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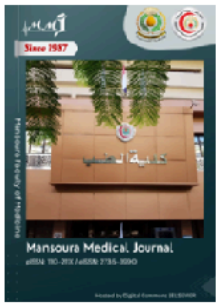

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Outcome of COVID-19 in patients with rheumatic diseases treated with immunosuppressive drugs

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ORIGINAL STUDY

Outcome of COVID-19 in Patients with Rheumatic Diseases Treated with Immunosuppressive Drugs

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Abstract

Background: **Rheumatologic disorders have been significantly impacted by the coronavirus disease 2019 (COVID-19) pandemic. The potential role of immunosuppressive drugs in the presentation, severity and even management of COVID-19 is still questionable. The aim of this work was to study the effect of immunosuppressive drugs on outcome of COVID-19 infection in patients with rheumatic diseases. 109 rheumatic patients (37 pediatrics and 72 adults) taking immunosuppressive treatment with confirmed COVID-19 infection were included in this study. Clinical, laboratory, radiological findings and outcome of these patients were retrospectively retrieved from hospital medical records.**

Results: **The majority of adult cases were rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), while juvenile idiopathic arthritis (JIA) represented the majority of pediatric cases. There were 13 deaths (18.1%) among adults. While, no recorded deaths among the pediatrics. There was significant correlation between the use of steroids, biologics and radiological findings among adults. Also, there was significant correlation between the need for oxygenation with the use of mycophenolate mofetil (MMF) and steroids.**

Conclusion: **The impact of the use of immunosuppressive therapies during the COVID-19 pandemic is variable depending on the type of drug and associated comorbidities. The decision whether to use these drugs or not must be tailored for each patient.**

Keywords: COVID-19, Immunosuppressive drugs, Rheumatic diseases

1. Background

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection presents with various clinical manifestations, ranging from asymptomatic to life-threatening multisystem ones. Most people only experience mild to moderate symptoms; however, respiratory failure, acute respiratory distress syndrome, and even death may occur (Wiersinga et al., 2020; Wong et al., 2020). The most severe cases of COVID-19 pneumonia are characterized by severe pulmonary oedema, inflammatory cell

Abbreviations: CSA, Cyclosporine; HCQ, Hydroxychloroquine; JIA, Juvenile idiopathic arthritis; MMF, Mycophenolate mofetil; RA, Rheumatoid arthritis; SLE, Systemic lupus erythematosus

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infiltration, extensive alveolitis, and concomitant pulmonary immunothrombosis. Furthermore, the immune reaction may be deleterious and overwhelming, where patients may experience a vicious cycle that includes the release of intrapulmonary proinflammatory mediators and abnormal immune cell activation (McGonagle et al., 2020; Alunno et al., 2020).

The majority of patients with rheumatic diseases, including SLE and RA, show immune dysregulation and need corticosteroids with or without other immunosuppressive drugs to stop the progression of the disease. It is widely accepted that patients receiving these medications are vulnerable to COVID-19 infection. Rheumatic diseases often exhibit clinical and laboratory findings that are similar to COVID-19 (such as fever and low lymphocyte count), it might be challenging to diagnose COVID-19 in individuals with rheumatic disorders (Ye et al., 2021).

There has been a lot of focus on the potential impact of immunosuppressive medications on the manifestations, severity and even treatment of COVID-19 (Siemieniuk et al., 2020). The 'cytokine storm' associated with COVID-19 is caused by a variety of cytokines, including tumor necrosis factor (TNF) and Interleukin 6 (IL-6) (Winthrop and Mariette, 2020). Therefore, research on cytokine inhibitors used in rheumatic diseases is important to determine whether they are effective therapies for severe COVID-19 and whether long-term use of these drugs in rheumatic disease patients may affect the course of infection (Leisman et al., 2020). According to several studies, patients with rheumatic disorders who are receiving immunosuppression don't appear to experience respiratory problems, life-threatening complications, or higher rates of SARS-CoV-2 related mortality as compared to general population. These results are not unexpected, as the severe respiratory complications caused by coronaviruses are thought to be caused by an abnormal inflammatory reaction (D'Antiga, 2020; Shi et al., 2020).

Data on COVID-19 in individuals with immunological disorders are controversial, and the role of the immune system and immunomodulatory drugs in the development of this infection is still debatable (Andersen et al., 2022). More research is still needed to fully comprehend the differential risk between rheumatic disorders, the individual risk linked to the use of different immunosuppressive medications for treatment of these disorders, and the long-term impacts of COVID-19 in this population (Akiyama et al., 2020). We decided to conduct this work to study the effect of immunosuppressive drugs on the outcome of COVID-19 infection in patients with rheumatic diseases.

2. Methods

2.1. Study design and overview

This observational retrospective study was done in the period between January and December 2021. The study protocol was approved by the Institutional Review Board (code no: R.21.03.1232). All patients included in the study, or their caring relatives, were well informed about the study, and a written informed consent was obtained.

The study included 109 rheumatic patients; 72 adults and 37 pediatrics (patients less than 16 years old) taking immunosuppressive treatment (for at least 3 months) and confirmed SARS-COV-2 infection with no original disease activity at time of infection. Data were collected from hospital medical records. These patients presented to our hospital with symptoms of COVID-19. These symptoms included fever higher than 37.5 °C, cough, dyspnea, anosmia, rhinorrhea, fatigue, myalgias, arthralgias, headache, nausea, abdominal pain, vomiting, or diarrhea.

For these cases, COVID-19 IgM and IgG were done by chemiluminescent immunoassay using automated assay (iFlash 1800-YHLO Biotech Co., Ltd., Shenzhen, China). The concentration of SARS-CoV-2 IgM or IgG Abs (AU/ml) was automatically calculated according to RLU and a built-in calibration curve, and 10.0 AU/ml was considered the positive cut-off; a reactive result for either IgG or IgM or both ($\geq$10.0 AU/ml) indicates potential infection by the SARS-CoV-2 virus, and non-reactive results (<10.0 AU/ml) indicate absence of SARS-CoV-2. The diagnosis of COVID-19 infection was confirmed if rhino-pharyngeal swabs were positive for SARS-CoV-2 RNA (total RNA was extracted from the clinical samples using a commercial RNA-extraction kit and was reverse transcribed; then, the cDNA was amplified by real-time qualitative RT-PCR, using a commercial kit in accordance with the manufacturer's instructions).

Patients with active disease at the time of COVID infection, other types of respiratory diseases including pneumonia induced by other microorganisms, bronchial asthma, or history of immune deficiencies, were excluded from this study.

Collected data included the onset and duration of symptoms, immunosuppressive drugs taken by the patients before infection and their doses, contact with infected cases, laboratory investigations (including hemoglobin, total leucocytic count,

neutrophilic count, lymphocytic count, ESR, CRP, ferritin, D-dimer, SGPT, SGOT, and serum creatinine), radiological findings (introduced by CO-RADS which indicates a level of suspicion for lung affection of COVID-19 based on the characteristics seen at non-contrast chest CT. The level of suspicion rises from very low (CO-RADS 1) to very high (CO-, hospitalization, need for oxygen administration, ICU admission, mechanical RADS 5) at the time of infection ventilation, and survival.

2.2. Statistical analysis and data interpretation

Data were fed to the computer and analyzed using IBM SPSS Corp. Released 2013. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp. Qualitative data were described using number and percent and compared using Chi–Square, Fischer exact and Monte Carlo tests as appropriate. Quantitative data were described using median (minimum and maximum) for non-normally distributed data and mean, standard deviation for normally distributed data after testing normality using Kolmogorov–Smirnov test. Significance of the obtained results was judged at the (0.05) level. Student t-test and Mann–Whitney U test were used to compare 2 independent groups as parametric and non-parametric test, respectively.

3. Results

Socio-demographic data, characteristics and immunosuppressive drugs (received by the patients before infection with COVID-19 and their doses) in both adult and pediatric groups are shown in Table 1. There was female dominance in both groups. For the adult group, the mean age was 42.65 ± 14.19 years. As regard the pediatric group, the mean age was 11.39 ± 4.17 years. From the 72 adult cases, 66 (91.6%) were RA and SLE. As regard the pediatric cases, the majority of cases; 23 (62.2%) were JIA. Five adults were on biological drugs before infection with COVID-19 (four were on anti-TNF, and one was on anti-IL-6), while three pediatric patients were on biological therapy before (two on anti-TNF and one on anti-IL-6). Table 2 shows the laboratory findings of the studied cases. There was a significant correlation between the types of medications and radiological findings as regard steroids and biologics among adult cases ($P = 0.03$, $P = 0.04$ respectively) (Table 3). Relation between diagnosis

Table 1. Characteristics of both adult and child groups.

	Adult group $N = 72$ (%)	Child group $n = 37$ (%)
Age/years (mean ± SD)	42.65 ± 14.19	11.39 ± 4.17
Min-Max	(22–78)	(2.5–17)
BMI (kg/m^2) mean ± SD	27.72 ± 4.28	20.24 ± 5.21
Min-Max	(20–38.28)	(14.1–36.48)
Sex		
Female	58 (80.6)	27 (73)
Male	14 (19.4)	10 (27)
Smoking	2 (2.8)	
Hypertension	33 (45.8)	1 (2.7)
DM	11 (15.3)	
Chronic Lung Disease	10 (13.9)	3 (8.1)
Diagnosis of cases		
RA	38 (52.8)	JIA: 23 (62.2)
Vasculitis	2 (2.8)	4 (10.8)
SLE	28 (38.9)	7 (18.9)
Ankylosing Spondylitis	2 (2.8)	–
Sarcoidosis	1 (1.4)	–
Dermatomyositis	1 (1.4)	3 (8.1)
Steroid	52 (72.2)	32 (86.5)
Steroid duration/month median (min–max)	9 (1–96)	3.5 (1–16)
Steroid dose mg/d median (min–max)	10 (2.5–60)	10 (2.5–60)
HCQ	46 (45.5)	11 (29.7)
Azathioprine	6 (5.9)	5 (13.5)
Cyclosporin	2 (1.9)	–
Cyclophosphamide	1 (0.9)	–
Leflunomide	20 (19.8)	1 (2.9)
MMF	15 (14.9)	–
Methotrexate	9 (8.9)	22 (59.5)
Sulfasalazine	2 (1.9)	1 (2.9)
Biological	5 (6.9)	3 (8.1)
Immunosuppressive dose		
Leflunomide (mg/day)	20 (20–20)	10
Azathioprine (mg/d)	100 (50–150)	100 (50–100)
Methotrexate (u/week)	15 (12.5–17.5)	65 (20–600)
MMF (mg/day)	2000 (1000–3000)	–
Sulfasalazine (mg/day)	2000 (2000–2000)	500
HCQ (mg/day)	386.95 (200–400)	200 (200–400)
Cyclosporine (mg/day)	175 (150–200)	–
Cyclophosphamide (mg/2 weeks)	500	–
Clinical presentation		
Fever	55 (76.4)	20 (54.1)
Cough	62 (86.1)	22 (59.5)
Rhinorrhea	15 (20.8)	22 (59.5)
Anosmia	18 (25)	2 (5.4)
Vomiting	17 (23.6)	8 (21.6)
Diarrhea	14 (19.4)	9 (24.3)
Abdominal pain	13 (18.1)	15 (40.5)
Myalgia	48 (66.7)	20 (54.1)
Hepatitis	6 (8.3)	1 (2.7)
Myocarditis	4 (5.6)	1 (2.7)
Guillain-Barre	1 (1.4)	

BMI, Body Mass Index; HCQ, Hydroxychloroquine; MMF, Mycophenolate Mofetil; RA, Rheumatoid arthritis; SLE, Systemic Lupus Erythematosus.

Table 2. Laboratory findings of the studied cases.

	Adult group ($n = 72$)	Child group ($n = 37$)
Hb (gm/dl) mean ± SD	10 ± 1.45	10.57 ± 0.89
TLC (10^3/ul) Median (Min-Max)	4.1 (1.5–27)	7.5 (3.8–11)
Neutrophils (10^3/ul) Median (Min-Max)	2.85 (0.6–2400)	4.8 (2.2–8.3)
Lymphocytes (10^3/ul) Median (Min-Max)	0.95 (0.3–900)	0.9 (0.2–2.3)
CRP (mg/l) Median (Min-Max)	24 (0–113)	20 (0–36)
ESR Median (Min-Max)	37 (6–100)	35 (20–58)
Ferritin (mic/l) Median (Min-Max)	161 (5–677)	150 (27–205)
D-dimer (μg/l) Median (Min-Max)	150 (6.3–1100)	77 (19–120)
SGOT (U/l) Median (Min-Max)	33 (15–2792)	25 (11–40)
SGPT (U/l) Median (Min-Max)	29 (16–406)	32 (13–45)
Creatinine mg/dl Median (Min-Max)	1.1 (0.4–10)	0.7 (0.4–0.9)

Hb: Hemoglobin, TLC: Total leucocytic count, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate.

and outcome among adult cases is shown in Table 4. There were 13 deaths (18.1%) among adult cases, with no recorded deaths among the pediatric group (Table 5). There was a significant correlation between the oxygen need with MMF and steroids ($P = 0.003$, $P = 0.026$, respectively) (Table 6).

4. Discussion

Our study included 109 patients (72 adults and 37 pediatrics) with rheumatic diseases who were receiving different types of immunosuppressive drugs and got infected with COVID-19. Main presenting symptoms in the adult group were cough (86.1%) and fever (76.4%). These findings are in line with the findings of the studies by Ye et al., and Pham et al., which showed that fever and cough were the most common symptoms (Ye et al., 2021; Pham et al., 2021). Cough and rhinorrhea were more common in the pediatric group (60% each). Each of myalgia and fever were presented in nearly half of the cases in the pediatric group. Pham et al., reported similar results regarding rhinorrhea (Pham et al., 2021).

Table 4. Relation between diagnosis and outcome among adult cases.

Diagnosis	Total number = 72	Alive $n = 59$ (%)	Dead $n = 13$ (%)	P value
RA	38	33 (55.9)	5 (38.5)	
Vasculitis	2	1 (1.7)	1 (7.7)	$\chi^{2MC} = 7.41$
SLE	28	22 (37.3)	6 (46.2)	$P = 0.192$
Ankylosing Spondylitis	2	2 (3.4)	0	
Sarcoidosis	1	0	1 (7.7)	
Dermatomyositis	1	1 (1.7)	0	

RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; Used test, Monte Carlo test.

Methotrexate is a commonly used drug in the treatment of autoimmune disorders. Infection risk is higher among methotrexate users than in the general population (Au et al., 2011). In our study, nine adult patients were on methotrexate therapy prior to infection, 44% (4 patients) of them were hospitalized (14.8% of total hospitalized patients), and 22% (2 patients) of them died (15% of total deaths). Our findings are in agreement with a study by Strangfeld et al., who reported that the use of methotrexate was linked to a higher percentage of death than other immunosuppressive medications, with the exception of sulfasalazine and rituximab (Strangfeld et al., 2021).

Among the studied patients, hydroxychloroquine (HCQ) was utilized by 46 adult patients; 32.5% (15 patients) of them needed hospitalization and Oxygen (55.5% of total hospitalized); and 24% of them died. HCQ was administered as an anti-SARS-CoV-2 treatment at the start of the pandemic because it seemed to be able to prevent SARS-CoV-2 from being endocytosed by alveolar epithelial cells (Colson et al., 2020). However, an observational study with 1446 patients found no association between HCQ administration and a significantly decreased or increased risk of intubation or death (Geleris et al., 2020). There is currently no evidence that

Table 3. Relation between use of medications and radiological findings among adult cases.

Immunosuppressive types	CORAD II $N = 4$ (%)	CORAD III $N = 5$ (%)	CORAD IV $N = 11$ (%)	CORAD V $N = 42$ (%)	P value
HCQ	1 (25)	3 (60)	5 (45.5)	31 (73.8)	$\chi^{2MC} = 6.10$, $P = 0.107$
Azathioprine	1 (25)	0	0	3 (7.1)	$\chi^{2FET} = 3.42$, $P = 0.332$
Cyclosporin	0	0	0	2 (4.8	$\chi^{2MC} = 0.984$, $P = 0.805$
Cyclophosphamide	0	0	0	1 (2.4)	$\chi^{2MC} = 0.484$, $P = 0.922$
Leflunomide	0	2 (40)	4 (36.4)	8 (19)	$\chi^{2MC} = 3.53$, $P = 0.317$
MMF	1 (25)	0	1 (9.1)	12 (28.6)	$\chi^{2MC} = 3.48$, $P = 0.323$
Methotrexate	1 (25)	1 (20)	1 (9.1)	5 (11.9)	$\chi^{2MC} = 0.924$, $P = 0.820$
Sulfasalazine	0	1 (20)	0	1 (2.4)	$\chi^{2MC} = 5.10$, $P = 0.164$
Steroid	4 (100)	1 (20)	9 (81.8)	31 (73.8)	$\chi^{2MC} = 8.96$, $P = 0.03$*
Biological treatment	0	2 (40)	0	3 (7.1)	$\chi^{2MC} = 8.24$, $P = 0.04$*

Used tests: Monte Carlo test, * if P value is significant. CORAD: COVID-19 Reporting and Data System, HCQ: Hydroxychloroquine, MMF: Mycophenolate Mofetil.

Table 5. Relation between COVID-19 and outcome among studied cases.

	Adult $N = 72$ (%)	Child $N = 37$ (%)
Hospitalization	27 (37.5)	0
ICU	15 (20.8)	0
Oxygen need	21 (29.2)	0
Mechanical ventilation	15 (20.8)	0
Multisystem	4 (5.6)	0
Multiorgan failure	5 (6.9)	0
Sepsis	10 (13.9)	0
AKI	19 (26.4)	0
Outcome		
Alive	59 (81.9)	37 (100%)
Dead	13 (18.1)	0
SO2 Mean ± SD (Min-Max)	88.78 ± 10.71	96 ± 1.37
RR Mean ± SD (Min-Max)	25.28 ± 8.25	18.65 ± 1.93
Hospitalization stay/days Median (Min-Max)	10 (5–21)	

AKI, Acute kidney injury; ICU, Intensive care unit; RR, Respiratory rate; SO2, Oxygen saturation.

HCQ regimens are beneficial for treating or preventing COVID-19 infection, according to data from a well-designed randomized controlled trial (Saghir et al., 2021). Additionally, in a cohort study done by Favalli et al. (2020), confirmed COVID-19 and respiratory symptoms of suspected COVID-19 were seen in patients using antimalarials, raising the question of the real preventative role of these medications. We have to mention that the findings observed in the current study can be attributed to the fact that HCQ is usually given in combination with other drugs in most of rheumatological diseases.

There were 3 deaths (15%) among the 20 patients taking leflunomide (23% of total deaths). Hu et al. (2020), found that COVID-19 patients who were taking leflunomide had a shorter hospital stay and a better clinical outcome. In addition, Strangfeld et al. (2021), reported that patients treated with leflunomide had lower death rate than those treated with methotrexate. However, for more reliable data regarding the use of leflunomide in COVID-19 infection, larger studies are needed.

The potent anti-oxidative, immunomodulatory and anti-inflammatory effects of sulfasalazine may be beneficial for treating COVID-19 patients, especially for reducing respiratory manifestations (Ghasemnejad-Berenji, 2022). Sulfasalazine acts by preventing the synthesis of many cytokines, as TNF-α, IL-1, IL-6, and IL-12 (Plosker and Croom, 2005). Only 2 patients receiving sulfasalazine were enrolled in our study; one of them needed hospitalization and oxygenation, but none of them died. However, Strangfeld et al. (2021), found that sulfasalazine was associated with higher rates of death in their study. Results from an international registry of individuals with inflammatory bowel disease and COVID-19 also showed this association, where sulfasalazine use was linked to severe COVID-19 (Brenner et al., 2020). This result was unexpected because sulfasalazine is typically thought to have a low immunosuppressive effect. In their study, Strangfeld et al. (2021), hypothesized that the relation between sulfasalazine and COVID-19 may be an association rather than a causal relationship.

Two out of 6 cases (33%) receiving Azathioprine died in our study (15% of total deaths). Azathioprine was reported to be linked to a higher risk of various viral infections and the reactivation of potential pathogens (Chen et al., 2011). Only few reports regarding the existence of an association between azathioprine use and COVID-19 infection or disease progression are available (Bakasis et al., 2021). On the contrary to our results, in the study by Strangfeld et al. (2021), seven out of 70 patients (1.8% of dead cases) receiving azathioprine died. This discrepancy could be explained by the small number of cases receiving azathioprine in our study. Also, the timing of stoppage of the drug after acquiring a COVID infection could affect the outcome of these patients.

Table 6. Relation between use of medications and different outcomes among adult cases.

Medications	Total number = 72	Hospitalization $N = 27$ (%)	need oxygenation $n = 21$ (%)	ICU admission $N = 15$ (%)	mechanical ventilation $n = 15$ (%)	Dead $n = 13$ (%)
HCQ	46	15 (55.5) $P = 0.862^{\#}$	15 (71.4) $P = 0.393^{\#}$	11 (73.3) $P = 0.801^{\#}$	11 (73.3) $P = 0.390^{\#}$	11 (84.6) $P = 0.086^{\#}$
Azathioprine	6	2 (7.4) $P = 1.0^{f}$	2 (9.5) $P = 0.815^{f}$	2 (13.3) $P = 0.598^{f}$	2 (13.3) $P = 0.430^{f}$	2 (15.4) $P = 0.0.295^{f}$
Cyclosporin	2	0 $P = 0.549^{f}$	0 $P = 1.0^{f}$	0 $P = 1.0^{f}$	0 $P = 1.0^{f}$	0 $P = 1.0^{f}$
Cyclophosphamide	1	1 (3.7) $P = 0.333^{f}$	1 (4.8) $P = 0.292^{f}$	1 (6.7) $P = 0.208^{f}$	1 (6.7) $P = 0.208^{f}$	1 (7.7) $P = 0.180^{f}$
Leflunomide	20	6 (22) $P = 0.710^{\#}$	3 (14.3) $P = 0.101^{\#}$	3 (20) $P = 0.160^{\#}$	3 (20.0) $P = 0.450^{\#}$	3 (23.1) $P = 0.678^{\#}$
MMF	15	9 (33.3) $P = 0.538^{\#}$	9 (42.9) $P = 0.003^{\#}$*	4 (26.7) $P = 0.532^{\#}$	4 (26.7), $P = 0.532^{\#}$	2 (15.4) $P = 0.593^{\#}$
Methotrexate	9	4 (14.8) $P = 0.450^{\#}$	2 (9.5) $P = 0.624^{\#}$	2 (13.3) $P = 0.913^{\#}$	2 (13.3) $P = 0.913^{\#}$	2 (15.4) $P = 0.728^{\#}$
Sulfasalazine	2	1 (3.7) $P = 0.612^{f}$	1 (4.8) $P = 0.511^{f}$	0 $P = 1.0^{f}$	0 $P = 1.0^{f}$	0 $P = 1.0^{f}$
Steroid	52	20 (74) $P = 0.137^{\#}$	19 (90.5) $P = 0.026^{\#}$*	13 (86.7) $P = 0.160^{\#}$	12 (80) $P = 0.450^{\#}$	10 (76.9) $P = 0.676^{\#}$
Biological treatment	5	2 (7.4) $P = 1.0^{f}$	3 (14.3) $P = 0.625^{f}$	1 (6.7) $P = 1.0^{f}$	1 (6.7) $P = 1.0^{f}$	1 (7.7) $P = 1.0^{f}$

Test of significance is Chi–Square test$^{\#}$ or Fisher's exact test^{f}, * if P value is significant.

In our study, 15 patients were receiving MMF; (60%) of them were hospitalized (33% of total hospitalized patients), and (26.6%) needed ICU admission and mechanical ventilation. Unfortunately, two of them died (15.4% of total deaths). In line with our findings are the results of the study by Bakasis et al. (2021), which showed that prior treatment with MMF was more prevalent in the hospitalized group (33.3 vs. 5.1%, $P = 0.001$). It is currently unclear if MMF should be reduced or stopped in individuals who were being treated with it when they got the COVID-19 infection. There isn't enough information in the literature about the relation between MMF use and COVID-19 (Değirmenci et al., 2021).

Two non-hospitalized adult patients were taking cyclosporine (CsA). None of these cases needed oxygen, mechanical ventilation, or died. Our results are in line with those of Strangfeld et al. (2021), who reported no deaths among 3 patients treated with CsA. Recent research has demonstrated that CsA has significant anti-SARS-CoV-2 antiviral activity due to its anti-inflammatory effects, which limit the production of proinflammatory cytokines and the development of the viral RNA synthesis complex (Fenizia et al., 2022). However, we cannot rely on these results due to the insufficient number of cases.

Only one patient in our study was receiving cyclophosphamide. This patient had severe infection, needed ICU admission, and died. Cyclophosphamide was reported to raise the risk of various viral infections and cause latent infections to reactivate (Chen et al., 2011). Although it was noticed that all 4 of the patients utilizing cyclophosphamide exhibited minor COVID-19 symptoms in a study by Kanellopoulos et al. (2020). To confirm if cyclophosphamide is linked to either moderate or severe symptoms and outcomes in patients infected with COVID, additional research with a larger sample size of patients is required.

Steroids were utilized by 52 adult patients (either alone or in combination with other immunosuppressive drugs) prior to infection in our study, 38.5% of them were hospitalized (74% of total hospitalized patients), and 19% died. According to a prior study, taking more than 7.5 mg of prednisone daily was linked to a six-fold increase in the incidence of serious infections that necessitated hospital admission (Au et al., 2011). Our findings are consistent with those of Strangfeld et al. (2021), who claimed that prednisolone equivalent dosages greater than 10 mg/day were related to death from COVID-19. Systemic corticosteroid exposure was linked to a 60% higher incidence of COVID-19 hospitalization, according to a Danish countrywide cohort study (Nørgård et al., 2021). According to more recent research, the use of corticosteroids in COVID-19 patients was linked to an increased risk of hospitalization and death (Strangfeld et al., 2021; Brenner et al., 2020; Gianfrancesco et al., 2020). In contrast to these studies, there are studies that have not found such an association, where Andersen et al. found no hazardous effect of exposure to systemic corticosteroids on in-hospital death among adults hospitalized with COVID-19 (Andersen et al., 2022). This beneficial effect may be attributed to the role of steroids in controlling the cytokine storm and also the proper timing of administration of steroids (Närhi et al., 2022). The discrepancy between the results of these studies may be due to the dose, duration of steroids usage before infection and drugs given in combination with steroids (Sun et al., 2022).

As regard biological therapy, we recorded 1 death out of 5 patients taking different types of biologics (4 cases were taking anti-TNF and 1 case was taking tocilizumab). This case was taking tocilizumab in combination with methotrexate prior to infection. Several studies reported that although anti-TNF-α and tocilizumab were linked to a higher risk of infection, they developed a milder form of COVID-19 infection without an increased risk of hospitalization or death and were associated with a favorable outcome, even they had protective effect against SARS-CoV-2 induced cytokine storm (Bakasis et al., 2021; Sun et al., 2022).

Our results showed that 31 out of 52 patients maintained on steroids had CORAD V on chest CT at presentation (59.6% of patients taking steroids and 73.8% of all patients had CORAD V, $P = 0.03$). This is matched with Tang et al. (2021), who reported that early use of low-dose methylprednisolone might not give any clinical benefits in the patients of COVID-19, even though it might prolong the virus shedding. It may be associated with immune cell suppression by the application of corticosteroids, so based on their result, corticosteroids administered in the selected patients might help them acquire a better prognosis, but early administration had a hazardous effect. Also, 3 patients treated with biological treatment had CORAD V on chest CT (60% of patients taking biological treatment; $P = 0.04$), 2 of them were taking anti-TNF and 1 was taking Tocilizumab which represents significant radiological progression with both drugs.

Although there were a variety of COVID-19 symptoms among the pediatric group, including fever, cough, rhinorrhea, myalgia, diarrhea, and abdominal pain, none of them needed hospitalization or ICU admission, and all cases were alive. This

is in line with the observation that children experience significantly better outcomes than adults, with a less than 1% mortality rate (Qiu et al., 2020). Data suggests that children treated with immunomodulators, biologics, or both for various indications appear to have a milder clinical course of COVID-19 (Marlais et al., 2020).

4.1. Conclusion

There are no definitive rules for the use of immunosuppressive therapy during the COVID-19 pandemic. The results are variable depending on the type of drug and associated comorbidities. The decision whether to use these drugs or not must be tailored for each patient. However, more randomized clinical trials are needed to assess the effect of these drugs on the outcome of COVID-19 infection in rheumatic patients.

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of Mansoura University (code no: R.21.03.1232). All patients included in the study, or their caring relatives were well informed about the study and a written informed consent was obtained. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Consent for publication

Not applicable.

Availability of data and material

The datasets generated and analyzed during the current study are not publicly available due to local university policy but are available from the corresponding author on reasonable request.

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Conflicts of interest

The authors declare that no conflict of interest.

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