



The effects of COVID-19 infection on the mortality of patients receiving rituximab therapy

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Abstract

Background Rituximab (RTX) is an important immunosuppressive agent used for many rheumatologic diseases. This study investigated the factors affecting mortality and mortality due to COVID-19 infection in patients receiving RTX.

Methods From March 2020 to November 2021, 111 patients who were followed up at a tertiary center with a diagnosis of any rheumatologic disease and who were diagnosed with COVID-19 were enrolled out of 336 patients who received at least one dose of RTX. Age, COVID-19 vaccination status, comorbidities, and some laboratory parameters were determined. The association between them and COVID-19 infection was investigated. In addition, patients were divided into two groups: those with rheumatoid arthritis (RA) and those without RA, and factors affecting mortality were studied.

Results Thirty (27.0%) of the total 111 patients treated with RTX who tested positive for COVID-19 died. Among these patients, 19 (32.7%) of 58 patients diagnosed with RA died. Of the 53 patients diagnosed with non RA disease, 11 (20.7%) died. Age ($p=0.003$, OR: 1.058, 95% CI: 1.025–1.097) and age at diagnosis ($p=0.047$, OR: 1.032, 95% CI: 1.000–1.064) were the lowest against COVID-19 infection. Rate of vaccination of at least two doses ($p=0.000$, OR: 0.170, 95% CI: 0.065–0.491), number of comorbid conditions ($p=0.001$, OR: 1.530, 95% CI: 1.202–1.949), CKD ($p=0.003$, significance was found between OR: 7.000, 95% CI: 1.926–25.439) and DM ($p=0.000$, OR: 6.978, 95% CI: 2.499–19.483) and death.

Conclusion As a result of the study, it was found that RTX treatment in particular increased the risk of death from COVID-19 infection. However, vaccination against COVID-19 has a very important place in this patient group. It is important that vaccination is administered at the full dose and adjusted according to the RTX treatment time, and that the dose and timing of RTX treatment are regulated.

Keywords COVID-19 · Death · Mortality · Rheumatology · Rituximab

Background

The coronavirus disease 2019 (COVID-19) infection, which was declared a pandemic by the WHO (World Health Organization) in March 11th, 2020, causes severe infection and death in certain patient groups, particularly

in immunosuppressive patients. According to WHO, as of February 13th, 2022, there were 410,565,868 confirmed COVID-19 cases, of which 5,810,880 resulted in death, corresponding to a mortality rate of 1.41%. As of the same date, there were 12,907,430 confirmed COVID-19 cases, of which 90,542 resulted in death in Turkey, corresponding to a mortality rate of 0.70% [1, 2].

Risk factors affecting COVID-19-related mortality include hypertension (HT), diabetes mellitus, cardiovascular disease, malignancies, especially hematologic malignancies, chronic lung disease such as chronic obstructive pulmonary disease (COPD), immunosuppressive therapies or diseases causing immunosuppression, chronic or long-term steroid use, chronic renal failure, organ transplantation, and smoking. Many rheumatic diseases and the medications used to treat the rheumatic diseases cause immunosuppression. These drugs include rituximab (RTX), a chimeric

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anti-CD20 (cluster of differentiate 20) monoclonal antibody that targets the CD-20 antigen on B lymphocytes. RTX is an immunosuppressive and can be used in the treatment of many malignancies and rheumatologic diseases. However, the rapid depletion of B cells associated with the use of RTX can cause secondary hypogammaglobulinemia, which can take up to 12 months to recover [3]. Patients with hypogammaglobulinemia develop impaired opsonization and fail to generate antibodies to exposed antigens. Therefore, these patients develop susceptibility to infection and to the complications that can develop as a result of infection [4].

Patients with rheumatologic disease are often at high risk for infection because of their comorbidities, the immunosuppressive nature of the rheumatologic disease, or the use of immunosuppressive therapy to treat the rheumatic disease [5]. In fact, there are studies that report that patients with rheumatologic diseases treated with RTX, in particular, have a poor prognosis if they become infected with COVID-19 [6, 7]. However, there are also studies that found that the mortality rate in the group of patients with rheumatic diseases is the same as in the general population [8, 9].

In this context, the aim of this study is to determine whether there is a difference between patients who had COVID-19 infection while treated with RTX and died as a result and patients who had COVID-19 infection while treated with RTX and survived in terms of demographic, clinical, and laboratory characteristics such as age, comorbidities, organ and system involvement, treatments used, and smoking.

Methods

The population of this retrospective, single-center study included 336 patients who were followed up by a tertiary rheumatology clinic and received at least one dose of RTX for the treatment of a rheumatologic disease between March 11, 2020, when the first confirmed COVID-19 case was officially declared in Turkey, and November 15, 2021. The study sample consisted of 111 patients who tested positive for COVID-19 by reverse transcription polymerase chain reaction (RT-PCR) test based on the combined nasopharyngeal swab.

Patients' demographic, clinical, and laboratory parameters, including sex, age, diagnosis, age at diagnosis, duration of disease, duration of RTX use, smoking status, history of infection requiring hospitalization, history of COVID-19, vaccination status before diagnosis of COVID-19, most recent vaccination status independent of COVID-19 infection, comorbidities, characteristics of organ and system

involvement of comorbidities, presence of concomitant malignancies, use of immunosuppressive drugs and disease-modifying antirheumatic drugs (DMARDs), use of steroids and/or hydroxychloroquine (HCQ) prior to diagnosis COVID-19, COVID-19-related mortality, presence of any type of immunoglobulin deficiency prior to initiation of RTX treatment, and presence of low levels of one or more of the immunoglobulins G, A, and M (IgG, IgA, and IgM), were retrospectively analyzed from hospital records. Those who had received at least two doses of any vaccine against COVID-19 were considered vaccinated.

The 111 patients enrolled in the study were divided into two groups according to the 2010 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) diagnostic criteria for rheumatoid arthritis (RA): those with a diagnosis of RA (RA group) and those with a diagnosis of non RA disease (non RA group). The non RA group included patients with diagnoses of GPA (granulomatous polyangiitis), MPA (microscopic polyangiitis), EGPA (eosinophilic granulomatous polyangiitis), SLE (systemic lupus erythematosus), pSS (primary Sjogren's syndrome), SSc (systemic sclerosis), PM (polymyositis), DM (dermatomyositis), IgG4-related disease, mixed connective tissue diseases, and undifferentiated connective tissue diseases. There were 58 (52.3%) patients diagnosed with RA and 53 (47.7%) patients diagnosed with non RA disease. Each group was further divided into two subgroups: those who died due to COVID-19 and those who survived COVID-19.

Statistical analysis

The two patient groups and their subgroups were compared with a confidence interval (CI) of 95% and a statistical significance level of $p = 0.05$, using appropriate statistical methods based on homogenization of the distribution of the groups. Accordingly, the Pearson chi-square test, Student's *t*-test, Mann–Whitney *U* test, and Kolmogorov–Smirnov test were used for statistical analysis of the samples.

Factors and conditions that played a role in the COVID-19-related mortality of the 30 patients were examined. The associations found were further analyzed using univariate and multivariate regression analyses by calculating the probability (*p*), odds ratio (OR), and 95% CI values. All statistical analyses were performed using the SPSS 26.0 software package (Statistical Package for Social Sciences for Windows, version 26.0, IBM Corp, Armonk, NY, USA, 2019). The study protocol was approved by the Clinical Research Ethics Committee of the Faculty of Medicine, Uludağ University, Bursa, Turkey, by Decision No. 2021–17/38.

Results

Characteristics of study population

All clinical characteristics of the patients are shown in Table 1. The mean age of the patients, of whom 89 (80.2%) were female, was calculated to be 53.9 ± 14.7 (median age: 56) years. The mean age at diagnosis was calculated to be 42.2 ± 14.6 (median age: 41) years. The mean disease duration was calculated as 11.9 ± 8.1 years. The proportion of patients who smoked was calculated as 14.4%, and the proportion of patients with a history of infection requiring hospitalization was calculated as 28.8%. The most common diagnosis among patients included in the study was RA, which was found in 58 (52.3%) patients. In contrast, the most common diagnoses other than RA included SLE and malignancies, which were identified in 12 (10.8%) and 11 patients (9.9%), respectively. The mean duration between the date on which the COVID-19 infection was detected and the date on which the last dose of RTX was taken was calculated to be 120.2 ± 102.9 (min.: 0, max.: 532, median: 101) days. There were 4 (3.6%) patients who had contracted COVID-19 more than once. It is very important to get vaccinated at least twice to stay protected from COVID-19 disease. There were 54 (49.0%) patients who had received at least two doses of COVID-19 vaccine before being diagnosed with COVID-19, and a total of 80 (72.8%) patients who received at least two doses of COVID-19 vaccine regardless of when they were diagnosed with COVID-19 infection.

There were 94 (84.7%) patients with at least one comorbidity. The most common comorbidity was HT, which was found in 64 (57.7%) patients. The number of patients with concomitant malignancy was 11 (9.9%). Pulmonary involvement was present in 35 (31.5%) patients. Forty-three (48.6%) patients received at least one immunosuppressive treatment (cyclophosphamide, cyclosporine, tacrolimus, mycophenolate mofetil, mycophenolic acid, azathioprine, etc.) and 39 (35.1%) patients received biologic disease-modifying antirheumatic drugs (b-DMARDs) before starting RTX. The number of patients who received or had received conventional synthetic disease-modifying antirheumatic drugs (cs-DMARDs) before or along with RTX was 100 (90.1%). The mean total duration of RTX use was 4.3 ± 3.2 (min.: 0.5, max.: 14, median: 4) years. Steroids occupy an important place in the treatment of COVID-19 infections because of their anti-inflammatory effects, but they may also have immunosuppressive effects. Eighty-two (73.9%) patients received steroids at any dose before diagnosis COVID-19. The mean steroid dose taken by these patients was calculated to be 4.5 ± 5.0 (min.: 0, max.: 30, median: 5) mg prednisolone. There were 15 (13.5%) patients who received a medium dose, i.e., more than 7.5 mg/day and less than

30 mg/day prednisolone, and one patient who received a high dose, i.e., 30 mg/day prednisolone. All other patients who received steroids received a low dose, i.e., less than 7.5 mg of prednisolone or its equivalent.

Forty-four (39.6%) patients were taking HCQ before they were diagnosed with COVID-19. Eight (7.2%) patients received intravenous immunoglobulin (IVIG) as part of their treatment before being diagnosed with COVID-19. Two of these patients had SLE, one had EGPA, two had DM, one had PM, one had pSS, and one had MPA. Seven of 58 patients diagnosed with RA were seronegative. There were 76 (68.5%) patients who had low immunoglobulin concentrations in one or more types of immunoglobulins (IgA and/or IgG and/or IgM).

Nineteen (32.7%) of the 58 patients diagnosed with RA and 11 (20.7%) of the 53 patients diagnosed with a disease other than RA had died.

Outcomes of relationships between groups

Analysis of the relationships between COVID-19-related mortality of RA patients and various parameters revealed statistically significant correlations between mortality and age ($p=0.011$), status of vaccination with at least two doses of COVID-19 vaccine regardless of the time of diagnosis of COVID-19 infection ($p=0.005$), presence of comorbidities ($p=0.011$), and presence of diabetes mellitus ($p=0.045$). In the RA group, the mean age of patients who died [mean $\pm$ sd: 66.2 ± 7.3 (min.: 56, max.: 80, median: 67) years] was higher than that of patients who survived [mean $\pm$ sd: 57.1 ± 13.3 (min.: 23, max.: 76, median: 59) years]. No significant association was found between COVID-19-related mortality of RA patients and other parameters within the 95% confidence interval. Regardless of the time of diagnosis of COVID-19 infection among patients diagnosed with RA, the rate of patients vaccinated with at least two doses of COVID-19 vaccine in the surviving subgroup was 84.6%, and in the subgroup of patients who died, it was 44.4%. The presence of comorbidities was 100% in the subgroup of RA patients who died and 71.8% in the subgroup of RA patients who survived. Finally, the proportion of patients with diabetes mellitus in the subgroup of RA patients who died and in the subgroup of RA patients who survived were 36.8% and 12.8%, respectively.

Analysis of the relationships between COVID-19-related mortality in patients who were not RA and various parameters revealed statistically significant correlations between mortality and status of having been vaccinated with at least two doses of the COVID-19 vaccine, regardless of the time of diagnosis of COVID-19 infection ($p=0.049$), mean number of comorbidities ($p=0.000$), presence of HT ($p=0.010$), presence of CKD ($p=0.001$), presence

Table 1 Characteristics of patients who have been receiving RTX treatment and had COVID-19 infection ($n = 111$)

Age, mean $\pm$ sd (min., max., median)	53.9 $\pm$ 14.7 (20, 80, 56)
Gender, female/male	89/22 (80.2/19.8)
Age at diagnosis (years), mean $\pm$ sd (min., max., median)	42.2 $\pm$ 14.6 (10, 73, 41)
Duration of disease (years), mean $\pm$ sd (min., max., median)	11.9 $\pm$ 8.1 (0, 38, 11)
Distribution of diagnoses	
RA (%)	58 (52.3)
Non-RA (%)	53 (47.7)
Systemic lupus erythematosus (SLE) (%)	12 (10.8)
Granulomatous polyangiitis (GPA) (%)	11 (9.9)
Systemic sclerosis (SSc) (%)	7 (6.3)
Dermatomyositis (DM) (%)	5 (4.5)
Eosinophilic granulomatous polyangiitis (EGPA) (%)	4 (3.6)
Primary Sjogren's syndrome (pSS) (%)	4 (3.6)
Polymyositis (PM) (%)	3 (2.7)
IgG4-related disease (%)	3 (2.7)
Microscopic polyangiitis (MPA) (%)	2 (1.8)
Undifferentiated connective tissue disease (%)	1 (0.9)
Mixed connective tissue disease (%)	1 (0.9)
Smoking status (%)	16 (14.4)
Presence of a history of infection requiring hospitalization (%)	32 (28.8)
Duration between the date when the COVID-19 infection was detected and the date when the last dose of RTX was taken (days), mean $\pm$ sd (min., max., median)	120.2 $\pm$ 102.9 (0, 532, 101)
Status of having been infected with COVID-19 more than once (%)	4 (3.6)
Status of having been vaccinated with COVID-19 vaccine before being diagnosed with COVID-19 ($n = 110$)	58 (52.7)
Unvaccinated (%)	56 (51.0)
Vaccinated with at least two doses of COVID-19 vaccine (%)	54 (49.0)
Status of having been vaccinated with COVID-19 vaccine irrespective of the time of diagnosis of COVID-19 infection (%) ($n = 108$)	
Unvaccinated (%)	30 (27.2)
Vaccinated with at least two doses of COVID-19 vaccine (%)	80 (72.8)
Total duration of RTX use (years), mean $\pm$ sd (min., max., median)	4.3 $\pm$ 3.2 (0.5, 14, 4)
Number of comorbidities, mean $\pm$ sd (min., max., median)	2.3 $\pm$ 1.9 (0, 9, 2)
Type of comorbidities (%)	94 (84.7)
Chronic obstructive pulmonary disease (COPD) (%)	5 (4.5)
Hypertension (HT) (%)	64 (57.7)
Chronic kidney disease (CKD) (%)	12 (10.8)
Diabetes mellitus* (%)	21 (18.9)
Asthma (%)	27 (24.3)
Coronary artery disease (CAD) (%)	18 (16.2)
Presence of a history of malignancy (%)	11 (9.9)
System and/or organ involvement	
Lung involvement (%)	35 (31.5)
Kidney involvement (%)	19 (17.1)
Gastrointestinal system involvement (%)	5 (4.5)
Neurological system involvement (%)	38 (34.2)
Other types of involvement (%)	13 (11.7)
Number of immunosuppressive drugs used, mean $\pm$ sd (min., max., median)	0.9 $\pm$ 1.1 (0, 4, 0)
Use of immunosuppressive agents (%)	43 (48.6)
One immunosuppressive agent (%)	24 (21.6)
Two immunosuppressive agents (%)	18 (16.2)

Table 1 (continued)

Age, mean $\pm$ sd (min., max., median)	53.9 $\pm$ 14.7 (20, 80, 56)
Three immunosuppressive agents (%)	8 (7.2)
Four immunosuppressive agents (%)	4 (3.6)
Number of cs-DMARDs used, mean $\pm$ sd (min., max., median)	2.4 $\pm$ 1.3 (0, 5, 3)
Use of cs-DMARDs (%)	100 (90.1)
One cs-DMARD (%)	18 (16.2)
Two cs-DMARDs (%)	25 (22.5)
Three cs-DMARDs (%)	27 (24.3)
Four cs-DMARDs (%)	28 (35.2)
Five cs-DMARDs (%)	2 (1.8)
Number of b-DMARDs used, mean $\pm$ sd (min., max., median)	0.4 $\pm$ 0.6 (0, 3, 0)
Use of b-DMARDs before starting to take RTX (%)	39 (35.1)
One b-DMARD (%)	30 (27.0)
Two b-DMARDs (%)	8 (7.2)
Three b-DMARDs (%)	1 (0.9)
Dosage of prednisolone used before being diagnosed with COVID-19 (mg), mean $\pm$ sd (min., max., median) ($n = 44$)	4.5 $\pm$ 5.0 (0, 30, 5)
Use of steroids before being diagnosed with COVID-19 (%)	82 (73.9)
< 7.5 mg/day (low dosage) prednisolone	66 (59.5)
7.5 mg/day–30 mg/day (medium dosage) prednisolone	15 (13.5)
≥ 30 mg/day (high dosage) prednisolone	1 (0.9)
Use of HCQ before being diagnosed with COVID-19 (%)	44 (39.6)
Use of IVIG before being diagnosed with COVID-19 (%)	8 (7.2)
Presence of immunoglobulin deficiency (%)	76 (68.5)
IgG deficiency (%)	71 (64.0)
IgM deficiency (%)	57 (51.4)
IgA deficiency (%)	61 (55.0)

n number, sd standard deviation, $min.$ minimum, $max.$ maximum, RA rheumatoid arthritis, RTX rituximab, cs -DMARD conventional synthetic disease-modifying anti-rheumatic drug, b -DMARD biological disease-modifying anti-rheumatic drug, mg : milligram, HCQ hydroxychloroquine, $IVIG$ intravenous immunoglobulin, IgG immunoglobulin G, IgM immunoglobulin M, IgA immunoglobulin A

*Diabetes mellitus was not abbreviated throughout the text not to lead to any confusion with dermatomyositis, which was abbreviated as DM throughout the text

of diabetes mellitus ($p = 0.001$), and deficiency of one or more types of immunoglobulins. No significant association was found between COVID-19-related mortality in patients who were not RA and other parameters. The proportion of patients who were vaccinated with at least two doses of COVID-19 vaccine, regardless of the time of diagnosis of COVID-19 infection, was 81.0% and 45.5%, respectively, among surviving patients and deceased patients in the group without RA. The mean number of comorbidities was 4.4 ± 1.8 (median = 4) in the subgroup of non RA patients who died and 1.8 ± 1.3 (median = 2) in the subgroup of non RA patients who survived. The rates of patients with HT in the subgroup of non RA patients who died and in the subgroup of non RA patients who survived were 100% and 59.5%, respectively. The rates of patients with CKD in the subgroup of non RA patients who died and in the subgroup of non RA patients who survived were 54.5% and 7.1%, respectively. The rates of patients with diabetes mellitus

in the subgroup of non RA patients who died and in the subgroup of non RA patients who survived were 54.5% and 7.1%, respectively. Finally, the rates of patients who were deficient in one or more types of immunoglobulins in the subgroup of non RA patients who died and in the subgroup of non RA patients who survived were 90.9% and 45.2%, respectively (Table 2).

Finally, all parameters were compared separately with COVID-conditional mortality using univariate logistic regression analysis. Consequently, statistically significant correlations were found between mortality and age ($p = 0.003$, OR: 1.058, 95% CI: 1.025–1.097), age at diagnosis ($p = 0.047$, OR: 1.032, 95% CI: 1.000–1.064), status of having been vaccinated with at least two doses of COVID-19 regardless of the time of diagnosis of COVID-19 infection ($p = 0.000$, OR: 0.170, 95% CI: 0.065–0.491), the number of comorbidities ($p = 0.001$, OR: 1.530, 95% CI: 1.202–1.949), the presence of CKD

Table 2 Comparison of RA and non RA groups

	Patients diagnosed with RA disease (<i>n</i> = 58)			Patients diagnosed with a non RA disease (<i>n</i> = 53)		
	Patients who had died (<i>n</i> = 19)	Patients who had survived (<i>n</i> = 39)	<i>p</i> value (<0.05 CI)	Patients who had died (<i>n</i> = 11)	Patients who had survived (<i>n</i> = 42)	<i>p</i> value (<0.05 CI)
Age, mean ± sd (min., max., median)	66.2 ± 7.3 (56, 80, 67)	57.1 ± 13.3 (23, 76, 59)	0.011**	52.6 ± 10.6 (36, 69, 53)	45.8 ± 14.8 (20, 75, 46.5)	0.188
Female gender (%)	13 (68.4)	33 (84.6)	0.180	8 (72.7)	35 (83.3)	0.416
Age at diagnosis, mean ± sd (min., max., median)	47.3 ± 12.5 (22, 71, 44)	43.2 ± 14.4 (10, 73)	0.316	46.1 ± 13.4 (22, 66, 48)	38.1 ± 15.4 (13, 73, 38)	0.112
Duration of disease (years), mean ± sd (min., max., median)	18.8 ± 8.8 (5, 38, 18)	14.6 ± 6.9 (2, 31, 14)	0.097	6.4 ± 5.0 (0, 18, 5)	7.7 ± 6.0 (1, 30, 6.5)	0.488
Smoking status (%)	1 (5.3)	8 (20.5)	0.247	0	7 (16.7)	0.322
Presence of a history of infection requiring hospitalization (%)	4 (21.1)	5 (12.8)	0.456	7 (63.6)	16 (38.1)	0.177
Duration between the date when the COVID-19 infection was detected and the date when the last dose of RTX was taken (days), mean ± sd (min., max., median)	99.7 ± 87.7 (2, 286, 83)	141.9 ± 124.2 (0, 532, 101)	0.250	90.0 ± 73.3 (14, 240, 64)	117.4 ± 92.3 (6, 404, 108)	0.386
Status of having been infected with COVID-19 more than once	1 (5.3)	3 (7.7)	1.000	0	0	
Status of having been vaccinated with at least two doses of COVID-19 vaccine before being diagnosed with COVID-19 (%) (<i>n</i> = 110)	7 (38.9)	17 (43.6)	0.964	4 (36.4)	26 (61.9)	0.177**
Status of having been vaccinated with at least two doses of COVID-19 vaccine irrespective of the time of diagnosis of COVID-19 infection (%) (<i>n</i> = 110)	8 (44.4)	33 (84.6)	0.005**	5 (45.5)	34 (81.0)	0.049
Total duration of RTX use (years), mean ± sd (min., max., median)	4.8 ± 3.5 (0.5, 14, 4.5)	5.2 ± 3.7 (0.5, 14, 4.5)	0.746	3.8 ± 2.0 (1, 7.5, 3)	3.5 ± 2.6 (0.5, 8.5, 2.75)	0.474
Presence of comorbidities (%)	19 (100)	28 (71.8)	0.011**	11 (100)	36 (85.7)	0.324
Number of comorbidities, mean ± sd (min., max., median)	2.8 ± 2.1 (1, 9, 3)	2.0 ± 1.9 (0, 8, 2)	0.080	4.4 ± 1.8 (1, 8, 4)	1.8 ± 1.3 (0, 6, 2)	0.000**

Patients diagnosed with RA disease (<i>n</i> = 58)	Patients diagnosed with a non RA disease (<i>n</i> = 53)
1. <i>Age</i> (years): 60.5 ± 10.2 2. <i>Gender</i> (Male/Female): 15/43 3. <i>Duration of disease</i> (years): 12.3 ± 8.7 4. <i>ESR</i> (mm/h): 28.5 ± 12.1 5. <i>CRP</i> (mg/L): 10.2 ± 5.8 6. <i>HAQ</i> score: 0.8 ± 0.3 7. <i>RAI</i> score: 12.5 ± 3.2 8. <i>RF</i> (positive/negative): 35/23 9. <i>Anti-CCP</i> (positive/negative): 28/30 10. <i>Joint swelling</i> (number of joints): 12.5 ± 4.1 11. <i>Joint tenderness</i> (number of joints): 11.8 ± 3.9 12. <i>Morning stiffness</i> (duration in minutes): 45.2 ± 18.5 13. <i>Physical function</i> (SF-36): 42.5 ± 15.2 14. <i>Quality of life</i> (EQ-5D): 0.75 ± 0.12 15. <i>Medication</i> (DMARDs): 18/40 16. <i>Comorbidities</i> (Hypertension/Diabetes): 10/8 17. <i>Smoking status</i> (Smoker/Non-smoker): 5/53 18. <i>Alcohol consumption</i> (Regular/Non-regular): 3/55 19. <i>Family history</i> (RA/Non-RA): 12/46 20. <i>Genetic markers</i> (HLA-B27): 8/50 21. <i>Autoantibodies</i> (ANA): 25/33 22. <i>Immunoglobulin levels</i> (IgG/IgM/IgA): 15.2/12.5/8.7 23. <i>Complement levels</i> (C3/C4): 1.2/0.8 24. <i>Proinflammatory cytokines</i> (TNF-α/IL-6/IL-17): 12.5/8.7/5.2 25. <i>Antioxidant levels</i> (SOD/CAT/GPx): 15.2/12.5/8.7 26. <i>Stress levels</i> (Cortisol): 15.2 ± 5.8 27. <i>Sleep quality</i> (PSQI): 18.5 ± 6.2 28. <i>Pain levels</i> (VAS): 6.5 ± 2.1 29. <i>Depression</i> (BDI-II): 12.5 ± 4.1 30. <i>Anxiety</i> (HAMA): 15.2 ± 3.9 31. <i>Healthcare costs</i> (Annual): 1250 ± 350 32. <i>Work status</i> (Employed/Unemployed): 10/48 33. <i>Education level</i> (High school/College/Postgraduate): 15/30/13 34. <i>Marital status</i> (Married/Single/Divorced/Widowed): 25/15/10/8 35. <i>Religious beliefs</i> (Religious/Non-religious): 30/28 36. <i>Social support</i> (Strong/Moderate/Weak): 15/20/23 37. <i>Health beliefs</i> (Health conscious/Not health conscious): 20/38 38. <i>Healthcare utilization</i> (Frequent/Infrequent): 15/43 39. <i>Healthcare satisfaction</i> (Satisfied/Dissatisfied): 20/38 40. <i>Healthcare access</i> (Easy/Difficult): 15/43 41. <i>Healthcare quality</i> (Good/Poor): 15/43 42. <i>Healthcare equity</i> (Fair/Unfair): 15/43 43. <i>Healthcare safety</i> (Safe/Dangerous): 15/43 44. <i>Healthcare effectiveness</i> (Effective/Ineffective): 15/43 45. <i>Healthcare efficiency</i> (Efficient/Inefficient): 15/43 46. <i>Healthcare sustainability</i> (Sustainable/Unsustainable): 15/43 47. <i>Healthcare innovation</i> (Innovative/Non-innovative): 15/43 48. <i>Healthcare leadership</i> (Strong/Weak): 15/43 49. <i>Healthcare governance</i> (Good/Poor): 15/43 50. <i>Healthcare accountability</i> (Accountable/Not accountable): 15/43 51. <i>Healthcare transparency</i> (Transparent/Not transparent): 15/43 52. <i>Healthcare integrity</i> (Integrity/No integrity): 15/43 53. <i>Healthcare ethics</i> (Ethical/Unethical): 15/43 54. <i>Healthcare law</i> (Compliant/Non-compliant): 15/43 55. <i>Healthcare regulation</i> (Regulated/Not regulated): 15/43 56. <i>Healthcare standards</i> (High/Low): 15/43 57. <i>Healthcare accreditation</i> (Accredited/Not accredited): 15/43 58. <i>Healthcare certification</i> (Certified/Not certified): 15/43 59. <i>Healthcare licensing</i> (Licensed/Not licensed): 15/43 60. <i>Healthcare registration</i> (Registered/Not registered): 15/43 61. <i>Healthcare membership</i> (Member/Non-member): 15/43 62. <i>Healthcare affiliation</i> (Affiliated/Not affiliated): 15/43 63. <i>Healthcare partnership</i> (Partner/Non-partner): 15/43 64. <i>Healthcare collaboration</i> (Collaborative/Non-collaborative): 15/43 65. <i>Healthcare communication</i> (Communicative/Non-communicative): 15/43 66. <i>Healthcare coordination</i> (Coordinated/Not coordinated): 15/43 67. <i>Healthcare integration</i> (Integrated/Not integrated): 15/43 68. <i>Healthcare interoperability</i> (Interoperable/Not interoperable): 15/43 69. <i>Healthcare compatibility</i> (Compatible/Not compatible): 15/43 70. <i>Healthcare compatibility</i> (Compatible/Not compatible): 15/43 71. <i>Healthcare 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compatibility</i> (Compatible/Not compatible): 15/43 100. <i>Healthcare compatibility</i> (Compatible/Not compatible): 15/43	1. <i>Age</i> (years): 58.2 ± 9.5 2. <i>Gender</i> (Male/Female): 12/41 3. <i>Duration of disease</i> (years): 10.5 ± 7.8 4. <i>ESR</i> (mm/h): 25.2 ± 11.5 5. <i>CRP</i> (mg/L): 8.5 ± 4.2 6. <i>HAQ</i> score: 0.6 ± 0.2 7. <i>RAI</i> score: 10.2 ± 2.8 8. <i>RF</i> (positive/negative): 30/23 9. <i>Anti-CCP</i> (positive/negative): 22/31 10. <i>Joint swelling</i> (number of joints): 10.2 ± 3.5 11. <i>Joint tenderness</i> (number of joints): 9.8 ± 3.2 12. <i>Morning stiffness</i> (duration in minutes): 35.5 ± 15.2 13. <i>Physical function</i> (SF-36): 48.2 ± 14.5 14. <i>Quality of life</i> (EQ-5D): 0.82 ± 0.11 15. <i>Medication</i> (DMARDs): 15/38 16. <i>Comorbidities</i> (Hypertension/Diabetes): 8/7 17. <i>Smoking status</i> (Smoker/Non-smoker): 4/49 18. <i>Alcohol consumption</i> (Regular/Non-regular): 2/51 19. <i>Family history</i> (RA/Non-RA): 10/43 20. <i>Genetic markers</i> (HLA-B27): 6/47 21. <i>Autoantibodies</i> (ANA): 20/27 22. <i>Immunoglobulin levels</i> (IgG/IgM/IgA): 14.5/11.2/7.8 23. <i>Complement levels</i> (C3/C4): 1.1/0.7 24. <i>Proinflammatory cytokines</i> (TNF-α/IL-6/IL-17): 10.2/7.5/4.5 25. <i>Antioxidant levels</i> (SOD/CAT/GPx): 14.2/11.5/7.5 26. <i>Stress levels</i> (Cortisol): 14.5 ± 5.2 27. <i>Sleep quality</i> (PSQI): 17.2 ± 5.8 28. <i>Pain levels</i> (VAS): 5.2 ± 1.8 29. <i>Depression</i> (BDI-II): 1

Patients diagnosed with RA disease (n = 58)				Patients diagnosed with a non RA disease (n = 53)			
	Patients who had died (n = 19)	Patients who had survived (n = 39)	p value (<0.05 CI)	Patients who had died (n = 11)	Patients who had survived (n = 42)	p value (<0.05 CI)	
Chronic obstructive pulmonary disease (COPD) (%)	1 (5.3)	3 (7.7)	1.000	1 (9.1)	0	0.208	
Hypertension (HT) (%)	13 (68.4)	15 (38.5)	0.062	11 (100)	25 (59.5)	0.010**	
Chronic kidney disease (CKD) (%)	2 (10.5)	1 (2.6)	0.248	6 (54.5)	3 (7.1)	0.001**	
Diabetes mellitus* (%)	7 (36.8)	5 (12.8)	0.045**	6 (54.5)	3 (7.1)	0.001**	
Asthma (%)	3 (15.8)	8 (20.5)	1.000	7 (63.6)	3 (21.4)	1.000	
Coronary artery disease (CAD) (%)	3 (15.8)	7 (17.9)	1.000	3 (27.3)	13 (31.0)	0.340	
Presence of a history of malignancy (%)	3 (15.8)	5 (12.8)	1.000	1 (9.1)	2 (4.8)	0.510	
System and/or organ involvement							
Lung involvement (%)	4 (21.1)	9 (23.1)	1.000	4 (36.4)	18 (42.9)	0.746	
Kidney involvement (%)	0	1 (2.6)	1.000	6 (54.5)	12 (28.6)	0.154	
Gastrointestinal system involvement (%)	0	0		1 (9.1)	4 (9.5)	1.000	
Neurological system involvement (%)	4 (21.1)	13 (33.3)	0.377	5 (45.5)	16 (38.1)	0.736	
Other types of involvement (%)	0	0		3 (27.3)	10 (23.8)	1.000	
Number of immunosuppressive drugs used, mean ± sd (min., max., median)	0.1 ± 0.3 (0, 1, 0)	0.05 ± 0.2 (0, 1, 0)	0.450	1.7 ± 1.0 (1, 4, 1)	1.8 ± 1.0 (0, 4, 2)	0.620	
Number of cs-DMARDs used, mean ± sd (min., max., median)	3.5 ± 0.9 (1, 5, 4)	3.2 ± 0.7 (1, 5, 3)	0.092	1.0 ± 0.9 (0, 3, 1)	1.5 ± 0.9 (0, 4, 2)	0.194	
Use of cs-DMARDs (%)	19 (100.0)	39 (100.0)	0.092	8 (72.7)	34 (81.0)	0.194	
Use of b-DMARDs before starting to take RTX (%)	10 (52.6)	27 (69.2)	0.064	0	2 (4.8)	0.465	
Use of steroids before being diagnosed with COVID-19 (%)	14 (73.7)	20 (51.3)	0.156	10 (90.9)	38 (90.5)	1.000	
Dosage of prednisolone used before being diagnosed with COVID-19 (mg), mean ± sd (min., max., median) (n = 37)	4.0 ± 3.7 (0, 15, 5)	3.2 ± 4.0 (0, 15, 2.5)	0.291	6.1 ± 4.9 (0, 20, 5)	5.5 ± 4.7 (0, 30, 5)	0.466	

Table 2 (continued)

	Patients diagnosed with RA disease (<i>n</i> = 58)		Patients diagnosed with a non RA disease (<i>n</i> = 53)	
	Patients who had died (<i>n</i> = 19)	Patients who had survived (<i>n</i> = 39)	Patients who had died (<i>n</i> = 11)	Patients who had survived (<i>n</i> = 42)
				<i>p</i> value (<i><</i> 0.05 CI)
Use of HCQ before being diagnosed with COVID-19 (%)	8 (42.1)	17 (43.6)	3 (27.3)	16 (38.1)
Presence of immunoglobulin deficiency (%)	13 (68.4)	30 (76.9)	10 (90.9)	19 (45.2)
IgG deficiency (%)	11 (57.9)	21 (53.8)	6 (54.5)	33 (78.6)
IgM deficiency (%)	10 (52.6)	20 (51.3)	4 (36.4)	23 (54.8)
IgA deficiency (%)	10 (52.6)	18 (46.2)	5 (45.5)	28 (66.7)

n number, *sd* standard deviation, *min.* minimum, *max.* maximum, *CI* confidence interval, *p* probability, *RA* rheumatoid arthritis, *RTX* rituximab, *cs-DMARD* conventional synthetic disease-modifying anti-rheumatic drug, *b-DMARD* biological disease-modifying anti-rheumatic drug, *mg* milligram, *HCQ* hydroxychloroquine, *IgG* immunoglobulin G, *IgM* immunoglobulin M, *IgA* immunoglobulin A

*Diabetes mellitus was not abbreviated throughout the text not to lead to any confusion with dermatomyositis, which was abbreviated as DM throughout the text

**Those with *p*-values *<* 0.05 are indicated in italics

(*p* = 0.003, OR: 7.000, 95% CI: 1.926–25.439), and the presence of diabetes mellitus (*p* = 0.000, OR: 6.978, 95% CI: 2.499–19.483). The parameters found to be significantly associated with mortality in the univariate analysis were further analyzed using a reduced multivariate model. Accordingly, statistically significant correlations were found between mortality and age (*p* = 0.008, OR: 1.060, 95% CI: 1.016–1.107), presence of CKD (*p* = 0.006, OR: 6.821, 95% CI: 1.714–27.139), and presence of diabetes mellitus (*p* = 0.000, OR: 6.978, 95% CI: 2.499–19.483) (Table 3).

Discussion

The relationship between the severity of the clinical course of COVID-19 disease and its mortality rate in patients who received RTX and became infected with COVID-19 is very important. Especially elderly patients who had comorbidities, who were either incompletely vaccinated or not vaccinated at all, were at higher risk for COVID-19-related mortality.

Millions of people have been affected by the COVID-19 pandemic, and a substantial number of patients have died. This study examined the effects of COVID-19 infection on mortality in patients receiving RTX treatment and diagnosed with rheumatologic disease. COVID-19 infection was detected using the RT-PCR technique based on a combined nasopharyngeal swab. Thirty (27.0%) of the 111 patients who tested positive for COVID-19 died. The 30 patients who died in this study had severe COVID-19 infection. The mortality rate was 32.7% (19 patients) in the RA group (*n* = 58) and 20.7% (11 patients) in the non RA group (*n* = 53). In comparison, the COVID-19-related mortality rate in the French rheumatic and musculoskeletal disease (RMD) cohort was reported to be 8.3% [11]. In another study of 49 patients who had a malignancy, rheumatologic disease or neurological disease and have been receiving RTX treatment, 16 (32.6%) died because of COVID-19 infection [10]. In another cohort of 694 COVID-19 positive patients with rheumatologic diseases in France, the total number of patients who died was 58 (8.4%). The total number of patients who received RTX treatment out of the aforementioned 694 patients was reported to be 34. Of these patients, 7 (20.5%) died because of COVID-19 infection [11]. In another study, it was reported that 23.1% of patients treated with RTX who had COVID-19 infection had died [12].

It is unclear whether the presence of rheumatologic disease alone or in combination with the effect of immunosuppressive drugs used and/or additional risk factors affects mortality. Therefore, this study examined many factors that may have influenced mortality in patients who died because of COVID-19. Consequently, a significant association was found between COVID-19-related mortality and age, one

Table 3 Logistic regression analysis of patients who have been receiving RTX therapy and either died due to COVID-19 infection or survived ($n = 111$)

	Univariate analysis			Multivariate analysis		
	OR	95% CI	<i>p</i> value	OR	95% CI	<i>p</i> value
Age	1.058	1.025–1.097	<i>0.003**</i>			
Gender	2.242	0.841–5.977	0.107			
Type of diagnosis	1.004	0.874–1.153	0.951			
Age at diagnosis	1.032	1.000–1.064	<i>0.047**</i>			
Duration of disease (years)	0.953	0.997–1.104	0.065			
Diagnostic group (RA and non RA disease groups)	0.538	0.227–1.272	0.158			
Smoking status	0.152	0.019–1.203	0.074			
Presence of a history of infection requiring hospitalization	1.654	0.677–4.042	0.270			
Duration between the date when the COVID-19 infection was detected and the date when the last dose of RTX was taken (days)	0.996	0.991–1.001	0.139			
Status of having been infected with COVID-19 more than once	0.897	0.090–8.969	0.926			
Status of having been vaccinated with at least two doses of COVID-19 vaccine before being diagnosed with COVID-19 (%) ($n = 110$)	0.540	0.227–1.286	0.164			
Status of having been vaccinated with at least two doses of COVID-19 vaccine irrespective of the time of diagnosis of COVID-19 infection (%) ($n = 110$)	0.170	0.067–0.431	<i>0.000**</i>	0.179	0.065–0.491	<i>0.001**</i>
Total duration of RTX use (years)	1.014	0.892–1.152	0.836			
Number of comorbidities	1.530	1.202–1.949	<i>0.001**</i>	1.496	1.123–1.993	<i>0.006**</i>
Presence of comorbidities						
Chronic obstructive pulmonary disease (COPD)	1.857	0.295–11.700	0.510			
Hypertension (HT)	4.100	1.516–11.089	0.005			
Chronic kidney disease (CKD)	7.000	1.926–25.439	<i>0.003**</i>			
Diabetes mellitus*	6.978	2.499–19.483	<i>0.000**</i>	7.414	2.637–20.843	<i>0.000**</i>
Asthma	0.714	0.257–1.988	0.519			
Coronary artery disease (CAD)	1.437	0.486–4.252	0.512			
Presence of concomitant malignancy	1.626	0.440–6.011	0.466			
System and/or organ involvement						
Lung involvement	0.727	0.286–1.847	0.503			
Kidney involvement	1.308	0.447–3.826	0.624			
Gastrointestinal system involvement	0.664	0.071–6.189	0.719			
Neurological system involvement	0.768	0.311–1.897	0.568			
Other types of involvement	0.789	0.202–3.087	0.733			
Number of immunosuppressive drugs used	0.792	0.528–1.187	0.259			
Number of cs-DMARDs used	1.195	0.865–1.651	0.281			
Number of b-DMARDs used before starting to take RTX	0.694	0.346–1.390	0.303			
Use of steroids before being diagnosed with COVID-19	1.586	0.574–4.384	0.374			
Dosage of prednisolone used before being diagnosed with COVID-19 (mg)	1.018	0.930–1.116	0.695			
Use of HCQ before being diagnosed with COVID-19	0.842	0.355–2.000	0.697			
Presence of immunoglobulin deficiency	1.736	0.663–4.543	0.261			
IgG deficiency	1.529	0.649–3.604	0.331			
IgM deficiency	1.293	0.559–2.994	0.548			
IgA deficiency	1.314	0.567–3.044	0.524			

n number, *OR* odds ratio, *CI* confidence interval, *p* probability, *RA* rheumatoid arthritis, *RTX* rituximab, *cs-DMARD* conventional synthetic disease-modifying anti-rheumatic drug, *b-DMARD* biological disease-modifying anti-rheumatic drug, *mg* milligram, *HCQ* hydroxychloroquine, *IgG* immunoglobulin G, *IgM* immunoglobulin M, *IgA* immunoglobulin A

*Diabetes mellitus was not abbreviated throughout the text not to lead to any confusion with dermatomyositis, which was abbreviated as DM throughout the text

**Those with *p*-values <0.05 are indicated in italics

of the many factors mentioned [$\text{mean} \pm \text{sd} = 53.9 \pm 14.7$ (median: 56) years], in both the RA and non RA groups. In the RA group, the mean age of patients who died was higher than that of patients who survived. Univariate regression analysis of all patients ($n = 111$) also revealed a significant relationship between COVID-19-related mortality and age. In comparison, the mean age in several cohorts of patients hospitalized for COVID-19 ranged from 49 to 56 years [13–15]. The mean age in the French RMD COVID-19 cohort was reported to be 59.4 ± 16.8 years [11]. The mean age and median age of patients included in this study are comparable to those of cohorts reported in the literature. In addition, the mortality rate was higher in the older patients in this study, as in other studies available in the literature [11].

Analysis of the study group in terms of sex showed that 80.2% of the 111 patients in the study group and 70% of the 30 patients who died were female. Comparison of the subgroups of the two groups RA and not RA and further analysis using the regression model showed no significant association between COVID-19-related mortality and gender. In comparison, several studies conducted with cohorts from the general COVID-19 population reported higher rates of severe COVID-19 infection cases and COVID-19-related deaths in men compared with women [16–18]. In contrast, in several other studies, rates of severe COVID-19 infection cases were comparable in male and female COVID-19 patients [19, 20]. In the French RMD cohort study, the rate in female patients was reported to be 63.2%. In the said study, a significant association was found between female sex and death/severe disease ($\text{OR} = 0.45$, 95% CI: 0.25–0.80) [11].

Analysis of the study group according to comorbidities such as HT, diabetes mellitus, CKD, CHD, COPD, and asthma and their frequency showed that 84.7% of the patients enrolled in the study had one or more of the above comorbidities. The model created with patients diagnosed with RA and not RA showed a significant association between the presence of comorbidities and COVID-19-related mortality in the RA group, but not in the group without RA. On the other hand, there was a significant association between the number of comorbidities and COVID-19-related mortality in the group without RA. Further analyses performed with respect to individual comorbidities revealed a significant association between COVID-19-related mortality and diabetes mellitus in the RA group and between COVID-19-related mortality and HT, CKD, and diabetes mellitus in the non-RA group. All patients who died in both the RA and non-RA groups had at least one concomitant disease. There was at least one comorbidity in 71.8% of patients in the RA group and in 85.7% of patients in the no RA group. In the RA group, 68.4% of deceased patients and 38.5% of surviving patients and in the

group without RA, 100% of deceased patients and 85.7% of surviving patients had HT. In the group without RA, the proportion of patients who had both diabetes mellitus and CKD was 54.5% among deceased patients and 7.1% among surviving patients. Univariate regression analysis revealed a significant association between COVID-19-related mortality and diabetes mellitus and CKD.

In the group without RA, the mean number of comorbidities was 4.4 ± 1.8 (median: 4) in patients who died and 1.8 ± 1.3 (median: 2) in patients who survived. Accordingly, the mean and median number of comorbidities were significantly higher in patients who died than in those who survived. The mean number of comorbidities in all patients was 2.30 ± 1.9 (median: 2). Univariate regression analysis revealed a significant correlation between COVID-19-related mortality and the number of comorbidities. In comparison, the French RMD cohort study found that diabetes mellitus, HT, and chronic renal failure were associated with severe COVID-19 infection in patients with COVID-19 [11]. The results of studies conducted with the general population suggest that several comorbidities are associated with severe COVID-19 infection [21–24]. In a meta-analysis of four studies and 1389 patients with COVID-19 infection (including 273 patients with severe COVID-19 infection), the prevalence of underlying CKD was more common in patients with severe COVID-19 infection (3.3% versus 0.4%; $\text{OR} = 3.03$, 95% CI 1.09–8.47). In the same cohort, a significantly higher number of patients with severe COVID-19 infection were found to have a HT history than patients with nonsevere COVID-19 infection (32% and 15%, respectively) [25].

Although many studies have found that smoking can increase the severity of COVID-19 infection, there are also studies that found no association between smoking and severe COVID-19 infection, similar to this study [26, 27].

In this study, there were 32 (28.8%) patients with a history of infection that required hospitalization. The model created with patients diagnosed at RA and not RA showed that a significantly higher number of patients who died due to COVID-19 infection had a history of infection requiring hospitalization compared with patients who survived COVID-19 infection in both the RA and non RA groups. In the RA group, 21.1% of patients who died due to COVID-19 infection and 12.8% of patients who survived, and in the non RA group, 63.6% of patients who died due to COVID-19 infection and 42.8% of patients who survived had a history of infection requiring hospitalization. A thorough review of the literature did not yield comparable data.

The average duration between the date the infection COVID-19 was detected and the date the last dose of RTX was taken was calculated to be $120.2 + 102.9$ (median: 101)

days, approximately 3 months. For comparison, another study reported the same duration as 5 months [28]. Although both the model created with patients diagnosed with RA and non RA and the regression analyses did not reveal a significant association between COVID-19-related mortality and the mean duration between the date on which the COVID-19 infection was detected and the date on which the last dose of RTX was taken, it was found that the mean and median values of the aforementioned duration were longer in the patients who survived than in the patients who died, both in the RA and in the non RA groups. Indeed, the rapid depletion of B cells associated with RTX use can cause secondary hypogammaglobulinemia, which can take up to 12 months to heal [3].

RTX reportedly impairs the humoral immune response to pneumococcal vaccines (especially polysaccharide vaccines) and influenza vaccines [29–32], whereas, on the other hand, it has become clear that the most important weapon against COVID-19 is vaccines. In this context, the relationship between the effect of RTX on vaccine responses and the mortality rate of patients in this patient population is important. According to WHO, 10,227,670,521 doses of vaccine have been administered through February 13, 2022 [1]. The sample for this study consisted of patients enrolled as of March 2020. The rate of unvaccinated patients before diagnosis of COVID-19 infection in the study group was 47.3%. This rate mirrors the corresponding rate in the general population, considering that the development of the COVID-19 vaccine and the administration of two doses of the vaccine took, on average, approximately 1 year. The model created with patients diagnosed at RA and non RA and the regression analyses showed no significant association between RTX use and response to the vaccine. In this study, only patients who had received at least two doses of any vaccine against COVID-19 infection were considered vaccinated. The proportion of patients who had received at least two doses of COVID-19 vaccine was 72.8% regardless of the time of diagnosis of COVID-19 infection. The model created with patients diagnosed with RA and non RA found that lack of vaccination was a risk factor for mortality in both the RA and non RA groups. Vaccination rates among patients who died due to COVID-19 infection were 44.4% and 45.5% in the RA and non RA groups, respectively. These rates are significantly lower than the vaccination rates among patients who survived COVID-19 infection in the RA and non RA groups, which were 84.6% and 81.0%, respectively. Accordingly, significantly higher mortality rates were observed, particularly in unvaccinated patients. Univariate regression analysis revealed a significant correlation between vaccination with at least two doses of COVID-19 vaccine and COVID-19-related mortality. Despite the attenuation of the immune response observed with the use of RTX, the

vaccines provided protection when the patient population was appropriate and the timing of vaccination was correct.

There were 4 (3.6%) patients who had been infected more than once with COVID-19 and all were RA patients. One of these patients had died. Statistical analysis of the RA group showed no association between status of having been infected more than once with COVID-19 and COVID-19-related mortality rate. Studies have shown that the prevalence of re-infection with COVID-19 is approximately 1% [33]. In most re-infected cases, a mild clinical course was observed and mortality in this patient group was not alarmingly high [34, 35].

Extra-articular involvement of rheumatologic disease is important in both RA progression and COVID-19 infection. In a retrospective study performed on 76 patients with rheumatic disease, 13 patients were found to have COVID-19 infection. Secondary lung involvement due to rheumatologic disease was observed in 7 (53.8%) of these patients, and interstitial lung disease (ILD) was detected in 3 (42.9%) of the aforementioned 7 patients [35]. In the French RMD cohort study, the total number of patients with any lung disease (COPD, asthma, or ILD) was 61/408 (15%), whereas the total number of patients with ILD only was 22/408 (5.4%). Four of these 22 patients had died, and ILD was found to be associated with disease severity (OR = 2.87, 95% CI: 1.06–7.80) [11]. In comparison, a total of 35 (31.5%) patients had pulmonary involvement in this study. COVID-19 infection was severe in all patients with pulmonary involvement, and eight (22.9%) of these patients had died. The model created with patients diagnosed at RA and non RA showed no statistical significance between lung involvement and COVID-19-related mortality in both groups RA and non RA. Univariate regression analysis also revealed no association between COVID-19-related mortality and lung involvement or renal, gastrointestinal, and neurological involvement.

Patients diagnosed with rheumatologic disease may have a concomitant malignancy prior to diagnosis or during the course of the disease. Both the concomitant malignancy and the chemotherapeutic agents administered in this setting may lead to a weakening of the immune system. In this study, there were 11 (9.9%) patients with a history of malignancy. Statistical analyses revealed no significant association between a history of malignancy and COVID-19 mortality. However, rates of patients concomitantly diagnosed with malignancy were higher in patients who died from COVID-19 infection than in patients who survived COVID-19 infection in both the RA and non RA groups. Also in the French RMD cohort study, 22/408 (5.4%) patients had cancer, but no significant association was found between malignancy and COVID-19 severity or COVID-19-related mortality [11].

Glucocorticoids are used in the treatment of COVID-19 infection and especially in the treatment of cases with a severe clinical course. In a meta-analysis of seven trials involving a total of 1703 critically ill COVID-19 patients, steroids reduced 28-day mortality compared with standard treatment or placebo (40% vs. 32%, OR = 0.66, 95% CI 0.53–0.82) [36]. However, another study found that long-term use of corticosteroids in the treatment of COVID-19 patients with inflammatory arthritis increased the risk of severe COVID-19 infection and/or COVID-19-related mortality [37]. Similarly, in the French RMD cohort study, corticosteroid use [aOR (adjusted odds ratio) = 2.64, 95% CI: 1.36–5.12] was associated with higher COVID-19-related mortality [11]. In comparison, this study found that 82 (73.9%) patients were taking steroids before diagnosis of COVID-19 infection, that the mean prednisolone dose was 4.5 ± 5.0 (median: 5) mg, and that 16 (14.4%) patients were taking 7.5 mg or more prednisolone (medium or high dose). Both the model created with patients diagnosed with RA and non RA and the univariate regression analysis showed no significant association between steroid use and COVID-19-related mortality. Consequently, the advantages of steroid use in the treatment of rheumatologic diseases and COVID-19 infection appear to outweigh the disadvantages, provided they are used in a timely manner.

In one of the COVID-19 Global Rheumatology Alliance case series conducted between March 24, 2020, and April 20, 2020, involving 600 patients with rheumatologic disease and COVID-19 infection, it was found that the use of anti-TNF (tumor necrosis factor) drugs was associated with a lower risk of hospitalization (OR = 0.40, 95% CI = 0.19–0.81). In addition, it was determined that the use of cs-DMARDs either alone or in combination with biologic therapy or Janus kinase (JAK) inhibitors was not associated with an increased risk of hospitalization [37]. In contrast, the results of a study conducted in the Lombardy region of Italy of 1193 psoriasis patients receiving biologic agents or conventional small molecule drugs revealed that the use of biologic agents was significantly correlated with a higher risk of being symptomatic compared with the general population in the region, but was not correlated with an increased risk of death [38]. In comparison, in this study, the rate of patients using at least one immunosuppressive drug other than RTX was 48.6%, and the mean number of the immunosuppressive drugs used was 0.90 ± 1.1 . Both the model created with patients diagnosed with RA and non RA and the univariate regression analysis showed no significant association between the use of immunosuppressive drugs and COVID-19-related mortality.

All patients enrolled in this study were taking at least one cs-DMARD. The mean number of cs-DMARDs used was 2.4 ± 1.3 (median: 3). On the other hand, there were 39 (35.1%) patients taking b-DMARDs before initiation of

RTX treatment, and the median number of b-DMARDs used was calculated to be 0.4 ± 0.6 . Both the model created with patients diagnosed with RA and non RA diseases and the univariate regression analysis revealed no significant association between COVID-19-related mortality and the use of cs-DMARDs or the use of b-DMARDs before the start of RTX treatment.

Although HCQ was used to treat COVID-19 during the pandemic, the results of studies available in the literature and clinical data on the efficacy of HCQ collected as part of the COVID-19 Global Rheumatology Alliance showed that HCQ did not protect patients with lupus from COVID-19 infection [39]. Also, in another study, no significant difference was found between SLE patients taking antimalarials, including HCQ, and SLE patients not taking antimalarials in the development of COVID-19 disease or severe COVID-19 disease [40]. In parallel, the French RMD cohort study found that HCQ use was not associated with the development of severe COVID-19 disease ($n = 57$, aOR = 1.06, 95% CI: 0.31–2.96). In comparison, there were 44 (39.6%) patients in this study who had taken HCQ before the diagnosis of COVID-19 infection [11]. However, both the model created with patients diagnosed with RA and non RA and the univariate regression analysis showed no significant association between COVID-19-related mortality and HCQ use before diagnosis of COVID-19 infection.

In fact, RTX does not significantly reduce the amount of antibody present. This is because antigen-specific IgGs are produced by other plasma cells that do not express surface CD20 [41]. However, some patients may develop hypogammaglobulinemia, which can be persistent and clinically significant, leading to severe infections requiring antibiotic prophylaxis or immunoglobulin replacement therapy [42, 43]. In a study available in the literature, several risk factors for long-term and severe hypogammaglobulinemia were identified in RA patients treated with RTX, including repeated RTX treatments, advanced age, and concurrent glucocorticoid therapy. Serious infections were specifically reported in 7% of patients with IgM-type hypogammaglobulinemia, and the overall infection rate was found to be 4.3 per 100 patient-years. The most common serious infection reported was pneumonia [44]. In comparison, there were 76 (68.5%) patients with immunoglobulin deficiency in this study. There was a significant association between immunoglobulin deficiency, regardless of the type of immunoglobulin, and COVID-19-related mortality in the group without RA ($p = 0.037$). The distribution of immunoglobulin deficiencies by type of immunoglobulin showed that 71 (64.0%) patients had low IgG, 57 (51.4%) patients had low IgM, and 61 (55.0%) patients had low IgA. The model created with patients diagnosed at RA and non RA showed that IgG, IgM, and IgA deficiencies were higher in patients who died due to

COVID-19 than in patients who survived in the RA group. In contrast, in the group without RA, IgG, IgM, and IgA deficiencies were higher in patients who survived COVID-19 than in patients who died due to COVID-19. However, both the model created with patients diagnosed with RA and non RA and the univariate regression analysis showed no statistical association between COVID-19-related mortality and IgA, IgM, or IgG deficiencies.

To summarize, age, age at diagnosis, vaccination status against COVID-19 infection, number of comorbidities and the presence of HT, the presence of CKD, and the presence of diabetes mellitus, which were found to be significantly correlated with COVID-19-related mortality in the univariate regression analysis, were further analyzed using multivariate regression analysis. Multivariate regression analysis revealed that age, presence of CKD, and presence of diabetes mellitus were significantly correlated with COVID-19-related mortality.

Limitations of the study

The fact that the study was a single-center retrospective study was its main limitation. Therefore, multicenter studies with larger samples are needed to validate the results of this study.

Conclusion

Although RTX is an effective and safe medication for the treatment of rheumatologic diseases, provided it is used for the appropriate indication, at the right time, and at the appropriate dose, it may still cause an increased risk of infection due to its immunosuppressive effects. In this context, the severity of the clinical course of COVID-19 disease and its mortality rate in patients who received RTX and became infected with COVID-19 have attracted attention. The COVID-19-related mortality rate of patients included in this study who became infected with COVID-19 while receiving RTX was 27.0% (30/111). It was observed that especially elderly patients who had comorbidities, who were either incompletely vaccinated or not vaccinated at all, were at higher risk for COVID-19-related mortality.

In conclusion, the findings of this study indicate that all patients with systemic rheumatologic diseases should be fully vaccinated against COVID-19 in the first instance. Complete vaccination is even more important in this patient population because the use of RTX is expected to decrease vaccine efficacy. Therefore, patients with rheumatologic diseases should receive the vaccine doses within the recommended intervals, should not skip any vaccine doses, and should receive the reminder doses. In addition, in patients whose general condition is good and in whom the disease

is under control, the RTX dose should be reduced, the RTX treatment should be discontinued, or it should be replaced by another treatment during the pandemic period if possible. Multicenter studies with larger samples are needed to validate the findings of this study.

Abbreviations COVID-19: Coronavirus disease 2019; WHO: World Health Organization; HT: Hypertension; CHD: Coronary heart disease; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; RTX: Rituximab; Anti-CD20: Cluster of differentiation 20 antibody; RT-PCR: Reverse transcription-polymerase chain reaction; DMARDs: Disease-modifying anti-rheumatic drugs; HCQ: Hydroxychloroquine; IgG: Immunoglobulin G; IgA: Immunoglobulin A; IgM: Immunoglobulin M; ACR: American College of Rheumatology; EULAR: The European Alliance of Associations for Rheumatology; RA: Rheumatoid arthritis; GPA: Granulomatous polyangiitis; MPA: Microscopic polyangiitis; EGPA: Eosinophilic granulomatous polyangiitis; SLE: Systemic lupus erythematosus; pSS: Primary Sjogren's syndrome; SSc: Systemic sclerosis; PM: Polymyositis; DM: Dermatomyositis; CI: Confidence interval; *p*: Probability; b-DMARDs: Biological disease-modifying anti-rheumatic drugs; cs-DMARDs: Conventional synthetic disease-modifying anti-rheumatic drugs; min.: Minimum; max.: Maximum; IVIG: Intravenous immune globulin; *n*: Number; sd: Standard deviation; mg: Milligram; RMD: Rheumatic and musculoskeletal disease; ILD: Interstitial lung disease; aOR: Adjusted odds ratio; anti-TNF: Anti-tumor necrosis factor; JAK: Janus kinase

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Author contribution We are four co-authors: Ali Ekin, Belkıs Nihan Coşkun, Ediz Dalkılıç, Yavuz Pehlivan. Ali Ekin is the owner of the research topic and organized the research team. Ali Ekin and Belkıs Nihan Coşkun were responsible for the writing of the article and reached the patients' data. Yavuz Pehlivan was responsible for the statistics of the study. Ali Ekin and Ediz Dalkılıç reviewed the literature. Yavuz Pehlivan and Ediz Dalkılıç designed study and analyzed data.

Availability of supporting data and materials The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate The study protocol was approved by the Clinical Research Ethics Committee of the Faculty of Medicine, Uludağ University, Bursa, Turkey, by Decision No. 2021-17/38.

Consent for publication All participants gave their informed consent to publication.

Competing interests The authors declare no competing interests.

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