortality according to histological subtype, including small cell lung cancer (SCLC), and non-small cell lung cancer (NSCLC).

Results: The predominant histological subtype was adenocarcinoma in both groups, however, a larger proportion of SCLC patients was noted in patients with both LC and RA, compared to those with LC but without RA (26.5% *vs.* 12.9%, respectively; P=0.0317). LC patients with RA had a significantly lower body mass index (P=0.0488), and a higher proportion of interstitial lung disease (P<0.0001), compared to patients without RA. There was no statistical difference in the distribution of smoking status, stage, or comorbidity index between groups. Overall survival did not differ between LC patients with and without RA. Mortality was significantly worse for RA patients with SCLC than those with NSCLC (P=0.0404), and RA was associated with a 3.26-fold increase in mortality for SCLC patients with versus without RA (P=0.0350; 95% confidence interval: 1.05–9.56). However, RA was not a risk factor for mortality in NSCLC and, even in histological subtypes including lung adenocarcinoma and squamous cell carcinoma.

Conclusions: RA was not associated with a lower overall survival rate for LC patients, irrespective of histological subtype. Because the effects of RA on LC mortality might differ between SCLC and NSCLC patients, future studies should recognize that the histological subtype may affect the outcome.

Keywords: Lung cancer; rheumatoid arthritis (RA); survival; small cell lung cancer (SCLC); non-small cell lung cancer (NSCLC)

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Introduction

Cancer and rheumatic disease sometimes coexist in the same patient, either simultaneously or sequentially. Although they can occur by accident, previous studies have reported that cancers may be closely linked to a state of continuous inflammation characterized by the production of cytokines, chemokines, and free radicals, thus contributing to an increased risk of carcinogenesis (1). Rheumatoid arthritis (RA)

is a systemic autoimmune disease with chronic inflammation involving multiple organs. RA can sometimes affect the lung, as a frequent site of extra-articular involvement. Treatments for RA, including methotrexate and anti-tumor necrosis factor (TNF) antagonists, may increase the risk of malignancy (2-4). In epidemiological studies conducted in several countries, a positive association between increased incidence of lung cancer (LC) and RA has been reported (5-8).

The survival rate of LC patients with RA may be worse than that of those without RA, because the administration of long-term immunosuppressive therapies and impaired immune surveillance associated with underlying RA may promote cancer cell proliferation and survival (7,9). Underlying immune conditions in RA may also increase the risk of infection and treatment-related toxicity, a major cause of death during cancer treatment (10). However, periodic monitoring and longitudinal follow-ups of RA patients might result in better outcomes because of the increased likelihood of early detection and prompt treatment of LC (11). Although previous studies have suggested a significant link between RA and the incidence of LC, data regarding survival of LC patients, with or without RA, are limited and often conflicting (12-16). LC manifests in various histological subtypes, such as small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), so it is necessary to assess the outcome measures histologically in LC patients with RA. However, previous studies that reported the outcomes of LC patients with RA did not include information about the histological subtypes. Thus, it is unknown whether there was a significant difference in survival of LC patients with RA by histological subtypes. The aim of this study was therefore to assess whether LC patients with RA, treated in a single tertiary university-affiliated hospital in South Korea, had worse outcomes than those without RA, by separately analyzing the results of SCLC and NSCLC patients, and identify potential factors, including the presence of RA, which might predict outcomes.

Methods

Study population and data collection

The medical records of patients with RA and concurrent LC diagnosed at Hanyang University Hospital, a tertiary referral hospital in South Korea, between January 1, 2011 and December 31, 2016, were retrospectively analyzed. We only included LC patients who received treatment for LC; we excluded patients with cancer diagnosed before RA diagnosis, because the aim of the study was to investigate the possible effect of RA on the survival of LC patients. Patients with other rheumatic diseases, except RA, HIV infections, or other active malignancies, were also excluded.

We identified 46 LC patients with rheumatic diseases, among whom 9 with other rheumatic diseases were excluded (4 with systemic sclerosis, 3 with systemic lupus erythematosus, 1 with overlap syndrome, and 1 with Behçet's disease). Three LC patients with RA were not treated. A total of 34 LC patients with RA were treated at our hospital. For comparative purposes, patients with newly diagnosed LC treated in our respiratory clinic during the same 6-year study period, without any evidence of systemic rheumatic diseases including RA, were matched and served as the control group. Four controls were randomly selected from among the LC patients without RA and matched to one patient with RA by age and sex. This ratio of 1:4 was used throughout, except in two RA cases with a ratio of 1:2. Finally, 132 age- and sex-matched patients without RA who received medical care at the same hospital were included in this study.

Data collection

The diagnosis of RA was established by a board certified rheumatologist, according to the 1987 American College of Rheumatology (formerly the American Rheumatism Association) revised classification criteria for RA (17) and the 2010 American College of Rheumatology /European League against Rheumatism criteria (18). The diagnosis of LC was confirmed by cytological or histological examination. Data on numerous factors associated with mortality were collected for the LC patients, including sex, body mass index (BMI), Charlson comorbidity index (CCI), smoking history, age at time of diagnosis of LC and RA, calendar year of LC diagnosis, tumor histology, cancer stage, genetic mutation status, underlying lung disease status, and treatments for LC and RA. We checked for the presence of interstitial lung disease (ILD) using chest computed tomography (CT), and for chronic lung diseases including asthma and chronic obstructive pulmonary disease (COPD). The CCI score, as a measure of comorbidity, encompasses 22 comorbid conditions, including cardiovascular disease, malignancy, and lung disease (19). The scores for connective tissue disease and LC were omitted from the CCI score in this study. The cancer stage was determined based on the international tumor-node-metastasis (TNM) criteria. Mutational analysis

was performed on DNA extracted from surgically resected, biopsied, or cytological specimens of NSCLC patients. Epidermal growth factor receptor (EGFR) mutational status was tested using quantitative real-time polymerase chain reaction (qPCR) with the PNAClamp EGFR Mutation Detection Kit (Panagene, Daejeon, South Korea).

Statistical analysis

We used SAS software (version 9.4; SAS Institute, Cary, NC, USA) for matching the patients, and R software (version 3.4.2; R Development Core Team, Vienna, Austria) for all other statistical analyses (after first assessing the normality of the data distribution using the Shapiro-Wilk test). Patient matching based on age and sex data extracted from medical records was conducted using the Greedy algorithm. We compared clinicopathological characteristics between LC patients with and without RA. Continuous variables were compared using the *t*-test or Mann-Whitney U test, and categorical variables using the χ^2 or Fisher's exact tests. All nominal variables are expressed as frequencies and percentages. Continuous variables are expressed as means ± SD if normally distributed, while non-normally distributed variables are expressed as medians with quartile range. Follow-up began at the time of cancer diagnosis and ended at the time of death or the last follow-up visit for patients without an event (whichever occurred first).

Survival curves were estimated using the Kaplan-Meier method, and differences in survival among groups were assessed using a two-sided log-rank test. We analyzed the univariate associations of mortality with clinicopathological variables of interest using a Cox proportional hazards regression model, and hazard ratios (HRs) and P values were calculated. Next, we applied the best subset selection method to build multivariate models including the variables that were significant in the univariate analysis, using the backward stepwise selection method. We computed the Akaike information criterion (AIC) for a set of candidate models with different numbers of variables and selected the one with the smallest AIC value. In the same manner, we also separately constructed best-fit models based on NSCLC and SCLC histologies. In addition, lung adenocarcinoma and squamous cell carcinoma represent the major subtypes in NSCLC, and these histologic features might be important to assess the outcome of NSCLC patients. Thus, an analysis was conducted on the impact of RA presence on mortality in two main histological types of NSCLC (lung adenocarcinoma and squamous cell carcinoma). All tests were two-sided, and a P value <0.05 was considered to reflect statistical significance.

Ethics statement

The study protocol was approved by the Institutional Review Board (IRB) of Hanyang University Hospital, Seoul, South Korea (IRB No. 2019-06-016). All data were anonymized before the analysis, and the requirement for informed consent from the study participants was waived because of the retrospective nature of the study.

Results

Baseline characteristics of RA patients with LC

The baseline characteristics of the 166 LC patients enrolled in this study are shown in *Table 1*. Of the 34 LC patients with RA, 55.9% were male, and 61.8% were active or former smokers; these proportions showed no statistical difference from the group of LC patients without RA. Lung adenocarcinoma predominated in both groups; however, a significant difference was found in the frequency thereof between the groups; adenocarcinoma was diagnosed in 35.5% of the RA patients, which was a lower proportion than in the LC patients without RA (60.6%; P=0.0317). A larger proportion of SCLC was noted in LC patients with versus without RA (26.5% *vs.* 12.9%). LC patients with RA had a significantly lower BMI than those without RA (P=0.0488). Although more LC patients with RA had a CCI ≥2 than those without RA, the difference was not significant (35.3% *vs.* 18.9%; P=0.0596). ILD was significantly more prevalent in LC patients with RA than in those without (26.5% *vs.* 1.5%; P<0.0001), whereas no significant between-group difference was noted in the frequency of chronic lung diseases, such as asthma or COPD. No group difference was seen in age at LC diagnosis, calendar year of LC diagnosis, TNM stage, EGFR mutant status in NSCLC, or anti-cancer treatment status. The proportion of extensive stage disease of SCLC, and of stage IV NSCLC, did not differ between the two groups. The LC treatment status was similar between the two groups. In particular, the rates of chemotherapy alone (38.2%) and combined therapy (23.5%) in LC patients with RA were comparable to those of patients without RA. Similar to the result in all LC patients, NSCLC with RA had lower BMI and higher prevalence of ILD, compared to those without RA. No significant between-group difference

Table 1 Baseline characteristics of 34 lung cancer patients with RA and 132 age- and sex- matched controls without RA

Variables	Lung cancer with RA (N=34), n (%)	Lung cancer without RA (N=132), n (%)	P value
Gender			1.0000
Female	15 (44.1)	56 (42.4)	
Male	19 (55.9)	76 (57.6)	
Body mass index	22.37±3.25	23.80±3.73	0.0488
Age at cancer diagnosis	67.12±8.35	66.58±7.89	0.7760
Calendar year at cancer diagnosis			0.7267
2011–2012	13 (38.2)	42 (31.8)	
2013–2014	11 (32.4)	43 (32.6)	
2015–2016	10 (29.4)	47 (35.6)	
Charlson Comorbidity Index			0.0596
0	9 (26.5)	60 (45.5)	
1	13 (38.2)	47 (35.6)	
≥2	12 (35.3)	25 (18.9)	
Smoking, ever	21 (61.8)	72 (54.5)	0.5738
Cancer type			0.0317
Small cell lung cancer	9 (26.5)	17 (12.9)	
Adenocarcinoma	12 (35.3)	80 (60.6)	
Squamous	11 (32.4)	26 (19.7)	
Others	2 (5.9)	9 (6.8)	
Stage			0.4089
I–III	20 (58.8)	90 (68.2)	
IV	14 (41.2)	42 (31.8)	
Stage (each cancer cell type)			
Small cell lung cancer			0.6828
Limited stage disease	3 (33.3)	8 (47.1)	
Extensive stage disease	6 (66.7)	9 (52.9)	
Non-small cell lung cancer			0.3421
I	14 (56.0)	53 (46.1)	
II	2 (8.0)	8 (7.0)	
III	1 (4.0)	21 (18.3)	
IV	8 (32.0)	33 (28.7)	
Underlying lung disease			
ILD	9 (26.5)	2 (1.5)	<0.0001
Chronic lung diseases, other than ILD*	9 (26.5)	26 (19.7)	0.5302

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Lung cancer with RA (N=34), n (%)	Lung cancer without RA (N=132), n (%)	P value
EGFR mutant**	5 (31.2)	25 (32.5)	1.0000
Treatment			
Surgery, only	10 (29.4)	41 (31.1)	1.0000
Chemotherapy, only	13 (38.2)	45 (34.1)	0.8024
Radiation, only	3 (8.8)	4 (3.0)	0.1522
2 or more treatments	8 (23.5)	42 (31.8)	0.4655
Survival			0.5766
Alive	12 (35.3)	56 (42.4)	
Death	22 (64.7)	76 (57.6)	

*Chronic lung diseases, other than ILD included asthma and chronic obstructive pulmonary diseases; **EGFR mutation test was performed in 16 patients with RA and 77 patients without RA. ILD, interstitial lung disease; RA, rheumatoid arthritis.

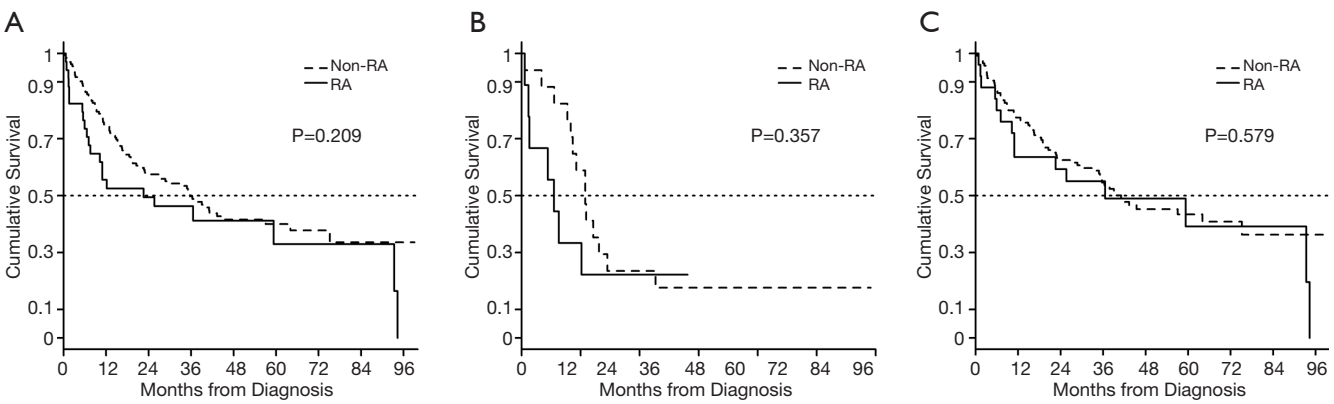

Figure 1 Survival curve using Kaplan-Meier plot for mortality by patients with and without RA. (A) All lung cancers, (B) small cell lung cancer, (C) non-small cell lung cancer.

was noted in TNM stage, EGFR mutation status, and anti-cancer treatment (*Table S1*). Only two LC patients without RA (one with adenocarcinoma and one with squamous cell carcinoma) were treated with immunotherapy, and none of the LC patients with RA were treated with immunotherapy. Among LC patients with RA, no difference was noted between the SCLC and NSCLC patients in the mean age at RA diagnosis, duration of RA before LC diagnosis, or RA treatment status. Three NSCLC patients with RA were treated with an anti-TNF antagonist (*Table S2*).

Overall survival by RA status

During the study period, 22 (64.7%) LC patients with RA and 76 (57.6%) LC patients without RA died (*Table 1*). The overall survival rate did not differ between LC patients with RA and age- and sex-matched LC patients without RA (*Figure 1A*), even when the survival analysis was conducted on SCLC and NSCLC patient subgroups (*Figure 1B,C*). Risk factors predictive of overall mortality based on multivariate Cox model analysis are listed in *Table 2*. Among LC patients of all histological subtypes, low BMI, older age at LC diagnosis, high CCI score, small cell histology, and advanced stage IV disease were significant risk factors for mortality. The status of RA was not a significant predictor of mortality after adjusting for other variables. SCLC is a more aggressive subtype of LC than NSCLC (20). As expected, mortality was significantly

Table 2 Univariable and multivariable Cox proportional hazards analysis

Variables	Mortality in all lung cancer				Mortality in SCLC				Mortality in NSCLC			
	Univariable		Multivariable		Univariable		Multivariable		Univariable		Multivariable	
	HR	P value	HR	P value	HR	P value	HR	P value	HR	P value	HR	P value
RA (*vs.* non-RA)	1.36	0.2098			1.53	0.3661	3.26	0.0350	1.18	0.5789		
Male gender (*vs.* female)	1.72	0.0114			0.58	0.2348			1.96	0.0051		
Body mass index (n=165)	0.93	0.0157	0.91	0.0088	1.19	0.0315	1.26	0.0275	0.89	0.0007	0.89	0.0019
Age at cancer diagnosis	1.04	0.0078	1.03	0.0241	1.06	0.0312	1.04	0.1620	1.03	0.0558	1.03	0.0942
CCI score												
CCI = 1 (*vs.* 0)	1.78	0.0145	1.71	0.0313	1.01	0.9873			1.88	0.0163	2.02	0.0208
CCI ≥ 2 (*vs.* 0)	1.70	0.0496	1.79	0.0420	1.70	0.3410			1.63	0.1146	1.96	0.0496
Smoking, ever	2.42	0.0001	1.63	0.0578	0.48	0.1590			2.61	0.0001	2.15	0.0063
SCLC (*vs.* NSCLC)	2.63	0.0001	1.75	0.0439	NA				NA			
Stage IV (*vs.* I–III)	5.80	<0.0001	4.24	<0.0001	5.39	0.0015	5.28	0.0033	5.33	<0.0001	3.52	<0.0001
Underlying lung disease												
ILD	1.65	0.1776			0.93	0.8845			1.21	0.7533		
Chronic lung disease, other than ILD	1.38	0.1703			3.19	0.0493			1.37	0.2336	0.55	0.0665
Treatment												
Surgery only	0.17	<0.0001	0.47	0.0505	NA				0.19	<0.0001	0.44	0.0346
Chemotherapy only	3.54	<0.0001	1.56	0.1209	2.34	0.0687			3.41	<0.0001	1.74	0.1145
Radiation only	3.92	0.0015	3.74	0.0086	11.99	0.0426			4.10	0.0029	4.14	0.0113
2 or more treatments	0.93	0.7550			0.35	0.0300			1.08	0.7494		

CCI, Charlson Comorbidity Index; HR, hazard ratios; ILD, interstitial lung disease; NA, not applicable; NSCLC, non-small cell lung cancer; RA, rheumatoid arthritis; SCLC, small cell lung cancer.

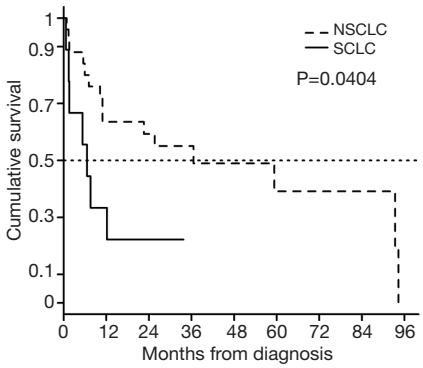

Figure 2 Survival curve using Kaplan-Meier plot for mortality in lung cancer patients with RA according to histological subtype.

worse in RA patients with small cell histology compared to those with NSCLC (P=0.0404, *Figure 2*). Risk factor analysis was therefore conducted regarding mortality in LC patients with RA according to histological subtype (SCLC *vs.* NSCLC). We found that RA (HR: 3.26; P=0.0350) was a poor prognostic indicator for SCLC patients, along with high BMI (HR: 1.26, P=0.0275) and stage IV disease (HR: 5.28; P=0.0033). However, RA did not influence the mortality risk in NSCLC patients. Low BMI, high CCI score, smoking, and advanced stage IV were significant risk factors for mortality in NSCLC patients. *Table 3* represents results from univariate and multivariate analysis of mortality according to the two main histological types of NSCLC (lung adenocarcinoma and squamous cell carcinoma). There were 92 (55.4% of total) patients for lung adenocarcinoma and 37 (22.3%) for squamous cell lung cancer. Lung adenocarcinoma histology was a more favorable risk factor predictive of mortality in NSCLC patients, compared to squamous cell carcinoma, but there was no statistical significance (HR: 0.53, P=0.0565). In multivariate analysis of patients with lung adenocarcinoma, male gender (HR: 0.25, P=0.0052), BMI (HR: 0.83, P=0.0002), ever smoking (HR: 4.20, P=0.0035), and advanced stage IV disease (HR: 2.76, P=0.0094) were significant factors associated with mortality. Among those with lung squamous cell carcinoma, only advanced stage IV disease was a significant factor for mortality. This study, however, the presence of RA had no significant impact on the mortality even in two subgroups with lung adenocarcinoma and squamous cell carcinoma.

Discussion

In this retrospective cohort study of Korean RA patients, we showed that RA did not reduce overall survival in LC patients. No difference in overall survival was found in survival analysis stratified by small cell versus non-small cell histology. However, RA patients with SCLC had significantly worse outcomes than those with NSCLC. We also found that the presence of RA was a significant predictor of mortality among SCLC patients, along with BMI and LC stage status, whereas RA among NSCLC patients was not associated with an increased mortality risk.

In an analysis of Korean patients with all types of rheumatic diseases, RA was associated with higher mortality in LC patients after adjusting for other variables (15). In contrast, a Chinese study reported that RA did not shorten the survival of LC patients with RA compared to the general population (21). Ji *et al.* (13) analyzed Swedish hospital discharge register data and reported no significant difference in overall survival between LC patients with versus without RA. However, these conflicting results regarding the effect of RA on the survival of LC patients might be related to heterogeneity in the definitions of LC. Small cell and non-small cell are the two main subtypes of LC, which have several key differences in terms of treatment response and prognosis (22). Most previous studies considered LC to be a single entity, with no distinction made between SCLC and NSCLC (13,15,21,23). Only a few studies have assessed survival rates in LC patients with RA according to histological subtype. Abasolo *et al.* (12) evaluated survival rates in Spanish RA patients of all subtypes, and reported that mortality was significantly higher than expected for lung adenocarcinoma in males, while in a Swedish national cancer registry-based study, Hemminki *et al.* (14) found a potential association of LC mortality with all types of autoimmune diseases, including RA, but failed to find a significantly increased HR for mortality in an analysis of the four main histological subtypes (adenocarcinoma, squamous, large cell, and small cell). Our study differed in several respects from the above two epidemiological studies, which evaluated LC survival in RA via subgroup analysis. To the best of our knowledge, our study is the first cohort study to analyze survival rates by histological subtype of LC, including SCLC and NSCLC, and to identify potential factors predicting the mortality of LC patients.

Our analyses revealed that RA was not associated with increased mortality in LC patients, irrespective of histological subtype. Cancer survival depends mainly on sex, age, cancer stage, smoking status, and comorbidities, all of which affect treatment outcomes. As reported in

Table 3 Univariable and multivariable Cox proportional hazards analysis in lung adenocarcinoma and squamous cell carcinoma

Variables	Mortality in lung adenocarcinoma and squamous cell carcinoma (N=129)				Mortality in lung adenocarcinoma (N=92)				Mortality in lung squamous cell carcinoma (N=37)			
	Univariable		Multivariable		Univariable		Multivariable		Univariable		Multivariable	
	HR	P value	HR	P value	HR	P value	HR	P value	HR	P value	HR	P value
RA (*vs.* non-RA)	1.09	0.7883	0.58	0.1294	1.44	0.4095			0.42	0.1024	0.45	0.1447
Male gender (*vs.* female)	1.88	0.0127			1.73	0.0738			1.29	0.6476		
Body mass index (n=165)	0.91	0.0060	0.92	0.0385	0.88	0.0030	0.85	0.0018	1.03	0.6787		
Age at cancer diagnosis	1.04	0.0319	1.05	0.0096	1.04	0.0614	1.05	0.0188	1.03	0.3612		
CCI score												
CCI = 1 (*vs.* 0)	1.87	0.0253	1.66	0.0841	2.33	0.0135			1.27	0.6426		
CCI ≥ 2 (*vs.* 0)	1.93	0.0442	2.28	0.0163	1.61	0.3009			2.08	0.1550		
Smoking, ever	2.65	0.0002	1.91	0.0411	2.72	0.0011			1.96	0.3646		
Adenoca (*vs.* Squamous)	0.60	0.0420	0.53	0.0565	NA				NA			
Stage IV (*vs.* I–III)	4.91	<0.0001	6.97	<0.0001	6.36	<0.0001	3.17	0.0009	10.63	0.0001	15.21	<0.0001
Underlying lung disease												
ILD	0.89	0.8689			10.87	0.0245			0.26	0.2012	0.17	0.1521
Chronic lung disease, other than ILD	1.46	0.1756			1.75	0.1115			1.06	0.8969	2.67	0.0642
Treatment												
Surgery only	0.19	<0.0001			0.05	<0.0001	0.07	0.0006	0.65	0.3577		
Chemotherapy only	3.54	<0.0001			4.45	<0.0001			5.14	0.0016		
Radiation only	3.72	0.0288			12.59	0.0013	4.89	0.0575	1.11	0.9181		
2 or more treatments	1.14	0.6075			1.43	0.2858			0.67	0.3450		

CCI, Charlson Comorbidity Index; HR, hazard ratios; ILD, interstitial lung disease; NA, not applicable; NSCLC, non-small cell lung cancer; RA, rheumatoid arthritis; SCLC, small cell lung cancer.

a previous epidemiological study, LC predominantly affected males (24). In contrast, Chen *et al.* (21) and Liu *et al.* (25) conducted cohort studies comparing LC patients with RA to those without RA, and reported that female patients accounted for nearly half of the LC patients with RA. Similarly, in our study 44.1% of the LC patients with RA were females, which might be attributed to the high prevalence of RA in females (26). Because sex differences in LC survival have been reported (27), we used a sex- and age-matched control group in the present study. The smoking rates were similar between the groups. There was no significant difference in CCI or TNM stage between LC patients with RA and age- and sex-matched controls, so these factors would not have affected the results regarding morality. However, ILD was observed in 26.5% of LC patients with RA, which was a much higher rate than in those without RA, despite the similar proportion of smokers between the groups. In a previous report (25), 40.9% of LC patients with RA had ILD, which was consistent with our findings. ILD is a well-known and frequently reported extraarticular manifestation of RA (28), and could negatively affect the survival of RA patients (29). Alternatively, LC in RA-associated ILD might be hidden until it manifests clinically, thus resulting in delayed detection (30), while ILD-associated accumulation of autoimmune cells in RA patients could create a harsh environment preventing cancer cell growth (31). We found that the presence of ILD was not significantly associated with a worse outcome in LC patients in a multivariable Cox regression analysis controlling other variables. One possible reason for these findings was that respiratory symptoms associated with LC, but not ILD, may facilitate diagnostic imaging for early detection of ILD or very mild ILD, which would otherwise be asymptomatic. Nonetheless, the impact of ILD on survival in LC patients with RA still needs further study.

Our analyses based on LC subtype revealed that RA was significantly associated with the lower survival rate of SCLC, but not NSCLC, patients. We also found that consistent results that RA had no large influence on the survival of NSCLC patients, irrespective of histological types including lung adenocarcinoma and squamous cell histology. Several potential mechanisms may explain the association of RA with the risk of mortality in SCLC patients, including the poor prognosis of SCLC. Because the main treatment for SCLC is chemotherapy, compared to surgery for NSCLC, it is possible that RA and its related comorbidities might be more treatment-limiting factors when the duration of treatment is extended. Second, the outcome of interest in the present study was all-cause mortality; the mortality of LC patients with RA may be affected by various factors, including cancer stage, comorbid conditions and treatment, and the effects of the RA itself. All of these factors could cause an increase in mortality. It is possible that the mortality of cases of LC discovered at an early stage may not be associated with LC itself, but rather with cardiovascular diseases and other non-RA-related causes. We found that 64% of NSCLC patients with RA were of stage I–II, which was a higher proportion versus those without RA (53.1%), although not significantly. However, two-thirds of SCLC patients with RA had extensive stage disease. Thus, the effects of RA on LC mortality could differ between SCLC and NSCLC. These intriguing findings provide the basis for future investigations.

Due to the regular follow-up of RA patients, we expected that earlier stage cancers would be detected (11). Surprisingly, however, the majority of SCLC cases were detected at an advanced stage in the LC with RA group. Because RA patients with advanced LC are more likely to be referred to our center, a selection bias may have existed. However, early detection of SCLC using imaging alone is challenging because SCLC can metastasize even when the primary lesion is very small. Our findings raise concerns regarding potential negligence of SCLC in RA patients attending regular follow-ups, and highlight the need for optimization of the LC screening program for RA patients. Further studies are also needed to compare cancer screening rates between patients with RA and the general population.

Our study had several limitations. First, it was performed at a single institution and included a relatively small sample size, so there may have been a bias in patient selection. Previous studies have described a few cases of SCLC in LC patients with RA, predominantly as adenocarcinomas (21,25); however, in this study, a significantly higher proportion of LC patients with RA had SCLC versus those without RA, which may have affected our results. Second, the use of LC immunotherapy has become clinically important in the treatment of LC patients with rheumatic diseases (32), including RA. In the present study, only two LC patients were treated with immunotherapy without RA. Thus, our findings cannot be generalized to other populations treated with immunotherapy. Third, we excluded patients who were untreated. Because LC patients with RA have been reported to be less likely to receive anti-cancer treatment (25), our results may not be fully applicable to clinical practice. Finally, our study was limited

by its retrospective nature; we had information only on all-cause mortality, and not on LC-specific mortality. Thus, our survival data should be interpreted with caution.

Conclusions

No significant difference in survival was found between LC patients with versus without RA, including in subgroup analysis of SCLC and NSCLC. Notably, regarding the association of RA with poor outcomes in LC patients, the presence of RA could be a significant factor impairing overall survival in SCLC, but not NSCLC, patients. Future studies assessing the relevance of RA to the prognosis of LC patients should recognize that the histological subtype may affect the outcome.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2020.03.02). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study protocol was approved by the Institutional Review Board (IRB) of Hanyang University Hospital, Seoul, South Korea (IRB No. 2019-06-016). All data were anonymized before the analysis, and the requirement for informed consent from the study participants was waived because of the retrospective nature of the study.

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Supplementary

Table S1 Characteristics of 25 non-small cell lung cancer patients with RA and 115 controls without RA

Variables	Lung cancer with RA (N=25)	Lung cancer without RA (N=115)	P value
Gender			0.8490
Female	12 (48.0)	50 (43.5)	
Male	13 (52.0)	65 (56.5)	
BMI	21.86±3.42	23.69±3.85	0.0275
Age at cancer diagnosis	66.80±7.84	66.38±7.66	0.8062
Calendar year at cancer diagnosis			0.5734
2011–2012	11 (44.0)	38 (33.0)	
2013–2014	6 (24.0)	35 (30.4)	
2015–2016	8 (32.0)	42 (36.5)	
Charlson Comorbidity Index			0.2508
0	7 (28.0)	53 (46.1)	
1	11 (44.0)	39 (33.9)	
≥2	7 (28.0)	23 (20.0)	
Smoking, ever	15 (60.0)	58 (50.4)	0.5177
Cancer type			0.0763
Adenocarcinoma	12 (48.0)	80 (69.6)	
Squamous	11 (44.0)	26 (22.6)	
Others	2 (8.0)	9 (7.8)	
Stage			0.3421
I	14 (56.0)	53 (46.1)	
II	2 (8.0)	8 (7.0)	
III	1 (4.0)	21 (18.3)	
IV	8 (32.0)	33 (28.7)	
Underlying lung disease			
ILD	4 (16.0)	0 (0.0)	0.0008
Chronic lung diseases, other than ILD*	6 (24.0)	25 (21.7)	1.0000
EGFR mutant**	5 (31.2)	25 (32.5)	1.0000
Treatment			
Surgery, only	10 (40.0)	41 (35.7)	0.8570
Chemotherapy, only	7 (28.0)	36 (31.3)	0.9319
Radiation, only	2 (8.0)	4 (3.5)	0.2911
2 or more treatments	6 (24.0)	34 (29.6)	0.7535
Survival			0.7394
Alive	10 (40.0)	53 (46.1)	
Death	15 (60.0)	62 (53.9)	

*Chronic lung diseases, other than ILD included asthma and chronic obstructive pulmonary diseases; **EGFR mutation test was performed in 16 patients with RA and 77 patients without RA. ILD, interstitial lung disease; RA, rheumatoid arthritis

Table S2 Characteristics of lung cancer patients with RA

Variables	SCLC with RA (N=9)	NSCLC with RA (N=25)	P value
Age of RA onset (year)	60.44±9.51	56.88±11.17	0.4041
RA duration before cancer diagnosis, median, (quartiles), months	53.3 (22.1–144.7)	82.7 (29.3–184.6)	0.4465
Used drugs for RA			
MTX	5 (55.6)	14 (56.0)	1.000
Steroid	6 (66.7)	20 (80.0)	0.6488
Other DMARDs	7 (77.8)	17 (68.0)	0.6921
TNF inhibitors	0 (0.0)	3 (12.0)	0.5488
Others*	1 (11.1)	2 (8.0)	1.000

*Others included tocilizumab, rituximab, abatacept, bucillamine, and cyclosporine. DMARDs, disease-modifying anti-rheumatic drugs; MTX, methotrexate; NSCLC, non-small cell lung cancer; RA, rheumatoid arthritis; SCLC, small cell lung cancer; TNF, tumor necrosis factor.