Twenty-Year Changes in Mortality Rates and Underlying Causes of Death in Patients with Rheumatoid Arthritis-Associated Interstitial Lung Disease, 1999–2018

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Abstract

Background: The treatment of rheumatoid arthritis (RA) has advanced considerably in the last 20 years. However, few population-based studies have assessed mortality rates and the underlying cause of death (UCD) in patients with RA and RA-associated interstitial lung disease (RA-ILD). We conducted a study to evaluate trends in mortality rates, demographic characteristics, and UCDs in patients with RA-ILD.

Methods: Through data from death certificates (1999-2018) acquired from the U.S. Centers for Disease Control and Prevention Multiple Cause of Death files, we explored trends in mortality rates and UCD for RA and RA-ILD patients. We evaluated trends in crude rates and age-standardised mortality rates (ASMR) for patients with RA and RA-ILD.

Results: In both RA and RA-ILD patients, ASMR variation trended downward over a 20-year period. The ASMR ratio of RA-ILD to RA decreased by 5.84%. The ASMR for RA and RA-ILD stratified by sex or age group also trended downward. The change in the ASMR ratio of RA-ILD to RA differed between men and women, trending downward in women and upward in men. Arthropathies and ILD were the two most frequent UCDs for RA-ILD, while the most frequent UCDs for RA were arthropathies and ischaemic heart disease.

Conclusions: Although both RA and RA-ILD showed a downward trend in mortality, RA combined with ILD may reduce patient life span. Specifically, the mortality rate for RA-ILD remained relatively stable during the study period when ILD was the UCD, which suggests the necessity of devoting resources to active prevention, early diagnosis, and effective management of RA-ILD.

Background

Approximately 0.5–1% of the global population has rheumatoid arthritis (RA) (1). RA affects not only joints but also multiple organs. This illness is sometimes fatal, and usually economically burdensome for the patient. One of the most frequent extra-articular manifestations of RA is interstitial lung disease (ILD), which is a leading cause of illness and death in patients with RA (2). ILD, which is clinically significant among only 10% of ILD cases, can be detected in 60% of patients with RA by high-resolution computed tomography (HRCT) (3). The prevalence of RA-ILD has increased year by year (4). An earlier study showed that certain autoantibodies can be detected in the serum of patients without evidence of joint involvement, and airway abnormalities can be identified on HRCT in patients with circulating RA-related antibodies in the absence of arthritis (5). Interestingly, one group reported a hypothesis that the lung may represent the initiating site of autoimmunity (6). In the last 20 years, new biological agents have been developed that control RA joint inflammation and improve joint symptoms; however, changes in mortality and underlying cause of death (UCD) in patients with RA-ILD have rarely been studied. Previous studies of RA-ILD mortality were primarily based on deaths in patient cohorts (7, 8), which did not capture changes in RA-ILD mortality over time and did not reflect the true burden and trends of RA-ILD mortality and UCD in the general population. One previous study examined RA-ILD mortality based on death certificate data on a large population-based scale. However, the data predated 2010, and there has not been any research on RA-related mortality trends in recent years. Therefore, we conducted a population-based study of temporal trends in mortality and changes in UCD associated with RA and RA-ILD in the United States from 1999 to 2018.

Methods

Data were obtained from the U.S. Centers for Disease and Control Prevention National Center for Health Statistics Multiple Cause of Death files (1999–2018) (10), which were compiled from data collected by 57 vital statistics jurisdictions. All data contained in these database files are public records; therefore, institutional review board approval for this research was not required.

We used the following ICD-10 codes to identify RA: M05.0 (Felty syndrome), M05.1 (rheumatoid lung disease (J99.0*)), M05.2 (rheumatoid vasculitis), M05.3 (rheumatoid arthritis with involvement of other organs and systems), M05.8 (other seropositive rheumatoid arthritis), M05.9 (seropositive rheumatoid arthritis, unspecified), M06.0 (seronegative rheumatoid arthritis), M06.1 (adult-onset Still disease), M06.2 (rheumatoid bursitis), M06.3 (rheumatoid nodule), M06.4 (inflammatory polyarthropathy), M06.8 (other specified rheumatoid arthritis), and M06.9 (rheumatoid arthritis, unspecified). ILD was defined by corresponding ICD-10 codes, which included J84.1 (a code that combined postinflammatory pulmonary fibrosis and idiopathic pulmonary fibrosis), and M05.1 or J99.0 (rheumatoid lung disease). To standardise mortality rate comparisons for each year, we calculated the overall age-standardised mortality rate (ASMR) of RA and RA-ILD based on the estimated population distribution for the year 2000.

We calculated yearly ASMRs of patients who died of RA or RA-ILD, as well as the ratio of the former to the latter. Among the abovementioned decedents, the trends of ASMR in both sexes and within each age group (0–54, 55–64, 65–74, 75–84, and > 84 years) were also summarised. To obtain rates of change and to highlight the trends in RA-ILD mortality compared with RA mortality, we divided patients according to two subperiods (1999–2003 and 2014–2018). We also examined change rates in the ratio of the RA-ILD ASMR to the RA ASMR overall, and according to gender. Finally, we ranked the top 10 UCDs according to the crude death rates found in the UCD-ICD sub-chapter.

Results

Overall mortality trends

From 1998 to 2018, there were 50,567,774 deaths in U.S. residents, of which 180,821 included mentions of RA on the death certificate. Of these RA deaths, 13,802 (7.6%) were of RA combined with ILD. The average age-adjusted mortality rate for RA was 36.2 per 1,000,000 people in the general population. The average age of patients with RA-ILD mentioned in death certificates from 1999 to 2018 was 74.4 years, compared with 77.0 years for patients with RA. The average age of death in patients with RA was 74.8 years for males and 77.7 years for females, and the average age of death in patients with RA-ILD was 73.3 years for males and 75.0 years for females.

We observed a downward trend for ASMR over the course of 20 years for both the RA and RA-ILD groups (Fig. 1A). The ASMR ratio of RA-ILD to RA without ILD showed an upward trend year by year (Fig. 1B). The ASMR in the RA-ILD group decreased from 0.24 per 100,000 people during 1999–2003 to 0.15 per 100,000 people during 2014–2018, for a rate of change of -37.50%; however, the rate of change for RA was − 33.62%. The change in the ASMR ratio of RA-ILD to RA was − 5.84%. The average age of death in patients with RA-ILD rose from 73.5 years in 1999–2003 to 75.2 years in 2014–2018, whereas the average age of death in patients with RA rose from 76.4 to 77.2 years.

Mortality trends by sex and age groups

When we stratified the data set according to sex, we observed a decreasing trend in the ASMR for both men and women. For RA-ILD, the change in trend among women was greater than among men, while for RA, the trend was more significant in men than in women (Table 1). The ASMR ratio of RA-ILD to RA trended differently in men and women, with a downward trend observed among women and an upward trend observed among men. The mortality analysis according to gender and age group (0–54, 55–64, 65–74, 75–84, and > 84 years) revealed decreasing trends for all groups, though to differing degrees (Fig. 1C-D, Fig. 2, and Fig. 3). The largest reduction occurred among females and in people ages 55–64 years for RA-ILD, and among males and in people ages 65–74 years for RA (Tables 1 and 2). The change rates in the mortality ratio of RA-ILD to RA showed downward trends in people ages 0–54 years (-46.67%), 55–64 years (-28.71%), and 65–74 years (-5.03%), as well as rising trends in people ages 75–84 years (5.80%) and > 84 years (15.75%).

Variable	RA-ILD					RA					ASMR ratio of RA-ILD to RA		
	1999-2003		2014-2018		change,%	1999-2003		2014-2018		change,%	Ratio×10^{-2}		Change,%
	Deaths	AMSR	Deaths	AMSR		Deaths	AMSR	Deaths	AMSR		1999-2003	2014-2018	
all	3450	0.24	2950	0.15	-37.50	48740	3.48	43959	2.31	-33.62	6.90	6.49	-5.84
Female	2212	0.31	1861	0.17	-45.16	35793	4.23	32139	2.95	-30.26	7.33	5.76	-21.37
Male	1238	0.18	1089	0.13	-27.78	12947	2.31	11820	1.44	-37.66	7.79	9.03	15.86
ASMR = age-standardized mortality rate (per 100 000 people)													

Table 1
Cumulative Percentage Change in ASMRs(deaths per 100,000 people) stratified by sex grouping of RA-ILD and RA, and ASMRs Ratio of RA-ILD to RA , 1999 –2018

Age groups	RA-ILD					RA					mortality ratio of RA-ILD to RA		
	1999-2003		2014-2018		change,%	1999-2003		2014-2018		change,%	Ratio×10^{-2}		Change,%
	Deaths	Rate	Deaths	Rate		Deaths	Rate	Deaths	Rate		1999-2003	2014-2018	
0-54 years	170	0.02	94	0.01	-50.00	1795	0.15	1636	0.14	-6.67	13.33	7.14	-46.47
55-64 years	464	0.37	352	0.17	-54.05	4422	3.46	4598	2.23	-35.55	10.69	7.62	-28.71
65-74 years	1021	1.11	870	0.61	-45.05	11301	12.27	10133	7.10	-42.14	9.05	8.59	-5.03
75-84 years	1357	2.16	1051	1.46	-32.41	19905	31.68	14559	20.24	-36.11	6.82	7.21	5.80
>84years	438	2.03	583	1.83	-9.85	11317	52.54	13031	40.92	-22.12	3.86	4.47	15.75

Table 2
Cumulative Percentage Change in mortality rates(deaths per 100,000 people) stratified by age grouping of RA-ILD and RA, and mortality ratio of RA-ILD to RA, 1999 –2018

Rank of UCD

For RA-ILD, arthropathies and ILD consistently ranked among the top two causes of death in both time periods. Ischaemic heart diseases, pulmonary heart disease, and diseases of pulmonary circulation all dropped in the rankings over the course of the follow-up period. Malignant neoplasms rose in rank from fifth to third, and chronic lower respiratory diseases became slightly more frequent (Table 3). Interestingly, influenza and pneumonia dropped from the 10th to the 13th place. In RA, the top five causes of death were arthropathies, ischaemic heart disease, malignant neoplasms, chronic lower respiratory disease, and other forms of heart disease in both time periods (Table 4).

Table 3
The top 10 underlying-cause-of-death of RA-ILD

1999–2003			2014–2018		
UCD - ICD Sub-Chapter	UCD - ICD Sub-Chapter Code	Crude Rates	UCD - ICD Sub-Chapter	UCD - ICD Sub-Chapter Code	Crude Rates
Arthropathies	M00-M25	0.136	Arthropathies→	M00-M25	0.097
Other respiratory diseases principally affecting the interstitium	J80-J84	0.042	Other respiratory diseases principally affecting the interstitium→	J80-J84	0.041
Ischaemic heart diseases	I20-I25	0.015	Chronic lower respiratory diseases↑	J40-J47	0.008
Chronic lower respiratory diseases	J40-J47	0.009	Malignant neoplasms↑	C00-C97	0.007
Malignant neoplasms	C00-C97	0.008	Ischaemic heart diseases↓	I20-I25	0.006
Other forms of heart disease	I30-I51	0.006	Other forms of heart disease→	I30-I51	0.003
Pulmonary heart disease and diseases of pulmonary circulation	I26-I28	0.003	Other bacterial diseases↑	A30-A49	0.002
Other bacterial diseases	A30-A49	0.003	Cerebrovascular diseases↑	I60-I69	0.001
Cerebrovascular diseases	I60-I69	0.002	Lung diseases due to external agents↑	J60-J70	0.001
Influenza and pneumonia	J09-J18	0.002	Systemic connective tissue disorders↑	M30-M35	0.001

Table 4
The top 10 underlying-cause-of-death of RA

1999–2003			2014–2018		
UCD - ICD Sub-Chapter	UCD - ICD Sub-Chapter Code	Crude Rates	UCD - ICD Sub-Chapter	UCD - ICD Sub-Chapter Code	Crude Rates
Arthropathies	M00-M25	0.955	Arthropathies→	M00-M25	0.679
Ischaemic heart diseases	I20-I25	0.603	Ischaemic heart diseases→	I20-I25	0.307
Malignant neoplasms	C00-C97	0.324	Malignant neoplasms→	C00-C97	0.306
Chronic lower respiratory diseases	J40-J47	0.194	Chronic lower respiratory diseases→	J40-J47	0.194
Other forms of heart disease	I30-I51	0.180	Other forms of heart disease→	I30-I51	0.139
Cerebrovascular diseases	I60-I69	0.170	Organic, including symptomatic, mental disorders↑	F01-F09	0.111
Diabetes mellitus	E10-E14	0.076	Other degenerative diseases of the nervous system↑	G30-G31	0.101
Other respiratory diseases principally affecting the interstitium	J80-J84	0.073	Hypertensive diseases↑	I10-I15	0.095
Other bacterial diseases	A30-A49	0.073	Cerebrovascular diseases↓	I60-I69	0.093
Hypertensive diseases	I10-I15	0.072	Diabetes mellitus↓	E10-E14	0.074

Discussion

The findings of this study indicate that in both RA and RA-ILD, mortality showed a significant decline in the last 20 years and the presence of ILD decreased survival in patients with RA. While RA is more common in women than in men, previous studies have suggested that the prevalence of RA-ILD was greater among men than among women or was similar between genders. In the present study, although the ASMR of females was greater than that of males, the ASMR ratio of RA-ILD to RA was higher in men than in women, trending upwards in men and downwards in women. This

observation suggests that the proportion of male patients with RA dying from ILD was higher than the proportion of female patients, and the proportion of male patients increased between 1999–2003 and 2014–2018. Hence, male patients with RA-ILD have an increased risk of death, and the risk has been increasing over the course of 20 years. These findings are consistent with those of previous cohort studies (11, 12).

Compared to other connective tissue diseases, patients with RA-ILD may be older, and exhibit a higher proportion of usual interstitial pneumonia (UIP). Owing to immunosenescence and inflammaging, the aged lung undergoes functional and structural changes that facilitate the occurrence of pulmonary fibrosis. Hence, ILD is more likely to occur in older patients with RA. In the present study, we found that the elderly accounted for the majority of patients with RA-ILD deaths, whereas RA-ILD patient mortality in the 55–64 years group showed significant reductions. Furthermore, the proportion of ILD cases increased in patients aged 55–74 years whose death certificates mentioned RA and decreased in patients aged > 74 years. This suggests that RA-ILD survival was extended. However, the reasons accounting for this increase in life expectancy are not well characterised.

To answer this question, we conducted an analysis of UCD in RA-ILD, which indicated that arthropathies and ILD are ranked as the top two most frequent UCDs in patients with RA and ILD mentioned in death certificates. This was the case during the entire 20-year follow-up period. Surprisingly, although there was a decrease in the death rate among patients with RA-ILD mentioned in death certificates, little significant changes occurred in the mortality rate when ILD was the UCD. Therefore, the decline in RA-ILD mortality may be more due to an improvement in living standards, control of other complications, and active treatment of primary diseases than due to treatment of ILD. One possible explanation is that there is a critical unmet need with respect to the management of RA-ILD patients. There is also evidence that treatment with methotrexate in patients with RA increased the prevalence of interstitial lung disease by approximately 0.3–11% based on numerous case reports and case series (13, 14). Other evidence suggests that treating with abatacept versus TNF inhibitors (TNF-Is) might be associated with the occurrence of ILD in RA patients, which can lead to more severe pulmonary symptoms and even death (15, 16). Further prospective cohort studies are warranted to better illustrate the association or causation between TNF-Is and ILD. A longitudinal multicenter study of 68 RA-ILD patients was conducted from 2007 until 2018 in Madrid. The results showed that patients receiving rituximab were less likely to develop functional respiratory impairment than were patients treated with other therapies (17). Tozumab showed a good safety profile in patients with RA-ILD and a potential effect on the stabilisation of pulmonary manifestations. Nevertheless, large sample-size randomised controlled trials and prospective studies are needed to validate these findings. In addition, there are a lack of sensitive and specific disease predictors. Studies showed that possible predictors of mortality include lung carbon monoxide diffusion function, high IgM rheumatoid factor levels (18), and UIP patterns (19). However, these indicators are not specific or are difficult to use for the early identification of a disease. A recent study indicated that the MUC5B promoter variant was the strongest genetic risk factor. The MUC5B promoter variant was strongly correlated with the occurrence of RA-ILD and with UIP on imaging (20). Nevertheless, the clinical application of this test appears to be far off. A prospective cohort study (21) showed that there was an association between active articular RA and development of RA-ILD, and decreasing systemic inflammation might modify the natural history of RA-ILD. Therefore, more attention should be paid to active prevention, early diagnosis, and effective management of this condition.

Ischaemic heart disease is a very common UCD in patients with RA or RA-ILD. A previous population-based cohort study indicated that ischaemic heart disease and congestive heart failure were more likely to occur in the RA-ILD group than patients with RA but not ILD, with the difference being more significant for congestive heart failure (8.5% in the RA-ILD group and 4.4% among those with RA but not ILD). A cross-sectional cohort study of 2013 patients with RA from 21 hospitals in China showed that treatment with hydroxychloroquine (HCQ) was a protective factor against cardiovascular disease, whereas ILD, hypertension, and hyperlipidemia were independent risk factors. In our study, the UCD ranking of ischaemic heart disease in RA-ILD patients decreased from third to fifth, probably owing to the widespread use of HCQ and the effective management of ischaemic heart diseases. In this study, malignant neoplasms ranked fourth on the UCD list in RA-ILD patients during 2014–2018, and compared with 1999–2003, they showed an increasing trend. In fact, certain meta-analyses have suggested that RA patients, compared with the general population, tend to have lymphomas and lung malignancies (22). RA patients with ILD and a UIP pattern were often subjected to higher mortality rates than those with other patterns and were also more likely to die of lung cancer (19). Systemic connective tissue disorders also showed an upward trend in the UCD ranking of RA-ILD, possibly because of the widespread use of various autoantibody detection techniques. Some studies indicated that infectious diseases were increasingly frequent causes of death associated with RA, and that the most common cause of death was pneumonia based on chronic ILD (19, 23). Our study reached similar conclusions. However, surprisingly, influenza and pneumonia dropped out of the top 10 most frequent UCDs during the study period. In contrast, the incidence of other bacterial diseases was elevated. This could be related to more attention being paid to lung infections based on ILD.

Conclusions

The mortality rates in both RA and RA-ILD showed downward trends from 1999–2003 to 2014–2018, with extended patient survival. However, RA in combination with ILD may reduce the life span of patients with RA. The ASMR was higher in women with RA-ILD than in men with RA-ILD; however, among patients whose death certificates mentioned RA, the proportion of men with ILD was higher than the proportion of women. Men and older adults are at a higher risk for RA-ILD death. Whether 20 years ago or more recently, arthropathies and ILD are the two most frequent UCDs in patients with RA and ILD mentioned in death certificates. HRCT can detect lung disorders in more than half of RA patients, and approximately 10% of these patients develop clinically significant ILD. It is difficult to identify the above patients for early intervention in the clinical course of their lung disorder, and even with early detection, available therapeutics do not have a clear beneficial effect on the prevention or delayed progress of ILD. Hence, it

remains urgent to identify new biological markers to help diagnose and predict disease progression, to study its pathogenesis, and to develop more targeted drugs against RA-ILD.

Abbreviations

ASMR: age-standardised mortality rates; ILD: interstitial lung disease; RA: rheumatoid arthritis; RA-ILD: rheumatoid arthritis-associated interstitial lung disease; UCD: underlying cause of death

Declarations

Ethics approval and consent to participate

The ethical review was exempted because of the use of open data.

Consent for publication

Not applicable.

Availability of data and materials

The data used in this study came from a national mortality database maintained by the CDC. The analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Jinfang Gao and Liyun Zhang conceived the study, guided the analyses, and wrote the article draft. Lei Xin, Qianyu Guo collected and analysed the data and critically revised the draft. Ke Xu and Gailian Zhang are the guarantors of the study. All authors have read and approved the manuscript, and ensure that this is the case.

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Figures

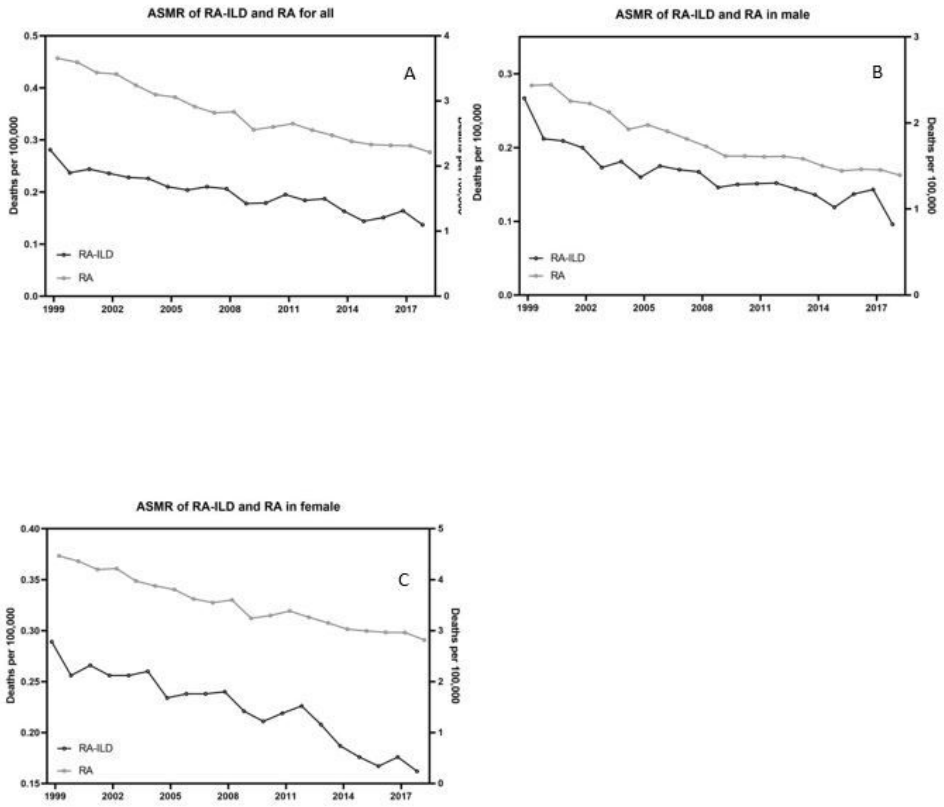

Figure 1

Age-standardised mortality rates for rheumatoid arthritis (RA) and RA with interstitial lung disease (RA-ILD), overall and among males and females, 1999–2018. The data of the RA-ILD group is referred to in the left Y axis, and that of RA is referred to in the right Y axis.

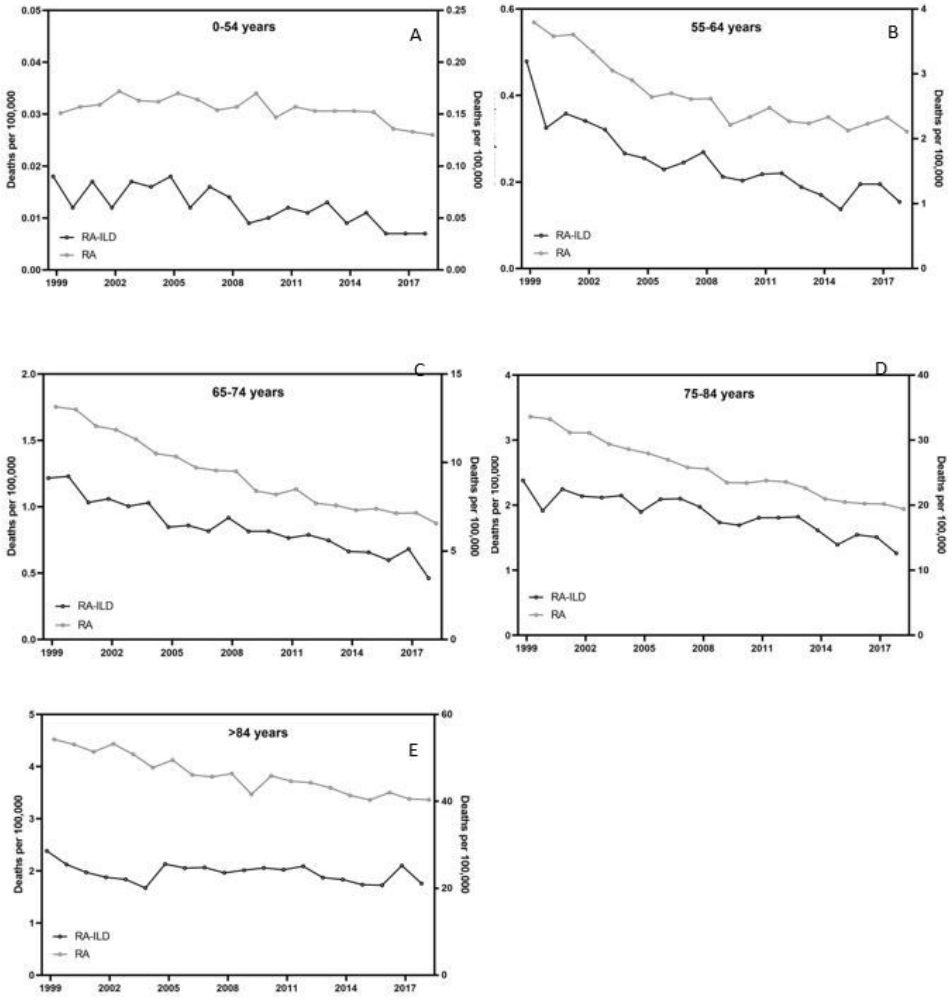

Figure 2

Trends in mortality rates of rheumatoid arthritis (RA) with and without interstitial lung disease (ILD) mentioned in death certificates by age group：0-54, 55-64, 65-74, and 75-84years，in the U.S., 1999–2018. The data of the RA-ILD group is referred to in the left Y axis, and that of RA is referred to in the right Y axis.