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Original Article

Hospitalization and mortality from COVID-19 of patients with rheumatic inflammatory diseases in Andalusia[☆]



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ABSTRACT

Objective: To describe whether rheumatic inflammatory diseases (RID) are associated with a higher risk of hospitalization and/or mortality from COVID-19 and identify the factors associated with hospitalization and mortality in RID and COVID-19 in different Hospitals in Andalusia.

Methods: Design: Multicentre observational case-Control study. Patients: RID and COVID-19 from different centres in Andalusia. Controls: patients without RIS matched by sex, age and CRP-COVID.

Protocol A list of patients with PCR for COVID-19 was requested from the microbiology service from March 14 to April 14, 2020. The patients who had RID were identified and then consecutively a paired control for each case.

Variables The main outcome variable was hospital admission and mortality from COVID-19.

Statistical analysis Bivariate followed by binary logistic regression models (DV: mortality/hospital admission).

Results: One hundred and fifty-six patients were included, 78 with RID and COVID-19 and 78 without RID with COVID-19. The patients did not present characteristics of COVID-19 disease different from the general population, nor did they present higher hospital admission or mortality. The factor associated with mortality in patients with RID was advanced age (OR [95% CI], 1.1 [1.0–1.2]; $P = .025$), while the factors associated with hospitalization were advanced age (OR [95% CI], 1.1 [1.0–1.1]; $P = .007$) and hypertension (OR [95% CI], 3.9 [1.5–6.7]; $P = .003$).

Conclusion: Mortality and hospital admission due to COVID-19 do not seem to increase in RID. Advanced age was associated with mortality in RID and, in addition, HTN was associated with hospital admission.

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Hospitalizaciones y mortalidad por COVID-19 en pacientes con enfermedades inflamatorias reumáticas en Andalucía

R E S U M E N

Objetivo: Describir si las enfermedades inflamatorias reumáticas (EIR) se asocian con mayor riesgo de hospitalización y/o mortalidad por COVID-19 e identificar los factores asociados a la hospitalización y mortalidad en EIR y COVID-19 en diferentes hospitales de Andalucía.

Palabras clave:

Enfermedad inflamatoria reumática

COVID-19

Hospitalización

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Métodos: Diseño: Estudio multicéntrico observacional de casos y controles. Pacientes Casos: EIR y COVID-19 de diferentes centros de Andalucía. Controles: pacientes sin EIR pareados por sexo, edad y PCR-COVID. Protocolo Se solicitó al Servicio de Microbiología un listado de pacientes con PCR para COVID-19 desde 14 de marzo al 14 de abril de 2020. Se identificaron los pacientes que tuvieran EIR y luego consecutivamente un control pareado para cada caso.

Variables La variable de desenlace principal fue ingreso hospitalario y mortalidad por COVID-19.

Análisis estadístico Bivariante seguida de modelos de regresión logística binaria (variable dependiente: mortalidad/ingreso hospitalario).

Resultados: Se incluyeron 156 pacientes con COVID-19, 78 con EIR y 78 sin EIR. Los pacientes con EIR no presentaron características de la enfermedad COVID-19 diferentes a la población general, tampoco mayor ingreso hospitalario ni mortalidad. El factor asociado con mortalidad en los pacientes con EIR fue edad (OR [IC 95%], 1,1 [1,0–1,2]; $p = 0,025$), mientras que los factores asociados con ingreso hospitalario fueron edad (OR [IC 95%], 1,1 [1,1–1,2]; $p = 0,007$) e hipertensión arterial (OR [IC 95%], 3,9 [1,5–6,7]; $p = 0,003$).

Conclusión: La mortalidad y el ingreso hospitalario por COVID-19 no parecen aumentados en las EIR. La edad se asoció con mortalidad en EIR y, además, la hipertensión arterial se asoció con ingreso hospitalario.

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Introduction

Coronavirus disease 2019 (COVID-19), caused by the novel type 2 coronavirus (SARS-CoV-2) that causes severe acute respiratory syndrome has spread rapidly as a pandemic. Asymptomatic infections are common;¹ a literature review estimated that up to 30%–40% may go undetected, based on data from three large cohorts that identified cases through population-based testing.² However, in other cases COVID-19 can cause severe acute respiratory infection that requires hospitalisation, intensive care and may result in death.³ Numerous studies have been published in recent months identifying risk factors for severe forms of the disease, such as age, male sex, hypertension, and immunosuppression.^{4–7}

Several studies have sought to determine how inflammatory rheumatic diseases (IRD) and previous use of immunosuppressive agents influence the frequency and severity of COVID-19.^{8–12} In a Spanish multicentre study,⁸ a higher risk of infection was observed in patients with systemic autoimmune diseases and in patients treated with biological disease-modifying drugs (bDMARDs) compared to the general population. However, there does not appear to be an increased risk of COVID-19 infection in chronic inflammatory arthritis.^{8,11} In terms of the severity of COVID-19, patients with chronic inflammatory arthritis have also been shown not to have higher mortality and more severe complications than the general population. In contrast, in hospitalised patients with rheumatic diseases, having a systemic autoimmune disease may be associated with higher mortality from COVID-19.¹⁰ However, general factors such as older age and male sex are also risk factors for higher COVID-19 mortality in patients with RID.^{8–12}

However, other variables of severity and care demand, such as hospital admission, have been less studied in these patients. Knowing the factors associated with hospital admission could help to identify vulnerable patients at an early stage. Therefore, the objectives of our study were: (1) to describe whether the presence of RID is associated with a higher risk of hospitalisation and/or mortality, and (2) to identify the risk factors associated with hospitalisation and mortality in patients with RID and COVID-19 in different university hospitals in Andalusia, compared to controls without RID.

Patients and methods

Design

Multicentre observational study of a case-control series with COVID-19 from four university hospitals in Andalusia, Spain. Recruitment took place between March and April 2020. The Research Ethics Committee of the Regional University Hospital of Malaga (Code 0868-N-20) approved the study.

Participants

Patients with RID and COVID-19 from rheumatology departments of different centres in Andalusia, who attended the emergency departments of each hospital from March 14 to April 14, 2020, were included. Cases and controls with a final diagnosis other than COVID-19 were excluded.

Cases: The RID included were rheumatoid arthritis (RA), spondyloarthritis (SpA), psoriatic arthritis (Pisa), juvenile idiopathic arthritis (JIA), and systemic autoimmune diseases (SAD): systemic lupus erythematosus (SLE), primary Sjögren's syndrome (pSS), systemic sclerosis (SS) and inflammatory myopathies (IM).

Controls: patients without RID attending the emergency department matched by sex, age, and diagnosis of COVID-19 (confirmed and probable).

Protocol

The microbiology service was asked to provide a list of patients for whom a PCR test for COVID-19 had been requested from each included centre's emergency department during the period from 14 March to 14 April, 2020. Patients with RID were identified and then a control was consecutively matched for each case. In all participating centres, patients with signs or symptoms of acute respiratory infection suspicious of COVID-19 in the emergency department's triage area were admitted to the COVID-19 patient pathway^{11,13} and then assessed by an ED physician, who requested the relevant laboratory, radiological or microbiological tests, as well as their hospital admission or outpatient management following the recommendations of the Government of Spain's Ministry of Health.¹⁴

The patients that we included in our study were those with a clinical acute respiratory infection compatible with COVID-19; Spain was considered a country of community transmission in that period. Following the recommendations of the Spanish government in force during the study period, patients with moderate-severe disease, or mild cases with any risk factor for possible severe COVID-19 disease underwent PCR testing.¹⁵

Variables and case definitions

The primary variable was COVID-19 severity, defined as the need for hospital admission or death due to COVID-19. Admission to the observation or inpatient area, including the intensive care unit for at least 24 h, was considered hospital admission. The diagnosis of COVID-19 was based on the classification of the Spanish Ministry of Health¹⁶ as a "confirmed case", for example, patients with a positive PCR for SARS-CoV-2, and a "probable case", patients with

acute respiratory infection with clinical and radiographic features compatible with COVID-19, without PCR confirmation.

Other variables collected were respiratory failure, defined as baseline oxygen saturation $\leq 92\%$ and pneumonia detected on chest X-ray. All COVID-19 treatments administered were collected: azithromycin, hydroxychloroquine/chloroquine, lopinavir/ritonavir, remdesivir, anti-IL6, anti-IL1, glucocorticoids, and immunoglobulins.

Epidemiological data and comorbidities such as sex, age, hypertension (HTN), diabetes mellitus, history of cardiovascular events or pulmonary disease were also collected. Duration of symptoms and treatment data were included for RID: synthetic disease-modifying drugs (DMARDs) (methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, chloroquine), biological DMARDs (infliximab, etanercept, adalimumab, golimumab, certolizumab, tocilizumab SC or IV, sarilumab SC, tocilizumab SC, tocilizumab SC or IV, tocilizumab SC, tocilizumab SC, tocilizumab SC, and tocilizumab SC), sarilumab SC, abatacept, ustekinumab, secukinumab), targeted synthetic DMARDs (baricitinib, tofacitinib), other immunosuppressive drugs (cyclophosphamide, mycophenolate, azathioprine, tacrolimus) and immunoglobulins.

Statistical analysis

We first performed a χ^2 and Student's t-test or Mann-Whitney test to compare the main characteristics between patients with RID and the matched controls without RID. Qualitative variables were expressed as absolute numbers and their percentages and quantitative variables as mean (SD) or median (IQR), according to their distribution. Normality fit was confirmed with the Kolmogorov-Smirnov test. Finally, several stepwise logistic regression models were performed to independently explore the variables associated with hospitalisation and mortality in patients with COVID-19, as well as to identify the factors associated with hospitalisation and mortality in the patients with RID. The variables included in the model were those of statistical significance or clinical interest. For all analyses, a *P*-value $< .05$ was considered significant. R commander version 2.4-0 was used to analyse all the data.

Results

Characteristics of the patients with COVID-19

One hundred and fifty-six patients with COVID-19, 78 patients with RID and 78 controls without RID were included. Table 1 shows the main characteristics of both groups. Most were women (70%), with a mean age of 60 years. Hypertension was the most frequent comorbidity, followed by diabetes mellitus. No epidemiological differences were found between cases and controls.

Of the 78 patients with RID, most had RA (44.95%), followed by SAD (28.2%), SpA (12.8%) and PsA (12.8%). A higher frequency of cases with RID and COVID-19 was observed in the province of Malaga, followed by Cordoba, Granada, and Seville. The median (p25–p75) duration of the RID was 8.0 (4.3–13.1) years. More than half the patients were on a conventional synthetic disease-modifying drug (csDMARDs) (61.6%), methotrexate being the most frequent; and almost 20% were on bDMARDs, TNF α inhibitors being the most frequent. Only seven patients with RID were not under treatment with a DMARD or immunosuppressive agent: five patients with SpA and one patient with PsA, with axial predominance who were being treated with non-steroidal anti-inflammatory drugs (NSAIDs); and one patient with antiphospholipid syndrome (APS) treated with oral anticoagulation.

No differences in COVID-19 characteristics were found between the cases and controls. Among the patients with RID, 59 were PCR-

confirmed cases (75.6%) and 19 (24.4%) were probable cases. There was no difference between cases and controls in hospital admissions (56.4 vs. 61.5%; *P* = .515) or mortality (4 vs. 7.6%; *P* = .298). Table 1 shows the treatments received for COVID-19.

Factors associated with hospitalisation and mortality in the full sample with COVID-19

Of the 156 patients with COVID-19 included in the study, 92 (59%) were hospitalised: 44/78 (56%) cases with RID y 48/78 (61%) controls. A total of nine patients died: 3/78 (4%) with RID and 6/78 (7%) controls.

Table 2 shows the multivariate logistic regression analysis (dependent variable: hospitalisation) for the full sample of patients with COVID-19. Age and male sex were the only variables associated with hospital admission. However, in the second multivariate model (Table 3), the only factor associated with COVID-19 mortality was age. The presence of an RID, however, was not associated with increased risk of hospitalisation or mortality in the COVID-19 patients overall. Neither was the presence of RID or SAD (independently) associated with increased hospitalisation or mortality.

Factors associated with hospitalisation and mortality in patients with RID and COVID-19

Of the group of patients with RID, 44/78 (56%) patients with COVID-19 required hospitalisation and 3/78 (4%) patients died. The three patients who died with RID were RA patients: one woman aged 84.4 years, one man aged 65.1 years, and one man aged 66 years. Most patients requiring hospital admission had a positive PCR result for COVID-19 (84%), including the three (100%) patients who died.

Unlike that observed in the group as a whole, in the patients with RID and COVID-19, age and HTN were independently associated with hospital admission (Table 4), but again, the only factor associated with mortality was age (Table 5).

Discussion

In our study, we sought to identify the risk factors associated with increased hospitalisation and mortality due to COVID-19 in RID. In this regard, we did not find that patients with RID had a higher risk of hospitalisation or mortality. This is in line with other published studies, which have not shown that patients with chronic inflammatory arthritis have higher mortality and/or serious complications compared to the general population.^{10,11} However, some studies have suggested a possible increased risk of mortality from COVID-19 in patients with rheumatic diseases, specifically systemic autoimmune diseases (SAD).¹⁷ In our study, the group of patients with SAD did not have a higher risk of hospitalisation or mortality compared to the controls. This could be because in our study we selected patients and controls who had attended hospital emergency departments, and the controls probably do not represent the general population, but rather a population group that are more vulnerable to severe disease and hospitalisation. In this regard, the percentage of hospitalised patients in our study was higher than in the COVID-19 patient cohorts, but this probably reflects the mechanism by which we collected the patient information and should not be interpreted as the actual rate of hospitalisation among COVID-19 patients with RID.^{8–12,16–18}

Previous studies have identified factors that are associated with increased severity of COVID-19 disease in patients with RID. Most have defined severity as mortality, intensive care need, mechanical ventilation, or a sum of these factors. Thus, age and male sex have been identified as factors associated with greater severity in patients with RID. In our study, age was independently associated

Table 1
Characteristics of the patients with RID-COVID-19 and controls with COVID-19.

Variables	RID n = 78	Controls n = 78	P-value
Epidemiological			
<i>Centres included</i>			
Hospital Universitario de Málaga	34 (43.5)	34 (43.5)	–
Hospital Universitario Reina Sofía, Córdoba	19 (24.3)	19 (24.3)	–
Hospital Universitario San Cecilio, Granada	15 (19.2)	15 (19.2)	–
Hospital Virgen de Valme, Seville	10 (12.8)	10 (12.8)	–
Age in years, mean (SD)	60.9 (14.2)	60.8 (14.8)	.959
Sex, female; n (%)	55 (70.5)	55 (70.5)	.999
Duration of disease (years), median (p25–p75)	8.0 (4.3–13.1)	–	–
Smoking, n (%)	12 (15.4)	7 (9.0)	.221
Hypertension, n (%)	32 (41.0)	40 (51.2)	.261
Diabetes mellitus, n (%)	12 (15.4)	15 (19.2)	.525
Heart disease, n (%)	7 (9.0)	11 (14.1)	.316
Lung disease, n (%)	9 (11.5)	15 (19.2)	.127
Characteristics of RD			
<i>Type of RD</i>			
RA, n (%)	35 (44.9)	–	–
AS, n (%)	10 (12.8)	–	–
PsA, n (%)	10 (12.8)	–	–
JIA, n (%)	1 (1.3)	–	–
SAD, n (%)	22 (28.2)	–	–
<i>Treatment of RD</i>			
GC, n (%)	26 (33.3)	–	–
Immunosuppressive agents, n (%)	7 (8.9)	–	–
Azathioprine, n (%)	5 (6.4)	–	–
Micophenolate, n (%)	2 (2.6)	–	–
DMARDs, n (%)	48 (61.6)	–	–
Leflunomide, n (%)	12 (15.4)	–	–
Methotrexate, n (%)	28 (35.9)	–	–
Sulfasalazine, n (%)	8 (10.3)	–	–
tsDMARDs, n (%)	2 (2.6)	–	–
Tofacitinib, n (%)	2 (2.6)	–	–
bDMARDs, n (%)	15 (19.2)	–	–
Anti-TNF, n (%)	12 (15.4)	–	–
Tocilizumab, n (%)	2 (2.6)	–	–
Abatacept, n (%)	1 (1.3)	–	–
COVID-19 diagnosis			.200
Probable; n (%)	19 (24.4)	27 (34.6)	
Confirmed, n (%)	59 (75.6)	51 (65.4)	
<i>Clinical characteristics of COVID-19</i>			
Hospitalisation, n (%)	44 (56.4)	48 (61.5)	.515
Admission to ICU, n (%)	4 (5.3)	4 (5.3)	.970
Death, n (%)	3 (4.0)	6 (7.6)	.298
<i>Treatment of COVID-19</i>			
Azithromycin, n (%)	39 (52.0)	45 (58.4)	.425
Lopinavir/Ritonavir, n (%)	22 (29.3)	11 (14.3)	.077
Hydroxychloroquine/chloroquine, n (%)	47 (62.7)	49 (63.6)	.901
IL-1 inhibitors, n (%)	1 (1.3)	2 (2.6)	.575
IL-6 inhibitors, n (%)	5 (6.7)	9 (11.7)	.284
Glucocorticoids, n (%)	20 (26.7)	23 (29.9)	.661

bDMARDs: Biological disease-modifying antirheumatic drugs; csDMARDs: Conventional synthetic disease-modifying antirheumatic drugs; ICU: Intensive Care Unit; JIA: Juvenile Idiopathic Arthritis; PsA: Psoriatic arthritis; RA: Rheumatoid arthritis; RID: Rheumatic Inflammatory Diseases; SA: Spondyloarthritis; SAD: Systemic Autoimmune Diseases; SD: Standard Deviation; tsDMARDs: Targeted synthetic disease-modifying antirheumatic drugs.

Table 2
Multivariate analysis of hospitalisation in patients with COVID-19.

Variable	Univariate OR (95% CI)	Multivariate OR (95% CI)	P-value
Age in years	1.119 (1.07–1.16)	1.125 (1.08–1.16)	< .001
Sex, male	1.600 (.78–3.25)	2.605 (1.06–6.39)	.037
Hypertension	5.081 (1.63–9.37)		
Diabetes mellitus	5.000 (1.64–11.27)		
Heart disease	1.106 (.40–3.02)		
Pneumopathy	1.052 (.44–2.51)		
Rheumatic inflammatory disease	.809 (.43–1.53)		

Nagelkerke's $R^2 = .326$. The variables included in the equation were: age, sex, hypertension, diabetes mellitus and rheumatic inflammatory disease.
CI: Confidence Interval; OR: Odds Ratio.

Table 3
Multivariate analysis of mortality in COVID-19 patients.

Variable	Univariate OR (95% CI)	Multivariate OR (95% CI)	P-value
Age in years	1.057 (1.01–1.10)	1.042 (1.01–1.15)	.025
Sex, male	1.048 (.26–4.24)		
Hypertension	5.16 (1.06–11.17)		
Diabetes mellitus	2.338 (.56–9.73)		
Heart disease	.875 (.10–7.36)		
Pneumopathy	2.46 (.59–10.31)		
Rheumatic inflammatory disease	.617 (.11–1.67)		

Nagelkerke's $R^2 = 0,124$. The variables included in the equation were: age, sex, hypertension, diabetes mellitus and rheumatic inflammatory disease. CI: Confidence Interval; OR: Odds Ratio.

with higher COVID-19 mortality in all the samples and in the group of patients with RID. Therefore, our data are consistent with previous studies.^{4–7,10,11,19,20} Male sex may not have been a risk factor for mortality in our study due to the higher frequency of females in the sample and the low mortality observed.

We also studied risk factors associated with increased hospitalisation for COVID-19 in patients with RID. In our study we observed that age and male sex were associated with a higher frequency of hospitalisation in the complete sample,^{21,22} whereas in patients with RID, age and HTN were the factors associated with hospitalisation. The fact that hypertension was not an independent factor for hospitalisation in the sample as a whole may be because more than half the controls were hypertensive. Some studies have reported that hypertension is the most common comorbidity associated with COVID-19.^{23,24} In the case of patients with RID, having another associated comorbidity such as hypertension may be associated with increased severity and hospital admission. It has been reported that SARS-CoV-2 virus uses angiotensin-converting enzyme 2 (ACE2) as a receptor to enter the host cell, and therefore overexpression of ACE2 in hypertensive patients could result in more severe disease.^{25,26} One of the largest registries of patients with RHD and COVID-19, led by Gianfrancesco M et al.,¹² examined demographic and clinical factors associated with COVID-19 hospitalisation status in 600 patients with RID from 40 countries. They found that patients with comorbidities such as hypertension and cardiovascular disease were more likely to be hospitalised, as were those with glucocorticoid exposure of ≥ 10 mg/day, while anti-TNFs were associated with a lower likelihood of hospitalisation in patients with RID. In our study, we found no association between the different drugs used for RID and hospitalisation or mortality. In fact, different studies have been contradictory regarding the effect of these drugs on COVID-19 infection in patients with RID.^{8,10–12,27,28} There could be several reasons for this controversy between studies, these drugs may increase the risk of infection on the one hand, but the potential benefit of biological drugs in the treatment of COVID-19 has also been shown in patients with more severe disease who have higher levels of cytokines, including IL-6 and TNF.^{24,29} Further studies and randomised placebo trials are needed to clarify the potential benefits or harm of RID therapies in the treatment of COVID-19.

Our study has several limitations. First, our group of RID patients was a small sample size and was matched at a 1:1 case: control ratio, and therefore the results should be interpreted with caution. Nevertheless, our data appear consistent with the COVID-19 severity factors described^{8–12,16–18} and support the recommendations of national and international scientific societies to maintain immunosuppressive treatment in patients with RID.^{9–13} On the other hand, the mechanism of selection of the patients and controls, through the hospital emergency department, could constitute selection bias. However, this study did not attempt to look at the rate of hospitalisation and mortality in these patients, but rather at the factors associated with increased hospitalisation and mortality in RID and to compare it with a control group. As for the

Table 4
Multivariate analysis of hospitalisation in patient with RD and COVID-19.

Variable	Univariate OR (95% CI)	Multivariate OR (95% CI)	P-value
Age in years	1.131 (1.06–1.20)	1.160 (1.10–1.20)	.007
Sex, male	1.771 (0.28–2.07)		
Hypertension	5.075 (1.82–7.11)	3.900 (1.50–6.70)	.003
Diabetes mellitus	4.800 (1.34–19.11)		
Heart disease	.549 (0.11–2.63)		
Pneumopathy	3.027 (0.58–15.67)		
Glucocorticoids	3.889 (1.34–11.25)		
sDMARDs	.955 (0.37–2.42)		
bDMARDs	.617 (0.21–1.81)		

Nagelkerke's $R^2 = .301$. The variables included in the equation were: age, sex, hypertension, diabetes mellitus and glucocorticoids. bDMARDs: Biological disease-modifying antirheumatic drugs; CI: Confidence Interval; OR: Odds Ratio; RE: Rheumatic Disease; sDMARDs: Synthetic disease-modifying antirheumatic drugs.

Table 5
Multivariate analysis of mortality in patients with RD and COVID-19.

Variable	Univariate OR (95% CI)	Multivariate OR (95% CI)	P-value
Age in years	1.127 (1.01–1.15)	1.11 (1.02–1.25)	.025
Sex, male	1.206 (.02–2.39)		
Hypertension	2.800 (.24–12.31)		
Diabetes mellitus	3.100 (.25–17.45)		
Heart disease	.901 (.10–15.45)		
Pneumopathy	4.000 (.325–19.24)		
Glucocorticoids	4.261 (.36–19.42)		
sDMARDs	1.130 (.09–11.07)		

Nagelkerke's $R^2 = .100$. The variables included in the equation were: age, sex, hypertension, and diabetes mellitus. CI: Confidence Interval; OR: Odds Ratio; RE: Rheumatic disease; sDMARDs: Synthetic disease-modifying antirheumatic drugs.

treatments used with DMARDs and/or immunosuppressive drugs, although we did not observe an association between these treatments and hospitalisation or mortality, we did not evaluate the duration of treatment with these drugs. However, as these are patients with chronic diseases, the duration of treatment is usually from diagnosis of the disease, and the duration of the disease did not show any association with hospitalisation or mortality. Finally, it should be noted that we included patients with a probable diagnosis of COVID-19, which may have resulted in some patients without COVID-19 being included in the study; however, to reduce this bias we ruled out patients with a confirmed aetiological diagnosis other than COVID-19.

In conclusion, the presence of RID did not increase the risk of hospitalisation or mortality due to COVID-19. As in the general population, people with RID who are older have higher COVID-19 mortality. Hypertension and age could be independent factors for hospitalisation in patients with RID and COVID-19. These data help to further identify risk factors related to severity factors (e.g., hospitalisation, mortality) for COVID-19 in patients with RID.

Ethical approval

The work was conducted under the protocol for the research project which was approved by a Provincial Ethics Committee of Malaga, and complies with the provisions of the Declaration of Helsinki.

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Conflict of interests

The authors have no conflict of interests to declare.

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