ORIGINAL ARTICLE

Comparing Survival in Patients With Lung Cancer With and Without a History of Common Autoimmune Disease

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ABSTRACT

Introduction: Autoimmune disease has both a predisposing and a protective effect toward malignancy. Though studies have investigated the risk of malignancy in patients with autoimmune disease, there is limited research on how autoimmunity affects survival.

Methods: This study compared survival in patients with lung cancer with and without autoimmune disease. Patients with lung cancer were culled from the Surveillance, Epidemiology, and End Results Medicare databases (2007–2014), and autoimmune diseases were identified using diagnosis codes.

Results: The overall prevalence of investigated autoimmune diseases among the 112,445 patients was 22.7%. Overall survival (OS) ($p < 0.0001$) was longer and cancer-specific mortality (CSM) ($p < 0.0001$) reduced among patients with autoimmune disease. Median OS was 5 months higher. Improved OS and CSM were also apparent in disease stages 1, 3, and 4 in the NSCLC and SCLC subgroups ($p < 0.0001$) and across most specific autoimmune diseases. After adjusting for the effects of age, sex, race, disease stage, and chronic kidney disease, autoimmune disease was still predictive of higher OS (hazard ratio = 1.23, 95% confidence interval: 1.21–1.25, $p < 0.0001$) and reduced CSM (hazard ratio = 1.16, 95% confidence interval: 1.14–1.18, $p < 0.0001$).

Conclusions: The prevalence of rheumatoid arthritis, inflammatory bowel disease, and systemic lupus erythematous was highly enriched compared with the general population. The improvement in OS and CSM was larger in NSCLC than in SCLC, suggesting a larger role for the immune system in NSCLC. Alternate explanations for the improved

survival include lead time bias, better access to health care, and a survival or autoimmunity-inducing genetic factor.

Introduction

There is a complex relationship between autoimmunity and malignancy. Patients with certain autoimmune diseases are at higher risk for developing specific malignancies, possibly owing to increased DNA damage and inflammation. Nevertheless, in other cases, autoimmune disease seems to be protective against the development of cancer. For example, epidemiologic studies reveal that patients with systemic lupus erythematous (SLE) have an overall increased risk of malignancy, but a protective effect in prostate, melanoma, colon, breast, endometrial, and ovarian cancers.[1,2] Interestingly, sometimes, malignancy can result in the development of autoantibodies and autoimmune disease.[3]

There are several proposed mechanisms for the protective effect of autoimmune disease against malignancy. It is well established that increased immune cell activity (B cells, T cells, plasma cells) within tumors is associated with improved survival in many forms of cancer.[4] The presence of autoantibodies could mediate increased immune cell activity inducing complement-mediated or antibody-dependent cytotoxicity on tumor cells. They could also enhance cellular immune response by priming antigen-presenting cells. Finally, autoantibodies could directly interfere with tumor progression by directly targeting receptors on the tumor cell surface, the same mechanism used by targeted immunotherapy.[4] For instance, the presence of a naturally occurring HER2 autoantibody was found to protect against the development of breast cancer.[5] Classically, autoantibodies were thought to function only on the surface of the cell, and not to enter living cells.[6,7] Nevertheless, an anti-dsDNA antibody 3E10 derived from a mouse model for SLE was found to penetrate the nucleus and bind to DNA, sensitizing tumor cells to radiation treatment by interfering with DNA repair.[8,9]

Though there have been several epidemiologic studies exploring the risk of developing malignancy in autoimmune disease,[1,2,10–12] there has been limited research in terms of how autoimmunity affects survival in a patient with a diagnosed malignancy. Given the integral role that immunotherapy plays in treatment of lung cancer,[13,14] it was natural to look at the potential effect that specific autoimmune conditions may have in lung cancer. This is especially true given the relatively high levels of autoimmune conditions found in patients with lung cancer, which is estimated to be between 14% and 25%.[15]

Materials and Methods

The data for this study were purchased from the Surveillance, Epidemiology, and End Results (SEER) Medicare database[16] after they had reviewed the study and approved the data request. Data were stored on a Health Insurance Portability and Accountability Act–compliant secure server behind the University Hospitals Seidman Cancer Center firewall with access controls and logging at all times. This study was reviewed by the University Hospitals Institutional Review Board and determined to be an exempt study.

This study used the linked SEER Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The authors acknowledge the efforts of the National Cancer Institute; the Office of Research, Development and Information, Centers for Medicare & Medicaid Services; Information Management Services Incorporated; and the SEER Program tumor registries in the creation of the SEER Medicare database.

The study population included patients residing in the geographic areas served by SEER registries who were diagnosed with having lung cancer, between 2007 and 2014, and who had a history of autoimmune disease. The following patients were excluded: patients more than 90 years of age on the date of their lung cancer diagnosis, patients with another lifetime cancer diagnosis, patients diagnosed with having lung cancer on autopsy, and patients with health maintenance organization insurance. Patients with a history of common autoimmune diseases were identified using relevant International Classification of Diseases, Ninth Revision (ICD-9), diagnosis codes (Supplementary Table 1). Patients with rheumatoid arthritis (RA) were also identified using chronic condition flags. A history of autoimmune disease was defined as having at least one relevant ICD-9 code or chronic condition flag within a two year lookback period preceding the lung cancer diagnosis or after the lung cancer diagnosis. The autoimmune diseases investigated were Crohn's disease (CD), dermatomyositis (DM), polymyositis (PM), psoriasis, RA, sarcoidosis, systemic scleroderma (SSc), Sjogren's syndrome, SLE, and ulcerative colitis (UC).

Baseline characteristics about the patients, their disease, and treatment were available. These baseline

characteristics included age, sex, race, degree of urban versus rural development within the locality, percentage of the population in poverty within the locality, presence of chronic kidney disease (CKD), tumor grade, disease stage, and treatment history (surgery, radiation, or chemotherapy). Lung cancer stage was defined per the American Joint Committee on Cancer Cancer Staging Manual, Sixth[17] and Seventh Editions.[18] The use of chemotherapy agents most often used to treat lung cancer during the relevant years was identified using Healthcare Common Procedure Coding System codes (Supplementary Table 2).

The study end points are overall survival (OS) and cancer-specific mortality (CSM). The OS was measured from the date of diagnosis to the date of death and was censored at the date of last follow-up for survivors. CSM was measured from the date of diagnosis to the date of death from cancer and was censored at the date of last follow-up for those alive with noncancer death as competing risk. Patients who died of their cancer were identified using the International Classification of Diseases, Tenth Revision, diagnosis codes (Supplementary Table 3). The survival rates of OS were estimated by the Kaplan-Meier method with log-rank test for the difference between groups.[19] The effect of autoimmune disease on OS was further estimated by multivariable Cox regression controlling the effects of age, sex, disease stage, and CKD.[20] The cumulative CSM was estimated taking noncancer death as competing risk into account.[21,22] The effect of autoimmune disease on CSM was estimated using Gray's method,[21] controlling the effects of age, sex, disease stage, and CKD. All tests were two sided, and *p* values less than or equal to 0.05 were considered statistically significant.

Results

From the SEER Medicare database, 212,484 patients with lung cancer were identified; 100,039 were excluded; and 112,445 were analyzed for this study (Fig. 1). Of the patients, 69,019 (61.4%) had NSCLC and 14,552 (12.9%) had SCLC, while 28,874 (25.7%) were unspecified. The overall prevalence of the noted autoimmune diseases among the 112,445 patients was 22.7%. The prevalence of specific autoimmune conditions is listed in Table 1; the most common were RA (18.8%), psoriasis (2.2%), and UC (1.2%).

The baseline patient characteristics of age, race, level of urban development, and poverty level were similar between the groups with a history of autoimmune disease and without autoimmune disease (Table 2). There was a higher percentage of females in the autoimmune history group (54.4% versus 45%). More patients with a history of autoimmune disease were diagnosed at stage

1 (25.6% versus 17.8%) than patients without autoimmune disease, and fewer were diagnosed at stage 4 (43.5% versus 50.7%). A higher percentage of patients with a history of autoimmune disease had CKD (40.3% versus 30.9%). Other disease characteristics including percentage of patients diagnosed at stages 2 and 3 and tumor grade were similar between the two groups. The percentage of patients who received radiation treatment was also similar in both groups, whereas a higher percentage of people in the autoimmune group were treated with chemotherapy (41.4% versus 30.1%) and surgery (25.4% versus 17.8%). Overall, this suggests that the populations in the autoimmune disease and non-autoimmune disease groups were well balanced in terms of baseline patient and disease characteristics.

In the entire cohort of patients with lung cancer, which included patients with SCLC, NSCLC, and unspecified cancers, OS ($p < 0.0001$) was significantly higher and CSM ($p < 0.0001$) was significantly reduced among patients with autoimmune disease. This difference seemed almost immediately after diagnosis and persisted to eight years, the end of the period for which survival data are available (Fig. 2A–F). Median OS (mOS) of patients in the autoimmune group was 12 months, compared with seven months in patients without autoimmune disease (Table 3). After adjusting for the effects of age, sex, race, stage, and CKD, a history of autoimmune disease was still predictive of OS ($p < 0.0001$). The hazard ratio (HR) of patients with no autoimmune disease to those with autoimmune disease was 1.23 with a 95% confidence interval (CI) of 1.21 to 1.25 (Supplementary Table 4). A similar relationship was found between autoimmune disease and CSM. After adjusting for the effects of age, sex, race, disease stage, and CKD, a history of autoimmune disease was still predictive of CSM ($p < 0.0001$). The cancer-specific HR of patients with no autoimmune disease compared with those with autoimmune disease was 1.16 with 95% CI of 1.14 to 1.18 (Supplementary Table 5).

OS was significantly higher and CSM significantly reduced for patients with autoimmune disease in stages 1, 3, and 4, with all *p* values less than 0.0001 (Fig. 3A–H). Stage 2 had a higher OS ($p = 0.15$) and reduced CSM ($p = 0.19$). The largest magnitude of difference in mOS was in stage 1 lung cancer, with mOS of 63 months in patients with autoimmune disease versus 46 months in patients without autoimmune disease (Table 3). For patients with SCLC or NSCLC, OS was significantly higher and CSM significantly reduced in patients with autoimmune disease (all $p < 0.0001$). The magnitude of the increase in OS and reduction in CSM were higher in NSCLC (Fig. 2).

OS was significantly higher in all cohorts of patients with a history of a specific autoimmune condition (all
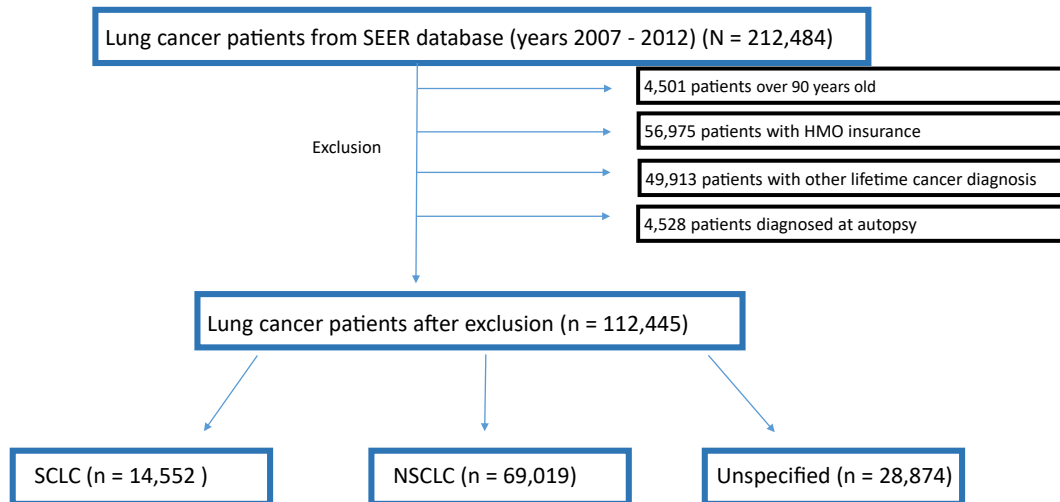
Figure 1. Consort flow diagram revealing the selection of eligible patients with lung cancer, including specific exclusions from the SEER Medicare Database (2007-2014). HMO, health maintenance organization.

$p < 0.0001$ except for DM $p = 0.02$ and SSc $p = 0.027$), except for patients with a history of PM who also had an improved OS ($p = 0.127$). The largest magnitude of difference in mOS was in patients with Sjogren's syndrome who had a mOS of 19 months compared with 8 months in patients without autoimmune disease. Likewise, CSM was significantly reduced in all cohorts of patients with a history of a specific autoimmune condition (all $p < 0.0001$ except for PM $p = 0.0029$ and SSc $p = 0.0023$), except for patients with a history of DM who also had a reduced CSM ($p = 0.11$) (Supplementary Table 6).

Discussion

This study was the first comprehensive analysis of the prognostic effect of specific autoimmune diseases on survival in patients with lung cancer using a large national database, such as the SEER Medicare. Several of the differences in baseline characteristics between the patients with and without a history of autoimmune disease can likely be explained by known phenomenon. For

instance, the higher rate of females in the autoimmune history group (54.4% versus 45%) is consistent with the higher prevalence of autoimmune disease among females in the general population.[23–25] The higher prevalence of CKD (40.3% versus 30.9%) in the autoimmune history group may reflect the renal sequelae of diseases, such as SLE. In addition, the higher prevalence of surgical treatment among the autoimmune group may reflect the lower stage at which this group's lung cancer was diagnosed.

Overall, this analysis revealed that autoimmune disease is associated with a longer OS and reduced CSM in patients with lung cancer. A higher OS and reduced CSM in a population with at least one additional comorbidity seem counterintuitive. Yet, this pattern emerged not only when broadly evaluating autoimmune diseases in patients with lung cancer but also specifically in both early stage and late-stage lung cancer and in most specific autoimmune diseases, including RA, psoriasis, CD, UC, and SLE. History of autoimmune disease continued to be predictive of improved survival even when age, sex, race, disease stage, and CKD were controlled.

In contrast, a small, single-center study found that patients with lung cancer and a history of RA or DM or PM had higher levels of mortality compared with patients with lung cancer without autoimmune disease. Nevertheless, this study did find lower mortality in patients with lung cancer and SSc.[26] Another single-center study revealed no significant difference in OS in patients with lung cancer with and without autoimmune disease.[27] Compared with the single-center studies, we used a larger sample size taken from a national cohort and investigated a larger number of specific autoimmune conditions.[26,27] An earlier study using the SEER Medicare cohort found no association between autoimmune

Table 1. Prevalence of Autoimmune Diseases in Lung Cancer by Specific Disease (N = 112,445)

Autoimmune Disease	Prevalence (%)
Crohn's disease	980 (0.87)
Dermatomyositis	109 (0.10)
Polymyositis	147 (0.13)
Psoriasis	2507 (2.23)
Rheumatoid arthritis	21,156 (18.81)
Sarcoidosis	454 (0.40)
Systemic scleroderma	267 (0.24)
Sjogren's syndrome	533 (0.47)
Systemic lupus erythematosus	1054 (0.94)
Ulcerative colitis	1295 (1.15)

Table 2. Patient, Disease, and Treatment Characteristics of Patients With Lung Cancer by Status of Autoimmune Disease (N = 112,445)

Variables	Median (Range) or Frequency (%)	
	Autoimmune Disease	
	No (n = 86,969)	Yes (n = 25,476)
Age (y)	72 (21, 90)	72 (24, 90)
Sex		
Female	39,108 (45)	13,863 (54.4)
Male	47,861 (55)	11,613 (45.6)
Race		
Black	8797 (10.1)	2520 (9.9)
White	72,919 (84)	21,745 (85.4)
Others	5140 (5.9)	1186 (4.7)
Rural or urban		
All urban	51,650 (59.5)	15,438 (60.7)
Mostly urban	19,119 (22)	5355 (21.1)
Mostly rural	7861 (9.1)	2236 (8.8)
All rural	8218 (9.4)	2406 (9.4)
Poverty		
0%-5%	15,872 (18.3)	4844 (19.1)
5%-10%	21,031 (24.2)	6127 (24.1)
10%-20%	27,233 (31.4)	7946 (31.2)
20%-100%	22,686 (26.1)	6512 (25.6)
Stage		
1	13,968 (17.8)	5920 (25.6)
2	3387 (4.3)	1174 (5.1)
3	21,234 (27.1)	5983 (25.9)
4	39,710 (50.7)	10,072 (43.5)
Grade		
1	3480 (9.1)	1404 (11.3)
2	11,767 (30.7)	4232 (34)
3	19,726 (51.4)	5818 (46.7)
4	3384 (8.8)	1008 (8)
CKD		
No	60,099 (69.1)	15,212 (59.7)
Yes	26,870 (30.9)	10,264 (40.3)
Chemotherapy		
No	60,777 (69.9)	14,941 (58.6)
Yes	26,192 (30.1)	10,535 (41.4)
Surgery		
No	71,464 (82.17)	18,996 (74.56)
Yes	15,505 (17.83)	6480 (25.44)
Radiation		
No	56,245 (64.67)	16,429 (64.49)
Yes	30,724 (35.33)	9047 (35.51)

CKD, chronic kidney disease.

disease and increased mortality in patients with lung cancer. Nevertheless, compared with our study, that study had a shorter minimum lookback period to identify patients with autoimmune disease and did not breakdown their survival analysis by specific autoimmune condition. We also identified a higher prevalence of autoimmune disease among patients with lung cancer (22.7%) than in that study (13.4%).[28] Possibly, this was because it used a more restrictive definition of autoimmune disease and did not use chronic condition flags to identify patients with RA.

We also observed an elevated prevalence of specific autoimmune diseases. An epidemiologic study using the Third National Health and Nutrition Examination Survey, a different national database, estimated the prevalence of RA in people aged more than 60 years in the United States to be approximately 2%, whereas our study found a prevalence of 18.81%, suggesting a high level of enrichment of RA in patients with lung cancer. That study identified patients with RA using clinical criteria rather than with diagnosis codes.[29] Our study population had a prevalence of 0.9% for CD and 1.2% for UC in comparison to 0.2% and 0.3%, respectively, in the general population more than 60 years of age.[30] This suggests an increased level of inflammatory bowel disease in lung cancer and possibly a relationship between inflammatory bowel disease and lung cancer. The study population had a 0.9% prevalence of SLE compared with 0.2% in the U.S. general population over the age of 65 years, also suggesting an association between SLE and lung cancer.[31]

A number of different explanations exist for why autoimmune disease may be associated with improved survival. Patients with autoimmune disease have increased antitumor immune effects compared with the general population, potentially resulting in better outcomes. Immunotherapy is a preferred first-line therapy either as a single agent or as combination therapy with chemotherapy in advanced or systemic NSCLC, whereas in SCLC, it is generally given with chemotherapy with only a modest impact on survival.[13,14] This suggests that NSCLC cells could be more sensitive to the cytotoxic attacks of a hyperactive immune system. We saw an analogous relationship between autoimmune disorders and survival in our cohort, with greater improvement in survival in NSCLC than SCLC. This greater improvement in the survival of a more immune-sensitive cancer supports the possibility that immune activity may be responsible for increased survival. It is also possible that patients with autoimmune disease were diagnosed with having lung cancer earlier, introducing lead time bias, or received treatment earlier because they were already established with health care providers and receiving more monitoring than the general population. The patients with autoimmune disease could also have had some other attribute such as an underlying genetic variant that independently predisposes this population to autoimmune disease and better survival of lung cancer.

Our study had several methodological strengths. The large study population decreased the likelihood that random chance caused the difference in survival between the autoimmune and nonautoimmune
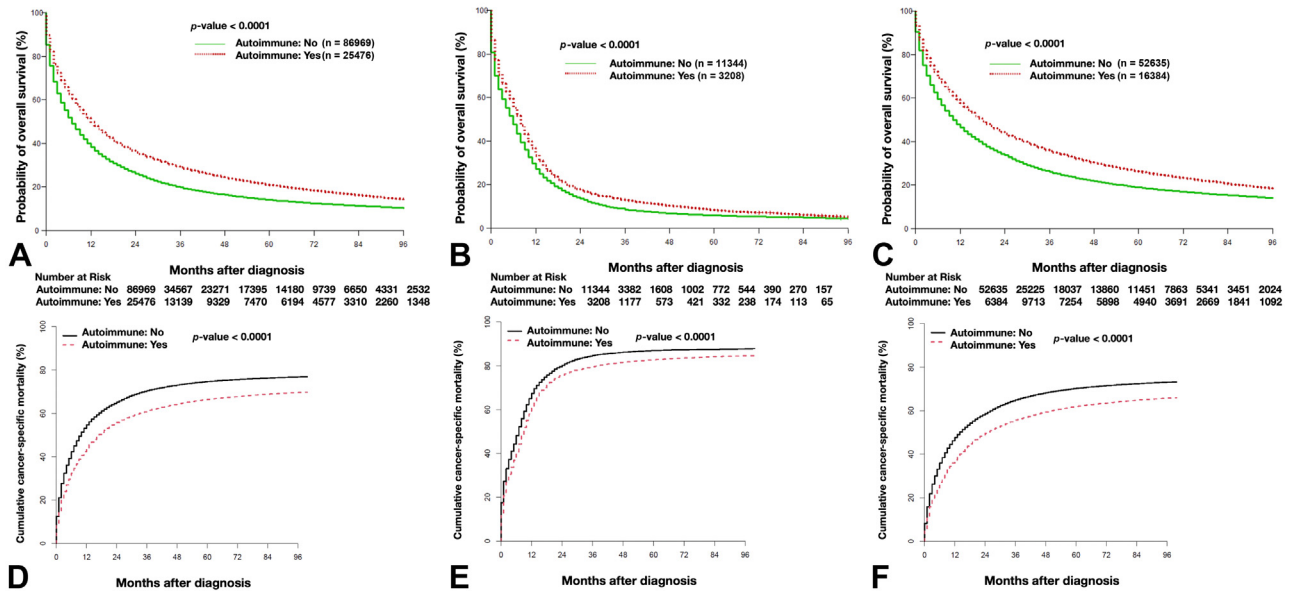
Figure 2. OS and CSM for lung cancer cohort, SCLC and NSCLC with and without a history of autoimmune disease: Kaplan-Meier estimation of OS for patients with (A) lung cancer, (B) SCLC, and (C) NSCLC with and without autoimmune disease. Cumulative incidence of CSM for patients with (D) lung cancer, (E) SCLC, and (F) NSCLC with and without autoimmune disease. OS, overall survival; CSM, cancer-specific mortality.

populations. The 7-year period for which data were analyzed allowed for long-term follow-up. In addition, our cohort predated the widespread use of immunotherapy in lung cancer, removing confounding effects that immunotherapy might have caused and making it

easier to isolate the effect of autoimmune disease on survival. There were also a number of limitations. SEER Medicare data largely include patients more than 65 years of age making it difficult to generalize these findings to a younger population. The use of ICD-9 codes, and chronic condition flags for RA, to identify a history of autoimmune disease may have allowed for patients that do not meet clinical and laboratory criteria for a particular disease to be included in the autoimmune disease group. Likewise, some patients with a genuine diagnosis may not have been captured. In addition, the National Cancer Institute and Charlson comorbidity indexes could not be used as a proxy to compare level of comorbidity in autoimmune and nonautoimmune patient groups because both of these indexes include "rheumatologic conditions," making it difficult to discern the significance of a difference in comorbidity index between the two populations. It is also not possible to reliably determine tobacco use using the SEER Medicare data, which does not include information on risk factors.[32] This makes it difficult to exclude a difference in the prevalence of tobacco use as an underlying cause for survival differences between autoimmune and non-autoimmune disease patients. Nevertheless, men use tobacco at higher rates than women.[33] If tobacco use was an underlying explanation of the survival differences, then controlling for sex should shrink the survival gap, whereas we report a significant increase ($p < 0.0001$) in survival with autoimmune disease regardless of sex.

Table 3. Median OS in Months by Status of Autoimmune Disease

| Factors	Median OS (mo) Without Autoimmune Disease	Median OS (mo) With Autoimmune Disease
Overall	7	12
SCLC	6	8
NSCLC	6	8
Stage 1	46	63
Stage 2	24	29
Stage 3	10	13
Stage 4	3	5
Crohn's disease	8	11
Dermatomyositis	8	10
Polymyositis	8	11
Psoriasis	8	13
Rheumatoid arthritis	7	13
Sarcoidosis	8	16
Systemic scleroderma	8	11
Sjogren's syndrome	8	19
Systemic lupus erythematosus	8	12
Ulcerative colitis	8	12

OS, overall survival.
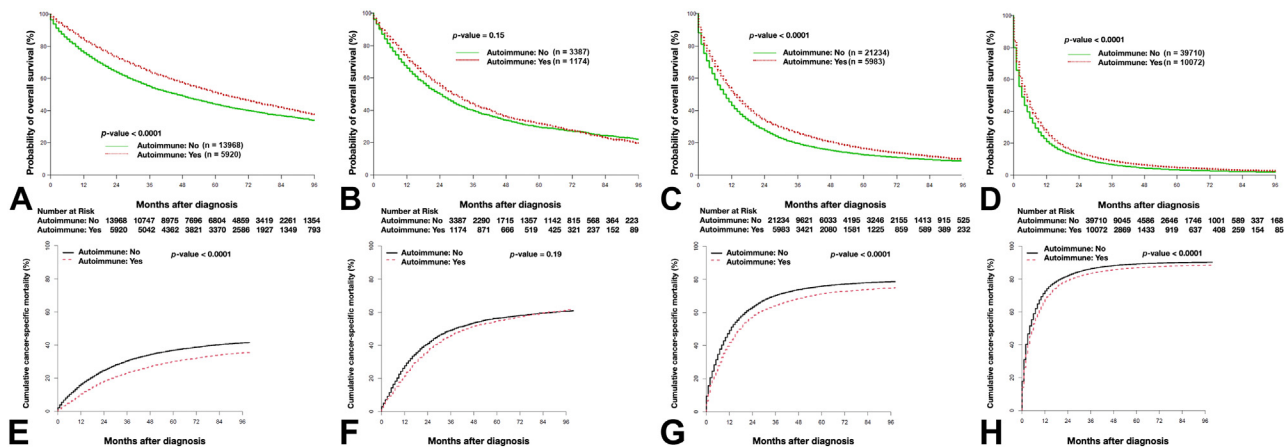
Figure 3. OS and CSM for lung cancer stages 1 to 4 with and without a history of autoimmune disease: Kaplan-Meier estimation of OS for patients with (*A*) stage 1, (*B*) stage 2, (*C*) stage 3, and (*D*) stage 4 lung cancer with and without autoimmune disease. Cumulative incidence of CSM for patients with (*E*) stage 1, (*F*) stage 2, (*G*) stage 3, and (*H*) stage 4 lung cancer with and without autoimmune disease. OS, overall survival; CSM, cancer-specific mortality.

In conclusions, this study revealed that patients in the SEER Medicare database with lung cancer and an autoimmune disease had significantly higher OS and significantly reduced CSM compared with patients with lung cancer and no autoimmune disease even when controlling for age, sex, race, disease stage, and CKD. This association between autoimmune disease and increased survival was not restricted to a particular stage of disease and was found in most specific autoimmune diseases included in this study. Ignoring the complex relationship between autoimmune disease and malignancy, it is unexpected that an additional comorbidity is associated with improved survival. Nevertheless, the larger increases in survival in NSCLC over SCLC suggest that immune activity in these patients could contribute to improved outcomes. Better access to care for patients with an autoimmune disease diagnosis or an independent factor resulting in higher rates of autoimmune disease and improved survival in lung cancer must also be considered. This study also revealed higher levels of autoimmune disease, and specific common autoimmune diseases, in patients with lung cancer compared with cohorts of similar age ranges in the general population. Increased survival in patients with malignancies other than lung cancer and autoimmune diseases would suggest that those malignancies could be amenable to treatment with immunotherapy. Similarly, autoimmune diseases that consistently are associated with improved survival in malignancies could offer future targets for immunotherapy drug development. Further research is needed to understand the relationship between lung cancer and autoimmune diseases and to explore the relationship between autoimmune diseases and survival in other malignancies.

CRediT Authorship Contribution Statement

Demitrios Dedousis: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration.

Anastasia N. Vassiliou: Software, Formal analysis, Investigation, Data curation, Writing - original draft, Visualization.

Shufen Cao: Methodology, Software, Validation, Formal analysis, Data curation, Writing - original draft, Visualization.

Deepthi Yammani: Software, Validation, Formal analysis, Data curation.

Ravi Kyasaram: Software, Data curation.

John P. Shanahan: Resources, Writing - original draft, Supervision.

Melissa C. Keinath: Visualization.

Annie L. Zhang: Writing - review & editing.

Melinda L. Hsu: Writing - review & editing, Supervision.

Pingfu Fu: Methodology, Software, Validation, Formal analysis, Resources, Data curation, Visualization, Supervision.

Afshin Dowlati: Conceptualization, Methodology, Validation, Formal analysis, Resources, Writing - review & editing, Supervision, Funding acquisition.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO*

Clinical and Research Reports at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2022.100375.

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