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Clinical profile and management of COVID-19 in unvaccinated patients with rheumatoid arthritis: A single-center study

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ABSTRACT

Aim. The present study aimed primarily to assess COVID-19 (COronaVIrus Disease 2019) course and management in unvaccinated patients with rheumatoid arthritis (RA). Secondary objectives included an analysis of the impact of RA disease activity, age, comorbidities, and DMARD treatment on COVID-19 course.

Materials and methods. We performed a prospective observational study on RA patients in the 1st Rheumatology Clinic of the Clinical Rehabilitation Hospital between February and July 2021. The criteria for inclusion in the study cohort were: confirmed RA diagnosis and SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) infection confirmed by rapid antigen test and/or RT-PCR (Real-Time Polymerase Chain Reaction) during hospitalization in our department. We excluded the patients who were vaccinated against SARS-CoV-2 and those with incomplete data regarding COVID-19 clinical features and management. Demographic characteristics, DAS28 (Disease Activity Score 28) and the treatment prior to SARS-CoV-2 infection, as well as the patients' comorbidities were taken from the subjects' charts completed on presentation in the 1st Rheumatology Clinic. COVID-19-related data were collected from the patients' release forms from specialized departments.

Results. The study group included 28 unvaccinated patients with RA who tested positive for SARS-CoV-2. All patients over 65 years of age were symptomatic for COVID-19. Moreover, this subgroup had an increased risk of pneumonia ($p = 0.047$) and a 217% risk increase for desaturation. Comorbid type 2 diabetes mellitus was associated with COVID-19 pneumonia ($p = 0.048$). Women needed less antiaggregant and anticoagulant medication ($p = 0.029$), antitussives ($p = 0.014$) and oxygen therapy ($p = 0.044$) compared to men. Patients with comorbid heart failure, valvulopathies and cardiac ischemia were more likely to require antiaggregant or anticoagulant medication during hospitalization for COVID-19 ($p = 0.003$, $p = 0.013$, and $p < 0.001$). DAS28 ≥ 5.1 prior to infection was associated with Tocilizumab therapy for COVID-19 pneumonia, results approaching statistical significance in this respect.

Conclusions. In the present study group, we found significant associations between COVID-19-related changes and advanced age, as well as certain comorbidities. Large comprehensive longitudinal studies may provide a more accurate representation of COVID-19 outcomes in unvaccinated patients with RA.

Keywords: rheumatoid arthritis, COVID-19, SARS-CoV-2, pneumonia, obesity, diabetes mellitus, systemic hypertension

INTRODUCTION

Since December 2019, humanity has been experiencing an unprecedented health crisis caused by SARS-CoV-2 (severe acute respiratory coronavirus-2), an infectious agent thought to originate from Wuhan (Hubei province, China) (1). Due to its rapid global spread, The World Health Organization (WHO) declared COVID-19 (COronaVIrus Disease 2019) a public health emergency of international concern on January 30th 2020 and a pandemic on

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March 11th 2020. From the initial outbreak, COVID-19 lead to over 200 million confirmed cases and over 4.5 million deaths worldwide (2).

The disease course may vary from asymptomatic to non-specific viral illness or mild upper/lower respiratory tract infection, to multisystem organ failure and consequent exitus (2,3). The clinical manifestation may vary from symptoms as fatigue, fever, nausea, diarrhoea, rhinitis, headache, dry cough, and dyspnea to acute respiratory distress syndrome (ARDS) requiring mechanical ventilation and admission to an intensive care unit (ICU) (4-6).

Similar to other viral infections, a robust immune response is associated, inflammatory markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and proinflammatory cytokines are elevated (7-10). The excessive or uncontrolled immune activation could lead to a so-called "cytokine storm" as observed in serious cases of COVID-19, this phenomenon is correlated with disease severity, viral replication, and lung injury (11,12).

Knowing that SARS-CoV-2 infection pathogenesis includes an immunological phase and immune disturbance being the main focus in inflammatory rheumatic diseases, it was hypothesised that the advances in the management of the latter could provide valuable insight for the development of effective therapies for COVID-19. Hydroxychloroquine and interleukin-6 (IL-6) inhibitors are disease-modifying antirheumatic drugs (DMARDs) used in various immune-inflammatory conditions. During the SARS-CoV-2 pandemic, these drugs were used to treat COVID-19, including in patients exhibiting a "cytokine storm" (12-15).

Furthermore, a high risk of COVID-19-associated complications and death was reported in patients considered vulnerable (the elderly and patients with significant comorbidities) (16,17). Rheumatoid arthritis (RA) patients are known to be a high-risk group for various infections compared to the general population due to both endogenous and exogenous risk factors such as the dysregulation of the immune system involved in the pathogenesis of the disease itself, the presence of immunocompromising comorbidities, and the therapeutic agents used in the management of RA: immunosuppressive agents such as conventional synthetic DMARDs (csDMARDs), biological DMARDs (bDMARDs), targeted synthetic DMARDs (tsDMARDs) and corticosteroids (18,19).

The present study aimed primarily to assess COVID-19 disease course and management in unvaccinated patients with RA. Secondary objectives included an analysis of the impact of RA disease activity, age, comorbidities, and DMARD treatment on COVID-19 course.

MATERIALS AND METHODS

We performed an observational study on RA patients in the 1st Rheumatology Clinic of the Clinical Rehabilitation Hospital between February and July 2021. The criteria for inclusion in the study cohort were: confirmed RA diagnosis according to the ACR 1987 diagnosis criteria (American College of Rheumatology) or the ACR/EULAR 2010 classification criteria (ACR/EUropean League Against Rheumatism) and SARS-CoV-2 infection confirmed by rapid antigen test and/or RT-PCR (real-time polymerase chain reaction) during hospitalization in our department. We excluded the patients who were vaccinated against SARS-CoV-2 and those with incomplete data regarding COVID-19 clinical features and management.

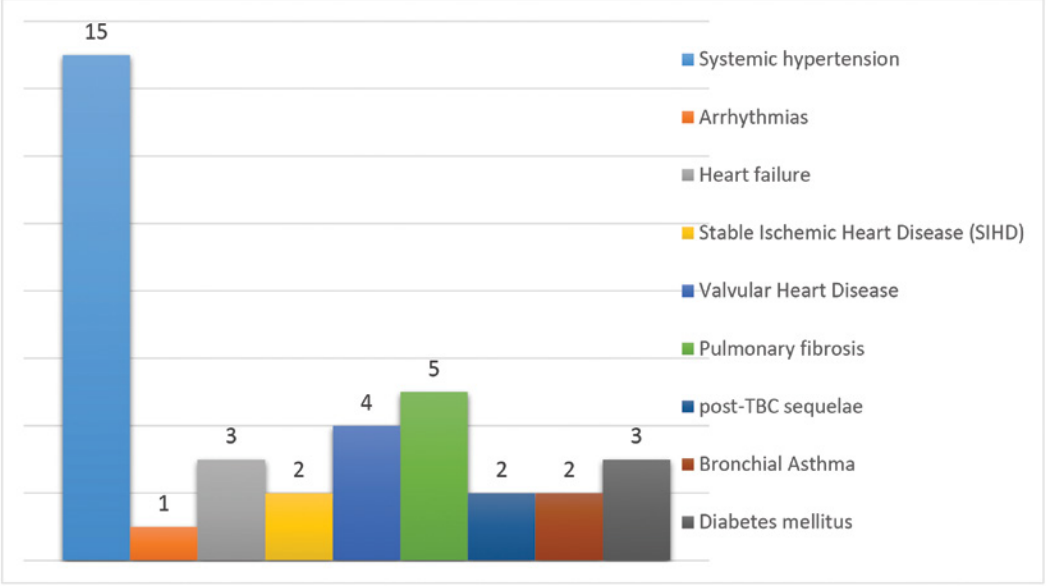

FIGURE 1. Comorbidities

TABLE 1. Characteristics of the study group

Parameter	Characteristics Number (%); Minimum-Maximum (Mean±SD)		
Age (years)	22-71 (58.00±11.99)		
Gender	Male	5 (17.86%)	
	Female	23 (82.14%)	
Area of residence	Urban	19 (67.86%)	
	Rural	9 (32.14%)	
BMI (kg/m2)	23.32–35.44 (29.18±3.27)		
RF	Positive	17 (60.7%)	
	Negative	11 (39.3%)	
ACPA	Positive	15 (53.6%)	
	Negative	13 (46.4%)	
Radiographic stage	II	7 (25%)	
	III	18 (64.3%)	
	IV	3 (10.7%)	
DAS28-ESR	1.41-6.66 (3.77±1.41)		
DAS28-CRP	1.89-6.67 (3.62±1.28)		
RA treatment	csDMARDs	Methotrexate	8 (28.6%)
		Leflunomide	12 (42.9%)
		Sulfasalazine	3 (10.7%)
		Hydroxychloroquine	8 (28.6%)
		Azathioprine	2 (7.1%)
	bDMARDs	Adalimumab	2 (7.1%)
		Etanercept	5 (17.9%)
		Rituximab	2 (7.1%)
		Tocilizumab	1 (3.6%)
		AntiTNF (total)	7 (25.0%)
		Biologics (total)	10 (35.7%)
	tsDMARDs	tsDMARDs	Baricitinib
		Glucocorticoids (GCS)	5 (17.9%)

Demographic characteristics, RA disease activity (DAS28, Disease Activity Score 28), the radiographic stage and treatment prior to SARS-CoV-2 infection, as well as the patients' comorbidities were taken from the subjects' charts completed on presentation in the 1st Rheumatology Clinic. COVID-19-related data were collected from the patients' release forms from specialized departments.

We performed the statistical analysis of the data using IBM SPSS Statistics version 23 for Windows. The statistical significance threshold was set at $p \leq 0.05$.

RESULTS

Over the 6-month duration of the study, 28 unvaccinated RA patients with a mean age of 58 years tested positive for SARS-CoV-2 during hospitalization in our department. The general characteristics of the study group are presented in Table 1.

The analysis of the serology panel revealed a 60.7% seropositivity for rheumatoid factor (RF), 53.6% seropositivity for anti-citrullinated protein antibodies (ACPA), while 38% of patients were both RF+ and ACPA+.

In terms of theassociated comorbidities, more than half of the patients had systemic hypertension (53.6%, 15 patients), whereas asthma was the least prevalent comorbidity in our study group (Figure 1). Notably, our study group did not include patients with type 1 diabetes mellitus.

Almost half of the patients (46.4%) had a known source of SARS CoV-2 infection in our study cohort, familial exposure to the virus being the most prevalent (Table 2).

TABLE 2. Source of SARS CoV-2 infection

Parameter	Characteristics Number (%);	
Source of infection	Workspace	5 (17.9%)
	Hospital	4 (14.3%)
	Family	6 (21.4%)
	Unknown	13 (46.4%)

The majority of our study group (26 patients, 92.9%) were symptomatic for COVID-19, of which 65.38% (17 patients) required hospitalization.

The most commonly reported symptom was fatigue, followed by fever, cough, and headache (Figure 2). Young patients (under 40 years of age) were more likely to be asymptomatic, results approaching statistical significance in this respect.

All patients over 65 years of age were symptomatic. Moreover, this subgroup had an increased risk of COVID-19-associated pneumonia ($p = 0.047$) and a 217% risk increase for desaturation. Female patients were less likely to have such COVID-19-associated symptoms as cough ($p = 0.047$) and cutaneous changes ($p = 0.029$).

The subjects with obesity were more likely to be symptomatic compared to non-obese individuals ($p = 0.045$). Comorbid type 2 diabetes mellitus was associated with the presence of dyspnea ($p = 0.019$) and pneumonia ($p = 0.048$).

In patients who were hospitalized for COVID-19, the length of stay varied between 2-16 days (7.75±5.22 days). Pneumonia was found in 9 patients (32.1%), of which 7 patients (25%) had lung opacities on chest X-rays.

The most frequently administered medication used to treat COVID-19 symptoms were non-steroidal antiinflammatory drugs (NSAIDs; 24 patients, 85.7%), followed by antibiotics (23 patients, 82.1%), anticoagulant therapy (17 patients, 60.7%), gluco-

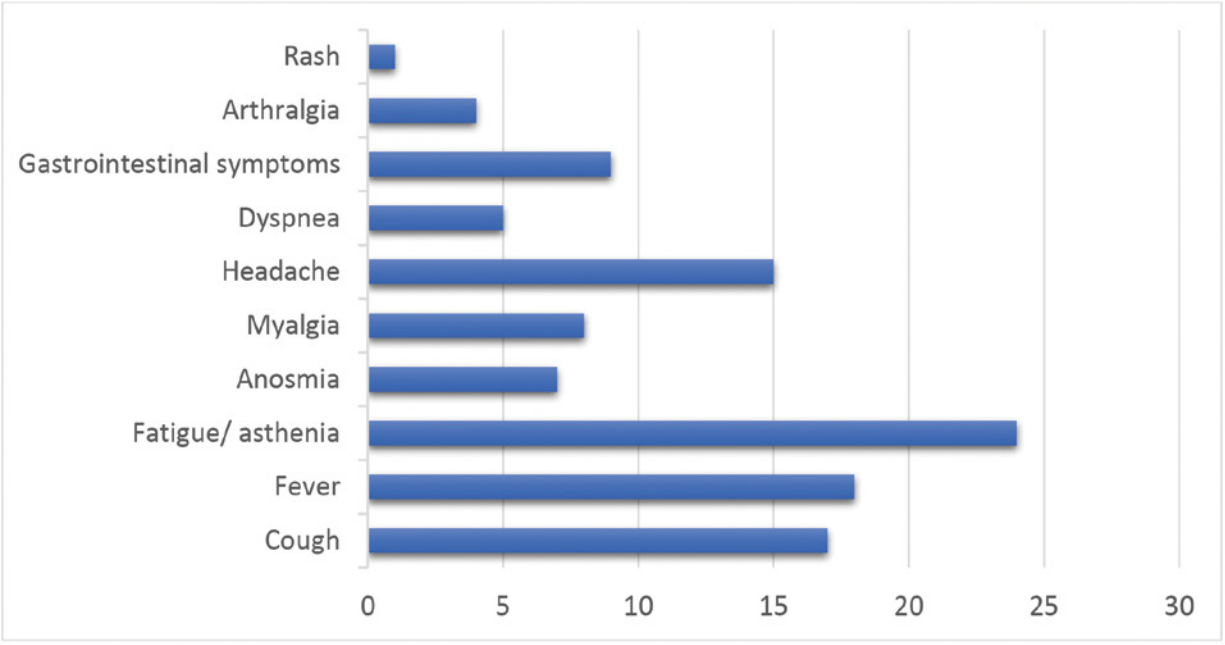

FIGURE 2. COVID-19 symptoms

corticoids (15 patients, 53.6%), and antitussives (14 patients, 50%). Only 25% of the group (7 patients) needed oxygen therapy, similar to antiviral medication (25%), while 10 subjects (35.7%) received Hydroxychloroquine for COVID-19, and 3 patients (7.14%) needed biological therapy with Tocilizumab and/or Anakinra. Patients with pneumonia had 4.2 times higher odds of needing oxygen therapy.

Women needed less antiaggregant and anticoagulant medication ($p = 0.029$), antitussives ($p = 0.014$) and oxygen therapy ($p = 0.044$) compared to men. In addition, we found that the subgroup aged over 65 years was more likely to require glucocorticoids ($p = 0.039$) and anticoagulant therapy ($p = 0.041$). Oxygen therapy was also administered significantly more frequently in elderly patients ($p = 0.008$).

Patients with comorbid heart failure, valvulopathies and cardiac ischemia were more likely to receive antiaggregant or anticoagulant medication during hospitalization for COVID-19 ($p = 0.003$, $p = 0.013$, and $p < 0.001$). We did not find significant associations between cardiovascular comorbidities and other therapeutic strategies commonly applied for COVID-19 (including oxygen therapy) in our study group. Moreover, we did not obtain significant relationships between pulmonary fibrosis or other chronic pulmonary conditions and the need for oxygen therapy, COVID-19-associated respiratory symptoms, or the risk of pneumonia. Comorbid type 2 diabetes mellitus was not significantly linked to a more extended hospital stay or the need for oxygen therapy, Tocilizumab and Anakinra, anticoagulants, or glucocorticoids for COVID-19 in our study group.

A highly active form of disease (DAS28 over 5.1) prior to infection was associated with Tocilizumab therapy for COVID-19 pneumonia (with results approaching statistical significance, $p = 0.06$), but not oxygen therapy or glucocorticoids. Nevertheless, we did not find a significant association between RF and ACPA seropositivity and COVID-19-related symptoms, pneumonia or the need for a more aggressive therapeutic approach.

More than half (60.71%) of the study group interrupted their DMARD medication after the confirmation of SARS-CoV-2 infection, with or without the attending doctor's recommendation. There was no signidicant association between Methotrexate treatment and pneumonia, COVID-19-related symptoms, the length of hospitalization or management, similar to other csDMARDs. Albeit without statistical significance, patients treated with Hydroxychloroquine were less likely to have radiographic evidence of pneumonia (12.5% versus 30%).

Although the patients who were under biological treatment for RA were more likely to receive either Tocilizumab or Anakinra to manage COVID-19 pneumonia (20% versus 5.6%), these results did not reach statistical significance. Regarding other types of therapeutic interventions for COVID-19, there were no differences between the subgroups with or without biological therapy for RA.

DISCUSSIONS

The currently ongoing pandemic has raised many questions regarding COVID-19-related outcomes in patients with important comorbidities and their specific treatments. Autoimmune diseases pose a high risk, especially in case of active disease or the presence of additional risk factors for poor outcomes of COVID-19. Advanced age is an important variable that negatively influences the evolution of COVID-19

both in the general population and in patients with RA, being considered a leading risk factor for hospital admission and mortality (20-23). Of the 28 patients with RA included in the present study, the elderly subjects had, indeed, a greater chance of desaturation as opposed to younger subjects. Additionally, the patients in this subgroup were more likely to need administration of glucocorticoids, anticoagulant treatment and oxygen therapy.

Another critical factor that affects the severity of infection is disease activity; more specifically, moderate to severe disease activity is assessed as an independent risk factor for hospitalization (20,24). Therefore, even more so than usual, strict management is essential, and clear-set goals must be established to control the disease.

Male gender has been described as a possible risk factor for a more severe SARS-CoV-2 infection, associated with a higher hospitalization rate and higher mortality. It has been reported that beyond the risk of hospital admission, the male gender was found to be more often in the group of patients that required oxygen therapy. Therefore, men may be prone to a more severe course of infection, as observed in the general population (20,23,25,26). Another study observed a higher rate of comorbidities among males with the result that, as opposed to female patients, these subjects had a slightly greater risk for poor outcomes (27). In our study group, women were at a lower risk of presenting such COVID-19-related symptoms as cough and required less anticoagulant medication, antitussives, and oxygen therapy compared to men.

Regarding comorbidities, the presence of obesity, hypertension, diabetes, and lung disease has been reported to be frequent among patients with virologically confirmed SARS-CoV-2 infection and is also correlated with more severe symptoms of COVID-19, a higher risk of hospitalization and, in general, with a poorer prognoses. (21,28-31). The present study supports the association between obesity and a higher likelihood of developing COVID-19. Regarding patients with comorbid heart failure, valvulopathies and cardiac ischemia, this subgroup had a higher change of receiving antiaggregant or anticoagulant medication, but no association with oxygen administration was observed. In our study, we did not observe a strong link between lung disease, such as pulmonary fibrosis, asthma and other chronic lung diseases with respiratory symptoms, risk of pneumonia and the administration of oxygen therapy for COVID-19. Furthermore, patients with type 2 diabetes mellitus were more likely to present dyspnea and COVID-19-associated pneumonia, but, interestingly, there was no link to a more extended hospital stay or oxygen administration necessity.

In a recent study on patients with RA evaluating for the risk of COVID-19, there was no statistically significant association with seropositivity and SARS-CoV-2 infection (32). This observation mirrors our results, as there was no significant link between seropositivity and COVID-19-associated parameters (symptoms or required treatment).

Prior or current treatment with glucocorticoids at ≥ 10 mg/day is considered an independent risk factor for COVID-19 severity and hospitalization (33-35). However, data must be analysed with caution since glucocorticoids are administered in some instances that may themselves have a strong influence on the outcome, for example, high disease activity, which, as mentioned above, is also considered an independent risk factor for SARS-CoV-2 infection. Consequently, glucocorticoids should be used in the lowest possible dose (20,34,36,37). In our study, all the patients who took prednisone in various doses ≥ 5 mg/day (or an equivalent) were symptomatic.

Methotrexate remains a widely used csDMARD in the treatment of RA and is known to exert an anti-inflammatory effect. Methotrexate reduces the expression of ACE2 (angiotensin-converting enzyme 2), being thought to have a protective effect against viral entry (38,39). In our group, Methotrexate treatment was not significantly associated with a decreased risk of pneumonia or other COVID-19-related manifestations in our study group.

Regarding Hydroxychloroquine, in vitro studies have shown its role in inhibiting SARS-CoV-2 into epithelial cells (40,41). Statements regarding the potential benefits of Hydroxychloroquine treatment for COVID-19 remain discrepant. In population-based study of patients with pre-exposure to Hydroxychloroquine, an association of its use and either a beneficial or harmful effect has not been established (42,43). In the current study, we found a lower frequency of radiologically confirmed pneumonia in the subgroup treated with Hydroxychloroquine prior to SARS-CoV-2 infection, yet without statistical significance.

The present study focused on SARS-CoV-2 infection in unvaccinated RA patients. The advantages of vaccination against SARS-CoV-2 in RA and other immune-inflammatory rheumatic conditions are still a matter of investigation, especially in case of active disease. However, it has been stated that the benefits of vaccination may outweigh the risks in autoimmune diseases (44).

Our study, however, faces certain limitations, including its observational nature and the lack of a control group of vaccinated RA patients. Another significant limitation is the small sample size, which may influence statistical results.

CONCLUSIONS

Knowledge regarding susceptibility to SARS-CoV-2 infection and COVID-19 and the risk factors linked to poor outcomes are of utmost importance in the current pandemic, particularly in patients with autoimmune diseases. In the present study group of unvaccinated patients with RA, we found associations between COVID-19-related changes and advanced age, as well as certain comorbidities. Large comprehensive longitudinal studies may provide a more accurate representation of COVID-19 outcomes in unvaccinated patients with RA.

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