



Mortality Trends Among Patients with Rheumatoid Arthritis in Western Australia

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ABSTRACT

Introduction: With scarce comparative data on mortality in Australian patients with rheumatoid arthritis (RA), we investigated temporal changes in standardized mortality rates for patients with RA using longitudinal linked population-wide health data in Western Australia (WA) over the period 1980 to 2015.

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Methods: The study included 17,125 patients with a first-time hospital contact for RA (ICD-10-AM M05.00–M06.99 and ICD-9-AM 714.00–714.99) in the study period. Standardized mortality rate ratios (SMRRs) for the RA cohort versus the WA general population was estimated using direct age standardization. We analyzed temporal trends over with dates and causes provided by the WA Death Registry.

Results: During 356,069 patient-years of follow-up, a total of 8955 (52%) deaths occurred in the RA cohort. The SMRR was 2.24 (95% CI 2.15–2.34) in males and 3.09 (95% CI 3.00–3.19) in females over the study period. SMRR decreased since 2000 to 1.59 (95% CI 1.39–1.81) for the period 2011–2015. Median survival was 26.80 years (95% CI 26.30–27.30), where age and comorbidity independently increased the risk of death. The leading causes of deaths were cardiovascular diseases (26.60%), cancer (16.80%), rheumatic diseases (5.80%), chronic pulmonary disease 491 (5.50%), dementia (3.00%), and diabetes 235 (2.6%).

Conclusions: The mortality rate in patients with RA in WA has decreased but remains 1.59-times higher than in community counterparts, suggesting that there is room for further improvement. Comorbidity is the main modifiable risk factor to further reduce mortality in patients with RA.

Keywords: Mortality; Arthritis; Rheumatoid; Survival analysis; Mortality rates; Death causes

Key Summary Points

Why carry out this study?

Rheumatoid arthritis (RA) contributes to excess morbidity and mortality in patients with RA compared with the general population.

The mortality rate of RA remains higher than the general population, reducing the life expectancy by approximately 10 years.

There is a paucity of published literature on mortality and morbidity rates in Australian patients with RA.

What was learned from the study?

The mortality rate of patients with RA in Western Australia has decreased but remains 1.5-times higher than in community counterparts, suggesting that improved management comorbidity can further reduce mortality in RA.

INTRODUCTION

Mortality rates for patients with rheumatoid arthritis (RA) have reportedly improved in the past decades due to increasing access to specialized rheumatology care [1], early introduction of DMARDs with combination regimens [2], and subsequent biologics therapies [3]. However, the mortality rate remains higher than the general population, reducing the life expectancy by approximately 10 years [4–9]. A review found the median standardized mortality rate ratios (SMRRs) for patients with RA between 1953 and 2008 varied from 1.20 and 1.30 in inception cohorts and 1.60 to 1.70 in observational cohorts including patients with longer disease duration [6, 10]. Thus, patients with RA have not experienced the same improvement in survival over time as the general population [11]. To close the mortality gap, it is critical to understand the trend in causes

and predictors of RA mortality in order to develop suitable measures [11]. The reported excess mortality in patients with RA may relate to disease severity, the higher prevalence and poorer outcome of cardiovascular disease (CVD) [12–14], and/or the total number of comorbidities [15, 16]. There is an evident disparity between patients with RA and the general population in terms of prevention and management of comorbidities [17, 18]. The updated Charlson Comorbidity Index (CCI) has validated International Classification of Diseases (ICD) coding algorithms to identify comorbid conditions as predictors of mortality to predict mortality in various disease sub-groups and the overall CCI and weight risk scores have been validated in hospital discharge data from six countries, including Australia [19]. As linked health data provide the best overall RA case ascertainment [20], and there is a paucity of published literature on mortality and morbidity rates in Australian patients with RA [21], this study estimated temporal standardized mortality rates over a 35-year period and identified survival predictors and leading causes of death in a large RA cohort.

METHODS

Study Design

This is a longitudinal population-based study using population-wide linked administrative health data to assess standardized mortality rates and comorbidity accrual for patients with RA in WA from 1980 to 2015.

Data Sources

The Western Australian Rheumatic Disease Epidemiological Registry (WARDER) [22, 23] contains longitudinally linked health data for all hospital-ascertained patients with RA in the WA Hospital Morbidity Data Collection, Emergency Department Data Collection, and the WA death registry. WARDER data were extracted and linked by the WA DLB through probabilistic matching with clerical review based on

patient's name, date of birth, sex, and residential address with high linkage accuracy (99.90%) [24]. These linked datasets provide the opportunity to analyze comorbidities and mortality for people with RA.

Participants

Patients with RA were identified from the WARDER with the ICD primary or secondary codes for RA (ICD-10-AM M05.00–M06.99 and ICD-9-AM 714.00–714.99) who as having had been admitted at least once in a public or private hospital in WA from 1 January 1980 to 31 December 2014. The WA clinical coding authority confirmed the relevant ICD codes used for extraction. To increase the RA diagnosis accuracy, patients with RA were excluded if they had at least two subsequent health contacts identifying other forms of arthritis, including psoriatic arthritis, ankylosing spondylitis, other spondyloarthropathies and systemic lupus erythematosus, or other connective tissue diseases [25]. This method has been shown to have greater than 90% positive predictive value for identifying patients with a rheumatologist-reported diagnosis of RA [26]. A summary of the characteristics of the RA cohort ($n = 17,125$, 68% female) is presented in Table 1.

Outcome Measures

The primary outcome was all-cause mortality. Dates and leading causes of deaths were obtained from the WA Death Registry. Crude mortality rates per 1000 person-years by sex and age were calculated for the whole study period and for each period of study entry. The period of study entry was divided into three decades [1980–1990, 1991–2000, and 2001–2010], and the most recent 5 years [2011–2015] in the study. The death rates for the WA general population were extracted from the Australian Bureau of Statistics [27] and SMRR with a 95% confidence interval (CI) were calculated per decade. We used the 2006 WA national census population as a reference, stratified by age and gender. We also examined survival rates for

patients with RA from entry into the study and categorized causes of death among patients with RA based on ICD chapter headings of leading causes of deaths.

Statistical Methods

Continuous parametric and nonparametric variables were reported differently as the mean value \pm SD and median values with IQR range, respectively. Continuous variables were analyzed using Student's *t* test (normally distributed data) and the Mann–Whitney *U* test (non-normally distributed data). Categorical variables were compared using the Pearson χ^2 test. Comorbidity was ascertained using the CCI coding algorithms for defining comorbidities in ICD-9 and ICD-10 administrative data based on last observation in each period of study (Supplementary Material Table S1) [19]. Multi-morbidity was defined as the presence of ≥ 2 CCI score. The ARIA is an index of remoteness derived from road distance measures between populated localities and service centers. For this study, the patient's residential postcode was used to calculate the ARIA + score, and patient records were subsequently assigned at baseline to one of three geographical population settings: urban (major cities), rural (inner and outer regional), and remote areas (remote and very remote areas). Survival analysis was conducted for the whole study cohort by the Kaplan–Meier method with follow-up from the first RA health contact until Dec 31, 2014, or death. We measured median years of life lost by subtracting an individual's death age from their remaining life expectancy based on the Australian Government Actuary Life Table [28]. Differences in survival times were assessed using the log-rank test and Cox proportional hazard model was used to estimate hazard ratios of death with corresponding 95% CI. The proportional hazards assumption was assessed by examining plots of the scaled Schoenfeld residuals against survival time for the predictors. Potential predictors of death assessed were sex, age, geographic location, admitted to intensive care units (ICU), number of comorbidities (CCI), and period of study entry [14–16, 29, 30].

Table 1 Patients characteristics at study entry for the Western Australia RA cohort

	<i>N</i> = 17,125	Male, <i>N</i> = 5416 (32%)	Female, <i>N</i> = 11,709 (68%)	<i>p</i> value
Age [median (IQR)]	57 (40, 69)	57 (42, 68)	57 (39, 69)	> 0.9
Age groups				< 0.01
≤ 19	1102 (6.40%)	348 (6.40%)	754 (6.40%)	
20–29	1385 (8.10%)	314 (5.80%)	1071 (9.10%)	
30–44	2865 (17.00%)	884 (16.00%)	1981 (17.00%)	
45–59	4293 (25.00%)	1557 (29.00%)	2736 (23.00%)	
60–69	3703 (22.00%)	1250 (23.00%)	2453 (21.00%)	
70–84	3506 (20.00%)	1020 (19.00%)	2486 (21.00%)	
85+	271 (1.60%)	43 (0.80%)	228 (1.90%)	
ARIA classification				< 0.01
Urban	13,410 (78.00%)	4088 (75.00%)	9322 (80.00%)	
Rural	2664 (16.00%)	941 (17.00%)	1723 (15.00%)	
Remote	1051 (6.10%)	387 (7.10%)	664 (5.70%)	
CCI score at baseline				< 0.01
0	3843 (22.00%)	1055 (19.00%)	2788 (24.00%)	
1	7030 (41.00%)	2095 (39.00%)	4935 (42.00%)	
2	4681 (27.00%)	1626 (30.00%)	3055 (26.00%)	
3	192 (1.10%)	85 (1.60%)	107 (0.90%)	
6	1379 (8.10%)	555 (10.00%)	824 (7.0%)	

RA rheumatoid arthritis, ARIA Accessibility/Remoteness Index of Australia, CCI Charlson Comorbidity Index, ICU intensive care units

Multivariate analysis was performed for variables that were significant on univariate analysis. All statistical analyses were performed in R version 4.0.2, with statistical significance set at two-tailed with the alpha level of 0.05.

Ethics Approval

Ethics approval for this study was granted by the WA Department of Health Human Research Ethics Committee (approval number 2016/24) and the Human Research Ethics Committee of UWA (approval number RA/4/20/4070). The study was conducted in accordance with the last revised Helsinki Declaration [31].

RESULTS

Standardized Mortality Rates for RA Cohort with Odds

A total of 17,125 patients with RA were included in the RA cohort, and 8955 (52.29%) deaths occurred during 356,069 patient-years of follow-up. Death percentage for female patients with RA was 51.40%, and with a median age at death of 82 years (IQR 75–88), while the death percentage for male patients with RA was 54.20%, and with a median age at death of 78 years. Over the study period, SMRR was 2.50-fold (95% CI 2.52–2.65) higher for patients with

Table 2 Mortality rates per 1000 person-years (95% CI) and standardized mortality rate ratio by sex and age groups in the Western Australia Rheumatoid Arthritis cohort (1980–2015)

Characteristics	Patients with RA				Control (WA general population)				SMRR (95% CI) ^a
	Patients with RA (n)	Deaths (n)	Person-years at risk	Mortality rate per 1000 person-years (95% CI Poisson)	Deaths (n)	Person-years at risk	Mortality rate per 1000 person-years (95% CI Poisson)		
Sex									
Female	11,709	6020	249,111	24.16 (23.55–24.78)	171,130	31,646,049	5.40 (5.38–5.43)	3.58 (2.51–2.65)	
Male	5416	2935	106,958	27.44 (26.45–28.45)	201,058	32,084,065	6.26 (6.23–6.29)	2.24 (2.15–2.34)	
Total	17,125	8955	356,069	25.15 (24.63–25.67)	372,188	63,730,114	5.84 (5.82–5.85)	2.58 (2.51–2.65)	
Age (years)									
≥ 19 ^b	1102	46	30,124	1.52 (1.11–2.03)	10,529	18,540,725	0.56 (0.55–0.57)	2.69 (1.97–3.59)	
20–29	1385	87	39,721	2.19 (1.75–2.70)	7872	9,895,584	0.79 (0.77–0.81)	2.75 (2.20–3.40)	
30–44	2865	521	78,087	6.67 (6.11–7.27)	16,057	14,519,509	1.10 (1.08–1.12)	6.03 (5.52–6.58)	
45–59	4293	2249	98,931	22.73 (21.80–23.69)	37,760	11,203,536	3.37 (3.33–3.40)	6.74 (6.46–7.04)	
60–69	3703	2861	64,550	44.32 (42.71–45.97)	53,506	4,920,557	10.87 (10.78–10.96)	4.08 (3.92–4.23)	
70–84	3506	2946	42,796	68.83 (66.37–71.37)	149,306	3,956,872	37.73 (37.54–37.92)	1.82 (1.76–1.89)	
85+	271	245	1861	131.65 (115.68–149.20)	97,158	693,331	140.13 (139.25–141.01)	0.94 (0.83–1.07)	
Total	17,125	8955	356,069	25.15 (24.63–25.67)	372,188	63,730,114	5.84 (5.82–5.85)	2.58 (2.51–2.65)	

^aUsing the 2006 population of Western Australia as standard population

^bThe age group included juvenile idiopathic arthritis, RA rheumatoid arthritis, CI confidence interval, SMRR standardized mortality rate ratio

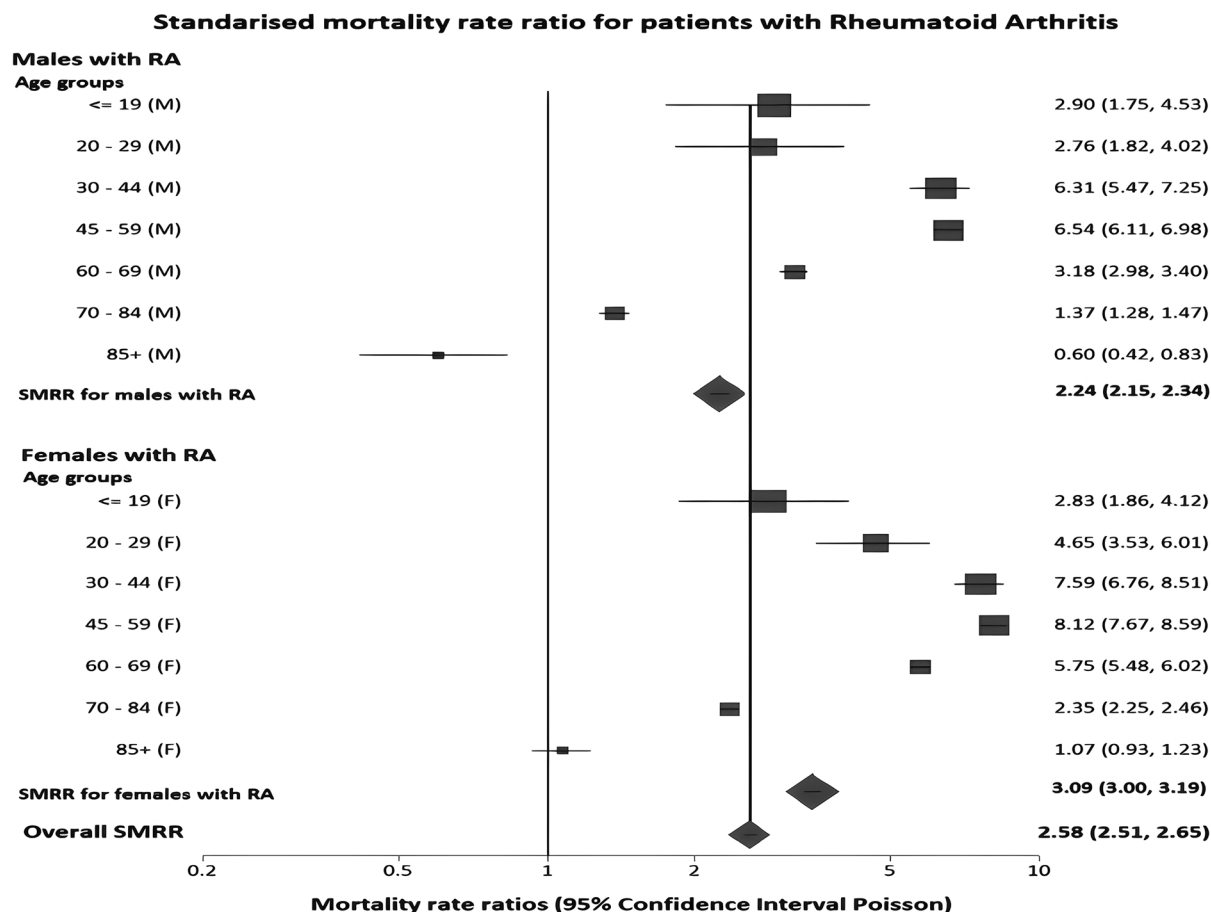


Fig. 1 Standardized mortality rate ratios for patients with rheumatoid arthritis by sex and age in Western Australia (1980–2015). RA rheumatoid arthritis, M male, F female, SMRR standardized mortality rate ratio

RA than for the general population (Table 2), with a sex- and age-specific SMRR of 2.24 (95% CI 2.15–2.34) in males and 3.09 (95% CI 3.00–3.19) in females (Fig. 1). SMRR was 2.50-fold higher than the general population during the first decade of the study, increased between 1991 and 2000 with fivefold higher than the general WA population, and then the SMRR decreased fourfold after in the 2001–2010 period, then dropping to 1.50-fold between 2011 and 2015 (Fig. 2).

Temporal Trends of Sex-Standardized Mortality Rates with Odds

In the earliest decade of study, SMRR for female patients with RA (3.51) was more than double that for males (1.82) in the RA cohort

(Supplementary Material Fig. S1–S2). The highest SMRRs stratified by sex were observed in 1991–2000 for both sexes, but with SMRRs were higher in females (5.68) than male patients with RA (4.62) (Supplementary Material Fig. S3–S4). However, SMRR for female patients with RA improved from 4.85-fold in 2001–2010 period to 1.80-fold in the 2011–2015 period (Supplementary Material Fig. S5).

Temporal Trends of Age-Standardized Mortality Rates with Odds

SMRR stratified by age (Fig. 3) was 2.50-fold and 5.00-fold higher in the first and second decades, respectively. In the following decade, SMRR reached fourfold the general population, and by the end of the study period, it was reduced to

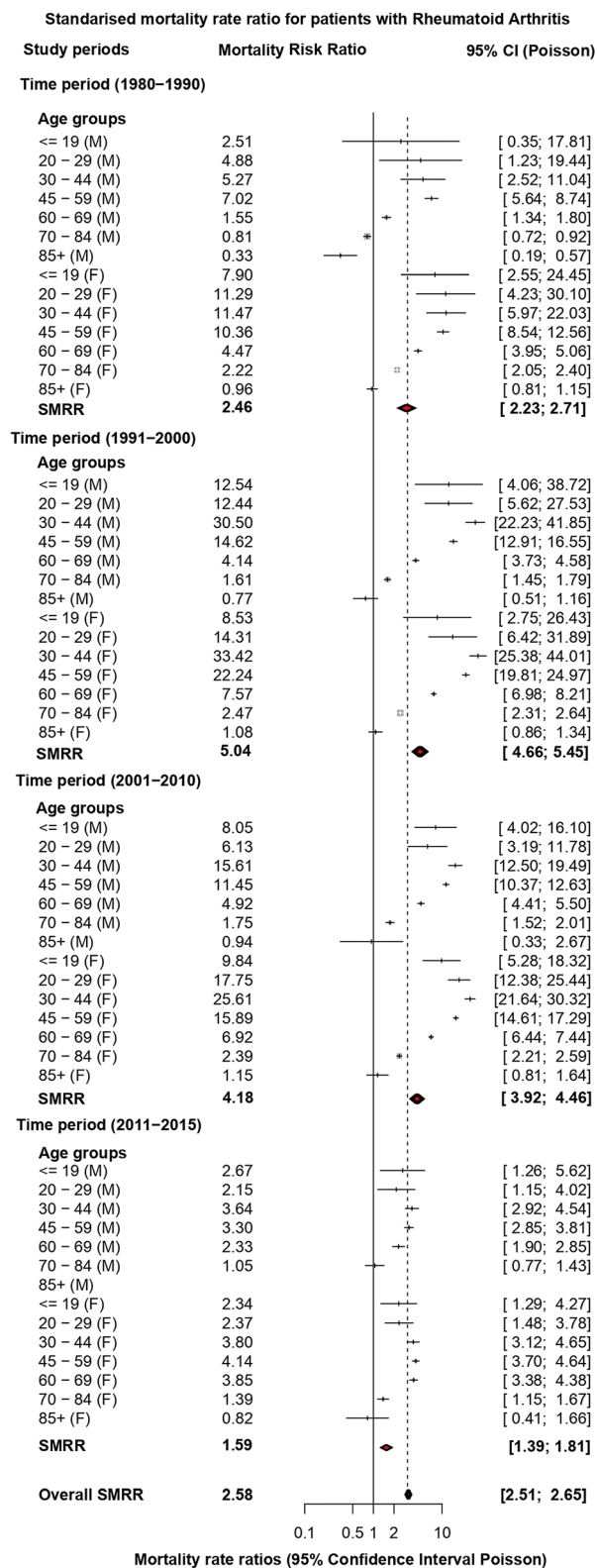


Fig. 2 Standardized mortality rate ratios for patients with rheumatoid arthritis by sex and age in Western Australia (1980–2015). *RA* rheumatoid arthritis, *M* male, *F* female, *SMRR* standardized mortality rate ratio

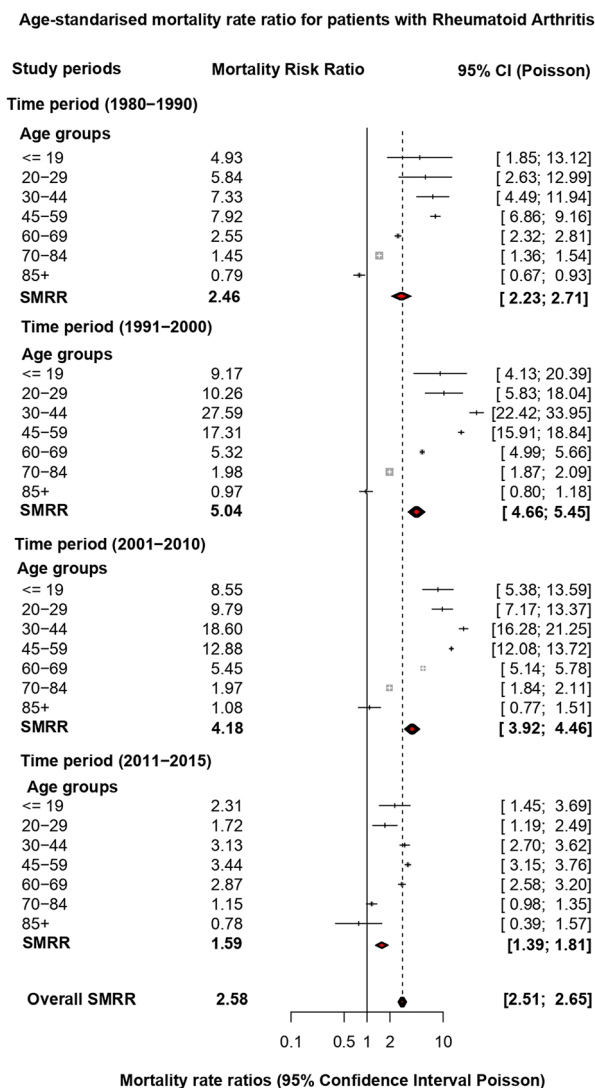


Fig. 3 Age-standardized mortality rate ratios for patients with rheumatoid arthritis in Western Australia (1980–2015). *RA* rheumatoid arthritis, *M* male, *F* female, *SMRR* standardized mortality rate ratio

1.50-fold (95% CI 1.39–1.81). The SMRRs were increased for patients with RA across all age groups up to the age of 85 (Fig. 3). The highest SMRRs were observed at 27.59 (95% CI

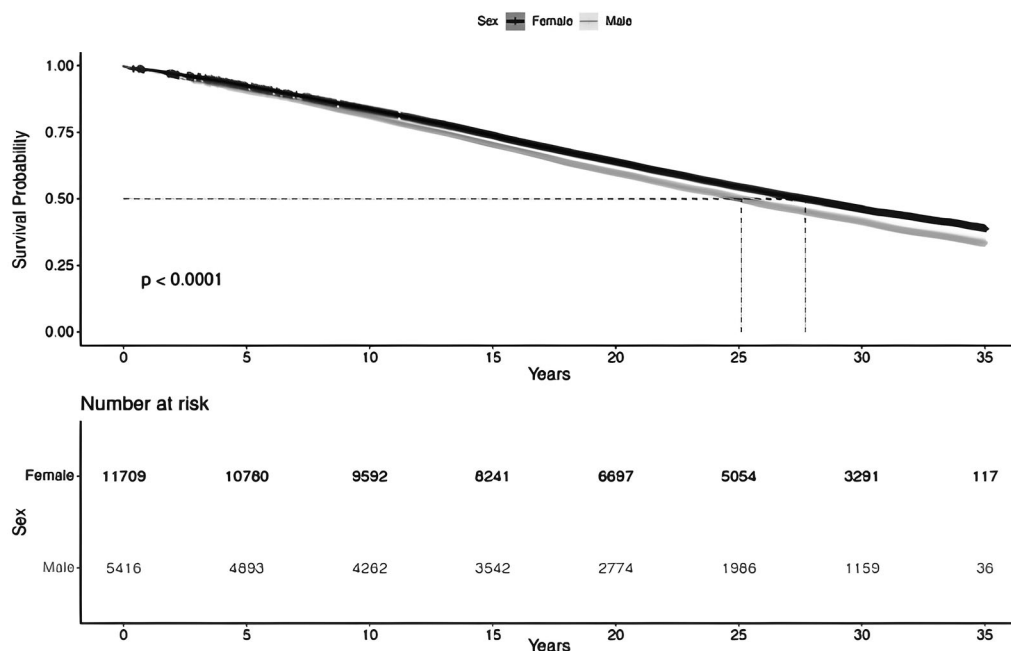


Fig. 4 Patient survival over 35 years in 17,125 people with rheumatoid arthritis according to sex

Table 3 Median life years lost for the rheumatoid arthritis cohort over study time periods

RA cohort	Females		Male	
	Median (IQR)	Percentage change (%)	Median (IQR)	Percentage change (%)
Study periods				
1980–2015	5.10 (3.40–8.0)	–	5.7 (3.90–9.10)	–
1980–1990	6.10 (4.40–9.40)	0.00	7.4 (5.00–10.2)	0.00
1991–2000	5.40 (3.70–8.00)	– 11.50	5.90 (4.10–9.30)	– 20.30
2001–2010	4.60 (3.20–7.30)	– 14.80	5.00 (3.60–8.30)	– 15.30
2011–2015	4.30 (3.10–7.70)	– 6.50	5.20 (3.40–9.10)	4.00

RA rheumatoid arthritis, IQR interquartile range

22.42–33.95) in the age group 30–44 years for the 1991–2000 period, then this risk of RA mortality reduced from 27.59-times to 18.60-times for 2001–2010 (Fig. 3). No increased risk of RA mortality was observed by age for 2011–2015.

Survival Analysis

Survival rates for patients with RA following index admission were 91.90% at 5 years,

82.90% at 10 years, 62.50% at 20 years, and 44.8% at 30 years. The median survival of the entire RA cohort was 26.80 years (95% CI 26.30–27.30) and was longer for females 27.7 years (95% CI 27.10–28.30) than males 25.1 years (95% CI 24.50–25.80) with significant difference ($p < 0.01$, Fig. 4). The estimated rates and median survival time according to patient demographic and clinical characteristics is shown in Supplementary Material Fig. S6–S8.

Table 4 Predictors of death in the Western Australia RA cohort by Cox regression

Characteristics	Univariate analysis			Multivariable analysis		
	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value
Sex						
Female	Reference	–	–	Reference	–	–
Male	1.16	1.11, 1.21	< 0.001	0.97	0.93, 1.01	0.20
Age groups						
≤ 19	Reference	–	–	Reference	–	–
20–29	1.37	0.96, 1.96	0.082	1.46	1.02, 2.09	0.037
30–44	4.31	3.19, 5.83	< 0.001	4.14	3.06, 5.61	< 0.01
45–59	16.30	12.10, 21.80	< 0.001	10.60	7.90, 14.2	< 0.01
60–69	36.80	27.50, 49.30	< 0.001	16.70	12.4, 22.3	< 0.01
70–84	64.80	48.40, 86.70	< 0.001	27.80	20.7, 37.4	< 0.01
85+	129.00	94.10, 177.00	< 0.001	57.80	42.0, 79.5	< 0.01
ARIA classification						
Urban (major cities)	Reference	–	–	Reference	–	–
Rural (inner and outer regional)	0.89	0.84, 0.94	< 0.001	1.09	1.03, 1.15	0.04
Remote (remote and very remote)	0.60	0.54, 0.66	< 0.001	1.06	0.96, 1.17	0.30
CCI score						
0	Reference	–	–	Reference	–	–
1	1.03	0.97, 1.09	0.30	0.66	0.62, 0.70	< 0.01
2	1.75	1.65, 1.85	< 0.001	1.21	1.14, 1.28	< 0.01
3	2.25	1.91, 2.66	< 0.001	2.05	1.73, 2.42	< 0.01
6	2.90	2.69, 3.12	< 0.001	1.76	1.63, 1.89	< 0.01
Multi-comorbidity						
No (CCI low score ≤ 1)	Reference	–	–	Reference	–	–
Yes (CCI high score ≥ 2)	1.94	1.86, 2.02	< 0.001	1.72	1.65, 1.80	< 0.01
Patients in ICU						
Never admitted to ICU	Reference	–	–	Reference	–	–
Ever Admitted to ICU	0.86	0.82, 0.92	< 0.001	1.28	1.20, 1.36	< 0.01
Period of study entry						
1980–1990	Reference	–	–	Reference	–	–
1991–2000	1.86	1.74, 1.98	< 0.001	2.12	1.97, 2.27	< 0.01
2001–2010	0.85	0.80, 0.90	< 0.001	1.05	0.98, 1.14	0.20

Table 4 continued

Characteristics	Univariate analysis			Multivariable analysis		
	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value
2011–2015	0.12	0.11, 0.13	< 0.001	0.25	0.23, 0.28	< 0.01

RA rheumatoid arthritis, ARLA Accessibility/Remoteness Index of Australia, CCI Charlson Comorbidity Index, ICU intensive care units, HR hazard ratio, CI confidence interval. Cox multivariable analysis adjusted for sex, age, number of comorbid conditions based on CCI, ICU admission, and period of study entry

Years of Life Lost for Patients with RA

Over the study period, the median life years lost for the RA cohort were 5.7 years for females and 5.1 years for males (Table 3). From 1991 to 2000, life-year loss decreased more in males than in females; the median loss of life decreased from 7.4 to 5.9 years. After 2000, the median lost life decreased further from 5.9 to 5.0 years (15.30%) for males and from 5.4 to 4.6 years (14.80%) for females. During 2011–2015, the median loss of life years in males increased to 5.20 years (4.00%), while in females it declined to 4.3 years (6.50%).

Predictors of RA Mortality

The assumption of proportional hazards was fulfilled for all selected predictors. In Cox multivariable analysis age ≥ 30 years, multimorbidity (CCI ≥ 2), ever ICU admission, living outside urban areas, and study entry before 2000 remained significant predictors of death (Table 4).

Causes of Death

The leading causes of death were diseases of the circulatory system ($n = 3646$, 40.70%); neoplasms ($n = 1586$, 17.70%); diseases of the respiratory system ($n = 1038$, 11.6%); diseases of the musculoskeletal system and connective tissue ($n = 599$, 6.70%); endocrine, nutritional, and metabolic diseases ($n = 414$, 4.60%); and diseases of the digestive system ($n = 410$, 4.60%) (Table 5). Within circulatory diseases, ischemic heart diseases (52.20%) and cerebrovascular diseases (20.10%) were the leading causes of

death (Table 5). Based on the age groups, the overall leading causes of death were diseases of the circulatory system, except among 30–44-year-olds in the 1991–2000 period; neoplasm was the leading cause of death (Supplementary Material Table S2–S3).

DISCUSSION

This study revealed that while the gap in mortality for patients with RA compared to the general population is narrowing over time (particularly since 2000), patients with RA remain at an increased risk of death. A higher comorbidity burden was associated with a greater risk of death in patients with RA where cardiovascular diseases remain the leading cause of death.

The SMRR was 2.58 (95% CI 2.52–2.65) higher for patients with RA in the whole study period. The age- and sex-specific SMRR were two times greater in males and three times greater in females during the study period, which is consistent with the literature [4–9]. The excess RA mortality risk in 1980–1990 may be related to less efficacious medications and potentially more toxic medications for patients with RA such as sodium aurothiomalate, penicillamine, and cyclophosphamide [32], before methotrexate became the standard of care and subsidized by Medicare Australia in 1992 [33].

In the current study, a decline in SMRRs was observed, especially after 2000. It is tempting but speculative to relate this narrowing of the mortality gap to changes in RA management toward early [34–36], aggressive treatment with DMARDs [37–39], the introduction of biological

Table 5 The overall leading causes of deaths based on International Classification of Diseases chapter (ICD) headings for the Western Australia RA cohort

Causes of death based on ICD-9 and ICD-10	Frequency	Percent
Diseases of the circulatory system	3643	40.70
Ischemic heart diseases	1903	52.20
Cerebrovascular diseases	735	20.10
Other and unspecified disorders of the circulatory system	583	16.00
Diseases of arteries, arterioles, and capillaries	239	6.60
Hypertensive diseases	77	2.10
Chronic rheumatic heart diseases	49	1.40
Pulmonary heart disease and diseases of pulmonary circulation	35	1.00
Diseases of veins and lymphatics, and other diseases of circulatory system	22	0.60
Neoplasms	1586	17.70
Diseases of the respiratory system	1038	11.60
Diseases of the musculoskeletal system and connective tissue	599	6.70
Endocrine, nutritional, and metabolic diseases	414	4.60
Diseases of the digestive system	410	4.60
External causes of morbidity	353	3.90
Diseases of the nervous system	266	3.00
Diseases of the genitourinary system	257	2.90
Certain infectious and parasitic diseases	148	1.70
Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified	79	0.90
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	60	0.70

Table 5 continued

Causes of death based on ICD-9 and ICD-10	Frequency	Percent
Mental, behavioral, and neurodevelopmental disorders	60	0.70
Diseases of the skin and subcutaneous tissue	37	0.40
Congenital malformations, deformations, and chromosomal abnormalities	5	0.10
Total	8955	100

ICD International Classification of Diseases

therapy in 2003 [40], and a treat-to-target strategy [41, 42].

Although the death rate of patients with RA has decreased over time, it remains higher than the general population, with 40–50% more fatalities [7]. In a Canadian study [7], the SMRRs were reduced from 1.50 (95% CI 1.43–1.57) in 2001 to 1.41 (95% CI 1.35–1.47) in 2009. Also, a recent Dutch study [8] found that the SMRR for all-cause mortality in the RA population was 1.54 (95% CI 1.41–1.67) in the period 1997–2012. The SMRR was reduced from 1.63 (95% CI 1.15–2.24) in 2003–2007 to 1.29 (95% CI 0.83–1.91) in 2008–2012 [8]. This is in accordance with our findings that the overall mortality of RA after age adjustment was 1.5-fold from 2011 to 2015 and despite a short timeframe. In accordance with our findings, these results suggest improved outcomes may be improved due to the combined changes in disease- and patient-related factors features and advances in specialist care and therapeutics.

The median survival time for the entire RA cohort was 26.80 years over the study period (1980–2015), with a 5-year survival rate of 91.90% for patients with RA. A recent study from Taiwan reported that the mean life expectancy for 29,355 new seropositive RA cases diagnosed between 2003 and 2016 was 26.30 years [43]. In Denmark, a recent study found a 5-year survival rate of 80% for people

with RA from national population-based registries in the period 1998–2009, while the 12-year probability of survival was 61% [44]. In the current study, the 12-year probability of survival was 78.90% for people with RA, indicating better survival for people with RA in Australia compared with Denmark in the last decades. However, this finding is dependent upon the extent validity of ICD diagnoses in Denmark-linked registries, which have not been tested yet [44]. The median years lost life was 5 years ranging from 3.50 to 9.00 years over the study period, which is consistent with a single-center observational study conducted in Australia [45].

Survival in patients with RA can be influenced by a range of factors, and we found the hazard of death was independently associated with increasing aged ≥ 30 years, living in rural areas, multi-morbidity (CCI score ≥ 2), and admissions before 2000 or to ICU or admissions before 2000. These results are in agreement with previous study predictors and suggests risk factors for death in RA are similar across regions where age > 50 years, presence of comorbid conditions, ICU admissions, and living in rural areas increased mortality risk in patients with RA [15, 16, 29, 46].

The accumulative multi-comorbidity was associated with a higher risk of mortality in our study. Using CCI, our study found that 37% of patients with RA had multi-comorbidity and they have a twofold increase in all-cause mortality compared with patients with a low CCI low (< 2 CCI score). These results are in agreement with a recent systematic review that found multimorbidity increases the risk of all-cause mortality in various RA populations [47]. In a UK study, patients with RA with multi-morbidity have a 2.20-fold increase in all-cause mortality compared to those without RA and heart disease [48]. Additionally, the study found that cardiovascular disease was associated with a more than twofold increase in all-cause mortality [48].

The cumulative burden of multi-morbidity in patients with RA is not only associated with an increased mortality rate but also a poorer quality of life and increased utilization of healthcare services [47, 49, 50]. A recent study has revealed a significant increase in

hospitalization duration for patients with RA plus two other long-term conditions as compared to those with only RA [49]. Therefore, it is important to regularly screen for common comorbidities in patients with RA and manage them adequately through collaboration between multiple care providers in order to improve patients' long-term outcomes [50]. The leading causes of death were not unexpectedly cardiovascular disease, in accordance with the literature [12–14, 51]. This relates to the accelerated rate and/or extent of atherosclerosis observed in patients with RA compared with RA tend to have a higher risk of cardiovascular morbidity than with the general population due to the accelerated atherosclerosis observed in RA [15]. Myocardial infarction (MI) was the most frequent fatal cardiovascular event as in previous studies that found the risk of MI was 1.60 compared with the general population [16, 52]. According to a recent meta-analysis, even after controlling for all traditional cardiovascular risk factors, the risk of incident MI was increased in patients with RA compared with the general population, suggesting that other variables such as systemic inflammation are involved [53].

We found that compared to a CCI score of 1, the hazard ratios for death in our patients with RA were 1.75, 2.25, and 2.90 for CCI scores of 2, 3, and 6, respectively. These findings are in agreement with the Swedish study [16] where the hazard ratios for mortality among patients with RA were increased by 50% per point increase of CCI score. Together, these data demonstrate the importance of screening and management for comorbidities in patients with RA, especially cardiovascular diseases [17].

Our study found an increase in mortality among male patients with RA compared with females in the last period (2011–2015). This was despite adequate treatment options, using treatment-to-target methods, improved cardiovascular comorbidity control in low RA activity [54]. This may be explained by gender differences in cardiovascular risk profile in patients with RA with low disease activity. Based on a recent study, there was significantly more atherosclerosis in male patients with RA despite being of similar age and moderate disease

activity (DAS28 3.20) compared to female patients with RA [55]. As a result of conventional CV risk factors, most male patients with RA with low disease activity are at high or extremely high risk of developing fatal cardiovascular disease deaths compared to female patients with RA [55].

The highest SMRRs were observed in patients with RA aged 30–44 years between 1991 and 2000, where malignant neoplasms were the leading causes of death, and lung cancer was the leading cause of cancer mortality. These results align with literature findings that indicate an increased risk of lung and lymphoma malignancies in RA compared with the general population [52]. This may be explained by higher smoking prevalence compared with smoking in other age groups or by more lung complications seen with less efficacious earlier RA therapy [56, 57]. While in later periods, earlier RA diagnosis and more aggressive management, use of biological DMARDs and smoking-cessation policies may have contributed to the reduction in mortality among patients with RA [58].

There are limitations to this study related to a case definition of patients with RA with hospital contacts (admission/ED visits) and did not cover patients with RA treated solely in outpatient settings. However, given the use of a reliable definition for RA in state-wide linked administrative health datasets combined with the finding that patients with RA are hospitalized at least once for any condition over 35-year study period [26], we feel the sample size and power of the study were sufficiently representative of the number of people with RA living in WA and the broader RA population for the whole of Australia [26].

In the literature, the mean number of hospital admissions for patients with RA for disease complications or comorbidity varies from 0.13 to 0.34 per year [59], which lies within the range of our previous published study's annual RA hospital separations (0.15%) [60]. The prevalence of RA [60] also matched the estimates prevalence derived from Australian general practice data [61]. This suggests that the long-term observation in this study covered the overwhelming majority of RA cases state-wide.

The cohort included patients with juvenile idiopathic arthritis, which can be different from adult RA with regards to symptoms, remission period, and disability [62]. However, we used this age group as an age reference for RA cases [63]. Also, the shorter last observation period (2011–2015) may have skewed our outcome data at the end of follow-up, even though we used SMRR to compensate. The incomplete data for the last period ended in 2015 instead of 2020, which is due to the lengthy and expensive process of accessing linked health data from WA Health (18–24 months). Our access was completed in 2018, but the linked datasets were only available to 2015. In the future, WARDER will be updated to include more recent data, with the latest available data up to 2019. Finally, the nature of this dataset precluded the inclusion of detailed descriptors such as clinical or biological markers of disease activity.

CONCLUSIONS

The mortality gap for patients with RA in WA has diminished since 2000, which is likely due to improvements in the management of RA and comorbid conditions. Nonetheless, the mortality rate in patients with RA in WA still remains 1.59-times higher than their community counterparts, indicating that improved management comorbidity can further reduce mortality in RA.

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Data Availability. All data generated or analysed are available in this article or the supplementary file.

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