

# Clinical Course and Outcomes of COVID-19 Infection in Patients Treated with Rituximab: A Tertiary Care Center Experience

Thamer S Alhawaish<sup>1,2</sup>, Moustafa S Alhamadh<sup>2,3</sup>, Alaa Mathkour<sup>4</sup>, Marwan Alamoudi<sup>2,5</sup>, Hossam Ali Alqahtani<sup>1,2</sup>, Abdulrahman Alrashid<sup>2,3,5</sup>

<sup>1</sup>Division of Neurology, King Abdulaziz Medical City, Ministry of the National Guard Health Affairs, Riyadh, Kingdom of Saudi Arabia; <sup>2</sup>King Abdullah International Medical Research Center, Ministry of the National Guard Health Affairs, Riyadh, 11481, Kingdom of Saudi Arabia; <sup>3</sup>College of Medicine, King Saud Bin Abdulaziz University for Health Sciences (KSAUHS), Ministry of the National Guard-Health Affairs, Riyadh, 14611, Kingdom of Saudi Arabia; <sup>4</sup>Ministry of Health, Riyadh, 12613, Kingdom of Saudi Arabia; <sup>5</sup>Department of Medicine, Division of Rheumatology, King Abdulaziz Medical City, Ministry of the National Guard-Health Affairs, Riyadh, Kingdom of Saudi Arabia

Correspondence: Thamer S Alhawaish, Division of Neurology, Department of Medicine, King Abdulaziz Medical City, Ministry of the National Guard Health Affairs, P.O. Box 22490, Riyadh, 11426, Kingdom of Saudi Arabia, Email Thamersa18@gmail.com

**Introduction:** Patients receiving rituximab (RTX) may be at increased risk for severe Coronavirus infections and worse outcomes compared with the general population. Because of the conflicting results concerning the effect of RTX on the clinical course and outcomes of COVID-19 infection, we aimed to share our experience with 35 patients infected with COVID-19 while treated with RTX for a variety of clinical indications.

**Methods:** This was a single-centre retrospective cohort study that included 35 patients. All patients aged  $\geq 14$  years who were treated with RTX for various conditions and were found to have COVID-19 infection were included. Patients with poor outcomes or patients with suspected COVID-19 infection were excluded.

**Results:** The patients' mean age was  $42.8 \pm 16.3$  years with an average BMI of  $29.9 \pm 11.4$  kg/m<sup>2</sup>. Over half (51.4%, n = 18) of the patients received RTX at a dose of 375 mg/m<sup>2</sup> with a median frequency of 4 doses. More than a third (37.1%, n = 13) of the patients had hypogammaglobulinemia and 25.7% had low CD19. Over a third (42.9%, n = 15) of the patients required hospitalization and almost a third (25.7%, n = 9) required treatment in the intensive care unit. There was a statistically significant association between intensive care unit admission and age, steroid use, and low CD19. The mortality rate was 25.7%, and it was significantly higher in elderly, diabetics, corticosteroid users, patients who were hospitalized, treated in the intensive care unit, and had low immunoglobulin or CD19.

**Conclusion:** Treatment with RTX seems to be a potential risk factor for unfavorable outcomes in COVID-19 patients. RTX should be used with caution or avoided unless the benefit clearly outweighs the risk.

**Keywords:** rituximab, SARS-CoV-2, COVID-19, autoimmunity, hypogammaglobulinemia, rheumatology

## Introduction

Coronavirus is an enveloped, single-stranded RNA virus. Infection with this virus was first reported in Wuhan, China, in December 2019, and it was declared a pandemic in March 2020. Coronavirus disease 2019 (COVID-19) may present as mild to moderate, self-limiting respiratory symptoms such as fever, loss of taste and smell, cough, and shortness of breath, but in some patients, it may be severe enough to require hospitalization and intubation with mechanical ventilation.<sup>1</sup>

Rituximab (RTX) is a monoclonal antibody that is used for the treatment of numerous diseases, including rheumatologic, hematologic, nephrologic, neurologic, and oncologic conditions.<sup>2</sup> RTX targets the B-cell transmembrane protein CD20, leading to B-cell destruction. As a result, RTX suppresses the humoral immunity via B-cell depletion. Although

generally well-tolerated with only mild adverse effects such as infusion reactions, headache, and chills, RTX can induce severe immunosuppression, resulting in hypogammaglobulinemia, neutropenia, and reactivation of viral infections.<sup>3</sup>

There is no consensus on whether immunosuppressive and immunomodulatory agents negatively affect the clinical course and outcome of COVID-19 infection.<sup>4</sup> To emphasize, some studies found that patients who were already taking immunosuppressive agents are more susceptible to COVID-19 infection and worse outcomes.<sup>1,5</sup> More specifically, multiple studies suggested that patients treated with RTX are at increased risk for severe COVID-19 infection and worse outcomes compared to the general population. Also, several reports revealed higher rates of COVID-19-related hospitalization, respiratory failure requiring intubation and mechanical ventilation, and mortality in patients treated with RTX.<sup>3,6,7</sup>

A descriptive study by Martos et al of SARS-CoV-2 infections in patients with rheumatic diseases treated with RTX showed a high rate of severe illness requiring hospitalization (61.5%) and a high mortality rate (23.1%). Similarly, a cohort study by Singh et al showed that the use of RTX in patients with rheumatoid arthritis was associated with worse COVID-19 outcomes such as hospitalization (26%) and ICU admission (6.6%) than in patients receiving conventional synthetic disease-modifying anti-rheumatic drugs.<sup>3</sup>

Because of the variable results of different studies on the effect of RTX on the course and outcome of COVID-19 infection and because of the limited literature in Saudi Arabia, we aimed to investigate the outcome of COVID-19 infection in patients who received RTX during the period of the COVID-19 pandemic in Saudi Arabia.

## Materials and Methods

### Aim

To evaluate the clinical course and outcomes of COVID-19 infection among patients treated with RTX for a variety of clinical indications.

### Study Design/Setting

This was a retrospective cohort study conducted at King Abdulaziz Medical City (KAMC), Ministry of National Guard-Health Affairs (MNG-HA), Riyadh, Kingdom of Saudi Arabia. KAMC is an academic, government-funded tertiary hospital that combines clinical care, training, and academics with research and state of the art medical technologies.

### Inclusion and Exclusion Criteria

Patients aged  $\geq 14$  years who were treated with RTX for autoimmune connective tissue diseases, hematologic malignancies, benign hematologic diseases, neurologic diseases, or glomerular diseases and had PCR-proven COVID-19 infection were included. Patients who had a poor outcome due to severe underlying disease before infection with COVID-19 or patients with suspected infection with COVID-19 were excluded. After applying the aforementioned criteria, only 35 patients were eligible for inclusion.

### Data Collection

Electronic medical records (via the KAMC electronic system - BestCare; Seoul, South Korea: ezCaretech Co) were used to obtain data of all patients who met our inclusion criteria, from 2019 to 2021. The data collected included the following: demographic data such as age, gender, and body mass index, comorbidities including diabetes mellitus (DM), hypertension (HTN), and chronic kidney disease (CKD), the primary diagnosis for which RTX was used, RTX dose, number of RTX doses, other immunosuppressants used, immunoglobulin (IgG, IgM, and IgA) levels, CD19 levels, presenting signs and symptoms of COVID-19, chest x-ray findings on admission, ferritin levels, site of treatment (outpatient, inpatient, or intensive care unit (ICU)), and outcomes (survival or death).

### Statistical Analysis

Statistical analysis was performed with SPSS version 28 (IBM Co., Armonk, NY, USA).

Quantitative nonparametric data were presented as median and interquartile range (IQR) and analyzed with the Mann Whitney test. Categorical variables were presented as frequency and percentage (%) and analyzed with the Chi-square test or Fisher's exact test, as appropriate. A two tailed P value < 0.05 was considered statistically significant.

## Ethical Considerations

This study was approved by the Institutional Review Board of the King Abdullah International Medical Research Center, Ministry of National Guard-Health Affairs, Riyadh, Kingdom of Saudi Arabia (RC20/693/R). Because this was a retrospective study, informed consent was waived. Access to the data was restricted to the investigators. Patient confidentiality and privacy were maintained, and no names or medical record numbers were used, and all data were stored in a secure location at National Guard-Health Affairs. This study complies with the Declaration of Helsinki.

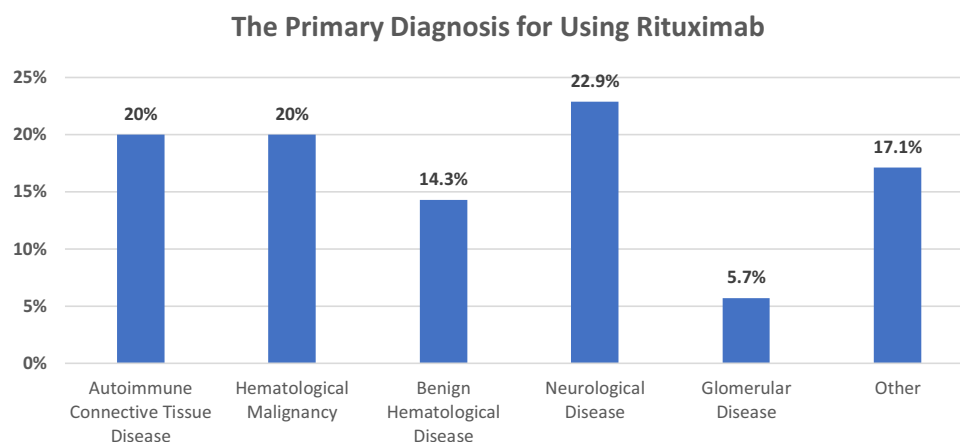
## Results

### Baseline Characteristics

A total of 35 patients (15 men and 20 women) were included. The patients' mean age was  $42.8 \pm 16.3$  years, and over two-thirds (65.9%,  $n = 23$ ) of them were  $\leq 50$  years old. About half of the patients (48.6%,  $n = 17$ ) were obese with an average BMI of  $29.9 \pm 11.4$  kg/m<sup>2</sup>. The most prominent comorbid condition was HTN, followed by DM and CKD, accounting for 28.6%, 25.7%, and 25.7%, respectively. The most common primary diagnoses for using RTX were neurologic diseases (22.9%), autoimmune connective tissue diseases (20%), and hematological malignancies (20%) [Figure 1](#). Over half (51.4%,  $n = 18$ ) of the patients received RTX at a dose of 375 mg/m<sup>2</sup>, around a third (37.1%,  $n = 13$ ) at a dose of 1000 mg/m<sup>2</sup>, and only a few (11.4%,  $n = 4$ ) at a dose of 500 mg/m<sup>2</sup>. The median frequency of RTX administration was 4 times with an IQR of 3 to 6 times. More than half (51.4%) of the patients were on corticosteroids, and a few were on azathioprine (14.3%), mycophenolate (14.3%), and hydroxychloroquine (11.4%). Hypogammaglobulinemia, defined as low IgG, IgM, and/or IgA, was diagnosed in 37.1% of the patients and 25.7% had low CD19. The mortality rate was 25.7% as shown in [Table 1](#)

### COVID-19 Data

As summarized in [Table 2](#), 22.9% of the patients had symptomatic COVID-19 infection. The most common presenting symptoms were lower respiratory symptoms, which were reported by more than half (60%,  $n = 21$ ) of the patients, followed by gastrointestinal and neurological symptoms, each reported by 17.1%. Chest radiography revealed pneumonia in 22.9% and bilateral airspace opacities in 17.1%. More than half (57.1%,  $n = 20$ ) of the patients were treated as outpatients, and 25.7% were admitted to ICU.



**Figure 1** The Primary Diagnosis for Using Rituximab.

**Table 1** Baseline Characteristics of the Studied Patients (n=35)

	<b>N</b>	<b>%</b>
<b>Age</b>		
≤30 Years	8	22.9
31–50 Years	15	42.9
≥51 Years	12	34.3
<b>Gender</b>		
Male	15	42.9
Female	20	57.1
<b>BMI</b>		
Non-obese	18	51.4
Obese	17	48.6
<b>Comorbidities</b>		
Diabetes Mellitus	9	25.7
Hypertension	10	28.6
Chronic Kidney Disease	9	25.7
Cr (μmol/L)	<b>Median</b>	<b>IQR</b>
	61	50–82
<b>Rituximab Dose</b>		
375 mg/m <sup>2</sup>	18	51.4
500 mg	4	11.4
1000 mg	13	37.1
<b>Number of rituximab doses</b>	<b>Median</b>	<b>IQR</b>
	4	3–6
<b>Immunosuppressants</b>		
Steroids	18	51.4
Methotrexate	2	5.7
Azathioprine	5	14.3
Mycophenolate	5	14.3
Hydroxychloroquine	4	11.4
Cyclophosphamide	2	5.7
Cyclosporine	2	5.7
Tocilizumab	3	8.6
R-CHOP Protocol	3	8.6

(Continued)

**Table 1** (Continued).

	N	%
<b>Immunoglobulins</b>		
Hypogammaglobulinemia	13	37.1
Low CD19	9	25.7
<b>Outcome</b>		
Alive	26	74.3
Dead	9	25.7

**Abbreviations:** BMI, Body mass index; R-CHOP, A protocol including rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

**Table 2** COVID-19 Data Among the Studied Patients (n=35)

	N	%
<b>Symptomatic COVID-19 Infection</b>		
No	27	77.1
Yes	8	22.9
<b>Presenting Signs and Symptoms</b>		
Lower Respiratory Symptoms	21	60.0
Gastrointestinal Symptoms	6	17.1
Other	6	17.1
Upper Respiratory Symptoms	5	14.3
Fever	3	8.6
<b>Chest X-Ray Findings</b>		
Not Done	16	45.7
Normal	5	14.3
Pneumonia	8	22.9
Bilateral Airspace Opacities	6	17.1
<b>Site of Care</b>		
Outpatients	20	57.1
Inpatients	15	42.9
Intensive Care Unit Admission	9	25.7

## Mortality

Comparison between survivors and nonsurvivors revealed a statistically significant difference in age, as nonsurvivors were older than those who recovered ( $P=0.016$ ). Compared with the recovered patients, the nonsurvivors had higher rates of DM (55.6% vs 15.4%,  $P=0.03$ ), steroid administration (88.9% vs 38.5%,  $P=0.018$ ), inpatient care (77.8% vs 30.8%,  $P=0.022$ ), and ICU admission (66.7% vs 11.5%,  $P=0.003$ ). Nonsurvivor patients had significantly lower immunoglobulins (hypogammaglobulinemia) than the survivors (77.8% vs 23.1%,  $P=0.006$ ), manifested by an abnormal decrease in

**Table 3** Association Between Mortality and Patients' Characteristics, Outcome

	Alive (n=26)	Dead (n=9)	P- value
Age			
≤30 Years	8 (30.8%)	0 (0%)	0.016
31–50 Years	12 (46.2%)	3 (33.3%)	
≥51 Years	6 (23.1%)	6 (66.7%)	
Gender			
Male	11 (42.3%)	4 (44.4%)	>0.999
Female	15 (57.7%)	5 (55.6%)	
BMI			
Non-obese (BMI less than 30)	13 (50%)	5 (55.6%)	>0.999
Obese (BMI of 30 or more)	13 (50%)	4 (44.4%)	
Comorbid Conditions			
Diabetes Mellitus	4 (15.4%)	5 (55.6%)	0.03
Hypertension	7 (26.9%)	3 (33.3%)	0.694
Chronic Kidney Disease	6 (23.1%)	3 (33.3%)	0.665
Creatine level (μmol/L)	63 (54.75–84.25)	58 (44–89.5)	0.282
Primary Diagnosis for Rituximab			
Autoimmune Connective Tissue Disease	3 (11.5%)	4 (44.4%)	0.083
Hematological Malignancy	4 (15.4%)	3 (33.3%)	
Benign Hematological Disease	4 (15.4%)	1 (11.1%)	
Neurological Disease	7 (26.9%)	1 (11.1%)	
Glomerular Disease	2 (7.7%)	0 (0%)	
Other	6 (23.1%)	0 (0%)	
Rituximab Dose			
375 mg/m <sup>2</sup>	14 (53.8%)	4 (44.4%)	0.866
500 mg/m <sup>2</sup>	3 (11.5%)	1 (11.1%)	
1000 mg/m <sup>2</sup>	9 (34.6%)	4 (44.4%)	
Number of rituximab Doses	4 (3–5)	5 (3–9)	0.277
Immunosuppressants			
Steroids	10 (38.5%)	8 (88.9%)	0.018
Methotrexate	1 (3.8%)	1 (11.1%)	0.454
Azathioprine	3 (11.5%)	2 (22.2%)	0.586
Mycophenolate	4 (15.4%)	1 (11.1%)	>0.999
Hydroxychloroquine	2 (7.7%)	2 (22.2%)	0.268

(Continued)

**Table 3** (Continued).

	<b>Alive (n=26)</b>	<b>Dead (n=9)</b>	<b>P- value</b>
Cyclophosphamide	2 (7.7%)	0 (0%)	>0.999
Cyclosporine	2 (7.7%)	0 (0%)	>0.999
R-CHOP Protocol	2 (7.7%)	1 (11.1%)	>0.999
<b>Ferritin level (ng/mL)</b>	273.6 (60.4–788.6)	1708.6 (269–12,130.3)	0.086
<b>Site of Care</b>			
Outpatient	18 (69.2%)	2 (22.2%)	<b>0.022</b>
Inpatient	8 (30.8%)	7 (77.8%)	
<b>ICU</b>	3 (11.5%)	6 (66.7%)	<b>0.003</b>
<b>Immunoglobulins</b>			
Hypogammaglobulinemia	6 (23.1%)	7 (77.8%)	<b>0.006</b>
Hypo-IgG	2 (7.7%)	4 (44.4%)	<b>0.027</b>
Hypo-IgM	6 (23.1%)	6 (66.7%)	<b>0.038</b>
Hypo-IgA	2 (7.7%)	1 (11.1%)	>0.999
Low CD19	4 (15.4%)	5 (55.6%)	<b>0.03</b>
<b>Duration between the last rituximab dose and COVID-19 infection (months). 6–12 month after ritx</b>	7.1 (3.8–12.04)	2.1 (0.25–19.4)	0.291

**Note:** Bold P-values indicate statistically significant.

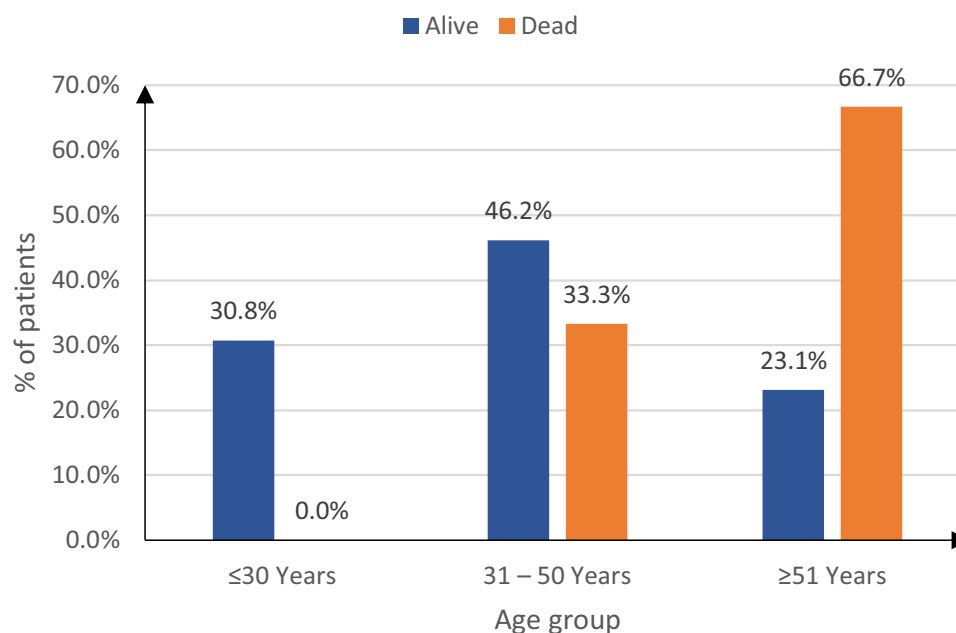
either IgG (44.4% vs 7.7%), IgM (66.7% vs 23.1%), or IgA (11.1% vs 7.7%, which was similar between the two groups). Moreover, nonsurvivors had lower CD19 levels than survivors (55.6% vs 15.4% respectively had low CD19,  $P=0.03$ ) as summarized in [Table 3](#), [Figures 2–4](#).

## Intensive Care Unit Admission

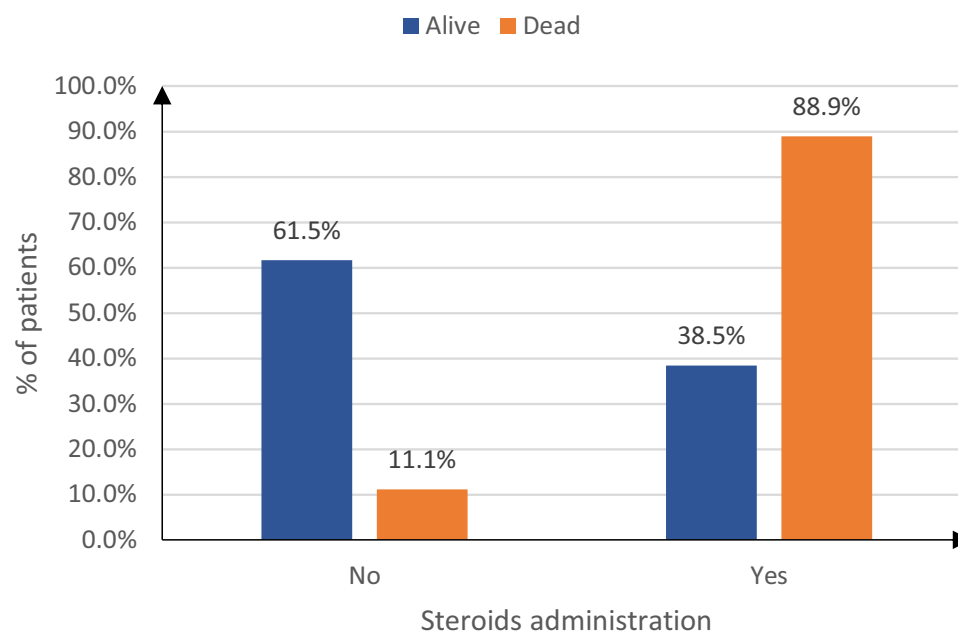
As shown in [Table 4](#), there was a statistically significant association between ICU admission and age, as patients who were admitted to the ICU were older than those who were not admitted ( $P=0.045$ ). Compared with patients who were not admitted to the ICU, patients admitted to the ICU had higher rates of steroid use (88.9% vs 38.5%,  $P=0.018$ ) and lower CD19 levels (55.6% vs 15.4%,  $P=0.03$ ). Patients admitted to the ICU had a higher mortality rate (66.7% vs 11.5%,  $P=0.003$ ) ([Figure 5](#)).

## Discussion

In this study, we sought to evaluate the outcome of COVID-19 infection in patients who received RTX for various underlying diseases in Saudi Arabia. We found that RTX at a dose of 375 mg/m<sup>2</sup> was the most commonly used protocol. Corticosteroids were used in more than half of the patients. This study showed that a large number of RTX receivers were found to have hypogammaglobulinemia and low CD19. Our study showed a relatively high mortality rate among patients treated with RTX. In addition, patients treated with RTX who did not survive tended to be older, diabetic, taking steroids, and hospitalized or admitted to ICU. Also, hypogammaglobulinemia and lower CD19 levels were found to be associated



**Figure 2** Association between mortality and age of the studied patients.



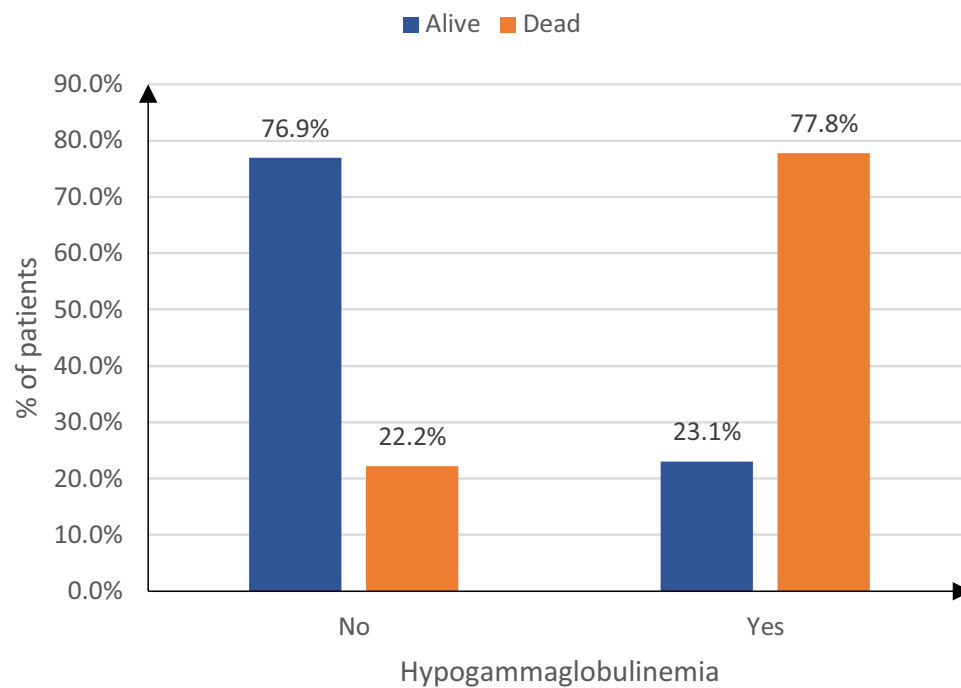
**Figure 3** Association between mortality and steroids administration of the studied patients.

with a high mortality rate. Moreover, this study showed that there was a statistically significant association between ICU admission and age, steroid use, and low CD19 levels.

Most of our patients were young females, and the most common cause of RTX use was autoimmune diseases such as multiple sclerosis and myasthenia gravis. This can be explained by the fact that autoimmune diseases tend to affect young individuals and have a female tendency.<sup>1,8</sup>

Some previous reports found that the use of RTX does not worsen the outcomes of patients with COVID-19 and is not associated with disease progression.<sup>9</sup> Our study shows a mortality rate of 25.7% in patients treated with RTX.<sup>1</sup> In





**Figure 4** Association between mortality and hypogammaglobulinemia rate of the studied patients.

addition, a large proportion of our cohort were hospitalized (42.9%) and required treatment in the ICU (25.7%). MacKenna et al reported that patients receiving RTX had an increased risk of COVID-19-related hospitalization, ICU admissions, and deaths compared with patients receiving standard systemic therapy.<sup>8</sup> Similarly, a cohort study by Singh

**Table 4** Association Between ICU Admission and Patients' Characteristics, Outcome

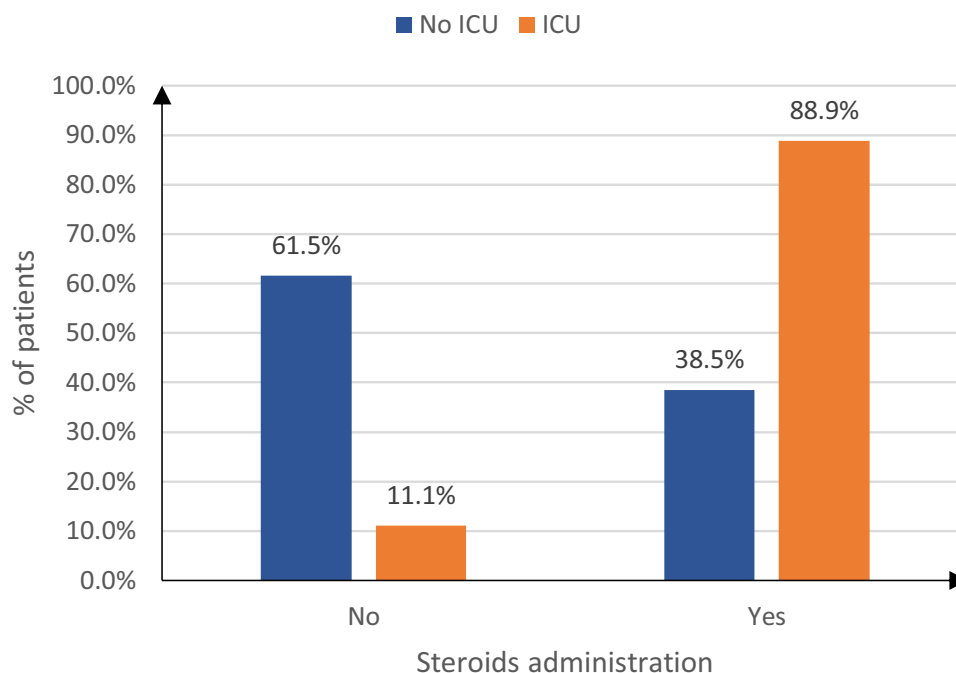
	No ICU (n=26)	ICU (n=9)	P- value
Age			
≤30 Years	8 (30.8%)	0 (0%)	0.045
31–50 Years	11 (42.3%)	4 (44.4%)	
≥51 Years	7 (26.9%)	5 (55.6%)	
Gender			
Male	12 (46.2%)	3 (33.3%)	0.7
Female	14 (53.8%)	6 (66.7%)	
BMI			
Non-obese (BMI less than 30)	11 (42.3%)	7 (77.8%)	0.121
Obese (BMI of 30 or more)	15 (57.7%)	2 (22.2%)	
Comorbid Conditions			
Diabetes Mellitus	6 (23.1%)	3 (33.3%)	0.665
Hypertension	8 (30.8%)	2 (22.2%)	>0.999
Chronic Kidney Disease	7 (26.9%)	2 (22.2%)	>0.999
Creatine level (μmol/L)	63 (50–101)	44 (34–72.75)	0.101

(Continued)

**Table 4** (Continued).

	No ICU (n=26)	ICU (n=9)	P- value
Primary Diagnosis for Rituximab			
Autoimmune Connective Tissue Disease	4 (15.4%)	3 (33.3%)	0.109
Hematological Malignancy	4 (15.4%)	3 (33.3%)	
Benign Hematological Disease	5 (19.2%)	0 (0%)	
Neurological Disease	6 (23.1%)	2 (22.2%)	
Glomerular Disease	1 (3.8%)	1 (11.1%)	
Other	6 (23.1%)	0 (0%)	
Rituximab Dose			
375 mg/m <sup>2</sup>	15 (57.7%)	3 (33.3%)	0.352
500 mg/m <sup>2</sup>	2 (7.7%)	2 (22.2%)	
1000 mg/m <sup>2</sup>	9 (34.6%)	4 (44.4%)	
No of Rituximab Doses	4 (2.7–5)	5 (3.5–7.5)	0.164
Immunosuppressants			
Steroids	10 (38.5%)	8 (88.9%)	0.018
Methotrexate	1 (3.8%)	1 (11.1%)	0.454
Azathioprine	3 (11.5%)	2 (22.2%)	0.586
Mycophenolate	4 (15.4%)	1 (11.1%)	>0.999
Hydroxychloroquine	2 (7.7%)	2 (22.2%)	0.268
Cyclophosphamide	2 (7.7%)	0 (0%)	>0.999
Cyclosporine	2 (7.7%)	0 (0%)	>0.999
R-CHOP Protocol	3 (11.5%)	0 (0%)	0.553
Ferritin level (ng/mL)	273.6 (60.4–935.4)	585.6 (269–2873.5)	0.252
Immunoglobulins			
Hypogammaglobulinemia	8 (30.8%)	5 (55.6%)	0.243
Hypo-IgG	3 (11.5%)	3 (33.3%)	0.162
Hypo-IgM	8 (30.8%)	4 (44.4%)	0.686
Hypo-IgA	1 (3.8%)	2 (22.2%)	0.156
Low CD19	4 (15.4%)	5 (55.6%)	0.03
Outcome			
Alive	23 (88.5%)	3 (33.3%)	0.003
Dead	3 (11.5%)	6 (66.7%)	
Duration between the last rituximab dose and COVID-19 infection (months)	6.67 (3.8–12.04)	2.1 (0.25–18.83)	0.497

**Note:** Bold P-values indicate statistically significant.



**Figure 5** Association between ICU admission and steroids administration of the studied patients.

et al showed that RTX use in patients with rheumatoid arthritis is associated with worse COVID-19 outcomes such as hospitalization (26%) and ICU admission (6.6%) compared to those on conventional synthetic disease modifying anti-rheumatic drugs. Likewise, a descriptive study by Martos et al of SARS-CoV-2 infections in patients with rheumatic diseases treated with RTX showed a high rate of severe illness requiring hospitalization (61.5%) and a high mortality rate (23.1%).<sup>3</sup> In agreement with ours, Tepasse et al, Stradner et al, and Alpizar-Rodriguez et al also reported that RTX use was associated with a higher risk of severe disease and/or mortality in patients with COVID-19 infection.<sup>9,10</sup>

Some immunosuppressants selectively target T lymphocytes and suppress their function, such as calcineurin inhibitors, while largely preserving B cell activity. However, other immunosuppressants, such as RTX, an anti-CD20 monoclonal antibody, result in complete depletion of B cells and suppress B cell functions such as immunoglobulin production. Therefore, the rapid depletion of B cells associated with RTX use can cause secondary hypogammaglobulinemia, which may be persistent or take up to 12 months to recover. Patients with hypogammaglobulinemia develop impaired opsonization and do not form antibodies to exposed antigens. Therefore, these patients develop susceptibility to infection and to the complications that can occur as a result of infection, which may necessitate hospitalization and/or ICU admission.<sup>9,11</sup> There are case reports of persistent COVID-19 infection or delayed serological response to COVID-19 vaccination in patients receiving RTX therapy. These data raise concerns that RTX may directly influence adaptive immune response, which is important for the control and clearance of viral infections.<sup>12</sup>

It is unclear whether the underlying primary diagnosis for which RTX is used alone or in combination with the effect of RTX use and/or additional risk factors, influences mortality. Suppressed immunity and comorbidities are considered the main reasons for the increased infection and mortality rates of COVID-19 in these patients.<sup>13,14</sup> Mortality was reported in a quarter (25.7%) of our patients who were treated with RTX. Also, Ekin et al showed that the mortality rate was 27% in patients with rheumatologic diseases who received RTX.<sup>11</sup> In a study of the outcomes of COVID-19 in patients with inflammatory rheumatic diseases, the mortality rate was 11.5% in patients on RTX, which is consistent with some other studies.<sup>1</sup> For clarification, Montero et al mentioned a mortality rate of 16%, and Sharmeen et al reported a mortality rate of 5.9%.<sup>15,16</sup> However, A cohort study by Singh et al and the French national study did not find an association with an increased risk of death in the RTX-exposed vs not-exposed group.<sup>12,17</sup> The differences between these

studies could be due to different underlying diseases for which RTX was used. This could also explain the high mortality rate in our study because we included different disease groups such as cancer patients and not only inflammatory rheumatic diseases. Moreover, from these studies, it appears that patients receiving RTX have a higher mortality rate than patients receiving other immunosuppressants. As in our study and in previous studies, patients receiving RTX may have other concomitant diseases, such as DM, HTN, and CKD, which also increase the risk of poor outcomes.<sup>1,11</sup> This study showed that the mortality rate was higher in RTX receivers if they were older, had diabetes, were taking steroids, were hospitalized, needed ICU, or had lower immunoglobulins or CD19. This is consistent with Ekin et al and the French RMD COVID-19 cohort, which also found a higher mortality rate in older patients. However, unlike our study, Ekin et al showed a significant association between COVID-19-related mortality and CKD.<sup>11</sup> Some studies have shown that steroids have no association with mortality. 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.<sup>18</sup> Gianfrancesco et al and the French RMD cohort study, however, found that long-term use of corticosteroids in the treatment of COVID-19 patients increased the risk of severe COVID-19 infection and/or COVID-19 mortality.<sup>19,20</sup> To be more specific in patients treated with RTX, unlike our study, Ekin et al showed no significant association between steroid use and COVID-19-related mortality in RTX patients. Therefore, they concluded that the advantages of steroid use in the treatment of rheumatologic diseases and COVID-19 infections seem to outweigh the disadvantages when used in a timely manner.<sup>11</sup>

Regarding sex and COVID-19 outcomes, there are some conflicting results in the literature. Several studies conducted in the general COVID-19 population reported higher rates of severe COVID-19 infections and COVID-19-related deaths in men compared with women.<sup>21,22</sup> In our study, no significant association was found between COVID-19-related mortality and gender, and the same was reported by Ekin et al. However, in the French RMD cohort study which investigated the impact of SARS-CoV-2 on patients with inflammatory rheumatic and musculoskeletal diseases, a significant association was found between female sex and death/serious illness.<sup>19</sup> Another cohort study on the outcomes of COVID-19 patients with inflammatory rheumatic diseases showed that women had a more better survival rate compared to men.<sup>1</sup> We believe that gender may not be directly related to severe COVID-19 infections. Rather, the underlying primary diagnosis for which RTX is used could play a role. To clarify this point, most of the available literature addressing RTX and the risk of severe COVID-19 infections and COVID-19-related deaths is related to a specific disease such as rheumatoid arthritis, or a group of diseases such as autoimmune diseases which could predominantly affect a specific gender. However, in our study, the fact that our patients had heterogeneous diagnoses could explain the even gender distribution in our study.

Some patients in RTX may develop hypogammaglobulinemia, which can be persistent and clinically significant and may require antibiotic prophylaxis or immunoglobulin replacement therapy to prevent severe infections and infection-related complications.<sup>23,24</sup> Several risk factors for hypogammaglobulinemia in patients treated with RTX have been reported in the literature including repeated RTX treatments, advanced age, and concurrent glucocorticoid therapy.<sup>25</sup> In our study, 37.1% of patients had hypogammaglobulinemia, and Casulo et al reported almost the same percentage (38.54%).<sup>26</sup> However, the incidence was higher in Roberts and Ekin et al, 56% and 68.5%, respectively. Unfortunately, not all patients in our study were tested for immunoglobulin levels, which may explain the difference in percentage between our study and the latter two studies. Both our study and Ekin et al showed that there was a significant association between hypogammaglobulinemia and COVID-19-related mortality.<sup>11</sup>

In our study, the hospitalization rate was 42.9%, which is higher than the general hospitalization rate in the general population.<sup>1</sup> In our study population, 25.71% of patients needed ICU. There was a statistically significant association between ICU admission and older age, steroid use, and lower CD19. In the study by Ekin et al 28.8% of patients with a history of infection required hospitalization. In the French RMD COVID-19 cohort study of 694 adults, 63% developed mild (not hospitalized), 24% developed moderate (hospitalized out of the ICU), and 13% developed severe (treated/died in the ICU) disease.<sup>19</sup> Previously published studies agree with the high rate of admission rate in people with immunotherapy.<sup>15,20</sup> COVID-19 patients in the general population, comorbidities such as chronic respiratory disease and DM could be the reason for admission.<sup>27,28</sup> In addition, disease-specific factors of the patients could be another explanation for admission as patients with cancer or autoimmune diseases

may require more medical attention. To clarify, Sahraian et al showed that in multiple sclerosis patients infected with COVID-19, the hospitalization rate was 25%, Which is higher than the admission rate in the age group of patients with multiple sclerosis in the general population.<sup>29</sup> MacKenna et al showed adults with immune-mediated inflammatory diseases are also at increased risk for COVID-19-related ICU admission and death.<sup>8</sup> Based on the literature, people with immune-mediated inflammatory diseases have a higher risk of COVID-19-related death, critical care admission or death, and hospital admissions than people without immune-mediated inflammatory diseases. The poor outcomes in these patients could be due to underlying diseases, immunotherapy, and/or other comorbidities.<sup>1,8</sup>

## Study Limitations and Future Directions

This study had some limitations. First, it was a retrospective study, and some defects in the study design cannot be ignored (eg, small sample size, single-center design). Second, some of the patients were not tested for immunoglobulins. Third, data on vaccination were not available, so the effects of vaccination on patient outcomes were ignored in the cohort. We plan to conduct two follow-up studies to assess the effects of vaccination on the outcomes of patients on RTX and the incidence of hypogammaglobulinemia in RTX receivers.

## Conclusion

We found that neurological disorders were the most common reason for RTX use. Approximately half of the patients received RTX at a dose of 375 mg/m<sup>2</sup>. Almost half of the patients received steroids. Hypogammaglobulinemia was seen in 37.1% of patients. ICU admission occurred in 25.7% of cases, and there was a statistically significant association between ICU admission and age, steroid use, and low CD19 levels. The mortality rate was 25.7%, and the mortality rate was higher in patients receiving RTX if they were older, had diabetes, were on steroids, were hospitalized or admitted to the ICU, or had low immunoglobulin or CD19 levels.

## Recommendation

Although RTX is an effective and safe medication for the treatment of various autoimmune diseases and hematologic malignancies, still RTX may cause an increased risk of infection and worse outcomes because of its immunosuppressive effects. Based on our findings, we recommend that patients who will start on RTX should be counseled regarding the risk of COVID-19 infection outcomes based on their individual risk factors. RTX should be used with caution or avoided unless the benefits clearly outweigh the risks. Finally, immunoglobulin testing should be performed in all patients started on RTX to know the baseline level of the patients. Multicenter studies with larger samples are needed to validate the results of this study.

## Abbreviations

RTX, Rituximab; COVID-19, Coronavirus disease 2019; KAMC, King Abdulaziz Medical City; DM, Diabetes Militias; CKD, Chronic Kidney Disease; ICU, Intensive Care Unit.

## Data and Materials Availability

The dataset used and/or analyzed to write the current study is available upon request.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

There is no funding to report.

## Disclosure

All authors declare no conflicts of interest in this work.

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