doi: 10.5937/opmed0-45923

Opšta medicina 2024;30 (1-2):29-40

UDC: 616.72-002-08
616.1/.7-08
616.98-085:578.834

Determinatori kliničkih ishoda kod obolelih od hroničnih artritisa i sistemskih bolesti vezivnog tkiva: fokus pandemija COVID-19

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Determinators of clinical outcomes in patients with chronic arthritis and systemic connective tissue disorders: COVID-19 pandemic focus

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Sažetak

Uvod. Rana dijagnoza i terapija poboljšavaju kliničke ishode, naročito kod hroničnih artritisa (HA) i sistemskih bolesti vezivnog tkiva (SBVT). Zahvaljujući kliničkim istraživanjima od 1990. godine, inovativnim lekovima sačuvano je 55 miliona godina života. Pandemija COVID-19 donela je medicinske izazove u reumatologiji.

Cilj istraživanja je bio da se kod obolelih od HA i/ili SBVT ispita rano uspostavljanje dijagnoze, vreme uvođenja inovativne terapije, učešće u kliničkim istraživanjima, uticaj pola, starosti i lečenje kortikosteroidima na stopu hospitalizacije usled COVID-19 infekcije.

Metod. U novembru 2022. godine sproveli smo studiju preseka kod obolelih od HA i/ili SBVT koristeći ''online'' upitnik. Prvi deo analiziranih pitanja odnosio se na socio-demografske karakteristike i podatke vezane za reumatsku bolest - reumatoidni artritis (RA)/ostale reumatske bolesti, a drugi deo na COVID-19. Podaci su analizirani deskriptivnom statistikom i Pirsonovim Hi-kvadrat testom korišćenjem SPSS 29.

Rezultati. Od ukupno 176 ispitanika, RA je imalo 60,8%. Vreme od prvih simptoma do dijagnoze bilo je duže od dve godine. U prvih šest meseci češće se dijagnostikovao RA ($p < 0,05$ - muškarci). Inovativnu terapiju koristilo je 59,7% ispitanika. Većini obolelih od RA inovativna terapija je uvedena nakon pet godina, kasnije u odnosu na ostale HA ($p < 0,05$ - žene). U kliničkim istraživanjima učestvovalo je 23,3% ispitanika, više oboleli od RA ($p < 0,05$ - žene). Kortikosteroidna terapija uticala je na višu stopu hospitalizacije tokom COVID-19 infekcije ($p < 0,05$ - žene).

Zaključak. Muškarcima obolelim od RA brže se postavlja dijagnoza, dok žene obolele od RA imaju veće učešće

Abstract

Introduction. Early diagnosis and treatment improve clinical outcomes, especially in chronic arthritis (CA) and systemic connective tissue disorders (SCTD). Thanks to clinical research from the 1990s on and innovative drugs, 55 million life-years have been saved. The COVID-19 pandemic brought on medical challenges in rheumathology.

Objective. The study objective was to research early diagnosis, time of the introduction of innovative therapy, participation in clinical research, influence of gender, age, and corticosteroid treatment on hospitalization rate due to COVID-19 infection in CA and SCTD patients.

Method. In November 2022 we performed the cross-sectional study in CA and/or SCTD patients using an online questionnaire. The first part of the analyzed questions referred to sociodemographic characteristics and data concerning rheumatic disease - rheumatoid arthritis (RA) and other rheumatic diseases. The second part referred to COVID-19. Data were analyzed by descriptive statistics and Pearson's Chi-square test using SPSS 29.

Results. Out of the total of 176 participants, RA was present in 60,8%. The time from the symptom onset to diagnosis was longer than two years. RA was more frequently diagnosed in the first six months ($p < 0,05$ - males). The innovative therapy was used by 59,7% of the participants. The majority of RA patients got innovative therapy after five years from disease onset, which is later than in other CAs ($p < 0,05$ - females). There were 23,3% of the participants who took part in clinical research, more those with RA ($p < 0,05$ - females). Corticosteroid therapy influenced a higher rate of hospitalization during COVID-19 infection ($p < 0,05$ - females).

Conclusion. Males suffering from RA were diagnosed sooner, while females with RA participated more in clini-

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u kliničkim istraživanjima, ali kasnije uvođenje inovativne terapije. Upotreba glukokortikoida u lečenju HA i SBVT povećava rizik za hospitalizaciju usled infekcije COVID-19.

Ključne reči: reumatske i mukuloskeletne bolesti, zakasnela dijagnoza, klinička istraživanja, kortikosteroidi, COVID-19, vakcinacija

Uvod

Prevalencija reumatskih i muskuloskeletnih bolesti (RMD) je u znatnom porastu, a kao glavni razlozi smatraju se starenje populacije, brža dijagnostika i duži životni vek obolelih od RMD[1]. RMD obuhvataju više od 200 bolesti koje karakterišu hronični i progresivni bol (zglobovi, mišići, kosti), ograničenje funkcionalnosti, invaliditet i značajno umanjenje kvaliteta života obolelih[2]. Evropska alijansa udruženja u reumatologiji (EULAR) izdala je 2010. godine Briselsku deklaraciju po kojoj svaki četvrti građanin u Evropi boluje od neke RMD (u Srbiji 1 700 000), od toga 150 000 boluje od hroničnih artritisa (HA) i sistemskih bolesti vezivnog tkiva (SBVT)[3]. U Kanadi kod obolelih od HA i/ili SBVT utvrđeno je da veći pristup specijalističkim pregledima ostvaruju žene, dok je korišćenje usluga hitne službe zbog RMD češće kod muškaraca[5]. Rana dijagnoza i terapija HA i/ili SBVT značajno poboljšavaju dugoročne kliničke ishode. Međutim, period između pojave simptoma i početka lečenja ovih bolesti je značajno odložen i predstavlja aktuelan problem širom sveta[5,6]. Usled heterogenosti manifestacija HA i/ili SBVT klinička istraživanja su neophodna za unapređenje i uvođenje inovativnih terapijskih mogućnosti, posebno ako se zna da je od 1990. godine inovativnim lekovima sačuvano 55 miliona godina života[7,8]. Porodični/izabrani lekar ima značajnu ulogu u obrazovanju i poboljšanju spremnosti pacijenata da učestvuju u kliničkim ispitivanjima[8]. Podršku pacijentima pruža EULAR preko projekta „Vreme je za istraživanje"[10].

Pandemija izazvana korona virusom SARS-CoV-2 doprinela je visokom stepenu obolevanja i smrtnosti od COVID-19, ali je donela i mnoge medicinske izazove za pacijente obolele od HA i/ili SBVT i reumatologe, što je značajno uticalo na zdravstvenu negu i praćenje ovih pacijenata[2]. Instituti specijalizovani za HA i/ili SBVT u Srbiji bili su deo kovid sistema i pacijenti su imali samo pristup u hitnim slučajevima, odnosno nije bilo redovnih pregleda. U tom periodu uspešno je funkcionisalo „Online savetovanje za pacijente sa artritisom" (Online Counselling for Arthritis Patients, OCAP), preko platforme „Lekarinfo". Kako ove grupe pacijenata spadaju u kategoriju pacijenata sa povećanim rizikom od težeg oblika obolevanja zaražavanjem COVID-19 i povećanim rizikom od smrtnog ishoda, reumatolozi su putem

cal research but were later introduced to innovative therapy. The use of glucocorticoid therapy in the treatment of CA and SCTD increased the risk of hospitalization due to COVID-19 infection.

Keywords: rheumatic and musculoskeletal diseases, late diagnosis, clinical research, corticosteroids, COVID-19, vaccination

Introduction

The prevalence of rheumatic and musculoskeletal diseases (RMD) is on the rise, and the main reasons are thought to be the aging population, faster diagnostics, and longer life span of RMD patients[1]. The RMD encompasses more than 200 diseases, characterized by chronic and progressive pain (joints, muscles, bones), functionality limitation, disability, and significant impairment of the patient's life quality[2]. European Alliance of Associations for Rheumatology (EULAR) published Brussels' Declaration in 2010 stating that every fourth European citizen was suffering from some form of RMD (in Serbia 1.700.000), out of whom 150.000 were suffering from chronic arthritis (CA) and systemic connective tissue disorders (SCTD)[3]. In Canada, in people suffering from CA and/or SCTD, it was found that females achieved higher access to specialist care, while using emergency care due to RMD was more often found in males[5]. Early diagnosis and treatment of CA and/or SCTD significantly improve long-term clinical outcomes. Nevertheless, the time between symptom onset and treatment start of these diseases is significantly postponed and it is an actual problem around the world[5,6]. Due to the heterogeneity of manifestations of CA and/or SCTD, further research is needed to improve and introduce innovative therapeutic possibilities, especially since it's widely known that since 1990 innovative drugs have saved 55 million life-years[7,8]. Family/general physician plays an important role in education and improvement of patient's readiness to participate in clinical research[8]. The EULAR gives its support to patients through the project „Time 2 research"[10].

The pandemic caused by the coronavirus SARS-CoV-2 contributed to a high prevalence of morbidity and mortality from COVID-19 but it also brought on many medical challenges for patients suffering from CA and/or SCTD, and rheumatologists, which significantly affected healthcare and follow-up of these patients[2]. The institutes specialized for CA and/or SCTD in Serbia were part of the COVID system and patients have had only emergency access and there were no regular check-ups. At the time, the Online Counselling for Arthritis Patients - OCAP worked successfully through the platform „Lekarinfo". Since these patient groups are consid-

„Online savetovanja za pacijente sa artritisom", a aktivisti ORS putem društvenih mreža upoznavali obolele sa značajem vakcinacije protiv SARS-CoV-2[11,12]. Ovim je potvrđeno da ulaganje u telemedicinske usluge može doneti izuzetnu dobrobit za pacijente u budućnosti[13].

Pacijenti sa HA i/ili SBVT uglavnom imaju povećan rizik za infekcije u poređenju sa opštim stanovništvom[14]. U tom smislu kod ovih pacijenata, vakcine protiv COVID-19 pokazale su efikasnost u smanjenju infekcije i težine bolesti[15]. Aktivnost HA i/ili SBVT, starost, komorbiditeti, terapija glukokortikoidima su nezavisni faktori rizika za hospitalizaciju usled infekcije COVID-19[16]. Poznato je da COVID-19 i reumatoidni artritis (RA) imaju slične imuno-inflamatorne puteve i proinflamatorne medijatore, od kojih IL-6 ima ključnu patofiziološku ulogu u obe bolesti. U RA odgovoran je za oštećenje zglobova, dok je u COVID-19 u korelaciji sa težim oštećenjem pluća i većom smrtnošću[17]. Iz tog razloga su neki antireumatski lekovi (tocilizumab, hidroksihlorohin) bili deo terapijskih protokola u lečenju COVID-19[18].

Ciljevi istraživanja

Ciljevi istraživanja bili su ispitivanje pravovremenog postavljanja dijagnoze HA i/ili SBVT, vreme do uvođenja inovativne terapije i učešće u kliničkim istraživanjima kod obolelih od HA i/ili SBVT, kao i uticaj pola, starosti pacijenta i primene kortikosteroidne terapije (u lečenju HA i/ili SBVT), na stopu hospitalizacije usled COVID-19 infekcije.

Metod

Sproveli smo studiju preseka među obolelima od RMD, članovima Udruženja obolelih od reumatskih bolesti RS (ORS) u novembru 2022. godine. Ukupno je bilo 176 ispitanika. Koristili smo "online" upitnik. Svim učesnicima je zagarantovana anonimnost i svi su dali informisani pristanak za učešće u našem istraživanju.

Prvi deo analiziranih pitanja iz upitnika odnosio se na socio-demografske karakteristike ispitanika (godine života, pol), kao i podatke vezane za HA i/ili SBVT koje su bile kategorisane kao: 1) RA i 2) ostale RMD (ankilozirajući spondilitis - AS, psorijazni artritis, juvenilni idiopatski artritis, sistemski eritemski lupus, Šjogrenov sindrom, sistemska skleroza, sistemski vaskulitis i sve dijagnoze označene kao "druge"). Analizirano je proteklo vreme od prvih simptoma bolesti do postavljanja dijagnoze, korišćenje glukokortikoida i inovativne terapije (biološki i biosлични lekovi, Janus kinase - JAK inhibitori) u lečenju HA i/ili SBVT i učešće u kliničkim istraživanjima.

Drugi deo pitanja, koja su analizirana, odnosio se na COVID-19: opšte mere zaštite protiv COVID-19 (nošenje

ered high risk for the severe forms of COVID-19 and dying of it, rheumatologists used „Online Counselling for Arthritis Patients", while the ORS activists used social networks to educate patients on the importance of vaccination against SARS-CoV-2[11,12]. This confirmed the investment in telemedical services may benefit patients in the future[13].

Patients with CA and/or SCTD are mostly at higher risk of infection compared to the general population[14]. Thus, in these patients, COVID-19 vaccines showed efficacy in decreasing morbidity and disease severity[15]. The activity of CA and/or SCTD, age, comorbidities, and glucocorticoid therapy are independent risk factors for hospitalization due to COVID-19 infection[16]. It is common knowledge that COVID-19 and rheumatoid arthritis (RA) have similar immuno-inflammatory pathways and proinflammatory mediators, of which IL-6 plays a key pathophysiologic role in both diseases. In RA, it is responsible for joint damage, while in COVID-19 it's correlated to more severe lung damage and higher mortality[17]. For that reason, some antirheumatic drugs (tocilizumab, hidroxichlorochin) were part of the treatment protocol for COVID-19[18].

Research objectives

The research objective was to find out the time for timely diagnosis of CA and/or SCTD, the time to introducing innovative therapy, and participation in clinical research on CA and/or SCTD, as well as the influence of gender, age, and use of corticosteroid therapy (in the CA and/or SCTD treatment) in hospitalization rate due to COVID-19 infection.

Method

We conducted the cross-sectional study among RMD patients, and members of the Association of Rheumatic Disease Patients of the RS (ORS) in November 2022. There were 176 participants in total. We used an online questionnaire. All the participants were guaranteed anonymity and all of them gave informed consent for participating in our research.

The first part of the analyzed questions from the questionnaire referred to socio-demographic characteristics of the participants (age, gender), as well as data referring to CA and/or SCTD categorized as: 1) RA and 2) other RMDs (ankilyzing spondylitis - AS, psoriatic arthritis, juvenile idiopathic arthritis, systemic erythematous lupus, Sjogren syndrome, systemic sclerosis, systemic vasculitis, and all diagnoses marked as "other"). We analyzed the time lapsed from first disease symptoms to diagnosis, use of corticosteroids and innovative therapy (biologic and biosimilar medications, Janus kinase - JAK inhibitors) in the treatment of CA and/or SCTD, and participation in clinical research.

The other part of the analyzed questions referred to COVID-19: general protective measures against COVID-19

maski, izbegavanje boravka u zatvorenom prostoru, izbegavanje skupova, držanje distance, pranje ruku, korišćenje vitamina C i D, Zn), vakcinacija protiv COVID-19, obolevanje od infekcije COVID-19, kao i potreba za hospitalizacijom u kovid bolnici.

Prikupljeni podaci su tabelarno obrađeni i analizirani korišćenjem statističkog paketa za društvene nauke (SPSS, verzija 29.0). Kategorijalne varijable su predstavljene kao frekvencije (učestalosti) i izražene su u procentima. Podaci su analizirani deskriptivnom statistikom, a za utvrđivanje razlike između varijabli od značaja korišćen je Pirsonov Hi-kvadrat test. Statistički značajnom se smatrala p vrednost < 0,05.

(wearing masks, avoiding indoor stays, avoiding gatherings, keeping distance, hands washing, use of vitamin C and D, Zn), vaccination against COVID-19, getting ill from COVID-19, as well as the need for hospitalization in COVID hospitals.

Gathered data were tabulated and analyzed using a statistical package for social sciences (SPSS, version 29.0). Categorical variables were presented as frequencies (of occurrence) and were presented as percentages. Data were analyzed using descriptive statistics and for determining the difference between variables of importance Pearson Chi-square test was used. P- value of < 0,05 was considered statistically significant.

Rezultati

U istraživanju je učestvovalo 176 obolelih od HA i/ili SBVT, od kojih je 126 (71,6%) osoba bilo ženskog pola, a 50 (28,4%) muškog pola. Najveći broj ispitanika, njih 51, odnosno 29% je imalo između 51–60 godina starosti. Najviše ispitanika (ukupno 107) bolovalo je od RA (60,8%), dok je ostale reumatske bolesti imalo 69 ispitanika (39,2%). Kod najvećeg broja ispitanika (44,3%) proteklo vreme od pojave prvih simptoma do postavljanja dijagnoze bilo je duže od dve godine, dok je kod 29% ispitanika to vreme bilo kraće od 6 meseci. Kortikosteroidnu terapiju u bilo kom trenutku bolesti dobijalo je 65,9% ispitanika. Na inovativnoj terapiji je bilo 59,7% ispitanika. U kliničkom istraživanju učešće je imalo 23,3% ispitanika (Tabela 1).

Results

The research included 176 patients with CA and/or SCTD, of whom 126 (71,6%) were females and 50 (28,4%) were males. The majority of participants, 51, who make 29%, were 51–60 years of age. The majority of participants (a total of 107) were suffering from RA (60,8%), while other rheumatic diseases were found in 69 participants (39,2%). In the majority of the participants (44,3%) the time lapsed from first symptoms onset to diagnosis was longer than two years, while in 29% of the participants, this time was less than 6 months. Corticosteroid therapy, at any time during the disease, got 65,9% of the participants. The innovative therapy was used by 59,7% of the participants. Participation in clinical research took 23,3% of the participants (Table 1).

Tabela 1. Socio-demografske karakteristike ispitanika i karakteristike vezane za reumatsku bolest
Table 1. *Socio-demographic characteristics of the participants and characteristics related to rheumatic disease*

Pol / Gender	**N (%)**
Ženski / Female	126 (71,6)
Muški / Male	50 (28,4)
Godine starosti / Age	**N (%)**
20–30	12 (6,8)
31–40	27 (15,3)
41–50	42 (23,9)
51–60	51 (29,0)
61–70	34 (19,3)
71–75	10 (5,7)
Reumatska bolest / Rheumatic disease	**N (%)**
RA / RA	107 (60,8)
Ostale / Other	69 (39,2)
Vreme od simptoma do postavljanja dijagnoze / Time lapsed from symptom onset to diagnosis	**N (%)**
Kraće od 6 meseci / Less than 6 months	51 (29,0)

6–12 meseci / 6–12 months	20 (11,4)
1–2 godine / 1–2 years	27 (15,3)
Duže od 2 godine / More than 2 years	78 (44,3)
Kortikosteroidna terpaija u lečenju bolesti / Corticosteroid therapy in disease treatment	**N (%)**
Da / Yes	51 (29,0)
Ranije / Previously	65 (36,9)
Ne / No	60 (34,1)
Inovativna terapija u lečenju bolesti / Innovative therapy in disease treatment	**N (%)**
Da / Yes	105 (59,7)
Ne / No	71 (40,3)
Učešće u kliničkom istrazivanju / Participation in clinical research	**N (%)**
Da / Yes	41 (23,3)
Ne / No	135 (76,7)

U našem uzorku pacijenata obolelih od HA i/ili SBVT, opšte mere zaštite protiv COVID-19 sprovodilo je 51,1% ispitanika (nošenje maski i ostale mere zaštite). Vakcinisano je 68,8% ispitanika, pri čemu je tri doze vakcine primilo 53,7% ispitanika. Od COVID-19 infekcije obolelo je 67%, dok je potrebu za hospitalizacijom tokom COVID-19 infekcije imalo 17,8% ispitanika (Tabela 2).

In our sample of patients suffering from CA and/or SCTD, general protective measures against COVID-19 were carried out by 51,1% of the participants (wearing masks and other protective measures). There were 68,8% vaccinated participants and three doses were received by 53,7% of the participants. There were 67% of the participants who got COVID-19 infection, while 17,8% needed to be hospitalized due to COVID-19 (Table 2).

Tabela 2. Podaci vezani za infekciju COVID 19 kod ispitanika sa RMD
Table 2. *Data related to COVID-19 infection in participants with RMD*

Opšte mere zaštite protiv COVID-19 / General protective measures against COVID-19	**N (%)**
Da / Yes	90 (51,1)
Ne / No	**86 (48,9)**
Vakcinacija protiv COVID-19 / Vaccination against COVID-19	**N (%)**
Da / Yes	121 (68,8)
Ne / No	55 (31,2)
Broj doza vakcine / Number of vaccine doses	**N (%)**
Jedna / One	3 (2,5)
Dve / Two	44 (36,4)
Tri / Three	65 (53,7)
Četiri / Four	9 (7,4)
COVID-19 infekcija / COVID-19 infection	**N (%)**
Da / Yes	118 (67)
Ne / No	58 (33)
Hospitalizacija tokom COVID-19 infekcije / Hospitalization during COVID-19 infection	**N (%)**
Da / Yes	21 (17,8)
Ne / No	97 (82,2)

U prvih šest meseci od pojave simptoma, statistički značajno češće se dijagnostikuje RA od ostalih reumatskih bolesti. Međutim, statistička značajnost je potvrđena samo kod muškog pola ($p < 0,05$). Takođe, kod osoba muškog pola najčešće je bilo potrebno duže od dve godine za dijagnozu ostalih reumatskih bolesti. Najvećem broju ispitanika obolelih od RA inovativna terapija je uvedena nakon pet godina od pojave prvih simptoma bolesti, što je statistički značajno duže u poređenju sa ostalim reumatskim bolestima, ali je statistička značajnost potvrđena samo za ženski pol ($p < 0,05$). Utvrđeno je statistički značajno veće učešće u kliničkom istraživanju kod obolelih od RA u odnosu na obolele od ostalih reumatskih bolesti, ali je samo kod osoba ženskog pola potvrđena statistička značajnost ($p < 0,05$) (Tabela 3).

During the first six months, since the symptom onset, RA was statistically significantly diagnosed more frequently than other rheumatic diseases. Nevertheless, statistical significance was confirmed only in males ($p < 0,05$). Also in males, it took more than two years to diagnose other rheumatic diseases. In the majority of the participants suffering from RA, innovative therapy was introduced five years from the symptom onset, which is statistically significantly longer compared to other rheumatic diseases, but statistical significance was confirmed only for females ($p < 0,05$). Statistically significant higher participation in clinical research was confirmed in RA patients compared to other rheumatic disease patients but only in females statistical significance was confirmed ($p < 0,05$) (Table 3).

Tabela 3. Proteklo vreme od prvih simptoma do postavljanja dijagnoze, uvođenja inovativne terapije i učešće u kliničkom istraživanju kod obolelih od RA i ostalih reumatskih bolesti
Table 3. *The elapsed time from first symptoms to diagnosis, introduction of innovative therapy and participation in clinical trials in patients with RA and other rheumatic diseases*

Vrsta reumatske bolesti / Type of rheumatic disease			
	RA / RA	**Ostale / Other**	
Vreme: simptomi-dijagnoza / Time: symptoms-diagnosis, N (%)			
Oba pola / Both genders			p=0,001
Kraće od 6 meseci / Less than 6 months	42 (23,9)	9 (5,1)	
6–12 meseci / 6–12 months	12 (6,8)	8 (4,5)	
1–2 godine / 1–2 years	16 (9,1)	11 (6,3)	
Duže od 2 godine / More than 2 years	37 (21)	41 (23,3)	
Ženski pol / Females			p=0,127
Kraće od 6 meseci / Less than 6 months	34 (27)	8 (6,3)	
6–12 meseci / 6–12 months	10 (7,9)	3 (2,4)	
1–2 godine / 1–2 years	14 (11,1)	6 (4,8)	
Duže od 2 godine / More than 2 years	30 (23,8)	21 (16,7)	
Muški pol / Males			**p=0,007**
Kraće od 6 meseci / Less than 6 months	8 (16,0)	1 (2,0)	
6–12 meseci / 6–12 months	2 (4,0)	5 (10,0)	
1–2 godine / 1–2 years	2 (4,0)	5 (10,0)	
Duže od 2 godine / More than 2 years	7 (14,0)	20 (40,0)	
Vreme: dijagnoza - inovativna terapija / Time: diagnosis - innovative therapy, N (%)			
Oba pola / Both genders			p=0,016
Kraće od 1 godine / Less than a year	6 (5,7)	11 (10,5)	
1–2 godine / 1–2 years	7 (6,7)	5 (4,8)	
2–5 godina / 2–5 years	12 (11,4)	13 (12,4)	

Duže od 5 godina / More than 5 years	38 (36,2)	13 (12,4)	
Ženski pol / Females			**p=0,015**
Kraće od 1 godine / Less than a year	1 (1,5)	4 (6,0)	
1–2 godine / 1–2 years	6 (9,0)	3 (4,5)	
2–5 godina / 2–5 years	12 (17,9)	9 (13,4)	
Duže od 5 godina / More than 5 years	27 (40,3)	5 (7,5)	
Muški pol / Males			p=0,189
Kraće od 1 godine / Less than a year	5 (13,2)	7 (18,4)	
1–2 godine / 1–2 years	1 (2,6)	2 (5,3)	
2–5 godina / 2–5 years	0 (0,0)	4 (10,5)	
Duže od 5 godina / More than 5 years	11 (28,9)	8 (21,1)	
Učešće u kliničkom istraživanju / Participation in clinical research, N (%)			p=0,042
Oba pola / Both genders			
Ne / No	76 (43,2)	59 (33,5)	
Da / Yes	31 (17,6)	10 (5,7)	
Ženski pol / Females			**p=0,019**
Ne / No	66 (52,4)	36 (28,6)	
Da / Yes	22 (17,5)	2 (1,6)	
Muški pol / Males			p=0,210
Ne / No	10 (20,0)	23 (46,0)	
Da / Yes	9 (18,0)	8 (16,0)	

p-vrednost (Pirsonov Hi-kvadrat test) / p-value (Pearson's Chi-square test)

Pol i starosna dob u našem uzorku nisu statistički značajno uticali na stopu hospitalizacije tokom COVID-19 infekcije, ali je stopa hospitalizacije bila veća u starijoj životnoj dobi. Primena kortikosteroidne terapije u lečenju reumatske bolesti je statistički značajno uticala na višu stopu hospitalizacije tokom COVID-19 infekcije, ali je statistička značajnost potvrđena samo kod žena ($p < 0,05$) (Tabela 4).

Gender and age, in our sample, didn't statistically significantly influence the hospitalization rate during COVID-19 infection but the hospitalization rate was higher in the elderly. The use of corticosteroid therapy in the treatment of rheumatic disease statistically significantly influenced higher hospitalization rates during COVID-19 infection but the statistical significance was confirmed only in females ($p < 0,05$) (Table 4).

Tabela 4. Uticaj pola, godina starosti i kortikosteroidne terapije u lečenju reumatske bolesti na hospitalizaciju usled infekcije COVID-19
Table 4. *Influence of sex, age and corticosteroid therapy in the treatment of rheumatic disease on hospitalization due to COVID 19 infection*

Hospitalizacija (usled COVID 19) / Hospitalization (due to COVID 19)			
	Ne / No	**Da / Yes**	
Pol / Gender, N (%)			p=0,842
Ženski / Females	69 (58,5)	16 (13,6)	
Muški / Males	28 (23,7)	5 (4,2)	
Godine starosti / Age, N (%)			p=0,072
20–30	6 (5,1)	0 (0,0)	
31–40	17 (14,4)	3 (2,5)	
41–50	28 (23,7)	2 (1,7)	
51–60	28 (23,7)	6 (5,1)	
61–70	14 (11,9)	8 (6,8)	
71–75	4 (3,4)	2 (1,7)	
Kortikosteroidna terapija / Corticosteroid therapy, N (%)			
Oba pola / Both genders			p=0,024
Da / Yes	27 (22,9)	10 (8,5)	
Ranije / Previously	31 (26,3)	9 (7,6)	
Ne / No	39 (33,1)	2 (1,7)	
Ženski pol / Females			**p=0,037**
Da / Yes	21 (24,7)	9 (10,6)	
Ranije / Previously	22 (25,9)	6 (7,1)	
Ne / No	26 (30,6)	1 (1,2)	
Muški pol / Males			p=0,448
Da / Yes	6 (18,2)	1 (3,0)	
Ranije / Previously	9 (27,3)	3 (9,1)	
Ne / No	13 (39,4)	1 (3,0)	

p-vrednost (Pirsonov Hi-kvadrat test) / p-value (Pearson's Chi-square test)

Diskusija

Najveći broj anketiranih boluje od RA (60,8%). Rezultati našeg istraživanja pokazuju da se kod oba pola češće dijagnostikuje RA od ostalih HA i SBVT u prvih šest meseci od pojave simptoma, naročito kod muškaraca. Dobijeni podatak je u korelaciji sa podacima iz literature koji navode da je kod obolelih od RA vreme postavljanja pravovremene dijagnoze relativno kraće u poređenju sa drugim HA i/ili SBVT[6,19]. Postoje istraživanja koja su pokazala da ne postoje razlike vezane za pol za vreme potrebno za postavljanje dijagnoze RA i za uvođenje sistemske terapije[4]. Posebno je uočeno kasnije

Discussion

The majority of the surveyed suffer from RA (60,8%). The results of our research show that RA was more frequently diagnosed than other CAs and SCTDs, in both genders, in the first six months from the symptom onset, especially in males. This datum correlates to literature data, stating that in patients suffering from RA time for timely diagnosis is relatively shorter when compared to other CAs and SCTDs[6,19]. Studies are showing there is no difference related to gender as far as RA diagnosis and introduction of the innovative therapy are concerned[4]. Later visits to a doctor stood out in patients

javljanje lekaru kod pacijenata obolelih od aksijalnog spondiloartritisa (axSpA), što se smatra delimično i posledicom kulturološkog obrasca ponašanja vezanim za zanemarivanje bola u donjem delu leđa[6]. Poznato je da žene sa AS imaju veće kašnjenje u postavljanju dijagnoze u poređenju sa muškarcima, tegobe su im blaže nego kod muškaraca, a često im se pogrešno dijagnostikuje fibromijalgija[4]. Istraživanje sprovedeno u Velikoj Britaniji ukazalo je na kašnjenje u postavljanju dijagnoze nakon početnih simptoma inflamatornog artritisa na više nivoa (nepravovremeno javljanje obolelog izabranom lekaru, kasno upućivanje reumatologu (približno četiri posete izabranom lekaru pre upućivanja reumatologu), čekanje na pregled kod reumatologa nakon upućivanja pacijenta od strane izabranog lekara ili drugih specijalista[5]. U našoj zemlji čekanje na poslednjem nivou je svedeno na minimum, jer kada izabrani lekar posumnja na HA i/ili SBVT, ima mogućnost da pacijenta najhitnije uputi reumatologu radi savetovanja. Da bi se smanjilo vreme od pojave simptoma do pregleda reumatologa, potrebna je obrazovanost građana, farmaceuta (sa kojima se najčešće građani prvo savetuju nakon pojave simptoma), kao i lekara u primarnoj i sekundarnoj zdravstvenoj zaštiti[5]. U Srbiji je posle obrazovanosti lekara, medicinskih sestara/tehničara i farmaceuta, u primarnoj zdravstvenoj zaštiti vreme od prvih simptoma do postavljanja dijagnoze RA skraćeno sa 24 na 12 meseci[20].

Rezultati našeg istraživanja ukazuju da su oboleli od RA, posebno žene, imali veće učešće u kliničkim istraživanjima u poređenju sa ostalim reumatskim bolestima. Prema podacima iz literature u mnogim kliničkim istraživanjima vezanim za axSpA žene su nedovoljno zastupljene, što ima za posledicu kašnjenje u primeni optimalnih strategija lečenja kod ovih pacijentkinja[21]. Najvećem broju ispitanika obolelih od RA, naročito žena, inovativna terapija je uvedena nakon pet godina od pojave prvih simptoma bolesti, što je statistički značajno kasnije od ostalih reumatskih bolesti. Zanemarivanje tegoba i navikavanje na bol kod žena u Srbiji povezano je, nažalost, i sa mentalitetom. Dostupnost biološke terapije u odnosu na 17 posmatranih evropskih zemalja je na pretposlednjem mestu, a po kašnjenju u dostupnosti nalazi se na prvom mestu u uzorku od 26 evropskih zemalja sa prosečnim kašnjenjem od 979 dana[22]. Socioekonomski faktori, kašnjenje u postavljanju dijagnoze HA i kasno uvođenje inovativne terapije ima za posledicu pojačan umor, anksioznost i depresiju kod pacijenata sa RA[23]. Da bi ublažili navedeno, a omogućili obolelima od HA blagovremeno uvođenje inovativne terapije ulaskom u Klinička istraživanja, Udruženje reumatologa Srbije i Udruženje obolelih od reumatskih bolesti Republike Srbije sproveli su EULAR projekat „Vreme je za istraživanje"[10]. Prema podatku iz istraživanja u Francuskoj, oko 30% pacijenata sa RA započne sa primenom biološke terapije u prvih 10 godina bolesti[24].

Hronična upotreba glukokortikoida kod obolelih od reumatskih bolesti povezana je sa većim rizikom za hospi-

suffering from axial spondyloarthritis (axSpA), which is partially blamed on the cultural behavioral pattern related to neglecting lower back pain[6]. It's widely known women with AS are much later diagnosed compared to men, their health problems are milder than in men, and very often they are wrongly diagnosed with fibromyalgia[4].

A study performed in Great Britain showed there was a delay in diagnosis on many levels after the first symptoms of inflammatory arthritis (untimely visit to a GP, late referral to a rheumatologist, (nearly four visits to a GP before the patient is referred to a rheumatologist), waiting for a rheumatologist consultation after GP's or other specialist's referral)[5]. In our country, waiting time on the last level is quite minimal because when a GP suspects CA and/or SCTD, he/she can refer the patient most urgently to a rheumatologist for consultation. To shorten the time from symptom onset to a rheumatologist's consultation it is necessary to educate people, pharmacists (whom people most often contact first after the onset of the symptoms), as well as physicians on primary and secondary healthcare levels[5]. In Serbia, after the education of physicians, nurses/medical technicians, and pharmacists in primary healthcare, the time from first symptoms onset to diagnosis of RA is shortened from 24 to 12 months[20].

The results from our research show RA patients, especially women, had a higher incidence of participation in clinical research compared to other rheumatic diseases. According to literature, in many studies concerning axSpA women are insufficiently represented which leads to a delay in introducing optimal treatment strategies in these patients[21]. In the majority of RA patients, especially women, the innovative therapy was introduced five years after the onset of the first symptoms of the disease and it is statistically significantly delayed than in other rheumatic diseases. Disregarding symptoms and getting used to pain, in women in Serbia, are unfortunately connected to mentality. Availability of biologic therapy, compared to 17 surveyed European countries, is second to last and the delay in availability puts it in the first place in the sample of 26 European countries, with an average delay of 979 days[22]. Socio-economic factors, delay in diagnosis of CA, and late introduction of innovative therapy lead to prominent fatigue, anxiety, and depression in RA patients[23]. To alleviate previously mentioned facts and enable CA patients to get innovative therapy on time by getting into clinical research, the Rheumatology Association of Serbia and the Association of Rheumatic Patients of the Republic of Serbia conducted the EULAR project ''Time 2 research"[10]. According to research data from France, about 30% of RA patients start with biologic therapy in the first ten years of the disease[24].

Chronic use of glucocorticoids in patients suffering from rheumatic diseases is related to a higher risk of hospitalization due to COVID-19 infection[16,25–27], which was confirmed in female patients from our study. After diagnosis of

talizaciju usled infekcije COVID-19[16,25–27], što je potvrđeno kod pacijentkinja uključenih u naše istraživanje. Po postavljanju dijagnoze HA i/ili SBVT, reumatolog uvodi u terapiju lekove koji menjaju tok bolesti (LMTB). U cilju smanjenja upale, posledičnih bolova i malaksalosti, prvih 6–8 nedelja reumatolog uvodi kortikosteroide u punoj dozi ili po potrebi u pulsnim dozama kako bi premostio tih 6–8 nedelja. Strategija korišćenja kortikosteroida, zbog jatrogenog delovanja, podrazumeva da se njihova doza što pre postepeno smanjuje. Dalja upotreba kortikosteroida podrazumeva davanje najniže aktivne doze u što kraćem periodu uz održavanje najniže moguće aktivnosti bolesti, kao i obrazovanost pacijenata o imunosupresivnom dejstvu navedene terapije[26,27]. U našem istraživanju od 176 anketiranih obolelih od HA i/ili SBVT, 65,9% je koristilo kortikosteroide, a u trenutku istraživanja 29% i dalje koristi.

HA i SBVT su u patogenetskom smislu autoimunske bolesti. Zbog poremećaja imunskog odgovora, ali i imunosupresivne terapije (LMTB, kortikosteroidi, biološka terapija…), koja se primenjuje u lečenju, osobe koje boluju od ovih bolesti su sklone infekcijama, uključujući infekciju SARS-CoV-2. Zbog toga se svim bolesnicima sa HA i SBVT preporučuje aktivna, a u slučajevima kada je to neophodno i pasivna imunizacija protiv SARS-CoV-2. Uočeno je da aktivna imunizacija (vakcinacija) protiv COVID-19 može kod nekih bolesnika (oko 10%) da dovede do prolaznog pogoršanja bolesti, zbog podsticanja imunskog odgovora. Zbog toga se aktivna imunizacija (vakcinacija) ne preporučuje dok bolest nije dobro kontrolisana, tj. dok je aktivna. Imunosupresivni lekovi i glukokortikoidi mogu da smanje odgovor bolesnika na primenjenu vakcinu, kako u smislu jačine tako i trajanja imunskog odgovora. Ipak ovi bolesnici treba da se vakcinišu, jer je bolje imati bilo kakvu nego nikakvu otpornost. Posebno treba biti obazriv kod bolesnika na terapiji rituximabom, koji deluje tako što dovodi do deplecije B-limfocita. Vakcinaciju treba sprovesti pre započinjanja terapije ovim lekom ili neposredno pred naredni ciklus. Kod bolesnika kod kojih se ne preporučuje aktivna imunizacija protiv SARS-CoV-2, a to su bolesnici sa aktivnom bolešću ili na terapiji visokim/pulsnim dozama glukokortikoida, ili na terapiji rituximabom, preporučuje se primena pasivne imunizacije monoklonskim antitelima[28].

Oko polovine anketiranih pridržavalo se opštih mera zaštite, a oko 69% je vakcinisano protiv COVID-19 infekcije, a od toga 53,7% sa tri doze vakcine. U kovid bolnici je lečeno 17,8% anketiranih. Mada je stopa hospitalizacije bila veća u starijoj životnoj dobi, interesantno je da kod pacijenata sa HA i SBVT u našem istraživanju nije potvrđeno da godine starosti utiču na stopu hospitalizacije usled infekciije COVID-19, što je u suprotnosti sa podacima iz literature[16]. Takođe ni pol nije imao uticaj na rizik za hospitalizaciju, što nije u skladu sa rezultatima istraživanja Montero i saradnika u kome je kod obolelih od HA i/ili SBVT muški pol povezan sa većim rizikom za teži oblik COVID-19[29].

CA and/or SCTD, a rheumatologist introduces Disease-modifying antirheumatic drugs (DMARs). To ease the inflammation, consequential pain, and malaise in the first 6–8 weeks, the rheumatologist introduces corticosteroids, full dose or when needed, in pulse doses, to bridge those 6–8 weeks. The strategy of corticosteroid use, due to their iatrogenic effect, implies a gradual dose step down, as soon as possible. Further use of corticosteroids implies giving the lowest active dose, in the shortest time, maintaining the lowest disease activity, as well as the patient's education on immunosuppressive effects of said therapy[26,27]. In our research, out of 176 surveyed patients with CA and/or SCTD, 65,9% used corticosteroids, and at the moment of the research, 29% were still using them.

CA and SCTD are pathogenetically autoimmune diseases. Due to disfunction of the immune response but immunosuppressive therapy, as well, (DMAR, corticosteroids, biologic therapy…) that is being used in the course of treatment, persons suffering from these diseases are prone to infections, including SARS-CoV-2 infection. Therefore, all patients with CA and SCTD are advised active immunization and in some cases, when necessary, passive immunization against SARS-CoV-2. It was observed that active immunization (vaccination) against COVID-19 may lead to transitory disease deterioration in some patients (about 10%) due to initiation of the immune response. Therefore, active immunization (vaccination) is not advised unless the disease is well-controlled or is still active. Immunosuppressive medications and glucocorticoids may reduce the patient's response to the vaccine, both, in the sense of strength and duration of the immune response. Nevertheless, these patients should get vaccinated because it's better to have any immunity than none at all. It is especially neccesary to be cautious in patients on rituximab therapy. This drug depletes B-lymphocytes. Vaccination should be performed before the therapy start, with this medication or just before the next round of the medication. In patients who are not advised active immunization against SARS-CoV-2, and those are the patients with active disease, or on the high/pulse doses of glucocorticoids, or rituximab therapy, passive immunization with monoclonal antibodies is advised[28].

Around half of the surveyed patients adhered to general protective measures and about 69% were vaccinated against COVID-19 infection, of whom 53,7% with three doses of the vaccine. Out of the surveyed patients, 17,8% were hospitalized in the COVID hospital. Although the hospitalization rate was higher in the elderly, it's interesting that our research didn't confirm this. In CA and SCTD patients in our research age didn't affect hospitalization rate due to COVID-19 infection, which is opposed to other data from the literature[16]. Gender also didn't influence the risk of hospitalization, which is opposed to the research findings of Montero et al. who found that male patients with CA and SCTD were at higher risk for the severe form of COVID-19[29].

Analizirani podaci oslanjaju se na memoriju pacijenta što je u skladu sa Međunarodnom razmenom iskustava sa organizacijama pacijenata (IEEPO), koja insistira na oblikovanju zdravstvenog okruženja, prikupljanju podataka o realnoj medicinskoj praksi, njihovoj zaštiti i dostupnosti uz poštovanja privatnosti pacijenata. Ono što u izvesnoj meri potvrđuje naš pristup proizilazi iz istraživanja u kome je ispitivano kašnjenje javljanja lekaru pacijenata sa RA nakon pojave prvih simptoma, pri čemu je istaknuta tačnost sećanja pacijenata proverom datuma koji su dokumentovani u kartonima primarne zdravstvene zaštite[30].

Zaključak

Kod muškaraca obolelih od RA češće se pravovremeno postavlja dijagnoza u odnosu na obolevanje od ostalih HA i/ili SBVT. Žene četiri puta češće od muškaraca obolevaju od RA, imaju veće učešće u kliničkim istraživanjima i period do uvođenja inovativne terapije je duži kod ovih pacijentkinja u odnosu na obolele od ostalih HA. I u našem istraživanja je potvrđeno da upotreba glukokortikoida u lečenju HA i/ili SBVT utiče na veći rizik za hospitalizaciju usled infekcije COVID-19.−

Analyzed data rely on the patient's memory which is in accordance with the International Experience Exchange with Patient Organizations (IEEPO), which insists on shaping health environment, gathering data on realistic medical practice, their protection, and availability while respecting patient's privacy. The thing that to some extent confirms our approach ensues from the research investigating RA patients' delays in visiting their physicians after the symptoms onset. The accuracy of the patient's memory is emphasized by checking their visit dates documented in their health charts in primary practice[30].

Conclusion

In men suffering from RA diagnosis is more often timely when compared to other CAs and/or SCTDs. Women are four times more likely to get RA than men, they participate more in clinical research, and time to introduction of the innovative therapy is longer in these patients than in other CA patients. Our research also confirmed that glucocorticoid use in the treatment of CA and/or SCTD leads to higher risk of hospitalization due to COVID-19 infection.−

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Primljen - Received - 10.08.2023.
Prihvaćen - Accepted - 30.10.2023.