

A long-term nationwide study on mortality associated to rheumatoid arthritis in Italy

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Received on December 1, 2019; accepted
in revised form on February 24, 2020.

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EXPERIMENTAL RHEUMATOLOGY 2020.

Key words: mortality, rheumatoid
arthritis, comorbidity, epidemiology,
causes of death

ABSTRACT

Objective. We aimed to evaluate trends of rheumatoid arthritis (RA) mortality reported as the underlying cause of death (UCD) and as multiple causes of death (MCD) in Italy between 2003 and 2015.

Methods. Analyses were carried out on the Italian National Cause of Death Register, managed by the Italian National Institute of Statistics (ISTAT). Deaths from January 1, 2003 to December 31, 2015 with any mention of RA were included. Diseases are coded according to the International Classification of Diseases, 10th Edition (ICD-10, 2009 version). Time trends of age-standardised rates were analysed for RA both as UCD and MCD, and the annual percent change (APC) was estimated.

Results. Overall, 26,564 deaths with a mention of RA were retrieved out of 7,595,214 deaths (0.35% of all certificates). The mention of RA as MCD increased throughout the study period, meanwhile the selection as the UCD decreased. RA mortality rates based on the UCD declined (males APC -3.1%, CI -3.9, -2.3; females APC -3.3%, CI -4.1, -2.4); while rates based on the MCD were stable. Specifically, rates were stable or declined among younger subjects and increased in subjects aged ≥80 years.

Conclusion. RA was found to be increasingly reported in death certificates in the last two decades in Italy, although it is less frequently reported as the UCD. Due to the increased survival of patients, we observed a shift of RA-related mortality towards the elderly, making RA a comorbidity contributing to death in these patients.

Introduction

Rheumatoid arthritis (RA) is the most common chronic inflammatory arthritis worldwide with a prevalence of 0.5–1% of the adult population (1). Mortality in RA is increased compared to the general population, mainly due to cardiovascular comorbidity and infections (2–5). Improved treatment strategies and better management of the cardiovascular morbidity have reduced mortality in RA patients in the last decades (6, 7). Nevertheless, reports on trends in RA

mortality are divergent. Meta-analyses failed to show a decrease of the mortality risk in cohorts of patients with RA between 1950 and 1995 (2). At the population level, one study based on the World Health Organisation (WHO) mortality database showed that mortality rates for RA selected as the underlying cause of death (UCD) in standard mortality statistics declined at a higher pace than all-cause mortality over the study period (3.1% vs. 1.7% annual reduction), with a mean age-standardised mortality rate reduced by 48.2% from 1987 to 2011 (8). However, only RA listed as the UCD was considered, which is widely underreported; analyses extended to all the conditions mentioned in the death certificate (multiple causes of death - MCD) can provide a more complete estimate of the burden of mortality related to RA (9). In fact, deaths associated to chronic pathologies such as rheumatic diseases are likely to result from a number of coexisting conditions that contribute to the outcome (10). Such analyses are available from a limited number of countries, and trends for RA mortality based on multiple causes have been reported as decreasing in some studies (4, 11), and stable in others (5, 10, 12).

The objective of the present analysis was to evaluate trends of RA mortality reported both as the UCD and MCD from the Italian National Cause of Death Register between 2003 and 2015.

Methods

All analyses were carried out on the Italian National Cause of Death Register, managed by the Italian National Institute of Statistics (ISTAT). Data are based on information reported in death certificates: all diseases mentioned in the certificate are coded according to the International Classification of Diseases, 10th Edition (ICD-10, 2009 version). Standard mortality statistics are based on internationally adopted algorithms which identify the UCD from all the MCD reported in the certificate according to the rules and provisions included in the ICD-10. Through the study period, the selection of the UCD has been performed by means of the Automated Classification of Medical

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Competing interests: none declared.

Entities software (13). The analyses based on the MCD data take into account all the death certificates with any mention of a specific disease, irrespective of its selection as UCD.

All deaths from January 1, 2003 to December 31, 2015 of subjects resident in Italy with any mention of RA (ICD-10 M05-M06) as MCD in the death certificate were extracted (RA-related deaths). The proportional mortality (share of all registered deaths) for RA mentioned as MCD was assessed by gender and age class. Time trends of directly age-standardised rates (European standard population) were analysed for RA both as UCD and MCD by means of the Joinpoint regression programme (14); the annual percent change (APC) with 95% Confidence Interval (CI) was estimated by fitting a linear regression to the natural logarithm of age-standardised rates, with calendar year as the predictor variable. Lastly, the distribution of selected UCD in certificates with any mention of RA was analysed. No patients or members of the public were involved in the research. All analyses were carried out on routinely collected aggregated data, therefore the study was exempt from institutional review board approval.

Results

Overall, 26,564 deaths with RA mentioned as MCD (RA-related deaths) were retrieved out of 7,595,214 deaths from all causes in Italy (0.35% of all death certificates, 0.52% in females and 0.17% in males). The proportional mortality was higher in the female gender across all ages; a peak was observed in the 70–79 years age class, where death certificates reporting RA accounted for 0.83% and 0.24% of all registered deaths in females and males, respectively.

The yearly number of deaths with RA reported as MCD increased in both genders throughout the study period, as well as the percentage represented over all causes of deaths. Meanwhile, the probability of selection of RA as the UCD decreased; as a consequence, age-standardised rates for RA as the UCD declined, while rates based on MCD remained stable (Table I). The ratio of

Table I. Rheumatoid arthritis-related number of deaths and mortality rates, based on underlying and multiple causes of death.

	2003-2006	2007-2011	2012-2015
Males			
Average annual number of deaths with RA as MCD (%, among all deaths)	441 (0.16)	502 (0.18)	535 (0.18)
Average annual number of deaths with RA selected as UCD (%, among deaths with RA selected as MCD)	117 (26)	116 (23)	113 (22)
MCD, average age-standardised rate (x100,000)	2.01	2.04	1.95
UCD, average age-standardised rate (x100,000)*	0.54	0.47	0.41
Females			
Average annual number of deaths with RA as MCD (%, among all deaths)	1392 (0.49)	1557 (0.52)	1699 (0.54)
Average annual number of deaths with RA selected as UCD (%, among deaths with RA selected as MCD)	463 (33)	458 (29)	423 (25)
MCD, average age-standardised rate (x100,000)	4.00	4.04	3.98
UCD, average age-standardised rate (x100,000)*	1.34	1.20	0.98

RA: rheumatoid arthritis; UCD: underlying cause of death; MCD: multiple cause of death.

*significant change over time.

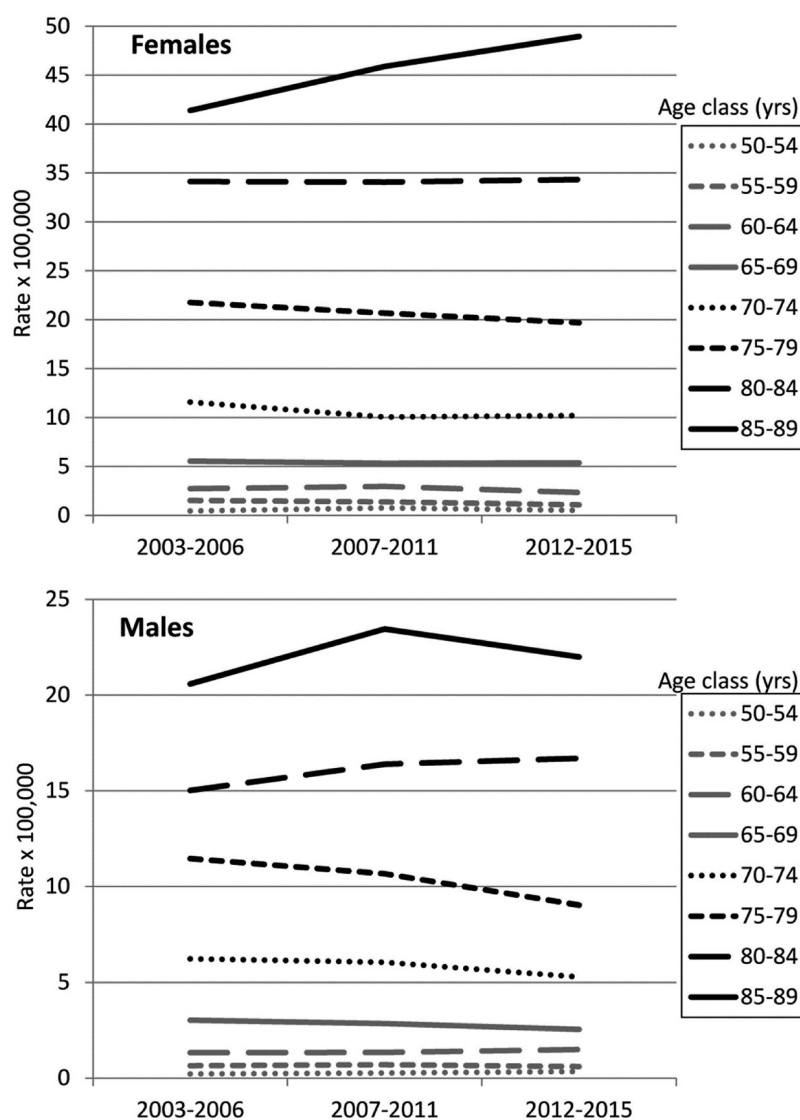


Fig. 1. Multiple causes of death: rheumatoid arthritis-related mortality rates (x100,000) by calendar period and age class.

MCD to UCD rate increased from 3.7 in 2003–2006 to 4.8 in 2012–2015 in males and from 3.0 to 4.1 in females.

RA mortality rates based on the UCD showed a constant linear decrease through the whole study period (males APC -3.1%, CI -3.9, -2.3; females APC -3.3%, CI -4.1, -2.4); the decline was more pronounced than for mortality from all causes (males APC -1.8%, CI -2.2, -1.5; females APC -1.5%, CI -2.0, -1.0). By contrast, RA mortality rates based on MCD showed no significant time trend. Figure 1 displays the trends in age-specific mortality rates for RA based on MCD: rates were stable or declined among younger subjects, whereas an increase was registered for the elderly. Out of all RA-related deaths, those accounted by subjects aged ≥ 80 years raised from 48% in 2003–2006 to 59% in 2012–2015.

RA was the UCD in 28% of RA-related deaths; the other most frequently selected UCD were circulatory diseases (21%, mainly ischaemic heart diseases), neoplasms (12%), and disorders of the respiratory (6%) and the digestive system (5%). Notably, respiratory diseases were frequently mentioned as contributory causes of death: among certificates with mention of AR, 13.0% listed also chronic obstructive pulmonary disease (COPD) and 4.4% interstitial lung diseases among reported conditions (data not shown).

Discussion

This is the first nationwide study on RA mortality in Italy. The analysis showed a reduction of mortality rates for RA selected as the UCD between 2003 and 2015 in the Italian population, while rates of RA-related mortality estimated by MCD remained unchanged. When considering different age classes, RA-related mortality increased among the elderly (80 years and more). There was a rising trend in the absolute number of deaths certificates with mention of RA; in particular, RA was increasingly mentioned as a contributory cause of death throughout the study period.

The 3% annual reduction in mortality from RA as the UCD is consistent with recently reported global trends (8). By contrast, RA-related mortality

based on MCD was stable in the Italian population, similarly to France and Brazil (5, 10, 11). Reports from Sweden and North America reported diverging results, with declining rates also for RA-related mortality (4, 11). These differences might be ascribed to a number of factors, including differences in death certification practices and also in the genetic and epidemiological characteristics of population in each country (15). Interestingly, the finding of stable age-standardised mortality rates for RA based on MCD in Italy, mainly due to the increased RA-related mortality in the elderly population, is similar to that already reported from France (10). The aging of the general population and the increased survival of RA patients are responsible for an increase in the number of old people affected by RA.

Through the study period, the percentage on total deaths of certificates with mention of RA increased. This can be explained by increased awareness and reporting of RA and possibly by increased prevalence of RA in high-income countries, such as Italy (16). The analyses based on MCD suggest a convergence of the percentage of RA in Southern Europe (0.2–0.4% in Italy and France, where MCD data were available) towards that observed in Northern Europe and the US (0.4–0.8%) (4, 10–12). The study by Kiadaliri, conducted on numerous countries, also revealed a tendency toward minor disparity in RA reporting rates in death certificates in the most recent years (8). This observation might reflect an improved diagnosis of RA and the adoption of common management strategies.

A main limit of the present study is represented by underreporting of RA in death certificates. Furthermore, this analysis did not take into account possible confounding factors such as ethnicity. Italian death certificates report only citizenship, thus, solely recent immigrants are identified according to country of origin (17). However, recent immigrants represent only a small fraction of deaths with mention of RA (<1%), preventing any analysis of RA-related mortality by ethnicity. Among potential confounders, severity and treatment were not taken into account

in the present study, nevertheless, patients usually receive treatment tailored on disease activity and have equal access to all treatments across the country. Nonetheless, the aim was not to investigate determinants of mortality but to assess time changes of overall RA-related mortality. Strengths of the study are the use of MCD and the adoption of the same classification of causes of death (ICD-10) and UCD selection method throughout the study period.

In conclusion, the progress in therapeutic strategies lead to increased survival and thus to increased prevalence of RA at older ages. The shift of RA-related mortality towards the elderly has already been suggested by analyses based on the UCD, showing rising age-specific RA mortality rates limited to older age classes (8). Although being less frequently selected as the UCD in Italy, RA is increasingly mentioned among diseases contributing to death, especially among older subjects. The growing burden on health care systems represented by elderly patients affected by RA associated to several comorbidities represents the epidemiological scenario currently faced by health care professionals and policy makers in Italy.

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