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The Association of Psoriatic Arthritis With All-cause Mortality and Leading Causes of Death in Psoriatic Arthritis

Amir Haddad[1], Walid Saliba[2], Idit Lavi[3], Amin Batheesh[4], Samir Kasem[5], Tal Gazitt[1], Ilan Feldhamer[6], Arnon Dov Cohen[6], and Devy Zisman[7]

ABSTRACT. ***Objective.*** To examine the association between psoriatic arthritis (PsA) and all-cause mortality from a large population-based database.

Methods. Patients with PsA from the Clalit Health Services database were identified between 2003–2018 and matched to 4 controls by age, sex, ethnicity, and index date. Patient demographics, comorbidities, and treatments were extracted. Mortality data were obtained from the Israeli Notification of Death certificate. The proportionate mortality rate (PMR) of the leading causes of death was calculated and compared to that of the general population. Cox proportional hazard regression models were used to estimate the crude and the multivariate adjusted HR for the association between PsA and all-cause mortality and for factors associated with mortality within the PsA group.

Results. There were 5275 patients with PsA and 21,011 controls included and followed for 7.2 ± 4.4 years. The mean age was 51.7 ± 15.4 years, and 53% were females. Among patients with PsA, 38.2% were on biologics. Four hundred seventy-one (8.9%) patients died in the PsA group compared to 1668 (7.9%) in the control group. The crude HR for the association of PsA and all-cause mortality was 1.16 (95% CI 1.04–1.29) and 1.02 (95% CI 0.90–1.15) on multivariate analysis. Malignancy was the leading cause of death (26%), followed by ischemic heart disease (15.8%); this is in keeping with the leading causes of death in the general population. Older age, male sex, lower socioeconomic status, increased BMI, increased Charlson comorbidity index scores, and history of psoriasis or hospitalization in 1 year prior to entry were positive predictors for mortality.

Conclusion. No clinically relevant increase in mortality rate was observed in patients with PsA, and specific PMRs were similar to those of the general population.

Key Indexing Terms: mortality, prognosis, psoriatic arthritis

Psoriatic arthritis (PsA) affects an estimated 0.3–1.0% of the general population, and occurs in up to 42% of patients with psoriasis.[1] Epidemiological studies have shown that patients with PsA are often affected by numerous comorbid conditions that carry significant associated disease burden and can lead to increased mortality.[2] This is supported by data showing clear association between increasing severity of psoriasis and increasing PsA disease activity, and a higher risk for metabolic syndrome and cardiovascular (CV)-related mortality.[3,4,5] Moreover, PsA is known to be associated with increased subclinical atherosclerosis[6] and active PsA is associated with atherogenic lipid profile.[7] Both accelerated atherosclerosis and PsA are mainly mediated by Th1 cells and have a common pattern of T cell activation. Tumor necrosis factor-α (TNF-α), interferon-γ, interleukin (IL)-1β, IL-6, IL-23, and Th17 are all inflammatory mediators associated with PsA that contribute to C-reactive protein elevation[8]. TNF-α and IL-1β promote inflammation of the vascular endothelium and synovial tissue in PsA, thus supporting the hypothesis that PsA might be associated with increased CV morbidity and mortality. Treatment with anti–TNF-α decreases CV events in patients with rheumatoid arthritis (RA), another inflammatory arthritis associated with increased CV morbidity and mortality as reported by the British[9] and Swedish[5] registries; the decrease in CV morbidity and mortality is possibly due to improvement in endothelial dysfunction[10] and insulin resistance.[11]

The current body of evidence remains conflicting with regard to the association between PsA and mortality.[12] Some of the previous studies have been hampered by small sample sizes with

[1]A. Haddad, MD, T. Gazitt, MD, MSc, Division of Rheumatology, Carmel Medical Center, Haifa; [2]W. Saliba, MD, Department of Internal Medicine, Carmel Medical Center, and Department of Epidemiology, Clalit Health Services, Haifa; [3]I. Lavi, MPH, Department of Internal Medicine, Carmel Medical Center, Haifa; [4]A. Batheesh, MD, Ruth and Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa; [5]S. Kasem, MD, PhD, Department of Epidemiology, Clalit Health Services, and Ruth and Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa; [6]I. Feldhamer, BSc, A.D. Cohen, MD, Clalit Health Services, Tel Aviv; [7]D. Zisman, MD, Division of Rheumatology, Carmel Medical Center, and Ruth and Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel.

A. Haddad and W. Saliba contributed equally to this work.

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Address correspondence to Dr. A. Haddad, Rheumatology Unit, Carmel Medical Centre, 7 Michal Street, Haifa, 3436212 Israel. Email: Amirha3@clalit.org.il.

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few events and the potential for confounders of selection and severity biases from clinic-based studies. In addition, in most of the previous studies, the investigators compared the observed all-cause mortality incidence in cohorts of PsA patients with the expected incidence in the general population and reported the standardized mortality ratio (SMR). Hence, due to the lack of a concurrent internal comparative study group with individual data, adjustment was, in general, limited to age and sex, raising real concerns about residual confounding factors.

In this study, we aim to examine the association between PsA and all-cause mortality in a cohort of patients with PsA and matched controls, using data from a large population-based medical record database.

METHODS

Setting and source of data. This study is based on the computerized database of Clalit Health Services (CHS), which is the largest healthcare provider in Israel, serving approximately 4.7 million members constituting ~52% of Israel's population and representing a diverse population from different ethnicities and from all socioeconomic statuses (SES). Healthcare coverage in Israel is mandatory according to the National Health Insurance Law (1995) and is provided by 4 groups akin to not-for-profit health maintenance organizations (HMOs), which are charged with providing a broad package of benefits stipulated by the government. The 4 HMOs are both healthcare insurers and providers, thus financing and supplying health services. Membership in a specific HMO is voluntary and members can freely switch to another HMO. All members of the different HMOs have similar health insurance plans and similar access to health services, including low medications copayment. CHS maintains a database that receives continuous real-time input from pharmaceutical, medical, and administrative digital systems. Designed for purposes of administrative and clinical management, the database is available for clinical studies.[13,14,15] The electronic medical records of CHS include data from multiple sources: records of primary care physicians (PCPs), community specialty clinics, hospitalizations, laboratories, and pharmacies. A registry of chronic disease diagnoses is compiled from these data sources. Diagnoses are captured in the registry by diagnosis-specific algorithms, employing International Classification of Diseases, 9th revision (ICD-9) code reading, text reading, laboratory test results, and disease-specific drug usage. A record is kept of the data sources and dates used to establish the diagnosis, with the earliest recorded date from any source considered to be the defining date of diagnosis. The validity of selected disease diagnoses in the CHS database was found to be high in previous studies.[15,16,17,18]

Study population and follow-up. In this cohort, we first identified all adult patients aged ≥ 18 years with a new diagnosis of PsA between January 1, 2003, and December 31, 2018 (n = 5275). The date of PsA diagnosis was defined as the index date. We used risk set sampling to select the comparative, unexposed group of patients without PsA; members of CHS who were still alive in each case of PsA index date constituted the risk set for the case. For each case of PsA, we randomly selected up to 4 controls without PsA from among CHS database members in the risk set (n = 21,011). These controls were matched to cases of PsA by age (within 1 yr), sex, ethnicity (Jewish vs non-Jewish), and index date. The 2 groups were followed from the index date until the first occurrence of death from any cause or end of follow-up on June 30, 2019, whichever came first.

Covariates. Data on mortality and on the immediate cause of death were based on the Notification of Death certificate legally required by the Israeli Ministry of the Interior for every deceased person in the country. Specific causes of death were available for the deceased PsA cohort of patients until December 31, 2017. Therefore, we were unable to investigate the association of PsA with specific causes of death and thus estimated the attributable fraction of the various causes of death in patients with PsA and compared it to the proportionate mortality rate (PMR) of the leading causes of death in Israel from 2014 to 2016 based on a recently published report by the Central Bureau of Statistics.[19]

The algorithm used to retrieve patients with PsA consisted of one of the following conditions: (1) PsA diagnosis (ICD-9 code 696.0) assigned at least once by a rheumatologist; (2) permanent diagnosis (ICD-9 code 696.0) assigned by a PCP combined with use of conventional (cDMARDs) or biologic disease modifying antirheumatic drugs (bDMARDs); (3) PsA diagnosis (ICD-9 code 696.0) listed in a hospitalization discharge summary. This algorithm has been previously validated by our group and found to have high sensitivity (88.7%), specificity (88.1%), and positive predictive value (90.5%).[20]

Demographic data including age, sex, ethnicity (Jewish or non-Jewish), and SES at inception (as determined according to the CHS categories of low, medium, and high, a classification system that has been shown to highly correlate with SES assigned by the Israel Central Bureau of Statistics[21]) were retrieved from the CHS database. Data regarding tobacco use (ever), obesity (defined as BMI ≥ 30 kg/m^2), diabetes mellitus, hyperlipidemia, hypertension, ischemic heart disease, prior cerebrovascular accident, congestive heart failure, chronic renal failure, chronic obstructive pulmonary disease (COPD), cirrhosis, prior malignancy, psoriasis, hospitalization during 1 year prior to entry, and the concomitant use of glucocorticoids as well as cDMARDs and bDMARDs were also extracted from the database. The Charlson comorbidity index[22] was calculated.

Statistical analyses. Continuous variables are summarized with mean ± SD, and categorical variables are presented as numbers and proportions. Comparisons of baseline characteristics between patients with and without PsA were performed using the chi-square test for categorical variables and *t* test for continuous variables. Cox proportional hazard regression models were used to estimate the crude and multivariate adjusted HR for the association between PsA and all-cause mortality, as well as for factors associated with mortality within the PsA group. All statistical analyses were performed using IBM SPSS Statistics for Windows 24.0 (IBM Corp.). In all analyses, $P < 0.05$ for the 2-tailed tests was considered statistically significant.

The study was approved by the Institutional Review Board of Carmel Medical Center, Haifa, Israel (CMC 0014-14).

RESULTS

A total of 5275 newly diagnosed patients with PsA were identified between 2003 and 2018 and were matched to 21,011 controls based on age, sex, and ethnicity. The mean age was 51.7 ± 15.4 years, and 53% were female.

More individuals in the PsA group were smokers and obese, with diabetes, hypertension, and dyslipidemia, and had a history of ischemic heart disease, cerebrovascular disease, congestive heart failure, COPD, chronic renal failure, and cirrhosis than patients in the control group. In patients with PsA, 38.2% were on biologics (Table 1).

Overall, 471 (8.9%) patients died in the PsA group compared to 1668 (7.9%) in the control group during a mean follow-up of 7.2 ± 4.4 years. Of the 471 patients with PsA who died by the end of follow-up (June 30, 2019), the specific cause of death was available for 385 patients with PsA who died by the end of December 31, 2017. In patients with PsA, malignancy was the leading cause of death, constituting 26% of all deaths, followed by ischemic heart disease (15.8%), diabetes (6.2%), cerebrovascular disease (5.5%), and septicemia (5.5%); this is in keeping with the order of the leading causes of death in the general

Table 1. Baseline demographic and clinical characteristics.

	PsA, n = 5275	Controls, n = 21,011	*P*
Age, yrs	51.7 ± 15.4	51.7 ± 15.5	0.99
Sex			0.96
Male	2468 (46.8)	9838 (46.8)	
Female	2807 (53.2)	11173 (53.2)	
Ethnicity			0.98
Jewish	4594 (87.1)	18296 (87.1)	
Arab	681 (12.9)	2715 (12.9)	
Socioeconomic status			< 0.0001
Low	1621 (30.7)	7169 (34.1)	
Medium	2043 (38.7)	8779 (41.8)	
High	1326 (25.1)	4922 (23.4)	
Tobacco use (ever)	2227 (42.2)	8311 (39.6)	< 0.0001
Obesity (BMI ≥ 30 kg/m^2)	1765 (33.5)	5411 (25.8)	< 0.0001
Diabetes mellitus	1781 (33.8)	5497 (26.2)	< 0.0001
Congestive heart failure	117 (2.2)	344 (1.6)	0.004
Chronic renal failure	159 (3.0)	529 (2.5)	0.04
COPD	465 (8.8)	824 (3.9)	< 0.0001
Cirrhosis	28 (0.5)	45 (0.2)	< 0.0001
Hyperlipidemia	2313 (43.8)	8223 (39.1)	< 0.0001
Hypertension	1589 (30.1)	5492 (26.1)	< 0.0001
Ischemic heart disease	542 (10.3)	1814 (8.6)	< 0.0001
Prior CVA	243 (4.6)	824 (3.9)	0.02
Malignancy	336 (6.4)	1284 (6.1)	0.49
Psoriasis	4244 (80.5)	337 (1.6)	< 0.0001
cDMARDs	2053 (38.9)	0 (0.0)	< 0.0001
bDMARDs	2015 (38.2)	107 (0.5)	< 0.0001

Values are expressed as mean ± SD or n (%). bDMARD: biologic disease-modifying antirheumatic drugs; cDMARD: conventional disease-modifying antirheumatic drug; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; PsA: psoriatic arthritis.

population of Israel from 2014 to 2016, as recently reported by the Central Bureau of Statistics[19] (Table 2).

The crude incidence mortality rate was higher in patients with PsA (1238 per 100,000 person-years [PY]) than in controls (1096 per 100,000 PY; $P = 0.007$) as depicted in Table 3. Although described as crude, the crude incidence rates cannot be considered purely crude as the 2 groups were matched for age, sex, and ethnicity. Thus, these rates should be considered as at least adjusted for these variables.

The univariate HR for the associations among PsA, potential confounders, and all-cause mortality are shown in Table 4. The crude HR for the association of PsA and all-cause mortality was 1.16 (95% CI 1.04–1.29). However, the association was not significant on multivariate analysis, with an HR of 1.02 (95% CI 0.90–1.15; Table 5).

Cox regression univariate and multivariate models were applied to look for factors associated with mortality within the PsA cohort. Older age, male sex, lower SES, increased BMI, increased Charlson comorbidity index scores, history of psoriasis, and history of hospitalization during the 1 year prior to entry were associated with higher mortality, whereas treatment with cDMARDs was associated with a lower relative risk of death (Table 6). Although treatment with bDMARDs had a similar trend, it was not statistically significant (HR 0.82, 95% CI 0.62–1.08). This trend did not change by age stratification, as the effect of bDMARDs in younger patients (age < 50 yrs) was 0.57 (0.26–1.25) and in older patients (age ≥ 50 yrs), the HR was 0.85 (95% CI 0.63–1.14).

DISCUSSION

Our study on all-cause mortality and leading causes of death among patients with PsA, which reflects mortality risk in the more recent era (2003–2018), showed that PsA is not associated with significant increased risk of all-cause mortality. Our findings are in line with more recent studies on PsA mortality. Notably, an increased SMR for patients with PsA was previously reported from early studies on 428[23] and 680 patients from a Toronto cohort[24] compared to the general population. The report by Ali, *et al* from the same cohort showed an improved mortality risk over time, with SMR for periods 1978–1986, 1987–1995, and 1996–2004 of 1.89, 1.83, and 1.21, respectively, which was speculated to be due to earlier diagnosis and more aggressive treatment in the more recent follow-up periods. CV-related disease was found to be the most common cause of death, followed by respiratory diseases, cancer, injuries, and poisoning, with deaths from respiratory disease, CV disease, injuries, and poisoning all found to be higher than those in the general population. Predictors for mortality in these early studies were a high erythrocyte sedimentation rate and radiological damage at presentation,[25] suggesting that disease severity markers associated with progression of damage predict mortality and thus proposing that treating patients aggressively could prevent these outcomes. A more recently published study from the same cohort at the PsA clinic at the University of Toronto[26] reported a SMR of 3.36 (95% CI 1.61–6.18) in young patients with PsA in the age group of 20–39 years; however, the overall SMR was not increased. Factors associated with increased mortality were elevated acute-phase reactants, presence of comorbidities such as ischemic heart disease and cancer, and lower level of education, again suggesting that better control of comorbidities may reduce this risk.[26] Notably, another hospital registry study by Mok, *et al*[27] on 778 patients with PsA from 1999 to 2008 in Hong Kong also reported increased mortality among patients with PsA relative to the general population with an age- and sex-adjusted SMR of 1.59; infection was the most common cause of death.

On the other hand, a study by Shbeeb, *et al*[28] based on the medical record system in Olmsted country from 1982 to 1991, and an additional study by Wilson, *et al*[29] conducted on the same database over 3 decades including 147 patients, did not find a significant increase in mortality among patients with PsA compared to the general population. Along these lines, a hospital-based study by Buckley, *et al*[30] on patients with PsA from 1985 to 2007 demonstrated no difference in the SMR. These results are in keeping with another recent large study by Ogdie, *et al*[31] on patients followed from 1994 to 2010, which reported increased mortality for patients with RA or psoriasis but not for the 8706 patients with PsA (in both DMARD users and nonusers) compared to the general population. The results of all

Table 2. The 10 leading causes of death in the general population and in the PsA cohort.

	Israel General Population (2014–2016)		PsA	
	Cause-specific Mortality	PMR, %	Cause-specific Mortality	PMR, %
1	Malignant neoplasms	25.5	Malignant neoplasms	26
2	Heart disease	15.3	Heart disease	15.8
3	Diabetes mellitus	5.5	Diabetes mellitus	6.2
4	Cerebrovascular disease	5.4	Cerebrovascular disease	5.5
5	Septicemia	4.6	Septicemia	5.5
6	Nephritis, nephrotic syndrome, and nephrosis	3.6	Nephritis, nephrotic syndrome, and nephrosis	3.4
7	Dementia	3.1	Chronic lower respiratory diseases	3.4
8	Chronic lower respiratory diseases	2.9	Liver disease	2.3
9	Pneumonia and Influenza	2.7	Dementia	2.1
10	Accidents	2.5	Accidents	2.1

PMR: proportionate mortality rate; PsA: psoriatic arthritis.

Table 3. Death summary in the 2 groups.

	No. of Deaths	Follow-up (PY)	Incidence Rate per 100,000 PY	Crude HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
PsA, n = 5275	471	38,057	1238	1.16 (1.04-1.29)	0.007	1.02 (0.90–1.15)	0.77
Controls, n = 21,011	1668	152,205	1096	Ref		Ref	

PsA: psoriatic arthritis; PY: person-years.

Table 4. Univariate association between PsA, potential confounders, and all-cause mortality.

	Survival, n = 24,142	Death, n = 2139	*P*	HR	95% CI
Age, yrs, mean ± SD	50.09 ± 14.64	69.33 ± 12.94	< 0.0001	1.16	1.08–1.23
PsA	4804 (19.9)	471 (22.0)	0.007	1.16	1.04–1.29
Tobacco use	9718 (40.2)	820 (38.3)	0.09	1.10	0.99–1.22
Diabetes mellitus	3093 (12.8)	732 (34.2)	< 0.0001	1.92	1.71–2.14
Congestive heart failure	203 (0.8)	258 (12.1)	< 0.0001	3.18	2.65–3.82
Chronic renal failure	410 (1.7)	278 (13.0)	< 0.0001	2.50	2.11–2.97
Cirrhosis	44 (0.2)	29 (1.4)	< 0.0001	5.17	2.92–9.18
Hyperlipidemia	9306 (38.5)	1230 (57.5)	0.02	1.13	1.02–1.26
Hypertension	5759 (23.8)	1322 (61.8)	< 0.0001	1.47	1.31–1.64
Ischemic heart disease	1677 (6.9)	679 (31.7)	< 0.0001	1.59	1.42–1.79
Malignancy	1242 (5.1)	378 (17.7)	< 0.0001	1.91	1.65–2.20
Psoriasis	4159 (17.2)	422 (19.7)	< 0.006	1.17	1.05–1.32

Values are expressed as n (%) unless otherwise indicated. PsA: psoriatic arthritis.

the aforementioned studies might have been confounded by a selection bias stemming from differences not only in study populations (community vs clinic/hospital-based) but also in the control population (regional vs national data). Clinic and hospital-based studies might capture a larger proportion of patients with severe disease, reflecting a selection bias. In comparison, our study was conducted on a large sample of patients with PsA from a national registry, reflecting a diverse population of patients with PsA. We did not find any increased risk in mortality compared to the general population. In the unadjusted model, the HR for mortality in PsA was statistically higher compared to the general population (1.16, 95% CI 1.04–1.29) but not clinically meaningful. This HR was not increased in the adjusted model when controlling for comorbidities, possibly pointing to the better management of comorbidities and better control of inflammation in the PsA population.

The potential limitations of this study include the retrospective analysis of a database, which lacks information on disease activity measures, as well as the missing information regarding causes of mortality in the control group and on 86/471 patients in the PsA cohort. However, as the specific causes of death were not different from the causes reported in the general population,

Table 5. Multivariable HRs for the association between PsA and all-cause mortality.

	HR (95% CI)
PsA	1.02 (0.90–1.15)
Age at entry, yrs	1.13 (1.06–1.21)
Socioeconomic status	
Low	Ref
Middle	0.77 (0.68–0.87)
High	0.60 (0.52–0.70)
Diabetes	1.57 (1.38–1.78)
Congestive heart failure	2.41 (1.95–2.97)
Chronic renal failure	1.71 (1.42–2.07)
Hyperlipidemia	0.93 (0.82–1.05)
Hypertension	1.20 (1.06–1.37)
Ischemic heart disease	1.17 (1.02–1.35)
Malignancy	1.96 (1.67–2.29)
Cirrhosis	4.79 (2.55–9.02)
Smoking	1.17 (1.04–1.31)
Obesity	
BMI < 30 kg/m^2	Ref
BMI ≥ 30 kg/m^2	1.10 (0.97–1.24)
Hospitalization during 1 year prior to entry	1.14 (1.01–1.30)

PsA: psoriatic arthritis.

Table 6. Multivariable Cox proportional hazard regression analysis for factors associated with death in the PsA cohort (n = 5275).

	HR (95% CI)
Age, yrs	1.09 (1.08–1.10)
Male sex	1.41 (1.17–1.69)
Socioeconomic status	
Low	Ref
Middle	0.89 (0.71–1.10)
High	0.56 (0.42–0.74)
Obesity	
BMI < 30 kg/m^2	Ref
BMI ≥ 30 kg/m^2	1.33 (1.09–1.62)
Hospitalization during 1 year prior to entry	1.91 (1.40–2.61)
Charlson comorbidity index	
< 3	Ref
≥ 3	2.13 (1.49–3.03)
Psoriasis	1.35 (1.04–1.76)
cDMARDs	0.70 (0.57–0.85)
bDMARDs	0.82 (0.62–1.08)

cDMARDs and bDMARDs were included in the multivariable model as time-dependent variables. bDMARD: biologic disease-modifying antirheumatic drugs; cDMARDs: conventional disease-modifying antirheumatic drug; PsA: psoriatic arthritis.

we do not expect that it would have changed the leading causes of death in the 2 groups. Moreover, only 40% of the patients with PsA were on biologic therapy; thus, the potential for exposure to sustained treatments that dampen the inflammatory state in later years was likely less pronounced.

Further, we report that treatment with cDMARDs was associated with a lower relative risk of death within the PsA cohort. A similar trend that was not statistically significant was noted with the use of biologics. This might suggest that optimal treatment and control of disease is associated with a lower relative risk of death, which is known to be less likely achieved in patients requiring biologics and supports our study conclusion of no relevant increase in mortality rate in patients with PsA from the period of 2003–2018. On the other hand, healthy adherer effect could have confounded the results as treated patients are more compliant with medical follow-up, visits, investigations, and medications that could have shifted toward better medical management and lower mortality.

The strength of our study lies in the nature of its design as we assessed the risk of all-cause mortality in PsA of an unexposed population rather than using SMR to compare to census statistics, especially as internal controls are generally felt to provide a better approximation of the true effect than SMR.[32] Moreover, the reliability of the diagnosis and data in the CHS database is high, as is that of the data on mortality from the Central Bureau of Statistics in the Ministry of Interior.

In our study, we found that the major causes of death in PsA did not differ from those most commonly reported in the general population, with malignancy as the leading cause of death. Of note, malignancy is known not to be increased in patients with PsA,[33] even in those treated with biologic therapy.[34] It is important to emphasize, however, that comparison data on the leading causes of death in PsA should be interpreted with caution, as a comparison was done with the general population and not with a control group, and was therefore indirect.

To conclude, in this study, we did not find a clinically relevant increase in mortality rate in patients with PsA from the period of 2003–2018. Although the most common causes of specific PMRs in our cohort were similar to those in the general population, it is still imperative to identify and treat comorbidities that could affect quality of life, cause medical complications, and increase mortality in our patients with PsA. Future research study designs are needed to shed more light on the effect of different confounders on mortality in patients with PsA.

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