



Araştırma

2023; 32(1): 106-112

AN OVERVIEW OF THE RHEUMATOLOGY OUTPATIENT CLINIC VISITS IN THE FIRST 16 MONTHS OF THE COVID-19 PANDEMIC: SINGLE-CENTRE EXPERIENCE
COVID-19 PANDEMİSİNİN İLK 16 AYINDA ROMATOLOJİ POLİKLİNİK VİZİTLERİNE GENEL BİR BAKIŞ: TEK MERKEZ DENEYİMİ

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ABSTRACT

The aim of this study is to present a general picture of patients who applied to the rheumatology outpatient clinic in the first 16 months of the COVID-19 pandemic. Patients who applied to the rheumatology outpatient clinic between March 2020 and August 2021 were included in the study. Patients' clinical and demographic characteristics, the received drug treatments at their last admissions, and the outpatient clinic visits of patients within the specified 16-month period were evaluated retrospectively. A total of 869 patients were included, and their mean age was 48.51 ± 12.84 years; of these, 658 (75.71%) were female and 211 (24.29%) were male. The most common disease diagnosis was rheumatoid arthritis (29.57%). The average number of hospital visits in 2021 was significantly higher than in 2020. Also, patients who received both biological disease-modifying antirheumatic drugs (bDMARDs) and conventional synthetic disease-modifying antirheumatic drugs (csDMARDs)/immunosuppressives had a significantly higher number of admissions than those who did not (for all, p<0.05). The patients were divided into two groups based on their age as over and under 65 years of age, the number of outpatient clinic admissions was similar between the groups (p=0.620). We determined that the year of admission, gender, and the drugs used had significant effects on the number of applications during this period. These and other effects of the pandemic on rheumatic diseases should be demonstrated in multicenter prospective studies.

ÖZ

Bu çalışmanın amacı, COVID-19 pandemisinin ilk 16 ayında romatoloji polikliniğine başvuran hastaların genel bir resmini sunmaktır. Mart 2020-Ağustos 2021 tarihleri arasında romatoloji polikliniğine başvuran hastalar çalışmaya dahil edildi. Hastaların klinik ve demografik özellikleri, son başvurularında kullandıkları ilaç tedavileri ve belirlenen 16 aylık süre içerisinde poliklinik ziyaretleri retrospektif olarak değerlendirildi. Toplam 869 hasta dahil edildi ve hastaların ortalama yaşları 48.51 ± 12.84, 658'i (%75.71) kadın, 211'i (%24.29) erkekti. En sık görülen hastalık tanısı romatoid artrit (%29.57) idi. 2021'deki ortalama hastane ziyareti sayısı 2020'den istatistiksel anlamlı olarak daha yüksekti. Ayrıca, hem biyolojik hastalık modifiye edici antiromatizmal ilaçlar (bDMARD'lar) hem de konvansiyonel sentetik hastalık modifiye edici antiromatizmal ilaçlar (csDMARD'lar)/immünosupresifler alan hastalar almayanlara göre daha yüksek başvuru sayısına sahipti (tümü için, p<0.05). Hastalar yaşlarına göre 65 yaş üstü ve altı olmak üzere iki gruba ayrıldığında poliklinik başvuru sayıları gruplar arasında benzerdi (p=0.620). Bu dönemde başvuru sayıları üzerine başvuru yılı, cinsiyet ve kullanılan ilaçların önemli etkileri olduğunu belirledik. Pandeminin romatizmal hastalıklar üzerindeki bu ve diğer etkileri çok merkezli prospektif çalışmalarla gösterilmelidir.

Keywords: COVID-19, outpatient clinic, rheumatology

Anahtar kelimeler: COVID-19, poliklinik, romatoloji

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Makale Geliş Tarihi : 13.09.2022
Makale Kabul Tarihi: 05.01.2023

INTRODUCTION

The COVID-19 disease caused by SARS-CoV2 (new corona virus), which first appeared in Wuhan, China, in December 2019, spread rapidly all over the world and became an important health problem by affecting millions of people (1). The clinical spectrum of the COVID-19 disease is highly heterogeneous and can range from asymptomatic infection to acute respiratory distress syndrome, multiorgan failure, or death (2). Due to respiratory tract infection, the main transmission route of the virus is through droplets, and close contact with infected individuals is critical for transmission (3). In this direction, the country administrations took precautionary measures to reduce the spread of the disease and the hospital burden. Practices such as stay-at-home calls, curfews, approaches to the importance of social isolation, and postponing elective procedures were some of them (4).

In various studies, mortality rates due to COVID-19 infection are estimated to be around 3.6%. When severe cases that need treatment in intensive care units and progress to acute respiratory syndrome (ARDS) are examined, it is reported that they are older and have at least one comorbidity (diabetes mellitus, hypertension, cardiovascular diseases, etc.). In some studies, immune dysregulation in COVID-19 infection is associated with comorbidities (5, 6). Rheumatic diseases have both a chronic course and a higher risk of comorbidities over the years than in the general population. It is known that cardiovascular diseases and also gastrointestinal diseases, metabolic diseases, malignancies, and infections may accompany these patients. The presence of comorbidities is extremely important as it may affect the hospitalization and death rates due to COVID-19 in rheumatology patients. Although no exacerbation of the disease was detected in short-term studies on rheumatic diseases in the COVID-19 pandemic, it was found that drug compliance in these patients was impaired. It was thought that this would contribute to an increase in exacerbations and the risk of comorbidity in the near future (7).

While the immunosuppressive effects of antirheumatic drugs cause concerns for COVID-19 infection, some of these [IL-6 antagonists, anakinra, intravenous immunoglobulin, chloroquine, and hydroxychloroquine (HCQ)] have become potential treatment options for patients infected with SARS-CoV2(5). In fact, some individuals with the rheumatic disease had difficulties in accessing HCQ treatment in the early stages of the pandemic (8). International rheumatology societies have published several guidelines on the management of rheumatic diseases during the COVID-19 pandemic. Here, opinions have been presented about which treatments will be discontinued, which ones can be continued, and when the treatments can be restarted after interruption due to COVID-19 infection (9). Also, within the scope of the measures taken by the Ministry of Health regarding chronic diseases in our country, during the pandemic period, the drugs that they used before were directly supplied from pharmacies without the need for renewing their drug reports and writing a prescription (10).

In line with the suggestions of the administrations, the hospitals left their routine practices aside and were

reorganized according to COVID-19 requirements. Non-urgent procedures were stopped or postponed, staff was assigned to COVID fields based on needs, and inpatient clinics were quickly allocated to COVID-19 services. This situation led to the categorization of patients concerning their priority status and the postponement or cancelation of some treatments (11). Also, telemedicine applications came to the fore for patients who could not reach the hospital (12). As a result, the COVID-19 pandemic has forced people to stay at home with social isolation. Due to the warnings by government agencies not to leave the house except in obligatory circumstances, the number of patient admissions and the demographic characteristics of the patients who applied to the hospitals changed significantly (2). Based on these, we thought that factors such as general infection spread precautions changes in the routine working of hospitals, patients' existing rheumatic or additional comorbid diseases, their concerns about the immunosuppressive treatments that they use, and the ease of access to drugs without hospital admission would have an impact on parameters including age and gender patterns, frequency of outpatient visits, and diagnosis distribution of individuals who apply to the hospital. Moreover, much needs to be addressed about the hospital admissions of rheumatology patients during the pandemic period. Therefore, in the current study, we aimed to present a general picture of patients who applied to the rheumatology outpatient clinic in the first 16 months of the COVID-19 pandemic.

MATERIALS and METHODS

In this retrospective cohort study, ethical approval was obtained from the Erciyes University Clinical Research Ethics Committee (Date: October 20, 2021, Approval Number: 2021/687) after the Ministry of Health gave permission (2021-09-15T11) for the study. Patients who applied to the rheumatology outpatient clinic at the Erciyes University Faculty of Medicine between March 11, 2020, and August 31, 2021, were included in the study. Due to the retrospective nature of this study, the requirement for informed consent was waived by the Ethics Committee. Data collected from the hospital electronic registration system, such as the patient's clinical (symptom duration and disease duration) and demographic (age and gender) characteristics, the drug treatments used in their last admission, and the number of outpatient visits within the specified 16-month period, were evaluated retrospectively. Duplicate applications were not included in the total number of applicants and were included in an additional heading under "application number". The number of applications was calculated both in total and separately for 2020 and 2021. However, it was required that the patients had visited the outpatient clinic for 1 or more times in one of two different years. Due to the curfews for individuals aged 65 and over in the COVID-19 pandemic, we divided the patients into two subgroups according to this age limit. Newly diagnosed patients during the evaluation period were not included in the study due to its effects on the number of applications. Patients without any rheumatic disease (fibromyalgia, osteoarthritis or patients with traumatic, paraneoplastic, and infectious arthritis) were excluded from the study. Also, no labora-

tory or imaging tests were requested from the patients.

Statistical analysis

The SPSS, Version 23 (IBM Corp., Armonk, NY, USA), was used for the statistical analysis. The normality of the distribution of data was tested using the Shapiro-Wilk test. The independent samples *t*-test was conducted to compare normally distributed data between the two independent groups. Paired-sample *t*-test was used to measure the differences between the number of admissions of the same patients in two different years. Relationships between numerical variables were assessed using Spearman's correlation coefficient. Descriptive statistics for numerical variables are expressed as means \pm standard deviations, while those for categorical variables are expressed as numbers and percentages. A *p*-value of <0.05 was considered statistically significant.

RESULTS

In the current study, 869 patient files that met the inclusion criteria between March 11, 2020, and August 31, 2021, were retrospectively evaluated. The number of patients with at least one outpatient visit was 635 and 726 for the year 2020 and 2021, respectively. The mean age of the patients was 48.51 ± 12.84 years. Also, 75.71% of the patients were female, and 24.29% were

male. Detailed demographic and clinical characteristics of the patients are shown in Table I.

When the diagnoses of the patients who applied to the rheumatology outpatient clinic were examined, the most common diagnosis was rheumatoid arthritis (RA) (29.57%). However, if the diagnoses in the spondyloarthritis (SpA) spectrum, such as axial SpA (axSpA), peripheral SpA (pSpA), coexistence of Behcet's disease and axSpA, and coexistence of familial Mediterranean fever (FMF) and axSpA, were combined, the rate of SpA increased to 35.67% (Table II).

The mean number of outpatient clinic visits of all patients who were admitted to the hospital during the evaluation period was 4.42 ± 3.16 . The average number of hospital visits in 2021 was significantly higher than admissions in 2020 ($p < 0.001$). The number of hospital applications of female patients was statistically significantly higher than that of male patients ($p = 0.010$). Also, patients who used both bDMARDs and csDMARDs/immunosuppressives had a significantly higher number of admissions than those who did not ($p < 0.001$ and $p = 0.026$, respectively). The fact that the patients were 65 years old and older or younger than 65 did not affect the number of outpatient visits ($p = 0.620$) (Table III).

In the correlation analysis, there was no statistically significant correlation between the number of hospital

Table I. Clinical and demographic characteristics of patients.

Number of total patients	869
year 2020	635*
year 2021	726*
Age, years	48.51 ± 12.84
Female/Male, n (%)	658/211 (75.71/24.29)
Patients < 65 years of age, n (%)	773 (88.95)
Patients \geq 65 years of age, n (%)	96 (11.05)
Symptom duration, years	10.0 ± 6.89
Disease duration, years	8.97 ± 6.82
Patients using csDMARDs/immunosuppressives, n (%)	547 (62.94)
HCQ	114 (20.96)
MTX	79 (14.52)
Sulphasalazine	52 (9.56)
Azathioprine	16 (2.94)
Leflunomide	13 (2.39)
Steroid alone	16 (2.94)
csDMARD monotherapy+steroid	102 (18.75)
csDMARD combination+steroid	68 (12.50)
csDMARD combination	56 (10.30)
Immunosuppressive+steroid	14 (2.57)
Other combinations	14 (2.57)
Patients using bDMARDs, n (%)	270 (31.07)
TNF inhibitors	207 (77.24)
IL-17 inhibitors	17 (6.34)
IL-6 inhibitors	13 (4.85)
T-cell costimulation modulator	12 (4.48)
JAK inhibitors	12 (4.48)
IL-1 inhibitors	6 (2.24)
Anti-CD20 agents	1 (0.37)

Data are expressed as n (%) if categorical, and mean \pm standard deviation if numerical.

SD, standard deviation; csDMARD, conventional synthetic disease-modifying antirheumatic drug; bDMARD, biological disease-modifying antirheumatic drug; TNF, tumor necrosis factor; IL, interleukin; JAK, Janus kinase.

*Without duplicate submissions.

Table II. The distribution of rheumatic diseases

Disease	n (%)
RA	257 (29.57)
AxSpA	212(24.39)
pSpA	67 (7.71)
SjS	67 (7.71)
FMF	51 (5.87)
SLE	38 (4.37)
Overlap syndromes	33 (3.80)
SSc	29 (3.34)
UCTD	26 (2.99)
BD	24 (2.76)
Gout	17 (1.96)
Coexistence ofBD+ and axSpA	17 (1.96)
Coexistence ofFMF and axSpA	14 (1.61)
Adult-onset Still's disease	7 (0.81)
Vasculitis	5 (0.58)
Polymyositis/dermatomyositis	4 (0.46)
Primary APS	1 (0.11)

Categorical data are expressed as n (%).

RA, rheumatoid arthritis; SjS, Sjogren's syndrome; Ax, axial; p, peripheral; SpA, spondyloarthritis; FMF, familial Mediterranean fever; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; UCTD, undifferentiated connective tissue disease;BD, Behcet's disease; APS, antiphospholipid syndrome.

Table III. Number of outpatient clinic applications and associated factors

Patient's characteristics	Number of applications	p-values
All patients	4.42 ± 3.16 (min:1 max:18)	-
By the year of application		
2020	1.84 ± 1.84	p<0.001
2021	2.58 ± 2.09	
Age		
<65 years of age	4.44 ± 3.21	p=0.620
≥65 years of age	4.27 ± 2.68	
Gender		
Female	4.57 ± 3.12	p=0.010
Male	3.93 ± 3.21	
bDMARD		
Yes	5.26 ± 4.03	p<0.001
No	4.04 ± 2.59	
csDMARD/immunosuppressive		
Yes	4.60 ± 3.08	p=0.026
No	4.11 ± 3.26	

Data are expressed as mean ± standard deviation if numerical.

SD, standard deviation; bDMARD, biological disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; min, minimum; max, maximum.

admissions and symptom duration ($r=0.027$, $p=0.418$). Similarly, no statistically significant correlation was found between the number of admissions and disease duration variables ($r=0.052$, $p=0.126$). There was a very weak positive correlation between age and the number of outpatient clinic applications ($r=0.130$, $p<0.001$).

DISCUSSION AND CONCLUSION

In the present study, we obtained some noteworthy results, especially regarding the number of hospital applications. We subdivided patients according to gender, bDMARD or csDMARD/immunosuppressive use, and year of admission; consequently, we found statisti-

cally significantly different results from each other. The most common diagnosis was RA. The majority of patients who applied to the outpatient clinic were women. A weak positive correlation was found between age and the number of outpatient visits, but when we grouped the patients according to the age limit of 65, we failed to find a statistically significant difference between the subgroups in terms of the number of admissions.

Studies on the incidence and prevalence of rheumatic diseases have shown that these two conditions are not static but dynamic processes and are affected by both genetic and environmental factors (13). In studies examining the distribution of diseases in rheumatology

outpatient clinics, different results have been revealed in different countries. Jokar et al. examined Iranian patients who applied to the rheumatology outpatient clinic and found the rate of women to be 64.20% in their study. Also, the most common diagnosis was RA (47.30%), followed by spondyloarthritis (AS, ReA, PsA, enteropathic arthritis, and undifferentiated SpA) with 17.23%. In the German data, where they compared their own results, the rate of women was 71%, and the rates of RA and SpA were 50.6% and 22.61%, respectively (14). In a prevalence study of some rheumatic diseases in Turkey, the most common inflammatory joint disease after osteoarthritis was RA (0.321%) (15). Similarly, we found the most common diagnosis to be RA (29.57%) in our study, followed by axSpA (24.39%) in the second line. However, when patients categorized across the entire SpA spectrum were combined, the rate rose to 35.67%. Considering the studies that found comorbidity clusters in RA patients higher than in axSpA patients (16), the fact that RA was behind axSpA in the patient hospital applications in the current study could be suggested as a result of these patients' fear of COVID-19 infection due to comorbidities. In the study of Esatoglu et al. (17), in which they reported the results of inflammatory rheumatic patients infected with COVID-19, the fact that RA is the most common diagnosis in infected patients and that comorbidities and glucocorticoid use are associated with poor outcome support the possibility of fear of COVID-19 in these patients. It has been shown that 80% of patients with RA develop one or more comorbidities due to ongoing systemic inflammation (18). In all inflammatory rheumatic diseases, how hospital admissions are affected during the COVID-19 pandemic and the factors that may be related to this can be revealed in future national studies.

After the first case in Turkey was identified on March 11, 2020, serious precautionary measures were taken to reduce the spread of the pandemic. Stopping the activities of some businesses, restricting the curfew of individuals over the age of 65, and making intercity travel conditional are some examples of these measures. Although some restrictions were reduced with the controlled normalization steps that started in May 2020, the restrictions came to the fore again with an increase in the spread of the virus as of September 2020 (19). In January 2021, COVID-19 vaccines began to be applied, and as of March, restrictions were determined according to the risk status (low, medium, high, very high) based on the number of cases in the provinces (19, 20). Undoubtedly, vaccination programs are an important practice in protecting susceptible individuals from infection and gaining mass immunity (21). Within this scope, we predicted that situations such as more isolation precautions and the fact that vaccinations were not available might have negative effects on patients' hospital admissions in 2020. For this purpose, we aimed to examine the number of outpatient clinic applications according to year, age, gender, and drugs used. The patients' mean admissions in 2021 were significantly higher than in 2020. Also, female gender and using DMARD/immunosuppressive group drugs were among the factors that increased the number of hospital admissions. When we divided the patients into two groups, considering the age of 65 as the limit, we found that the

number of applications was not statistically different from each other. The fact that the number of applications is similar to individuals under the age of 65, despite the curfews for the people aged 65 years and over, can be due to the given opportunity to apply to hospitals by making an appointment. Also, although 88.95% of the patients who applied to the hospital were under the age of 65, the frequency of outpatient visits was similar to those over the age of 65. This can be attributed to the more frequent disease exacerbations of older individuals due to additional comorbidities. The weak positive correlation between age and the number of applications in our study also supports this finding. In the effect of gender on hospital admissions, factors such as RA being the most common diagnosis in our patient group, frequent incidence of RA and other connective tissue diseases in women (22, 23), and higher disease perception scores in women than men in studies conducted in some chronic diseases (24) can be considered. HCQ, used extensively in the early stages of pandemic and anticytokine therapies in COVID-19 infected patients who are unresponsive to glucocorticoid therapy and have a cytokine storm, caused difficulties in the supply of these drugs in rheumatic diseases. Necessities about the medication reports and prescriptions required more referrals to the following rheumatologist (8, 25). The high number of hospital applications for DMARD or immunosuppressive treatments in our study may reflect drug supply problems. The real reasons for this issue can be clarified in prospective studies.

Although several recommendations were developed by international associations regarding the treatment management of rheumatologists during the pandemic period, the final decision had to be determined according to the clinical condition of the patients or sometimes specific to that particular case. On the other hand, some patients who did not apply to hospitals decided to continue or discontinue the treatment themselves (26). While it is easier to monitor by extending the outpatient visit intervals or routine laboratory tests with telemedicine as long as possible in patients using oral or subcutaneous treatment, this is unlikely in patients using intravenous bDMARDs, and if the treatments are delayed, negative effects related to existing disease may occur. To minimize this, opinions such as switching to subcutaneous formulations of IV treatments, if available, have been reported (27). When viewed from the patient's perspective, in some rheumatology clinics, there has been a decrease in the number of patients of around 70% and appointment delays of up to 15%. Singh et al. attributed these effects to factors such as patients' fear of contracting COVID-19 infection from healthcare facilities, difficulties in transferring them to the hospital due to public transport measures, and quarantine due to COVID-19 infection (28). Also, although rheumatologists are unanimous around the continuation of immunosuppressive treatments, Pineda et al. stated that patients' own beliefs, perceptions, and knowledge of their diseases affected treatment compliance (29). Fragoulis et al. reported that the number of patients who discontinued treatment for fear of immunosuppression was very low in their cohort (30). Conversely, Michaud et al. found that up to 42% of patients had changes in some of their medications (31). Also, some studies have shown

that patients change their current treatment not due to fears of COVID-19 but because of difficulties in accessing drugs (29). In an article about rheumatology patients in Turkey, Akkoç emphasized the price paid by patients for access to medication (8). When the drug treatments of the patients admitted to our study were examined, the most frequently used csDMARD/immunosuppressive group drug was HCQ. In our patient cohort, csDMARD/immunosuppressive therapy users had more outpatient admissions than nonusers. This could be attributed to HCQ supply problems in the early part of the pandemic. Patients using bDMARD have a higher number of outpatient visits, and being informed by our physicians about complications beforehand, not wanting to stop treatment due to bad experiences related to active disease, or their established habits in strict follow-up can be considered factors. In addition to these, we think that the drug use behaviors of patients during the COVID-19 pandemic may vary from country to country, city in the same country, and education level in the city where they live. The real reason for these trends should be investigated in prospective studies.

This study has some limitations. First, its retrospective nature may lead to errors in the information obtained about patients. The tendency of patients to apply to the nearest health institution due to the COVID-19 pandemic may cause differences in the distribution of patients in the current study. Also, the effect of deaths due to COVID-19, the possibility of patients changing cities, the difficulties of reaching our center for patients coming from outside the province, and the use of telemedicine are factors that have the potential to affect both the diagnosis distribution and the frequency of admissions. Finally, the fact that the study was carried out in a tertiary university hospital prevents having an opinion about the general population.

In this study, we have presented a general picture of patients who applied to the rheumatology outpatient clinic by examining the period of approximately 16 months after the onset of the COVID-19 pandemic. We determined that the year 2020 (when the pandemic first showed its effects in Turkey), gender, and the drug being used had significant effects on the number of applications in this period. More realistic effects of the pandemic in rheumatic diseases should be revealed in multicenter prospective studies. We recommend that rheumatologists encourage patients to apply to the hospital to prevent complications due to a lack of follow-up in patients under long-standing pandemic conditions.

Acknowledgements

Not available.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

None.

Ethical approval

Ethical approval was obtained from the Erciyes University Clinical Research Ethics Committee (Date: October 20, 2021, Approval Number: 2021/687) after the Minis-

try of Health gave permission (2021-09-15T11) for the study.

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