Cause-specific mortality in a large population-based cohort of patients with rheumatoid arthritis in Italy

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Abstract

Objective

The aim of our study was to investigate cause-specific mortality in rheumatoid arthritis (RA) subjects living in Italy.

Methods

We identified in the electronic archive of the Veneto Region patients aged 20–89 years who were exempt from co-payment for RA in January 2010, and linked them with the archive of causes of deaths of the period 2010-2015. Causes of death were coded according to the International Classification of Diseases, 10th Edition. Standardised mortality ratios (SMRs) with 95% confidence intervals were computed as the ratios between deaths observed in the cohort, and those expected according to age- and gender-specific regional mortality rates.

Results

Overall, 16,098 residents diagnosed with RA and aged 20–89 years were enrolled in the cohort. The overall follow-up amounted to 88,599 person-years, with 2,142 registered decedents. The most common causes of death were circulatory diseases (36.6%), neoplasms (24.2%), and respiratory diseases (8.3%). Overall mortality was increased in RA subjects (SMR=1.42, confidence interval 1.36–1.48). Mortality was significantly increased from circulatory (SMR=1.56, 1.45–1.67), respiratory (SMR=1.83, 1.57–2.12), digestive (SMR=1.93, 1.60–2.32), infectious (SMR=2.34, 1.88-2.89), haematological diseases (SMR=3.22, 2.04-4.83), and falls (SMR=1.95, 1.19–3.01). RA was the underlying cause of death in 6.1% of all deaths in the cohort and was mentioned in 25.4% of death certificates.

Conclusion

In our study, a 42% excess risk of death was observed among subjects with RA compared with the general population. Cardiovascular disease is the primary cause of premature death in RA. Adverse effects of therapy and comorbidities should be adequately monitored in RA subjects.

Key words

rheumatoid arthritis, mortality, multiple causes of death, Italy, musculoskeletal disorders

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Introduction

Rheumatoid arthritis (RA) is a common chronic inflammatory disease characterised by persistent synovitis, which leads to joint disruption and eventually disability. RA prevalence is estimated at 0.5% to 1% of the adult population around the world (1). Patients with RA are known to have an increased mortality compared to the general population, although such increased risk is often underrecognised in the medical community (2). The reasons for increased mortality in RA are multifactorial and include the effects of chronic persistent inflammation, disability, and comorbidity (3).

The introduction of new effective treatments, namely biological drugs, and the improvement in the management of the disease seem to have reduced mortality rates in patients with RA (4). Treatments for RA and the achievement of a lower disease activity state proved to be associated with lower mortality (2, 4-6). However, studies on trends in RA mortality over time have produced inconsistent results. Some studies have reported a decrease in mortality in the last decades (6-9), while others have not (2, 4, 10, 11). The improvement in RA mortality might be partly explained by the improvement of survival in the general population, with mortality rates still remaining higher in subjects with RA than in the general population (4, 6, 7, 9).

The distribution of the most common causes of death in RA, similarly to that in the overall population, includes cardiovascular diseases, cancer, and respiratory diseases (2, 4). However, after adjusting for sex and age, mortality among RA patients has been reported to be increased for circulatory, respiratory, musculoskeletal, infectious and digestive system diseases (2, 12). Notwithstanding the fact that data on RA mortality are valuable to physicians, most of the rheumatology centres do not collect data on mortality, and information on the causes of death are sparse (2). Furthermore, in the majority of studies investigating cause-specific mortality, only a limited number of causes were studied, the number of subjects who died during follow-up was small, and most studies were carried out in the past decades (4). There is thus a need to investigate the cause-specific mortality for a wide range of causes, in a large cohort, using more recent data.

Studies on mortality in RA from Italy are completely lacking. The Veneto Region (northeastern Italy), has about 4.9 million inhabitants, with a life expectancy slightly higher than national figures (80 and 85 years in males and females, respectively). The main aim of our study was to investigate cause-specific mortality in RA subjects living in the Veneto Region through the years 2010–2015.

Materials and methods

Hospital care is free of charge in Italy, although patients must contribute to out-of-hospital care and drug costs. Upon certification from an hospitalist, subjects with chronic diseases such as RA receive disease-specific care without any contribution to the costs. Although the archive does not include all patients (for example, patients can be exempt also based on combinations of age, income, and disability), it can be used to identify a sub-set of subjects with confirmed RA. We identified in the electronic archive of the Veneto Region a cohort of patients aged 20–89 years who were exempt from co-payment for RA in January 2010, and linked them with the archive of causes of deaths of the period 2010–2015. The record-linkage was performed on previously anonymised records, without any possibility of identification of individuals. Each subject was followed from 1st January 2010 either until death, or 90 years of age, or 31st December 2015, whichever came first. No approval from the ethical committee was required in accordance with the policy of our institution. The study was carried out in accordance with the ethical standards of the Declaration of Helsinki (1983).

In the Veneto Region a copy of all death certificates is transmitted to the Regional Epidemiology Service for coding of causes of death according to the International Classification of Diseases, 10th Edition (ICD-10). The certifying physician is required to report those conditions involved in the causal chain of events leading to death in Part I of

the death certificate, and other significant conditions contributing to death in Part II. Standard mortality statistics are based on internationally adopted algorithms which identify the underlying cause of death (UCOD) from all the conditions reported in the certificate. The UCOD generally corresponds to the underlying cause stated by the certifier, but could also be another disease reported in Part I or Part II, or a derived condition (13). In the Veneto region, the archive of causes of death includes all diseases mentioned in the death certificate, and the selection of the UCOD is performed by means of the Automated Classification of Medical Entities, which is a computer programme developed by the US National Center for Health Statistics to standardise assignment of the UCOD (14).

Standardised mortality ratios (SMRs) with 95% confidence intervals, based on the Poisson distribution, were computed as the ratios between deaths observed in the cohort, and those expected according to age- and gender-specific regional mortality rates. SMRs were computed for both total mortality and main nosologic categories on the basis of the UCOD. SMRs were assessed both in the whole cohort, and separately by gender and three age classes (adults, <65 years; young-old, 65–74 years; and elderly, ≥75 years). Lastly, among all deaths in the cohort, the prevalence of common chronic comorbidities and acute complications was investigated not only by analyses of the selected UCOD, but also based on any mention of the condition in the death certificate.

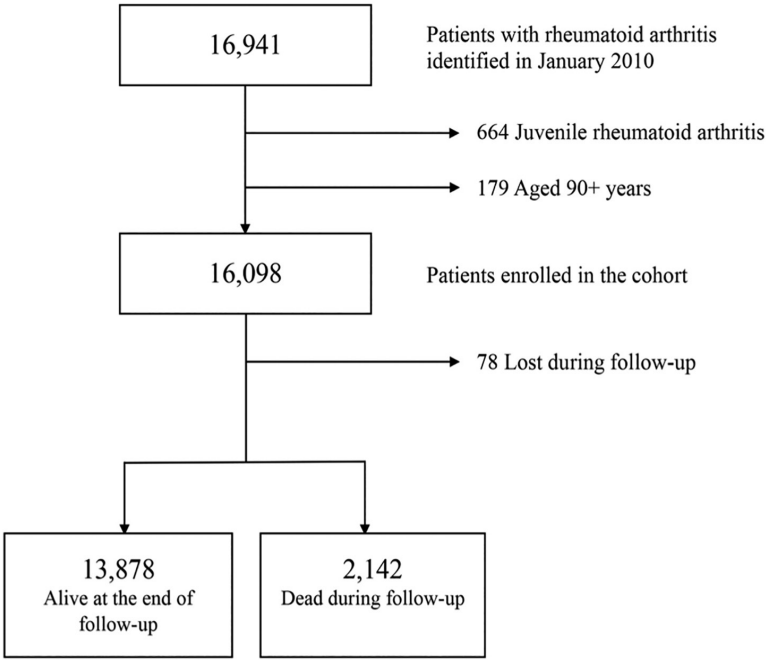

Fig. 1. Schematic design of enrolment and follow-up of patients with rheumatoid arthritis.

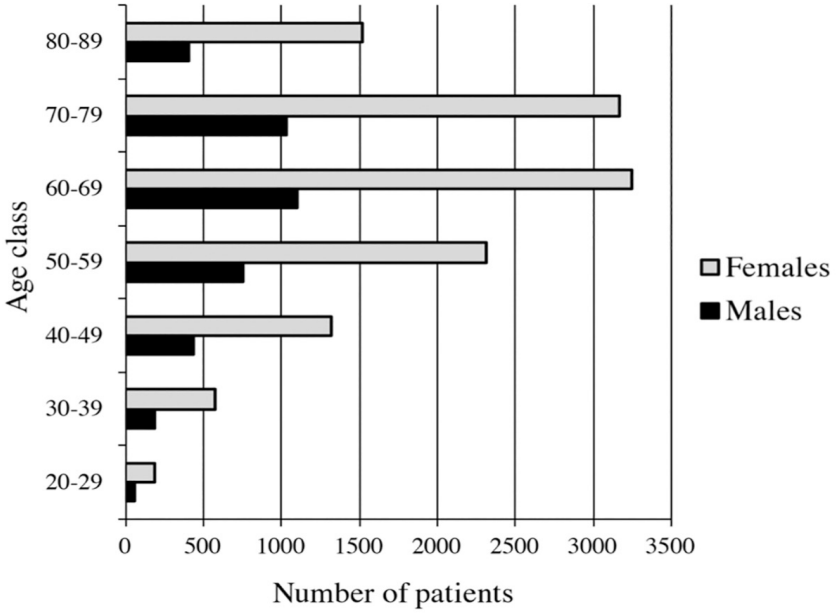

Fig. 2. Demographics of the study population at the beginning of follow-up: 16,098 patients with rheumatoid arthritis aged 20-89 years, Veneto Region (Italy), January 2010.

Results

Overall, 16,098 residents diagnosed with RA and aged 20–89 years were enrolled in the cohort; few patients were censored because of emigration out of the region, and follow-up was complete for above 99% of study subjects (Fig. 1). The majority of patients was represented by females (76%), and by subjects aged 50–79 years (Fig. 2). From January 2010 to December 2015, the overall follow-up amounted to 88,599 person-years, with 2,142 registered decedents. The most common causes of death among RA patients were circulatory diseases (36.6%), neoplasms (24.2%), and respiratory diseases (8.3%).

Table I shows SMRs computed for broad nosologic sectors and specific causes with at least 20 observed deaths. Overall, a 42% excess risk of death could be observed among patients with RA. Mortality from neoplasms overall and for the most common sites of cancer was similar to that expected based on rates from the general population; a slight, non-significant excess was found limited to lymphoma and leukaemia. By contrast, mortality was significantly increased from all other main nosological sectors, including circulatory, respiratory, digestive, and infectious diseases.

Mortality was increased from all circulatory diseases, and from the main subcategories including ischaemic heart and cerebrovascular diseases. Among respiratory diseases, increased mortality

Table I. Number of deaths and standardised mortality ratio (SMR) with 95% Confidence Interval (CI) in a cohort of 16,098 patients with rheumatoid arthritis. Reference = expected deaths based on gender- and age-specific mortality rates in the Veneto Region (Italy), 2010-2015.

	n. deaths	SMR (CI)
Certain infectious and parasitic diseases (A00-B99)	88	2.34 (1.88-2.89)
Septicaemia (A40–A41)	66	3.07 (2.37-3.90)
Neoplasms (C00-D48)	519	0.98 (0.90-1.07)
Malignant neoplasm of stomach (C16)	25	1.04 (0.67-1.54)
Malignant neoplasms of colon, rectum and anus (C18-C21)	51	0.96 (0.71-1.26)
Malignant neoplasm of pancreas (C25)	45	1.04 (0.76-1.39)
Malignant neoplasms of trachea, bronchus and lung (C33-C34)	102	1.10 (0.89-1.33)
Malignant neoplasm of breast (C50)	44	0.87 (0.63-1.16)
Non-Hodgkin's lymphoma (C82-C85)	21	1.36 (0.84-2.08)
Leukaemia (C91-C95)	22	1.31 (0.82-1.99)
Diseases of the blood and blood-forming organs (D50-D89)	23	3.22 (2.04-4.83)
Endocrine, nutritional and metabolic diseases (E00-E90)	57	0.96 (0.73-1.25)
Diabetes mellitus (E10-E14)	43	0.93 (0.67-1.26)
Mental and behavioural disorders (F00-F99)	50	0.90 (0.67-1.18)
Dementia (F00-F03)	44	0.86 (0.62-1.15)
Diseases of the nervous system (G00-G99)	61	0.89 (0.68-1.14)
Alzheimer's disease (G30)	27	0.90 (0.59-1.31)
Diseases of the circulatory system (I00-I99)	783	1.56 (1.45-1.67)
Hypertensive diseases (I10-I15)	101	1.51 (1.23-1.83)
Ischaemic heart diseases (I20-I25)	247	1.51 (1.33-1.71)
Other heart diseases (I00-I09, I26-I51)	201	1.64 (1.42-1.88)
Cerebrovascular diseases (I60-I69)	182	1.43 (1.23-1.65)
Diseases of the respiratory system (J00-J99)	177	1.83 (1.57-2.12)
Pneumonia (J12-J18)	61	2.22 (1.70-2.86)
Chronic lower respiratory diseases (J40–J47)	54	1.47 (1.10-1.92)
Interstitial pulmonary diseases (J84)	20	3.47 (2.12-5.36)
Diseases of the digestive system (K00-K93)	117	1.93 (1.60-2.32)
Vascular disorders of intestine (K55)	21	2.40 (1.48-3.66)
Diseases of liver (K70-K76)	20	0.95 (0.58-1.47)
Diseases of the musculoskeletal system (M00-M99)	149	17.3 (14.7-20.4)
Rheumatoid arthritis (M05-M06)	130	63.3 (52.9-75.2)
Diseases of the genitourinary system (N00-N95)	27	1.29 (0.85-1.88)
External causes of mortality (V01-Y84)	70	1.65 (1.28-2.08)
Falls (W00-W19)	20	1.95 (1.19-3.01)
All causes	**2142**	**1.42 (1.36-1.48)**

rates were observed for chronic obstructive pulmonary disease (COPD), pneumonia, and, with a three-fold excess, interstitial pulmonary disease. Mortality from digestive diseases was two-times higher than in the general population; such finding was not accounted by liver diseases (with a SMR close to unity), but by an heterogeneous group of intestinal diseases, the most common being ischemic and other vascular disorders of the intestine. The excess risk in mortality from infectious diseases was explained by the very high rate of sepsis. An increased mortality was observed from haematological diseases; among 23 registered deaths, 8 were from aplastic anaemia, 5 from other anaemia, 4 from coagulation or platelet disorders, and 6 from agranulocytosis or immunodeficiency. Lastly, it is worth noting that also the risk of death from accidental falls was significantly increased.

All-causes mortality and mortality from circulatory diseases were significantly increased in both genders and all analysed age classes (Table II). For circulatory diseases, observed relative risks were higher among younger patients. Due to few observed deaths among younger age classes, respiratory diseases mortality was significantly increased among males and females aged ≥75 years and ≥65 years, respectively.

Overall, RA was selected as the UCOD in 6.1% of all deaths in the cohort (Table III), mainly registered as unspecified RA (ICD-10 M06.9), or as RA with involvement of other organs and systems (M05.3). However, overall the disease was mentioned in about one out four death certificates. Other diseases often reported in the certificate without being selected as the UCOD where sepsis, pneumonia, diabetes mellitus, and hypertensive diseases.

Discussion

This is the first report on mortality in an Italian RA population, and it provides data on causes of death in a large cohort in recent years. We reported a 42% increased risk of death in subjects with RA compared to the general population. The most common causes of death were circulatory diseases, neoplasms and respiratory diseases. With respect to the general population, subjects with RA were affected by an increased mortality from these causes -except for neoplasms- and also from digestive, infectious, hematological diseases and falls. RA was mentioned in only one fourth of the death certificates. Only a few studies investigating cause-specific mortality took into account a broad number of diseases (12, 15-20), most being limited to cardiovascular death and cancer (2). Furthermore, only a few of them were carried out on a large population-based cohort.

Our data confirm the increased SMR in RA subjects compared to the general population. Median SMRs in previous studies were in the range of 1.5 to 1.6 overall, with lower SMRs in inception cohorts (limited to incident RA cases), and higher in non-inception cohorts (including also prevalent RA cases) (2, 4). Possible explanation for this differences is that mortality rates increase with the length of follow-up due to chronic inflammation and comorbidities (4). Our study population included prevalent RA cases, and an increased risk of overall mortality could be confirmed irrespective of gender and age class. It must be remarked that the absolute risk of death in almost all series of patients with RA is greater in older people and in males, but the relative risk of death tends to be higher in younger people and females (who have a lower absolute risk of death in the general population) (2). Age-specific relative risks in this study are also slightly higher in the female gender (Table II).

In studies on causes of mortality in RA, the source of information may be a death certificate or a medical record. A death certificate is often completed by a non-rheumatologist and may omit to mention RA. Nonetheless, the advantages of considering death certificates

Table II. Number of deaths and standardised mortality ratio (SMR) with 95% Confidence Interval (CI) in patients with rheumatoid arthritis, by gender and age class. Reference = expected deaths based on gender- and age-specific mortality rates in the Veneto Region (Italy), 2010-2015.

	Males		Females	
	n	SMR (CI)	n	SMR (CI)
All causes				
20-64 yrs	62	1.50 (1.15-1.93)	106	1.54 (1.26-1.86)
65-74 yrs	141	1.30 (1.10-1.54)	235	1.41 (1.23-1.60)
75-89 yrs	452	1.32 (1.20-1.45)	1146	1.47 (1.39-1.56)
Neoplasms (C00-D48)				
20-64 yrs	21	1.03 (0.64-1.58)	52	1.17 (0.87-1.53)
65-74 yrs	50	0.91 (0.67-1.20)	79	0.87 (0.69-1.09)
75-89 yrs	117	1.03 (0.85-1.23)	200	0.98 (0.85-1.12)
Circulatory system (I00-I99)				
20-64 yrs	16	1.86 (1.06-3.02)	18	2.07 (1.23-3.28)
65-74 yrs	43	1.62 (1.17-2.18)	62	1.80 (1.38-2.30)
75-89 yrs	179	1.48 (1.27-1.71)	465	1.53 (1.40-1.68)
Respiratory system (J00-J99)				
20-64 yrs	3	2.94 (0.59-8.59)	4	2.62 (0.71-6.71)
65-74 yrs	6	1.31 (0.48-2.85)	14	2.23 (1.22-3.74)
75-89 yrs	54	1.76 (1.33-2.30)	96	1.82 (1.47-2.30)

Table III. Contribution of specific diseases selected as the underlying cause of death, or mentioned anywhere in the death certificate, among 2,142 decedents from a cohort of 16,098 patients with rheumatoid arthritis.

	Underlying cause	Any mention
Septicaemia (A40–A41)	3.1%	13.6%
All neoplasms (C00-D48)	24.2%	29.8%
Diabetes mellitus (E10-E14)	2.0%	11.8%
Dementia, Alzheimer (F01-F03, G30)	3.3%	7.0%
Hypertensive diseases (I10-I15)	4.7%	17.4%
Ischaemic heart diseases (I20-I25)	11.5%	20.7%
Cerebrovascular diseases (I60-I69)	8.5%	14.7%
Pneumonia (J12-J18)	2.8%	11.6%
Chronic lower respiratory diseases (J40–J47)	2.4%	8.4%
Interstitial pulmonary diseases (J84)	0.9%	1.9%
Rheumatoid arthritis (M05-M06)	6.1%	25.4%

are coverage, continuity, uniform classification of diseases according to the ICD-10 (21), and proper comparisons with mortality figures from the general population. The size of the cohort and the use of the regional population as a reference provided the study enough statistical power to demonstrate an increased risk of death for several specific causes.

The patterns of causes of death in the general population and in the RA cohort were similar to that reported in other studies (2, 4, 9, 12, 20, 22-25). As expected, circulatory diseases were the most common causes of death and the risk was higher in RA subjects. Hypertensive disease, ischaemic heart disease and cerebrovascular disease accounted for one fourth of the UCOD in RA, similarly to previous reports (2, 9, 12, 23, 24). SMR for circulatory disease was higher in younger patients in whom death from this cause is less frequent (2, 26, 27). These data support the evidence that RA is a risk factor for premature cardiovascular death. Persistent inflammation contributes to the atherosclerotic process together with traditional cardiovascular risk factors, which also appear to be more frequent in RA patients (28).

Vascular disorders of the intestine contributed to the increased mortality from digestive system diseases. A similar two-fold increased risk was observed in a few studies considering digestive diseases, but no report on vascular disorders is available (12, 18). An early investigation with follow-up spanning from 1964 to 1995 reported an highly increased risk from gastrointestinal disorders mainly explained by peptic ulcer disease (15). However, the epidemiology of peptic ulcer has completely changed in the general population and among RA patients, and now ischemic intestinal diseases might be regarded as a complication of RA, particularly in patients with other vasculitic manifestations (29).

Respiratory diseases presented a higher mortality risk compared with the general population. Similarly to other reports, the most frequent among them was pneumonia, which is related to the immunosuppressive treatment (30). Mortality from COPD was the second more common respiratory cause of death in the RA cohort and was increased by 50% as in other studies (23, 25, 31). We observed a three-fold increased risk of death because of interstitial lung disease. Interstitial lung disease is an extraarticular manifestation of RA and has been associated to increased mortality, but it is often underrecognised in RA patients (16, 17, 20, 23, 26, 31-33). Immunosuppressive treatments, especially biologics, are implicated in the development and the exacerbation of interstitial lung disease and the larger use of biologics in the last decades might also explain the higher mortality from this complication (34).

The increase in mortality from infections was expected (2, 4, 9, 12, 23). Sepsis was mentioned in 13.6% of death certificates of RA patients. Severe and opportunistic infections are strongly related to treatment especially with chronic corticosteroid use and biologics (30). Furthermore, we observed an increased mortality risk from hematological diseases, which has been reported in few previous studies (9, 15, 22). Immunosuppression and blood dyscrasias might be manifestations of the autoimmune disease, but more likely, they represent a severe complication of the treatment. Lastly, we found an almost two-fold increased risk of mortality from accidental falls. Falls are generally associated to fractures which are independently related to mortality in the general population (35). Osteoporosis

is common in RA patients and, together with disability, increases the likelihood of mortality due to frailty fractures (5, 36, 37).

By contrast, mortality from neoplasms in RA was not increased and lymphoproliferative neoplasms, which are classically related to RA, showed a non-significant increased risk of death. These findings are also consistent with other studies (2, 9, 12, 16-18, 23).

Analyses of the UCOD provide important insights in understanding the impact of RA on mortality; nonetheless, particularly with the aging of the population, several comorbidities are involved in the causal pathway to death (13). Comorbidities might be associated with the rheumatic condition or might be a consequence of disease progression or of treatment (2, 38). Thus, deaths in these patients are the consequence of a number of coexisting conditions, and the study of all the diseases reported in the death certificate allows a more comprehensive understanding of the pathological burden contributing to death (13). In the present study, chronic diseases such as diabetes, COPD, and hypertensive diseases were frequently mentioned in death certificates without being selected as the UCOD. Specifically, diabetes was often reported in death certificates in association to circulatory diseases, which are frequently selected as the UCOD in patients with both comorbidities. Furthermore, the burden of acute infectious complications such as pneumonia and sepsis, already evident by computing SMRs based on the UCOD, could be more fully appreciated by analysis of any mention of such diseases in death certificates. It is worth noting that RA was reported in only 25% of deaths. Certifying physicians might not mention RA because unaware of the disease in the patient, or may not consider that it substantially contributed to the patient's death, or may not have listed it because of space constraints. Based on early small studies, Sokka and colleagues reported that RA was included in fewer than 25% of death certificates (2), and such underreporting has been confirmed by more recent investigation from Australia (16%) and the US (18%) (19, 39). All the above reinforce the evidence of an overall underestimation by the medical community about the role of RA in increasing the risk of death.

The study presents some limits. Firstly, identification of RA patients was based on the exemption from co-payment of health-care costs in January 2010. The number of patients with exemption for RA in the Veneto Region suggests that the prevalence of RA might be slightly lower to that reported in other studies (1, 40). Actually, the cohort included in this study does not allow an estimation of RA prevalence, because subjects with exemption for RA do not include all subjects affected by the disease. The exemption for RA is based on the judgment of a physician, with no adopted standardised diagnostic criteria. Nevertheless, an Italian study proved that using an administrative healthcare database – including exemptions for chronic diseases – was effective in estimating RA prevalence (41). All series of patients with RA include a proportion of patients who do not have progressive inflammatory arthritis (42). Nevertheless, using data on prevalent RA might have reduced the number of patients with early self-limited disease who do not progress to RA. The inclusion of these patients in inception cohorts might also explain the lower SMR compared to that observed in non-inception cohorts (2). Second, the use of age- and sex-standardisation alone does not take into account other potential confounders for mortality. SMR could not be adjusted by determinants of mortality such as socio-economic level, comorbidities, disease characteristics and treatment. The study included patients from all clinical settings, not limited to tertiary care centres, and patients might have been treated according to any therapeutic approach before or during the study period. A considerable difference in RA severity and duration, which might affect mortality, was also possible. Notwithstanding the lack of these data, analysis of the impact of disease severity on overall mortality was not an objective of the present study.

In conclusion, this study provides information on mortality in a large cohort of RA subjects in Italy and the study size allowed to investigate the risk from several specific causes of death. Mortality is still increased compared with the general population and the awaited benefit of innovative treatments will be evident in the future years. Cardiovascular disease is the primary cause of premature death in RA patients. The agreement with studies conducted in different geographic areas suggests that the increased mortality from cardiovascular disease is primarily related to the pathogenic mechanism intrinsic to RA and not to genetic or environmental factors. Likewise, our data confirmed that certain comorbidities, such as respiratory and infectious diseases, are associated to RA and are partly due to immunosuppressive therapy. Along with the optimal control of disease activity, monitoring of comorbidities and adequate surveillance of treatment is needed in RA subjects.

References

1. SCOTT DL, WOLFE F, HUIZINGA TW: Rheumatoid arthritis. *Lancet* 2010; 376: 1094-108.
2. SOKKA T, ABELSON B, PINCUS T: Mortality in rheumatoid arthritis: 2008 update. *Clin Exp Rheumatol* 2008; 26: S35-61.
3. MIKULS TR, FAY BT, MICHAUD K *et al*.: Associations of disease activity and treatments with mortality in men with rheumatoid arthritis: results from the VARA registry. *Rheumatology* (Oxford) 2011; 50: 101-9.
4. DADOUN S, ZEBOULON-KTORZA N, COMBESCURE C *et al*.: Mortality in rheumatoid arthritis over the last fifty years: systematic review and meta-analysis. *Joint Bone Spine* 2013; 80: 29-33.
5. LISTING J, KEKOW J, MANGER B *et al*.: Mortality in rheumatoid arthritis: the impact of disease activity, treatment with glucocorticoids, TNF alpha inhibitors and rituximab. *Ann Rheum Dis* 2015; 74: 415-21.
6. ZHANG Y, NA LU, PELOQUIN C *et al*.: Improved survival in rheumatoid arthritis: a general population based cohort study. *Ann Rheum Dis* 2017; 76: 408-13.
7. WIDDIFIELD J, BERNATSKY S, PATERSON JM *et al*.: Trends in excess mortality among patients with rheumatoid arthritis in Ontario, Canada. *Arthritis Care Res* 2015; 67: 1047-53.
8. LACAILLE D, AVINA-ZUBIETA JA, SAYRE EC, ABRAHAMOWICZ M: Improvement in 5-year mortality in incident rheumatoid arthritis compared with the general population-closing the mortality gap. *Ann Rheum Dis* 2017; 76: 1057-63.
9. KIADALIRI AA, TURKIEWICZ A, ENGLUND M: Mortality from Musculoskeletal Disorders Including Rheumatoid Arthritis in Southern Sweden: a multiple cause of death analysis, 1998–2014. *Rheumatology* 2017; 44: 5.

10. GONZALEZ A, MARADIT K, REMERS H *et al*.: The widening mortality gap between rheumatoid arthritis patients and the general population. *Arthritis Rheum* 2007; 56: 3583-7.
11. HUMPHREYS JH, WARNER A, CHIPPING J *et al*.: Mortality trends in patients with early rheumatoid arthritis over 20 years: results from the Norfolk Arthritis Register. *Arthritis Care Res* 2014; 66: 1296-301.
12. VAN DEN HOEK J, BOSHUIZEN HC, ROORDA LD *et al*.: Mortality in patients with rheumatoid arthritis: a 15-year prospective cohort study. *Rheumatol Int* 2017; 37: 487-93.
13. ISRAEL RA, ROSENBERG HM, CURTIN LR: Analytical potential for multiple cause of death data. *Am J Epidemiol* 1986; 124: 161-79.
14. LU TH, ANDERSON RN, KAWACHI I: Trends in frequency of reporting improper diabetes-related cause-of-death statements on death certificates, 1985–2005: An algorithm to identify incorrect causal sequences. *Am J Epidemiol* 2010; 171: 1069-78.
15. BJORNADAL L, BAECKLUND E, YIN L, GRANATH F, KLARESKOG L, EKBOM A: Decreasing mortality in patients with rheumatoid arthritis: results from a large population based cohort in Sweden, 1964–95. *J Rheumatol* 2002; 29: 906-12.
16. YOUNG A, KODURI G, BATLEY M *et al*.: Mortality in rheumatoid arthritis. Increased in the early course of disease, in ischaemic heart disease and in pulmonary fibrosis. *Rheumatology* 2007; 46: 350-7.
17. KIM YJ, SHIM JS, CHOI CB, BAE SC: Mortality and incidence of malignancy in Korean patients with rheumatoid arthritis. *J Rheumatol* 2012; 39: 226-32.
18. KUO CF, LUO SF, SEE LC, CUOU IJ, CHANG HC, YU KH: Rheumatoid arthritis prevalence, incidence, and mortality rates: a nationwide population study in Taiwan. *Rheumatol Int* 2013; 33: 355-60.
19. LASSERE MN, RAPPO J, PORTEK IJ, STURGESS A, EDMONDS JP: How many life years are lost in patients with rheumatoid arthritis? Secular cause-speficic and all cause mortality in rheumatoid arthritis, and their predictors in a long term Australian cohort study. *Intern Med J* 2013; 43: 66-72.
20. AVOUAC J, AMROUCHE F, MEUNE C, REY G, KAHAN A, ALLANORE Y: Mortality profile of patients with rheumatoid arthritis in France and its change in 10 years. *Semin Arthritis Rheum* 2016; 46: 537-43.
21. SOUZA DC, SANTO AH, SATO EI: Mortality profile related to systemic lupus erythematosus: a multiple cause of death analysis. *J Rheumatol* 2012; 39: 496-503.
22. ZIADÉ N, JOUGLA E, COSTE J: Population level impact of osteoporotic fractures on mortality and trends over time: a nationwide analysis of vital statistics for France, 1968-2004. *Am J Epidemiol* 2010; 172: 942-51.
23. PINHEIRO FA, SOUZA DC, SATO EI: A study of multiple causes of death in rheumatoid arthritis. *J Rheumatol* 2015; 42: 2221-8.
24. VAN DEN HOEK J, ROORDA LD *et al*.: Trend in and predictors for cardiovascular mortality in patients with rheumatoid arthritis over a period of 15 years: a prospective cohort study. *Clin Exp Rheumatol* 2016; 34: 813-9.
25. MASI AT, REHMAN AA, JORGENSO LC, ALDAG JC: Increased mortality of incident rheumatoid arthritis versus matched non-RA control subjects: a community-based long-term prospective cohort study. *Clin Exp Rheumatol* 2017; 35: 277-87.
26. NAKAJIMA A, INOUE E, TANAKA E *et al*.: Mortality and cause of death in Japanese patients with rheumatoid arthritis based on a large observational cohort, IORRA. *Scand J Rheumatol* 2010; 39: 360-7.
27. MYASOEDOVA E, GABRIEL SE, MATTESON EL, DAVIS JM III, THERNEAU TM, CROWSON CS: Decreased cardiovascular mortality in patients with incident rheumatoid arthritis (RA) in recent years: dawn of a new era in cardiovascular disease in RA? *J Rheumatology* 2017; 44: 6.
28. DEL RINCÓN I, POLAK JF, O'LEARY DH *et al*.: Systemic inflammation and cardiovascular risk factors predict rapid progression of atherosclerosis in rheumatoid arthritis. *Ann Rheum Dis* 2015; 74: 1118-23.
29. EBERT EC, HAGSPIEL KD: Gastrointestinal and hepatic manifestations of rheumatoid arthritis. *Dig Dis Sci* 2011; 56; 295-302.
30. WOLFE F, CAPLAN L, MICHAUD K: Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. *Arthritis Rheum* 2006; 54: 628-34.
31. NANNINI C, RYU JH, MATTESON EL: Lung disease in rheumatoid arthritis. *Curr Opin Rheumatol* 2008; 20: 340-6.
32. OLSON AL, SWIGRIS JJ, SPRUNGER DB *et al*.: Rheumatoid arthritis interstitial lung disease associated mortality. *Am J Respir Crit Care Med* 2011; 183: 372-8.
33. HYLDGAARD C, HILBERG O, PEDERSEN AB *et al*.: A population-based cohort study of rheumatoid arthritis-associated interstitial lung disease: comorbidity and mortality. *Ann Rheum Dis* 2017; 0: 1-7.
34. MORI S: Management of rheumatoid arthritis patients with interstitial lung disease: safety of biological antirheumatic drugs and assessment of pulmonary fibrosis. *Clin Med Insights Circ Respir Pulm Med* 2015; 9: 41-9.
35. WHO scientific group on the assessment of osteoporosis at primary health care level; 2015.
36. MHUIRCHEARTAIGH ON, CROWSON CS, GABRIEL SE *et al*.: Fragility fractures are associated with an increased risk for cardiovascular events in women and men with rheumatoid arthritis: a population-based study. *J Rheumatol* 2017; 44: 4.
37. PROVAN SA, OLSEN IC, AUSTAD C, HAUGEBERG G, KVIEN TK, UHLIG T: Calcium supplementation and inflammation increase mortality in rheumatoid arthritis: A 15-year cohort study in 609 patients from the Oslo Rheumatoid Arthritis Register. *Semin Arthritis Rheumatism* 2017; 45: 411-7.
38. LAAKSO M, ISOMÄKI H, MUTRU O, KOOTA K: Death certificate and mortality in rheumatoid arthritis. *Scand J Rheumatol* 1986; 15: 129-33.
39. MOLINA E, DEL RINCÓN I, RESTREPO JF, BATTAFARANO DF, ESCALANTE A: Mortality in rheumatoid arthritis (RA): factors associated with recording RA on death certificates. *BMC Muskuloskelet Disord* 2015; 16: 277.
40. ROSSINI M, ROSSI E, BERNARDI D *et al*.: Prevalence and incidence of rheumatoid arthritis in Italy. *Rheumatol Int* 2014; 34: 659-64.
41. CARRARA G, SCIRÈ CA, ZAMBON A *et al*.: A validation study of a new classification algorithm to identify rheumatoid arthritis using administrative health databases: case–control and cohort diagnostic accuracy studies. Results from the RECord linkage On Rheumatic Diseases study of the Italian Society for Rheumatology. *BMJ Open* 2015; 5: e006029.
42. VAN AKEN J, VAN BILSEN JHM, ALLAART CF, HUIZINGA TWJ, BREEDVELD FC: The Leiden Early Arthritis Clinic. *Clin Exp Rheumatol* 2003; 21 (Suppl. 31): S100-5.