Increased COVID-19 mortality in patients with rheumatic diseases: results from the CONTROL-19 study by the Italian Society for Rheumatology

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Abstract

Objective

To investigate differences in coronavirus disease 2019 (COVID-19) mortality between patients with rheumatic musculoskeletal diseases (RMD) and the general population in Italy.

Methods

We analysed the data from the national surveillance study promoted by the Italian Society for Rheumatology (CONTROL-19 database) including patients with RMD and COVID-19 between 26 March 2020 and 29 November 2020, compared with official data from the Italian population (within the same period) adjusted for age, sex and geographic location. The main outcome of the analyses was mortality. The relationship between RMD and mortality was analysed using adjusted logistic models and sensitivity analyses were conducted to support the robustness of our results.

Results

We included 668 RMD patients (62.7% with inflammatory arthritis, 28.6% with systemic autoimmune diseases), who had a mean age of 58.4 years and of which 66% were female. Compared to the general population, the RMD population showed an increased risk of death (OR 3.10 (95% CI 2.29–4.12)), independently from the differences in age and sex distribution. Even after considering the potential influence of surveillance bias, the OR was 2.08 (95% CI: 1.55–2.73). Such excess of risk was more evident in the subgroup of younger patients, and more consistent in women. Subjects with systemic autoimmune diseases showed a higher risk of death than patients with any other RMDs.

Conclusions

Patients with RMD and COVID-19 infection evidenced a significant increase in mortality during the first pandemic phases in Italy. These findings support the need for strong SARS-CoV-2 prevention in patients with rheumatic diseases.

Key words

rheumatic diseases, COVID-19, mortality

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection is responsible for the Coronavirus Disease (COVID-19) pandemic, which arose in late 2019 in the Chinese city of Wuhan.

Among other epidemiological contexts, Italy was one of the countries hit first and hardest by the COVID-19 epidemic. Taking advantage of a strong network of rheumatological units across the country – under the aegis of the Italian Society for Rheumatology (SIR) – all the members of SIR were involved in an active surveillance system (the so-called, CONTROL-19 surveillance database). Such initiative was also connected from the earliest phase to the European and Global registries (1). CONTROL-19 aims to deepen the knowledge about patients with immune-mediated rheumatic diseases (RMDs) affected by COVID-19, in order to describe the clinical course of these diseases, compare the given outcome in the general population and identify the major factors associated with more severe prognosis (2).

In the last year, a huge amount of data was accumulated, and most of these research questions have been resolved. However, one of the most urgent and controversial clinical questions is whether or not the severity of COVID-19 is different between the RMD patients and the overall population.

The meta-analysis of controlled studies suggests a marginal increase in mortality (OR[95% CI]: 1.43 [0.89–2.30]) (3). This meta-analysis comprises 3 controlled studies: a study with enrolling patients followed in a rheumatology setting (4); another study based on a healthcare provider electronic medical records (5); finally, a population-based study on administrative healthcare databases (6). Further data support an excess of mortality in patients affected by rare autoimmune rheumatic diseases (7). By comparing mortality of inflammatory arthritis patients with 2015–2019 data, a Sweden record linkage study discovered an age-sex adjusted 1.99 hazard ratio for mortality in rheumatoid arthritis patients, and a UK population study found an age-sex 1.30 hazard ratio for death in patients with rheumatoid arthritis, lupus or psoriasis. (8) Despite the substantial methodological heterogeneity, these data suggest an increase in the risk of death in patients affected by RMDs and COVID-19. Yet, such increased mortality is still a matter of debate (9, 10).

The present analysis has been planned to test the hypothesis that RMDs were not associated with an increased mortality due to COVID-19 compared to the general population.

Methods

Data

The CONTROL-19 registry is a retrospective, multicentre, national study; it complies with the Declaration of Helsinki and was approved on March 24th, 2020 by the "Area Vasta Emilia Centrale" Ethics Committee (288/2020/Oss/AOUFe).

The data collection was carried out by a sample of Italian rheumatology centres (universities, hospitals, outpatient clinics etc.), which are distributed throughout the national territory and involved in the care of patients with RMDs and COVID-19. Patients included in the present analysis were enrolled between March 26th, 2020 and November 29th,2020, and were selected based on the: i) molecular diagnosis for SARS-CoV-2 (determined by real-time polymerase-chain-reaction, RT-PCR) identified by nasopharyngeal swab test, ii) clinical diagnosis of RMD and iii) availability of COVID-19 outcome data (recovered or deceased subjects).

Anonymised data were collected in an online database, created on the REDCap platform and hosted on SIR servers (11). Information on non-rheumatic patients with SARS-CoV-2 (sex, age classes and COVID-19 outcome) was obtained by the Italian National Institute of Health (12). To make the general population comparable with the RMD population, only subjects over 19 years old were enrolled.

The analyses included the following variables: i) presence of RMDs (as covariate), ii) death due to COVID-19 (as response variable), iii) sex and age classes (as adjustment and stratification variables); iv) Italian region of diagnosis.

To estimate the potential impact of differential misclassification (under-reporting of non-fatal cases), all the recruiting centres were asked to respond to a survey to define the percentage of patients having COVID-19 but not reported in our registry and the percentage of death for these patients.

Statistical analysis

Descriptive analyses are reported as absolute and relative frequencies. To evaluate the differences in COVID-19 lethality between RMD patients and the general population, Pearson's Chi-squared or Fisher's exact tests, stratified by sex and age classes, were performed. The association between the presence of RMDs and death due to COVID-19 was assessed by logistic regression model, adjusted for sex and age classes, and results were presented as odds ratio (OR) and 95% confidence intervals (CIs).

A first sensitivity analysis assessed the impact of possible under-reporting of patients with RMD and non-fatal COVID-19 outcome. Keeping constant the RMD population structure by sex and age, we simulated the progressive increase of subjects with RMD and recovered from COVID-19. Considering one-unit increment for every 20 patients, a logistic regression model with specified covariates and outcome was performed in order to quantify how much under-reporting would be sufficient to change the significance and the direction of the association between RMD and death due to COVID-19.

Since the COVID-19 mortality was different between northern, southern, and central regions of Italy (13), a second sensitivity analysis was performed to verify if the area-dependent difference between RMD population and non-rheumatic population could have an impact on the association of RMD with COVID-19 outcome. To balance area distribution, a subset of the original RMD patients was chosen and a logistic regression model (with the same above-mentioned structure) was performed. To validate the result, a thousand bootstrap samples were extracted, and the bootstrap estimation and CIs were calculated. All data were processed and analysed with the statistical analysis software R (Foundation for Statistical Computing, Vienna, Austria)

Table I. Description of the RMD population characteristics.

	Total (n=668)	
Age, mean (SD)	58.4	(14.5)
Female, n (%)	441	(66%)
Smokers, n (%)	58	(9.1%)
Comorbidities, median (IQR)	1	(0 - 3)
RMD, n (%)		
Rheumatoid arthritis	228	(34.1%)
Spondyloarthritis	191	(28.6%)
Connective tissue disease	133	(19.9%)
Vasculitis	58	(8.7%)
Other	58	(8.7%)
Disease activity, n (%)		
Remission	247	(37.2%)
Hospitalisation due to SARS-CoV-2 infection, n (%)	291	(43.6%)
RMD treatment, n (%)		
Glucocorticoids	281	(42.1%)
cDMARDs	267	(40%)
Immunosuppressants	58	(8.7%)
bDMARDs	282	(42.2%)

Table II. Description of deaths by COVID-19 in RMD and the general population, stratified by sex and age classes.

	Deaths in RMD population	Deaths in general population	*p*-value
Male, age 20-49, n (%)	0 (0%)	445 (0.1%)	<0.001
Male, age 50-59, n (%)	1 (1.5%)	1422 (1%)	0.480
Male, age 60-69, n (%)	12 (18.5%)	4113 (4.2%)	<0.001
Male, age 70-79, n (%)	10 (25%)	9767 (13.6%)	0.062
Male, age >79, n (%)	7 (43.8%)	16470 (27.8%)	0.251
Female, age 20-49, n (%)	3 (2.3%)	192 (0.06%)	<0.001
Female, age 50-59, n (%)	4 (3.3%)	471 (0.3%)	<0.001
Female, age 60-69, n (%)	9 (10.2%)	1339 (1.6%)	<0.001
Female, age 70-79, n (%)	10 (14.1%)	4375 (6.9%)	0.030
Female, age >79, n (%)	6 (20.7%)	17209 (16.2%)	0.691

Results

On November 29th, 2020, 668 patients with RMD and confirmed SARS-CoV-2 infection were registered in the CONTROL-19 database. The RMD population was predominantly composed of female (66%); 26.1% of subjects were younger than 50, 50.6% were between 50 and 69, while 23.3% were older than 69 years old. 291 (44%) patients were hospitalised due to SARS-CoV-2 infection. RMD population characteristics are shown in Table I.

Since the beginning of the pandemic in Italy, 1,429,386 subjects have contracted the SARS-CoV-2 infection over the same period; 48% of them were male, 45.8% were younger than 50, 33.1% were between 50 and 69, and 21.1% were older than 69 years old.

Sixty-two subjects (9%) of the RMD population and 55,803 patients (4%) of the non-rheumatic population died of COVID-19.

For all the age and sex classes (except for the young men), the crude mortality rate of the RMD population is greater than the corresponding rate in the non-rheumatic population; such difference has a high significance and is especially notable in the female categories. In particular, the deaths distribution in RMD population compared with that in non-rheumatic population is:

i. in males 60–69 years old, 18.5% *vs*. 4.2% respectively ($p<0.001$);

ii. in females younger than 50 years old, 2.3% *vs*. 0.1%, respectively ($p<0.001$);

iii. in females 50–59 years old, 3.3% *vs*. 0.3% respectively ($p<0.001$);

iv. in females 60-69 years old, 10.2% *vs*. 1.6%, respectively ($p<0.001$);

v. in females 70–79 years old, 14.1% *vs*.

6.9%, respectively (p=0.03) (Table II). By analysing mortality rates by region, we found a higher excess of mortality rates in the Northern regions (RMD *vs*. general population: North 12.7% *vs*. 4.3%, Centre 2.5% *vs*. 2.4%, and South 1.6% *vs*. 1.8%).

The association between any RMD (Fig. 1A) or between different RMDs (Fig. 1B) and the risk of death by COVID-19 was explored using two multivariable-adjusted analyses, as reported in Figure 1.

Independently of the differences in the age and sex distribution, the RMD population exhibited a higher risk of death when compared to non-rheumatic patients, being characterised by an OR of 3.10 (95% CI: [2.30–4.12], p-value<0.001). The increased risk of death is even greater in patients affected by vasculitis and connective tissue diseases (OR [95% CI]: 6.09 [2.87–12.19] and 5.32 [2.65–9.98] respectively). COVID-19 mortality was significantly lower in women than in men (OR [95% CI]: 0.47 [0.46–0.48] and p-value <0.001).

Sensitivity analysis

Figure 2 shows the number of RMD patients - recovered from COVID-19 but not reported to our registry - who were sufficient to change the direction and the significance of the OR referred to RMD variable (model in Figure 1A). 648 patients (with the above-specified characteristics) were needed to make the OR statistically non-significant, while 1426 were required to reverse the direction of the OR. Based on the survey results, a 35% difference in the reporting of non-fatal versus fatal cases was estimated, which gave about 235 non-fatal cases not reported. Under this assumption, by taking into account the non-fatal cases which were not reported, the adjusted OR obtained from the model is 2.08 (95% CI: 1.55–2.73).

When compared to the non-rheumatological population areas distribution, the RMD population is mainly located in the northern Italy. To balance the area distribution, a random sample of subjects (equal to 68%) from the northern area of Italy was selected and the logistic regression model was per-

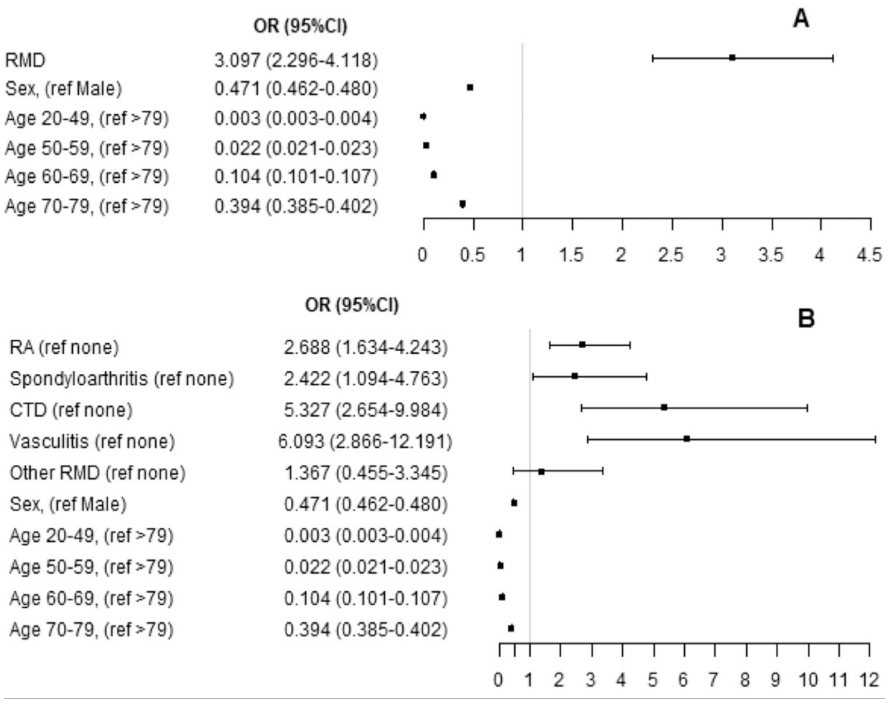

Fig. 1. Association between the risk of death by COVID-19 and RMDs.
A: shows any RMD and risk of death by COVID-19, adjusted for sex and age classes;
B: shows different RMDs and risk of death by COVID-19, adjusted for the same covariates.
RMD: rheumatic and musculoskeletal disease; OR: odds ratio; CI: confidence intervals; RA: rheumatoid arthritis; CTD: connective tissue disease.

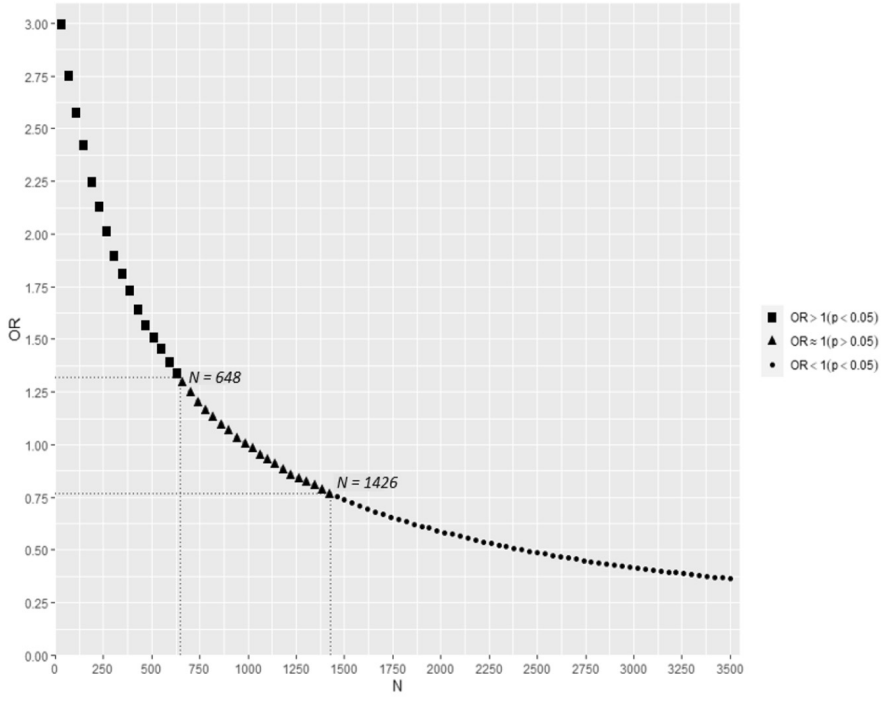

Fig. 2. Simulation of differential misclassification in the presence of under-reporting of cases.
The horizontal axis displays the potential number of non-fatal cases for RMD patients that were not reported (and therefore added to the database), while the vertical axis shows the OR values derived from the simulated logistic regression models of such cases. Despite the under-reporting of non-fatal cases, in all cases with OR values >1 (squares), the presence of RMD is considered a significant risk factor for deaths induced by COVID-19. In all cases with OR values around 1 (triangles), the presence of RMD is not significantly associated with deaths induced by COVID-19. Finally, in all cases with OR values <1 (dots), the presence of RMD prevents from deaths induced by COVID-19. OR: odds ratio.

formed. The bootstrap estimate of OR confirmed the significant effect of the RMD variable on death due to COVID-19 with an OR equal to 2.81 (95% CI: [1.90–3.88]).

Discussion

Based on our findings, during the first phases of the COVID-19 pandemic in Italy, the mortality rate of the RMD population was greater than the mortality rate in the general population – even after adjusting for age and sex. These results are in line with data from previous studies (4-8), including meta-analysis (3). However, the dimension of the observed effect is higher. Differences in the study design and strategy of analysis may have had an impact. Our data source for RMD was mainly from hospital-based rheumatology centres and a selection bias may have enriched the RMD population of more active and severe patients, leading to an intrinsic worse prognosis. Indeed, the percentage of cases with systemic, rare and complex autoimmune diseases is much higher than the expected frequency in the general RMD population. This imbalance can only be partially attributed to an increase in the susceptibility of the infection and more likely caused by a selection bias, which is mainly linked to secondary or tertiary hospitals. However, after stratification by diagnosis, chronic inflammatory arthritis was still associated with a statistically significant increase in mortality. On the other hand, the excess of risk appeared much higher in patients with vasculitis and CTD, in line with what previously reported (7).

The data collection was not exhaustive, and a surveillance bias may have occurred, leading to the registration of cases with worse outcomes. For instance, symptomatic patients could have sought contact with the rheumatologist more frequently than those asymptomatic. For this reason: i) we used a wide window of enrolment that required a routine consultation, in order to intercept most of the patients, even after the first wave; ii) we tried to measure the magnitude of the differential misclassification in terms of reporting of deaths; we then adjusted the final estimates of excess mortality accordingly. Even after this simulation, the OR of mortality resulted still significant with an almost double risk of death in RMD patients. We also simulate the case of non-difference in mortality and the scenario of a lower mortality than expected, finding that 100% of selective non reporting about non-fatal cases would have been needed to make our results not significant and more than 200% to reverse the association. Data acquired from the simulation would therefore support the hypothesis that RMD patients affected by COVID-19 have a greater risk of death than non-RMD patients (*i.e.* the general population) affected by COVID-19.

Other previous studies (8,14) made a fully adjusted comparison between RMD patients and the general population, including comorbidities as controlling factors, which showed marginal lower mortality in RMD. Contrarily to the other studies, data regarding comorbidities were not available in our data sources for the general population, which prevented from making such comparisons in our analysis. It is also important to highlight that comorbidities in RMD patients are correlated to the RMD itself, as they are an integral and inseparable part of such disease. Although controlling for them would help to dissect the impact of the RMD itself, clinicians are much more interested in the patient's level of risk related to RMD (rather than the disease itself), which is intrinsically linked to the concurrent conditions. For this reason, we are confident that the absence of comparison between the comorbidities in the RMD patients and the general population should not lead to an incorrect interpretation of our findings.

The distribution of RMD cases may be an additional potential factor associated with an inflation of the effect. The geographical distribution of RMD patients in the CONTROL-19 registry did not match the non-rheumatic population distribution reported by the Italian National Institute of Health. Again, the higher number of rheumatology centres in northern Italy may have increased reporting in these areas. The large number of RMD patients from the northern areas (with a high mortality rate) (15) may have led to an overestimation of the RMD effect on the risk of death. However, the sensitivity analysis indicates that results are consistent, even after having included a subset of RMD patients from the northern areas.

The reasons of such increased lethality of the SARS-COV-2 infection in RMD patients may be related to many factors, including the intrinsic higher mortality due to organ damage, disease-related and iatrogenic immunosuppression, and hypothetically to geographic heterogeneity of barriers to intensive care due to multimorbidity. Based on the global rheumatology alliance multi-national database, major determinants of death were identified. Beyond age and gender, the presence of organ involvement (cardiovascular, lung o kidney), the exposure to major immunosuppressants and rituximab and high dose glucocorticoids, accounted for an additional excess of mortality in the RMD population (1). For this reason, the excess of mortality should not be generalised to the entire population of RMD, but particularly to those patients with additional risk factors.

In conclusion, our data support the increased risk of death in patients affected by RMD and COVID-19 during the first year of the pandemic in Italy, before the beginning of the vaccination campaign. Although these findings mainly describe the outcome of a national context in a defined period, they support the idea that RMD patients may have a worse prognosis when also affected by SARS-CoV-2 disease; the level of alertness must therefore remain high for these patients. Prevention through vaccination is the most suitable way to control this increase of mortality.

Acknowledgements

The list of our collaborators is available as an online supplementary file.

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