Reumatizam 2022;69(1):32–40
https://doi.org/10.33004/reumatizam-69-1-4

PROFESSIONAL PAPER STRUČNI RAD

COVID-19 COURSE AND OUTCOME IN PATIENTS WITH INFLAMMATORY RHEUMATIC DISEASES WHO ARE ON BIOLOGICAL OR TARGETED SYNTHETIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS – RESULTS FROM A SINGLE RHEUMATOLOGY CENTRE

ISHOD I TIJEK BOLESTI COVID-19 KOD BOLESNIKA S UPALNIM REUMATSKIM BOLESTIMA KOJI SU NA BIOLOŠKOJ ILI CILJANOJ SINTETSKOJ MODIFICIRAJUĆOJ TERAPIJI – REZULTATI JEDNOGA REUMATOLOŠKOG CENTRA

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Received / Primljeno: 17th February 2022 / 17. 2. 2022.
Accepted / Prihvaćeno: 5th May 2022 / 5. 5. 2022

Abstract

The aim of this study was to investigate the course and outcome of COVID in patients with inflammatory rheumatic diseases (IRD) who are on biological disease-modifying antirheumatic drugs (bDMARDs) or targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs). In this study, we used the data of patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA) who had been treated at the Department of Rheumatology, Physical and Rehabilitation Medicine of the Sestre milosrdnice University Hospital in Zagreb (Croatia) and in whose case the SARS-CoV-2 infection was proven in the period from February 2020 until the end of July 2021. In order to analyse this data, we have used the methods of descriptive statistics. Out of a total of 28 patients, 6 had a severe or critical case of COVID-19, but only one subject was hospitalized. All 6 patients were treated with bDMARDs before the onset of infection. Most of them (4/6) had moderate to high disease activity of IRD, as well as multiple comorbidities. No deaths were recorded in this cohort of patients. The results of this study suggest that the course of COVID-19 is associated with the disease activity of IRD and accompanying comorbidities, whereas the use of specific biological drugs might be associated with a more favourable outcome of the infection. Therefore, a better follow-up process and management of disease activity in patients with IRD should be implemented during the period of this pandemic, as well as the modification of specific therapy.

Key words: COVID-19, inflammatory rheumatic disease, outcome, bDMARD, tsDMARD

Sažetak

Cilj ovog istraživanja bio je istražiti tijek i ishod bolesti COVID-19 kod ispitanika s upalnim reumatskim bolestima koji su liječeni biološkim lijekovima koji mijenjaju tijek bolesti (engl. *biologic disease modifying antirheumatic drugs*, skr. bDMARDs) i ciljanim sintetskim lijekovima koji mijenjaju tijek bolesti (engl. *targeted synthetic disease mo-*

difying antitheumatic drugs, skr. tsDMARDs). U istraživanju smo analizirali podatke bolesnika s reumatoidnim artritisom (RA), psorijatičnim artritisom (PsA) i aksijalnim spondiloartritisom (axSpA) koji su se kontrolirali na Klinici za reumatologiju, fizikalnu medicinu i rehabilitaciju Kliničkoga bolničkog centra Sestre milosrdnice u Zagrebu i koji su imali dokazanu infekciju virusom SARS-CoV-2 u razdoblju od veljače 2020. do kraja srpnja 2021. godine. Od ukupno 28 bolesnika njih šestoro je imalo teški ili kritični oblik bolesti COVID-19, a samo jedna osoba je bila hospitalizirana. Svih tih šest bolesnika bilo je liječeno bDMARDs-ima. Većina bolesnika (4 od 6) s teškim i kritičnim oblikom bolesti COVID-19 imali su umjereni do visoki stupanj aktivnosti upalne reumatske bolesti, kao i više komorbiditeta. Smrtnog ishoda u ovoj kohorti bolesnika nije bilo. Rezultati ovog istraživanja sugeriraju da je tijek bolesti COVID-19 povezan sa stupnjem aktivnosti upalne reumatske bolesti i popratnim komorbiditetima, a mogući povoljniji ishod s upotrebom specifične biološke terapije. Stoga je u ovo doba pandemije potrebna bolja kontrola aktivnosti upalne reumatske bolesti, kao i modifikacija specifične terapije.

Ključne riječi: COVID-19, upalna reumatska bolest, ishod, bDMARD, tsDMARD

INTRODUCTION

The COVID-19 pandemic, which predominantly affects the clinical features of acute respiratory syndrome, brought about a series of economic, social and political consequences from its very beginning, and due to this disease numerous health systems around the world have experienced and are still experiencing numerous problems in their operation. (1–4) The impact of COVID-19 on patients with inflammatory rheumatic diseases is the subject of numerous studies, in terms of detecting risk factors, evaluating the consequences of the disease, the impact of pharmacological therapy on COVID-19, as well as the dosage and timing of disease-modifying anti-rheumatic drugs. Although there is some general knowledge about these interrelationships, the results are contradictory. (5–7) Therefore, the aim of this research was to examine whether the use of biological disease-modifying antirheumatic drugs that change the course of the disease (bDMARDs) or conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) affects the course and outcome of the COVID-19 infection in patients with the most common inflammatory rheumatic diseases.

METHODS AND SUBJECTS

Patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and radiographic and non-radiographic axial spondyloarthritis (axSpA), who had COVID-19 and who were treated with bDMARDs and tsDMARDs at the time of the disease, along with a possible background therapy with csDMARDs, were included in this retrospective study. Patient follow-up was performed at the Department of Rheumatology, Physical and Rehabilitation Medicine of the Sestre milosrdnice University Hospital Centre in Zagreb. The cohort consisted of a total of 28 subjects, 13 men and 15 women, who have had COVID-19 in the period from February 2020 until the end of July 2021. The follow-up of the outcome of COVID-19 included a period of at least 2 months from the onset of the infection. Medical his-

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Pandemija COVID-19, koja dominantno izaziva kliničku sliku akutnoga respiratornog sindroma, od samog početka donijela je niz ekonomskih, društvenih i političkih posljedica, a brojni zdravstveni sustavi diljem svijeta imali su i još uvijek imaju brojnih problema u funkcioniranju. (1–4) Utjecaj bolesti COVID-19 na bolesnike s upalnim reumatskim bolestima predmet je mnogobrojnih istraživanja, a u smislu detektiranja rizičnih čimbenika, evaluacije posljedica bolesti, utjecaja farmakološke terapije na bolest COVID-19 kao i doziranja i tempiranja same antireumatske terapije. Iako postoje neka opća saznanja o tim međuodnosima, rezultati su proturječni. (5–7) Stoga je cilj ovog istraživanja bio ispitati utječe li primjena bioloških antireumatika koji mijenjaju tijek bolesti (bDMARDs, engl. *biological disease modifying antiheumatic drugs*) ili sintetskih lijekova koji utječu na tijek reumatske bolesti (csDMARDs, engl. *conventional synthetic disease modifying antirheumatic drugs* i tsDMARDs, engl. *targeted synthetic disease modifying antirheumatic drugs*) na tijek i ishod infekcije COVID-19 u bolesnika s najčešćim upalnim reumatskim bolestima.

METODE I ISPITANICI

U ovom retrospektivnom istraživanju uključeni su bolesnici s reumatoidnim artritisom (RA), psorijatičnim artritisom (PsA) i radiografskim i neradiografskim aksijalnim spondiloartritisom (axSpA), koji su imali bolest COVID-19, a koji su u vrijeme bolesti liječeni bDMARDs-ima i tsDMARDs-ima, uz eventualnu pozadinsku terapiju csDMARDs-ima, a praćeni su u Klinici za reumatologiju, fizikalnu medicinu i rehabilitaciju KBC-a Sestre milosrdnice u Zagrebu. Kohortu je činilo ukupno 28 ispitanika, 13 muškaraca i 15 žena, koji su imali COVID-19 bolest u periodu od veljače 2020. do kraja srpnja 2021. godine. Praćenje ishoda bolesti COVID-19 bilo je najmanje dva mjeseca od početka infekcije. Kao izvor podataka korištene su povijesti bolesti. Od ukupnog broja ispitanika, deset ih je bolovalo od RA, deset od PsA, a osam od axSpA (uklju-

tory was used as a data source. Out of the total number of subjects, 10 suffered from RA, 10 from PsA, and 8 from axSpA (including ankylosing spondylitis). The following data were used in the research: age and gender of the subject, data regarding SARS-CoV-2 infection (place of infection, method of diagnosis, data on the existence of symptoms and type of symptoms, data regarding the implementation of hospital treatment, treatment and outcome of the infection, data regarding COVID-19 complications), data related to an existing inflammatory rheumatic disease (disease activity graded as remission, low, moderate and high), treatment with bDMARDs or tsDMARDs, systemic glucocorticoid therapy, administration of methotrexate (or other csDMARD) along with biological therapy, line of bDMARDs and tsDMARDs administration, presence of comorbidities, data regarding pregnancy. The activity of inflammatory rheumatic disease is graded according to the DAS 28 score (Disease Activity Score Calculator for Rheumatoid Arthritis) for RA, the BASDAI questionnaire (Bath Ankylosing Spondylitis Disease Activity Index) for axSpA and the DAPSA questionnaire Disease Activity Index for Psoriatic Arthritis) for PsA. The criteria for grading the severity of COVID-19 (asymptomatic, mild, moderate, severe and critical form of the disease) are determined according to the *Guidelines for the treatment of patients with coronavirus disease 2019 (COVID-19) version no. 3 as of 21st October 2021* published by the Ministry of Health of the Republic of Croatia (in Croatian: *Smjernice za liječenje oboljelih od koronavirusne bolesti 2019. (COVID-19) verzija 3 od 21. listopada 2021. Ministarstva zdravstva Republike Hrvatske*).(8)

Descriptive statistics methods were used in the analysis of the available data, and the data were presented in the form of ranges, medians and mean values, and in the form of shares/percentages.

RESULTS

The age of the subjects ranged from 28 to 80, with a median value of 56.5 and a mean value of 54.5±14.5. There were 15 (53.57%) women and 13 (56.43%) men in the cohort, with an average age of 52.7±14.8 for men and 56±14.6 for women. For all patients, the source of infection was a close contact with a previously confirmed infection or suspected infection, with the exception of one patient for whom the source of infection was nosocomial, since this patient was a healthcare professional who was in close contact with another healthcare professional who was infected with the SARS-CoV-2 virus. In 26 patients (92.86%), the diagnosis of infection was established on the basis of a positive PCR test, and in 2 subjects (7.14%) it was a probable case of COVID-19 infection because the diagnosis was made solely on the basis of the clinical features and epidemiological history without microbiological diagnostics,

čivo ankilozantni spondilitis). U istraživanju su se koristili sljedeći podatci: dob i spol ispitanika, podatci o infekciji SARS-CoV-2 (mjesto zaraze, način postavljanja dijagnoze, podatci o postojanju simptoma te vrsti simptoma, podatci o provođenju bolničkog liječenja, liječenje i ishod infekcije, podatci o komplikacijama bolesti COVID-19), podatci vezani uz postojeću upalnu reumatsku bolest (aktivnost bolesti stupnjevana kao remisija, niska, umjerena i visoka), liječenje bDMARDs-ima ili tsDMARDs-ima; sistemska terapija glukokortikoidima; primjena metotreksata (ili drugog csDMARD-a) uz biološku terapiju; linija primjene bDMARDs-a i tsDMARDs-a; postojanje komorbiditeta; podatak o trudnoći. Aktivnost upalne reumatske bolesti stupnjevana je prema DAS 28 (engl. *disease activity score calculator for rheumatoid arthritis*) indeksu za RA, BASDAI (engl. *bath ankylosing spondylitis disease activity index*) upitniku za axSpA i DAPSA (engl. *disease activity in psoriatic arthritis*) upitniku za PsA. Kriteriji za stupnjevanje težine bolesti COVID-19 (asimptomatski, blagi, srednje teški, teški i kritični oblik bolesti) određeni su prema *Smjernicama za liječenje oboljelih od koronavirusne bolesti 2019. (COVID-19) verzija 3 od 21. listopada 2021. Ministarstva zdravstva Republike Hrvatske.* (8)

U analizi dostupnih podataka korištene su metode deskriptivne statistike, a podatci su prikazani u obliku raspona, medijana i srednje vrijednosti te u obliku udjela/postotka.

REZULTATI

Životna dob ispitanika bila je raspona od 28 do 80 godina, s medijanom vrijednosti 56,5 i uz srednju vrijednost je 54,5 ± 14,5 godina. U kohorti je bilo 15 (53,57%) žena i 13 (56,43%) muškaraca, s prosječnom životnom dobi od 52,7 ± 14,8 godina u muškaraca i 56 ± 14,6 godina u žena. U svih je bolesnika izvor zaraze bio bliski kontakt kojemu je prethodno potvrđena infekcija ili je postojala sumnja na infekciju, s tim da je u jednog bolesnika izvor zaraze bio intrahospitalni, budući da se radilo o zdravstvenom djelatniku koji je bio u bliskom kontaktu s drugim zdravstvenim djelatnikom zaraženim virusom SARS-CoV-2. Dijagnoza infekcije je kod 26 bolesnika (92,86%) utvrđena temeljem pozitivnog PCR testa, a kod dvaju ispitanika (7,14%) radilo se o vjerojatnom COVID-19 jer je dijagnoza postavljena isključivo na temelju kliničke slike i epidemiološke anamneze bez mikrobiološke dijagnostike, što je bilo u skladu s tada važećim preporukama Hrvatskog zavoda za javno zdravstvo (HZJZ-a). Dvadeset i pet bolesnika imali su simptome bolesti COVID-19 (89,29%), a tri bolesnika su bili asimptomatski (10,71%). Glede liječenja niti jedan ispitanik nije bio liječen remdesivirom, 25 bolesnika (89,29%)

which was in accordance with the recommendations of the Croatian Institute of Public Health (HZJZ) that were current at the time. Twenty-five patients had COVID-19 symptoms (89.29%), and 3 were asymptomatic (10.71%). Regarding treatment, not a single subject was treated with remdesivir, 25 patients (89.29%) received symptomatic therapy, and 2 of these patients (7.14%) were additionally treated with an antibiotic. Out of the total number of patients, only one patient (3.57%) received hospital treatment. Twenty-two patients (78.57%) fully recovered from COVID-19, 6 (21.43%) partially recovered and had prolonged symptoms of the disease (the symptoms lasted longer than 2 months from the onset of the disease), most often accompanied with the symptom of chronic fatigue, and with a median duration of 92.5 days. Regarding disease activity at the time of infection with the SARS-CoV-2 virus, 5 patients with RA had low or moderate disease activity (17.86% and 17.86%). In the case of PsA, 2 patients (7.14%) were in remission, 3 patients (10.71%) had low disease activity, 4 patients (14.29%) had moderate disease activity and 1 patient (3.57%) had high disease activity. Furthermore, in the case of axSpA, 3 patients (10.71%) had low disease activity, 4 patients (14.7%) had moderate disease activity, and 1 patient (3.57%) had high disease activity. Treatment with bDMARDs was represented in our cohort in the following way: 17 patients (60.71%) were treated with TNF-alpha inhibitors (tumour necrosis factor), 5 patients (17.86%) were treated with IL-17 inhibitors (interleukin 17), 2 patients (7.14%) were treated with IL-6 inhibitors (interleukin 6), 1 patient (3.57%) was treated with CD20 inhibitor, while 3 patients (10.71%) were treated with a tsDMARD, upadacitinib. Regarding the line of bDMARDs administration, 20 patients (71.43%) received them as the first-line treatment, 6 patients (21.43%) received them as the second-line treatment, and in two cases they were administered as the third-line treatment (7.14%). Three patients received systemic glucocorticoids (10.71%) in a low dose of up to 8 milligrams, while 6 patients (21.43%) received csDMARDs (methotrexate) as adjunctive therapy in addition to bDMARDs. None of the patients with PsA had clinically visible signs of psoriasis. In addition to that, there were no patients with inflammatory bowel disease in this cohort. In addition to inflammatory rheumatic disease, accompanying comorbidities were present in 17 patients (60.71%), the most common of which were: arterial hypertension, type II diabetes and hypercholesterolemia.

According to the severity of the clinical features of COVID-19, 3 patients in this cohort (10.71%) had symptoms of a mild form of COVID-19 (2 patients suffered from RA, 1 suffered from axSpA), 19 patients (67.86%) had a moderate form of COVID-19 (7 patients suffered from RA, 7 suffered from PsA, 5 suffered from axSpA), 5 patients (17.86%) had a severe form of

su dobivali simptomatsku terapiju, od čega je kod dvaju bolesnika (7,14%) u liječenje dodatno uključen i antibiotik. Od ukupnog broja bolesnika bolničko liječenje je provedeno samo kod jedne bolesnice (3,57%). Dvadeset i dva bolesnika (78,57%) potpuno su se oporavili od bolesti COVID-19, šest (21,43%) ih se djelomično oporavilo te su imali produljene simptome bolesti (dulje od dva mjeseca od početka bolesti), najčešće sa simptomom kroničnog umora, s medijanom trajanja 92,5 dana. U pogledu aktivnosti bolesti u trenutku zaraze virusom SARS-CoV-2, pet bolesnika s RA-om imalo je nisku odnosno umjerenu aktivnost bolesti (17,86% i 17,86%); u slučaju PsA dva bolesnika (7,14%) su bila u remisiji, tri bolesnika (10,71%) su imala nisku, četiri bolesnika (14,29%) umjerenu i jedan bolesnik (3,57%) visoku aktivnost bolesti; dok su u slučaju axSpA tri bolesnika (10,71%) imala nisku, četiri bolesnika (14,7%) umjerenu, a jedan bolesnik (3,57%) visoku aktivnost bolesti. Liječenje bDMARDs-ima u našoj je kohorti bilo zastupljeno na sljedeći način: 17 bolesnika (60,71%) je bilo liječeno TNF-alfa inhibitorima (engl. *tumor necrosis factor*), pet bolesnika (17,86%) IL-17 inhibitorima (engl. *interleukin 17*), dva bolesnika (7,14%) IL-6 inhibitorima (engl. *interleukin 6*), jedan bolesnik (3,57%) CD20 inhibitorom, dok su tri bolesnika (10,71%) liječena tsDMARD-om, updacitinibom. U pogledu linije primjene bDMARDs-a, 20 bolesnika (71,43%) ih je primalo kao prvu liniju liječenja, šest bolesnika (21,43%) kao drugu liniju, a kod dvoje je ona bila treća linija (7,14%). Tri su bolesnika kao popratnu terapiju uzimali sistemske glukokortikoide (10,71%) u niskoj dozi do 8 miligrama, dok je csDMARD (metotreksat) kao popratnu terapiju uz bDMARDs primalo šest bolesnika (21,43%). Nijedan od bolesnika s PsA-om nije imao klinički vidljivu psorijazu. Također, u ovoj kohorti nije bilo bolesnika s upalnom bolesti crijeva. Uz upalnu reumatsku bolest, popratni je/su komorbiditet/-i bio/-li zastupljen/-i kod 17 bolesnika (60,71%), od kojih su najčešći bili: arterijska hipertenzija, šećerna bolest tipa 2 i hiperkolesterolemija.

Prema težini kliničke slike COVID-19 bolesti, u ovoj kohorti tri bolesnika (10,71%) su imali simptome blagog oblika bolesti COVID-19 (dva bolesnika RA, 1 axSpA), 19 bolesnika (67,86%) srednje teški oblik (sedam bolesnika RA, sedam bolesnika PsA, pet bolesnika axSpA), pet bolesnika (17,86%) teški oblik (jedan bolesnik RA, tri bolesnika PsA, jedan bolesnik axSpA) i jedna bolesnica s axSpA (3,57%) kritični oblik bolesti COVID-19. Važno je napomenuti kako su se temeljem smjernica za liječenje oboljelih od bolesti COVID-19 bolesnici koji uzimaju imunosupresivne lijekove svrstavali u jednu kategoriju više (teže bolesti).(8) Uspoređujući težinu kliničke slike bolesti

Table 1 Demographic and clinical features of patients with severe and critical COVID-19 and inflammatory rheumatic disease
Tablica 1. Demografska i klinička obilježja ispitanika s teškim i kritičnim oblikom bolesti COVID-19 i upalnom reumatskom bolesti

Inflammatory rheumatic disese / Upalna reumatska bolest	Disease activity / Aktivnost bolesti	Gender / Spol	Age / Dob	Comorbidities / Pridružene bolesti	Severity of COVID-19 / Težina COVID-19	Hospital treatment / Bolničko liječenje	bDMARD	Glucocorticoids in therapy / Glukokortikoidi u terapiji	Methotrexate in therapy / Metotreksat u terapiji
axSpA	high / visoka	F/Ž	80	yes / da	critical / kritični	yes / da	IL-17 inhibitor	no / ne	no / ne
	moderate / umjerena	M/M	42	yes / da	severe / teški	no / ne	TNF-alfa inhibitor	no / ne	no / ne
PsA	high / visoka	F/Ž	66	yes / da	severe / teški	no / ne	TNF-alfa inhibitor	no / ne	no / ne
	moderate / umjerena	F/Ž	52	yes / da	severe / teški	no / ne	TNF-alfa inhibitor	yes / da	no / ne
	remission / remisija	F/Ž	31	no / ne	severe / teški	no / ne	IL-17 inhibitor	no / ne	no / ne
RA	low / niska	F/Ž	69	no / ne	severe / teški	no / ne	TNF-alfa inhibitor	no / ne	no / ne

Legend / Legenda: COVID: Coronavirus disease / koronavirusna bolest; bDMARD: biological disease modifying antirheumatic drug / biološka antireumatska terapija koja mijenja tijek bolesti; AxSpA: axial spondyloarthritis /aksijalni spondyloarthritis; PsA: psoriatic arhtritis / psorijatični artritis; RA: rheumatoid arthritis / reumatoidni artritis; F / Ž: female / ženski; M: male / muški; IL: interleukin; TNF: tumor necrosis factor / čimbenik nekroze tumora

COVID-19 (1 patient suffered from RA, 3 suffered from PsA, 1 suffered from axSpA) and 1 axSpA who suffered from axSpA (3.57%) had a critical form of COVID-19. It is important to note that, based on the guidelines for the treatment of patients with COVID-19, patients taking immunosuppressive drugs were classified in a higher category (severe disease).(8) Comparing the severity of the clinical features of COVID-19 and the activity of inflammatory rheumatic disease, in this cohort of 5 patients with a severe form of COVID-19, 1 patient (20.00%) was in remission, 1 patient (20.00%) had low disease activity, 2 patients (40.00%) had moderate disease activity, and 1 patient (20.00%) had a high inflammatory rheumatic disease activity. One patient (3.57%) with a critical form of COVID-19 also had a high inflammatory rheumatic disease activity and was the only one in this cohort who was hospitalized and oxygen therapy had to be administered to him. In relation to the patients with a severe and critical form of COVID-19, 4 patients had accompanying comorbidities, while 2 patients were without comorbidities. The aforementioned data are presented in Table 1. The median age of patients with a severe and critical form of COVID-19 was 59, with an average value of 56.67±18.32, which does not significantly deviate from the average age of all subjects in our cohort.

DISCUSSION AND CONCLUSION

This research indicated that the degree of inflammatory rheumatic disease activity, older age, gender and

COVID-19 i aktivnost upalne reumatske bolesti, u ovoj je kohorti od pet bolesnika s teškim oblikom bolesti COVID-19 jedan bolesnik (20,00%) bio u remisiji, jedan bolesnik (20,00%) je imao nisku aktivnost bolesti, dva bolesnika (40,00%) su imala umjerenu aktivnost bolesti, a jedan bolesnik (20,00%) je imao visoku aktivnost upalne reumatske bolesti. Jedan bolesnik (3,57%) s kritičnim oblikom bolesti COVID-19 imao je ujedno i visoku aktivnost upalne reumatske bolesti te je jedini u ovoj kohorti bio hospitaliziran i zahtijevao terapiju kisikom. Od bolesnika s teškim i kritičnim oblikom bolesti COVID-19, četiri bolesnika su imala prateće komorbiditete, dok su dva bolesnika bila bez komorbiditeta. Navedeni podatci su prikazani u tablici 1. Životna dob bolesnika s teškim i kritičnim oblikom bolesti COVID-19 bila je medijane vrijednosti 59 godina, uz prosječnu vrijednost 56,67 ± 18,32 godina, što ne odskače značajno od prosječne životne dobi svih ispitanika u našoj kohorti.

RASPRAVA I ZAKLJUČAK

Ovo istraživanje je ukazalo da stupanj aktivnosti upalne reumatske bolesti, starija životna dob, spol i popratni komorbiditeti utječu na težinu kliničke slike bolesti COVID-19 kod ispitanika u ovoj kohorti. Većina ispitanika je imala popratne komorbiditete poput arterijske hipertenzije ili šećerne bolesti, što su poznati rizični čimbenici u razvoju težeg oblika bolesti i lošijeg ishoda COVID-a. Budući da su upalne reumatske bolesti češće zastupljene kod žena, veća je prevalencija

accompanying comorbidities impact the severity of the clinical features of COVID-19 in subjects in this cohort. Most of the subjects had accompanying comorbidities such as arterial hypertension or diabetes, which are well-known risk factors in the development of a more severe form of the disease and an adverse outcome of COVID. Since inflammatory rheumatic diseases are more common in women, the prevalence of COVID is higher in women with inflammatory rheumatic diseases. Taking comorbidities into account, the most common comorbidities in people with inflammatory rheumatic diseases infected with SARS-CoV-2 are cardiovascular diseases, endocrine diseases and respiratory diseases. According to the available literature, there is no significant difference in the prevalence of COVID in individuals with inflammatory rheumatic diseases compared to the general population. (9) The results of this research confirm data from the literature which point to the fact that in general there is no difference in the symptoms and rate of hospitalizations due to COVID-19 between individuals with inflammatory rheumatic diseases and the general population, although some literature data indicate that patients with inflammatory rheumatic diseases have a higher chance of ending up in intensive care and on mechanical ventilation, while on the other hand the mortality between the groups is at the same level. (10) There were no deaths in the cohort of our subjects, and only one person who was elderly, with accompanying comorbidities, receiving IL-17 inhibitor therapy and with a high degree of inflammatory rheumatic disease activity had to be hospitalized and oxygen therapy had to be administered to them. Our research indicated that the degree of activity of inflammatory rheumatic disease affects the severity of the clinical features and the course of COVID-19, which is in accordance with the research available in global medical literature. General risk factors for an adverse course and outcome of COVID-19 in people with inflammatory rheumatic diseases, as well as a higher rate of hospitalization and mortality, are the following: male gender, older age, cardiovascular and pulmonary diseases, chronic kidney disease, moderate to high level of inflammatory rheumatic disease activity and the diagnosis of inflammatory rheumatic disease. (11–14) Some studies have found that patients with PsA had a more favourable outcome of COVID-19 compared to patients with RA, but the real reason for this has not yet been determined. (12) It is an interesting fact that none of our subjects diagnosed with PsA had psoriatic manifestations on the skin and/or nails. This fact could be explained by the low to moderate inflammatory rheumatic disease activity of most of our subjects with PsA, but also by the likely beneficial effect of biological therapy or targeted synthetic drugs on cutaneous manifes-

COVID-a kod osoba ženskog spola s upalnim reumatskim bolestima. Uzimajući u obzir komorbiditete, najčešći komorbiditeti kod osoba s upalnim reumatskim bolestima inficiranih virusom SARS-CoV-2 jesu kardiovaskularne bolesti, endokrinološke bolesti i respiratorna oboljenja. Prema dostupnoj literaturi, ne postoji značajna razlika u prevalenciji COVID-a kod osoba s upalnim reumatskim bolestima u usporedbi s općom populacijom. (9) Rezultati ovog istraživanja potvrđuju podatke iz literature da općenito ne postoji razlika u simptomima i stopi hospitalizacija od bolesti COVID-19 između osoba s upalnim reumatskim bolestima i opće populacije, iako neki literaturni podatci ukazuju da bolesnici s upalnim reumatskim bolestima imaju veći rizik da završe na intenzivnom liječenju i mehaničkoj ventilaciji, dok je s druge strane mortalitet među grupama jednak. (10) Smrtnih ishoda u kohorti naših ispitanika nije bilo, dok je samo jedna osoba koja je starije životne dobi, s pratećim komorbiditetima, na terapiji inhibitorom IL-17 i s visokim stupnjem aktivnosti upalne reumatske bolesti bila zahtijevala hospitalizaciju i terapiju kisikom. Naše je istraživanje ukazalo da stupanj aktivnosti upalne reumatske bolesti utječe na težinu kliničke slike i tijek bolesti COVID-19, što je u skladu s istraživanjima dostupnima u svjetskoj literaturi. Opći rizični čimbenici za lošiji tijek i ishod bolesti COVID-19 kod osoba s upalnim reumatskim bolestima, pa tako i veću stopu hospitalizacija i smrtnosti, jesu muški spol, starija životna dob, kardiovaskularne i plućne bolesti, kronična bolest bubrega, umjereni do visoki stupanj aktivnosti upalne reumatske bolesti te sama dijagnoza upalne reumatske bolesti. (11–14) Pojedina istraživanja su utvrdila da su bolesnici s PsA-om imali bolji ishod bolesti COVID-19 u usporedbi s bolesnicima s RA-om, ali pravi razlog tome još nije utvrđen. (12) Zanimljiva je činjenica kako nitko od naših ispitanika s dijagnozom PsA nije imao psorijatične promjene po koži i/ili noktima. Sama činjenica mogla bi se objasniti niskom do umjerenom aktivnošću upalne reumatske bolesti većine naših ispitanika sa PsA-om, ali i vjerojatnim povoljnim učinkom biološke terapije ili ciljanih sintetskih lijekova na kožne promjene. Proučavanjem patofizioloških mehanizama infekcije SARS-CoV-2 ustanovljeno je kako ekscesivni upalni odgovor organizma na SARS-CoV-2 (tzv. citokinska oluja) dovodi do razvoja težeg oblika bolesti i veće smrtnosti. Riječ je naime o pretjeranoj aktivaciji monocitno-makrofagnog sustava kod određenog dijela oboljelih, iz još nepoznatog razloga, koji posljedično dovodi do difuznog oštećenja različitih tkiva i organa. Kako kod bolesnika s upalnim reumatskim bolestima u organizmu već postoji upalno zbivanje, dodatna upala mogla bi dovesti do dodatnih oštećenja. Pritom je također ustanovljeno kako infekcija SARS-CoV-2 ima slične patofiziološke upalne mehanizme kao i RA

tations. By studying the pathophysiological mechanisms of SARS-CoV-2 infection, it was established that the body's excessive inflammatory response to SARS-CoV-2 (the so-called cytokine storm) leads to the development of a more severe form of the disease and higher mortality rate. It is an excessive activation of the monocyte-macrophage system in a certain part of the patients, for a reason that still remains unknown, which consequently leads to diffuse damage to various tissues and organs. Since in patients with inflammatory rheumatic diseases inflammation is already present in the body, additional inflammation could lead to additional damage. It was also established that SARS-CoV-2 infection has similar pathophysiological inflammatory mechanisms as RA in terms of cytokine imbalance, and this opened up the possibility of using similar and the same drugs that are used in the treatment of inflammatory rheumatic diseases. (15,16) Treatment, as well as the choice of different therapy in the treatment of inflammatory rheumatic disease, can have an impact on the course and outcome of COVID-19. Given that the majority of patients in our cohort were treated with a TNF-alpha inhibitor and that there was no fatal outcome, it could be concluded that the use of TNF-alpha inhibitors is associated with a more favourable outcome of the infection. Since targeted synthetic molecules and biological drugs act as inhibitors of certain parts of the immune mechanisms, which favourably affects the course of the inflammatory disease, there has been concern about their further use in the course of COVID-19 when the activity of the immune system is crucial for the resolution of the infection. However, research from the available world literature supports the fact that the use of TNF-alpha inhibitors is associated with a better outcome of infection, while the use of JAK-inhibitors and rituximab compared to TNF-alpha inhibitors is associated with an adverse outcome of infection, i.e., there is a significantly higher likelihood of hospitalization or death. Moreover, the use of immunosuppressants (e.g. methotrexate, azathioprine) as monotherapy or in combination with other drugs and the use of high doses of glucocorticoids in the treatment of inflammatory rheumatic diseases have been detected as factors that result in an adverse outcome of COVID-19, and consequently in an increased mortality rate. (5,6,11,12) The absence of deaths caused by COVID-19 in our cohort can also be explained by the fact that only one severely ill patient was receiving glucocorticoid therapy at the time. It has been shown that exposure of patients to glucocorticoids in a dose greater than 10 milligrams per day is associated with a higher rate of hospitalization in patients with COVID-19, especially in patients with systemic connective tissue disease and vasculitis. (17) Although we do not have data on the vaccination u pogledu disbalansa citokina, a to je otvorilo mogućnost korištenja sličnih i istih lijekova koji se koriste u liječenju upalnih reumatskih bolesti. (15,16) Liječenje, kao i odabir diferentne terapije u liječenju upalne reumatske bolesti, može imati utjecaj na tijek i ishod bolesti COVID-19. S obzirom na to da je većina bolesnika u našoj kohorti bila liječena blokatorom TNF-alfa te da nije bilo smrtnog ishoda, moglo bi se zaključiti da je upotreba TNF-alfa inhibitora povezana s boljim ishodom infekcije. Budući da ciljane sintetske molekule i biološka terapija djeluju kao blokatori pojedinih dijelova imunoloških mehanizama, što povoljno utječe na tijek upalne bolesti, pojavila se bojazan o njihovoj daljnjoj upotrebi u tijeku bolesti COVID-19 kada je aktivnost imunološkog sustava krucijalna za rezoluciju infekcije. Međutim, istraživanja iz dostupne svjetske literature govore u prilog tomu da je upotreba inhibitora TNF-alfa povezana s boljim ishodom infekcije, dok je upotreba JAK-inhibitora i rituksimaba u usporedbi s inhibitorima TNF-alfa povezana s lošijim ishodom infekcije, odnosno prisutna je značajno veća vjerojatnost za hospitalizaciju ili smrtni ishod. Također, upotreba imunosupresivnih lijekova (npr. metotreksat, azatioprin) kao monoterapije ili u kombinaciji s drugim lijekovima te upotreba visokih doza glukokortikoida u liječenju upalnih reumatskih bolesti detektirani su kao čimbenici koji rezultiraju lošijim ishodom COVID-19, a posljedično i povišenom stopom mortaliteta. (5,6, 11,12) Izostanak smrtnih ishoda od bolesti COVID-19 u našoj kohorti može se objasniti i činjenicom da je samo jedan teže oboljeli bolesnik tada bio na glukokortikoidnoj terapiji. Naime, pokazalo se da je izlaganje bolesnika glukokortikoidima u dozi većoj od 10 miligrama na dan povezano s većom stopom hospitalizacija kod oboljelih od bolesti COVID-19, pogotovo kod bolesnika sa sistemskom bolesti vezivnog tkiva i vaskulitisom. (17) Iako u našoj kohorti nemamo podataka o cijepnom statusu svih ispitanika, cijepljenje je zasigurno najučinkovitija metoda prevencije i zaštite od lošijeg tijeka i ishoda bolesti COVID-19. Od izuma cjepiva protiv SARS-CoV-2 u određenog broja bolesnika postojao je strah od negativnih posljedica cjepiva na aktivnost osnovne bolesti, međutim podatci iz literature govore kako se egzacerbacija upalne reumatske bolesti pojavila kod manje od 5% ispitanika. Većina ispitanika je pritom bila voljna privremeno obustaviti terapiju DMARD-ovima u svrhu poboljšanja učinkovitosti cjepiva. Isto tako, nuspojave cjepiva bile su tipične kao i u općoj populaciji, a to su redom umor, malaksalost, groznica, tresavica, glavobolja, mialgije, artralgije. (18) U našoj je kohorti samo šest ispitanika (pet žena i jedan muškarac) imalo težak i kritični oblik bolesti COVID-19, od kojih je samo jedan ispitanik hospitaliziran i zahtijevao terapiju kisikom. Prednost je ovog istraživanja da se radi o uzorku ispitanika iz

status of all subjects in our cohort, vaccination is certainly the most effective method of prevention and protection against an adverse course and outcome of COVID-19. Since the invention of the vaccine against SARS-CoV-2, in a certain number of patients there has been a fear of adverse consequences of the vaccine on the activity of the underlying disease. However, data from literature show that an exacerbation of inflammatory rheumatic disease occurred in less than 5% of subjects. The majority of respondents were willing to temporarily stop taking DMARDs in order to improve the effectiveness of the vaccine. Also, the side effects of the vaccine were typical, as those in the general population. They included fatigue, malaise, fever, chills, headache, myalgias, and arthralgias. (18) In our cohort, only 6 subjects (5 women and 1 man) had a severe and critical form of COVID-19, and out of these subjects only one subject was hospitalized and oxygen therapy had to be administered to him. The advantage of this research is that it includes a sample of subjects from everyday clinical practice which reflects the real situation, while the main limitation is the small number of subjects, which prevents a more detailed analysis of the interrelationship of individual parameters of interest. We must note that most of the subjects recovered from COVID-19 at a time when the vaccine was not yet developed and widely available on the market, that is, before mass vaccination of the population began. Furthermore, those who recovered from the disease could be vaccinated at the earliest 3 to 6 months after recovery. Therefore. vaccination was not an analysed variable in this study. Smoking as an analysed variable was not included due to insufficient data in relation to it.

In conclusion, the results of our retrospective study suggest that higher inflammatory rheumatic disease activity and accompanying comorbidities are associated with a severe and critical form of SARS-CoV-2 virus infection, but without a fatal outcome. A more favourable outcome of the infection may be associated with the use of specific biological therapy. For a more detailed insight into this, research needs to be conducted on a larger sample of subjects, preferably with a prospective design. Therefore, during this pandemic, it is necessary to monitor patients and perform the follow-up of patients with inflammatory rheumatic diseases more intensively in order to control and manage disease activity and modify the therapy in a more efficient way.

Conflict of interest statement: The authors declare no conflict of interest.

svakodnevne kliničke prakse koja odražava realno stanje, dok je glavno ograničenje mali broj ispitanika, što onemogućuje detaljniju analizu međuodnosa pojedinih parametara od interesa. Napominjemo da je većina ispitanika preboljela bolest COVID-19 u vrijeme dok cjepivo još nije bilo razvijeno i široko dostupno na tržištu, odnosno dok nije počelo masovno procjepljivanje populacije. Nadalje, oni koji su preboljeli bolest mogli su se cijepiti najranije tri do šest mjeseci nakon preboljenja, stoga cijepljenje nije bilo analizirana varijabla u ovom istraživanju. Pušenje kao analizirana varijabla nije bilo uključeno s obzirom na nedostatne podatke.

Zaključno, rezultati našega retrospektivnog istraživanja sugeriraju da su viša aktivnost upalne reumatske bolesti i popratni komorbiditeti povezani s teškim i kritičnim oblikom infekcije virusom SARS-CoV-2, ali bez smrtnog ishoda. Povoljniji ishod infekcije može biti povezan s upotrebom specifične biološke terapije. Za detaljniji uvid u to potrebna su istraživanja na većem uzorku ispitanika, poželjno prospektivnog nacrta. Stoga je u vrijeme ove pandemije potrebno intenzivnije pratiti i nadzirati bolesnike s upalnim reumatskim bolestima radi bolje kontrole aktivnosti bolesti i modifikacije same terapije.

Izjava o sukobu interesa: Autori izjavljuju da nisu u sukobu interesa.

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