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COVID-19 infection among autoimmune rheumatic disease patients: Data from an observational study and literature review

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ABSTRACT

The impact of SARS-CoV-2 infection in patients with autoimmune/auto-inflammatory rheumatic diseases (AARD) under immunomodulatory treatment has been a focus of interest during the COVID-19 pandemic. In this observational study, demographic data, disease related features and comorbidities, COVID-19 manifestations and outcome as well as antibody responses to SARS-CoV-2 were recorded among 77 consecutive patients with underlying AARD infected by SARS-CoV-2. Analysis of data was performed using univariate and multivariate models. Most patients (68.8%) had a mild COVID-19 course. The predominant clinical manifestations were fatigue (58.4%), low grade fever (45.4%) and upper respiratory tract symptoms (68.8%). About a quarter of patients required hospitalization (23.3%) and the mortality rate was 1.3%. Regarding COVID-19 severity, prior treatment with corticosteroids, mycophenolate mofetil or rituximab was more common in patients who developed a more serious disease course (60.0 vs 29.9%, $p = 0.003$, 40.0 vs 7.5%, $p = 0.003$, 10.0 vs 0.0%, $p = 0.009$, respectively). When disease related features and comorbidities were considered in multivariate models, older age and lung disease in the context of the AARD were found to be independent predictive factors for hospitalization (OR [95%]: 1.09 [1.03–1.15] and 6.43 [1.11–37.19]). Among COVID-19 related features, patients with shortness of breath and high-grade fever were more likely to get hospitalized (OR [95%]: 7.06 [1.36–36.57], 12.04 [2.96–48.86]), while anosmia was independently associated with lower hospitalization risk (OR [95%]: 0.09 [0.01–0.99]). Though the majority of AARD patients displayed a mild COVID-19 course, certain underlying disease features and COVID-19 related manifestations should prompt alertness for the physician to identify patients with AARD at high risk for severe COVID-19 and need for hospitalization.

1. Introduction

Almost one year after the World Health Organization declared the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) pandemic, an ever-increasing amount of data has expanded our knowledge of how to cope with it. For patients with autoimmune/autoinflammatory rheumatic diseases (AARD), the initial fears regarding the effect of immunosuppressive therapy on the immune system's ability to cope well with the "unknown" viral invader have been significantly alleviated. Given the independent association between rheumatic disease activity and increased mortality from Corona Virus Disease 2019 (COVID-19), the importance of continuing the medications and systematic close monitoring to keep the disease in remission is of great significance [1].

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Despite the initial concerns regarding susceptibility to SARS-CoV-2 infection among patients with AARD, a growing body of data -mostly observational in nature- is reassuring and detects similar or slightly elevated risk for serious/fetal COVID-19 compared to the general population [2–6]. Of interest the use of immunosuppressive therapy and adherence to treatment has been shown to be associated with lower frequency of COVID-19 related symptoms [5] and lower risk for developing severe acute respiratory distress syndrome (ARDS) [7]. Small series and case reports of patients with AARD infected with SARS-CoV-2 revealed that the treatment with tumor necrosis factor a (TNFα) antagonists, anakinra or tocilizumab develop a milder form of SARS-CoV-2 infection [8]. These observations, although limited, suggest that these biologic agents, used chronically, can ameliorate the burden of cytokine storm induced by SARS-CoV-2, and thus mitigate the severity of this infection. In addition, another study showed that patients on cytokine inhibitors display lower rates of serum IgG antibody titers against SARS-CoV-2 compared to healthy individuals as well as to patients with immune mediated inflammatory disease not receiving anti-cytokine therapies [9].

In the current observational study, the clinical features as well as the outcome of COVID-19 are described in a cohort of patients with AARD infected by SARS-CoV-2 and we aim to identify risk factors leading to hospitalization. Moreover, a thorough literature review regarding the clinical expression and outcome of COVID-19 among immunosuppressed AARD patients was performed.

2. Materials and methods

2.1. Study population

From the beginning of COVID-19 pandemic patients followed in four outpatient rheumatology clinics in the area of Athens, Greece were instructed to notify their treating physician in case of infection with SARS-CoV-2, confirmed by either a positive PCR on the nasal-pharyngeal swab material or a positive serology for the specific IgG antibodies to SARS-CoV-2 in association with typical COVID-19 symptomatology. The study population included 77 self-referred consecutive AARD patients infected by SARS-CoV-2 between March 2020 and March 2021. Demographic data, comorbidities and baseline medications were extracted from their medical records.

Completion of a structured questionnaire was performed including the date of documented SARS-CoV-2 infection, presence of high (more than 38 °C) or low-grade (up to 38 °C) fever, myalgias, arthralgias, fatigue, nasal congestion, sore throat, anosmia, loss of taste, headache, cough (dry or productive), shortness of breath (SOB), diarrhea, vomiting, confusion, rash or seizures. For patients who required hospitalization, information was obtained by the medical report upon discharge. Patients' disease course was scored as mild: presence of any of the various signs and symptoms of COVID-19 but lack of dyspnea or abnormal chest imaging; moderate: presence of lower respiratory disease during clinical assessment or imaging but sustained oxygen saturation above 94% on room air; severe: hypoxic patients with oxygen saturation below 94% on room air or imaging assessed lung infiltrates above 50%; critical: individuals with respiratory failure, septic shock, and/or multiple organ dysfunction [10]. Antibodies were measured in 29 patients approximately 2 months after recovery. Antibody detection of IgG anti-SARS- CoV-2 antibody in sera samples was performed using a chemiluminescence immunoassay kit for 2019-nCov detection from Xiamen Innodx Biotech, according to the manufacturer's instruction. A recombinant nucleoprotein of SARS-CoV-2 was expressed in *Escherichia coli* to be used as coating antigen.

Anemia is defined as hemoglobin levels below 12.5 and 11.5 g/dL for men and women, respectively. Leukocytosis and leukopenia are defined as total white blood cells above 11.0×10^9/L and below 4.5×10^9/L of circulating blood, respectively. Lymphopenia is defined as lymphocytes fewer than 1.0×10^9/L of circulating blood. Thrombocytosis and thrombocytopenia are defined as platelet counts fewer than 150×10^9/L and more than 450×10^9/L of circulating blood, respectively. Total creatine phosphokinase (CK) and lactate dehydrogenase (LDH) normal value ranges were considered as follows: a) males: 55–170 units/L and females: 30–135 units/L and b) LDH: 50–150 units/L, respectively. Erythrocyte sedimentation rate (ESR) was considered abnormal when it was more than age/2 mm/h.

All patients gave written informed consent prior to participation in the study and the study conformed with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of "Laikon" Hospital.

2.2. Statistics

All statistical analyses were performed using SPSS v.25.0 (IBM, Armonk, NY, U.S.) and GraphPad Prism 8 (GraphPad Software, San Diego, CA, U.S.), with the level of statistical significance being set at 0.05. Chi square or Fisher's exact test was performed to compare the frequencies of categorical variables and Mann-Whitney or *t*-test was employed for detecting significant differences in numerical variables. To explore independent predictors for hospitalization and severity outcomes, univariate and multivariate logistic regression models were implemented. We classified predictors for hospitalization into 2 major groups including a. AARD related features and comorbidities and b. COVID-19 related features. A P-value <0.05 and 0.1 for univariate and multivariate analysis was considered statistically significant, respectively.

3. Results

3.1. Distribution of underlying diagnoses and clinical characteristics of COVID-19 patients

Diagnoses were distributed as follows: 61 patients with systemic autoimmune rheumatic diseases (presence of serum autoantibodies including rheumatoid factor, antinuclear, anti-citrullinated peptide, antiphospholipid, myositis specific and anti-neutrophil cytoplasmic antibodies (ANCA) as well as antibodies against extractable antigens); more specifically, our study cohort included 16 patients with systemic lupus erythematosus (SLE), 18 patients with rheumatoid arthritis (RA), 8 with Sjogren's syndrome (SS), 11 with systemic sclerosis (SSC), 2 with ANCA-associated vasculitis (AAV), 3 with idiopathic inflammatory myopathy (IIM), 1 with antiphospholipid syndrome (APS), 1 with mixed connective tissue disease (MCTD) and 1 with undifferentiated connective tissue disease (UCTD). The remaining 16 patients had an autoinflammatory background in the absence of serum autoantibodies [11 patients with seronegative arthritis (6 psoriatic arthritides, 1 ankylosing spondylitis, 2 seronegative arthritides, 2 Still's diseases), 1 with relapsing polychondritis, 1 with cutaneous polyarteritis nodosa, 1 with polyarteritis nodosa and 2 with autoinflammatory syndromes (1 cryopyrin-associated periodic syndrome (CAPS) and 1 TNF receptor–associated periodic syndrome (TRAPS)], fulfilling internationally accepted classification criteria.

As shown in Supplementary Table 1, the mean age of patients was 49.5 ± 16.8 years, with the majority being females (80,5%). Fatigue and low-grade fever were the predominant symptoms detected in 58.4% and 45.4% of patients, respectively. Cough, myalgias, anosmia, high-grade fever, loss of taste, diarrhea, headache and sore throat were the second most commonly occurring set of complaints at a range from 22.1% to 41.5%, while infrequent complaints (less than 14.3%) included SOB, nasal congestion, arthralgias, vomiting, confusion, seizures and rash. Methylprednisolone was the most frequent medication used at 33.8% of patients with a mean dose of 5.4 ± 3.4 mg per day. Hydroxychloroquine, azathioprine or mycophenolate mofetil and methotrexate or leflunomide were used by 20.8%, 20.8%, and 22.1% of patients, respectively. Anti-TNF agents were the fourth most common prescribed drug in

19.5% of the cases. Anti-TNF or anti-cytokine agents monotherapy was observed at 10.4% of all. Cyclosporine, thalidomide, tocilizumab, cyclophosphamide, rituximab, belimumab, anakinra and canakinumab were the least used medication regimens ranging between 1.3% and 5.2%. The two most common comorbidities observed were hypothyroidism and lung disease related with the AARD at 16.7% and 14.2% of the cases, respectively; most of the cases with lung disease concerned patients with interstitial lung disease. Prior medical history of hypertension, diabetes mellitus, cardiovascular disease and dyslipidemia were less common, ranging from 6.9% to 12.5%.

Laboratory examination, shown in Supplementary Table 2, was available for approximately 34.2% of the patients and the main abnormalities referred to the complete blood count and liver function tests (LFTs). Anemia was present in 28.6% of cases, while 28.6% and 42.9% of the infected individuals revealed leukopenia and lymphopenia, respectively. Liver enzymes were elevated in 28.6% of cases. 63% of the patients presented increased C reactive protein (CRP) values.

In the current study, 2 patients out of the total of 77 (2.5%) remained asymptomatic during follow up, 53 patients (68.8%) showed mild symptomatology, 12 patients (15.5%) developed a moderate course, 8 patients (10.3%) experienced a severe disease activity and 2 patients (2.5%) developed critical disease. In the 2 asymptomatic individuals, SARS-CoV-2 nasopharyngeal PCR test was performed, due to previous contact with individuals with documented infection.

3.2. Distinctive features among patients with asymptomatic, mild or moderate and those with severe or critical COVID-19

As shown in Table 1, when patients with severe or critical disease ("serious illness" group) were compared to those with asymptomatic, mild or moderate disease, the former were significantly older (mean age of patients 68.9 ± 12.8 vs 46.6 ± 15.4, $p < 0.001$) and had lung disease related with the AARD (50.0 vs 9.0%, $p < 0.001$). Considering drugs use for therapy of a given disease, prior treatments with corticosteroids, mycophenolate mofetil and rituximab were more common in patients ultimately experiencing a more serious disease course (60.0 vs 29.9%, $p = 0.003$, 40.0 vs 7.5%, $p = 0.003$, 10.0 vs 0.0%, $p = 0.009$, respectively). SOB and age have been shown to be independently associated with severe/critical outcomes, following adjustment for both disease related features/medications/comorbidities and COVID-19 manifestations [OR 95% (CI): 12.7 (1.7–96.0), $p = 0.014$ for SOB and 1.1 (1.0–1.2), $p = 0.003$ for age, respectively].

3.3. Outcomes - predictors for hospitalization

Regarding the need for hospitalization, 18 of the patients (23.4%) required inpatient treatment, with a mean duration of 9.4 ± 4.1 days. Among the two patients in critical condition, one death was reported. The main diagnoses in the hospitalized patients were RA, SSC and SS. As shown in Table 2, while there was no difference in sex distribution between hospitalized and non-hospitalized patients (% of females: 83.3 vs 79.7, respectively), patients requiring hospitalization were older (mean ± SD: 63.9 ± 14.4 vs 45.1 ± 15.0 years, $p < 0.001$, respectively) and had more frequently evidence of lung disease related with the AARD and dyslipidemia (44.4 vs 5.1%, $p < 0.001$ and 22.2 vs 3.7%, $p = 0.014$, respectively). Among COVID-19 related features, high-grade fever, SOB and confusion occured more frequently in patients requiring hospitalization compared to infected patients recovering at home (72.2 vs 18.6%, $p < 0.001$, 38.9 vs 6.8%, $p < 0.001$ and 5.5 vs 0%, $p = 0.016$, respectively). On the other hand, anosmia was significantly more common among non-hospitalized patients compared to those requiring hospitalization (37.3 vs 5.6%, $p = 0.01$). Regarding the therapeutic scheme among those requiring hospitalization, more frequent use of mycophenolate mofetil (33.3 vs 5.1%, $p = 0.001$) and corticosteroids (61.1 vs 25.4%, $p = 0.005$) was detected. Following multivariate analyses, older age and lung disease related with the AARD were identified as independent predictors for hospitalization: (OR [95%]: 1.09 [1.03–1.15], 6.43 [1.11–37.19]). Among COVID-19 related features, independent associations with hospitalization included anosmia, SOB and high-grade fever (OR [95%]: 0.09 [0.01–0.99], 7.06 [1.36–36.57], 12.04 [2.96–48.86]). In the subgroup of hospitalized patients, with available laboratory findings for 77% of them, the most common abnormalities were anemia (46.7%), lymphopenia (53.3%), increased LFTs (40%) with mean levels being 2.1 times higher than the normal upper limit, increased CRP (78.6%) with mean levels being 8.9 times higher than the normal upper limit, increased ferritin (25%) with mean levels being 2.7 times higher than the normal upper limit, increased CK and/or LDH (41.7%) and increased D-dimers (55.5%) with mean levels being 2.8 times higher than the normal upper limit. Chest X-ray (CXR) abnormalities were noticed in 57.1% of the hospitalized patients, while chest computed tomography (CT) pathology was described in 92.9%. The extend of lung infiltrates (LI) in CT was further classified, with 21.4% of

Table 1
Statistically significant comparisons in demographics, main COVID-19 related symptoms, medications and comorbidities between patients with asymptomatic, mild or moderate disease and those with severe or critical disease.

	Patients with asymptomatic, mild or moderate disease (n = 67)	Patients with severe or critical disease (n = 10)	p-value
Demographics			
Age (mean ± SD, years)	46.6 ± 15.4	68.9 ± 12.8	<0.001
COVID-19 symptoms			
Fever low grade (%)	50.7	10.0	0.016
Fever high grade (%)	25.4	70.0	0.008
Headache (%)	29.0	0.0	0.045
Shortness of breath (%)	9.0	50.0	<0.001
Seizures (%)	0.0	10.0	0.009
Medications			
Methylprednisolone (%)	29.9	60.0	0.003
Azathioprine or Mycophenolate mofetil (%)	17.9	40.0	0.005
Mycophenolate mofetil (%)	7.5	40.0	0.003
Rituximab (%)	0.0	10.0	0.009
Comorbidities			
Lung disease (%)	9.0	50.0	<0.001

Table 2
Statistically significant comparisons in demographics, main COVID-19 related symptoms, medications and comorbidities between patients requiring hospitalization and those recovered at home.

	Patients required hospitalization (n = 18)	Patients recovered at home (n = 59)	p-value
Demographics			
Age (mean ± SD, years)	63.9 ± 14.4	45.1 ± 15.0	<0.001
COVID-19 symptoms			
Fever low grade (%)	16.7	54.2	0.005
Fever high grade (%) (>38 °C, %)	72.2	18.6	<0.001
Anosmia (%)	5.6	37.3	0.01
Shortness of breath (%)	38.9	6.8	<0.001
Confusion (%)	5.5	0.0	0.016
Medications			
Methylprednisolone (%)	61.1	25.4	0.005
Azathioprine or Mycophenolate mofetil (%)	44.4	13.6	0.005
Mycophenolate mofetil (%)	33.3	5.1	0.001
Comorbidities			
Lung disease (%)	44.4	5.1	<0.001
Dyslipidemia (%)	22.2	3.7	0.014

Table 3
Laboratory and radiological findings among hospitalized patients.

	Patients required hospitalization (n = 18)
Laboratory findings	
Anemia (%)	46.7
Leukocytosis (%)	20.0
Leukopenia (%)	20.0
Lymphopenia (%)	53.3
Thrombocytosis (%)	0.0
Thrombocytopenia (%)	6.7
LFTs (%)	40.0
Number of times AST above UNL (mean ± SD)	2.1 ± 1.4
Number of times ALT above UNL (mean ± SD)	1.9 ± 1.6
CK/LDH (%)	41.7
CRP (%)	78.6
Number of times CRP above UNL (mean ± SD)	8.9 ± 8.5
ESR (%)	40.0
Ferritin (%)	25.0
Number of times Ferritin above UNL (mean ± SD)	2.7 ± 0.3
D-Dimers (%)	55.5
Number of times D-Dimers above UNL (mean ± SD)	2.8 ± 1.2
Hypoxia (%)	52.9
O_2 Saturation (mean ± SD)	89.6 ± 4.6
Radiological Findings	
CXR	
CXR pathology (%)	57.1
CT	
No LI (%)	7.1
LI < 15 (%)	21,4
LI 15–25 (%)	35.7
LI 25–50 (%)	28.5
LI > 50 (%)	7.1

LFTs: liver function tests, AST: aspartate transaminase, ALT: alanine transaminase, UNL: upper normal limit, CK: creatine phosphokinase, LDH: lactate dehydrogenase, CRP:C-reactive protein, ESR: erythrocyte sedimentation rate, CT: computed tomography, CXR: chest x-ray, LI: Lung infiltrates.

patients presenting with <15% LI, 35.7% with 15–25% LI, 28.5% with 25–50% LI and 7.1% with >50% LI (Table 3).

3.4. Distinctive COVID-19 related features between AARD patients of systemic autoimmune vs inflammatory background

Next was sought to explore whether the underlying pathogenetic (systemic autoimmune vs autoinflammatory) background of AARD could influence the clinical expression of COVID-19 in these patients. Of interest, patients with systemic autoimmune background experienced more frequently fatigue and less frequently seizures (65.6 vs 31.1%, p = 0.013 and 0.0 vs 6.3%, p = 0.04) and developed higher rates of anti-SARS-CoV-2 IgG seroconversion compared to those with auto-inflammatory background (80.0 vs 25.0%, p = 0.02) (data not shown).

3.5. Antibody responses against SARS-CoV-2

IgG antibody titers against SARS-CoV-2 were measured approximately 2 months (62.6 ± 36.51, days) after the detection of a positive PCR nasopharyngeal swab for SARS-CoV-2. Antibody data was available for 29 patients and IgG were detected in 72.4% of them. No significant associations were found between antibody response and demographics, medications, clinical manifestations or outcomes.

4. Discussion

In the current observational study, we present the clinical spectrum related to COVID-19 in a cohort of AARD patients of Greek descent infected by SARS-CoV-2 observed from March 2020 to March 2021. The majority of patients had a mild course mainly presenting with fatigue, low grade fever and upper respiratory tract symptoms, which subsided within 9–10 days. Quite interestingly, fatigue tended to be more common among patients with AARD with a systemic autoimmune background (presence of serum autoantibodies). About a quarter of patients required hospitalization and only one death was reported. When taking into consideration AARD related features and comorbidities, older age and lung involvement were found to be independent predictive factors for hospitalization. Among COVID-19 related features, SOB and high-grade fever were independently associated with hospitalization, while anosmia was linked to lower hospitalization rates. Similar were the results when patients with severe or critical disease were compared to the ones with milder disease courses.

Immune dysfunction in the context of autoimmunity and immunosuppressive treatment has raised concerns about the possibility of increased disease severity and subsequent hospital admission. The findings in our study indicate a lower rate of hospitalization (23.3%, adjusted to 26.7%, following inclusion of 9 more cases during the evaluation of the current manuscript), quite similar to the general population [11,12,21], compared to other published literature reporting a need for hospital care for 30–72% of infected AARD patients [13–15,18–20,22,23] (Table 4). It is worth mentioning that this rather favorable observation regarding COVID-19 outcomes might reflect that most of our patients were in remission, not treated with rituximab or high doses of corticosteroids. In the same context, another possible explanation for the variation between the studies might be the availability of additional therapeutic options for COVID-19 in the later stages of the pandemic compared to the beginning, as well as potential reporting and recruitment biases leading to heterogeneous study populations.

In line with previous studies in both AARD patients and the general population, we found that older age and lung disease in the context of

Table 4
Summary of COVID-19 related outcomes of studies recruiting more than 100 AARD patients.

First author	Number of participants with AARD	Rate of severe disease, %[a]	Rate of hospitalization, %	Rate of mortality, %
Pablos et al [4]	228	13.5	71.1	18.1
French RMD COVID-19 cohort [34]	694	12.5	37.0	8.3
Strangfeld et al [37]	3729	N/A	49.0	10.5
Gianfrancesco et al [13]	600	N/A	46.0	9.0
Attauabi et al [15]	184	N/A	41.8	13.6
Marques et al [31]	334	N/A	33.0	8.4
Scirè et al [19]	232	N/A	69.8	19.0
Freites Nuñez et al [20]	123	N/A	43.9	22.2
Xu et al [22]	1138[b]	N/A	58.0	7.0
Akiyama et al [25]	2766[b]	N/A	35.0	6.6

AARD: autoimmune/auto-inflammatory rheumatic diseases N/A: Not applicable.
[a] Where applicable, different disease severity classification criteria were used.
[b] Systematic review and meta-analysis.

the underlying AARD were significantly more common among the hospitalized patients [13,16,24–27]. Interestingly, anosmia was significantly more common in non-hospitalized patients and turned to be an independent protective factor for hospitalization, as previously suggested [28,29]. Moreover, since male sex seems to associate with higher death rates and more severe course than females [30], the female predominance in systemic autoimmunity could have been a protective factor for the favorable outcomes. Within the current cohort, there was a higher proportion of patients receiving corticosteroids among those within the "serious illness" group and those who were hospitalized compared to those recovering at home, which is in agreement with prior studies showing an increased risk of severe infection for patients under corticosteroid treatment [12,13,15,31].

Disease severity in patients with AARD has been a focus of interest during the pandemic, with implications for hospitalization risk and outcome. In accord with previously published data in general population and rheumatic disease cohorts with reported rates of moderate and severe disease ranging from 22 to 24% and 8 to 13%, respectively [32–35], most of our patients experienced a rather uncomplicated disease course. The COVID-19 related death rate was 1.2% (adjusted to the new cases as previously mentioned), quite similar to that of the general population [1,36] and slightly lower than that previously reported in rheumatic diseases [12,22,31,34,37,38]. However, although neither our study nor the above-mentioned ones were designed to calculate the morbidity and mortality rates, the current data on overall disease course and outcome is rather reassuring.

Regarding previous use of immunomodulatory therapies by patients with AARD, our study shows that prior treatment with corticosteroids, mycophenolate mofetil and rituximab was more frequent in the "serious illness" or the hospitalization group, in line with most of the previous published data [4,14,17,25,26,39–41]. It is though important to emphasize that any possible association between rituximab and COVID-19 could have also been influenced by the typical coadministration of corticosteroids [14,37,42–44]. Notably, the majority of our patients treated with anti-cytokine monotherapy developed a mild disease course, while among the two patients in critical condition, the one who finally died presented almost all risk factors associated with hospitalization and death. He was a 57-year-old patient with seropositive RA, severe previous lung disease and concomitant presence of anti-NOR90 autoantibodies, who was treated with rituximab, mycophenolate mofetil and low doses of corticosteroids. The second critical patient who recovered was an 86-year-old female with SLE, concomitant lung disease treated with mycophenolate mofetil and corticosteroids and non-responder to SARS-CoV-2 vaccination [45,46]. Taking other studies and ours into consideration, corticosteroids and rituximab use is associated with worse outcomes while targeted synthetic immunomodulatory drugs or biologics monotherapy, and particularly anti-TNF agents, seem to relate with a favorable outcome. These findings highlight the different ways drugs might modify the disease course and warrants furthers studies to confirm these results.

Patients with SSC, SLE, SS and IMM are characterized by heightened type I interferon (IFN) signature [47–50]. The latter is also increased in patients with early treatment-naive rheumatoid arthritis and predicts a poorer response to initial therapy [51]. On the other hand, severe COVID-19 disease has been associated with defective type I interferon production at earlier disease stages [52–54]. Taken together this data could imply that endogenous type I IFN production in the setting of AARDs could lead to effective viral clearance and prevention of exaggerated inflammatory responses.

Regarding symptomatology, most patients presented with fatigue, fever, cough, anosmia and myalgias, similarly to what previously reported [14,16,41,55,56]. Fatigue was the predominant clinical feature in our cohort affecting 58.4% of patients though previous studies reported similar rates between AARD patients and controls at a range of 20–25% [55,57]. This could be attributed to overrepresentation of patients with systemic autoimmune origin, which was found to be associated with heightened fatigue rates in our SARS-CoV-2 infected patients compared to those with inflammatory background. Though intriguing and not entirely clear, this observation could be related to similar mechanisms leading to high fatigue rates among patients with SLE and SS [27,58–60] Modulation of COVID-19 symptoms and outcomes by the underlying disease has been previously reported. Thus, the risk for hospital admission and severe disease has been shown to be higher in patients with prior autoimmune systemic disease rather than chronic inflammatory arthritis [3,20]. In contrast, Benjamin Fernandez-Gutierrez et al. found no difference in hospitalization comparing the two groups [26].

It is worth mentioning that patients may present with non-specific symptomatology and especially without respiratory involvement and thus COVID-19 diagnosis could be misinterpreted with a disease flare, which seems to be a rather infrequent phenomenon [27,58,61]. In our case series there was only one disease flare regarding a 17-year-old male diagnosed with TRAPS who was in remission on colchicine. The patient experienced generalized skin rash accompanied by arthralgias at the peak of the fever, a symptomatology that completely subsided following an increase in colchicine dose.

To date, there are limited studies characterizing the adaptive immune responses to SARS-CoV-2 in patients with AARD. Compared to approximately 90% of seroconversion at 3 months post infection in the general population, our patients displayed a lower rate of antibody responses [62–68]. Our finding is consistent with the study by D'Silva et al., in which 77% of PCR-confirmed COVID-19 and rheumatic disease patients had positive antibodies for SARS-CoV-2 [69]. Similar to our results, no associations were so far found with prior immunosuppressive therapy including tocilizumab, anakinra, rituximab or prednisolone [68,70], except for a recent study which showed attenuated antibody responses in patients with inflammatory bowel syndromes treated with an anti-TNF agent [71].

There were some limitations in this study. First, this is an observational study where participants were recruited based on self-referral. Second, non-hospitalized individuals self-reported their symptomatology, which might have led to recall bias in terms of onset and duration of symptoms and we might have missed asymptomatic or very mild cases. Third, evidence-based treatment protocols had not been developed and any differences in disease management might have led to different outcomes, introducing bias. Finally, this study includes a broad range of AARDs and due to the limited number of patients in certain disease type, we did not subcategorize the AARDs when analyzing some parameters.

5. Conclusions

In conclusion, this cohort study demonstrates that most patients with AARD infected with SARS-CoV-2 have a rather mild disease course and finally recover from COVID-19. Nonspecific symptomatology like fatigue, low grade fever and musculoskeletal complaints are common among infected individuals and as such physicians should continue to be highly alert. As in the general population, AARD patients who are older and have lung disease are of a greater risk of severe COVID-19 and related hospitalization. Additionally, although exposure to specific medication classes, such as mycophenolate mofetil and corticosteroids, is more common among hospitalized patients and therefore a potential risk factor, such finding should be interpreted with caution. These risks so far do not seem to overweight the benefits of maintaining the underlying disease in remission and any possible associations between immunomodulatory drugs and vaccination responses should be interpreted thoroughly as we pass in a new post vaccination era.

Credit author statement

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Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaut.2021.102687.

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