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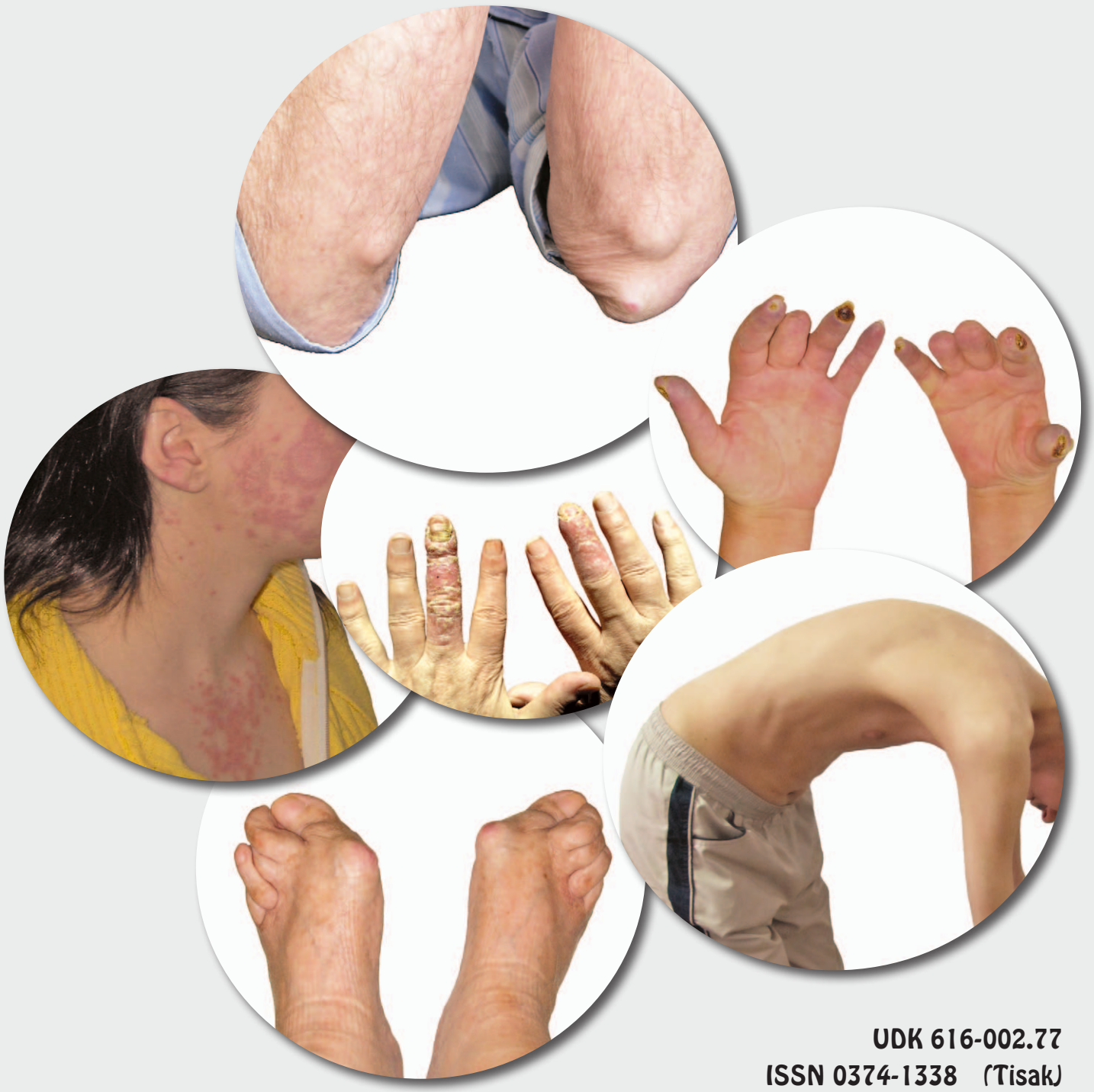

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Reumatizam, službeno glasilo Hrvatskoga reumatološkog društva Hrvatskoga liječničkog zbora, je recenzirani časopis, koji redovito izlazi dva puta godišnje.

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ORIGINAL SCIENTIFIC ARTICLE ORIGINALNI ZNANSTVENI RAD

GENDER DIFFERENCES IN PATIENTS WITH SJÖGREN'S SYNDROME: A 10-YEAR SINGLE CENTRE EXPERIENCE

SPOLNE RAZLIKE U SJÖGRENOVU SINDROMU – DESETOGODIŠNJE ISKUSTVO JEDNOG CENTRA

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Abstract

Objectives: The objective of this study was to examine the differences in clinical manifestations and comorbidities in men and women with Sjögren's syndrome (SS) treated at the University Hospital Centre Split. *Methods:* The data were collected from outpatient clinics, inpatient facilities and the day hospital of the Department of Rheumatology and Clinical Immunology of the Department for Internal Medicine of the University Hospital Centre Split. By inspecting the protocol and archive of the medical history of the disease, we have collected various data such as the demographic characteristics and the accompanying clinical manifestations and comorbidities. The SPSS 20 software for Windows (IBM, New York, USA), χ^2 test, Fisher's test, Fisher-Freeman-Halton test, univariate logistic regression, Firth univariate logistic regression and multivariate logistic regression were used in the statistical analysis. *Results:* Out of a total of 317 patients with SS, there were 17 (5.4%) men and 300 (94.6%) women. The median age of the patients was 64 (min-max: 19–89 years of age, Q1- Q3: 54–2 years of age). We have obtained a statistically significantly higher chance of developing lung diseases, vasculitis and lymphoma in men, and a statistically significantly higher chance of developing hypothyroidism in women. By using the Fisher-Freeman-Halton test we have proved a statistically significant association of the younger age group with thrombocytopenia and APS. In multivariate logistic regression in which age and gender were taken as independent variables, we have confirmed the association of the primary SS (pSS) with the male gender and the younger age group. *Conclusion:* Our study showed that men with Sjögren's disease had a higher incidence of lymphoma, vasculitis and lung involvement, while women had a higher incidence of hypothyroidism. Furthermore, thrombocytopenia and APS were more common in younger patients. In contrast, cardiovascular diseases, hypertension, diabetes, dyslipidemia, osteoporosis, rheumatoid arthritis (RA), systemic sclerosis (SSc) and secondary SS (sSS) were characteristically more common in elderly patients. Despite the fact that men are less likely to develop pSS, our research shows that at the time of diagnosis, male patients have a more serious form of the disease than women. Nevertheless, in order to draw precise conclusions on this issue, it is necessary to include the wider population in this research and perform its follow-up over a longer time period.

Keywords: Sjögren's syndrome, gender, clinical manifestations, vasculitis; lymphoma, lung diseases, comorbidities, Croatia

Sažetak

Cilj istraživanja: Cilj istraživanja bio je ispitati razlike u kliničkim manifestacijama i komorbiditetima između muškaraca i žena oboljelih od Sjögrenova sindroma (SS) liječenih u KBC-u Split. *Materijali i metode:* Podatci su prikupljeni iz ambulanta, stacionara i dnevne bolnice Zavoda za reumatologiju i kliničku imunologiju Klinike za unutarnje bolesti KBC-a Split. Iz arhive medicinske dokumentacije prikupljena su demografska obilježja te popratne kliničke manifestacije i komorbiditeti. U statističkoj analizi korišten je paket *SPSS 20 for Windows* (IBM, New York, SAD), χ^2 test, Fisherov test, Fisher-Freeman-Haltonov test, univarijantna logistička regresija, Firth univarijantna logistička regresija i multivarijantna logistička regresija. *Rezultati:* Istraživanje je obuhvatilo 317 ispitanika s dijagnozom SS-a: 17 (5,4%) muškaraca i 300 (94,6%) žena. Medijan životne dobi ispitanika iznosio je 64 godine (min-maks: 19 – 89 god., Q1-Q3: 54 – 72 god.). Dobili smo statistički značajno veće izglede za nastanak plućnih bolesti, vaskulitisa i limfoma u muškaraca te statistički značajno veće izglede za pojavnost hipotireoze u žena. Fisher-Freeman-Haltonovim testom dokazali smo statistički značajnu povezanost mlađe dobne skupine s trombocitopenijom i antifosfolipidnim sindromom (APS). Multivarijantnom logističkom regresijom u kojoj smo kao nezavisne varijable uzeli dob i spol, potvrdili smo povezanost primarnog SS-a (pSS) s muškim spolom i mlađom dobnom skupinom. *Zaključci:* Istraživanje je pokazalo da je u muškaraca sa SS-om bila veća pojavnost limfoma, vaskulitisa i zahvaćenosti pluća, dok je u žena bila veća učestalost hipotireoze. Trombocitopenija i APS češće su se javljali u bolesnika mlađe životne dobi. Nasuprot tomu, kardiovaskularne bolesti, hipertenzija, šećerna bolest, dislipidemija, osteoporoza, reumatoidni artritis (RA), sistemska skleroza (SSc) i sekundarni SS (sSS) karakteristično su bili češći u bolesnika starije životne dobi. Unatoč činjenici da su muškarci manje skloni razvoju pSS-a, naše istraživanje pokazuje da muškarci imaju veći izgled za ozbiljniji oblik bolesti naspram žena. Ipak, za preciznije zaključke potrebno bi bilo obuhvatiti širu populaciju i pratiti je tijekom duljeg razdoblja.

Ključne riječi: Sjögrenov sindrom, kliničke manifestacije, spol, vaskulitis, limfom, plućne bolesti, komorbiditeti, Hrvatska

INTRODUCTION

Sjögren's syndrome (SS) is a chronic, slowly progressive autoimmune disease characterized by lymphocytic infiltration of exocrine glands resulting in dry mouth (xerostomia) and dry eyes (xerophthalmia). The syndrome has unique clinical features, from organic autoimmune exocrinopathy to systemic disease (1). Lungs, kidneys, thyroid gland, muscles, heart, nervous system and skin can be affected and symptoms of fatigue, depression, cognitive disorders, pain and mild arthritis are present (2). A small but significant number of patients develop lymphoma (1). The condition can be primary or secondary — as part of some other autoimmune event (3). The prevalence of primary Sjögren's syndrome (pSS) is ~ 0.5–1%, while secondary SS (sSS) develops in 5–20% of patients with other autoimmune diseases (1). Women develop SS significantly more often than men; the gender difference ranges between 9:1 and 19:1. Average age at first diagnosis of pSS is 56 years old. However, the first symptoms may appear several years before diagnosis (4). Some studies indicate that the gender ratio and age distribution depend on the ethnicity and geographical area of the researched population. SS rarely occurs in children, and the onset has been described as early as the fifth year of life (3). Most patients with SS have symptoms related to impaired salivary gland function. Patients mostly complain of difficulty swallowing food, altered sense of taste, burning sensation in the mouth and more frequent occurrence of cavity. Oral candidiasis stands out as another

UVOD

Sjögrenov sindrom (SS) kronična je, polako napredujuća autoimuna bolest koju karakterizira limfocitna infiltracija egzokrinih žlijezda što rezultira suhoćom usta (kserostomijom) i suhim očima (kseroftalmijom). Sindrom ima jedinstvene kliničke značajke, od organske autoimune egzokrinopatije do sistemske bolesti (1). Mogu biti zahvaćena pluća, bubrezi, štitnjača, mišići, srce, živčani sustav i koža te su prisutni simptomi umora, depresije, kognitivnih poremećaja, boli i blagog artritisa (2). Mali, ali značajan broj bolesnika razvije limfom (1). Stanje može biti primarno ili sekundarno – u sklopu nekog drugoga autoimunog zbivanja (3). Prevalencija primarnoga Sjögrenovog sindroma (pSS) je ~ 0,5 – 1%, dok se sekundarni SS (sSS) razvija u 5 – 20% bolesnika s drugim autoimunim bolestima (1). Žene razvijaju SS znatno češće od muškaraca; razlika u spolu kreće se između 9:1 i 19:1. Prosječna dob u vrijeme prve dijagnoze pSS-a je 56 godina. Međutim, prvi simptomi mogu se pojaviti godinama prije dijagnoze (4). Pojedina istraživanja ukazuju da omjer spolova i dobna raspodjela ovise o etničkoj pripadnosti i geografskom području ispitane populacije. SS se rijetko javlja u djece, a opisani su početci već u petoj godini života (3). Većina bolesnika sa SS-om ima simptome povezane s poremećenom funkcijom žlijezda slinovnica. Bolesnici se najviše žale na poteškoće prilikom gutanja hrane, izmijenjen osjet okusa, osjećaj žarenja u ustima te učestalije pojave karijesa. Oralna kandidijaza ističe se kao još jedna komplikacija kserostomije (5).

complication of xerostomia (5). Ocular involvement is the second main manifestation of SS (3). Almost three-quarters of pSS patients present with signs or symptoms of extraglandular disease, but only approximately 25% of pSS patients develop moderate or severe extraglandular disease (6). SS is associated with various respiratory symptoms. The most typical manifestations are chronic interstitial lung disease (ILD) and tracheobronchial disease. The most common manifestation of ILD is nonspecific interstitial pneumonia with fibrosis (NSIP). Tracheobronchial disease is common and is characterized by diffuse lymphocytic infiltration of the airways. It can appear in the form of bronchial hyperreactivity, bronchiectasis, bronchiolitis or repeated respiratory infections (7).

It is important to emphasize the association of SS with other autoimmune diseases, especially with primary biliary cholangitis (PBC) and Hashimoto's thyroiditis. PBC and SS are described as autoimmune epithelitis in which apoptosis in both cases may be a key element to explain the organic immune-mediated injury of biliary epithelium and epithelium of exocrine glands. Antimitochondrial antibodies in the serum of patients with

SS detected by indirect immunofluorescence highly predict the development of PBC during a five-year follow-up period (8). Various studies have established the coexistence of SS and autoimmune thyroid diseases (AITD) and pointed to the fact that both diseases are characterized by the presence of lymphocytic infiltrates, especially CD4+ T lymphocytes and activation of B cells. The presence of specific chemokines, such as CXCL10, have been described in AITD as markers of an inflammatory response leading to tissue destruction and consequent hypothyroidism, while in SS it has been shown that glandular epithelial cells produce CXCL9 and CXCL10, thereby contributing to the damage of the salivary glands (9).

The development of B-cell non-Hodgkin's lymphoma is the main complication of the disease and can occur in 5–7% of patients with SS, usually within 10 years of diagnosis (6). In one study, an almost sevenfold higher risk of developing lymphoma was found in SS patients compared to the healthy population (10).

A meta-analysis of observational cohort studies showed that pSS is characterized by an almost one and a half times higher risk of cardiovascular diseases, including coronary artery disease, acute coronary syndrome, angina pectoris, ischemic heart disease and cerebrovascular disease, compared to control subjects (11).

The goals of this paper were to examine the differences in clinical manifestations and comorbidities between men and women with SS treated at UHC Split and to compare the results of our study with results from the available literature.

Zahvaćenost očiju druga je glavna manifestacija SS-a (3). Gotovo tri četvrtine bolesnika s pSS-om očituje se znakovima ili simptomima izvanžljezdane bolesti, ali samo približno 25% bolesnika s pSS-om razvija umjerenu ili tešku izvanžljezdanu bolest (6). SS je povezan s različitim respiratornim simptomima. Najtipičnije manifestacije su kronična intersticijska bolest pluća (ILD) i traheobronhalna bolest. Najčešća je manifestacija ILD-a nespecifična intersticijska pneumonija s fibroznim promjenama (NSIP). Traheobronhalna bolest je česta, a karakterizirana je difuznom limfocitnom infiltracijom dišnih putova. Može se pojaviti u obliku bronhalne hiperreaktivnosti, bronhiektazija, bronhiolitisa ili ponovljenih respiratornih infekcija (7).

Bitno je istaknuti povezanost SS-a s drugim autoimunim bolestima, posebno s primarnim bilijarnim kolangitisom (PBC) i Hashimotovim tireoiditisom. PBC i SS opisuju se kao autoimuni epitelitis u kojem apoptoza u oba slučaja može biti ključni element za objašnjenje organske imunološki posredovane ozljede bilijarnog epitela i epitela egzokrinih žlijezda. Antimitohondrijska protutijela u serumu bolesnika sa SS-om otkrivena neizravnom imunofluorescencijom visoko predviđaju razvoj PBC-a tijekom petogodišnjeg razdoblja promatranja (8). Razna istraživanja utvrđivala su koegzistenciju SS-a i autoimunih bolesti štitnjače (AITD) te su ukazala na činjenicu da obje bolesti karakterizira prisutnost limfocitnih infiltrata, posebno CD4+ T-limfocita i aktivacija B-stanica. Prisutnost specifičnih kemokina, kao što je CXCL10, opisani su u AITD-u kao biljezi upalnoga odgovora koji dovode do uništenja tkiva i posljedične hipotireoze, dok je u SS-u pokazano da žljezdane epitelne stanice stvaraju CXCL9 i CXCL10 pridonoseći time oštećenju žlijezda slinovnica (9).

Razvoj non-Hodgkinovog limfoma B-stanica predstavlja glavnu komplikaciju bolesti i može se javiti u 5 – 7% bolesnika sa SS-om, obično unutar deset godina od dijagnoze (6). U jednom istraživanju utvrđen je gotovo sedmerostruko veći rizik razvoja limfoma u SS pacijenata u usporedbi sa zdravom populacijom (10).

Metaanaliza opservacijskih kohortnih studija pokazala je da pSS karakterizira gotovo jedan i pol puta veći rizik od kardiovaskularnih bolesti, uključujući bolest koronarnih arterija, akutni koronarni sindrom, anginu pectoris, ishemijsku bolest srca te cerebrovaskularnih bolesti, u usporedbi s kontrolnim ispitanicima (11).

Ciljevi ovoga rada bili su ispitati razlike u kliničkim manifestacijama i komorbiditetima između muškaraca i žena sa SS-om liječenih u KBC-u Split te usporediti rezultate našeg istraživanja s rezultatima iz literature.

ISPITANICI I METODE

Provedeno istraživanje je retrospektivno, opažajno i presječno. Korišteni su podatci iz ambulanta, stacionara i dnevne bolnice Zavoda za reumatologiju i kliničku

SUBJECTS AND METHODS

The conducted research is retrospective, observational and cross-sectional. Data from outpatient clinics, inpatient facilities and day hospitals of the Division of Rheumatology and Clinical Immunology of the Department of Internal Medicine, Split University Hospital Centre were used. All patients older than 18 years of age who were registered at the Division of Rheumatology and Clinical Immunology from January 1st, 2010 to December 31st, 2020, and who had at least two visits, examinations or hospitalizations at the Division during the follow-up period. As an inclusion criterion, we used the diagnosed SS according to the 2016 ACR/EULAR criteria. By inspecting the patients' medical history, we collected data on age, gender, clinical manifestations and comorbidities. From the clinical manifestations, we took into account the following: the existence of cutaneous manifestations, vasculitis, lymphoma, haematological and immunological manifestations, involvement of the joints, nervous system, kidneys, lungs and gastrointestinal system. From the group of comorbidities, we recorded the following: cardiovascular diseases, hypertension, degenerative diseases of the spine, hypothyroidism, diabetes (DM), dyslipidemia, systemic infections, associated neoplasms and accompanying autoimmune diseases (rheumatoid arthritis – RA, systemic lupus erythematosus – SLE, systemic sclerosis – SSc).

We made a basic division of SS into pSS and sSS, whereby we described each SS with an additional diagnosis of SLE, RA or SSc as secondary. We singled out the overlap syndrome as a separate category and evaluated it when it was prominent in the clinical findings. In the cardiac involvement variable, we included diseases of the pericardium, myocardium, endocardium, heart valves and coronary blood vessels, as well as heart rhythm disorders. Under haematological manifestations we included anaemia, leukopenia and thrombocytopenia, and under immunological manifestations we included polyclonal hypergammaglobulinemia, IgA and IgG immunodeficiency, common variable immunodeficiency, monoclonal gammopathy and monoclonal gammopathy of undetermined significance (MGUS). The study was approved by the Ethics Committee of UHC Split.

Statistical processing

The collected data were entered into a computer database, using the SPSS 20 software for Windows (IBM, New York, USA). We used the χ^2 test, Fisher's test, Fisher-Freeman-Halton test, univariate logistic regression, Firth univariate logistic regression and multivariate logistic regression. A P-value of less than 0.05 was considered as statistically significant. Data are presented as absolute values, percentages, OR odds ratio and 95% confidence intervals 95% CI).

imunologiju Klinike za unutarnje bolesti KBC-a Split. U istraživanje su uključeni svi bolesnici stariji od 18 godina koji su evidentirani u Zavodu za reumatologiju i kliničku imunologiju od 1. siječnja 2010. do 31. prosinca 2020., a koji su u ispitivanom razdoblju imali barem dva posjeta, pregleda ili hospitalizaciju u Zavodu. Kao kriterij uključenja uzeli smo dijagnosticirani SS prema zajedničkim ACR/EULAR kriterijima iz 2016. godine. Iz povijesti bolesti prikupili smo podatke o dobi, spolu te kliničkim manifestacijama i komorbiditetima. Od kliničkih manifestacija u obzir smo uzeli: postojanje kožnih promjena, vaskulitisa, limfoma, hematoloških i imunoloških manifestacija, zahvaćenost zglobova, živčanog sustava, bubrega, pluća i gastrointestinalnog sustava. Iz skupine komorbiditeta zabilježili smo: kardiovaskularne bolesti, hipertenziju, degenerativne bolesti kralježnice, hipotireozu, šećernu bolest, dislipidemiju, sistemske infekcije, pridružene neoplazme te popratne autoimune bolesti (reumatoidni artritis – RA, sistemski eritemski lupus – SLE, sistemska skleroza – SSc).

Napravili smo osnovnu podjelu SS-a na pSS i sSS, pri čemu smo svaki SS uz koji je postojala još dijagnoza SLE, RA ili SSc opisali kao sekundarni. Sindrom preklapanja (*sy overlap*) izdvojili smo kao posebnu kategoriju i evaluirali smo ju onda kada je bila istaknuta u kliničkim nalazima. U varijablu zahvaćenosti srca uključili smo bolesti perikarda, miokarda, endokarda, srčanih zalistaka i koronarnih krvnih žila te poremećaj srčanog ritma. Pod hematološke promjene uvrstili smo anemiju, leukopeniju i trombocitopeniju, a pod imunološke manifestacije ubrojili smo poliklonsku hipergamaglobulinemiju, imunodeficijenciju IgA i IgG, običnu varijabilnu imunodeficijenciju, monoklonalnu gamapatiju te monoklonalnu gamapatiju neodređenog značenja (MGUS). Istraživanje je odobrilo Etičko povjerenstvo KBC-a Split.

Statistička obrada

Prikupljeni podatci uneseni su u računalnu bazu podataka pri čemu smo koristili program *SPSS 20 for Windows* (IBM, New York, SAD). Koristili smo χ^2 test, Fisherov test, Fisher-Freeman-Haltonov test, univarijantnu logističku regresiju, Firth univarijantnu logističku regresiju i multivarijantnu logističku regresiju. P-vrijednost manja od 0,05 uzeta je za statistički značajnu. Podatci su prikazani kao apsolutne vrijednosti, postotci, omjer izgleda (engl. *odds ratio*, OR) i 95-postotni intervali pouzdanosti (engl. 95% CI).

REZULTATI

Istraživanjem je obuhvaćeno 317 bolesnika sa SS-om. Medijan životne dobi ispitanika iznosio je 64 godine (min-maks: 19 – 89 god.). Ispitanike smo prema dobi podijelili u tri skupine: < 59 godina, 59 – 69 godina,

Table 1 Distribution of patients by age groups and type of clinical manifestations that did not differ significantly between the genders

Tablica 1. Raspodjela bolesnika prema dobnim skupinama i vrsti kliničkih manifestacija koje se nisu statistički značajno razlikovale među spolovima

		Total/Ukupno (n=317)	Gender/Spol		P
			Men/Muškarci (n=17)	Women/Žene (n=300)	
Age groups (in yrs.) / Dobne skupine (god.)	< 59	111 (35)	9 (52.9)	102 (34)	0.281[a]
	59–69	101 (31.9)	4 (23.5)	97 (32.3)	
	> 69	105 (33.1)	4 (23.5)	101 (33.7)	
Cutaneous manifestations / Kožne promjene	yes / da	115 (36.3)	7 (41.2)	108 (36)	0.666[a]
Kidneys / Bubrezi	yes / da	41 (12.9)	1 (5.9)	40 (13.3)	0.327[b]
GI system / GI sustav	yes / da	70 (22.1)	7 (41.2)	63 (21)	0.068[b]
Nervous system / Živčani sustav	yes / da	43 (13.6)	3 (17.6)	40 (13.3)	0.712[b]
Depression / Depresija	yes / da	34 (10.7)	3 (17.6)	31 (10.3)	0.408[b]
Joints / Zglobovi	yes / da	117 (36.9)	5 (29.4)	112 (37.3)	0.51[a]
Haematological manifestations / Hematološke promjene	yes / da	49 (15.5)	4 (23.5)	45 (15)	0.312[b]
Anaemia / Anemija	yes / da	33 (10.4)	2 (11.8)	31 (10.3)	0.693[b]
Thrombocytopenia / Trombocitopenija	yes / da	9 (2.8)	2 (11.8)	7 (2.3)	0.078[b]
Leukopenia / Leukopenija	yes / da	5 (1.6)	1 (5.9)	4 (1.3)	0.242[b]
Immunological manifestations / Imunološke promjene	yes / da	19 (6)	2 (11.8)	17 (5.7)	0.271[b]

Legend / Legenda: GI system = gastrointestinal system / gastrointestinalni sustav. [a]χ^2-test, [b]Fisher's test / Fisherov test. Data are presented as absolute value and percentage / Podatci su prikazani kao apsolutna vrijednost i postotak.

RESULTS

The research included 317 patients with SS. The median age of the subjects was 64 (min-max: 19–89). We divided the subjects into 3 groups according to age: < 59, 59–69, > 69. Out of the total number of subjects there were 17 (5.4%) men and 300 (94.6%) women.

Table 1 shows that there was no statistically significant association of clinical manifestations with gender. Nevertheless, it is worth emphasizing that the most common cutaneous manifestations were Raynaud's phenomenon (RP) (15%), discoid lupus (11%), erythematous cutaneous manifestations (8%) and alopecia (7%). The share of other recorded cutaneous manifestations is shown in Figure 1.

Likewise, in the category of nervous system diseases, which we divided into central and peripheral nervous system, the prevalence of central nervous system involvement (epilepsy, demyelinating diseases, cerebrovascular disease, condition following meningoencephalitis, CNS vasculitis, central vertigo, extrapyramidal disorders, cerebrovascular insult, headache) was 5.7%, and the share of peripheral neuropathies was 7.6%.

From the data shown in Table 2, it can be seen that men have a higher frequency of lung diseases, vasculitis, lymphoma and primary SS, while women have a higher incidence of hypothyroidism.

Our results indicate a significant association between vasculitis and the male gender, with the proportion

> 69 godina. Od ukupnog broja ispitanika bilo je 17 (5,4%) muškaraca i 300 (94,6%) žena.

Iz tablice 1 primjećuje se da nije bilo statistički značajne povezanosti kliničkih manifestacija sa spolom. Unatoč tomu, vrijedi naglasiti da su najčešće kožne promjene bile Raynaudov fenomen (RF) (15%), diskoidni lupus (11%), eritematozne promjene kože (8%) i alopecija (7%). Udio ostalih zabilježenih kožnih promjena prikazan je na slici 1.

Jednako tako, u kategoriji bolesti živčanog sustava, koju smo podijelili na središnji i periferni živčani sustav, prevalencija zahvaćenosti središnjega živčanog sustava (epilepsija, demijelinizacijske promjene, cerebrovaskularna bolest, stanje po meningoencefalitisu, CNS vaskulitis, centralni vertigo, ekstrapiramidni poremećaji, cerebrovaskularni inzult, glavobolja) iznosila je 5,7%, a udio perifernih neuropatija 7,6%.

Iz podataka prikazanih u tablici 2 uočava se da je u muškaraca veća učestalost plućnih bolesti, vaskulitisa, limfoma i primarnog SS-a, dok je u žena veća pojavnost hipotireoze.

Naši rezultati ukazuju na značajnu povezanost vaskulitisa i muškog spola, pri čemu je udio vaskulitisa četiri puta veći u muškaraca nego u žena. Kao najčešći oblik ističe se krioglobulinemički vaskulitis s prevalencijom od 29%, potom leukocitoklastični vaskulitis (17%) te CNS i sistemski oblik vaskulitisa (12%). Nodularni i urtikarijalni vaskulitis imali su najmanju pojavnost (6%).

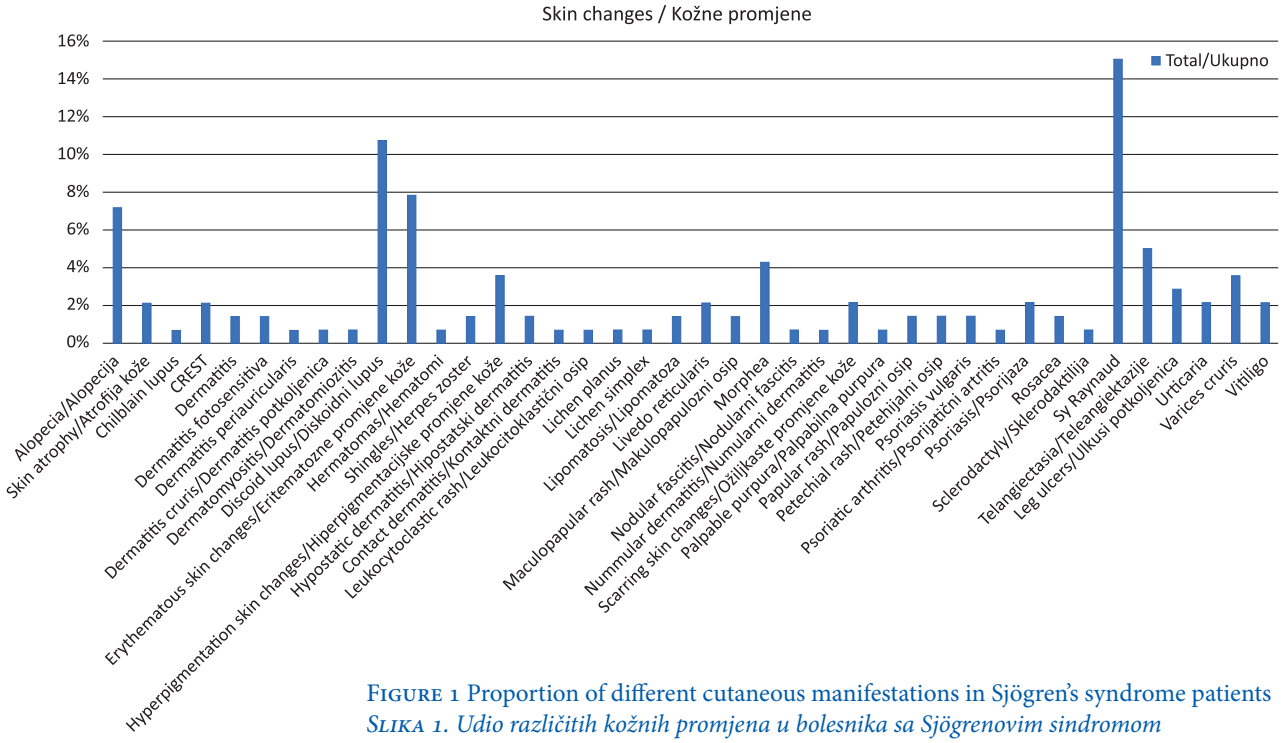


Figure 1 Proportion of different cutaneous manifestations in Sjögren's syndrome patients
Slika 1. Udio različitih kožnih promjena u bolesnika sa Sjögrenovim sindromom

Table 2 Distribution of Sjögren's syndrome patients according to type of disease and clinical manifestations where a significant difference between the genders was proven.
Tablica 2. Raspodjela bolesnika prema vrsti kliničkih manifestacija gdje je nađena značajna razlika među spolovima

		Total / Ukupno	Men / Muškarci	Women / Žene	P	OR (95% CI)	P
Primary SS / Primarni SS	yes / da	204 (64.4)	16 (94.1)	188 (62.7)	**0.008**[a]	9.5 (1.2–72.9)	**0.03**[d]
Vasculitis / Vaskulitis	yes / da	16 (5)	3 (17.6)	13 (4.3)	**0.047**[b]	4.7 (1.2–18.5)	**0.026**[d]
Lymphoma / Limfom	yes / da	9 (2.8)	3 (17.6)	6 (2)	**0.009**[b]	10.5 (2.4–46.4)	**0.002**[d]
Lung diseases / Plućne bolesti	yes / da	46 (14.5)	6 (35.3)	40 (13.3)	**0.024**[b]	3.5 (1.2–10.1)	**0.018**[d]
Hypothyroidism / Hipotireoza	yes / da	89 (28.1)	0 (0)	89 (29.7)	**0.004**[b]	14.8 (0.8–271.1)	0.07[e]

Legend/ Legenda: SS = Sjögren's syndrome / Sjögrenov sindrom. [a]χ2-test, [b]Fisher's test / Fisherov test, [c]Fisher-Freeman-Halton test, [d]logistic regression / logistička regresija, [e]Firth logistic regression / Firth logistička regresija. Data are presented as absolute value and percentage / Podatci su prikazani kao apsolutna vrijednost i postotak

tion of vasculitis being 4 times higher in men than in women. The most common form is cryoglobulinemic vasculitis with a prevalence of 29%, followed by leukocytoclastic vasculitis (17%) and CNS and systemic vasculitis (12%). Nodular and urticarial vasculitis had the lowest incidence (6%).

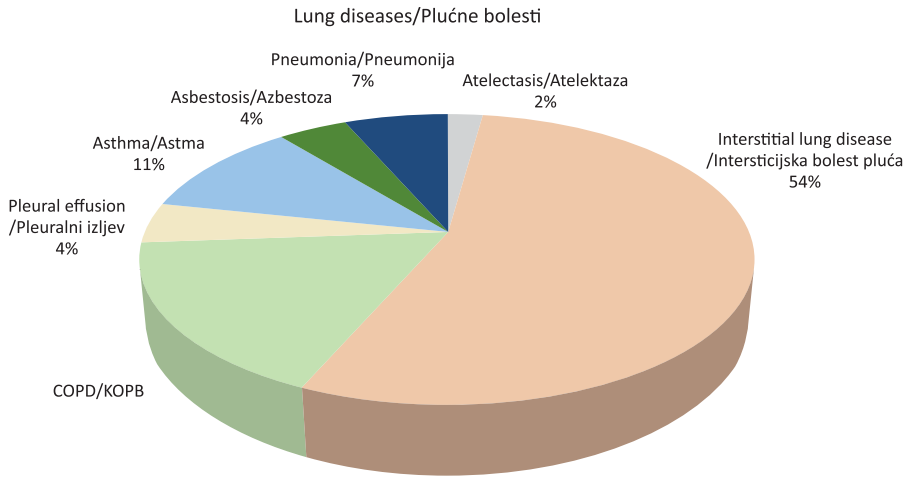
The frequency of lung diseases is 2.7 times higher in men than in women. Figure 2 shows the share of different lung diseases, of which we single out interstitial lung disease as the most represented entity. It should be emphasized that pulmonary fibrosis was the most common form of ILD with a 40% incidence, followed immediately by idiopathic interstitial pneumonia with a 20% incidence and sarcoidosis with a 16% incidence, while the fewest recorded cases were bronchiolitis obliterans with organized pneumonia (8%).

Table 2 also shows that the proportion of lymphoma is 8.8 times higher in men than in women, while the

Učestalost plućnih bolesti veća je 2,7 puta u muškaraca nego u žena. Na slici 2 prikazan je udio različitih plućnih bolesti od kojih izdvajamo intersticijsku bolest pluća kao najzastupljeniji entitet. Valja naglasiti da je plućna fibroza bila najčešći oblik ILD-a s 40-postotnom pojavnošću, a odmah nakon nje slijedi idiopatska intersticijska pneumonija s 20-postotnom i sarkoidoza sa 16-postotnom učestalošću, dok je najmanje bilo zabilježenih slučajeva bronhiolitisa obliteransa s organiziranom pneumonijom (8%).

Iz tablice 2 također je vidljivo da je udio limfoma 8,8 puta veći u muškaraca nego u žena, dok je vjerojatnost limfoma 10,5 puta veća u muškaraca nego u žena. Svi evaluirani limfomi u istraživanju bili su upravo non-Hodgkinov tip limfoma.

Od ukupno 89 slučajeva dijagnoze hipotireoze svih 89 dijagnosticirano je u žena pa je time udio žena s hipotireozom bio 29,7%, a u muškaraca u našem uzorku



Legend/ Legenda: COPD / KOPB = chronic obstructive pulmonary disease / kronična opstruktivna plućna bolest

Figure 2 Proportion of certain lung diseases in Sjögren's syndrome patients
Slika 2. Udio pojedinih plućnih bolesti u bolesnika sa Sjögrenovim sindromom

Table 3 Odds ratio (OR) with 95% confidence interval for clinical manifestations significantly associated with age groups.
Tablica 3. Omjer izgleda (OR) uz 95-postotni interval pouzdanosti za kliničke manifestacije koje su statistički značajno povezane s dobnim skupinama

Age groups / Dobne skupine					
Haematological manifestations / Hematološke promjene	Reference level / Referentni nivo	OR for group / OR za skupinu 59–69	P	OR for group / OR za skupinu > 69	P
	Group / Skupina < 59	0.8 (0.6–1.1)	0.206[d]	0.6 (0.4–0.9)	**0.02**[d]
Thrombocytopenia / Trombocitopenija	Reference level / Referentni nivo	OR for group / OR za skupinu < 59	P	OR for group / OR za skupinu > 69	P
	Group / Skupina 59–69	14.6 (0.8–262.1)	0.07[e]	4.9 (0.2–104.9)	0.31[e]

Legend / Legenda: OR = odds ratio / omjer izgleda. [d]logistic regression / logistička regresija, [e]Firth logistic regression / Firth logistička regresija

chance of lymphoma is 10.5 times higher in men than in women. All lymphomas evaluated in the study were non-Hodgkin's lymphoma.

Out of a total of 89 cases of diagnosis of hypothyroidism, all 89 were diagnosed in women, so the proportion of women with hypothyroidism was 29.7%, and taking into account the men in our sample it was 0%. Thus, by the resulting calculation, it can be concluded that the chance of hypothyroidism is 14.8 times higher in women than in men.

We also analysed clinical manifestations and comorbidities in relation to three age groups (<59, 59–69 and > 69) because these three age groups are adjusted according to gender. Out of the clinical manifestations, haematological manifestations including thrombocytopenia were statistically significantly different between age groups (Table 3).

The attached table shows that the chance of occurrence of haematological manifestations in the group of patients aged 59–69 years old is 20% lower compared to the group of patients <59 years old (P= 0.206), while the chance of occurrence of haematological manifestations in the group of patients > 69 years old is by 40% 0%, a posljedičnim izračunom vjerojatnost hipotireoze je 14,8 puta veća u žena nego u muškaraca.

Analizu kliničkih manifestacija i komorbiditeta napravili smo i u odnosu na tri dobne skupine (< 59, 59 – 69 i > 69 godina) jer su te tri dobne skupine usklađene prema spolu. Od kliničkih manifestacija, hematološke promjene uključujući trombocitopeniju statistički su se značajno razlikovale među dobnim skupinama (tablica 3).

Iz priložene tablice vidljivo je da je vjerojatnost pojavnosti hematoloških promjena u skupini bolesnika dobi od 59 – 69 godina za 20% niža u odnosu na skupinu bolesnika <59 godina (P = 0,206), dok je vjerojatnost pojavnosti hematoloških promjena u skupini bolesnika > 69 godina za 40% niža u odnosu na skupinu bolesnika < 59 godina (P = 0,02). Nastavno na analizu zastupljenosti kliničkih manifestacija, vjerojatnost pojavnosti trombocitopenije u skupini bolesnika < 59 godina viša je 14,6 puta nego u skupini bolesnika dobi od 59 – 69 godina (P = 0,07), dok je vjerojatnost pojavnosti trombocitopenije u skupini bolesnika > 69 godina za 4,9 puta veća nego u bolesnika dobi od 59 – 69 godina (P = 0,31).

Table 4 Odds ratio (OR) with 95% confidence interval for comorbidities significantly associated with age groups.
Tablica 4. Omjer izgleda (OR) uz 95-postotni interval pouzdanosti za komorbiditete koji su značajno povezani s dobnim skupinama

	Age groups / Dobne skupine				
	Reference level / Referentni nivo group / skupina <59	OR for group / OR za skupinu 59–69	P	OR for group / OR za skupinu >69	P
Cardiovascular diseases / Kardiovaskuarne bolesti		1.6 (1.04–2.5)	**0.03**[d]	2.9 (1.9–4.3)	**<0.0001**[d]
Hypertension / Hipertenzija		2.5 (1.8–3.4)	**<0.0001**[d]	4.3 (3.1–6.1)	**<0.0001**[d]
Degenerative diseases of the spine / Degenerativne bolesti kralježnice		1.5 (1.1–2.01)	**0.004**[d]	1.9 (1.4–2.5)	**<0.0001**[d]
Osteoporosis / Osteoporoza		2.1 (1.3–3.3)	**0.0012**[d]	2.5 (1.6–3.9)	**<0.0001**[d]
DM		2.9 (0.0–8.2)	0.051[d]	3.8 (1.3–10.5)	**0.011**[d]
RA		1.6 (1.1–2.3)	**0.015**[d]	1.7 (1.2–2.5)	**0.002**[d]
SSc		1.7 (0.7–3.9)	0.219[d]	2.4 (1.1–5.1)	**0.027**[d]
Secondary SS / Sekundarni SS		1.7 (1.2–2.4)	**0.003**[d]	1.9 (1.3–2.6)	**0.0004**[d]
Dyslipidemia / Dislipidemija		1.9 (1.2–2.9)	**0.008**[d]	2.3 (1.5–3.6)	**0.0002**[d]
APS		0.6 (0.3–1.24)	0.178[d]	0.35 (0.12–1)	0.0508[d]

Legend / Legenda: DM= diabetes mellitus / šećerna bolest; RA= rheumatoid arthritis / reumatoidni artritis; SSc = systemic sclerosis / sistemska skleroza ; SS= Sjögren's syndrome / Sjögrenov sindrom ; APS= antiphospholipid syndrome / antifosfolipidni sindrom. [d] logistic regression / logistička regresija

lower compared to the group of patients <59 years old (P=0.02). Following the analysis of the prevalence of clinical manifestations, the chance of occurrence of thrombocytopenia in the group of patients <59 years is 14.6 times higher than in the group of patients 59–69 years old (P= 0.07), while the chance of occurrence of thrombocytopenia in the group of > 69 years old by 4.9 times higher than in patients 59–69 years old (P=0.31).

Although there was no statistically significant correlation in the prevalence of kidney diseases with gender (Table 1) and among the observed age groups, it is certainly important to point out that in the study we had a total of 41 (12.9%) patients with one of the diagnosed kidney diseases, of which one (5.9%) was a man, and 40 (13.3%) were women. Out of the 41 cases of kidney disease, there was one biopsy-confirmed tubulointerstitial nephritis (TIN) with renal tubular acidosis type I and one TIN with mesangio proliferative glomerulonephritis.

All significantly associated comorbidities with SS, shown in Table 4, were associated with age groups in a positive direction, i.e. with increasing age, the proportion of patients also increased, with the exception of APS, which in our cohort was recorded in 3.8% cases, which was negatively related to age groups. For this reason, when performing the logistic regression for these comorbidities, we used the group < 59 years old as the reference level. The probability of occurrence of APS in the group of patients aged 59–69 years old is 40% lower compared to the group of patients <59 years old (P=0.178), while the probability of APS in the group of patients >69 years old is 65% lower compared to the group patients <59 years old (P=0.0508).

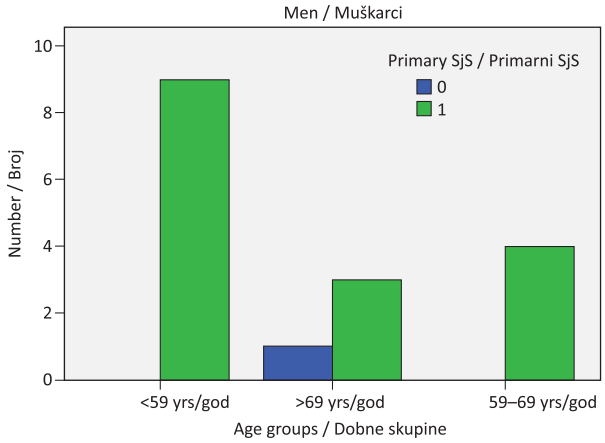
Iako nije bilo statistički značajne povezanosti u prevalenciji bubrežnih bolesti sa spolom (tablica 1) i među promatranim dobnim skupinama, svakako je važno istaknuti da smo u istraživanju ukupno imali 41 (12,9%) pacijenta s jednom od dijagnosticiranih bubrežnih bolesti, od čega je jedan (5,9%) bio muškarac, a 40 (13,3%) žena. Od 41 slučaja bubrežne bolesti, bio je jedan biopsijom potvrđen tubulointersticijski nefritis (TIN) s renalnom tubularnom acidozom tipa I i jedan TIN s mezangioproliferativnim glomerulonefritisiom.

Svi komorbiditeti značajno povezani sa SS-om, prikazani u tablici 4, bili su povezani s dobnim skupinama u pozitivnom smjeru, tj. s porastom dobi rastao je i udio bolesnika, s iznimkom APS-a koji je u našoj kohorti zabilježen u 3,8% slučajeva, a koji je s dobnim skupinama bio povezan u negativnom smjeru. Zbog toga smo kod izvođenja logističke regresije za ove komorbiditete kao

Table 5 Results of multivariate logistic regression between Sjögren's syndrome, age and gender.
Tablica 5. Rezultati multivarijantne logističke regresije između primarnog Sjögrenova sindroma, dobi i spola

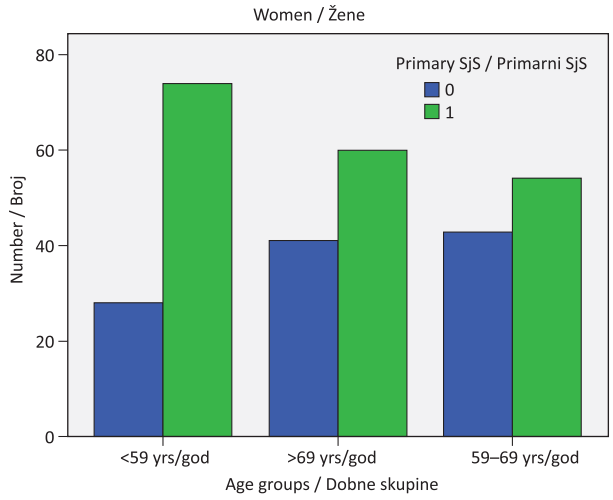
Dependent variable / Zavisna varijabla	Independent variable / Nezavisne varijable	OR (95% CI)	P**
Primary SS/ Primarni SS	Gender/ Spol (women / žene*)	8.7 (1.1–66.9)	**0.038**
	Age groups / Dobne skupine (59–69 years of age / godina*)	2.1 (1.2–3.8)***	**0.013**

*Legend / Legenda: SS = Sjögren's syndrome / Sjögrenov sindrom. * reference level / referentni nivo, ** logistic regression / logistička regresija, *** for the group <59 years / za skupinu < 59 godina*



Age /Dob < 59 g.: *N pSS=9;*
Age / Dob > 69 g.: *N pSS=3;*
Age / Dob 59 – 69 g.: *N pSS = 4*
0 = *absence of pSS in one male of the age group > 69 years / odsustvo pSS kod jednog muškarca iz dobne skupine > 69 godina (diagnosis / dijagnoza: sSS)*
Legend / Legenda: N = number /broj ; pSS = primary Sjögren's syndrome / primarni Sjögrenov sindrom ; sSS = secondary Sjögren's syndrome / sekundarni Sjögrenov sindrom

FIGURE 3 Distribution of primary Sjögren's syndrome (pSS) according to the age groups among males
SLIKA 3. Raspodjela bolesnika s primarnim Sjögrenovim sindromom (pSS) u muškaraca prema dobnim skupinama



Age / Dob < 59 yrs. of age /god.: *N pSS=74;*
Age / Dob > 69 yrs. of age / god.: *N pSS= 60;*
Age / Dob 59–69 yrs. of age /god.: *N pSS= 54*
0 = *absence of pSS in a certain number of women in all age groups / izostanak pSS-a kod određenog broja žena u svim dobnim skupinama (diagnosis /dijagnoza: sSS and / i syndrome overlap)*
Legend/Legenda: pSS = primary Sjögren's syndrome / primarni Sjögrenov sindrom ; sSS = secondary Sjögren's syndrome / sekundarni Sjögrenov sindrom

FIGURE 4 Distribution of primary Sjögren's syndrome (pSS) according to age groups among females
SLIKA 4. Raspodjela bolesnika s primarnim Sjögrenovim sindromom u žena prema dobnim skupinama

Using multivariate logistic regression in which we took each of the observed clinical manifestations and comorbidities as dependent variables, and gender and age groups as independent variables, we confirmed the association of pSS with gender and age groups (Table 5, Figures 3 and 4).

From the presented results, it can be concluded that the probability of primary SS in the group of patients <59 years old is 2.1 times higher compared to the group of patients 59–69 years old (P=0.013). The chance of occurrence of primary SS in men is 8.7 times higher than in women (P=0.038). From the results of the multivariate logistic regression (Figures 3 and 4), it can be seen that in men, once they develop SS, it is usually pSS without other associated autoimmune diseases, in contrast to women who often already have a known diagnosis of RA or SLE which is often followed by sSS. In our study, the number of diagnosed sSS was 79, of which only one was male and 78 were female.

DISCUSSION

The main results of our research indicate the existence of obvious differences in clinical manifestations and comorbidities between men and women suffering from SS. With statistical significance, we proved that gender and lung diseases are related in our sample of subjects. The more frequent incidence of lung disease in men with SS was also confirmed by a study conducted by Swedish authors (12). Male gender is widely rec-

referentni nivo uzimali skupinu < 59 godina. Izgled za pojavnost APS-a u skupini bolesnika dobi od 59 – 69 godina 40% je manji u odnosu na skupinu bolesnika < 59 godina (P = 0,178), dok je vjerojatnost APS-a u skupini bolesnika > 69 godina 65% manja u odnosu na skupinu bolesnika < 59 godina (P = 0,0508).

Multivarijantnom logističkom regresijom u kojoj smo kao zavisnu varijablu uzeli svaku od promatranih kliničkih manifestacija i komorbiditeta, a kao nezavisne varijable spol i dobne skupine, potvrdili smo povezanost pSS-a sa spolom i s dobnim skupinama (tablica 5, slike 3 i 4).

Iz prikazanih rezultata može se zaključiti da je vjerojatnost primarnog SS-a u skupini bolesnika < 59 godina 2,1 puta viša u odnosu na skupinu bolesnika dobi od 59 – 69 godina (P = 0,013). Vjerojatnost pojavnosti primarnog SS-a u muškaraca viša je 8,7 puta u odnosu na žene (P = 0,038). Iz rezultata multivarijantne logističke regresije (slike 3 i 4) može se vidjeti da se u muškaraca, jednom kad razviju SS, obično radi o pSS-u bez drugih pridruženih autoimunih bolesti, za razliku od žena koje često već od ranije imaju poznatu dijagnozu RA ili SLE-a, nakon kojih nerijetko uslijedi i sSS. U našem je istraživanju broj dijagnosticiranih sSS-a bio 79, od čega je bio samo jedan muškarac, a 78 žena.

RASPRAVA

Glavni rezultati našeg istraživanja ukazuju na postojanje značajnih razlika u pojavnosti pojedinih klinič-

ognized as a risk factor for the development of interstitial lung disease. The reasons for such male dominance are poorly understood, however, they could be the result of higher seropositivity, exposure to environmental pollutants and more frequent smoking. Idiopathic pulmonary fibrosis is the most common form of interstitial lung disease detected in pSS and is more preventable in men (13, 14).

In the study, we also proved a significant association of lymphoma with gender. A study of almost 1,000 patients with pSS reported a higher incidence of lymphoma in men, while a study by Vasaitis et al. showed that men compared to women had a shorter average time from pSS diagnosis to lymphoma diagnosis (1 vs. 8 years) and more often had lymphoma localized in the salivary glands (56% vs. 29%) (12, 15).

Horvath et al. found that autoimmune thyroiditis is highly prevalent in women and, according to our study, no cases were found in men, in contrast to 7% occurrence in women (16). Such results are explained by the fact that systemic autoimmune diseases characteristically appear more often in women, which emphasizes the importance of female sex hormones in the pathogenesis of these diseases. Estrogen metabolites, especially their hydroxylated forms, increase the rate of B-cell differentiation leading to increased production of autoantibodies and activation of T-cells with consequent secretion of pro-inflammatory cytokines.

The study by Strikić Đula et al also testifies to the higher prevalence of thyroid disease in women in general. in which it was noted that women have a 47% lower chance of euthyroidism than men. In addition, women had 1.57 times the odds of antibody-positive euthyroidism, 2.1 times the odds of subclinical hyperthyroidism, 2.37 times the odds of clinical hypothyroidism, and 1.58 times the odds of subclinical hypothyroidism (17).

We showed a significant association between vasculitis and male gender, but the small number of men in the sample should be taken into account. A higher frequency of vasculitis in men was also recorded in a study in which men presented more often with La/SSB, Ro/SSA and ANA positivity, which resulted in higher immune activity (18). This increased response of the immune system could have contributed to the more frequent occurrence of vasculitis. This is supported by the observations of Scofield's study, in which a connection was observed between the occurrence of vasculitis and certain immunological changes, such as hypocomplementemia, cryoglobulinemia, and the presence of anti-Ro and La antibodies (19).

The most common observed cutaneous manifestation was RP, which was present in a total of 22 (7%) patients and with a higher frequency in women. Here we also included patients who were diagnosed with CREST syndrome. In other studies, this prevalence

kih manifestacija i komorbiditeta između muškaraca i žena oboljelih od SS-a. Sa statističkom značajnošću dokazali smo da su u našem uzorku ispitanika spol i plućne bolesti povezani. Češću pojavnost bolesti pluća u muškaraca sa SS-om potvrdila je i studija švedskih autora (12). Muški spol široko je prepoznat kao čimbenik rizika za razvoj intersticijske bolesti pluća. Razlozi za takvu dominaciju muškog spola slabo su shvaćeni, međutim, mogli bi biti posljedica veće seropozitivnosti, izloženosti okolišnim zagađivačima i češćeg pušenja. Idiopatska plućna fibroza najčešći je oblik intersticijske bolesti pluća otkriven u pSS-u i ima veću prevalenciju u muškaraca (13, 14).

U istraživanju smo također dokazali značajnu povezanost limfoma sa spolom. Studija na gotovo 1000 bolesnika s pSS-om izvijestila je o većoj učestalosti pojave limfoma u muškaraca, dok je istraživanje Vasaitisa i suradnika pokazalo da su muškarci u usporedbi sa ženama imali kraće prosječno vrijeme od dijagnoze pSS-a do dijagnoze limfoma (jedna godina nasuprot osam godina) i češće su imali limfom lokaliziran u slinovnicama (56% naspram 29%) (12, 15).

Horvath i suradnici utvrdili su da je autoimuni tiroiditis visoko prevalentan u žena te, sukladno našem istraživanju, nije pronađen nijedan slučaj u muškaraca, za razliku od 7% pojave u žena (16). Ovakvi rezultati objašnjavaju se činjenicom da se sistemske autoimune bolesti karakteristično češće pojavljuju u žena, čime se naglašava važnost ženskih spolnih hormona u patogenezi ovih bolesti. Metaboliti estrogena, posebno hidroksilirani oblici, povećavaju brzinu diferencijacije B-stanica, što dovodi do povećanog stvaranja autoprotutijela i aktivacije T-stanica s posljedičnim lučenjem proupalnih citokina.

O većoj prevalenciji bolesti štitnjače u žena općenito, također, svjedoči i studija Strikić Đula i suradnika u kojoj je zabilježeno da žene imaju 47% niže izglede za eutireozu od muškaraca. Uz to, žene su imale 1,57 puta veće izglede za eutireozu s pozitivnim antitijelima, 2,1 puta veće izglede za subkliničku hipertireozu, 2,37 puta veće izglede za kliničku hipotireozu i 1,58 puta veće izglede za subkliničku hipotireozu (17).

Prikazali smo značajnu povezanost vaskulitisa i muškog spola, no treba uzeti u obzir premali broj muškaraca u uzorku. Veća učestalost vaskulitisa u muškaraca zabilježena je i u studiji u kojoj su se muškarci češće prezentirali s La/SSB, Ro/SSA i ANA pozitivnošću, što je rezultiralo većom imunološkom aktivnošću (18). Upravo taj pojačani odgovor imunološkog sustava mogao je pogodovati češćoj pojavnosti vaskulitisa. Tomu u prilog idu opažanja Scofieldove studije u kojoj je uočena povezanost između nastanka vaskulitisa i određenih imunoloških promjena kao što su hipokomplementemija, krioglobulinemija te prisutnost anti-Ro i La-protutijela (19).

Najčešća uočena kožna promjena bio je RF, koji je bio prisutan u ukupno 22 (7%) pacijenta i s većom

was up to 33% (20, 21). The different geographical areas where the research was conducted could explain this difference in results. It is known that a colder climate can exacerbate the development of RP along with other risk factors, such as emotional stress. A higher frequency of RP in women was also proven in the studies of Brandt et al. and Horvath et al. (2, 16). Sex hormones are considered to play an important role in the pathogenesis of RP, whereby the incidence of RP-like vasospastic reactions increases with oestrogen administration and in the preovulatory period (22).

In the study by Narváez et al. the prevalence of kidney diseases in pSS was 9%, where 38 cases out of 39 were in women, according to the results of our research (23). It should be emphasized that our study included patients with pSS and with sSS that developed as part of some other autoimmune disease. We emphasize this especially in the analysis of kidney diseases, where certainly a good part of the total kidney disorders can be attributed to the primary disease, for example SLE, in which sSS developed, and kidney involvement is a consequence of lupus nephritis. To determine the true prevalence of kidney involvement in pSS, while excluding the influence of associated diseases, such as SLE, it is necessary to perform kidney biopsy more often.

In the Sjögrenser study, which included 437 patients with pSS, the prevalence of gastrointestinal complaints was 16.2% (24). Gastritis was the most recorded (29.5%), which was also the case in our study, but with an even higher percentage (48.6 %). Atrophic gastritis appears to be age-related as its incidence increases with age, which may explain the different research results. Under gastrointestinal diseases, we also classified PBC, of which there were four in total, and all PBCs were diagnosed in women.

Numerous sources report CNS involvement in pSS with a frequency of 2–5% (25, 26). Similar results were shown by our research, in which the prevalence of CNS involvement was 5.7%, of which all forms of CNS involvement were also diagnosed in women. The same observations were made by the study of Ramírez Sepúlvedo et al. (18). Peripheral neuropathies are a more common form of neurological manifestations in pSS and occur in 5–15% of cases (27). In a cohort study in which there were 400 patients with pSS, a frequency of peripheral neuropathies of 7% was recorded, which is almost equal to the result of our research, where this incidence was 7.6% (28).

In the analysis of haematological manifestations in relation to age groups, we found a statistically significant association between thrombocytopenia and age. The more frequent incidence of thrombocytopenia at a younger age was also proven by the study by Maria Ramos-Casals et al. which was conducted on a Spanish cohort (29). In her research, Ro/La positive patients

učestalošću u žena. Ovdje smo ubrojili i pacijente kojima je evidentiran CREST sindrom. U drugim istraživanjima ta je prevalencija iznosila do 33% (20, 21). Različita geografska područja u kojima su se provodila istraživanja mogla bi objasniti ovakvu razliku u rezultatima. Poznato je da hladnija klima može pogodovati razvoju RF-a zajedno s drugim čimbenicima rizika, kao što je npr. emocionalni stres. Veća učestalost RF-a u žena dokazana je i u studijama Brandta i suradnika te Horvatha i suradnika (2, 16). Smatra se da spolni hormoni imaju važnu ulogu u patogenezi RF-a, pri čemu se incidencija vazospastičnih reakcija sličnih RF-u povećava primjenom estrogena i u preovulacijskom razdoblju (22).

U studiji Narváeza i suradnika prevalencija bubrežnih bolesti u pSS-u iznosila je 9%, pri čemu je 38 od 39 slučajeva bilo u žena, sukladno rezultatima našeg istraživanja (23). Potrebno je naglasiti da su u našem istraživanju bili uključeni pacijenti s pSS-om i sSS-om koji se razvio u sklopu neke druge autoimune bolesti. To posebno ističemo kod analize bubrežnih bolesti, gdje se zasigurno dobar dio ukupnih bubrežnih poremećaja može pripisati primarnoj bolesti, primjerice SLE-u u sklopu kojeg se razvio sSS, a zahvaćenost bubrega posljedica je lupusa nefritisa. Kako bi se utvrdila prava prevalencija zahvaćenosti bubrega u pSS-u, a pritom isključio utjecaj pridruženih bolesti, poput SLE, nužno je češće provoditi biopsiju bubrega.

U studiji Sjögren SER, koja je obuhvatila 437 pacijenata s pSS-om, prevalencija gastrointestinalnih tegoba iznosila je 16,2% (24). Najviše je bilo zabilježenih gastritisa (29,5%), što je također bio slučaj i u našem istraživanju, ali s još većim postotkom (48,6%). Čini se da je atrofični gastritis povezan s dobi jer se njegova učestalost povećava s godinama, što može objasniti različite rezultate istraživanja. Pod gastrointestinalne bolesti svrstali smo i PBC kojih je ukupno bilo četiri, pri čemu su svi PBC dijagnosticirani u žena.

Brojni izvori navode zahvaćenost CNS-a u pSS-u s učestalošću od 2 – 5% (25, 26). Slične je rezultate pokazalo i naše istraživanje u kojem je prevalencija zahvaćenosti CNS-a iznosila 5,7% od čega su svi oblici zahvaćenosti CNS-a također dijagnosticirani u žena. Jednaka opažanja imala je i studija Ramíreza Sepúlveda i suradnika (18). Periferne neuropatije češći su oblik neuroloških manifestacija u pSS-u i javljaju se u 5 – 15% slučajeva (27). U kohortnom istraživanju u kojem je bilo 400 pacijenata s pSS-om zabilježena je učestalost perifernih neuropatija od 7% , što je gotovo jednako rezultatu našeg istraživanja, gdje je ta pojavnost iznosila 7,6% (28).

U analizi hematoloških manifestacija u odnosu na dobne skupine statistički značajnu povezanost dobili smo između trombocitopenije i dobi. Češću pojavnost trombocitopenije u mlađoj dobi dokazalo je i istraživanje Marie Ramos-Casals i suradnika na španjolskoj

were recognized at a younger age with a higher frequency of positive diagnostic tests (parotid scintigraphy, salivary gland biopsy), enlarged parotid glands, more frequent extraglandular manifestations (Raynaud's phenomenon – RP, arthralgias, arthritis, vasculitis, kidney involvement and peripheral neuropathy) and cytopenia (leukopenia and thrombocytopenia) and positive immune markers (ANA, RF and cryoglobulins) in univariate analysis (29).

Out of the comorbidities that we observed in the research, namely cardiovascular diseases, hypertension, degenerative diseases of the spine, diabetes, dyslipidemia and associated autoimmune diseases (RA, SLE, SSc), all of them occurred significantly more often in older patients. In addition to age, which is one of the key risk factors for the development of the above-mentioned conditions, the characteristics of SS, including inflammation and specific treatment, which contribute to the development of concomitant diseases, also stand out. In a study by Pérez-De-Lis et al. it was found that elevated levels of CRP in patients with pSS may contribute to a higher frequency of atherosclerotic cardiovascular damage, and glucocorticoid therapy was clearly associated with a higher prevalence of cardiovascular risk factors, especially diabetes, hypertension and hypertriglyceridemia (30).

In our study, APS showed a negative correlation with age groups, i.e., with increasing age, the proportion of patients decreased. In a Brazilian study, the frequency of APS in patients with pSS was 3%, which is in accordance with our results (3.8%). Prolonged lupus anticoagulant (LAC) in pSS is a predictor of stroke and deep vein thrombosis, especially in young patients (31). This is consistent with our observations where APS occurs more often in younger age groups with statistical significance.

CONCLUSION

The results of our research indicate the existence of obvious differences in clinical manifestations and comorbidities between women and men suffering from SS. Lung diseases, lymphoma and vasculitis occurred many times more often in men than in women, in contrast to hypothyroidism, which is significantly associated with the female gender. All cases of PBC and CNS involvement were recorded in women, while pSS was significantly associated with male gender and younger age. Thrombocytopenia and APS also had a higher incidence in younger age groups. The probability of developing SS is lower in men than in women, but men who develop SS are more likely to have a more severe form of the disease.

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kohorti (29). U njenom su istraživanju Ro/La-pozitivni pacijenti bili prepoznati u mlađoj životnoj dobi s većom učestalošću pozitivnih dijagnostičkih testova (parotidna scintigrafija, biopsija žlijezda slinovnica), povećanim parotidama, češćim izvanžljezdanim manifestacijama (Raynaudov fenomen – RF, artralgije, artritis, vaskulitis, zahvaćenost bubrega i periferna neuropatija) i citopenijom (leukopenija i trombocitopenija) te pozitivnim imunološkim biljezima (ANA, RF i krioglobulini) u univarijantnoj analizi (29).

Od komorbiditeta koje smo promatrali u istraživanju, a to su kardiovaskularne bolesti, hipertenzija, degenerativne bolesti kralježnice, šećerna bolest (ŠB), dislipidemija te pridružene autoimune bolesti (RA, SLE, SSc), svi su se značajno češće javljali u bolesnika starije životne dobi. Osim dobi, koja je jedan od ključnih čimbenika rizika za razvoj navedenih stanja, ističu se i osobine SS-a uključujući upalu i specifično liječenje koji doprinose nastanku popratnih bolesti. U istraživanju Pérez-De-Lis i suradnika utvrđeno je da povišene razine CRP-a u bolesnika s pSS-om mogu doprinijeti većoj učestalosti aterosklerotskih kardiovaskularnih oštećenja, a terapija glukokortikoidima bila je očito povezana s većom prevalencijom kardiovaskularnih čimbenika rizika, posebno šećerne bolesti, hipertenzije i hipertrigliceridemije (30).

APS je u našem istraživanju pokazao negativnu korelaciju s dobnim skupinama, tj. s porastom dobi smanjivao se udio bolesnika. U brazilskom istraživanju učestalost APS-a u pacijenata s pSS-om iznosila je 3%, što je sukladno našim rezultatima (3,8%). Produljen lupus antikoagulans (LAC) u pSS-u prediktor je moždanog udara i duboke venske tromboze, posebno u mladih bolesnika (31). To je u skladu s našim opažanjima u kojima se APS sa statističkom značajnošću češće javlja u mlađim dobnim skupinama.

ZAKLJUČAK

Rezultati našeg istraživanja upućuju na postojanje očitih razlika u kliničkim manifestacijama i komorbiditetima između žena i muškaraca oboljelih od SS-a. Plućne bolesti, limfom i vaskulitis višestruko su se češće javljali u muškaraca nego u žena, za razliku od hipotireoze koja je značajno povezana sa ženskim spolom. Svi slučajevi PBC-a i zahvaćenosti CNS-a zabilježeni su u žena, dok je pSS značajno povezan s muškim spolom i mlađom životnom dobi. Trombocitopenija i APS također su imali češću pojavnost u mlađim dobnim skupinama. Vjerojatnost obolijevanja od SS-a manja je u muškaraca nego u žena, ali muškarci koji obole od SS-a imaju veće izglede za teži oblik bolesti.

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

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ORIGINAL SCIENTIFIC PAPER ORIGINALNI ZNANSTVENI RAD

ASSOCIATION BETWEEN CUTANEOUS MANIFESTATIONS AND CLINICAL FEATURES OF IgA VASCULITIS

POVEZANOST KOŽNIH MANIFESTACIJA I KLINIČKIH ZNAČAJKI IgA VASKULITISA

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Abstract

Introduction: IgA vasculitis (IgAV) is the most common systemic vasculitis in childhood. Purpuric rash is a mandatory criterion for diagnosing IgAV, it is mostly localized on the lower extremities and gluteal region, although it can also appear atypically affecting the face, trunk and upper extremities. In the most severe cases, ulcerations, necrosis and bullae can be present. *Objectives:* To evaluate the characteristics of cutaneous manifestations in patients with IgAV and to examine its association with clinical features. *Subjects and methods:* Retrospective analysis of data from patients with IgAV diagnosed and treated at the Referral Centre for Paediatric and Adolescent Rheumatology of the Ministry of Health of the Republic of Croatia, in the period from January 2009 to December 2021. *Results:* IgAV was diagnosed in 234 patients, 124 boys and 110 girls with the median (range) age at the time of diagnosis of 6.5 (4.5–8.2) years. All patients had a purpuric rash, and in 127 of them (54.3%) IgAV began with a rash. Cutaneous manifestations were most often presented in the form of palpable purpura and/or petechiae (87.2%) and in all patients were localized on the lower extremities. In 103 patients (44%) purpuric rash spread further to the upper extremities, trunk and/or face. At least one skin relapse occurred in 47 patients (20.1%). The most severe cutaneous manifestations which included ulcerations and necrosis developed in 11 patients (4.7%). Patients with cutaneous manifestations spread above the waist had a more statistically significant gastrointestinal involvement compared to patients with cutaneous manifestations affecting the lower extremities and gluteal region (50.5% vs. 36.6%, p=0.033), higher incidence of IgA vasculitis nephritis (IgAVN) (31.1% vs. 19.8%, p=0.048) and were more frequently treated with systemic glucocorticoids (68% vs. 52.7%, p=0.018) and angiotensin-converting enzyme inhibitors (14.5% vs. 5.3%, p=0.016). Almost all patients with ulcerations and necrosis required treatment with systemic glucocorticoids compared to the rest (90.9% vs. 57.8%,p=0.031). *Conclusion:* We observed that patients with purpuric rash spread above the waist have more frequently affected gastrointestinal system and a higher incidence of IgAVN. The prevalence of ulcerations and necrosis in IgAV is less common than the standard purpuric rash and this group of patients required systemic glucocorticoid therapy.

Key words: IgA vasculitis, cutaneous manifestations, children

Sažetak

Uvod: IgA vaskulitis (IgAV) najčešći je sistemski vaskulitis dječje dobi. Purpurični osip ključan je kriterij za dijagnozu IgAV-a, a najčešće je rasprostranjen po donjim udovima i gluteusima, iako može biti proširen i na atipičnim mjestima poput lica, trupa i gornjih udova. U najtežim slučajevima mogu biti prisutne ulceracije, nekroze i bule. *Cilj:* Utvrditi osobitosti kožnih promjena u bolesnika s IgAV-om te ispitati njihovu povezanost s kliničkim značajkama. *Ispitanici i metode:* Retrospektivna analiza podataka bolesnika s IgAV-om dijagnosticiranih i liječenih u Referentnom centru za pedijatrijsku i adolescentnu reumatologiju Ministarstva zdravstva RH, u razdoblju od siječnja 2009. do prosinca 2021. godine. *Rezultati:* IgAV je dijagnosticiran u 234 bolesnika, 124 dječaka i 110 djevojčica s medijanom (rasponom) dobi u trenutku dijagnoze 6,5 (4,5 – 8,2) godina. Svi su bolesnici imali kožni osip, a u njih 127 (54,3%) IgAV je i započeo osipom. Kožne promjene najčešće su bile zastupljene u obliku palpabilne purpure i/ili petehija (87,2%) i u svih bolesnika bile su lokalizirane po donjim udovima. U 103 bolesnika (44%) kožni osip se dalje proširio na ruke, trup i/ili lice. U 47 bolesnika (20,1%) došlo je do barem jednog recidiva kožnih promjena. Najteže kožne promjene u vidu ulceracija i nekroza razvilo je 11 bolesnika (4,7%). Bolesnici s kožnim promjenama proširenim iznad donjih udova imali su statistički značajno češće zahvaćen gastrointestinalni sustav u odnosu na bolesnike s kožnim osipom ograničenim na donje udove i glutealno (50,5% u odnosu na 36,6%, p=0,033), veću pojavnost nefritisa (IgAVN) (31,1% u odnosu na 19,8%, p=0,048) te su češće liječeni sistemskim glukokortikoidima (68% u odnosu na 52,7%, p=0,018) i inhibitorima angiotenzin konvertaze (14,5% u odnosu na 5,3%, p=0,016). Gotovi svi bolesnici s ulceracijama i nekrozama zahtjevali su liječenje sistemskim glukokortikoidima u odnosu na sve preostale bolesnike (90,9% u odnosu na 57,8%, p=0,031). *Zaključak:* Uočili smo da bolesnici s kožnim osipom proširenim iznad donjih udova imaju češće zahvaćen gastrointestinalni sustav i češću pojavu IgAVN-a. Učestalost ulceracija i nekroza u IgAV-u rjeđa je od klasične slike kožnog osipa i takvi bolesnici zahtijevali su liječenje sistemskim glukokortikoidima.

Ključne riječi: IgA vaskulitis, kožne manifestacije, djeca

INTRODUCTION

IgA vasculitis (IgAV), formerly known as Henoch-Schönlein purpura (HSP), is the most common form of childhood vasculitis with an estimated worldwide annual incidence of 3–55.9 cases per 100,000 children (1–3). In the Republic of Croatia, the average annual incidence of IgAV is 6.79 per 100,000 children (4). Palpable purpura and/or petechiae without thrombocytopenia and other underlying coagulation disorders are a recognizable feature of the disease and at the same time a necessary criterion in making a diagnosis (5). The purpuric rash is most often spread on the extensor sides of the lower extremities and the gluteal region, although it can also be spread to the upper extremities, abdomen, face and ears. In the beginning, the skin lesions appear as clusters of erythema, urticaria and maculopapular rash, and then they turn into petechiae, ecchymoses and purple induration up to 1 cm in diameter, which are distributed on the previously changed skin. The skin lesions then change colour from red and purple to brownish and fade after ten days, leaving some patients with areas of gradual hyperpigmentation (6). Less than 5% of children may develop necrosis, ulceration and bullae on the skin, while the appearance of such skin forms has been described in as many as 60% of adult patients (7). In such cases, as well as with skin lesions that are diffusely distributed, it is recommended to perform a skin biopsy to rule out other forms of vasculitis, especially ANCA-associated vasculitis (8). A skin biopsy in patients with IgAV shows leukocytoclastic vasculitis characterized by fibrinoid ne-

UVOD

IgA vaskulitis (IgAV), otprije poznat kao Henoch-Schönleinova purpura (HSP), najčešći je vaskulitis dječje dobi s procijenjenom svjetskom godišnjom incidencijom između 3 i 55,9 na 100.000 djece (1-3). U Republici Hrvatskoj prosječna godišnja incidencija IgAV-a je 6,79 na 100.000 djece (4). Palpabilna purpura i/ili petehije bez trombocitopenije i drugoga podležećeg koagulacijskog poremećaja prepoznatljivo su obilježje bolesti te ujedno i neophodan kriterij u postavljanju dijagnoze (5). Purpurični osip najčešće je rasprostranjen po ekstenzornim stranama donjih udova i gluteusima, premda može biti proširen i na gornje udove, trbuh, lice i uške. U početku se kožne lezije očituju kao grozdovi eritema, urtike i makulopapulozni osip, a potom prelaze u petehije, ekhimoze i ljubičaste induracije promjera do 1 cm koje su raspoređene između prethodno promijenjene kože. Kožne lezije potom mijenjaju boju od crvene i ljubičaste do smeđkaste boje, da bi nakon desetak dana izblijedjele ostavljajući kod pojedinih bolesnika područja postupalne hiperpigmentacije (6). U manje od 5% djece može doći i do razvitka nekroza, ulceracija i bula na koži, dok je pojava takvih kožnih oblika opisana u čak 60% odraslih bolesnika (7). U takvim slučajevima, kao i kod kožnih lezija koje su difuzno rasprostranjene, preporučeno je napraviti i biopsiju kože kako bi se isključili drugi vaskulitisi, posebno vaskulitisi povezani s ANCA-om (8). Biopsija kože u bolesnika s IgAV-om pokazuje leukocitoklastični vaskulitis koji obilježava fibrinoidna nekroza malih krvnih žila papilarnog der-

crosis of the small blood vessels of the papillary dermis (capillaries, venules and arterioles), perivascular oedema and neutrophil infiltration with neutrophil nucleus fragmentation, while direct immunofluorescence of the skin shows predominant IgA deposits and complement component C3 in the dermis. (5). And while the purpuric rash usually passes spontaneously, that is, with the application of short-term symptomatic treatment, the most severe cutaneous forms require special therapy. In addition to that, some previous studies have already shown that the prevalence of purpuric rash as well as recurrences of purpura can significantly contribute to the increased risk for the occurrence of more severe gastrointestinal forms of the disease as well as the development of IgA vasculitis nephritis (IgAVN), the most significant chronic complication of the disease (9–12). The aim of this paper is to show the cutaneous manifestations in IgAV and to determine the association of their characteristics with the clinical and laboratory features of the disease and the selection of therapy.

SUBJECTS AND METHODS

In the period from January 2009 to December 2021, a retrospective study was conducted at the Division of Clinical Immunology, Allergology and Rheumatology at the Department of Paediatrics, University Hospital Centre Zagreb, the Referral Centre for Paediatric and Adolescent Rheumatology of the Ministry of Health of the Republic of Croatia, which included patients younger than 18 years of age who are diagnosed with IgAV according to the EULAR/PRINTO/PRES criteria (5). The research was approved by the Ethics Committee of the University Hospital Centre Zagreb and the School of Medicine, University of Zagreb. Demographic, clinical and laboratory data on patients were collected from a database based on medical records. Demographic data included the patient's gender and age at the time of IgAV diagnosis, while clinical data included the duration of hospitalization expressed in days, the leading initial symptom of the disease, the presence and type of prodromal infection, isolated microbiological agents, the prevalence of purpuric rash, joint involvement, gastrointestinal, renal and urogenital system, the presence of severe cutaneous changes (ulcerations, necrosis, bullae), time from the onset of the disease to the onset of nephritis (in days), systolic blood pressure values, skin biopsy, kidney biopsy, type of medication and number of relapses. Purpuric rash is categorized into one of two groups according to its prevalence: 1. purpuric rash localized on the lower extremities and the gluteal region; 2. purpuric rash spread above the lower extremities to the upper extremities, trunk and face (generalized purpura). Disease relapse was defined as the recurrence of symptoms and signs

misa (kapilare, venule i arteriole), perivaskularni edem i neutrofilna infiltracija s fragmentacijom njihovih jezgara, dok nalaz direktne imunofluorescencije kože pokazuje predominantne IgA depozite i C3 komponente komplementa u dermisu (5). I dok purpurični osip uobičajeno prolazi spontano, odnosno na primjenu kratkotrajnoga simptomatskog liječenja, najteži kožni oblici zahtijevaju posebnu terapiju. Osim toga, već su neka prethodna istraživanja pokazala da rasprostranjenost purpuričnog osipa kao i recidivi purpure mogu značajno pridonositi povećanom riziku za nastanak težih gastrointestinalnih oblika bolesti, kao i razvitku IgA vaskulitis nefritisa (IgAVN), najznačajnije kronične komplikacije bolesti (9-12). Cilj ovog rada jest prikazati kožne manifestacije u IgAV-u te utvrditi povezanost njihovih osobitosti s kliničkim i laboratorijskim značajkama bolesti te odabir terapije.

ISPITANICI I METODE

U razdoblju od siječnja 2009. do prosinca 2021. u Zavodu za kliničku imunologiju, reumatologiju i alergologiju Klinike za pedijatriju Kliničkoga bolničkog centra Zagreb, Referentnom centru za pedijatrijsku i adolescentnu reumatologiju Ministarstva zdravstva Republike Hrvatske, provedeno je retrospektivno istraživanje u koje su uključeni bolesnici mlađi od 18 godina s postavljenom dijagnozom IgAV-a sukladno EULAR/PRINTO/PRES kriterijima (5). Istraživanje je odobrilo Etičko povjerenstvo Kliničkoga bolničkog centra Zagreb i Medicinskog fakulteta Sveučilišta u Zagrebu. Demografski, klinički i laboratorijski podatci o bolesnicima prikupljeni su iz baze podataka temeljene na medicinskoj dokumentaciji. Demografski podatci uključivali su spol i dob pri dijagnozi IgAV-a, dok su klinički podatci uključivali trajanje hospitalizacije izražene u danima, vodeći početni simptom bolesti, postojanje i vrstu prodromalne infekcije, izolirane mikrobiološke uzročnike, rasprostranjenost purpuričnog osipa, zahvaćenost zglobova, gastrointestinalnog sustava, bubrega i urogenitalnog sustava, prisutnost teških kožnih promjena (ulceracije, nekroze, bule), vrijeme od početka bolesti do pojave nefritisa (u danima), vrijednosti sistoličkoga krvnog tlaka, biopsiju kože, biopsiju bubrega, vrstu lijekova i broj relapsa. Purpurični je osip prema rasprostranjenosti kategoriziran u jednu od dvije skupine: 1. purpurični osip lokaliziran na donjim udovima i glutealno; 2. purpurični osip proširen iznad donjih udova na gornje udove, trup i lice (generalizirana purpura). Relaps bolesti definiran je kao ponovna pojava simptoma i znakova karakterističnih za IgAV nakon asimptomatskog razdoblja u trajanju od najmanje jednog mjeseca. Laboratorijski nalazi uključivali su upalne pokazatelje: sedimentaciju eritrocita (SE), C-reaktivni protein (CRP) i feritin; broj eritrocita, hemoglobin, hematokrit, broj leukocita, broj trombocita; biokemijske pretrage krvi: kreatinin,

characteristic of IgAV after an asymptomatic period of at least one month. Laboratory findings included inflammatory indicators: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and ferritin; red blood cell count, haemoglobin, haematocrit, white blood cell count, platelet count; biochemical blood tests: creatinine, urea, estimated glomerular filtration rate (eGFR), total proteins, serum albumins; coagulation factor tests: prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, D-dimers; urine tests: presence of erythrocyturia (defined as >5 erythrocytes in urine sediment) and/or proteinuria (defined as ≥2+ proteins in urine sediment), albumin/creatinine ratio in urine (values >3 mg/mmol were considered pathological); 24-hour urine analysis for quantification of proteinuria (defined as >0.15 g/day of total excreted proteins); immunological tests: immunoglobulin classes (IgA, IgG, IgM, total IgE), antinuclear antibodies (ANA), complement components C3 and C4, total complement activity (CH50), antistreptolysin O titer (ASTO) and faecal occult blood test (FOBT). Microbiological tests performed on patients with a history of infection included a nasopharyngeal swab.

Statistical processing of the data was performed using the MedCalc program for the Windows operating system, and the data were presented in tables and graphics. The normality of data distribution was tested using the Shapiro–Wilk test. Continuous variables for values that do not have a normal distribution are shown as the median and interquartile range (25 to 75 percentiles), and categorical variables are shown as percentages. Differences in categorical variables between two groups of patients were examined using the $\chi 2$ test and Fisher's exact test, and in quantitative variables using the Mann-Whitney U test. All p-values lower than 0.05 were considered as statistically significant.

RESULTS

In the period from 1st January 2009 to 31st December 2021, 234 patients were diagnosed with IgAV, among whom there were 124 boys and 110 girls, in a ratio of 1.13:1 with a median age of 6.5 (4,5–8,2) years of age at the time of the diagnosis. Table 1 shows the demographic and clinical characteristics of patients with IgAV.

The most common skin efflorescences in the mentioned cohort of patients were papules in combination with purpuric changes, which were present in 122 patients (52.2%). The next most frequent occurrences were isolated petechiae, which were present in 82 patients (35%), while the rarest was a combination of purpuric and macular changes (in 15 patients, or 6.4%). Purpuric changes with hematomas were present in 4 patients (1.7%). 11 patients (4.7%) had severe cutaneureju, procijenjenu glomerularnu filtraciju (engl. *estimated glomerular filtration rate*, eGFR), ukupne proteine, serumske albumine; koagulacijske pretrage: protrombinsko vrijeme (PV), aktivirano parcijalno tromboplastinsko vrijeme (APTV), fibrinogen, D-dimere; pretrage urina: prisutnost eritrociturije (definirane kao >5 eritrocita u sedimentu urina) i/ili proteinurije (definirane kao ≥2+ proteina u sedimentu urina), omjer albumin/kreatinin u urinu (vrijednosti >3 mg/mmol smatrane su patološkim); analizu 24-satnog urina za kvantifikaciju proteinurije (definirane kao >0,15 g/dU sveukupno izlučenih proteina); imunološke pretrage: razrede imunoglobulina (IgA, IgG, IgM, ukupni IgE), antinuklearna antitijela (ANA), C_3 i C_4 komponente komplementa, razinu ukupnog komplementa (CH_{50}), antistreptolizinski O titar (ASTO) i analizu stolice na okultno krvarenje. Mikrobiološke pretrage u bolesnika s anamnezom infekcije uključivale su obrisak nosne sluznice i ždrijela.

Statistička obrada podataka izvršena je pomoću programa *MedCalc* za operativni sustav *Windows*, a podatci su prikazani tablično i grafički. Normalnost raspodjele podataka ispitivana je pomoću Shapiro-Wilkovljevog testa. Kontinuirane varijable za vrijednosti koje nemaju normalnu distribuciju prikazane su kao medijan i interkvartilni raspon (od 25 do 75 centile), a kategoričke varijable prikazane su u postotcima. Razlike u kategorijskim varijablama između dviju grupa pacijenata ispitivane su pomoću $\chi 2$ testa i Fisherovog egzaktnog testa, a u kvantitativnim pomoću Mann-Whitneyjevog U-testa. Sve p-vrijednosti manje od 0,05 smatrane su statistički značajnima.

REZULTATI

U razdoblju od 1. siječnja 2009. do zaključno 31. prosinca 2021. dijagnosticirano je 234 bolesnika s IgAV-om, među kojima je bilo 124 dječaka i 110 djevojčica, u omjeru 1,13:1 s medijanom dobi od 6,5 (4,5 – 8,2) godina u trenutku dijagnoze. U tablici 1 prikazane su demografske i kliničke karakteristike bolesnika s IgAV-om.

Najčešće kožne eflorescencije u navedenoj kohorti bolesnika bile su papule u kombinaciji s purpuričnim promjenama, koje su bile prisutne u 122 bolesnika (52,2%). Sljedeće su po učestalosti bile izolirane petehije, koje je imalo 82 bolesnika (35%), dok je najrjeđe bila zastupljena kombinacija purpuričnih i makuloznih promjena (u 15 bolesnika odnosno njih 6,4%). Purpuричne promjene uz hematome bile su prisutne u četiri bolesnika (1,7%). Teške kožne promjene, ulceracije i nekroze imalo je 11 bolesnika (4,7%). U 47 bolesnika (20,1%) kožne promjene imale su barem jedan recidiv. Kožni osip lokaliziran po nogama i glutealno imao je 131 bolesnik (56%), u 50 bolesnika je osip osim donjih udova zahvatio i ruke (21,4%), dok su 53 bolesnika imala za-

Table 1 Demographic and clinical features in IgAV patients, N=234
Tablica 1. Demografska i klinička obilježja bolesnika s IgAV-om, N = 234

Characteristic / Obilježje	IgAV patients with skin lesions only on the lower extremities (N=131) / IgAV bolesnici s kožnim lezijama samo po donjim ekstremitetima (N=131) N (% or/ili range/raspon)	IgAV patients with skin lesions spread above the lower extremities (N=103) / IgAV bolesnici s kožnim lezijama proširenim iznad donjih ekstremiteta (N=103) N (% or/ili range/raspon)	p-value / p vrijednost
Gender / Spol			
F / Ž	63 (48,1%)	47 (45,6%)	0,708[a]
M	68 (51,9%)	56 (54,4%)	
Age (in years) / Dob (godine)	6,5 (4,5-8,1)	6,5 (4,5-8,3)	0,7[a]
First symptom of the disease / Prvi simptom bolesti			
Skin rash / Kožni osip	67 (51,1%)	60 (58,3%)	0,278[a]
Arthritis/arthralgia / Artritis/artralgije	46 (35,1%)	26 (25,2%)	
GI system involvement / Probavni sustav	18 (13,8%)	17 (16,5%)	
Hospitalization (in days) / Hospitalizacija (dani)	10 (5-13)	12 (8-18)	**0,006**[a]
Infection / Infekcija	90 (68,7%)	67 (65%)	0,554[a]
Clinical features / Klinička slika			
Subcutaneous oedema / Subkutani edem	25 (19,1%)	18 (17,5%)	0,753[a]
Recurrent rash / Recidivirajući osip	25 (19,1%)	22 (21,4%)	0,666[a]
Severe cutaneous manifestations (ulcerations, necrosis) / Teške kožne promjene (ulceracije, nekroze)	6 (6,2%)	5 (4,8%)	0,922[b]
Skin biopsy / Biopsija kože	0 (0%)	1 (0,97%)	0,258[b]
Arthritis/arthralgia / Artritis/artralgije	102 (77,8%)	69 (67%)	0,063[a]
GI system involvement / Zahvaćanje GI sustava	48 (36,6%)	52 (50,5%)	**0,033**[a]
Severe GI complications (gastrointestinal bleeding, intussusception, intestinal invagination) / Teške GI komplikacije (krvarenje iz probavnog sustava, intususcepcija, invaginacija crijeva)	9 (6,9%)	11 (10,7%)	0,301[a]
IgAVN	26 (19,8%)	32 (31,1%)	**0,048**[a]
Time from diagnosis to onset of IgAVN: median (IQR) / Vrijeme od dijagnoze do pojave IgAVN-a: medijan (IR)	2,5 (0-5,25)	7,5 (3,25-24)	0,007[c]
Kidney biopsy / Biopsija bubrega	9 (6,8%)	16 (15,5%)	**0,033**[a]
Involvement of the scrotum and urogenital system (N= number of boys) / Zahvaćenost skrotuma i urogenitalnog sustava (N= broj dječaka)	9 (13,2%)	5 (9%)	0,573[b]
Therapy / Terapija			
NSAID	79 (60,3%)	56 (54,4%)	0,361[a]
Glucocorticoids / Glukokortikoidi	69 (52,7%)	70 (68%)	**0,018**[a]
ACE inhibitors / ACE inhibitori	7 (5,3%)	15 (14,5%)	**0,016**[a]
Immunosuppressants / Imunosupresivi	4 (3%)	8 (7,8%)	0,137[b]
Disease relapse / Relaps bolesti	25 (19,1%)	25 (24,3%)	0,336[a]

*Legend / Legenda: IgAV: IgA vasculitis / IgA vaskulitis; F/Ž: female gender / ženski spol; M: male gender / muški spol; GI: gastrointestinal / gastrointestinalni; IgAVN: IgA vasculitis nephritis / IgA vaskulitis nefritis; IQR/IR: interquartile range / interkvartilni raspon; NSAID: non-steroidal anti-inflammatory drugs / nesteroidni protuupalni lijekovi. Data are presented as percentages, statistical significance set at *P<0.05 / Podatci su prikazani u postotcima, statistička značajnost postavljena na *P<0,05. [a]X^2 test / X^2 test; [b]Fisher's exact test / Fisherov egzaktni test; [c]Mann-Whitney U-test / Mann-Whitneyjev U-test*

ous manifestations, ulcerations and necrosis. In 47 patients (20.1%), cutaneous manifestations had at least one recurrence. 131 patients (56%) had a skin rash localized on the legs and gluteal area, in 50 patients the

hvaćenu kožu nogu, ruku, trupa i lica (22,6%). Biopsija kože učinjena je u samo jednog bolesnika koji je po koži ruku i nogu imao gust purpuričan osip s eflorescencijama promjera 1 cm i centralnim nekrozama te papule po

rash affected not only the lower extremities but also the hands (21.4%), while in 53 patients the skin on the legs, arms, trunk and face was affected (22, 6%). A skin biopsy was performed on only one patient who had a dense purpuric rash on the skin of the arms and legs with efflorescences 1 cm in diameter and central necrosis and papules on the skin of the face. The skin biopsy indicated leukocytoclastic vasculitis with neutrophil infiltration, especially in the small blood vessels of the dermis and deposits of IgA and C3, and thus the histopathological finding with the clinical features of the patient was included in the diagnosis of IgAV.

A statistically significantly higher proportion of patients with skin rash spread over the lower extremities suffered from gastrointestinal system involvement (50.5% compared to 36.6%, p=0.033), they developed IgAVN (31.1% compared to 19.8%, p=0.048), they had a large amount of protein in urine (24.3% versus 12.2%, p=0.016) and underwent a kidney biopsy (15.5% versus 6.8%, p=0.033) compared to patients with a skin rash affecting the lower extremities. Patients with skin rashes spread over the lower extremities were more often treated with glucocorticoids (68% versus 52.7%, p=0.018) and antihypertensives from the group of angiotensin-converting enzyme inhibitors (14.5% versus 5.3%, p=0.016) with a longer duration of hospitalization (p=0.006), and the time to onset of IgAVN was also longer (p=0.007). No statistically significant differences between the groups were observed in laboratory findings (Table 2). Also, no statistically significant difference was observed in the involvement of the gastrointestinal system (45.5% versus 42.6%, p=0.852) and the incidence of IgAVN (45.5% versus 23.8%, p=0.146) in patients with severe cutaneous manifestations compared to the rest of the patients. Among 11 patients with severe cutaneous manifestations, 10 of them (90.9%) were treated with systemic glucocorticoids, while only one patient was treated with local glucocorticoid therapy for ulcerations. Patients with ulcerations and necrosis were statistically more significantly treated with systemic glucocorticoids compared to all other patients (90.9% vs. 57.8%, p=0.031). In 1 patient (9.1%) scars remained after ulcerations, and in 3 patients (27.3%) hyperpigmentation remained. The follow-up of all patients was performed for at least 6 months, during which time recurrences of skin rash occurred in 47 patients (20.1%). In 224 patients (95.8%) with IgAV complete recovery was achieved, while 10 of these patients (4.3%) had IgAVN with proteinuria <1 g/dU and their clinical follow-up was continued.

DISCUSSION

The purpose of this retrospective study conducted at the Referral Centre for Paediatric and Adolescent Rheumatology of the Ministry of Health of the Republ-

koži lica. Bioptat kože ukazivao je na leukocitoklastični vaskulitis s neutrofilnom infiltracijom, posebno u malim krvnim žilama dermisa i depozitima IgA i C3, te je time patohistološki nalaz s kliničkom slikom bolesnika uklopljen u dijagnozu IgAV-a.

Statistički značajno veći udio bolesnika s kožnim osipom proširenim iznad donjih udova imao je zahvaćen gastrointestinalni sustav (50,5% u odnosu na 36,6%, p=0,033), razvio je IgAVN (31,1% u odnosu na 19,8%, p=0,048), imao proteinuriju u nalazu urina (24,3% u odnosu na 12,2%, p=0,016) te bio podvrgnut biopsiji bubrega (15,5% u odnosu na 6,8%, p=0,033) u odnosu na bolesnike s kožnim osipom ograničenim samo na donje udove. Bolesnici s kožnim osipom proširenim iznad donjih udova češće su liječeni glukokortikoidima (68% u odnosu na 52,7%, p=0,018) i antihipertenzivima iz skupine inhibitora angiotenzin konvertaze (14,5% u odnosu na 5,3%, p=0,016) uz dulje trajanje hospitalizacije (p=0,006), a vrijeme do nastupa IgAVN-a također je bilo dulje (p=0,007). U laboratorijskim nalazima nisu uočene statistički značajne razlike između skupina (tablica 2). Također nije uočena statistički značajna razlika u zahvaćanju gastrointestinalnog sustava (45,5% u odnosu na 42,6%, p=0,852) i pojavnosti IgAVN-a (45,5% u odnosu na 23,8%, p=0,146) u bolesnika s teškim kožnim promjenama u odnosu na sve preostale bolesnike. Među 11 bolesnika s teškim kožnim promjenama njih 10 (90,9%) liječeno je sistemskim glukokortikoidima, dok je u samo jednog bolesnika za ulceracije primijenjena lokalna glukokortikoidna terapija. Bolesnici s ulceracijama i nekrozama su statistički značajnije liječeni sistemskom glukokortikoidnom terapijom u odnosu na sve ostale bolesnike (90,9% u odnosu na 57,8%, p=0,031). Kod jednog bolesnika (9,1%) nakon ulceracija zaostali su ožiljci, a kod troje bolesnika (27,3%) hiperpigmentacije. Svi bolesnici praćeni su u vremenskom intervalu od barem šest mjeseci, tijekom kojega su se recidivi kožnog osipa javili kod 47 bolesnika (20,1%). U 224 bolesnika (95,8%) s IgAV-om došlo je do potpunog izlječenja, dok je njih 10 (4,3%) imalo IgAVN s proteinurijom <1 g/dU te je dalje nastavljeno njihovo kliničko praćenje.

RASPRAVA

Svrha ovoga retrospektivnog istraživanja provedenog u Referentnom centru za pedijatrijsku i adolescentnu reumatologiju Ministarstva zdravstva Republike Hrvatske bila je analizirati kožne manifestacije, ključni klinički kriterij za dijagnozu ovoga najčešćeg vaskulitisa dječje dobi te ukazati na moguću povezanost osobitosti kožnih promjena s drugim kliničkim i laboratorijskim značajkama bolesti. U najvećeg broja djece s IgAV-om kožne promjene su tipične u vidu palpabilne netrombocitopenične purpure lokalizirane po donjim udovima i glutealno (5,6). U našoj kohorti od 234 bolesnika svi su imali kožni osip u predjelu donjih udova, najčešće po potko-

Table 2 Laboratory findings in IgAV patients, (N=234)
Tablica 2. Laboratorijski nalazi bolesnika s IgAV-om, (N=234)

Characteristic / Obilježje	IgAV patients with skin lesions only on the lower extremities (N=131) / IgAV bolesnici s kožnim lezijama samo po donjim ekstremitetima (N=131) N (% or/ili range/raspon)	IgAV patients with skin lesions spread above the lower extremities (N=103) / IgAV bolesnici s kožnim lezijama proširenim iznad donjih ekstremiteta (N=103) N (% or/ili range/raspon)	p-value / p vrijednost
/ ESR (mm/hr): median (IQR) SE (mm/h): medijan (IR)	17 (11-32)	17 (10.4-26.5)	0.685[c]
CRP (mg/L): median (IQR) / CRP (mg/L): medijan (IR)	6.2 (1.9-13.9)	7.5 (2.4-16.8)	0.423[c]
Erythrocytes (10^{12}/L): median (IQR) / Eritrociti (10^{12}/L): medijan (IR)	4.65 (4.41-5)	4.65 (4.43-5)	0.704[c]
Hemoglobin (g/L): Median (IQR) / Medijan (IR)	126 (118-133)	127.5 (118-133)	0.354[c]
Hematocrit: median (IQR) / Hematokrit: medijan (IR)	0.36 (0.34-0.39)	0.37 (0.35-0.39)	0.629[c]
Leukocytes (10^9/L): median (IQR) / Leukociti (10^9/L): medijan (IR)	10.1 (7.9-12.5)	10.8 (8.2-13.2)	0.442[c]
Thrombocytes (10^9/L): median (IQR) / Trombociti (10^9/L): medijan (IR)	369 (307-439)	347 (279-384.5)	**0.044**[c]
Creatinine (µmol/L): median (IQR) / Kreatinin (µmol/L): medijan (IR)	42 (31-54)	41 (32-59.5)	0.859[c]
Urea (mmol/L): median (IQR) / Ureja (mmol/L): medijan (IR)	4.1 (3.3-4.7)	4 (3.4-4.8)	0.227[c]
eGFR: median (IQR) / eGFR: medijan (IR)	128.5 (115.3-147)	129 (116.5-150)	0.979[c]
Ferritin (ng/mL): median (IQR) / Feritin (ng/mL): medijan (IR)	65.3 (43.9-102.8)	70.5 (50.9-97.9)	0.895[c]
PT: median (IQR) / PV: medijan (IR)	1.0 (0.9-1.1)	0.9 (0.8-1.1)	0.179[c]
aPTT (s): median (IQR) / APTV (s): medijan (IR)	25.8 (23.8-27.7)	25.2 (23.4-26.6)	0.545[c]
Fibrinogen (g/L): median (IQR) / Fibrinogen (g/L): medijan (IR)	3.4 (2.9-4)	3.3 (2.7-4.1)	0.606[c]
D-dimer test (µg/L): median (IQR) / D-dimeri (µg/L): medijan (IR)	2.1 (0.9-4.2)	2.5 (0.7-5.1)	0.413[c]
Erythrocyturia: n(number) / Eritrociturija: n (broj)	22 (16.8%)	22 (21.4%)	0.375[a]
Proteinuria: n (number) / Proteinurija: n (broj)	16 (12.2%)	25 (24.3%)	**0.016**[a]
Urinary albumin/creatinine ratio: median (IQR) / Omjer albumin/kreatinin u urinu: medijan (IR)	6.2 (1.4-22.3)	15.7 (3.2-52.6)	0.327[c]
Proteinuria – 24 hour urine protein test (g/day): median (IQR) / Proteinurija – 24-satna (g/dU): medijan (IR)	0.09 (0.06-0.14)	0.13 (0.07-0.27)	0.836[c]
Total protein test (g/L): median (IQR) / Ukupni proteini (g/L): medijan (IR)	70 (67-74)	69.5 (65-73)	0.243[c]
Albumin test (g/L): median (IQR) / Albumini (g/L): medijan (IR)	38.5 (35.1-41.3)	38.8 (35.9-42.4)	0.865[c]
IgA (g/L): median (IQR) / IgA (g/L): medijan (IR)	1.9 (1.4-2.6)	1.8 (1.3-2.4)	0.383[c]
IgG (g/L): median (IQR) / IgG (g/L): medijan (IR)	10.2 (8.7-12.4)	9.7 (7.7-11.7)	0.312[c]
IgM (g/L) median (IQR) / IgM (g/L): medijan (IR)	0.9 (0.7-1.2)	0.9 (0.7-1.2)	0.678[c]
Total IgE (g/L): median (IQR) / ukupni IgE (g/L): medijan (IR)	85.8 (16.4-217.5)	36.2 (24.6-79.8)	0.315[c]
ANA (+/-): n (number) / (broj)	8 (6.1%)	12 (11.6%)	0.132[a]
C_3 (g/L): median (IQR) / medijan (IR)	1.26 (1.11-1.42)	1.31 (1.12-1.41)	0.749[c]
C_4 (g/L): median (IQR) / medijan (IR)	0.26 (0.21-0.31)	0.24 (0.18-0.3)	0.502[c]
CH_{50} (%): median (IQR) / medijan (IR)	97 (85-111)	94 (79-110)	0.860[c]
ASTO: median (IQR) / medijan (IR)	161 (69-492)	155 (22-421.8)	0.161[c]
Positive faecal occult blood test (+/–): n(number) / Stolica pozitivna na okultno krvarenje (+/-): n (broj)	26 (19.8%)	26 (25.2%)	0.324[a]

*Legend / Legenda: ESR/SE: erythrocyte sedimentation rate / sedimentacija eritrocita; CRP: C-reactive protein / C-reaktivni protein; eGFR: estimated glomerular filtration rate / procijenjena glomerularna filtracija; PT/PV: prothrombin time / protrombinsko vrijeme; APTT/APTV: activated partial thromboplastin time / aktivirano parcijalno tromboplastinsko vrijeme; IgA: immunoglobulin A / imunoglobulin A; IgG: immunoglobulin G / imunoglobulin G; IgM: immunoglobulin M / imunoglobulin M; total IgE / uIgE: total immunoglobulin E / ukupni imunoglobulin E; ANA: antinuclear antibodies / antinuklearna antitijela; C_3: complement component C_3 / C_3 komponenta komplementa; C_4: complement component C_4 / C_4 komponenta komplementa; CH_{50}: total complement activity / ukupni komplement; ASTO: antistreptolysin O titer / antistreptolizinski titar; IQR/IR: interquartile range / interkvartilni raspon. Data are presented as a median (interquartile range) as well as percentages, statistical significance set at *P<0.05 / Podatci su prikazani kao medijan (interkvartilni raspon) i u postotcima, statistička značajnost postavljena na *P<0,05. [a]X^2 test / X^2 test [b]Fisher's exact test / Fisherov egzaktni test [c]Mann-Whitney U-test / Mann-Whitneyjev U-test*

lic of Croatia was to analyse the cutaneous manifestations, the key clinical criterion for the diagnosis of this most common childhood vasculitis, and to point out the possible connection between the characteristics of the cutaneous manifestations and other clinical and laboratory features of the disease. In the majority of children with IgAV, cutaneous manifestations are typical in the form of palpable non-thrombocytopenic purpura localized on the lower extremities and the gluteal region (5,6). In our cohort of 234 patients, all had a case of skin rash in the area of the lower extremities, most often on the lower extremities and feet, and a typical palpable skin rash was present in 204 patients (87.2%), which in practical terms allows the clinician to diagnose the disease with great certainty. However, the appearance of slightly less common cutaneous manifestations such as papules, macules or haematomas in combination with a typical rash is also possible. The most severe cutaneous manifestations in the form of ulcerations and necrosis were developed by 11 patients (4.7%), which is in accordance with the literature data (6,7). The exact cause and mechanism of such skin changes in IgAV are not clear, and include trauma, pressure, skin fragility, immune dysregulation, local action of leukocyte esterase and matrix metalloproteinases 2 and 9 (MMP-2 and MMP-9) leading to proteolysis of collagen in the skin (13). Studying the possible connection between more severe cutaneous manifestations and the clinical features of the disease, we noticed that literature data is scarce and contradictory (9,14–16). In this cohort of 234 patients with IgAV, in which 11 (4.7%) developed the most severe cutaneous manifestations, no significant association was observed with other clinical manifestations of the disease, primarily gastrointestinal manifestations and IgAVN.

Several studies have investigated whether there is an association between the prevalence of skin rash and systemic manifestations in IgAV (9–12,17,18). Some studies have shown that cutaneous manifestations spread above the waist level significantly increase the risk of gastrointestinal system involvement (9,11,12) and the development of IgAVN (9,10,17), while studies conducted on a group of adult patients with IgAV showed significant association with the development of arthritis (17). On the other hand, Poterucha et al did not find a connection between the prevalence of skin rash and systemic manifestations in IgAV (18). We observed that patients with purpuric rash spread above the waist have more frequently affected gastrointestinal system and a higher incidence of IgAVN. Another association between cutaneous manifestations spread over the lower extremities and IgAVN is manifested in the higher frequency of proteinuria and the longer time required for the onset of IgAVN. These patients were more likely to undergo invasive procedures such as kidney biopsy. Since the skin rash that has spread

ljenicama i stopalima, a tipičan palpabilni kožni osip sveukupno je imalo 204 bolesnika (87,2%), što u praktičnom smislu kliničaru omogućuje dijagnosticiranje bolesti s velikom sigurnošću. Međutim, moguća je i pojava nešto manje uobičajenih kožnih promjena poput papula, makula ili hematoma u kombinaciji s tipičnim osipom. Najteže kožne promjene u vidu ulceracija i nekroza razvilo je 11 bolesnika (4,7%), što je u skladu s literaturnim podatcima (6,7). Točan uzrok i mehanizam nastanka takvih kožnih promjena u IgAV-u nisu jasni, a uključuju traumu, pritisak, fragilitet kože, imunološku disregulaciju, lokalno djelovanje leukocitne esteraze i matriks metaloproteinaza 2 i 9 (MMP-2 i MMP-9) koje dovode do proteolize kolagena u koži (13). Proučavajući moguću povezanost težih kožnih manifestacija s kliničkim osobitostima bolesti uočili smo da su literaturni podatci oskudni i kontradiktorni (9,14-16). U ovoj kohorti od 234 bolesnika s IgAV-om, u kojoj je njih 11 (4,7%) razvilo najteže kožne promjene, nije uočena značajna povezanost s drugim kliničkim manifestacijama bolesti, ponajprije gastrointestinalnim manifestacijama i IgAVN-om.

Više istraživanja je ispitivalo postoji li povezanost između rasprostranjenosti kožnog osipa i sistemskih manifestacija u IgAV-u (9-12,17,18). Neka istraživanja pokazala su da kožne promjene raširene iznad razine struka značajno povećavaju rizik za zahvaćanje gastrointestinalnog sustava (9,11,12) i razvoj IgAVN-a (9,10,17), dok su istraživanja provedena na skupini odraslih bolesnika s IgAV-om pokazala značajniju povezanost s razvojem artritisa (17). S druge strane, Poterucha i suradnici nisu pronašli vezu između rasprostranjenosti kožnog osipa i sistemskih manifestacija u IgAV-u (18). U našoj kohorti bolesnika također je uočeno da bolesnici s kožnim osipom proširenim iznad donjih udova imaju češće zahvaćen gastrointestinalni sustav i veću pojavnost IgAVN-a. Druga povezanost između kožnih promjena proširenih iznad donjih udova i IgAVN-a očituje se i u većoj učestalosti proteinurije i duljem vremenu potrebnom za nastanak IgAVN-a. Ovi bolesnici bili su češće podvrgnuti invazivnim postupcima poput biopsije bubrega. Budući da kožni osip koji se proširio od donjih udova i gluteusa na ruke, trup i lice označava da upalni proces u malim krvnim žilama tinja uz kontinuirano otpuštanje medijatora upale, čini se logičnim zaključiti da takvi bolesnici s većom učestalošću razvijaju gastrointestinalne manifestacije i IgAVN, imaju značajno dulju hospitalizaciju, kao i potrebu za liječenjem sistemskim glukokortikoidima i antihipertenzivnim lijekovima. Prema SHARE (engl. *Single-Hub Access for Pediatric Rheumatology in Europe*) preporukama peroralni prednizolon indiciran je u liječenju blagog i umjerenog IgAVN-a, dok je antihipertenzive iz skupine inhibitora angiotenzin konvertaze poželjno uključiti u svih bolesnika u kojih se u sklopu IgAVN-a pojavila proteinurija radi povoljnog učinka na prevenciju ili ograničavanje sekundarnoga

from the lower extremities and the gluteal region to the arms, trunk and face indicates that the inflammatory process in small blood vessels is developing with the continuous release of inflammatory mediators, it seems logical to conclude that such patients develop gastrointestinal manifestations and IgAVN with greater frequency, have significantly longer hospitalization time, and require treatment with systemic glucocorticoids and antihypertensive drugs. According to the recommendations of the Single Hub and Access Point for Pediatric Rheumatology in Europe (SHARE), oral prednisolone is indicated in the treatment of mild and moderate IgAVN, while antihypertensives from the group of angiotensin-converting enzyme inhibitors should preferably be included in the treatment of all patients in whom proteinuria has appeared as part of IgAVN for the sake of achieving a favourable effect on the prevention or limitation of secondary glomerulonephritis (8). Although the SHARE recommendations do not specify any guidelines for the treatment of spread cutaneous manifestations as well as the most severe ones, most of our patients received systemic glucocorticoids in such cases, especially patients with ulcerations and necrosis. Since in a large number of patients the diagnosis of IgAV is already clear on the basis of the clinical features, a skin biopsy is rarely indicated. This is also indicated by the SHARE recommendations, according to which a skin biopsy is required in the case of an atypical rash to exclude other diagnoses, especially ANCA-associated vasculitis, which in older children may present with symptoms and signs compatible with IgAV at the onset of the disease. In case there is an indication for a skin biopsy, it should be done at the site of the newly appeared cutaneous manifestations (8). In our study, a skin biopsy was performed in only one patient with severe cutaneous manifestations and an atypical appearance of a purpuric rash. Therefore, it can be said that skin biopsy in children with IgAV is an exception rather than the rule. The follow-up of all patients was performed for at least 6 months and all of them recovered from the cutaneous manifestations, except for one patient with ulcerations who developed scars. Ten patients are still under clinical follow-up and treated for IgAVN.

The main limitation of this paper is the retrospective nature of the research, as well as the small number of patients with the most severe cutaneous manifestations in the form of ulcerations and necrosis, on the basis of which recommendations related to therapy and follow-up of such patients could be made, which certainly remains one of the future challenges. Nevertheless, we gave an overview of the cutaneous manifestations of the most common childhood vasculitis in the Republic of Croatia, in which we observed that the frequency of severe cutaneous manifestations in IgAV is less frequent than the standard clinical features of glomerularnog oštećenja (8). Premda u SHARE preporukama nisu navedene smjernice za liječenje proširenih kožnih promjena kao i onih najtežih, većina naših bolesnika i u takvim je slučajevima dobivala sistemske glukokortikoide, osobito bolesnici s ulceracijama i nekrozama. Budući da je u velikog broja bolesnika dijagnoza IgAV-a jasna već na osnovi kliničke slike, biopsija kože rijetko je indicirana. O tome također govore i SHARE preporuke prema kojima je biopsija kože potrebna u slučaju atipičnog osipa kako bi se isključile druge dijagnoze, osobito vaskulitisi povezani s ANCA-om koji se u starije djece u početku bolesti mogu očitovati simptomima i znakovima kompatibilnim s IgAV-om. U slučaju da postoji indikacija za biopsiju kože, ona se treba napraviti na mjestu najsvježijih kožnih promjena (8). U našem istraživanju biopsija kože je učinjena u samo jednog bolesnika s teškim kožnim promjenama i atipičnim izgledom purpuričnog osipa. Stoga se može reći da je biopsija kože u djece s IgAV-om izuzetak, a ne pravilo. Svi bolesnici praćeni su barem šest mjeseci i kod svih je došlo do oporavka kožnih promjena, osim u jednog bolesnika s ulceracijama koji je razvio ožiljke. Deset bolesnika i nadalje se klinički prati i liječi zbog IgAVN-a.

Glavno ograničenje u ovom radu retrospektivna je priroda istraživanja kao i mali broj bolesnika s najtežim kožnim manifestacijama u vidu ulceracija i nekroza, na osnovi čega bi se mogle donijeti preporuke vezane uz terapiju i praćenje takvih bolesnika, što svakako ostaje jedan od budućih izazova. Ipak, dali smo pregled kožnih manifestacija najčešćeg vaskulitisa dječje dobi u Republici Hrvatskoj u kojem smo uočili da je učestalost teških kožnih promjena u IgAV-u rjeđa od klasične slike purpuričnog osipa i/ili petehija. Također smo uočili da su bolesnici s kožnim osipom koji se proširio od donjih udova na ruke, trup i lice imali češće sistemske manifestacije bolesti, odnosno češće zahvaćen gastrointestinalni sustav i veću pojavnost IgAVN-a, što svakako nalaže pomnije kliničko praćenje takvih bolesnika kako bi se na vrijeme prepoznale i liječile moguće komplikacije IgAV-a.

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purpuric rash and/or petechiae. We also observed that patients with a skin rash that spread from the lower extremities to the hands, trunk and face had more frequent systemic manifestations of the disease, i.e. more often the gastrointestinal system was involved along with a higher incidence of IgAVN, which certainly requires a closer clinical follow-up of such patients in order for the possible complications of IgAV to be recognized and treated in time.

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ORIGINAL SCIENTIFIC PAPER ORIGINALNI ZNANSTVENI RAD

INCIDENCE OF THROMBOEMBOLIC EVENTS IN PATIENTS WITH A SYSTEMIC FORM OF VASCULITIS AND CUTANEOUS VASCULITIS

UČESTALOST TROMBOEMBOLIJSKIH DOGAĐAJA U SISTEMSKOM OBLIKU VASKULITISA I LOKALIZIRANOM KOŽNOM VASKULITISU

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Sažetak

Uvod: Vaskulitis je rijetka bolest karakterizirana upalom i nekrozom krvnih žila. Upalom inducirana tromboza smatra se svojstvom nekoliko autoimunosnih bolesti poput sistemskog eritemskog lupusa (SLE), reumatoidnog artritisa (RA), Sjögrenova sindroma (SS) te sistemskih vaskulitisa. U ovom istraživanju nastojali smo utvrditi učestalost tromboembolijskih (TE) događaja kod sistemskog oblika vaskulitisa i vaskulitisa ograničenog na kožu te procijeniti koji su mogući rizični čimbenici za razvoj tromboembolijskih (TE) događaja. *Ispitanici i metode:* U ovoj retrospektivnoj studiji sudjelovali su bolesnici s dijagnozom sistemskog vaskulitisa i vaskulitisa ograničenog na kožu liječenih u Zavodu za reumatologiju, kliničku imunologiju i alergologiju Kliničkoga bolničkog centra Osijek u razdoblju od 30 mjeseci (od studenog 2016. do lipnja 2019. godine). Klinički podatci prikupljeni su pretraživanjem medicinske dokumentacije. *Rezultati:* U studiju je uključeno ukupno 46 bolesnika, 30 s dijagnozom sistemskog vaskulitisa i 16 s vaskulitisom ograničenim na kožu. Među dvjema skupinama bilo je statistički značajne razlike po spolu (sistemski vaskulitis vs vaskulitis ograničen na kožu – ženski spol 76,67% vs 43,75%; p=0,026), no među grupama nije bilo razlike u dobi pojave bolesti. Tromboembolijski događaji bili su češći u bolesnika sa sistemskim oblikom vaskulitisa (p=0,0321). Pri analizi bolesnika sa sistemskim vaskulitisom kao rizični čimbenici za razvoj TE događaja utvrđeni su zahvaćanje više organskih sustava bolešću te mlađa životna dob. *Zaključak:* U našem istraživanju pokazali smo da bolesnici sa sistemskim vaskulitisom, mlađe životne dobi, uz visoku aktivnost bolesti i zahvaćanje više organskih sustava imaju povećan rizik za nastanak tromoebolijskih događaja te bi se kod takvih bolesnika trebala posvetiti posebna pozornost u otkrivanju dodatnih rizičnih čimbenika kao što je genetska predispozicija u svrhu sprječavanja neželjenih događaja te primjenu pravovremene TE profilakse.

Ključne riječi: sistemski vaskulitis, vaskulitis ograničen na kožu, tromboembolija

Abstract

Objectives: Vasculitis is a rare disease characterized by inflammation and necrosis of blood vessels. Inflammation-induced thrombosis is a hallmark of several autoimmune diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's syndrome (SS), and systemic vasculitis. In this study, we aimed to investigate the frequency of thromboembolic (TE) events in the systemic form of vasculitis and cutaneous vasculitis and to determine

the possible risk factors for developing thromboembolic events. *Methods:* In this single-centre retrospective study, the patients diagnosed with systemic vasculitis and cutaneous leukocytoclastic vasculitis were included. Medical records of the patients that were treated at the Division of Rheumatology, Clinical Immunology, and Allergology University Hospital Centre Osijek in the period of 30 months (from November 2016. to June 2019.) were analysed. *Results:* Out of a total of 46 patients who were included in the study, 30 were diagnosed with systemic vasculitis, and 16 with cutaneous vasculitis. Statistically significant differences in relation to gender were found between the two groups (systemic vasculitis vs cutaneous vasculitis: the female gender 76.67% vs 43.75%; p=0.026), but there was no difference between the groups in relation to the age of disease onset. Thromboembolic events were found to be more frequent in the systemic form of the disease (p=0.0321). In the systemic vasculitis group, TE events were found in patients who suffered from involvement of multiple organ systems and in younger patients. *Conclusion:* Our research found that patients with systemic vasculitis, who are younger, with high disease activity, and who suffered from the involvement of multiple organ system, have an increased risk for developing TE events. In those patients, special attention should be paid to searching for additional TE risk factors, such as genetics, for the purpose of preventing unwanted events and applying TE prophylaxis on time.

Keywords: Systemic vasculitis, cutaneous leukocytoclastic vasculitis, thromboembolism

INTRODUCTION

Vasculitis is a rare disease characterized by inflammation and necrosis of blood vessels. Inflammation-induced thrombosis is a hallmark of several autoimmune diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's syndrome (SS), and systemic vasculitis (2,3). The incidence of thromboembolic (TE) events is an important clinical manifestation of systemic vasculitis. The reason for this incidence is due to the pathomechanism of the disease and it is also related to the pathogenesis of thrombosis (2–6).

Previous research has led to gaining new insights about the prothrombotic effect of systemic inflammation in vasculitis. In the pathophysiology of thrombosis in Behçet's syndrome (BS), a generalized disorder of CD4+ lymphocytes, monocytes, neutrophils is observed, as well as an increased production of pro-inflammatory cytokines such as interferon gamma (IFN-γ), tumour necrosis factor alpha, TNF-α), interleukin-1 (IL-1), IL-6, IL-8, IL-12 which causes the occurrence of the prothrombotic state (2). The incidence of TE events in vasculitis associated with antineutrophil cytoplasmic autoantibodies (ANCA) and large-vessel vasculitis has been confirmed (1,2). The highest frequency of ANCA-associated vasculitis occurs in eosinophilic granulomatosis with polyangiitis (EGPA) (1, 7, 8). One of the possible reasons is the role of eosinophils in the release of major basic protein as well as eosinophil cationic protein, which inhibit natural anticoagulant activity and activate platelets, leading to increased thrombin generation (1, 2). Endothelial dysfunction is also a characteristic of ANCA-associated vasculitis and is most likely caused by the interaction between neutrophils (activated by TNF-α and ANCA antibodies) and endothelial cells, with consequent massive oxidative stress leading to atherothrombotic complications (1, 2, 8–11).

In large-vessel vasculitis, anti-endothelial cell antibodies play a possible role in endothelial damage

UVOD

Vaskulitis je rijetka bolest karakterizirana upalom i nekrozom krvnih žila (1). Upalom inducirana tromboza smatra se svojstvom nekoliko autoimunih bolesti, poput sistemskog eritemskog lupusa (SLE), reumatoidnog artritisa (RA), Sjögrenova sindroma (SS), ali i sistemskih vaskulitisa (2,3). Pojavnost tromboemobolijskih (TE) događaja bitna je klinička manifestacija sistemskih vaskulitisa, što leži u patomehanizmu nastanka same bolesti, a povezana je i s patogenezom tromboze (2–6).

Dosadašnja istraživanja dovela su do spoznaja o protrombotskom učinku koji ima sustavna upala u vaskulitisima. U patofiziologiji tromboze u Behçetovu sindromu (BS) zamijećen je generalizirani poremećaj CD4+ limfocita, monocita, neutrofila i prekomjerna proizvodnja proupalnih citokina kao što su interferon gama (IFN-γ), čimbenika tumorske nekroze alfa (engl. *tumor necrosis factor alpha*, skr. TNF-α), interleukina (IL) 1, IL-6, IL-8, IL-12 što dovode do protrombotskog stanja (2). Potvrđena je pojavnost TE događaja u vaskulitisu povezanim s antineutrofilnim citoplazmatskim autoantitijelima (ANCA) i vaskulitisu velikih krvnih žila (1,2). Među ANCA-vaskulitisima najveća učestalost je u eozinofilnoj granulomatozi s poliangiitisom (EGPA) (1,7,8). Jedan od mogućih razloga jest uloga eozinofila u oslobađanju glavnoga bazičnog proteina kao i eozinofilnoga kationskog proteina koji inhibiraju prirodnu antikoagulantnu aktivnost i aktiviraju trombocite, dovodeći do prekomjernog stvaranja trombina (1,2). Disfunkcija endotelnih stanica također je svojstvo ANCA-vaskulitisa i najvjerojatnije je uzrokovana interakcijom između neutrofila (aktiviranih TNF-α i ANCA-protutijelima) i endotelnih stanica, s posljedičnim masivnim oksidativnim stresom što vodi prema aterotrombotskim komplikacijama (1,2,8–11).

Kod vaskulitisa velikih krvnih žila moguću ulogu u oštećenju endotela imaju antiendotelna protutijela

(12,13). One of the possible vascular complications is the development of aneurysms as a consequence of inflammatory damage (12, 13). Reshaping of the blood vessel wall begins in the adventitia with an infiltrate consisting mainly of auxiliary lymphocytes (T-helper cells, Th) Th1 /Th17 that activate residual dendritic cells and macrophages, which produce pro-inflammatory cytokines and growth factor that causes intimal hyperplasia (12, 13, 14, 15). The objective of this paper was to compare the incidence of TE events in systemic vasculitis and localized cutaneous vasculitis and to determine the possible risk factors for the development of TE events on a sample of patients in a tertiary care rheumatology centre.

SUBJECTS AND METHODS

In this research, a retrospective, systematic analysis and comparison of two groups of patients diagnosed with systemic vasculitis and cutaneous vasculitis are carried out, in order to determine the incidence of TE events in each group. The inclusion criterion for the study was the diagnosis of primary vasculitis according to the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasulitides (16) set by a rheumatologist/immunologist, and the exclusion criterion was the occurrence of another inflammatory rheumatic disease, malignant disease or proven infection at the time of diagnosis. 46 patients with diagnosed systemic vasculitis and cutaneous vasculitis, who were treated at the University Hospital Centre Osijek during a period of 30 months (from November 2016 to June 2019) were included in the study. Retrograde assessment was used to determine disease activity in patients with systemic vasculitis by using medical records according to the Birmingham Vasculitis Activity Score (BVAS). Data from the patient's medical history and clinical status at the time of diagnosis were analysed in relation to the incidence and type of cutaneous manifestations and manifestations on visible mucous membranes, muscle involvement, symptoms related to the respiratory and cardiovascular systems, neurological symptoms and symptoms of gastrointestinal system involvement, as well as laboratory findings (including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), detection of nitrogen-containing metabolites, etc.) in addition to various imaging methods that were performed depending on the symptoms (e.g. echocardiogram, multislice computed tomography (MSCT) of the thorax and abdomen, positron emission tomography / computed tomography (PET/CT), electromyography, etc.). The data were collected from the available medical documentation of the Division of Rheumatology, Clinical Immunology and Allergology at the University Hospital Centre Osijek (outpatient clinics, day hospitals and inpatient facilities). The research was conducted in accordance

(12,13). Jedna od mogućih vaskularnih komplikacija jest razvoj aneurizmi kao posljednice upalnog oštećenja (12,13). Preoblikovanje zida krvne žile započinje u adventiciji s infiltratom koji se uglavnom sastoji od pomoćničkih limfocita (engl. *T-helpper*, skr. Th) Th1/Th17 koji aktiviraju rezidualne dendritičke stanice i makrofage, a koji proizvode proupalne citokine i čimbenik rasta koji uzrokuje hiperplaziju intime (12–15). Cilj ovog rada bio je usporediti pojavnost TE događaja u sistemskom obliku vaskulitisa i u lokaliziranom kožnom vaskulitisu te utvrditi moguće rizične čimbenike za razvoj TE događaja u uzorku bolesnika jednoga tercijarnog reumatološkog centra.

ISPITANICI I METODE

U ovom istraživanju radi se retrospektivnoj, sistematskoj analizi i usporedbi dviju skupina bolesnika s dijagnozom sistemskog vaskulitisa i vaskulitisa ograničenog na kožu, u svrhu utvrđivanja pojavnosti TE događaja u pojedinoj skupini. Uključni kriterij za istraživanje bila je dijagnoza primarnog vaskulitisa sukladno Međunarodnom Chapel Hill konsenzusu iz 2012. godine (engl. *2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides*) (16), postavljena od strane reumatologa/imunologa, a isključni kriterij bila je prisutnost druge upalne reumatske bolesti, zloćudne bolesti ili dokazane infekcije u trenutku dijagnoze. U studiju je uključeno 46 bolesnika s dijagnosticiranim sistemskim vaskulitisom i vaskulitisom ograničenim na kožu liječenih u KBC-u Osijek u razdoblju od 30 mjeseci (od studenog 2016. do lipnja 2019. godine). Aktivnost bolesti u pacijenata sa sistemskim vaskulitisom procijenjena je retrogradno koristeći se medicinskom dokumentacijom prema skali *Birmingham Vasculitis Activity Score* (BVAS). Analizirani su podatci iz anamneze i kliničkog statusa pacijenta u trenutku dijagnoze o pojavi i vrsti kožnih promjena i promjena na vidljivim sluznicama, zahvaćanju mišića, simptomima vezanim uz dišni, srčani i krvožilni sustav, neurološkim simptomima te simptomima zahvaćanja probavnog sustava, potom laboratorijski nalazi (uključujući C-reaktivni protein [CRP], sedimentaciju eritrocita [SE], nalaz dušičnih metabolita itd.) te različite slikovne metode koje su se provodile ovisno o simptomima (npr. ultrazvuk srca, višeslojna kompjutorizirana tomografija [MSCT] prsnog koša i abdomena, pozitronska emisijska tomografija i kompjutorizirana tomografija [PET CT], elektromiografija itd.). Podatci su prikupljeni iz dostupne medicinske dokumentacije Zavoda za reumatologiju, kliničku imunologiju i alergologiju Kliničkoga bolničkog centra Osijek (ambulanti, dnevne bolnice i stacionara). Istraživanje je provedeno sukladno etičkim standardima institucije i Etičkom kodeksu udruge *World Medical Association* (Helsinška deklaracija iz 1964. i njezine

with the ethical standards of the institution and with the International Code of Medical Ethics of the World Medical Association (1964 Declaration of Helsinki and its updated versions) (17) with the approval of the institution's Ethics Committee (approval no. R2-13170/2020).

In terms of statistical methods for testing the difference in distributions for two variables, the Mann-Whitney test was used. Chi-squared test and Fisher's exact test were used to test the dependence between two categorical variables. The threshold value for the significance of the difference was set at $p<0.05$.

RESULTS

Out of a total of 46 patients, 30 were diagnosed with systemic vasculitis, and 16 with cutaneous vasculitis. Statistically significant differences in relation to gender were found between the two groups (systemic vasculitis vs cutaneous vasculitis: the female gender 76.67% vs 43.75%; p=0.026), but there was no difference between the groups in relation to the age of disease onset. A total of 5 TE events were recorded, 2 of which were a case of deep vein thrombosis, 1 was a case of arterial thrombosis, 1 was a case of pulmonary embolism and 1 was a case of cerebrovascular insult. TE events occurred more often in patients with systemic vasculitis (16.67% vs 0%; p=0.032). (Table 1). When analysing patients with systemic vasculitis, it became apparent that TE events occurred in those who suffered from the involvement of multiple organ systems (4 vs 3; p=0.0425) and in those patients who were younger (47 vs 65 years of age, p=0.018). No difference was found in relation to BVAS in the two groups of patients (19 vs 12, p=0.169) (Table 2). Distribution of patients by gender, age and occurrence of thromboembolic events (TE) according to the basic diagnosis is presented in Table 3. All patients who experienced a TE event were diagnosed with hereditary thrombophilia, which is defined by the lack of antithrombin, protein C, protein S, and mutation of factor V Leiden and prothrombin variants.

DISCUSSION

In our research, we analysed patients with systemic vasculitis and cutaneous vasculitis. Between the two groups, the incidence of TE events was exclusively characteristic of patients with systemic vasculitis.

According to the data published so far in the literature, when it comes to vasculitis, the incidence of TE events in Behçet's syndrome is the most frequently researched topic, in addition to the incidence of venous thromboembolism and arterial thrombosis (2, 18–20). According to our results, in accordance with previous knowledge, in one patient, who is also the only one diagnosed with Behçet's syndrome during that period, a TE event was determined as the outcome of an active disease.

In their retrospective cohort study, Kang et al. studied the incidence of TE events in patients with ANCA-

kasnije inačice) (17), uz odobrenje Etičkog povjerenstva institucije (br odobrenja R2-13170/2020.).

Od statističkih metoda za testiranje razlike u distribucijama za dvije varijable upotrijebljen je Mann-Whitneyev test. Za testiranje zavisnosti između dvije kategorijalne varijable upotrijebljen je Chi-2 test i Fisherov egzaktni test. Granična vrijednost za značajnost razlike je utvrđena na $p<0,05$.

REZULTATI

Od ukupno 46 bolesnika, 30 je imalo dijagnozu sistemskog vaskulitisa, a 16 vaskulitisa ograničenog na kožu. Među dvjema skupinama nađena je statistički značajna razlika po spolu (sistemski vaskulitis vs vaskulitis ograničen na kožu – ženski spol 76,67% vs 43,75%; p=0,026), no među grupama nije bilo razlike u dobi pojave bolesti. Zabilježeno je ukupno pet TE događaja, od kojih su dvije duboke venske tromboze, jedna arterijska tromboza, jedna plućna tromboemobolija i jedan cerebrovaskularni inzult. TE događaji su se češće javljali u bolesnika sa sistemskim oblikom (16,67% vs 0%; p=0,032) (tablica 1). Pri analizi bolesnika sa sistemskim vaskulitisom, TE događaji su se pojavili u onih koji su imali više zahvaćenih sustava (4 vs 3; p=0,0425) te u onih bolesnika koji su mlađe dobi (47 vs 65 godina, p=0,018). Nije nađena razlika u odnosu na BVAS u dvije skupine bolesnika (19 vs 12, p=0,169) (tablica 2). Raspodjela bolesnika po spolu i dobi i pojavnosti tromboembolijskih događaja (TE) s obzirom na osnovnu dijagnozu prikazana je u tablici 3. U svih bolesnika s TE događajem utvrđena je hereditarna trombofilija koja je definirana nedostatkom antitrombina, proteina C, proteina S te mutacijom faktora V Leiden i protrombinskih varijanti.

RASPRAVA

U našem istraživanju analizirali smo bolesnike sa sistemskim vaskulitisom i vaskulitisom ograničenim na kožu. Između dvije grupe, pojava TE događaja bila je isključivo obilježje bolesnika sa sistemskim oblikom vaskulitisa.

Prema do sada objavljenim podatcima iz literature među vaskulitisima najistraženija je pojava TE događaja u Behçetovu sindromu, uz pojavu i venskih i arterijskih tromboza (2,18–20). U našim je rezultatima, sukladno dosadašnjim spoznajama, kod jedne bolesnice, koja je ujedno i jedina kojoj je u tom razdoblju postavljena dijagnoza Behçetova sindroma, kao ishod aktivne bolesti utvrđen TE događaj.

U svojoj retrospektivnoj kohortnoj studiji Kang i suradnici proučavali su incidenciju TE događaja u bolesnika s ANCA-vaskulitisima i dokazali povećanu incidenciju TE incidenata u odnosu na opću populaciju Velike Britanije, posebno u prvoj godini dijagnoze, što

Table 1 Comparison of the main features of interest to a group of patients with systemic vasculitis and cutaneous vaculitis
Tablica 1. Usporedba glavnih obilježja od interesa skupine bolesnika sa sistemskim vaskulitisom i vaskulitisom ograničenim na kožu

		Thromboembolic events in patients with vasculitis / TE događaj u bolesnika sa vaskulitisom		P*
		Cutaneous vasculitis / Vasulitis ograničen na kožu (N=16)	Systemic vasculitis / Sistemski vaskulitis (N=30)	
Gender / Spol	Women / Žene	43,75%	76,67%	**0,0266**
	Men / Muškarci	56,25%	23,33%	
Age (Median, Interquartile range) / Dob (medijan, interkvartilni raspon IQR)		59 (±16)	62 (±14)	0,7643
Thromboembolic event / TE	Yes / Da	0%	16,67%	**0,0321**
	No / Ne	100%	83,33%	

P < 0.05

Table 2 Features of patients with Systemic Vasculitis
Tablica 2. Osobitosti bolesnika sa sistemskim vaskulitisom

		Thromboembolic event / TE događaj (N=5)	Without thromboembolic event / Bez TE događaja (N=25)	P*
Gender / Spol	Woman / Žene	80%	76%	0,6711
	Men / Muškarci	20%	24%	
Age (Median, lQR) / Dob (medijan, IQR)		47 (±15)	65 (±15)	**0,0189**
Median (IQR) / BVAS (medijan, lQR)		19 (11)	12 (11)	0,1694

P < 0.05; BVAS – Birmingham Vasculitis Activity Score

Table 3 Distribution of patients by gender, age and occurrence of thromboembolic events (TE) according to the basic diagnosis
Tablica 3. Raspodjela bolesnika po spolu i dobi i pojavnosti tromboembolijskih događaja (TE) s obzirom na osnovnu dijagnozu

	IgA vasculitis / IgA vaskulitis	GPA	EGPA	GCA	MPA	Bechet's disease / Behcetova bolest	In total / Ukupno
Men / Muškarci	3	4	0	0	0	0	7
Woman / Žene	1	8	6	3	4	1	23
In total / Ukupno	4	12	6	3	4	1	30
TE	1	1	2	/	/	1	5

GPA – granulomatosis with polyangiitis / granulomatoza s poliangiitisom; EGPA – eosinophilic granulomatosis with polyangiitis / eozinoflina granulomatoza s poliangiitisom; GCA – giant cell arteritis / gigantoceulularni arteritis; MPA – microscopic polyangiitis / mikroskopski poliangitis

associated vasculitis and demonstrated an increased incidence of TE events in comparison to the reported rates of the general population of UK, especially in the first year of diagnosis, which they associate with disease activity or with treatment (21). In our research, TE events occurred in those patients who suffered from multiple organ systems involvement and in patients who were younger. Similar observations were published by Salmela et al. in their observational study in which they demonstrated increased D-dimer values during active disease in ANCA-associated vasculitis, and in correlation with BVAS, they suggested that activation of coagulation is associated with ANCA-associ-

povezuju s aktivnošću bolesti ili s liječenjem (21). U našem istraživanju TE događaji pojavili su se u onih bolesnika koji su imali više zahvaćenih sustava te u onih bolesnika koji su mlađe dobi. Slična zapažanja objavili su Salmela i suradnici u svojoj opservacijskoj studiji u kojoj su dokazali povišene vrijednosti D-dimera tijekom aktivne bolesti u ANCA-vaskulitisu, a u korelaciji s BVAS-om sugerirali su da je aktiviranje koagulacije povezano s ANCA-vaskulitisom koji zahvaća više organskih sustava (22). Studija iz Nizozemske izvijestila je o incidenciji venskih TE incidenata od 1,8 na 100 osoba godišnje, povećavajući se na 6,7 po 100 osoba godišnje tijekom aktivne bolesti koja je defi-

ated vasculitis which involves multiple organ systems (22). A similar study from the Netherlands reported an incidence of venous TE events of 1.8 per 100 person-years, increasing to 6.7 per 100 person-years during active disease, which was characterized by a time interval of two months before and after diagnosis, or relapse in patients with ANCA-associated vasculitis, excluding eosinophilic granulomatosis with polyangiitis (EGPA) (3). The data from that study confirm that active disease is a risk factor for the incidence of TE events (3). According to a study conducted in 2007 by Stassen et al., they found that the risk of developing venous TE events in ANCA-associated vasculitis is increased, especially in active disease, which they associated with endothelial dysfunction and hypercoagulability (5). The results of the 2017 Kronbichler report highlight the role of C-reactive protein, baseline creatinine, cutaneous and gastrointestinal involvement in risk stratification associated with thromboembolic events (23).

In a 2016 meta-analysis, Ungprasert and Koster showed a significantly increased risk of venous TE events in patients suffering from granulomatosis with polyangiitis (GPA), polyarteritis nodosa (PAN) and giant cell arteritis (GCA) (6). They also showed that the frequency of hereditary thrombophilia is not increased in patients with GPA and GCA and that it is not a risk factor in the incidence of TE (6). In our study, genetic diagnosis of hereditary thrombophilia was not performed routinely in all patients, but only in patients with a proven TE event. Given that the results of our research showed an increased TE event in patients with high disease activity, hereditary haemophilia was an additional factor that contributed to the development of thrombosis in patients with a more severe clinical features with involvement of multiple organ systems.

Hereditary thrombophilia is a known factor in the incidence of venous thromboembolism in the general population (24, 25, 26). In their research, Sebastian et al. proved that the prevalence of cardiolipin antibodies as a prothrombin gene mutation (PGM) and methylenetetrahydrofolate reductase mutation (MTHFR) is not higher in patients with GPA in comparison to the general population, and they proved that the increased risk of TE events is not explained by the increased prevalence of anticardiolipin antibodies (aCL), anti-beta-2-glycoproteins or PGM and MTHFR mutations (26). In their paper, Espinosa et al. proved that patients with GCA have a high prevalence of antiphospholipid antibodies (aPL) which is not related to ischemic manifestations and that ischemic manifestations in GCA patients are not related to congenital thrombophilic risk factors (27).

The ageing process in humans is accompanied by changes in the coagulation system and thereby the risk of thrombosis is increased in older people (24). Concentrations of coagulation factors such as factor V, factor

nirana vremenskim intervalom dva mjeseca prije i nakon dijagnoze, ili recidiva u bolesnika s ANCA-vaskulitisom, a isključujući eozinofilnu granulomatozu s poliangitisiom (engl. *eosinophilic granulomatosis with polyangiitis* – EGPA) (3). Podatci te studije potvrđuju da je aktivna bolest rizični čimbenik za nastanak TE događaja (3). Stassen i suradnici u studiji iz 2007. godine otkrili su da je povećan rizik razvoja venskih TE događaja u ANCA-vaskulitisu, posebice u aktivnoj bolesti, što su povezali s endotelnom disfunkcijom i hipekoagulabilnošću (5). Rezultati izvješća Kronbichlera iz 2017. godine ističu ulogu C-reaktivnog proteina, početnog kreatinina, uključenosti kože i probavnog sustava u stratifikaciji rizika povezanih s trombembolijskim događajima (23).

U metaanalizi iz 2016. godine Ungprasert i Koster prikazali su značajno povišen rizik venskih TE događaja u pacijenata koji boluju od granulomatoze s poliangitisom (engl. *granulomatosis with polyangiitis* – GPA), nodoznog poliarteritisa (engl. *polyarteritis nodosa* – PAN) i gigantocelularnog arteritisa (engl. *giant cell arteritis* – GCA) (6). Prikazali su također da učestalost nasljedne trombofilije nije povećana u pacijenata s GPA i GCA te nije rizični čimbenik u nastanku TE (6). U našem istraživanju genetska dijagnostika hereditarne trombofilije nije rađena rutinski u svih pacijenata, već samo u onih kod kojih je dokazan TE događaj. S obzirom na to da su rezultati našeg istraživanja prikazali povećan TE događaj u pacijenata s visokom aktivnosti bolesti, nasljedna hemofilija bila je dodatni čimbenik koji je kod bolesnika s težom kliničkom slikom uz zahvaćanje više organskih sustava pridonio razvoju tromboze.

Hereditarna trombofilija je inače poznati čimbenik nastanka venskih tromboembolija u općoj populaciji (24,25,26). Sebastian i suradnici u svojem su istraživanju dokazali da prevalencija kardiolipinskih protutijela kao mutacija protrombinskog gena (engl. *prothrombin gene mutation* – PGM) i mutacija metilenhidrofolat reduktaze (engl. *methylenetetrahydrofolate reductase* – MTHFR) nije veća u pacijenata s GPA nego u općoj populaciji, te su dokazali da povećan rizik TE događaja nije objašnjen povećanom prevalencijom antikardiolipinskih protutijela (engl. *anti-cardiolipin antibody* – aCL), anti-beta2 glikoproteinom ili mutacijama PGM i MTHFR (26). Espinosa i suradnici u svojem su radu dokazali da pacijenti s GCA imaju visoku prevalenciju antifosfolipidnih proutijela (aPL) koja nije povezana s ishemijskim manifestacijama; također, ishemijske manifestacije u pacijenata s GCA nisu povezane ni s urođenim trombofilnim čimbenicima rizika (27).

Proces starenja kod ljudi popraćen je preinakama u sustavu zgrušavanja i time povećava rizik od tromboze u starijih ljudi (24). Koncentracije faktora koagulacije kao što su faktor V, faktor VII, faktor VII, faktor IX i

VII, factor VII, factor IX and fibrinogen gradually increase with age (24, 28). In our study, thromboembolic events occurred in younger patients, and a possible explanation for this lies in the increased activity of the disease and involvement of multiple organ systems in younger patients in comparison to the older population.

In our study, not a single thromboembolic event was recorded in patients with cutaneous vasculitis. By researching the available literature, no study was found that would compare the incidence of thromboembolic events in patients with cutaneous vasculitis. To our knowledge, we are the first to report an increased risk of thromboembolic events in systemic vasculitides compared to cutaneous vasculitides, so we were unable to compare our results to results from other studies.

The limitation of this research study is the small sample of subjects, considering that it is a study of a disease with a low incidence conducted in one hospital centre. Therefore, it would be preferable to expand it in the future by including more centres in the study. In addition to that, another limitation of this study is that it is a retrospective study. Also, considering that the genetic diagnosis of hereditary thrombophilia was performed only in patients with a proven TE event, so in future trials it would be necessary to determine the frequency of hereditary thrombophilia in all subjects.

CONCLUSION

Our research shows that younger patients with systemic vasculitis, high disease activity and involvement of multiple organ systems have an increased risk of thromboembolic events. The results of our research may have several clinical implications for the treatment of systemic vasculitis, and the most important objective of this research is to increase awareness of the risks for TE development. In addition to that, the objective is to propagate the performance of additional clinical trials in order to determine the need for the introduction of prophylactic anticoagulant and/or antiplatelet therapy for the prevention of TE event development.

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

fibrinogen povećavaju se postupno s godinama (24,28). U našem istraživanju tromboembolijski događaji pojavili su se u bolesnika koji su mlađe životne dobi, a moguće objašnjenje leži u većoj aktivnosti bolesti i zahvaćenosti više organskih sustava u mlađih pacijenata u odnosu na stariju populaciju.

U našem istraživanju u bolesnika s vaskulitisom ograničenim na kožu nije zabilježen niti jedan tromboembolijski incident. Pretraživanjem dosadašnje literature nije nađeno istraživanje koje bi usporedilo pojavnost tromboembolijskih incidenata bolesnika s vaskulitisima ograničenim na kožu. Prema našim saznanjima, prvi smo koji smo prijavili povećan rizik tromboembolijskih incidenata u sistemskim vaskulitisima u odnosu na vaskulitise ograničene na kožu, stoga nismo uspjeli usporediti naše rezultate.

Ograničenje ovog istraživanja jest mali uzorak ispitanika, budući da se radi o istraživanju bolesti s malom incidencijom provedenom u jednom centru; bilo bi poželjno proširiti ga uključivanjem više centara u istraživanje. Osim toga, ograničenje studije je i retrospektivno istraživanje. Također, s obzirom na to da je genetska dijagnostika hereditarne trombofilije rađena samo kod pacijenata s dokazanim TE događajem, u budućim ispitivanjima bilo bi potrebno utvrditi učestalost hereditarne trombofilije među svim ispitanicima.

ZAKLJUČAK

Naše istraživanje pokazuje da bolesnici sa sistemskim vaskulitisom mlađe životne dobi uz visoku aktivnost bolesti i zahvaćanje više organskih sustava imaju povećan rizik za nastanak tromboebolijskih događaja. Rezultati našeg istraživanja mogu imati nekoliko kliničkih implikacija za liječenje sistemskih vaskulitisa, a najvažniji cilj ovog istraživanja jest povećati svijest o rizicima za TE, te potaknuti dodatne kliničke studije kako bi se utvrdila potreba profilaktičkog uvođenja antikoagulantne i/ili antiagregacijske terapije u svrhu sprječavanja razvoja TE događaja.

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

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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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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-

UVOD

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.

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REVIEW PAPER PREGLEDNI RAD

DIAGNOSIS AND CLASSIFICATION CRITERIA OF SJÖGREN'S SYNDROME

DIJAGNOZA I KLASIFIKACIJSKI KRITERIJI SJÖGRENOVOG SINDROMA

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Abstract

Sjögren's syndrome (SS) is a chronic, systemic autoimmune disease of unknown aetiology that manifests with various clinical manifestations. It is characterized by dense lymphocytic infiltration of exocrine glands which leads to functional impairment. Involvement of the salivary and lacrimal glands, and the consequent dryness of the eyes and mouth, are among the most common clinical manifestations of the disease. SS may occur as a primary disease or secondary to another organ-specific autoimmune disease or overlap with other rheumatic conditions. The disease is named after the Swedish ophthalmologist Henrik Sjögren. The diagnosis of SS is made based on clinical and laboratory indicators and objective findings of involvement of the salivary glands and lacrimal glands. In clinical practice, classification criteria often help in making a diagnosis, although they were initially developed and validated to standardize a cohort of patients for inclusion in the clinical trials and studies. Over the years, more than ten different classification criteria for SS have been proposed. In 1993, the first multicentric preliminary European classification criteria for SS were proposed. These criteria were subsequently revised by the American-European Consensus Group (AECG) in 2002. In 2012, the new modified classification criteria of the American College of Rheumatology (ACR) for SS were published, which did not provide any significant diagnostic changes. The 2016 criteria of the ACR and the European Alliance of Associations for Rheumatology (EULAR) are currently used for the classification of the disease. A significant shift with the new criteria is that symptoms of dry eyes or mouth are not necessary for classification, and it is sufficient to have only one of the systemic manifestations of the disease.

Key words: Sjögren's syndrome, diagnosis, classification criteria

Sažetak

Sjögrenov sindrom (SS) je kronična, sustavna autoimunosna bolest nepoznate etiologije koja se manifestira širokim rasponom kliničkih očitovanja. Histološki je karakterizirana gustom limfocitnom infiltracijom egzokrinih žlijezda, što pridonosi oštećenju njihove funkcije. Zahvaćanje žlijezda slinovnica i suznih žlijezda te posljedična suhoća očiju i usta spadaju u najčešće kliničke manifestacije bolesti. SS se može pojaviti kao primarna bolest ili sekundarno uz drugu organ-specifičnu autoimunu bolest te u preklapanju s drugim reumatološkim stanjima. Bolest je ime dobila po švedskom oftalmologu Henriku Sjögrenu. Dijagnoza SS-a postavlja se na temelju kliničkih i laboratorijskih pokazatelja te objektivnih nalaza zahvaćenosti žlijezda slinovnica i suznih žlijezda. Najčešće u kliničkoj praksi za postavljanje dijagnoze pomažu klasifikacijski kriteriji, iako su oni prvotno razvijeni i validirani u svrhu standardiziranja kohorti bole-

snika za uključivanje u klinička ispitivanja i studije. Tijekom godina je predloženo više od deset različitih klasifikacijskih kriterija za SS. Godine 1993. predloženi su prvi multicentrični preliminarni europski klasifikacijski kriteriji za SS. Te kriterije naknadno je revidirala 2002. godine Američko-europska grupa stručnjaka (AECG – prema engl. *American-European Consensus Group*). Godine 2012. objavljeni su novi, dosta izmijenjeni klasifikacijski kriteriji Američkoga reumatološkog društva za SS koji nisu donijeli velikih dijagnostičkih pomaka. Za klasifikaciju bolesti trenutno se koriste kriteriji iz 2016. godine Američkog reumatološkog društva (ACR – prema engl. American College of Rheumatology) i Europskog saveza udruga za reumatologiju (EULAR – prema engl. *European Alliance of Associations for Rheumatology*). Značajna je izmjena u novim kriterijima da za klasifikaciju nije nužna prisutnost simptoma suhoće očiju ili usta, već je dovoljno imati neku od sustavnih manifestacija bolesti.

Ključne riječi: Sjögrenov sindrom, dijagnoza, klasifikacijski kriteriji

INTRODUCTION

Sjögren's syndrome (SS) is a chronic systemic autoimmune inflammatory disease characterised by dense lymphocytic infiltration of the exocrine glands, as well as other tissues and organs (1). Depending on whether it is a case of an isolated entity or an entity within another systemic inflammatory disease, it is divided into primary (pSS) and secondary Sjögren's syndrome (sSS) (1). Sjögren's syndrome is a disease with extremely heterogeneous clinical features and a variable course and prognosis. There is no single clinical, pathological or radiological marker that would serve as a "gold standard" for the diagnosis or classification of the disease. Involvement of the salivary and lacrimal glands, and the consequent dryness of the eyes and lack of saliva are among the most common clinical manifestations of the disease. The course and long-term prognosis of the disease as well as the clinical features depend on the distribution of inflammatory activity. Symptoms of dryness, pain and fatigue are benign manifestations of the disease that are present in the majority of patients and significantly affect the quality of life, while severe systemic manifestations occur in 20 to 40% of patients, and some patients will also present with lymphoma (2,3). SS is a relatively common autoimmune disease, the second most common after rheumatoid arthritis (1,4). In over 95% of cases, patients with primary SS are women(5), and the ratio of female to male patients varies depending on different studies, from 20:1 to 9:1 in favour of the female gender. It most often occurs in patients who are in their 40s or 50s (1). The prevalence of secondary SS depends on the diseases with which it occurs. Thus, the prevalence of sSS in systemic lupus erythematosus varies from 6.5 to 19%, in rheumatoid arthritis from 4 to 31%, and in systemic sclerosis from 14 to 20.5%. In patients with rheumatoid arthritis, it usually occurs as a late manifestation of the disease, while in patients with systemic lupus erythematosus, SS precedes the diagnosis of lupus by about two years. It is not uncommon that sSS also occurs as part of autoimmune events specific to a particular organ, such as primary biliary cirrhosis and Graves' disease. (1).

Although the drugs used can relieve the symptoms and prevent the development of complications in this

UVOD

Sjögrenov sindrom (SS) je kronična sustavna autoimunosna upalna bolest koja je obilježena gustom limfocitnom infiltracijom egzokrinih žlijezda, ali i drugih tkiva i organa (1). Ovisno o tome radi li se o izoliranom entitetu ili entitetu u sklopu druge sustavne upalne bolesti, dijelimo ga na primarni (pSS) i sekundarni Sjögrenov sindrom (sSS) (1). Sjögrenov sindrom je bolest izrazito heterogene kliničke slike te varijabilnog tijeka i prognoze. Ne postoji jedan klinički, patološki ili radiološki znak koji bi služio kao „zlatni standard" za dijagnozu ili klasifikaciju bolesti. Zahvaćanje suznih žlijezda i žlijezda slinovnica te posljedična suhoća očiju i manjak sline ubrajaju se u najčešće kliničke manifestacije bolesti. Tijek i dugoročna prognoza bolesti kao i klinička slika ovise o distribuciji upalne aktivnosti. Simptomi suhoće, bol i umor su dobroćudne manifestacije bolesti koje su prisutne u većine oboljelih i značajno utječu na kvalitetu života, dok se u 20 – 40% bolesnika javljaju teške sustavne manifestacije, a dio bolesnika će se prezentirati i limfomom (2,3). SS je relativno česta autoimunosna bolest, druga po učestalosti nakon reumatoidnog artritisa (1,4). U više od 95% slučajeva oboljeli od primarnog SS-a su žene (5), a odnos ženskih i muških bolesnika varira ovisno o različitim studijama, od 20:1 do 9:1 u korist žena. Najčešće se javlja u 4. i 5. desetljeću života (1). Prevalencija sekundarnog SS-a ovisi o bolestima uz koje se javlja. Tako prevalencija sSS-a u sistemskom eritematoznom lupusu varira od 6,5% do 19%, u reumatoidnom artritisu od 4% do 31%, a u sistemskoj sklerozi od 14% do 20,5%. U bolesnika s reumatoidnim artritisom obično se javlja kao kasna manifestacija bolesti, dok u bolesnika sa sistemskim eritematoznim lupusom SS prethodi dijagnozi lupusa za oko dvije godine. Nerijetko se sSS javlja i u sklopu autoimunosnih zbivanja specifičnih za pojedini organ poput primarne bilijarne ciroze i Gravesove bolesti (1).

Iako primijenjeni lijekovi mogu olakšati simptome i spriječiti razvoj komplikacija u sklopu ove bolesti, često ne dovode do zadovoljavajuće remisije, odnosno izlječenja. Međutim, razvoj novih terapijskih opcija za liječenje raznih autoimunosnih bolesti pa tako i SS-a te

disease, they often do not lead to a satisfactory remission or cure. However, the development of new therapeutic options for the treatment of various autoimmune diseases, including SS, and numerous clinical trials have highlighted the need for a better definition and earlier recognition of this disease.

HISTORY OF SJÖGREN'S SYNDROME

Anecdotal records of the condition we know today as Sjögren's syndrome date back to the second half of the 19th century. In 1882, in his lecture "On the origin of retinal detachment", Thomas Leber described three patients with dry inflammation of the cornea and conjunctiva with the formation of filaments, and he called this condition filamentary keratitis (6). Although he did not associate it with ocular surface dryness, his observations played an important role in the later definition of SS. In the late 1880s, Hutchinson and Hadden independently published reports of patients with severe dry mouth and consequent oral complications. Hutchinson is the author of the term "xerostomia" (6–8). Polish surgeon Johann Mikulicz-Radecki was born in 1892. described the case of a patient with painless symmetrical enlargement of the lacrimal and salivary glands, and the histopathological record of the salivary gland samples today fits the clinical features of MALT lymphoma (mucosa-associated lymphoid tissue) infiltration. In the mid-20s of the 20th century, the dermatologist Gougerot described the cases of three patients with progressive and chronic dryness of the mouth due to atrophy of the salivary glands and associated dryness of the eyes, nose, larynx and vagina. At the end of the 1920s, Houwer described cases of patients with chronic and bilateral filamentary keratitis, and half of these patients also suffered from associated arthritis. (7,8).

Although numerous authors "paved the way" for Henrik Sjögren, he was the only one who concluded that it is a systemic disease and not just an ocular disorder in his 1933 doctoral dissertation "Zur Kenntnis der Keratoconjunctivitis Sicca Keratitis filiformis bei hypofunction der Tranendriisen". He came to the above conclusions based on the follow-up of 19 patients with keratoconjunctivitis, 13 of whom also had associated arthritis. (8).

The opinion that it is an autoimmune disease first appeared in the 1950s, and this position was supported by Alspaugh's discovery of anti-SSA (anti-Ro) and anti-SSB (anti-La) antibodies. Through the efforts of a working group led by Haralampos Moutsopoulos in the 1970s and 1980s, it was discovered that SS is a chronic autoimmune disease characterized by infiltration of exocrine glands with B and T-lymphocytes, that the risk of developing lymphoma is up to 44 times higher than in the general population, and that certain

brojna klinička ispitivanja istaknuli su potrebu boljeg definiranja i ranijeg prepoznavanja ove bolesti.

POVIJEST SJÖGRENOVOG SINDROMA

Anegdotalni opisi stanja koje danas poznajemo pod nazivom Sjögrenov sindrom datiraju iz druge polovice 19. stoljeća. Thomas Leber je 1882. godine u predavanju *O porijeklu ablacije retine* opisao i tri bolesnika sa suhom upalom rožnice i spojnice uz formiranje filamenata te je navedeno stanje nazvao filamentozni keratitis (6). Iako ga nije povezao sa suhoćom površine oka, njegova su zapažanja odigrala važnu ulogu u kasnijoj definiciji SS-a. Krajem 1880-ih Hutchinson i Hadden, neovisno jedan o drugom, objavili su prikaze bolesnika s teškom suhoćom usta i posljedičnim oralnim komplikacijama. Hutchinson je autor pojma „kserostomija" (6–8). Poljski je kirurg Johann Mikulicz-Radecki 1892. godine opisao slučaj bolesnika s bezbolnim simetričnim povećanjem suznih i slinovnih žlijezda, a patohistološki opis uzoraka slinovnica danas se uklapa u sliku infiltracije MALT limfomom (engl. *mucosa-associated lymphoid tissue*). Sredinom 20-ih godina 20. stoljeća dermatolog Gougerot je opisao slučajeve troje bolesnika s progresivnom i kroničnom suhoćom usta uslijed atrofije slinovnica te pridruženom i suhoćom očiju, nosa, grkljana i vagine. Krajem 1920-ih Houwer opisuje slučajeve bolesnika s kroničnim i obostranim filamentoznim keratitisom od kojih polovica ima i pridruženi artritis (7,8).

Iako su brojni autori „utrli put" Henriku Sjögrenu, tek je on u svojoj doktorskoj disertaciji *Zur Kenntnis der Keratoconjunctivitis Sicca Keratitis filiformis bei hypofunction der Tranendriisen* iz 1933. godine zaključio da je riječ o sustavnoj bolesti, a ne samo o okularnom poremećaju. Do navedenih je zaključaka došao temeljem praćenja 19 bolesnica s keratokonjunktivitisom sika od kojih je 13 imalo i pridruženi artritis (8).

Mišljenje da je riječ o autoimunosnoj bolesti prvi put se javlja 1950-ih, a ta postavka je potkrijepljena Alspaughovim otkrićem protutijela anti-SSA (anti-Ro) i anti-SSB (anti-La) protutijela. Naporima radne skupine pod vodstvom Haralamposa Moutsopulosa 1970-ih i 1980-ih godina otkriveno je da je SS kronična autoimunosna bolest karakterizirana infiltracijom egzokrinih žlijezda B i T-limfocitima, da je rizik razvoja limfoma i do 44 puta veći u odnosu na opću populaciju te da se može govoriti o primarnom i sekundarnom SS-u ovisno o prisutnosti ili odsutnosti pridružene sustavne kolagenoze (8).

POSTAVLJANJE DIJAGNOZE SJÖGRENOVOG SINDROMA

Raznolikost i kompleksnost kliničke slike SS-a otežava dijagnostički i terapijski proces. Postavljanje dija-

characteristics could point to a case of primary and secondary SS depending on the presence or absence of associated systemic collagenosis (8).

ESTABLISHING DIAGNOSIS OF SJÖGREN'S SYNDROME

The diversity and complexity of the clinical features of SS complicates the process of diagnosis and therapy. The diagnosis of SS is often delayed, and the disease is often misdiagnosed as another autoimmune disease, most often systemic lupus erythematosus or rheumatoid arthritis. Certain subtypes of the disease (especially those without sicca symptoms) are more challenging to establish an accurate diagnosis, and due to a lack of understanding of the entire spectrum, the disease may remain undiagnosed. The diagnosis of SS should be suspected in individuals with persistent symptoms of dry eyes or oral cavity, enlargement of the parotid glands, and pathological findings of serological tests (e.g. anti-SS-A, anti-SS-B, rheumatism factor, hyperglobulinemia)(9). Dryness of the mouth often leads to a significant worsening of cavities, especially in the area of chewing surfaces or tooth cervix, hyperlobulated tongue (Figure 1), chronic erythematous oral candidiasis.

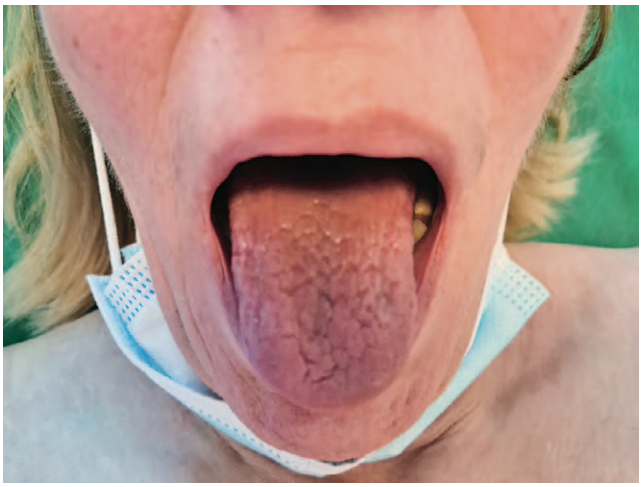


Figure 1 Dry mouth and hyperlobulated tongue in patient with primary Sjögren's syndrome (author's personal arhive)
Slika 1. Suhoća usta i hiperlobulirani jezik u bolesnice s primarnim Sjögrenovim sindromom (vlastita arhiva autora)

Making a diagnosis only on the basis of positive SS-A and SS-B antibodies is not advisable, considering that the said antibodies can be detected in other autoimmune diseases, but also in healthy individuals (10). Although medicine advances every day with the development of new diagnostic methods and tools, there is still no single diagnostic test that would confirm or exclude the diagnosis of SS, but it is established based on a combination of clinical and laboratory indicators.

gnoze SS-a često je zakašnjelo, a bolest se nerijetko pogrešno dijagnosticira kao druga autoimunosna bolest, najčešće sistemski eritematozni lupus ili reumatoidni artritis. Određeni podtipovi bolesti (pogotovo oni bez sika-simptoma) izazovniji su za postavljanje točne dijagnoze, a zbog nerazumijevanja cijelog spektra bolest može ostati i nedijagnosticirana. Na dijagnozu SS-a treba posumnjati kod pojedinaca s trajno prisutnim simptomima suhoće očiju ili usne šupljine, uvećanja parotidnih žlijezda te patoloških nalaza serološkim testova (npr. anti SS-A, anti-SS-B, reuma faktora, hiperglobobulinemije) (9). Suhoća usta nerijetko dovodi do izrazitog pogoršanja karijesa, posebice u području zagriznih ploha ili zubnih vratova, hiperlobuliranog jezika (slika 1) i kronične eritematozne oralne kandidijaze.

Postavljanje dijagnoze samo na temelju pozitivnih protutijela SS-A i SS-B protutijela nije uputno s obzirom na to da se navedena protutijela mogu detektirati kod drugih autoimunosnih bolesti, ali i kod zdravih osoba (10). Iako medicina svakodnevno napreduje uz razvoj novih dijagnostičkih metoda i sredstava, još uvijek ne postoji jedinstveni dijagnostički test kojim bi se potvrdila ili isključila dijagnoza SS-a, već se ona postavlja na temelju kombinacije kliničkih i laboratorijskih pokazatelja.

Dijagnoza SS-a postavlja se kod objektivnih pokazatelja suhoće oka i/ili usta ili oštećenja žljezdanog parenhima (nakon isključenja drugih mogućih uzroka) uz prisutnost serološkog ili histološkog dokaza autoimunosti. U pojedinim dobnim skupinama klasična klinička slika SS-a varira, pa je tako u djece znatno češća prisutnost rekurentnog parotitisa, dok objektivni pokazatelji suhoće očiju i usta nisu uvijek prisutni (11). Novija multicentrična studija na velikom broju bolesnika pokazala je da su mladi bolesnici (do 35. godine starosti) imali veću učestalost povećanja slinovnica, limfadenopatije, leukopenije, hipokomplementemije te hipergamaglobulinemije i limfoma u odnosu na kontrolnu populaciju bolesnika sa Sjögrenovim sidromom koji su bili srednje dobi. Stariji su bolesnici (dob iznad 65. godine) imali češće sika-simptome i intersticijsku patologiju pluća te također veću pojavnost limfoma (12). Poznato je da oko 20% bolesnika neće razviti sika-simptome, već će se prezentirati šarolikom paletom sustavnih manifestacija (2,4,5). Većina sustavnih manifestacija uključena je u *Indeks aktivnosti Sjögrenovog sindroma* (ESSDAI – prema engl. EULAR *Sjögren's syndrome disease activity index*). Nova istraživanja pokazuju da više od četvrtine bolesnika s pSS-om može imati manifestacije koje nisu obuhvaćene navedenim indeksom od kojih je najčešći Raynaudov sindrom koji je u nedavnom istraživanju bio prisutan u 15% bolesnika (5). Nadalje, brojni radovi pokazuju da se sustavne manifestacije mogu javiti i znatno prije sika-simptoma, što često značajno odgađa postavljanje točne dija-

Table 1 Questionnaire on dry mouth and eyes with suspected Sjögren's syndrome. (adapted according to reference No 16)
Tablica 1. Upitnik o suhoći usta i očiju kod sumnje na Sjögrenov sindrom (prilagođeno prema referenciji br. 16)

Questions about the symptoms of tear gland involvement / Pitanja o simptomima zahvaćanja suznih žlijezda	Questions about the symptoms of salivary gland involvement / Pitanja o simptomima zahvaćanja žlijezda slinovnica
1. Have you had daily, persistent, problematic dry eyes for > 3 months? / Jeste li imali svakodnevnu, trajnu, problematičnu suhoću očiju >3 mjeseca?	1. Have you had a daily feeling of dry mouth > 3 months? / Jeste li imali svakodnevni osjećaj suhoće usta >3 mjeseca?
2. Do you have a recurrent sensation of sand or gravel in the eyes? / Imate li ponavljajući osjećaj pijeska ili šljunka u očima?	2. Do you have to wake up at night to drink water because of dry mouth? / Morate li se buditi noću piti vodu zbog suhoće usta?
3. Do you use tear substitutes more than 3 times a day? / Koristite li umjetne suze?	3. Do you frequently drink liquids to aid in swallowing dry foods? / Pijete li često tekućinu za lakše gutanje hrane?
	4. Have you had recurrent or permanently swollen salivary glands as an adult? / Jeste li imali ponavljajuće ili trajno otečene žlijezde slinovnice u odrasloj dobi?

The diagnosis of SS is established with objective indicators of dry eyes and/or mouth or damage to the glandular parenchyma (after excluding other possible causes) with the presence of serological or histological evidence of autoimmunity. In certain age groups, the standard clinical features of SS varies, so the presence of recurrent parotitis is much more common in children, while objective indicators of dry eyes and mouth are not always present (11). A recent multicentre trial conducted on a large number of patients showed that young patients (up to 35 years of age) had a higher frequency of salivary gland enlargement, lymphadenopathy, leukopenia, hypocomplementemia, and hypergammaglobulinemia and lymphoma compared to a control population of middle-aged patients with Sjögren's syndrome. Older patients (over the age of 65) had more frequent sicca symptoms and interstitial lung pathology, as well as a higher incidence of lymphoma (12). It is known that about 20% of patients will not develop sicca-symptoms, but will present themselves with a colourful palette of systemic manifestations. (2,4,5). Most systemic manifestations are included in the Sjögren's syndrome disease activity index (ESSDAI, EULAR Sjögren's syndrome disease activity index). New research shows that more than a quarter of patients with pSS may have manifestations that are not covered by the mentioned index, the most common of which is Raynaud's syndrome, which was present in 15% of patients according to a recently conducted research (5). Furthermore, numerous works show that systemic manifestations can occur well before sicca symptoms, which often significantly delays the establishment of an accurate diagnosis (13). However, due to the non-specificity of systemic manifestations, the diagnosis can be made in the case of a positive finding of anti-SSA antibodies and other laboratory indicators characteristic of the disease.

Typical sicca symptoms will often be present in pSS at the time of diagnosis, and the percentage of patients varies between 86–95% in published studies (5,12). Other clinical manifestations that occur in more than 10% of

gnoze (13). Međutim, zbog nespecifičnosti sustavnih manifestacija dijagnoza se može postavi u slučaju pozitivnog nalaza antitijela anti-SSA te drugih laboratorijskih pokazatelja karakterističnih za bolest.

Klasični će sika-simptomi često biti prisutni u pSS-u u trenutku postavljanja dijagnoze, a postotak bolesnika varira u objavljenim studijama između 86 i 95% (5,12). Ostale kliničke manifestacije koje se javljaju u više od 10% bolesnika s pSS-om su zglobne (41%), plućne manifestacije (12%), limfadenopatija (11%), opći simptomi, umor te u 10% slučajeva kožne manifestacije poput palpabilne purpure potkoljenica (5,14). Zahvaćanje perifernoga živčanog sustava (periferna neuropatija) javlja se u 10% bolesnika, zahvaćanje bubrega u oko 5%, dok se kronični gastritis i disfagija pojavljuju u oko 2 – 3% bolesnika. Prema dostupnim studijama procjene zahvaćanja središnjega živčanog sustava značajno variraju, jer nema jasno postavljenih kriterija za dijagnozu (15).

Na simptome suhoće oka u sklopu sika-sindroma treba posumnjati kada bolesnici navode svakodnevne tegobe s očima u trajanju više od tri mjeseca, kontinuirano imaju osjećaj pijeska ili stranog tijela u očima te ako trebaju koristiti umjetne suze više od tri puta dnevno. Kserostomija i simptomi sijaloadenitisa suspektni su ako bolesnici navode osjećaj suhoće usta u trajanju više od tri mjeseca, buđenje noću kako bi popili vode, konzumaciju tekućine kako bi mogli jesti suhu hranu te epizodno ili konstantno oticanje u području slinovnica (16). U svrhu ispitivanja sika-simptoma napravljen je validirani upitnik (16) koji je prikazan u tablici 1.

Naravno, ovakve su tegobe subjektivne naravi te ih je za postavljanje dijagnoze nužno objektivizirati. Tri najčešće pretrage za objektiviziranje suhog oka jesu: Schirmerov test, test vremena pucanja suznog filma (TBUT – engl. *tear break-up time*) i ocjena bojenja površine oka (OSS – engl. *ocular staining test*) (9). OSS i Schirmerov test čine dva kriterija u zajedničkim kriterijima EULARA-a i ACR-a. iz 2016. godine (17). Kse-

patients with pSS are joint manifestations (41%), pulmonary manifestations (12%), lymphadenopathy (11%), general symptoms, fatigue and in 10% of cases skin manifestations such as palpable purpura of the lower legs (5,14). Involvement of the peripheral nervous system (peripheral neuropathy) occurs in 10% of patients, kidney involvement in about 5%, while chronic gastritis and dysphagia occur in about 2–3% of patients. According to the available studies, estimates of involvement of the central nervous system vary significantly, as there are no clearly established criteria for diagnosis (15).

Symptoms of dry eye as part of sicca syndrome should be suspected when patients report daily eye problems lasting more than 3 months, have a continuous feeling of sand or a foreign body in the eyes, and if they need to use artificial tears more than 3 times a day. Xerostomia and symptoms of sialoadenitis are suspected if patients report a feeling of dry mouth lasting more than 3 months, waking up at night to drink water, consuming liquids to be able to eat dry food, and episodic or constant swelling in the salivary gland area (16). For the purpose of examining sicca symptoms, a validated questionnaire (16) was created, which is shown in the Table 1.

Of course, these complaints are subjective in nature and it is necessary to objectivize them in order to establish a diagnosis. The three most common tests for the objectivization of dry eye: Schirmer's test, tear break-up time test (TBUT) and ocular staining test (OSS) (9). OSS and Schirmer's test are two criteria in the 2016 joint criteria of EULAR and ACR. (17). Xerostomia and salivary gland changes are objectivized by sialometry, imaging methods and biopsy (18). Sialometry is used to quantify or measure the amount of saliva produced. If 0.1 mL of saliva or less is secreted in one minute without stimulation, the criteria for xerostomia are met. The sensitivity of sialometry is 56%, and the specificity is 81%. (9). It should be kept in mind that sialometry is not valid if the patient is chronically taking drugs with anticholinergic effects such as some antihistamines, benzodiazepines, antidepressants. Technetium Tc-99m pertechnetate salivary scintigraphy and contrast sialography are no longer frequently used. The imaging methods that are preferred today are magnetic resonance imaging and easily available ultrasound, and they are supported by the specificity for SS greater than 90%, i.e. 93% and 92% respectively in the case of an ultrasound (19). The advantage of ultrasound is that it can be used in diagnosis, but also in disease follow-up. Moreover, salivary gland ultrasound has been shown to be a diagnostic tool comparable to salivary gland biopsy. Biopsy, i.e. histopathological analysis of small salivary glands (sensitivity 80%, specificity 82%) is still the gold standard in the diagnosis of SS, and in the 2016 classification criteria it has the highest number of points (17). Sialometry and biopsy are the only methods listed in the latest classification criteria for assessing salivary gland function (17). Laboratory, sero-

Table 2 Laboratory, serological, radiological and histopathological findings characteristic of the diagnosis of Sjögren's syndrome.

Tablica 2. Laboratorijski, serološki, radiološki i patohistološki nalazi karakteristični za dijagnozu Sjögrenovog sindroma

Laboratory findings / Laboratorijski nalazi: • ESR, CRP / **SE**, CRP • CBC, biochemical findings, urine / KKS, biokemijski nalazi, urin • **hypergammaglobulinemia**/hypogammaglobulinemia / **hipergamaglobulinemija**/hipogamaglobulinemija • C3, C4
Serological evidence of autoimmunity / Serološki dokaz autoimunosti: • **ANA** • **SSA** +/– SSB antibodies (50–70%) / **protutijela SSA** +/– SSB (50 – 70%) • RF (40–50%) • cryoglobulinemia / krioglobulinemija • anticentromere antibodies / anticentromerna protutijela
Objective evidence of dryness of the eyes or mouth or involvement of the glandular parenchyma / Objektivni dokaz suhoće očiju ili usta ili zahvaćanja žljezdanog parenhima • Schirmer test, TBUT, OSS, unstimulated salivation ≤0,1 mL/min / Schirmerov test, TBUT, OSS, nestimulirano lučenje sline ≤0,1 mL/min • MR or US evidence of gland parenchyma changes characteristic of SSj / MR ili UZV dokaz promjena parenhima žlijezda karakerističnih za SS • **salivary gland biopsy** with focal lymphocytic sialadenitis and focus score ≥ 1 focus / 4 mm^2 / **biopsija žlijezda slinovnica** s fokalnim limfocitnim sijaladenitisom i fokus skorom ≥ 1 fokus /4 mm^2

Legend / Legenda: ESR / SE – erythrocyte sedimentation rate / brzina sedimentacije eritrocita; CRP – C reactive protein / C-reaktivni protein; CBC / KKS – complete blood count / kompletna krvna slika; C3, C4 – complement / komplement; ANA – antinuclear antibodies / antinuklearna antitijela; RF – rheumatoid factor / reumatoidni faktor; TBUT – tear break-up time; OSS – ocular staining score / ocjena bojenja površine oka; MR – magnetic resonance imaging / magnetska rezonancija; US / UZV – ultrasound / ultrazvuk

rostomija i promjene slinovnica objektiviziraju se sijalometrijom, slikovnim metodama te biopsijom (18). Sijalometrija se koristi za kvantificiranje odnosno mjerenje količine proizvedene sline. Ako se bez stimulacije u jednoj minuti luči 0,1 mL sline ili manje od toga, ispunjeni su kriteriji za kserostomiju. Osjetljivost je sijalometrije 56%, a specifičnost 81%. (9). Treba imati na umu da sijalometrija nije mjerodavna ako bolesnik kronično uzima lijekove s antikolinergičkim djelovanjem poput nekih antihistaminika, benzodizepina, antidepresiva. Scintigrafija slinovnica tehnecij-pertehnetatom te kontrastna sijalografija više se ne koriste često. Slikovne metode koje se danas preferiraju jesu magnetska rezonancija te lako dostupan ultrazvuk, a u prilog im idu specifičnost za SS veća od 90%, tj. 93% odnosno 92% u slučaju ultrazvuka (19). Prednost ultrazvuka je to što se može koristiti u postavljanju dijagnoze, ali i u praćenju bolesti. Štoviše, ultrazvuk slinovnica se pokazao kao dijagnostičko sredstvo usporedivo s biopsijom

logical, radiological and histopathological findings characteristic for the diagnosis of Sjögren's syndrome are presented in Table 2.

To establish a diagnosis, after the objectivization of sicca-symptoms or in the case of systemic manifestations of the disease, it is necessary to perform an immunoserological test. It should be emphasized that testing for the presence of autoantibodies should be used to confirm a working diagnosis, and not be used as a screening test, considering that a healthy part of the population may have a positive finding of autoantibodies. Therefore, in the context of objectivized sicca-symptoms and a negative finding of antinuclear antibodies (ANA), it is unlikely that this is a patient with SS. In addition to autoantibodies (ANA positive in over 85% of cases, anti-SSA in 50 to 70%, rheumatoid factor (RF) in 50 to 60%, anti-SSB in 33 to 50%), there are other laboratory indicators indicative of SS such as which are accelerated erythrocyte sedimentation rate in 80 to 90% of cases, hypergammaglobulinemia in 80%, anaemia of chronic disease in a quarter of cases and leukopenia in 10% of cases. Thrombocytopenia is rarely present. A rare serological finding is anticentromeric antibodies that can be detected in up to 5% of cases, without or only with some clinical characteristics for systemic sclerosis, and anti-CCP without other elements for rheumatoid arthritis (20). New research shows the importance of new antibodies in predicting certain disease manifestations and long-term complications, which could have great clinical significance in the future (21).

Part of the patients will be diagnosed in the stage of developed lymphoproliferative disease, considering that compared to other systemic inflammatory diseases, SS has the highest risk for the development of lymphoma, according to the standardized incidence of 9 to 44 or 5 to 15, depending on whether these were published before the year 2000 or in the later period. The most common histological subtype of lymphoma are MALT lymphomas (2). Certain clinical and laboratory characteristics are associated with an increased risk of developing lymphoma. Due to the large clinical spectrum of this disease, the differential diagnosis of Sjögren's syndrome is very broad and includes other systemic autoimmune diseases (primarily systemic lupus erythematosus and rheumatoid arthritis), infections (hepatitis C virus (HCV), human immunodeficiency virus (HIV), cytomegalovirus (CMV), various non-autoimmune causes of dry mouth or eyes (age, medications), IgG4-related disease, sarcoidosis, amyloidosis, lymphoma, Graft vs. Host Disease (GVHD) and other diseases.

CLASSIFICATION CRITERIA OF SJÖGREN'S SYNDROME

Classification criteria that were originally developed and validated for the purpose of standardizing cohorts

slinovnica. Biopsija, odnosno patohistološka analiza malih žlijezda slinovnica (osjetljivost 80%, specifičnost 82%) i dalje je zlatni standard u postavljanju dijagnoze SS-a te u klasifikacijskim kriterijima iz 2016. nosi najveći broj bodova (17). Sijalometrija i biopsija su jedine od svih nabrojanih metoda za procjenu funkcije žlijezda slinovnica sadržane u najnovijim klasifikacijskim kriterijima (17). Laboratorijski, serološki, radiološki i patohistološki nalazi karakteristični za dijagnozu Sjögrenovog sindroma prikazani su u tablici 2.

Za postavljanje dijagnoze, nakon objektivizacije sika-simptoma ili u slučaju sustavnih očitovanja bolesti potrebno je učiniti imunoserološko testiranje. Potrebno je naglasiti da testiranje prisutnosti autoantitijela treba koristiti za potvrdu radne dijagnoze, a ne koristiti kao probirni test s obzirom na to da zdravi dio populacije može imati pozitivan nalaz autoantitijela. Stoga je u kontekstu objektiviziranih sika-simptoma i negativnog nalaza antinuklearnih antitijela (ANA) malo vjerojatno da je riječ o bolesniku sa SS-om. Osim autoantitijela (ANA pozitivna u više od 85% slučajeva, anti-SSA u 50 – 70%, reumatoidni faktor (RF) u 50 – 60%, anti-SSB u 33 – 50%), postoje i drugi laboratorijski pokazatelji indikativni za SS kao što su ubrzana sedimentacija eritrocita u 80 – 90% slučajeva, hipergamaglobulinemija u 80%, anemija kronične bolesti u četvrtini slučajeva i leukopenija u 10% slučajeva. Trombocitopenija je rijetko prisutna. Rijedak serološki nalaz jesu anticentromerna protutijela koja se mogu detektirati u do 5% slučajeva, bez kliničkih karakteristika za sistemsku sklerozu ili tek s nekima od njih, te anti-CCP bez drugih elemenata za reumatoidni artritis (20). Nova istraživanja pokazuju važnost novih protutijela u predviđanju pojedinih manifestacija bolesti te dugoročnih komplikacija, što bi moglo imati velik klinički značaj u budućnosti (21).

Dijelu bolesnika dijagnoza će biti postavljena u fazi razvijene limfoproliferativne bolesti, s obzirom na to da SS u usporedbi s drugim sistemskim upalnim bolestima ima najviši rizik za razvoj limfoma i to prema standardiziranoj incidenciji od 9 do 44 odnosno od 5 do 15, ovisno je li riječ o studijama prije ili poslije 2000. godine. Najčešći histološki podtip limfoma jesu MALT limfomi (2). Pojedine kliničke i laboratorijske karateristike povezane su s povećanim rizikom razvoja limfoma. Diferencijalna dijagnoza Sjögrenovog sidroma vrlo je široka zbog velikoga kliničkog spektra ove bolesti i obuhvaća druge sustavne autoimune bolesti (prvenstveno sistemski eritematozni lupus i reumatoidni artritis), infekcije (virus hepatitisa C [HCV], virus humane imunodeficijencije [HIV – prema engl. *human immunodeficiency virus*], citomegalo virus [CMV]), različite neautoimune uzroke suhoće usta ili očiju (starost, lijekovi), bolest IgG4, sarkoidozu, amiloidozu, limfom, bolest presatka protiv primatelja (GVHD – prema engl. *graft versus host disease*) i drugo.

of patients for inclusion in clinical trials and studies, often serve as an aid in clinical practice when establishing a diagnosis. Given the extremely heterogeneous clinical features of SS, it is understandable why more than eleven different classification criteria for SS have been proposed over the years since 1960. Figure 2 shows the development of individual classification criteria for Sjögren's syndrome throughout history.

The classification criteria that were developed until 1993 were mostly based on the clinical experience of leading experts or on the data of individual centres, and therefore none of them were accepted by the wider scientific community (22,23). When it comes to the older criteria for the diagnosis of SS, the most used were: the San Francisco criteria (proposed in 1975 and subsequently revised in 1984), the Copenhagen criteria (proposed in 1976) and the Japanese criteria (published in 1978), as well as the Greek and the Californian criteria proposed in 1986. (22–27). The Japanese criteria have been updated several times, the last time being in 1999.

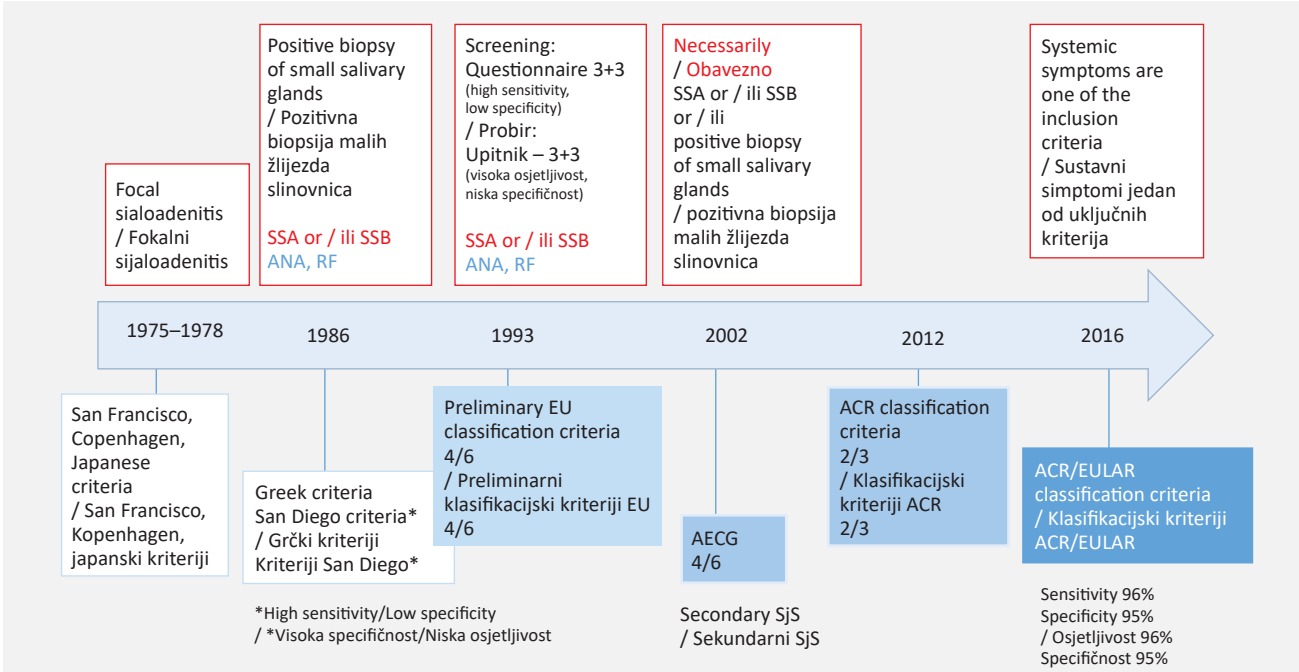
In the San Francisco criteria that were proposed in 1965, the introduction of a new diagnostic criterion was recommended – the presence of focal sialoadenitis in the biopsy samples of the minor salivary glands to determine the presence of the oral component of Sjögren's syndrome instead of the subjective assessment of xerostomia based on the presented research conducted on 100 patients (22). The criteria were revised in 1984, when it was confirmed in 362 patients that focal sialoadenitis in an adequate sample is an objective criterion specific for SS (23). The Copenhagen criteria required at least two pathological objective tests for the assessment of dry eye and mouth for classification (24). The first Japanese criteria were published in 1978 and were used in Japan for over 20 years. For classification, it was necessary to have a subjective feeling of dry mouth or eyes and at least one of the following: a) two pathological eye tests, b) focal sialoadenitis or c) abnormal sialography/scintigraphy (25). In the last revised Japanese criteria from 1999, which were formed as a result of the work of the Japanese working group for SS, it was not necessary to have subjective symptoms of dryness for classification, and serological findings and stimulated sialometry were introduced as criteria for assessing saliva secretion. These classification criteria contained four major components: histology, oral tests (sialography/scintigraphy/stimulated sialometry), ocular tests (Schirmer's test + Rose Bengal staining test/fluorescein) and serology (SS-A or SS-B). For classification, it was necessary to have at least two of the four criteria (28). According to the data recorded on 900 patients, it was estimated that the criteria have a sensitivity of 96%, a specificity of 90.5% and an accuracy for the diagnosis of SS of 94.5%. (28). These latest Japanese criteria were quite similar to the preliminary European classification criteria published 6 years

KLASIFIKACIJSKI KRITERIJI SJÖGRENOVOG SINDROMA

Klasifikacijski kriteriji koji su prvotno razvijeni i validirani u svrhu standardiziranja kohorti bolesnika za uključivanje u klinička ispitivanja i studije često služe kao pomoć u kliničkoj praksi pri postavljanju dijagnoze. S obzirom na izrazito heterogenu kliničku sliku SS-a razumljivo je zašto je tijekom godina predloženo više od jedanaest različitih klasifikacijskih kriterija za SS od 1960. godine. Na slici 2. prikazan je razvoj pojedinih klasifikacijskih kriterija za Sjögrenov sindrom kroz povijest, do 1993. god.

Klasifikacijski kriteriji koji su bili razvijeni do 1993. godine većinom su se bazirali na kliničkom iskustvu vodećih eksperata ili na podatcima pojedinih centara te stoga niti jedan od njih nije bio prihvaćen u široj znanstvenoj zajednici (22,23). Od kriterija starijeg datuma za dijagnozu SS-a najviše su se koristili: kriteriji San Francisco (predloženi 1975. i naknadno revidirani 1984. godine), kopenhagenski (predloženi 1976.) te japanski (objavljeni 1978.), grčki i kalifornijski kriteriji koji su predloženi 1986. godine. (22–27). Japanski kriteriji su u nekoliko navrata ažurirani, zadnji put 1999. godine.

U kriterijima San Francisco koji su predloženi 1965. godine preporučeno je uvođenje novog dijagnostičkog kriterija – prisutnost fokalnog sijaloadenitisa u uzorcima biopsije malih žlijezda slinovnica za utvrđivanje prisutnosti oralne komponente Sjögrenovog sindroma umjesto subjektivne procjene kserostomije na temelju prikazanog istraživanja provedenog na 100 bolesnika (22). Kriteriji su revidirani 1984. godine, kada je na 362 bolesnika potvrđeno da je fokalni sijaloadenitis u adekvatnom uzorku objektivan kriterij specifičan za SS (23). Kopenhagenski kriteriji za klasifikaciju su tražili najmanje dva patološka objektivna testa za procjenu suhoće oka i usta (24). Prvi japanski kriteriji objavljeni su 1978. godine i koristili su se u Japanu preko 20 godina. Za klasifikaciju je bilo potrebno imati subjektivan osjećaj suhoće usta ili očiju te najmanje jedno od slijedećeg: a) dva patološka očna testa, b) fokalni sijaloadenitis ili c) abnormalnu sijalografiju/scintigrafiju (25). U posljednjim revidiranim japanskim kriterijima iz 1999., koji su formirani kao rezultat rada japanske radne skupine za SS, za klasifikaciju nije bilo nužno imati subjektivne simptome suhoće, a kao kriterij uvedeni su serološki nalazi te stimulirana sijalometrija kao metoda procjene izlučivanja sline. Ti klasifikacijski kriteriji sadržavali su četiri velike komponente: histologiju, oralne testove (sijalografija/scintigrafija/stimulirana sijalometrija), očne testove (Schirmerov test + test Rose Bengal/florescein) te serologiju (SS-A ili SS-B). Za klasifikaciju je bilo potrebno imati najmanje dva od četiri kriterija (28). Prema podatcima napravljenim na 900 bolesnika procijenjeno je da kriteriji imaju osjetlji-



Legend /Legenda: ANA – antinuclear antibodies / antinuklearna antitijela; RF – rheumatoid factor / reumatoidni faktor; AECG – American-European Consensus Group / American-European Consensus Group; ACR – American Rheumatological Society / Američko reumatološko društvo; EULAR – European Association of Rheumatology Associations / Europski savez udruga za reumatologiju; SS – Sjögren's syndrome / Sjögrenov sindrom

Figure 2 Development of classification criteria for Sjögren syndrome throughout history
Slika 2. Razvoj klasifikacijskih kriterija za Sjögrenov sindrom kroz povijest

earlier. The Greek criteria published in 1986 were based on a study of 52 patients with sicca symptoms. According to them, for classification it was necessary to have focal sialoadenitis (≥2 focus/4 mm2) with one of the following criteria: a) subjective dryness of the eye plus a pathological finding of the Schirmer's test plus a pathological finding of the Rose Bengal staining test, b) anamnestic or current enlargement of the parotid glands and c) sensation of dry mouth and pathological finding of stimulated sialometry (26). The Californian criteria, also called the San Diego criteria, also published in 1986, are criteria of a more restrictive nature. According to these criteria, for the diagnosis it was necessary to have focal sialoadenitis (≥2 foci/4 mm2), a feeling of dry mouth with a pathological finding of stimulated and non-stimulated sialometry, a pathological finding of the Schirmer's test and one of the dye tests (Rose Bengal staining or fluorescein test) and a positive finding of one of the serological tests (IgM-RF [titer ≥ 160] or ANA [titer ≥ 160] or SS-A or SSB antibodies) (27). Exclusion criteria (lymphoma, chronic Graft vs. Host Disease – GVHD), acquired immunodeficiency syndrome, sarcoidosis are also listed in them for the first time. The differences and similarities of individual criteria up to 1993 are presented in Table 3.

In 1993, preliminary European classification criteria for SS were proposed (7). They were widely used for the next ten years, both in clinical practice and in ob-

vost 96%, specifičnost 90,5% te točnost za dijagnozu SS-a 94,5% (28). Ovi najnoviji japanski kriteriji dosta su sličili preliminarnim europskim klasifikacijskim kriterijima objavljenim šest godina ranije. Grčki kriteriji objavljeni 1986. godine napravljeni su na istraživanju 52 bolesnika sa sika-simptomima. Prema njima za klasifikaciju je bilo nužno imati fokalni sijaloadenitis (≥2 fokus/4 mm^2) uz neki od slijedećih kriterija: a) subjektivnu suhoću oka plus patološki nalaz Schirmerovog testa plus patološki nalaz Rose bengal testa, b) anamnestički ili trenutno povećanje parotidnih žlijezda i c) osjećaj suhoće usta i patološki nalaz stimulirane sijalometrije (26). Kalifornijski kriteriji koji se još nazivaju kriteriji San Diego, objavljeni također 1986., restriktivnije su naravi. Prema tim kriterijima za dijagnozu je bilo potrebno imati fokalni sijaloadenitis (≥2 fokus/4 mm^2), osjećaj suhoće usta uz patološki nalaz stimulirane i nestimulirane sijalometrije, patološki nalaz Schirmerovog testa i nekog od testa s bojama (Rose Bengal ili floresceinskog testa) te pozitivan nalaz nekog od seroloških testova (IgM-RF [titar ≥ 160] ili ANA [titar ≥ 160] ili SS-A ili SSB antitijela) (27). U njima su također po prvi put navedeni i isključni kriteriji (limfom, kronična bolest presatka protiv primatelja – GVHD, sindrom stečene imunodeficijencije, sarkoidoza). Razlike i sličnosti pojedinih kriterija do 1993. prikazane su u tablici 3.

Table 3 Differences and similarities of classification criteria proposed up to 1993 (adapted according to reference No 27)
Tablica 3. Razlike i sličnosti klasifikacijskih kriterija predloženih do 1993. godine (prilagođeno prema referenciji br. 27).

	San Francisco (1975, 1984)	Copenhagen (1976)	Japanese (1978)	Japanese (1999)	Greek (1986)	San Diego (1986)
References / Referenca	(22,23)	(24)	(25)	(28)	(26)	(27)
Subjective dryness of the eyes / Subjektivna suhoća oka	–	–	required / obvezna	–	+	–
Subjective dryness of the mouth / Subjektivna suhoća usta	–	–	required / obvezna	–	+	+
History of parotid gland swelling / Anamneza oticanja parotida	–	–	–	–	+	–
Ocular tests / Očni testovi:						
Schirmer's test / Schirmerov test	+ (< 10 mm /5 min)	+ (≤10 mm /5 min)	+ (≤10 mm /5 min)	+ (≤5 mm /5 min)	+ (≤5 mm /5 min)	+ (<9 mm /5 min)
Break-up time	+	+(≤10 s)	–	–	–	–
Rose Bengal	+	+(≥4)	+ (≥2)	+ (≥3)	+ (≥4)	+ (≥4)
Florescein test / Test floresceinom	–	–	+	+	–	+
Oral tests / Oralni testovi:						
Unstimulated whole saliva / Nestimulirano izlučivanje sline	+	+	–	–	–	+
Stimulated salivary flow / Stimulirano izlučivanje sline	–	–	+	+	+	+
Scintigraphy / Scintigrafija	–	+	–	+	–	–
Sialography / Sijalografija	–	–	+	+	–	–
Biopsy of small salivary glands / Biopsija malih žlijezda slinovnica	≥1 focus on 4 mm^2 / ≥1 fokus na 4 mm^2	≥1 focus / fokus /4 mm^2	≥1 focus on the lobe / ≥1 fokus po lobusu	≥1 focus / fokus /4 mm^2	≥2 focus / fokus /4 mm^2	≥2 focus / fokus /4 mm^2
Biopsy of small salivary gland mandatory criterion / Biopsija malih žlijezda slinovnica obvezan kriterij	Yes / Da	No / Ne	No / Ne	No / Ne	Yes / Da	Yes / Da
ANA	–	–	–	–	–	+
Anti-SSA	–	–	–	–	–	+
Anti-SSB	–	–	–	+	–	+
IgM-RF	–	–	–	+	–	+
pSS/sSS terminology / Terminologija pSS/sSS	+	+	–	–	+	–

Legend / Legenda: ANA – antinuclear antibodies / antinuklearna antitijela; IgM-RF – rheumatoid factor – imunoglobulin M / reumatoidni faktor imunoglobulin M; pSS – primary Sjögren's syndrome / primarni Sjögrenov sindrom; sSS – secondary Sjögren's syndrome / sekundarni Sjögrenov sidrom

servational and interventional studies. During the development of the classification criteria in 1993, a questionnaire on dry eyes and mouth was designed and validated, which is used in a minimally modified form in the current classification criteria. Three questions for dry eye and three questions for dry mouth were chosen, which had high sensitivity and low specificity and so well discriminated patients from controls and served as screening (Table 1) (7). For the classification of primary SS, the patient had to have four out of six criteria present. In addition to symptoms of dry eyes and mouth, the criteria included an objective finding of dry eye (Schirmer's test ≤ 5 mm/5 min, Rose Bengal

Godine 1993. predloženi su preliminarni europski klasifikacijski kriteriji za SS (7). Oni su se uvelike koristili sljedećih deset godina, kako u kliničkoj praksi, tako i u opservacijskim i intervencijskim studijama. Tijekom razvoja klasifikacijskih kriterija 1993. godine osmišljen je i validiran upitnik o suhoći oka i usta koji se u minimalno izmijenjenom obliku koristi i u trenutnim klasifikacijskim kriterijima. Izabrana su tri pitanja za suhoću oka te tri pitanja za suhoću usta koja su imala visoku osjetljivost i nisku specifičnost te tako dobro distingvirala bolesnike od kontrola i služila kao probir (tablica 1) (7). Bolesnik je za klasifikaciju primarnog SS-a trebao imati prisutna četiri od šest kriterija. Osim

score ≥ 4), then histological evidence of salivary gland involvement, one of the objective tests of salivary gland involvement (salivary gland scintigraphy, parotid sialography and unstimulated saliva secretion (≤ 1.5 ml/15 min) and serological proof of autoimmunity (presence of SSA or SSB antibodies, ANA or RF). Table 4 shows the differences and similarities of the classification criteria published from 1993 until today. Although the above classification criteria were widely accepted, they had several problems. A combination of ocular and oral symptoms and dry eye tests and salivary gland involvement tests could also be found in patients with sicca symptoms who did not necessarily have SS. Patients with true primary SS, but without subjective sicca-symptoms, could just as easily be omitted from the classification.

These criteria were subsequently revised by the American-European Consensus Group (AECG) and published new revised criteria in 2002 (8). In order to correct the problems with the earlier criteria, the patient had to have one of the following two findings characteristic of the disease for classification: a) positive antibodies characteristic of the disease (SSA or SSB) or b) a positive biopsy of minor salivary glands. These classification criteria, unlike the previous ones, introduced the classification of sSS in patients with another autoimmune disease with the presence of sicca symptoms and with two additional criteria from the group (III, IV or V). In 2012, the new, somewhat modified classification criteria of the ACR were published, which did not bring major news or diagnostic advances (30). For classification, it was necessary to have at least two of the three criteria: 1. serological criterion (positive anti SSA and/or anti SSB antibodies or positive rheumatism factor and ANA in a titer greater than 1:320), 2. ophthalmological criterion (ocular staining score, OSS ≥ 3), 3. presence of lymphocytic sialedenitis in the biopsy of minor salivary glands. In a study that compared the classification criteria AECG and ACR, matching results of these two sets of criteria were shown, and no clear evidence was presented for the increased value of the new ACR criteria compared to the old AECG criteria from a clinical perspective (31).

The joint criteria of ACR and EULARA from 2016 are currently used to classify the disease. They can be used in patients with at least one symptom of dry eyes or mouth according to the AECG questionnaire or in suspected systemic disease. The new parameter in the current criteria is that each criterion does not have the same weight, that is, it does not signify the same number of points. The classification is based on the weighted sum of five criteria: positive SSA antibodies and focal lymphocytic sialoadenitis with focus sum ≥1 focus/4 mm2, consisting of three points each, then Schirmer's test and OSS ≥5 for the objectivization of dry eyes and unstimulated salivation ≤0, 1 mL/min

simptoma suhoće očiju i usta, u kriterije su ulazili objektivni nalaz suhoće oka (Schirmerov test ≤ 5 mm/5 min, zbroj Rose Bengal ≥ 4), zatim histološki dokaz zahvaćanja žlijezda slinovnica, jedan od objektivnih testova zahvaćanja žlijezda slinovnica (scintigrafija žlijezda slinovnica, sijalografija parotida i nestimulirano lučenje sline [≤ 1,5 ml/15 min] te serološki dokaz autoimunosti [prisutnost antitijela SSA ili antitijela SSB, ANA ili RF]). Tablica 4 prikazuje razlike i sličnosti klasifikacijskih kriterija objavljenih od 1993. godine do danas. Iako su navedeni klasifikacijski kriteriji bili naširoko prihvaćeni, imali su nekoliko problema. Kombinacija okularnih i oralnih simptoma te testova suhoće očiju i testova zahvaćanja slinovnica mogla se također naći i u bolesnika sa sika-simptomima koji nisu morali imati SS. Isto tako, lako se moglo ispustiti iz klasifikacije bolesnike s pravim primarnim SS-om, ali bez subjektivnih sika-simptoma.

Ove kriterije naknadno je revidirala američko-europska skupina (AECG – prema engl. *American-European Consensus Group*) i 2002. godine objavila nove revidirane kriterije (8). Da bi se ispravili problemi s ranijim kriterijima, bolesnik je za klasifikaciju morao obvezno imati jedan od sljedeća dva nalaza karakteristična za bolest: a) pozitivna protutijela karakteristična za bolest (SSA ili SSB) ili b) pozitivnu biopsiju malih žlijezda slinovnica. Ovi klasifikacijski kriteriji za razliku od prethodnih uveli su klasifikaciju i sSS u bolesnika s prisutnom drugom autoimunosnom bolesti uz prisutnost sika-simptoma te uz dodatna dva kriterija iz grupe (III, IV ili V). Godine 2012. objavljeni su novi ponešto izmijenjeni klasifikacijski kriteriji ACR-a koji nisu donijeli velikih novosti niti dijagnostičke pomake (30). Za klasifikaciju bilo je potrebno imati najmanje dva od tri kriterija: 1. serološki kriterij (pozitivna protutijela anti-SSA i/ili anti-SSB ili pozitivan reuma faktor i ANA u titru većem od 1:320), 2. oftalomološki kriterij (OSS ≥ 3), 3. prisutnost limfocitnog sijaledenitisa u bioptatu malih žlijezda slinovnica. U studiji koja je uspoređivala klasifikacijske kriterije AECG i ACR pokazani su podudarni rezultati ovih dvaju skupova kriterija te nisu predočeni jasni dokazi za povećanu vrijednost novih kriterija ACR-a u odnosu na stare kriterije AECG-a iz kliničke perspektive (31).

Za klasifikaciju bolesti trenutno se koriste zajednički kriteriji ACR-a i EULARA-a iz 2016. godine. Oni se mogu koristiti u bolesnika s najmanje jednim simptomom suhoće očiju ili usta prema upitniku AECG-a ili kod sumnje na sustavnu bolest. Ono što je novo u trenutnim kriterijima jest da svaki kriterij nema istu težinu, odnosno ne nosi isti broj bodova. Klasifikacija se temelji na ponderiranom zbroju pet kriterija: pozitivna antitijela SSA i fokalni limfocitni sijaloadenitis s fokus zbrojem ≥1 fokus/4 mm^2, svaki nosi po tri boda, zatim Schirmerov test i OSS ≥5 za objektivizaciju suhoće oči-

Table 4 Differences and similarities of classification criteria published between 1993 and 2016.
Tablica 4. Razlike i sličnosti klasifikacijskih kriterija objavljenih 1993. – 2016. godine

	Classification criteria / Klasifikacijski kriteriji	Preliminary european (1993) / Preliminarni europski (1993.) (16)	AECG (2002) / AECG (2002.) (29)	ACR (2012) / ACR (2012.) (30)	ACR/EULAR (2016) / ACR/EULAR (2016.) (17)	
	Number of criteria for classification / Kriterij za klasifikaciju	4/6 criteria / 4/6 kriterija	4/6 criteria – mandatory criterion 4. or 6. 3/4 objective criteria (3., 4., 5., ili 6.) / 4/6 kriterija – obvezan kriterij 4. ili 6. 3/4 objektivna kriterija (3., 4., 5., ili 6.)	2/3 criteria / 2/3 kriterija	≥ 4 points in patients with sicca symptomes or ESSDAI ≥1 / ≥ 4 boda u bolesnika sa sika simptomima ili ESSDAI ≥1	
1.	Eye dryness / Suhoća oka	+	+	+	–	
2.	Oral symptoms / Oralni simptomi	+	+	–	–	
3.	Eye tests / Očni testovi	Schirmer's test (≤ 5 mm/ 5 min) or / Schirmer test (≤ 5 mm/ 5 min) ili Rose Bengal ≥4 / Rose Bengal zbroj ≥4	Schirmer's test (≤ 5 mm/5 min) or / Schirmer test (≤ 5 mm/5 min) ili van Bijsterveld ≥4 / van Bijsterveld zbroj ≥4	OSS ≥ 3	OSS ≥ 5 Schirmer's test (≤ 5 mm / 5 min) / Schirmer test (≤ 5 mm / 5 min)	1 point / 1 bod 1 point / 1 bod
4.	Biopsy of small salivary glands / Biopsija malih žlijezda slinovnica	≥ 1 focus / fokus / 4 mm^2	≥ 1 focus / fokus / 4 mm^2	≥ 1 focus / fokus / 4 mm^2	≥ 1 focus / fokus / 4 mm^2	3 points / 3 boda
5.	Involvement of salivary glands / Zahvaćanje žlijezda slinovnica	salivary gland scintigraphy or parotid sialography or unstimulated salivary flow (≤ 1.5 ml in 15 min) / scintigrafija žlijezda slinovnica ili sijalografija parotida ili nestimuliran protok sline (≤ 1,5 ml u 15 min)	salivary gland scintigraphy or parotid sialography or unstimulated saliva flow (≤ 1.5 ml in 15 min) / scintigrafija žlijezda slinovnica ili sijalografija parotida ili nestimuliran protok sline (≤ 1,5 ml u 15 min)	–	unstimulated saliva flow (≤ 0.1 ml in 1 min) / nestimuliran protok sline (≤ 0,1 ml u 1 min)	1 point / 1 bod
6.	Antibodies / Antitijela	SSA or SSB or ANA or RF / SSA ili SSB ili ANA ili RF	SSA and/or SSB / SSA i/ili SSB	SSA or SSB or RF and ANA titer >1:320 / SSA ili SSB ili RF i ANA titar >1:320	SSA	3 points / 3 boda
	Exclusion criteria / Isključni kriteriji	lymphoma, AIDS, sarcoidosis, GVHD / limfom, AIDS, sarkoidoza, GVHD	Previous head and neck radiotherapy, HCV infection, AIDS, lymphoma, sarcoidosis, GVHD, use of anticholinergics / Prethodna radioterapija glave i vrata, infekcija HCV, AIDS, limfom, sarkoidoza, GVHD, korištenje antikolnergika	Previous head and neck radiotherapy, HCV, AIDS, sarcoidosis, amyloidosis, GVHD, IgG4 – related disease / Prethodna radioterapija glave i vrata, infekcija HCV AIDS, sarkoidoza, amiloidoza,GVHD, IgG4 – vezana bolest	Previous radiotherapy of the head and neck, HCV AIDS, amyloidosis, GVHD, IgG4 – related disease / Prethodna radioterapija glave i vrata, infekcija HCV, AIDS, amiloidoza, GVHD, IgG4 – vezana bolest	
	Terminology pSS / sSS / Terminologija pSS/sSS		+		–	

Legend / Legenda: ANA – antinuclear antibodies / antinuklearna antitijela; RF – rheumatoid factor / reumatoidni faktor; TBUT – tear break-up time; OSS – ocular staining score / ocjena bojenja površine oka; AIDS –aquired immunodeficiency syndrome / sindrom stečene imunodeficijencije; GVHD – graft versus host disease / kronična bolest presatka protiv primatelja; HCV – hepatitis C virus / virus hepatitisa C; IgG4 – immunoglobulin G4 / imunoglobulin G4.

consisting of one point each. The patient must have 4 or more points in order for the classification to be successful. Positive SSB antibodies in the absence of SSA antibodies are no longer a criterion, and ANA and RF have also been dropped from the criteria. The reason for this decision was that a very small number of patients who met the ACR criteria had negative SSA and SSB antibodies, and positive ANA and RF (21).

A comparison of the AECG classification criteria from 2002 and the latest ACR/EULAR classification criteria showed excellent agreement between them (κ = 0.92). (32). However, the ACR/EULAR classification criteria were still more sensitive and additionally classified patients without sicca symptoms, who had systemic manifestations as pSS, which once again confirms the importance of including systemic manifestations in the classification criteria. This study showed that the sensitivity of the new ACR/EULAR criteria is 87.4%, and the specificity is 95.4% when the physician's diagnosis is taken as the standard. (32). It has also been shown that the inclusion of salivary gland ultrasound in the ACR/EULAR criteria can further increase their sensitivity (32). Summary of main features of classification criteria from 1993 to 2016 are presented in table 4.

CONCLUSION

Over the years, significant progress has been made in the understanding of Sjögren's syndrome as a systemic disease. This is especially outlined in the latest ACR/EULAR classification criteria from 2016, where the classification includes patients with systemic manifestations of the disease without sicca symptoms. However, the complexity of the clinical features of this disease still makes timely diagnosis and early recognition difficult. Therefore changes are not expected in a future in this field.

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ju te nestimulirano lučenje sline ≤0,1 mL/min nose svaki po jedan bod. Za klasifikaciju bolesnik treba imati četiri ili više bodova. Pozitivna antitijela SSB u odsutnosti antitijela SSA više nisu kriterij, a također su iz kriterija izbačeni ANA i RF. Razlog za ovu odluku bio je taj što je vrlo mali broj bolesnika koji su ispunili kriterije ACR imao negativna protutijela SSA i SSB, a pozitivna ANA i RF (21).

Usporedba klasifikacijskih kriterija AECG iz 2002. godine i najnovijih klasifikacijskih kriterija ACR/EULAR-a pokazala je odličnu suglasnost među njima (κ = 0,92) (32). Međutim, klasifikacijski kriteriji ACR/EULAR-a bili su ipak osjetljiviji i klasificirali su dodatno bolesnike bez sika-simptoma, koji su imali sustavne manifestacije kao pSS, što ponovno potvrđuje važnost uključivanja sustavnih manifestacija u klasifikacijske kriterije. Ova studija je pokazala da je osjetljivost novih kriterija ACR/EULAR-a 87,4%, a specifičnost 95,4% kada se dijagnoza liječnika uzme kao standard (32). Također, pokazano je da uključenje ultrazvuka žlijezda slinovnica u kriterije ACR/EULAR-a može dodatno povećati njihovu osjetljivost. (32). Sažetak glavnih obilježja kriterija od 1993. do 2016. godine je prikazan na tablici 4.

ZAKLJUČAK

Tijekom godina je napravljen značajan pomak u razumijevanju Sjögrenovog sindroma kao sustavne bolesti. To se posebno ocrtava u najnovijim klasifikacijskim kriterijima ACR/EULAR-a iz 2016. godine, gdje su klasifikacijom obuhvaćeni i bolesnici sa sustavnim manifestacijama bolesti bez sika-simptoma. No, kompleksnost kliničke slike ove bolesti i dalje otežava pravovremenu dijagnozu i rano prepoznavanje. Stoga ne očekuju promjene u ovom području.

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REVIEW PAPER PREGLEDNI RAD

ASSOCIATION OF BIOLOGICAL THERAPY AND MALIGNANCY IN INFLAMMATORY RHEUMATIC DISEASES

POVEZANOST BIOLOŠKE TERAPIJE I MALIGNIH BOLESTI U UPALNIM REUMATSKIM BOLESTIMA

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Abstract

Inflammatory rheumatic diseases are chronic, progressive autoimmune diseases which affect the musculoskeletal system and other organ systems. Nowadays, a large number of patients is treated with biological therapy. Although biological drugs selectively affect specific molecules of the immune system, they weaken the overall immune system of the body. Therefore, the patients are more susceptible to infections and other diseases such as lymphomas, breast and skin cancers and melanomas. Chronic inflammation which occurs due to autoimmune disease is also a risk factor for malignant development. So far, studies have not proven direct correlation between biological therapy and solid or haematologic tumours. On the other hand, the increased risk for developing skin cancer in patients on tumour necrosis factor alpha inhibitors has been described. In this review paper we analysed the available medical literature on the risks for malignant disease development in patients with rheumatic diseases who are on biological disease – modifying anti-rheumatic drugs.

Key-words: inflammatory rheumatic disease, biological therapy, malignant disease

Sažetak

Sistemske upalne reumatske bolesti jesu kronične, progresivne autoimunosne bolesti koje zahvaćaju lokomotorni sustav i druge organske sustave. Danas je sve više bolesnika liječeno biološkom terapijom. Iako biološki lijekovi selektivno djeluju na specifične molekule imunosnog sustava, oni smanjuju opću obrambenu funkciju organizma, zbog čega su bolesnici podložniji infekcijama, ali i nekim malignim bolestima poput limfoma, karcinoma kože, dojke ili melanoma. Također, sama kronična upala u sklopu autoimunosne bolesti jest rizični čimbenik za razvoj tumorske bolesti. Prema do sada objavljenim studijama, nije dokazana jednoznačna povezanost primjene bioloških lijekova s razvojem solidnih i hematoloških tumora. Suprotno tomu, istraživanja su pokazala povezanost primjene inhibitora tumorske nekroze alfa i razvoja tumora kože. U ovom preglednom radu analizirana je dostupna medicinska literatura o rizicima za razvoj malignih bolesti u bolesnika s reumatološkim bolestima koji su liječeni biološkim antireumatskim lijekovima koji mijenjaju tijek bolesti.

Ključne riječi: upalna reumatska bolest, biološki lijekovi, maligna bolest

INTRODUCTION

Systemic inflammatory rheumatic diseases are a group of chronic inflammatory diseases of unknown aetiology that affect the musculoskeletal system, but also other organ systems. They are characterised by an inadequate immune reaction of the human body (1,2). In medical treatment, the basis of therapy are non-steroidal anti-inflammatory drugs NSAIDs), glucocorticoids and drugs that modify the course of the disease (disease-modifying antirheumatic drugs, DMARDs) (3,4). The so-called conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) have been used in treatment for several decades, and due to the progress of science and a better knowledge of the pathophysiology of these diseases, the new generations of drugs, biological and targeted synthetic disease-modifying antirheumatic drugs (bDMARDs and tsDMARDs) were developed. Their effects are primarily achieved by blocking certain proinflammatory cytokines. In addition, some of them also inhibit the signal required for the activation of T lymphocytes or act on the depletion of B lymphocytes. Care should be taken when prescribing therapy because, although these drugs act specifically and selectively on the immune system, they reduce the general defence function of the body, so patients are more susceptible to infections, but also to some malignant diseases such as lymphoma, skin cancer, breast cancer or melanoma. Due to the immune background in pathogenesis and the predominantly immunosuppressive approach in the treatment of systemic autoimmune diseases, the risk of malignancy is increased (5). Chronic inflammation can contribute to the process of tumorigenesis (6). It has been proven in animal models that tumour necrosis factor alpha (TNF-α) can inhibit, but also promote tumour development depending on the dose and biological conditions (7). The connection between biological therapy and the development of malignant diseases is the topic of continuous interest of many researchers, considering the pronounced immunomodulatory effect of biological drugs during their long-term use. Tumour necrosis factor inhibitors (TNFi) are associated with a variety of potentially dangerous adverse effects, but the risks must be interpreted in the context of the beneficial effects that are experienced with TNFi use. It is important to keep in mind that conventional drugs used for the treatment of inflammatory rheumatic diseases come with their own harmful effects, just like the disease itself (8). A list of biological DMARDs used in the treatment of inflammatory rheumatic diseases is shown in Table 1. In this paper, which is part of the master's thesis written at the School of Medicine of the University of Zagreb, the available medical literature (with a special emphasis on more recent works) from the most important databases was analysed, covering the topic of the risks for the development of malignant diseases in

UVOD

Sistemske upalne reumatske bolesti skupina su kroničnih upalnih bolesti nepoznate etiologije koje zahvaćaju lokomotorni sustav, ali i druge organske sustave. Karakterizirane su neadekvatnom imunološkom reakcijom u vlastitom organizmu (1,2). U medikamentnom liječenju osnova terapije su nesteroidni protuupalni lijekovi (skr. NSAR; engl. *non-steroid anti-inflammatory drugs*, skr. NSAIDs), glukokortikoidi i lijekovi koji mijenjaju tijek bolesti (DMARD; prema engl. *disease modifying antirheumatic drugs*) (3,4). Već nekoliko desetljeća primjenjuju se tzv. konvencionalni sintetski DMARD-ovi (csDMARD, prema engl. *conventional synthetic DMARD*), a zahvaljujući napretku znanosti i boljem poznavanju patofiziologije ovih bolesti razvijene su nove generacije lijekova, biološki (bDMARD) i ciljani sintetski DMARD-ovi (tsDMARD, prema engl. *targeted synthetic DMARD*). Njihovi učinci prvenstveno se ostvaruju blokadom pojedinih proinflamatornih citokina. Osim toga, neki od njih inhibiraju i signal potreban za aktivaciju limfocita T ili pak djeluju na depleciju limfocita B. Pri propisivanju terapije treba biti oprezan jer, iako ovi lijekovi djeluju specifično selektivno na imunološki sustav, oni smanjuju opću obrambenu funkciju organizma pa su bolesnici podložniji infekcijama, ali i nekim malignim bolestima poput limfoma, karcinoma kože, dojke ili melanoma. Zbog imunosne podloge u patogenezi i pretežno imunosupresivnog pristupa u liječenju sistemskih autoimunosnih bolesti, povećan je rizik za pojavu malignoteta (5). Kronična upala može pridonijeti procesu tumorogeneze (6). Na životinjskim modelima je dokazano da čimbenik tumorske nekroze alfa (TNF-α; prema engl. *tumor necrosis factor alpha*) može inhibirati, ali i promovirati razvoj tumora ovisno o dozi i biološkim uvjetima (7). Povezanost biološke terapije i razvoja malignih bolesti predmet je kontinuiranog interesa brojnih istraživača, s obzirom na izražen imunomodulatorni učinak bioloških lijekova tijekom njihove dugoročne primjene. Inhibitori čimbenika tumorske nekroze (TNFi) povezuju se s različitim potencijalno opasnim štetnim učincima, no rizici se moraju interpretirati u kontekstu korisnih učinaka uz primjenu TNFi. Važno je imati na umu da i konvencionalni lijekovi koji se koriste u liječenju upalnih reumatskih bolesti imaju svoje štetne učinke, kao i sama bolest (8). Popis bioloških DMARD-ova koji se koriste u liječenju upalnih reumatskih bolesti prikazan je u tablici 1. U ovom radu, koji je dio diplomskog rada na Medicinskom fakultetu Sveučilišta u Zagrebu, analizirana je dostupna medicinska literatura iz najvažnijih baza, s posebnim naglaskom na recentnije radove, o rizicima za razvoj malignih bolesti u bolesnika s reumatološkim bolestima koji su liječeni biološkim DMARD-ovima.

Table 1 Biologic disease modifying drugs used in rheumatology
Tablica 1. Biološki lijekovi koji se koriste u reumatološkim indikacijama

Name of the drug (abbreviated) / Ime lijeka (skraćenica)	Action mechanism / Mehanizam djelovanja	Molecule / Molekula	Route of administration / Put primjene	Indication in rheumatology / Indikacija u reumatologiji	Remark / Napomena
Adalimumab (ADA)	TNF-alpha inhibitor / Blokator TNFα	Monoclonal antibody, human Ig / Monoklonsko protutijelo, humani Ig	SC / s.c.	RA, AS, nr-axSpA, PsA	
Infliximab (IFX) / Infliksimab (IFX)			IV/SC / i.v./s.c.	RA, AS, PsA	
Certolizumab pegol (CZP)			SC / s.c.	RA, AS, nr-axSpA, PsA	
Golimumab (GOL)			SC / s.c.	RA, AS, nr-axSpA, PsA	
Etanercept (ETA)		Soluble receptor / Solubilni receptor	SC / s.c.	RA, AS, nr-axSpA, PsA	
Tocilizumab (TCZ)	IL-6 receptor inhibitor / Blokator receptora IL-6	Monoclonal antibody, human Ig / Monoklonsko protutijelo, humani Ig	i.v./s.c.	RA, GCA, JIA, CRS	
Sarilumab (SAR)			SC / s.c.	RA	
Abatacept (ABT)	It binds to the CD80/CD86 complex / Veže se na kompleks CD80/CD86	Soluble fusion protein / Solubilni fuzijski protein	IV / SC / i.v. / s.c.	RA	
Secukinumab (SEC) / Sekukinumab (SEC)	IL-17A inhibitor / Inhibitor IL-17A	Monoclonal antibody, human immunoglobulin / Monoklonsko protutijelo, humani imunoglobulin	SC / s.c.	AS, nr-axSpA, PsA	It binds to and neutralizes IL-17A with high affinity / S visokim afinitetom se veže i neutralizira IL-17A
Ixekizumab (IXE) / Iksekizumab (IXE)			SC / s.c.	AS, nr-axSpA, PsA	
Anakinra (ANA)	IL-1 receptor antagonist (IL-1Ra) / Blokator receptora za IL-1 (IL-1Ra)	Receptor antagonist / Antagonist receptora	SC / s.c.	RA, sJIA, Still's disease, adult Still's disease, CAPS, FMF / RA, sJIA, Stillova bolest, Stillova bolest odraslih, CAPS, FMF	
Ustekinumab (UST)	IL-12/IL-23 inhibitor / Inhibitor IL-12/IL-23	Monoclonal antibody / Monoklonsko protutijelo	SC / s. c.	PsA	It binds to the p40 subunit of both cytokines and blocks their binding to receptors / Veže se na podjedinicu p40 obaju citokina i blokira njihovo vezanje za receptore.
Rituximab (RTX) / Rituksimab (RTX)	CD20 positive B-lymphocite inhibitor / Inhibitor CD20+ B-limfocita	Monoclonal antibody, chimera (human-mouse) / Monoklonsko protutijelo, kimera (humano-mišje)	IV (SC*) / i.v. (s.c.*)	RA, GPA, MPA	*SC administration only in haematological indications / *s.c. primjena samo u hematološkoj indikaciji

Abbreviations / Skraćenice: AS – ankylosing spondylitis / ankilozantni spondilitis, CAPS – cryopyrin-associated autoinflammatory syndrome / autoinflamatorni sindrom povezan s kriopirinom (engl. cryopyrin associated autoinflammatory syndrome), CRS – cytokine release syndrome / sindrom otpuštanja citokina (engl. cytokine release syndrome), FMF – familial Mediterranean fever / obiteljska mediteranska vrućica (engl. familial mediterranean fever), GCA – giant cell arteritis / gigantocelularni arteritis, GPA – granulomatosis with polyangiitis / granulomatozni poliangiitis, Ig – immunoglobulin / imunoglobulin, IL – interleukin, IV/i.v. – intravenous / intravenski, JIA – juvenile idiopathic arthritis / juvenilni idiopatski artritis, jPsA – juvenile psoriatic arthritis / juvenilni psorijatički artritis, MPA – microscopic polyangiitis / mikroskopski polinagiitis, nr-axSpA – non-radiographic axial spondyloarthritis / neradiografski aksijalni spondiloartritis, PO/p.o. – peroral / peroralno, PsA – psoriatic arthritis / psorijatični artritis, RA – rheumatoid arthritis / reumatoidni artritis, SC/s.c. – subcutaneous / supkutano.

patients with rheumatic diseases who were treated with biological DMARDs.

RISK OF DEVELOPING MALIGNANT DISEASES

According to data from the literature, patients suffering from rheumatoid arthritis (RA) have a 10–15%

RIZIK ZA OBOLIJEVANJE OD MALIGNIH BOLESTI

Prema podatcima iz literature, bolesnici koji boluju od reumatoidnog artritisa (RA) imaju 10–15% veći ukupni rizik za razvoj nekih malignoma u usporedbi s općom populacijom, primjerice karcinoma pluća i limfoma (standardizirani omjer incidencije; skr. SIR,

higher total risk of developing some malignancies compared to the general population, for example lung cancer and lymphoma (standardized incidence ratio 1, 2–4), non-melanoma skin cancers (SIR 1–3) and possible melanoma and leukaemia (9). The increased risk may be related to the simultaneous use of other drugs, but also the result of chronic, poorly controlled inflammation (10). On the other hand, due to the chronic use of NSAIDs, including cyclooxygenase-2 (COX-2) inhibitors, a lower incidence of colon adenocarcinoma and breast cancer is noted (11). According to some studies, methotrexate, which is often used in combination with TNF-alpha inhibitors may also be associated with an increased risk of developing lymphoma (5). Many of the conducted studies do not include a sufficient number of subjects in order to obtain a reliable result about a higher risk for the development of a malignant disease. Unlike RA, which was the topic of numerous studies in relation to the impact of TNF-alpha inhibitors, when it comes to other autoimmune diseases, as well as some biological drugs, the data on the increased risk are still insufficient. We must highlight the paper written by Kwan et al. in 2020, in which the risk for the development of a malignant disease in patients with seronegative spondyloarthropathies (SnSpA) was analysed (12). It is a systematic review article and meta-analysis that included 14,245 patients. Demographic and pathogenetic differences between patients with seronegative spondyloarthropathy (SnSpA) and RA are highlighted. Patients with SnSpA, especially those with the axial form of the disease, are mainly affected much earlier than patients with RA. In addition to that, considering the treatment guidelines, they were previously exposed to biological therapy. The pathophysiological aspect is also significant, considering the role of Th17 cells in the development of the disease, but also in tumorigenesis. The authors analysed the risk for the development of malignant disease depending on the type of SnSpA, which can be axial (e.g. ankylosing spondylitis, AS and non-radiographic axial spondyloarthritis, nr-axSpA) or peripheral (e.g. psoriatic arthritis, PsA or enteropathic arthritis, EA) and on therapy (biological drug vs. csDMARD and other types of biological drugs, TNF-alpha inhibitors, IL-17 inhibitors and others). Despite a comprehensive and detailed analysis, ultimately no increased risk was proven in patients with SnSpA, both with the disease itself and with biological therapy, regardless of the biological drug. The paper notes the need for trials that would include patients in a longer follow-up period. With psoriasis, independent of the development of PsA, an increased risk for the development of non-melanoma skin cancers, lymphomas and lung cancers has been described. There is speculation about the effect of IL-17, which promotes angiogenesis, but is also a mediator in immune defence processes against tumours. An

prema engl. *standardized incidence ratio*) (1,2–4), nemelanomskih karcinoma kože (SIR 1–3) te moguće melanoma i leukemije (9). Povišeni rizik može biti povezan s istodobnim uzimanjem drugih lijekova, ali i posljedica kronične, slabo kontrolirane upale (10). S druge strane, zbog kronične upotrebe NSAR-a (engl. NSAID), uključujući inhibitore ciklooksigenaze-2, bilježi se niža incidencija adenokarcinoma kolona i karcinoma dojke (11). Prema nekim studijama metotreksat (skr. MTX, prema engl. *methotrexate*), koji se često koristi u kombinaciji s TNF-alfa inhibitorima, također može biti povezan s povišenim rizikom za razvoj limfoma (5). Mnoge provedene studije ne obuhvaćaju dovoljan broj ispitanika da bi se sa sigurnošću dobio pouzdan rezultat o višem riziku za razvoj maligne bolesti. Za razliku od RA, vezano za koji su provedene brojne studije o utjecaju TNF-alfa inhibitora, za ostale autoimunosne bolesti, kao i za neke biološke lijekove, podatci o povišenom riziku još su uvijek nedostatni. Izdvajamo rad Kwana i sur. iz 2020. godine u kojemu je analiziran rizik za razvoj maligne bolesti u bolesnika sa seronegativnim spondiloartropatijama (skr. SnSpA) (12). Riječ je o sustavnom preglednom članku i meta-analizi kojom je bilo obuhvaćeno 14.245 bolesnika. Ističu se demografske i patogenetske razlike između bolesnika sa seronegativnom spondiloartropatijom (SnSpA) i RA. Naime, bolesnici oboljeli od SnSpA, posebice aksijalnim oblikom bolesti, obolijevaju znatno ranije nego bolesnici s RA. Također, obzirom na smjernice liječenja, ranije su izloženi biološkoj terapiji. Patofiziološki aspekt je također značajan, s obzirom na ulogu Th17-stanica u razvoju bolesti, ali i u tumorogenezi. Autori su analizirali rizik za razvoj maligne bolesti ovisno o tipu SnSpA, aksijalni (npr. ankilozantni spondilitis, skr. AS i neradiografski aksijalni spondiloartritis) ili periferni oblik (npr. psorijatički artritis, skr. PsA ili enteropatski artritis) i o terapiji (biološki lijek vs. csDMARD te vrste bioloških lijekova; TNF-alfa inhiitori, inhibitori IL-17 i ostali). Unatoč sveobuhvatnoj i detaljnoj analizi, u konačnici nije dokazan povišen rizik u bolesnika sa SnSpA, kako uz samu bolest, tako i uz biološku terapiju, bez obzira na biološki lijek. U radu se napominje potreba za ispitivanjima koja bi obuhvatila bolesnike u duljem razdoblju praćenja. Uz psorijazu, neovisno o razvoju PsA, opisuje se povišeni rizik za razvoj nemelanomskih kožnih karcinoma, limfoma i karcinoma pluća. Spekulira se o učinku IL-17 koji potiče angiogenezu, no ujedno je i medijator u imunosnim procesima obrane od tumora. Povišen rizik za razvoj gore navedenih tumorskih bolesti, uključivo i tumor mokraćnog mjehura, u bolesnika sa psorijazom, opisuje se i u drugom preglednom radu iz 2020. godine, no nije pronađena povezanost s biološkom terapijom, kao niti povišen rizik za razvoj tumora

increased risk for the development of the above-mentioned tumour diseases, including bladder tumours, in patients with psoriasis is also described in another review from 2020, but no connection with biological therapy was found, nor was there an increased risk for the development of tumours in patients with psoriatic arthritis (13). In studies that researched the risk of malignancy in inflammatory rheumatic diseases, SIR was predominantly used, which is obtained by comparing the recorded and expected incidence of malignancy, the relative risk (RR) and the odds ratio (OR). The advantage of using RR over SIR is higher specificity in the analysis of the risk associated with the therapy.

STUDIES OF OVERALL RISK FOR MALIGNANT DISEASE

The results of the studies published so far are conflicting. Some speak in favour, and others against the increased overall risk for the development of a malignant disease, regardless of its site. Initial concern about a possible association between TNF-alpha inhibitors and malignancy was based on a report by the Food and Drug Administration (FDA) from the United States of America (USA) which was published in 2002 and which included 26 cases of lymphoma, predominantly non-Hodgkin's lymphoma (NHL) in patients with RA and Crohn's disease who were treated with etanercept (ETN) or infliximab (IFX). Lymphoma remission was verified in 2 of the mentioned 26 patients after discontinuing the use of TNF-alpha inhibitors. However, in the aforementioned report, data were presented without comparison with a control group (14). A subsequent FDA report further raised concerns over the alleged association between malignancies and the listed drugs in children and adolescents treated for juvenile idiopathic arthritis (JIA) and inflammatory bowel disease (IBD) (8). The FDA analysis indicated a total of 48 cases of malignant diseases in a 10 year period (1998–2008) in patients treated with TNF-alpha inhibitors. Almost half of the 48 patients suffered from lymphoma (Hodgkin and non-Hodgkin type), and the rest had leukaemia, melanoma and solid tumours. Based on these reports, a meta-analysis was performed that included 9 clinical studies with a total of 3,493 RA patients who were treated with TNF-alpha inhibitors, drugs such as adalimumab (ADA) or infliximab (IFX). The results showed that the risk of developing malignancy in patients treated with these drugs was 3.3 times higher than in patients on placebo (OR 3.3; 95% confidence interval (CI, 1.2–9.1) (15). The frequency of cancer was higher in patients treated with higher doses of drugs. Out of the 26 malignant diseases registered in patients treated with TNF-alpha inhibitors, 15 had solid tumours. Only one solid tumour was recorded in the control group (patients on placebo).

u bolesnika sa psorijatičkim artritisom (13). U studijama koje su proučavale rizik pojave malignih bolesti u upalnim reumatskim bolestima pretežno se koristio SIR, koji se dobiva usporedbom zabilježene i očekivane incidencije maligniteta, relativni rizik (RR) i omjer šansi (OR, prema engl. *odds ratio*). Prednost korištenja RR pred SIR jest viša specifičnost u analizi rizika povezanog s terapijom.

STUDIJE UKUPNOG RIZIKA ZA MALIGNU BOLEST

Rezultati do sada objavljenih studija su oprečni. Neki govore u prilog, a drugi protiv povišenoga ukupnog rizika za razvoj maligne bolesti, neovisno o njenom sijelu. Početna zabrinutost o mogućoj povezanosti TNF-alfa inhibitora i maligniteta temeljila se na izvješću Agencije za hranu i lijekove (skr. FDA, prema engl. *Food and Drug Administration*) iz Sjedinjenih Američkih Država (skr. SAD; engl. USA) iz 2002. godine o 26 slučajeva limfoma, pretežno non-Hodgkin limfoma (NHL) u bolesnika s RA i Crohnovom bolesti koji su bili liječeni etanerceptom (ETN) ili infliksimabom (IFX, prema engl. *infliximab*). U dva od navedenih 26 bolesnika verificirana je remisija limfoma nakon prekida primjene TNF-alfa inhibitora. Međutim, u spomenutom izvješću, prikazani su podatci bez usporedbe s kontrolnom skupinom (14). Sljedeći izvještaj FDA još je više povećao zabrinutost zbog navoda o povezanosti malignih bolesti i navedenih lijekova u djece i adolescenata koji su bili liječeni od juvenilnoga idiopatskog artritisa (JIA) i upalnih bolesti crijeva (skr. IBD, prema engl. *inflammatory bowel disease*) (8). Analiza FDA je ukazala na ukupno 48 slučajeva malignih oboljenja u razdoblju od 10 godina (1998. – 2008.) u bolesnika liječenih TNF-alfa inhibitorima. Gotovo polovica od 48 bolesnika oboljela je od limfoma (tipa Hodgkin i non-Hodgkin), a ostali su imali leukemiju, melanom i solidne tumore. Na temelju tih izvješća učinjena je metaanaliza koja je uključivala devet kliničkih studija s ukupno 3,493 bolesnika oboljelih od RA koji su bili liječeni TNF-alfa inhibitorima, lijekovima adalimumabom (skr. ADA) ili IFX. Rezultati su pokazali da je rizik za razvoj maligniteta u bolesnika liječenih tim lijekovima 3,3 puta viši nego u onih na placebu (OR 3,3; 95% CI [prema engl. *confidence interval*, interval pouzdanosti]) 1,2 – 9,1) (15). Učestalost karcinoma je bila veća u bolesnika liječenih višim dozama lijekova. Od 26 malignih bolesti registriranih u bolesnika liječenih TNF-alfa inhibitorima, njih 15 su imali solidne tumore. U kontrolnoj skupini (na placebu) zabilježen je samo jedan solidni tumor.

Protivno navedenom, druge studije su pokazale da nema povišenog rizika za razvoj malignih tumora u bolesnika oboljelih od RA liječenih TNF-alfa inhibitorima u usporedbi s konvencionalnom terapijom ili

Contrary to the aforementioned, other studies have shown that there is no increased risk for the development of malignant tumours in RA patients treated with TNF-alpha inhibitors compared to conventional therapy or the general population. The safe use of ADA in RA, PsA, AS, JIA and IBD was demonstrated in a study that included data from 71 clinical trials (16). This study included 23458 patients treated with ADA. The risk of developing tumours in patients treated with ADA, regardless of the inflammatory rheumatic disease for which they were treated, was almost the same as in the reference general population. The SIR for RA was 0.93 (95% CI, 0.82–1.06), for AS it was 0.51 (95% CI, 0.16–0.19), and for PsA it was 0.68 (95% CI, 0.22–1.59). Not a single incidence of cancer was recorded among patients with JIA. Considering the age of the affected population, JIA is certainly of particular interest when it comes to the risk of developing malignant diseases. According to data from the Swedish registry from 2019, for all cancers, regardless of their site, the HR was 1.4 (95% CI, 0.7–2.9), and for lymphoproliferative diseases the HR was 3.6 (95% CI, 1.1–11.2). The data indicate a mildly increased risk for the development of lymphoproliferative disease in patients with JIA, but not for other cancers. Also, the risk does not change depending on the treatment modality (17). In Sweden, a study was conducted in 2009 with the aim of assessing the overall risk for the development of cancer related to the use of TNFi (9). Data from the Swedish registers of biological drugs, rheumatic diseases and cancer were analysed, and the results showed that there was no difference in the risk of developing malignant diseases in patients treated with TNF-alpha inhibitors and csDMARDs (RR = 1.0; 95% CI 0.86–1.15). The study conducted on the basis of data from the Danish Registry for Biological Therapies in Rheumatology (DANBIO) in the period 2000–2008 yielded similar results (18). The data collected from 3347 RA patients who were treated with TNF-alpha inhibitors and 3812 RA patients who were not treated with biological therapy were compared, and overall, no increased risk of malignancy was found in patients treated with TNF-alpha inhibitors (RR=1.02; 95% CI 0.80–1.30). Compared to the general population, the risk of developing malignant diseases was slightly higher (SIR = 1.27; 95% CI 1.08–1.49). According to published meta-analyses and cohort studies on patients with RA, there are similar data for the drugs: abatacept, anakinra, rituximab (RTX) and tocilizumab (TCZ) (19–21). A higher incidence rate of solid or haematological neoplasm and skin cancer in patients on biological therapy compared to patients treated only with csDMARDs was not proven, except for an increased risk of developing squamous cell carcinoma with the use of abatacept (hazard ratio, (HR) was 2.12; 95% CI 1.14–3.95) (21). In a study from Finland, based on data from the national registry, the frequency of oc-

općom populacijom. Sigurnost primjene ADA u RA, PsA, AS, JIA i IBD prikazana je u studiji koja je obuhvatila podatke iz 71 kliničkog istraživanja (16). Obuhvaćeno je bilo 23.458 bolesnika liječenih ADA. Rizik za razvoj bilo kojeg tumora u bolesnika liječenih primjenom ADA, neovisno o upalnoj reumatskoj bolesti od koje su liječeni, bio je gotovo isti kao u referentnoj općoj populaciji. SIR za RA iznosio je 0,93 (95% CI 0,82 – 1,06), za AS je bio 0,51 (95% CI 0,16 – 0,19), a za PsA 0,68 (95% CI 0,22 – 1,59). Među oboljelima od JIA nije zabilježen ni jedan karcinom. S obzirom na dob zahvaćene populacije JIA je svakako od posebnog interesa kada je u pitanju rizik za razvoj malignih bolesti. Prema podatcima iz švedskog registra iz 2019. godine, za sve karcinome, neovisno o sijelu, HR je 1,4 (95% CI 0,7 – 2,9), a za limfoproliferativne bolesti HR iznosi 3,6 (95% CI 1,1 – 11,2). Podatci ukazuju na blaže povišen rizik za razvoj limfoproliferativne bolesti u bolesnika s JIA, no ne i za ostale karcinome. Također, rizik se ne mijenja s obzirom na modalitet liječenja (17). U Švedskoj je 2009. godine provedena studija s ciljem procjene ukupnog rizika za razvoj karcinoma vezanih uz primjenu TNFi (9). Analizirani su podatci iz švedskih registara bioloških lijekova, reumatskih bolesti i karcinoma, a rezultati su pokazali da nema razlike u riziku od obolijevanja od malignih bolesti u bolesnika liječenih TNF-alfa inhibitorima i csDMARD-ovima (RR = 1,0; 95% CI 0,86 – 1,15). Studija provedena na temelju podataka iz Danskog registra za biološku terapiju u reumatologiji (DANBIO) u razdoblju od 2000. do 2008. godine dala je slične rezultate (18). Uspoređeni su podatci 3.347 bolesnika oboljelih od RA koji su liječeni TNF-alfa inhibitorima i 3.812 bolesnika s RA koji nisu liječeni biološkom terapijom te sveukupno nije nađen povišeni rizik za malignitet u bolesnika liječenih TNF-alfa inhibitorima (RR=1,02; 95% CI 0,80 – 1,30). Uspoređujući s općom populacijom, rizik obolijevanja od malignih bolesti bio je nešto viši (SIR = 1,27; 95% CI 1,08 – 1,49). Prema objavljenim metaanalizama i kohortnim istraživanjima na bolesnicima s RA, slični su podatci za lijekove: abatacept, anakinru, rituksimab (RTX, prema eng. *rituximab*) i tocilizumab (TCZ) (19–21). Nije dokazana viša stopa incidencije solidne ili hematološke neoplazme te karcinoma kože u bolesnika na biološkoj terapiji u odnosu na bolesnike koji su liječeni samo csDMARD-ovima, izuzev povišenog rizika za razvoj karcinoma skvamoznih stanica uz primjenu abatacepta (HR [prema engl. *hazard ratio*, omjer rizika] koji je bio 2,12; 95% CI 1,14–3,95) (21). U istraživanje iz Finske, na temelju podataka iz nacionalnog registra, analizirana je učestalost pojave malignih bolesti u bolesnika oboljelih od RA liječenih TNF-alfa inhibitorima (IFX, ETN, ADA), RTX ili csDMARD-ovima (22). Stopa incidencije (IR, prema engl. *incidence rate*) malignoma bila je najviša u bole-

currence of malignant diseases in RA patients treated with TNF-alpha inhibitors (IFX, ETN, ADA), RTX or csDMARDs was analysed (22). Incidence rate (IR) of malignancy was the highest in patients treated with csDMARDs (IR = 12; 95% CI 8.6–17) and RTX (IR = 9.5; 95% CI 3.8–2.0), and the lowest in patients treated with IFX (IR = 5.8; 95% CI 2.8–11). Comparing biological drugs and csDMARDs, the risk of developing a malignant disease is lower with biological drugs, with the exception of RTX. However, as it was concluded in the study, after adjusting the data according to age and gender, no statistically significant difference was found in the rate of incidence of malignant diseases during treatment with any combination of drugs, and the only risk factor associated with the development of a malignant disease was age.

The safety of secukinumab, which is increasingly used in the treatment of SnSpA, PsA and psoriasis, has been investigated in several large studies. The 2021 study included data from 49 clinical trials that included a total of 14,519 patients whose follow-up was performed over a five-year period (23). The results showed that there is no increased risk for the development of malignant disease (SIR 0.99; 95% CI 0.82–1.19).

RISK FOR THE DEVELOPMENT OF HAEMATOLOGICAL MALIGNANCIES

Data on the association between TNF-alpha inhibitors and the risk of developing haematological malignancies in patients suffering from systemic inflammatory rheumatic diseases, especially lymphoma, are different. Some authors believe that chronic inflammation, and not its treatment, is associated with an increased risk of lymphoma in RA patients (24). Thus, data from the South Swedish Arthritis Treatment Group indicate a possible increased risk for the development of lymphoma (25). For the development of any malignant disease with the use of TNF-alpha inhibitors (ETN and IFX) the SIR was 1.1 (95% CI 0.6–1.8), and for the control group treated with csDMARDs it was 1.4 (95% CI 1.1–1.8). For lymphoma in the group treated with TNF-alpha inhibitors the SIR was 11.5 (95% CI 3.7–26.9), which is a significantly different result compared to the SIR for the group treated with csDMARDs, which was 1.3 (95 % CI 0.2–4.5). The previously mentioned retrospective cohort study in Sweden conducted on RA patients, which included more than 50,000 subjects, showed that RA patients have an increased risk of developing lymphoma (SIR 1.9) and leukaemia (SIR 2.1) compared to the general population (24). Data collected from the Swedish national registries of patients with AS and PsA in the period 2001–2011 did not show an increased risk for the development of lymphoma in patients with AS compared to the general population (HR 0.9; 95% CI 0.5 – 1.6),

snika liječenih csDMARD-ovima (IR = 12; 95% CI 8,6 – 17) i RTX (IR = 9,5; 95% CI 3,8 – 2,0), a najniža u bolesnika liječenih IFX (IR = 5,8; 95% CI 2,8 – 11). Usporedivši biološke lijekove i csDMARD-ove, rizik za razvoj maligne bolesti niži je uz biološke lijekove, izuzev RTX-a. Ipak, kako je u studiji zaključeno, nakon prilagodbe podataka prema dobi i spolu, nije nađena statistički značajna razlika u stopi incidencija malignih bolesti tijekom liječenja bilo kojom kombinacijom lijekova te je jedini čimbenik rizika povezan s razvojem maligne bolesti bila dob.

Sigurnost primjene sekukinumaba, koji se sve više koristi u liječenju SnSpA, PsA te psorijaze, ispitivana je u nekoliko velikih studija. Studija iz 2021. godine obuhvatila je podatke 49 kliničkih studija koje su uključivale ukupno 14.519 bolesnika praćenih u petogodišnjem razdoblju (23). Rezultati su pokazali da nema povišenog rizika za razvoj maligne bolesti (SIR 0,99; 95% CI 0,82 – 1,19).

RIZIK ZA RAZVOJ MALIGNIH HEMATOLOŠKIH BOLESTI

Podatci koji govore o povezanosti TNF-alfa inhibitora i riziku za razvoj malignih hematoloških bolesti u bolesnika oboljelih od sistemskih upalnih reumatskih bolesti, posebice limfoma, različiti su. Neki autori smatraju da je kronična upala, a ne njezino liječenje, povezana s povišenim rizikom od nastanka limfoma u oboljelih od RA (24). Tako, podatci iz regionalnog registra u južnoj Švedskoj (eng. *The South Swedish Arthritis Treatment Group*) upućuju na mogući povišeni rizik za razvoj limfoma (25). SIR za razvoj bilo koje maligne bolesti uz primjenu TNF-alfa inhibitora (ETN i IFX) bio je 1,1 (95% CI 0,6 – 1,8), a za kontrolnu skupinu liječenu csDMARD-ovima iznosio je 1,4 (95% CI 1,1 – 1,8). SIR za limfom u skupini liječenih TNF-alfa inhibitorima bio je 11,5 (95% CI 3,7 – 26,9), što je značajno različit rezultat u odnosu na SIR za skupinu liječenu csDMARD-ovima koji je iznosio 1,3 (95% CI 0,2 – 4,5). Ranije spomenuto retrospektivno kohortno istraživanje u Švedskoj provedeno na oboljelima od RA, koje je uključivalo više od 50.000 ispitanika, pokazalo je da bolesnici oboljeli od RA imaju povišen rizik za razvoj limfoma (SIR 1,9) i leukemije (SIR 2,1) u usporedbi s općom populacijom (24). Prikupljeni podatci iz švedskih nacionalnih registara oboljelih od AS i PsA u razdoblju od 2001. do 2011. godine nisu pokazali povišeni rizik za razvoj limfoma u bolesnika s AS u odnosu na opću populaciju (HR 0,9; 95% CI 0,5 – 1,6), dok je u oboljelih od PsA nađen blago povišeni rizik (HR 1,2; 95% CI 0,9 – 1,7) (26). Uspoređujući oboljele od PsA liječene TNF-alfa inhibitorima s bolesnicima liječenim MTX-om ili sulfasalazinom, rizik je bio nešto viši uz konvencionalnu terapiju (HR 1,7; 95% CI 1,0 – 3,1).

while a slightly increased risk was found in patients with PsA (HR 1.2; 95 % CI 0.9–1.7) (26). By comparing PsA patients treated with TNF-alpha inhibitors to patients treated with MTX or sulfasalazine, it was revealed that the risk was slightly higher with conventional therapy (HR 1.7; 95% CI 1.0–3.1).

A study from Japan conducted on a sample of 5,573 patients analysed the safety profile of TCZ in the treatment of patients suffering from inflammatory rheumatic diseases (27). In analysing the number of recorded malignancies, it was revealed that only the incidence of lymphoma was significantly increased in patients treated with TCZ compared to the general population (SIR = 3.13; 95% CI 1.82–5.39). The incidence of leukaemia was not higher compared to the general population (SIR 0.54; 95% CI 0.08–3.83).

A study was conducted in the USA based on data available from the National Databank for Rheumatic Diseases (5). Separate research revealed that neither IFX nor ETN were associated with an increased risk for lymphoma.

The RATIO registry in France was established with the aim of collecting data on all cases of opportunistic infections and lymphomas associated with the treatment with TNF-alpha inhibitors regardless of the underlying disease, and to identify risk factors and compare the risk among different biological drugs (28). Based on the analysis of data collected from 2004–2006 a case control was conducted in which 38 cases of lymphoma (29 non-Hodgkin lymphomas, 5 Hodgkin lymphomas and 2 Hodgkin-like lymphomas) were recorded in patients suffering from inflammatory rheumatic diseases treated with TNF-alpha inhibitors. The risk of developing lymphoma in these patients was elevated compared to the general population (SIR 2.4; 95% CI 1.7–3.2), almost the same as in those who were not treated with drugs of this group. Thus, the study failed to demonstrate an increased risk for the development of lymphoma in patients suffering from inflammatory rheumatic diseases treated with TNF-alpha inhibitors.

RISK FOR THE DEVELOPMENT OF SOLID MALIGNANT TUMOURS

Most of the extensive studies published so far, mostly meta-analyses, which examined the safety of TNF-alpha inhibitor use, did not show a significantly increased risk for the development of solid tumours (5,29). In 20–50% of cases the risk is increased for cancers related to smoking and in 70% of cases there is an increased risk for all skin cancers except melanoma. In contrast, a reduced risk of developing breast cancer by 20% and colorectal cancer by 25% is reported, which was explained in the aforementioned part of the paper.

Furthermore, according to BSRBR-RA data (the British Society for Rheumatology Biologics Register

Studija iz Japana na uzorku od 5,573 pacijenata analizirala je sigurnosni profil TCZ-a u liječenju bolesnika oboljelih od upalnih reumatskih bolesti (27). Analizirajući sijela zabilježenih malignih bolesti, samo je učestalost limfoma bila znatno povišena u bolesnika liječenih TCZ-m u usporedbi s općom populacijom (SIR = 3,13; 95% CI 1,82 – 5,39). Učestalost leukemije nije bila veća u usporedbi s općom populacijom (SIR 0,54; 95% CI 0,08 – 3,83).

U SAD-u je provedeno istraživanje na temelju podataka dostupnih iz Nacionalnog registra za reumatske bolesti (5). Promatrano zasebno, niti IFX niti ETN ne povezuju se s povišenim rizikom za limfom.

Registar RATIO u Francuskoj osnovan je s ciljem da se skupe podatci o svim slučajevima oportunističkih infekcija i limfoma povezanih s liječenjem TNF-alfa inhibitorima neovisno o osnovnoj bolesti, te da se identificiraju rizični čimbenici i usporedi rizik među različitim biološkim lijekovima (28). Na temelju analize podataka prikupljenih od 2004. do 2006. godine provedeno je istraživanje parova (engl. *case-control)* u kojem je zabilježeno 38 slučajeva limfoma (29 non-Hodgkin limfoma, pet Hodgkin limfoma i dva limfoma slična Hodgkinovom) u bolesnika oboljelih od upalnih reumatskih bolesti liječenih TNF-alfa inhibitorima. Rizik za razvoj limfoma u ovih bolesnika bio je povišen u odnosu na opću populaciju (SIR 2,4; 95% CI 1,7 – 3,2), gotovo isti kao i u onih koji nisu liječeni lijekovima te grupe. Dakle, studija nije uspjela dokazati povišen rizik za razvoj limfoma u bolesnika oboljelih od upalnih reumatskih bolesti na terapiji TNF-alfa inhibitorima.

RIZIK ZA RAZVOJ SOLIDNIH MALIGNIH TUMORA

Većina do sada objavljenih opsežnih studija, pretežito metaanaliza, koje su ispitivale sigurnost primjene TNF-alfa inhibitorima nije pokazala značajno povišen rizik za razvoj solidnih tumora (5,29). U 20–50% slučajeva rizik je povišen za karcinome povezane s pušenjem te čak 70% povišen rizik za sve kožne karcinome osim melanoma. Nasuprot tomu, navodi se sniženi rizik za razvoj karcinoma dojke za 20%, a za kolorektalni karcinom 25%, što je objašnjeno ranije u tekstu.

Nadalje, prema podatcima BSRBR-RA (engl. *British Society for Rheumatology Biologics Register for Rheumatoid Arthritis*) nema povišenog rizika za solidne tumore u bolesnika liječenih TNFi u usporedbi s bolesnicima koji nikad nisu primili biološku terapiju (HR 0,83; 95% CI 0,64 – 1,07) (30). Studija je obuhvatila 11.767 bolesnika s RA liječenih TNF-alfa inhibitorima i 3.249 bolesnika s RA koji su liječeni csDMARD-ovima. Studija iz 2015. godine koju su proveli švedski istraživači nije našla povišeni rizik za razvoj solidnih malignih tumora. U kliničkoj studiji koja je trajala 11

for Rheumatoid Arthritis) there is no increased risk for solid tumours in patients treated with TNFi compared to patients who were never treated with biological drugs (HR 0.83; 95% CI 0.64–1.07) (30). The study included 11,767 RA patients treated with TNF-alpha inhibitors and 3,249 RA patients treated with csDMARDs. A 2015 study by Swedish researchers found no increased risk for developing solid malignancies. In a clinical trial that lasted 11 years, a follow-up was performed on the population of RA patients treated with RTX. The aim of the trial was to determine the possible long-term consequences of this therapy. The most common solid tumour was breast cancer (0.14/100 patient-years; 95% CI 0.08–0.22) (31). The SIR for breast cancer was 0.63 (95% CI 0.79–0.90) suggesting no increased risk compared to previous epidemiological studies of the safety of RTX in RA (SIR = 0.84; 95% CI 0.79–0.90) (32).

RISK FOR THE DEVELOPMENT OF SKIN CANCER AND MELANOMA

Research conducted so far has shown an increased risk for the development of non-melanoma skin cancer (NMSC) in patients suffering from RA (33,34). According to the study results, the use of TNF-alpha inhibitors and prednisone increases the risk of developing NMSC, which is confirmed by the results of a recent meta-analysis from 2020 which included 123,031 patients (35). It is emphasized that there is a statistically significantly higher risk for the development of squamous cell carcinoma (SCC) in RA patients treated with TNF-alpha inhibitors. In contrast, a British study that analysed data from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA) from 2001–2008 did not show an additional increased risk for NMSC when using drugs from the group of TNF-alpha inhibitors (36). The results of the study showed that the risk of developing basal cell carcinoma (BCC) and SCC is increased in RA patients compared to the general population, regardless of whether they were treated with TNF-alpha inhibitors (SIR 1.72; 95% CI 1.43–2.04) or csDMARDs (SIR 1.83; 95% CI 1.30–2.50). The previously mentioned systematic literature review and meta-analysis based on the data collected from various databases (MEDLINE, EMBASE, Cochrane Database of Systematic Reviews) and from the data published by rheumatology societies yielded very comprehensive results on the risk of treatment with TNF-alpha inhibitors and skin cancers (27). The results of 4 studies involving over 28,000 patients showed that patients treated with TNF-alpha inhibitors have a higher risk of developing BCC and SCC (RR 1.45; 95% CI 1.15–1.76). In addition to that, the study presented data for the development of invasive melanoma, according

godina praćena je populacija oboljelih od RA liječenih RTX-om. Cilj studije bio je ustanoviti eventualne dugoročne posljedice terapije. Najčešći solidni tumor bio je karcinom dojke (0,14/100 bolesnik-godina; 95% CI 0,08 – 0,22) (31). SIR za karcinom dojke iznosio je 0,63 (95% CI 0,79 – 0,90), što govori da nema povišenog rizika u usporedbi s prethodnim epidemiološkim istraživanjima sigurnosti RTX-a kod RA (SIR = 0,84; 95% CI 0,79 – 0,90) (32).

RIZIK ZA RAZVOJ KARCINOMA KOŽE I MELANOMA

Do sada provedena istraživanja pokazala su povišen rizik za razvoj nemelanomskih tumora kože (NMSC, prema engl. *non-melanoma skin cancer*) u bolesnika koji boluju od RA (33,34). Prema rezultatima studija, primjena TNF-alfa inhibitora i prednizona povećava rizik za razvoj NMSC-a, što potvrđuju i rezultati novije metaanalize iz 2020. godine koja je obuhvatila 123.031 bolesnika (35). Ističe se kako je statistički značajno viši rizik za razvoj karcinoma skvamoznih stanica (SCC, prema engl. *squamous cell carcinoma*) u bolesnika s RA liječenih TNF-alfa inhibitorima. Suprotno tomu, britanska studija koja je analizirala podatke iz britanskog registra biološke terapije za bolesnike oboljele od RA (BSRBR-RA) od 2001. do 2008. godine nije pokazala dodatni povišeni rizik za NMSC pri primjeni lijekova iz skupine TNF-alfa inhibitora (36). Rezultati studije pokazali su da je rizik za razvoj bazocelularnog karcinoma (BCC, prema engl. *basal cell carcinoma*) i SCC-a povišen u bolesnika oboljelih od RA u usporedbi s općom populacijom, nevezano jesu li liječeni TNF-alfa inhibitorima (SIR 1,72; 95% CI 1,43 – 2,04) ili csDMARD-ovima (SIR 1,83; 95% CI 1,30 – 2,50). Ranije spomenuti sistematski pregled literature i meta-analiza na temelju podataka koji su prikupljeni iz raznih baza podataka (*MEDLINE, EMBASE, Cochrane Database of Systematic Reviews*) te iz podataka koje su objavila reumatološka društva dali su vrlo iscrpne rezultate o riziku liječenja TNF-alfa inhibitorima i kožnih karcinoma (27). Rezultati četiriju studija koje su uključivale više od 28.000 bolesnika pokazali su da bolesnici koji su liječeni TNF-alfa inhibitorima imaju viši rizik za razvoj BCC-a i SCC-a (RR 1,45; 95% CI 1,15 – 1,76). Osim toga, studija je prikazala podatke i za razvoj invazivnog melanoma, prema kojima je viši relativni rizik za njihov razvoj u bolesnika liječenih TNF-alfa inhibitorima (RR = 1,79; 95% CI 0,92 – 2,67). Europska agencija za lijekove (EMA; prema engl. *European Medicines Agency*) zatražila je u svrhu boljeg prepoznavanja nuspojava liječenja TNF-alfa inhibitorima da se provedu istraživanja o mogućim štetnim učincima. Provedena je metaanaliza podataka 74 randomizirane kliničke studije o TNF-alfa inhibitorima koja je

to which the relative risk for their development is higher in patients treated with TNF-alpha inhibitors (RR = 1.79; 95% CI 0.92–2.67). The European Medicines Agency (EMA) requested that research be conducted on possible adverse effects in order to better recognize the side effects of treatment with TNF-alpha inhibitors. A meta-analysis of data from 74 randomized clinical trials on TNF-alpha inhibitors was conducted, which included 15,418 patients. The results showed a significantly increased risk for the development of skin cancer in patients treated with TNF-alpha inhibitors (RR = 2.02; 95% CI 1.11–3.95) (37). The study of the Danish Registry for Biological Therapies in Rheumatology (DANBIO) compared data for 3347 patients treated with TNF-alpha inhibitors and 3812 patients who were not treated with biological drugs. Patients suffering from RA, PsA and AS were included in the study. The data showed that there is no significantly increased risk for the development of skin cancer in patients treated with TNF-alpha inhibitors compared to patients treated with csDMARDs (HR = 1.10; 95% CI 0.69–1.76), while the risk compared to the general population was still increased (SIR = 1.92; 95% CI 1.42–2.59) (18). A large prospective cohort study conducted in Sweden, in the period from 2001–2010, which included patients with RA, studied the risk of developing skin melanoma (38). In patients who did not receive biological therapy, 113 cases of invasive melanoma were recorded (HR 1.2; 95% CI 0.9–1.5). In the group of patients treated with TNF-alpha inhibitors, 38 cases of melanoma were recorded (HR 1.5; 95% CI 1.0–2.2), which indicates an increased risk for the development of invasive melanoma. The authors of the study conclude that patients with RA who were not treated with TNF-alpha inhibitors are not at a significant risk for developing invasive melanoma compared to the general population, while patients treated with TNF-alpha inhibitors are exposed to a 50% higher risk for developing invasive melanoma.

RISK FOR THE DEVELOPMENT OF NEW MALIGNANCIES IN PATIENTS WITH PREVIOUSLY DIAGNOSED MALIGNANCIES

There are numerous studies whose goal was to determine whether there is an increased risk of developing another malignant tumour in RA patients with a previously diagnosed malignant disease if they are treated with biological drugs. The lack of data on this group of patients could not produce significant results, which is understandable because these patients are at an exceptional risk (5). In Great Britain, based on the data collected from the BSRBR-RA, a study was conducted that dealt with this very issue (39). This study included 14,000 patients with RA, and 293 of these patients suffered from primary cancer. In the group of patients

uključivala 15.418 bolesnika. Rezultati su pokazali značajno povećan rizik za razvoj karcinoma kože u bolesnika liječenih TNF-alfa inhibitorima (RR = 2,02; 95% CI 1,11 – 3,95) (37). Studija danskog registra DANBIO usporedila je podatke za 3.347 bolesnika na terapiji TNF-alfa inhibitora i 3.812 bolesnika koji nisu liječeni biološkim lijekovima. U studiju su uključeni bolesnici oboljeli od RA, PsA i AS. Podatci su pokazali da nema značajno povišenog rizika za razvoj karcinoma kože u bolesnika liječenih TNF-alfa inhibitorima u odnosu na bolesnike liječene csDMARD-ovima (HR = 1,10; 95% CI 0,69 – 1,76), dok je rizik u odnosu na opću populaciju ipak bio povišen (SIR = 1,92; 95% CI 1,42 – 2,59) (18). Velika prospektivna kohortna studija provedena u Švedskoj u razdoblju od 2001. do 2010. godine, koja je uključivala bolesnike oboljele od RA, proučavala je rizik za razvoj melanoma kože (38). U bolesnika koji nisu primali biološku terapiju zabilježeno je 113 slučaja invazivnog melanoma (HR 1,2; 95% CI 0,9 – 1,5). U skupini koja je primala TNF-alfa inhibitore zabilježeno je 38 slučajeva melanoma (HR 1,5; 95% CI 1,0 – 2,2), što ukazuje na povišen rizik za razvoj invazivnog melanoma. Autori studije zaključuju da bolesnici oboljeli od RA koji nisu liječeni TNF-alfa inhibitorima nisu pod značajnijim rizikom za razvoj invazivnog melanoma u usporedbi s općom populacijom, dok su bolesnici liječeni TNF-alfa inhibitorima izloženi 50% većem riziku za razvoj invazivnog melanoma.

RIZIK ZA RAZVOJ NOVIH MALIGNOMA U BOLESNIKA S RANIJE DIJAGNOSTICIRANIM MALIGNOMOM

Brojna su istraživanja kojima je cilj bio utvrditi postoji li u osoba oboljelih od RA s već dijagnosticiranom malignom bolešću povećan rizik od nastanka nekog drugog malignog tumora ako primaju biološku terapiju. Manjak podataka o toj skupini bolesnika nije mogao iznjedriti značajnije rezultate, što je i razumljivo jer su ti bolesnici pod iznimnim rizikom (5). U Velikoj Britaniji na osnovi podataka prikupljenih u BSRBR-RA provedena je studija koja se bavila upravo tom problematikom (39). U studiju je bilo uključeno 14.000 bolesnika s RA, od kojih je njih 293 imalo primarni karcinom. U grupi liječenih TNF-alfa inhibitorima bolesnici koji su već od ranije bolovali od melanoma češće su razvili novi karcinom (3 od 17 osoba, 18%) u usporedbi s bolesnicima na terapiji csDMARD-ovima u kojih nije zabilježen razvoj niti jednoga novog karcinoma. Prema ovoj studiji nema povišenog rizika za primjenu TNF-alfa inhibitora u oboljelih od RA i maligne bolesti, iako je potreban velik oprez. Autori zaključuju da je moguće da rezultati nisu reprezentativni zbog pogreške prilikom određi-

treated with TNF-alpha inhibitors, patients who already suffered from melanoma developed a new cancer more frequently (3 out of 17 people, 18%) than patients treated with csDMARDs in whose case no incidence of new cancer was recorded. According to this study, there is no increased risk for the use of TNF-alpha inhibitors in patients with RA and malignant disease, although great caution is required in the use of this therapy. The authors conclude that it is possible that the results are not representative due to an error when determining the criteria for the inclusion of patients in the clinical trial and thus the selection of patients. Future studies will reveal whether a diagnosis of melanoma in itself represents an increased risk for the development of another malignancy.

Although the data from the existing studies are actually few, they still indicate that the use of TNF-alpha inhibitors does not affect the prognosis in patients who develop cancer during treatment. Another Swedish study found no difference in the risk of cancer progression or death in cancer patients, whether treated with TNF-alpha inhibitors or csDMARDs (RR = 1.1; 95% CI 0.8–1.6) (40).

SMALL MOLECULES, INFLAMMATORY RHEUMATIC DISEASES AND THE RISK OF DEVELOPING MALIGNANCIES

Although the main purpose of this paper was to analyse the risk for the development of malignancies in patients with inflammatory rheumatic diseases treated with biological DMARDs, we shall briefly review the conventional therapy with targeted synthetic tsDMARDs that is commonly used today. Janus kinase inhibitors (JAKi), baricitinib, upadacitinib, tofacitinib and filgotinib (the latter is not yet registered in the Republic of Croatia) and the phosphodiesterase-4 inhibitor, apremilast, are used in the treatment of inflammatory rheumatic diseases. According to the data published so far in the available medical literature, adjusted for age, gender, other demographic data and anamnestic specifics, no increased signals for the risk of developing malignant diseases were detected compared to biological drugs (41–44). More detailed analysis of the mentioned literature goes beyond the scope of this paper.

CONCLUSION

The introduction of biological therapy as a standard treatment modality for inflammatory rheumatic diseases significantly improved the quality of life of patients and the functional status of patients. The study included 14,000 patients with RA. Numerous epidemiological studies were conducted that investigated the safety of the use of biological drugs in patients with various inflammatory rheumatic diseases, precisely in

vanja kriterija za uključivanje bolesnika u kliničko ispitivanje i samim time odabira bolesnika. Buduće studije pokazat će predstavlja li dijagnoza melanoma sama za sebe povišen rizik za razvoj nekog drugog malignoma.

Iako su podatci iz postojećih studija zapravo malobrojni, oni ipak ukazuju da primjena TNF-alfa inhibitora ne utječe na prognozu u bolesnika koji razviju karcinom tijekom liječenja. Prema još jednom istraživanju provedenom u Švedskoj nije nađena razlika u riziku za napredovanje stadija karcinoma ili smrti u oboljelih od karcinoma, bilo da su liječeni TNF-alfa inhibitorima ili csDMARD-ovima (RR = 1,1; 95% CI 0,8 – 1,6) (40).

MALE MOLEKULE, UPALNE REUMATSKE BOLESTI I RIZIK ZA RAZVOJ MALIGNOMA

Iako je glavna namjena ovog rada bila analizirati rizik za razvoj malignoma u bolesnika s upalnim reumatskim bolestima na biološkim DMARD-ovima, kratko se osvrćemo na danas već standardnu terapiju ciljanim sintetskim tsDMARD-ovima. U liječenju upalnih reumatskih bolesti koriste se inhibitori janus kinaza (JAKi), baricitinib, upadacitinib, tofacitinib i filgotinib (potonji još nije registriran u RH) te inhibitor fosfodiesteraze-4, apremilast. Prema do sada objavljenim podatcima u dostupnoj medicinskoj literaturi, prilagođeno za dob, spol, ostale demografske podatke i anamnestičke specifičnosti, nisu detektirani pojačani signali za rizik od razvoja malignih bolesti u usporedbi s biološkim lijekovima (41–44). Detaljnije analize navedene literature nadilaze opseg ovoga rada.

ZAKLJUČAK

Uvođenjem biološke terapije kao standardnog modaliteta liječenja upalnih reumatskih bolesti značajno se poboljšala kvaliteta života bolesnika i funkcionalni status bolesnika. Provedene su brojne epidemiološke studije koje su istraživale sigurnost primjene bioloških lijekova u oboljelih od različitih upalnih reumatskih bolesti upravo u kontekstu rizika za razvoj maligniteta. Najviše je studija dostupnih u literaturi provedeno za TNF-alfa inhibitore, budući da su to lijekovi koji su najduže u primjeni. Rezultati su različiti ovisno o tome koji je biološki lijek korišten i koje je sijelo maligne bolesti promatrano. Prema navedenim istraživanjima postoji određen rizik za obolijevanje od hematološke bolesti, kožnih tumora te razvoja nove maligne bolesti u bolesnika s već ranije dijagnosticiranim malignom. Međutim, vrlo je važno naglasiti da tumačenju rezultata treba pristupati oprezno, te između ostalog u obzir uzeti vrstu istraživanja (npr. deskriptivna studija, kohortna studija, randomizirana studija itd.), način prikupljanja podataka, veličinu uzorka i moguću pogrešku u uzorkovanju. Pitanje je potrebe sustavnog probira

the context of the risk of developing malignancy. Most of the studies available in the literature were conducted on TNF-alpha inhibitors, given that these are the drugs that have been in use the longest. The results are different depending on which biological drug was used and which site of the malignant disease was observed. According to the aforementioned research, there is a certain risk of developing a haematological disease, skin tumours, and the development of a new malignant disease in patients with a previously diagnosed malignant disease. However, it is particularly important to highlight the fact that the results of these studies should be interpreted very cautiously, taking into account, among other things, the type of research (e.g., descriptive study, cohort study, randomized trial, etc.), the method of data collection, sample size and possible sampling error. The question is the need for systematic screening for malignant diseases in patients with rheumatic diseases, for which there are currently no clear, i.e., generally accepted, guidelines. Bearing in mind the previously mentioned tumour diseases, it is possible to screen patients with an increased risk once a year (for example, ultrasound of the abdomen and lymph nodes, serum protein electrophoresis and serum immunofixation test, examination by a dermatologist). Considering that it is a matter of risk assessment on an individual level, it is the duty of the treating physician to adapt the diagnostic procedure depending on that risk. The effectiveness and good safety profile of biological drugs are unquestionable if they are used according to the guidelines of the national rheumatology societies, and thus the risks associated with their use are minimized.

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

na maligne bolesti u reumatoloških bolesnika, o čemu za sada nema jasnih, tj. općeprihvaćenih smjernica. Imajući u vidu ranije spomenute tumorske bolesti, u obzir dolazi jednom godišnje učiniti probir u bolesnika s povišenim rizikom (primjerice, ultrazvučni pregled abdomena i limfnih čvorova, elektroforezu serumskih proteina i imunofiksaciju, pregled dermatologa). Budući da je riječ o procjeni rizika na individualnoj razini, zadaća je ordinarijusa da ovisno o tom riziku prilagodi dijagnostički postupak. Učinkovitost i dobar sigurnosni profil bioloških lijekova nedvojbeni su ako se primjenjuju prema smjernicama nacionalnih reumatoloških društava te su samim time rizici povezani s njihovom primjenom minimizirani.

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

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LIST OF REVIEWERS **POPIS RECENZENATA**

LIST OF REVIEWERS for articles in volume 68 (2021) / POPIS RECENZENATA za članke u volumenu 68 (2021.)

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The editorial board thanks colleagues for the reviews, which raised the quality of the journal. / Uredički odbor zahvaljuje kolegama na recenzijama, čime su podigli kvalitetu časopisa.

INSTRUCTIONS FOR AUTHORS

ABOUT THIS JOURNAL

Reumatizam (Rheumatism) is the platinum open-access peer-reviewed biannual journal of the Croatian Society for Rheumatology. The journal publishes practice guidelines, editorials, original research, reviews, expert opinion pieces, case reports, letters, interviews, meeting reports, and news items. Priority is given to evidence-based research reports in rheumatology, physical medicine and rehabilitation, orthopedics, and allied health specialties to provide the readership with new scientific information on diagnostic and therapeutic procedures as well as comprehensive care for patients with autoimmune and autoinflammatory rheumatic diseases.

Although the journal primarily serves the interests of rheumatologists and physiatrists from Croatia and other Adriatic-Ionian countries, the editors welcome high-quality submissions from all over the world. The aim of the journal's internationalization is to publicize the best rheumatology research and practice, and monitor the progress in rheumatology and allied health professions in Croatia and neighboring countries.

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UPUTE AUTORIMA

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Kliničke smjernice (Practical Guidelines), pregledni radovi (Review) i radovi temeljeni na mišljenju eksperata (Expert Opinion Articles): maksimalno 6 000 riječi; 5 slika i 5 tablica; neograničeni broj referencija; 3-6 ključnih riječi, strukturirani sažetas sa do 300 riječi (izuzetak su radovi iz povijesti medicine koji mogu imati nestrukturirani sažetak).

Kratko priopćenje (*Short Communication*, *Brief Report*): maksimalno 1500 riječi; do 3 slike ili tablice; do 15 referencija; 3 – 6 ključnih riječi.

Prikaz bolesnika(*Case Based Review)* maksimalno 6000 riječi; do 5 slika ili tablica; neograničeni broj referencija; 3 – 6 ključnih riječi; nestrukturirani sažetak do 300 riječi.

Ispravak (*Erratum*): omogućuje korekciju pogrješaka koje su se pojavile kod pisanja, printanja ili u procesu publikacije članaka. Šalje se na adresu: *Reumatizam*, Uredništvo, Klinika za reumatologiju, fizikalnu medicinu i rehabilitaciju, Klinički bolnički centar Sestre milosrdnice, Vinogradska 29, 10000 Zagreb, Hrvatska ili elektroničkom poštom na: glavni-urednik-reumatizam@reumatologija.org i urednik-reumatizam@reumatologija.org.

PRIPREMA RADA / RUKOPISA

U časopisu *Reumatizam* objavljuju se članci na hrvatskom jeziku, s naslovom, sažetkom, ključnim riječima te s naslovom i legendom tablica i slika na engleskom jeziku ili članci na engleskom jeziku (*UK spelling*), s naslovom, sažetkom, ključnim riječima te s naslovom i legendom tablica i slika na hrvatskom jeziku. Stil pisanja treba biti jasan i jezgrovit. Radovi trebaju biti strukturirani sukladno principima EQUATOR Networka (http://www.equator-network.org).

Tekst treba biti napisan slovima veličine 12 točaka na bijelom papiru formata A4 (210 × 297 mm) s dvostrukim proredom, s najviše 30 redaka po stranici, uključujući i naslovnu stranicu, sažetak, tekst, zahvale, izjavu o sukobu interesa, referencije, tablice i legende. Lijeva margina treba biti široka 35 mm, a desna margina te gornji i donji rub 25 mm. Sve stranice, uključujući naslovnu, trebaju imati redni broj u donjem desnom kutu.

Pri potrebi izražavanja podataka rabe se SI mjerne jedinice. Kod naziva koji se mogu pisati kraticom pri prvom je pojavljivanju potrebno napisati puni naziv, s kraticom, a u daljnjem tekstu samo kraticu. Latinski nazivi pišu se načinom Italic, i to puni naziv kod prvog pojavljivanja u tekstu, a u daljnjem tekstu navodi se kratica. Lijekovi se navode generičkim imenom, a ako je nužno, može se u zagradi navesti tvorničko ime, s imenom proizvođača. Proizvođače specifičnih instrumenata ili reagensa (naziv i lokacija) treba navesti u zagradi.

Izuzev preglednih radova i pisama uredniku radovi trebaju imati slijedeće elemente: naslovna stranica (posebna stranica), sažetak i ključne riječi (posebna stranica), glavni tekst rada (s dijelovima: uvod, ispitanici i metode, rezultati, rasprava i zaključak), zahvale, financiranje, izjava o sukobu interesa, literatura, popis tablica i slika te tablice i slike.

Naslovna stranica

Na naslovnoj stranici trebaju biti naslov rada (sažet, jasan i informativan) na hrvatskom i engleskom jeziku te puno ime svakog od autora. U sljedećem retku treba navesti puni naziv ustanove, ulicu i broj, grad i državu. Ako su u izradi rada sudjelovali autori iz različitih ustanova, za svakog od njih poslije imena i prezimena te prije navoda ustanove treba napisati odgovarajući broj u superskriptu.

Slijede ime i prezime te puna adresa autora za dopisivanje u vezi s radom, njegov/njezin telefonski broj, broj faksa i e-mail adresa.

The abstract should emphasize new and important aspects of the study, or observations. Below the abstract, three to six keywords or short terms should be listed, both in Croatian and in English, to help index the article. The keywords may be published with the abstract. Terms from the Medical Subject Headings (MeSH) list of the National Library of Medicine of US should be used for the keywords. General and plural terms, and multiple concepts (e.g., using "and", "or") should be avoided. The abstract should not include references.

Introduction

The introduction provides a brief outline of the context/background of the topic, as well as the purpose and rationale for conducting the study/research. It is recommended to cite only relevant references, which should be well-balanced and recent (not older than 10 years, if possible). At the end, the objective(s) of the study/research should be stated clearly and precisely. No data from the paper or conclusions should be given in the introduction.

Materials and methods

This section provides details about how the study/research was conducted: the place and time, as well as the eligibility criteria for selecting the experimental or observational participants (or laboratory animals), with all their important characteristics. The author(s) should provide a detailed outline of the study (e.g., a randomized–controlled study, an observational study, a prospective/retrospective study, etc.), the data collection methods applied, the meaning of the descriptors, and explain and identify the methods, devices (including the manufacturer's name in parentheses), and procedures, sufficiently detailed to enable others to reproduce the results. References should be given for established methods, and new or substantially modified methods should be described in detail, stating the reasons for using them, and evaluating their limitations.

Generic names should be used for drugs and chemicals. All measurements should be given in SI units. In Croatian texts a decimal comma should be used, and in texts in English a decimal point.

Ethics / Ethical standards

Studies involving human subjects or animals should have received the approval of the respective ethics committee. The work described should have been carried out in accordance with the ethical standards of an institutional or national committee responsible for experiments involving human subjects, as well as with The Code of Ethics of the World Medical Association (Declaration of Helsinki 1964 and its revisions) for experiments involving humans http://www.wma.net/en/30publications/10policies/b3/index.html; EU Directive 2010/63/EU and for animal experiments http://ec.europa.eu/environment/chemicals/lab_animals/legislation_en.htm. Also, it should be stated explicitly that informed consent was obtained from all participating adult subjects or from parents or legal guardians for minors or incapacitated adults, together with the manner in which informed consent was obtained (i.e., oral or written).

Participants' names and/or surnames should not appear, particularly in figurative/illustrative materials.

Statistics

Statistical methods should be described in detail, to enable a knowledgeable reader with access to the original data to verify the reported results. Where possible, findings should be quantified and presented with appropriate indicators of measurement error or uncertainty. The statistical software used should be specified.

Results

Results should be presented in a logical sequence in the text, tables, and figures. In this section, the results are not interpreted nor are their implications discussed. In addition to absolute numbers

Sažetak i ključne riječi

Druga stranica treba sadržavati sažetak na engleskom i hrvatskom jeziku (do 300 riječi) u kojem su navedeni cilj studije/istraživanja, materijal (ispitanici) i metode, rezultati i zaključci.

U sažetku valja naglasiti nove i važne aspekte studije ili opservacije. Ispod sažetka autori trebaju navesti tri do šest ključnih riječi ili kratkih pojmova na hrvatskom i engleskom jeziku koji će pomoći pri indeksiranju članka. Ključne riječi se mogu objaviti uz sažetak. Za ključne riječi treba se koristiti pojmovima iz popisa *Medical Subject Headings* (MeSH) Indexa Medicusa. Općenite, množine i mnogostruke koncepte (primjerice uz uporabu „i", „ili") treba izbjegavati. Sažetak ne smije sadržavati navode referencija.

Uvod

U uvodu se ukratko navode kontekst/pozadinsko znanje o temi, svrha i razlog provođenja studije/istraživanja. Preporučuje se navesti samo relevantne referencije, koje trebaju biti uravnotežene i recentne (po mogućnosti ne starije od 10 godina). Na kraju treba jasno i točno navesti cilj/-eve studije/istraživanja. U uvodu se ne navode podatci iz rada niti zaključci.

Materijal i metode

Navode se detalji provedbe studije/istraživanja: gdje i kad je provedena, na koji je način učinjen odabir i sve važne karakteristike ispitanika (ili laboratorijskih životinja) koje su studirane ili opservirane. Treba detaljno specificirati nacrt studije (npr., randomizirana-kontrolirana studija, opservacijska studija, prospektivna/retrospektivna itd.), način prikupljanja podataka, značenje deskriptora te objasniti, identificirati metode, aparate (s nazivom proizvođača u zagradi) i postupke, dovoljno detaljno kako bi se rezultati mogli reproducirati. Za poznate metode treba navesti referencije, a nove metode ili metode koje su znatnije modificirane detaljno opisati, navodeći razlog njihove primjene i procjene njihovih ograničenja.

Za lijekove i kemikalije moraju se rabiti generička imena. Sve veličine trebaju biti izražene u SI jedinicama. U tekstovima na hrvatskom jeziku rabi se decimalni zarez, a u tekstovima na engleskome decimalna točka.

Etika / Etički standardi

Radovi koji uključuju ljude ili životinje trebaju imati odobrenje od odgovarajućeg etičkog povjerenstva. Takav rad treba biti proveden sukladno etičkim standardima intitucije ili nacionalnom povjerenstvu odgovornom za eksperimente koji uključuju ljude i s Etičkim kodeksom udruge World Medical Association (Helsinška deklaracija iz 1964. i njezine kasnije inačice) za istraživanja koja uključuju ljude http://www.wma.net/en/30publications/10policies/b3/index.html; EU Direktiva 2010/63/EU I za istraživanja na životnjama http://ec.europa.eu/environment/chemicals/lab_animals/legislation_en.htm. Također, treba jasno navesti da je dobiven informirani pristanak od strane svih odraslih ispitanika ili od strane roditelja ili zakonskih skrbnika za maloljetne ispitanike ili nesposobne odrasle osobe, kao i način na koji je taj pristanak dobiven (npr. usmeno ili pismeno).

Imena i /ili prezimena ispitanika ne smiju biti obznanjena, naročito u grafičkim/slikovnim materijalima.

Statistika

Treba iscrpno opisati statističke metode kako bi se obrazovanom čitatelju koji ima pristup originalnim podatcima omogućilo da potvrdi navedene rezultate. Gdje god je to moguće zaključke treba kvantificirati i prezentirati odgovarajućim indikatorima pogrješke ili odstupanja od mjerenja. Treba navesti upotrijebljeni računalni program.

Rezultati

Rezultati se izlažu logičnim slijedom u tekstu, tablicama i slikama. U ovom se dijelu rezultati ne tumače niti se raspravlja o njiho-

and percentages, it is necessary to include the results of statistical analysis, by stating, for example, P values or other parameters. All the data from the tables or figures should not be repeated in the text, but rather only the most important observations should be emphasized or summarized. Redundant tables and figures (e.g., presenting the same data in different formats) should be avoided, as should the use of figures and tables when it is better to include the data in the textual part (e.g., when there is insufficient data for tables or figures).

Discussion

Most of this section is the interpretation of results. New and important aspects of the study, and its implications, should be emphasized. It is not recommended to repeat in detail data or any other material given in the Introduction or in the Results section. Own findings should be compared with the findings of other studies/research, showing the similarities and differences. It is also important to explain the significance of the results obtained, their limitations, and implications for future research, avoiding, however, making statements and drawing conclusions not completely confirmed by the obtained data. When necessary, new hypotheses may be given, but clearly labelled as such.

Conclusions

The main conclusions are drawn based on the author's or authors' own results (3 – 5 sentences maximum).

Abbreviations

Only standard abbreviations should be used. The spelled-out abbreviation followed by the abbreviation in parentheses should be used at the first mention unless the abbreviation is a standard unit of measurement. Abbreviations should be avoided in the manuscript title.

Symbols

Symbols used in the text should be explained. A detailed list of symbols may be given in an appendix.

Tables

Tables should be presented on a separate page. They should not be submitted as images/photographs. Each table should have a title and be numbered consecutively in the order it appears in the text. Tables should be self-explanatory and as simple as possible. Table legends should be given below the table, and may include a reference to data in the table indicated by a superscript figure or letter. Results presented elsewhere in the article (e.g., in an illustration), should not be repeated in the table. If a table originating from other sources is used, permission for such publication should be obtained from the respective publisher/author.

Figures / Illustrations

All figures should be professionally drawn or photographed. Letters, numbers, and symbols on figures should be clear enough to remain legible when the figure is reduced for publication. Figure titles and descriptions are considered to be a part of the text, and not part of the figure/illustration. Each figure/illustration should be numbered consecutively according to the order in which it appears in the text, and have a clear mark showing which is the upper side. Figures/illustrations should appear in a quality appropriate for print publication. Photocopied images or photographs are not suitable for reproduction. If submitted in electronic format, figures/illustrations should be in a high resolution TIFF or JPEG file format, a minimum of 1,500 pixels wide. Figures/illustrations submitted in other formats may be accepted only with the prior consent of the editorial board. The editorial board reserves the right not to publish any figures/illustrations that fail to meet the above requirevim implikacijama. Uz apsolutne brojeve i postotke potrebno je uključiti rezultate statističke analize, navođenjem obično p-vrijednosti ili drugog parametra. U tekstu se ne ponavljaju svi podatci iz tablica ili slika, već se naglašavaju ili sažimaju samo bitna opažanja. Potrebno je izbjegavati suvišne tablice i slike (npr. prikaz istih podataka u različitim formatima) ili uporabu slika i tablica u slučaju kada je informacije bolje uključiti u tekstualni dio (npr. kada nema dovoljno podataka za tablice ili slike).

Rasprava

Većina ovog dijela odnosi se na interpretaciju rezultata. Potrebno je naglasiti nove i bitne aspekte studije te implikacije koje iz nje proistječu. Ne preporučuje se detaljno ponavljati podatke ni bilo koje druge materijale koji su navedeni u uvodnom dijelu ili u dijelu s rezultatima. U dijelu za raspravu treba usporediti vlastite rezultate s rezultatima iz drugih studija/istraživanja te navesti sličnosti i razlike. Također, važno je objasniti značenje dobivenih rezultata, njihova ograničenja i implikacije vezane uz buduća istraživanja, ali uz izbjegavanje izjava i zaključaka koji nisu potpuno potvrđeni dobivenim podatcima. Kad je potrebno, mogu se navesti nove hipoteze uz jasno naglašavanje da su nove.

Zaključci

Na osnovi vlastitih rezultata izvode se glavni zaključci (maksimalno 3 – 5rečenica).

Kratice

Treba rabiti samo standardne kratice. Puni pojam za koji se rabi kratica mora biti naveden pri prvoj uporabi kratice u tekstu, osim ako je riječ o standardnim kraticama mjernih jedinica. Kratice treba izbjegavati u naslovu rada.

Simboli

U tekstu se simboli moraju objasniti. U dodatku se može navesti iscrpan popis simbola.

Tablice

Tablice se pišu na posebnoj stranici. Ne smiju se slati kao slike/fotografije. Svaka tablica mora imati naslov i redni broj prema redoslijedu pojavljivanja u tekstu. Tablica mora biti pregledna i jednostavna. Legende tablica trebaju biti napisane ispod tablice, uz oznaku u tablici u superskriptu. Tablice ne bi trebale ponavljati rezultate koji su prezentirani bilo gdje drugdje u radu (npr. u slici). Tablice preuzete iz drugih izvora treba popratiti dopuštenjem za objavu njihovih izdavača/autora.

Slike / Ilustracije

Sve slike trebaju biti profesionalno nacrtane ili snimljene. Slova, brojevi i simboli moraju biti čitki i u smanjenom obliku u kojem će se objaviti. Svaka slika mora imati broj prema redoslijedu pojavljivanja u tekstu, ime autora i označenu gornju stranu. Svaki crtež mora imati broj prema redoslijedu pojavljivanja u tekstu i označenu gornju stranu. Crteži trebaju biti dovoljno kvalitetno izrađeni za objavu u tisku. Fotokopije slika ili fotografija nisu pogodne za reprodukciju. Ako se dostavljaju u elektroničkom obliku, slike/ilustracije moraju biti u formatu TIFF ili JPEG visoke kvalitete, najmanje širine 1500 piksela. Slike/ilustracije u ostalim formatima mogu biti prihvaćene samo uz prethodni dogovor s uredništvom. Uredništvo pridržava pravo ne objaviti slike/ilustracije koje ne zadovoljavaju ove uvjete. Fotografije osoba mogu se objavljivati samo uz pismeno dopuštenje osobe na fotografiji (ili skrbnika) ili osoba mora biti neprepoznatljiva (prekrivanje očiju, lica i sl.). Slike preuzete iz drugih izvora treba popratiti dopuštenjem za objavu njihova izdavača/autora.

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Acknowledgments

All contributors who do not meet the ICMJE authorship criteria, such as persons who provide technical help, special equipment or materials, and statistical analyses should be listed in the Acknowledgments section. Funding and material support should also be listed, with details of the institution/organization/company that provided such support (including the grant numbers), and the beneficiary (a project, a program, an individual). The International Committee of Medical Journal Editors – ICMJE provides detailed guidelines as to who to list under this section (https://bit.ly/36oo0UZ).

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The Statement will be included in a separate section of the paper before the References.

References

Comprehensive and systematic searches through Scopus, Web of Science, PubMed, Directory of Open Access Journals (DOAJ), and specialist bibliographic databases are strongly encouraged to cite highly relevant, updated, and evidence-based items. The following relevant recommendations could be consulted at https://rdcu.be/bVOOt and https://bit.ly/2PxEGDz.

References should be presented using the Vancouver style, a numeric citation style as recommended by the US National Library of Medicine. The most frequent examples can be consulted in the following recommendations: ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals: Samples of Formatted References for Authors of Journal Articles (https://www.nlm.nih.gov/bsd/uniform_requirements.html). Detailed instructions can be found in the following book: Citing Medicine (https://www.ncbi.nlm.nih.gov/books/NBK7256).

References in the text, tables, and legends should be numbered in Arabic numerals, in parentheses, consecutively in the order of appearance in the text. When more than one reference is given, these should be separated by a comma.

In the list of references, **authors** and/or **editors** are cited with the surname(s) and followed by the initial(s) of the name(s). Initials do not end with a full stop, unless the initial comes immediately before the title. For several authors/editors, their names are separated by a comma. For more than six authors/editors, the first six should be listed with surnames and initials followed by "et al.", and the others omitted. In **titles**, only the first word is capitalized, and any other words that are usually written with a capital. In pagination, repeated identical initial digits for page numbers are omitted (for example: 123-125 becomes 123-5). Each reference should end with a full stop.

For articles in **English**, it is recommended that titles of references published in other languages are cited in English (if available), or an English translation of the title provided (placed in square brackets), with an indication of the language of the original placed at the end.

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Izjava će stajati u posebnom dijelu prije navoda literature.

Literatura

Preporuča se sistematično pretraživanje u bazama Scopus, Web of Science, PubMed i Directory of Open Access Journals (DOAJ) i specijaliziranim bazama podataka s ciljem citiranja relevantnih, novijih i radova utemeljenih na dokazima. Takve relevantne preporuke mogu se naći na http://rdcu.be/bVOOt i https://bit.ly/2PxEGDz.

Literatura se navodi primjenom Vancouverskih pravila koja propisuju numerički način citiranja, prema preporukama američke *National Library of Medicine*. Najčešći primjeri mogu se naći u preporukama: *ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals: Samples of Formatted References for Authors of Journal Articles* (https://www.nlm.nih.gov/bsd/uniform_requirements.html). Detaljne upute mogu se naći u knjizi *Citing Medicine* (https://www.ncbi.nlm.nih.gov/books/NBK7256).

Literaturu u tekstu, tablicama i legendama treba navoditi arapskim brojevima u zagradi, prema redoslijedu pojavljivanja. Ako brojeva ima više, odvajaju se zarezima.

U popisu literature autori i/ili urednici navode se prezimenom/prezimenima i inicijalima imena. Iza inicijala ne stavlja se točka osim ako je riječ o inicijalu neposredno prije naslova. Ako autora/urednika ima više, odvajaju se zarezima. Ako ih ima više od šest, nakon prvih šest treba napisati „i sur.", a ostale ispustiti. U naslovu se velika slova rabe samo za početno slovo prve riječi u naslovu i u riječima koje se uobičajeno pišu velikim slovima. Kad se navode brojevi stranica, treba ispustiti iste početne znamenke stranica (npr. 123–125 postaje 123–5). Na kraju svake referencije stavlja se točka.

U tekstovima na engleskom jeziku pri navođenju radova objavljenih na drugim jezicima preporučuje se navesti naslov na engleskom (ako postoji) ili ga prevesti na engleski (u tom slučaju treba ga staviti u uglate zagrade), a na kraju se navodi izvorni jezik rada.

Pri navođenju prihvaćenih, ali još neobjavljenih radova na kraju treba dodati: „U tisku." Autori trebaju dobiti pismeno odobrenje za citiranje takvog rada zajedno s potvrdom da je rad prihvaćen za objavu.

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When referencing an accepted, but not yet published, article, "Forthcoming" should be added at the end. Authors should have written consent to cite such an article, with confirmation that the article has been accepted for publication.

Journal article

Journal titles should be cited with the usual abbreviations (NLM Title Abbreviation), to be found in the *National Library of Medicine Catalog* (https://www.ncbi.nlm.nih.gov/nlmcatalog/journals). Journal references omit information about the publisher. It is required to include the year of publication, volume, and page numbers. If the journal uses continuous pagination, the month/volume number of the journal indicated in parentheses may be omitted.

[Example] Journal article, more than six authors:

1. Ćurković B, Babić-Naglić Đ, Morović-Vergles J, Anić B, Grazio S, Martinović Kaliterna D et al. Proposal for biologic drugs therapy in rheumatoid arthritis. Reumatizam. 2010;57(1): 29–35. Croatian.

[Example] Journal article, continuous pagination:

2. Ritchlin CT. From skin to bone: translational perspectives on psoriatic disease. J Rheumatol. 2008;35:1434–7.

[Example] Supplement article:

3. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis. 2005;64(Suppl 2):ii14–7.

Books

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[Example] Book (authors):

4. Walker JM, Helewa A. Physical rehabilitation in arthritis. 2nd ed. St. Louis: Saunders; 2004.

[Example] Book (editors):

5. Isenberg DA, Maddison PJ, Woo P, Glass D, Breedveld FC, editors. Oxford textbook of rheumatology. 3rd ed. New York: Oxford University Press; 2004.

[Example] Chapter in a book:

6. Vasey FB, Espinoza LR. Psoriatic arthritis. In: Calin A, editor. Spondyloarthropathies. Orlando: Grune and Stratton; 1984. pp. 151–85.

Papers presented at meetings

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[Example] Papers presented at meetings, published in a supplement:

7. Matucci Cerinic M, Pignone A. The early diagnosis of rheumatoid arthritis (RA). Reumatizam. 1997;44(Suppl):1.

[Example] Papers presented at meetings, published in a book:

8. Babić-Naglić Đ. Fizička aktivnost i vježbe [Physical activities and exercises]. In: Ivanišević G, editor. Talasoterapija, kineziterapija i aromaterapija u Hrvatskoj [Thalassotherapy, kinesitherapy and aromatherapy in Croatia]. Proceedings of the 14th Lošinj School of Natural Remedies; 2013 Sep 6–7; Veli Lošinj, Croatia. Zagreb: Hrvatski liječnički zbor; 2013, pp. 49–55. Croatian.

[Example] Conference proceedings (book):

9. Gordon DA, editor. Immune reactions and experimental models in rheumatic diseases. Proceedings of the Fourth Ca-

[Primjer] Članak iz časopisa, više od šest autora:

1. Ćurković B, Babić-Naglić Đ, Morović-Vergles J, Anić B, Grazio S, Martinović Kaliterna D i sur. Prijedlog primjene bioloških lijekova u reumatoidnom artritisu. Reumatizam. 2010; 57(1):29–35.

[Primjer] Članak iz časopisa, kontinuirana paginacija:

2. Ritchlin CT. From skin to bone: translational perspectives on psoriatic disease. J Rheumatol. 2008;35:1434–7.

[Primjer] Članak iz suplementa:

3. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis. 2005;64(Supl 2):ii14–7.

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4. Walker JM, Helewa A. Physical rehabilitation in arthritis. 2. izd. St. Louis: Saunders; 2004.

[Primjer] Knjiga (urednici):

5. Isenberg DA, Maddison PJ, Woo P, Glass D, Breedveld FC (ur.). Oxford textbook of rheumatology. 3. izd. New York: Oxford University Press; 2004.

[Primjer] Poglavlje u knjizi:

6. Vasey FB, Espinoza LR. Psoriatic arthritis. U: Calin A (ur.). Spondyloarthropathies. Orlando: Grune and Stratton; 1984., str. 151–85.

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[Primjer] Izlaganje na znanstvenom skupu, objavljeno u knjizi:

8. Babić-Naglić Đ. Fizička aktivnost i vježbe. U: Ivanišević G (ur.). Talasoterapija, kineziterapija i aromaterapija u Hrvatskoj. Zbornik izlaganja na 14. lošinjskoj školi prirodnih ljekovitih činitelja; 2013 Ruj 6–7; Veli Lošinj, Hrvatska. Zagreb: Hrvatski liječnički zbor; 2013., str. 49–55.

[Primjer] Zbornik izlaganja na znanstvenom skupu (knjiga):

9. Gordon DA (ur.). Immune reactions and experimental models in rheumatic diseases. Zbornik izlaganja na Četvrtoj kanadskoj konferenciji o istraživanju reumatskih bolesti; 1970 Lis 15–17; Toronto, Kanada. Toronto: University of Toronto Press; 1972.

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[Primjer] Članak iz časopisa na internetu, sadržava DOI:

11. Vivar N, Van Vollenhoven RF. Advances in the treatment of rheumatoid arthritis. F1000Prime Rep. 2014 Svi 6;6:31. doi:

nadian Conference on Research in Rheumatic Diseases; 1970 Oct 15–17; Toronto, Canada. Toronto: University of Toronto Press; 1972.

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10. Mak A, Kow NY. The pathology of T cells in systemic lupus erythematosus. J Immunol Res [Internet]. 2014;2014:419029. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4017881. [cited: 2014 May 25].

[Example] Journal article on the Internet, with a DOI:

11. Vivar N, Van Vollenhoven RF. Advances in the treatment of rheumatoid arthritis. F1000Prime Rep. 2014 May 6;6:31. doi: 10.12703/P6-31. PubMed PMID: 24860653; PubMed Central PMCID: PMC4017904.

[Example] Book/monograph on the Internet:

12. Chen Q, editor. Osteoarthritis – diagnosis, treatment and surgery [Internet]. Rijeka: InTech; 2012. Available from: http://www.intechopen.com/books/osteoarthritis-diagnosis-treatment-and-surgery. [2013 Oct 8].

[Example] Web page:

13. Hrvatsko reumatološko društvo [Internet]. Zagreb: Croatian Society for Rheumatology of the CMA; c2014. Available from: http://www.reumatologija.org/Pocetna.aspx. [cited: 2014 Apr 1].

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[Primjer] Mrežna stranica:

13. Hrvatsko reumatološko društvo [Internet]. Zagreb: Hrvatsko reumatološko društvo HLZ-a; c2014. Dostupno na: http://www.reumatologija.org/Pocetna.aspx. [Pristupljeno: 1. 4. 2014.].

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