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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%).

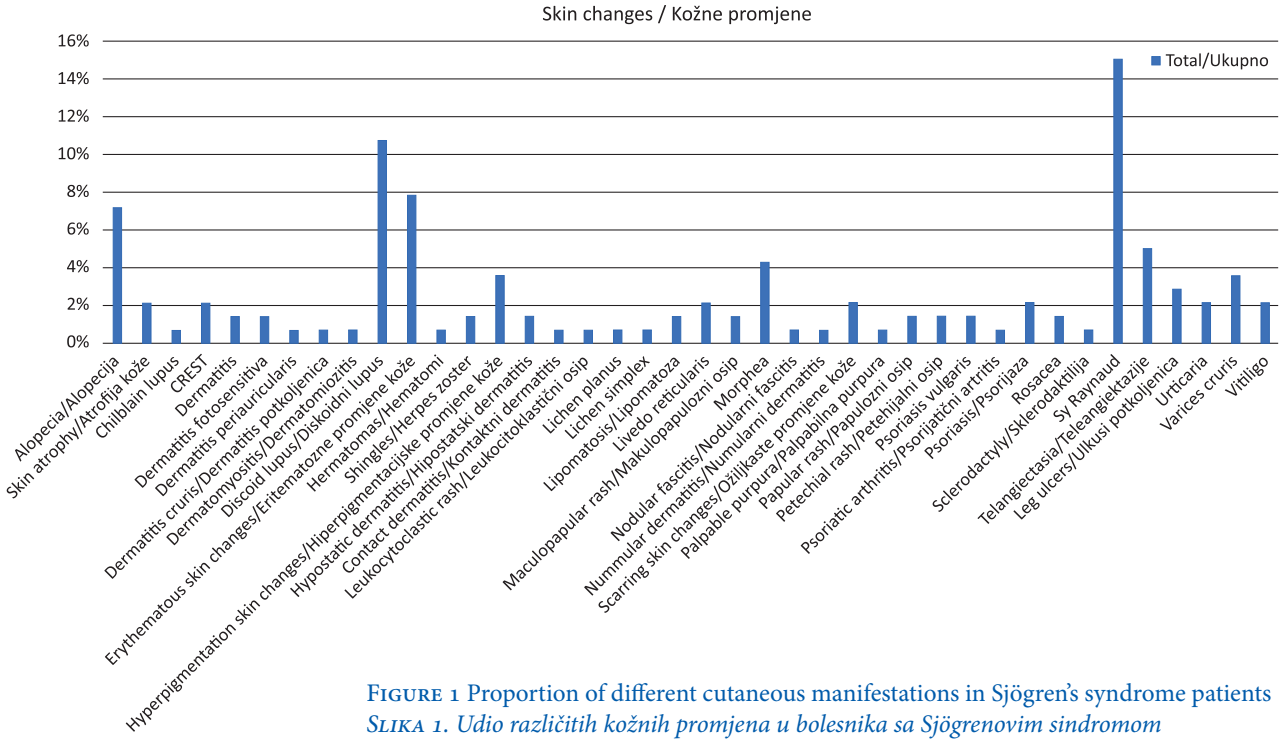


Figure 1 Proportion of different cutaneous manifestations in Sjögren's syndrome patients
Slika 1. Udio različitih kožnih promjena u bolesnika sa Sjögrenovim sindromom

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%).

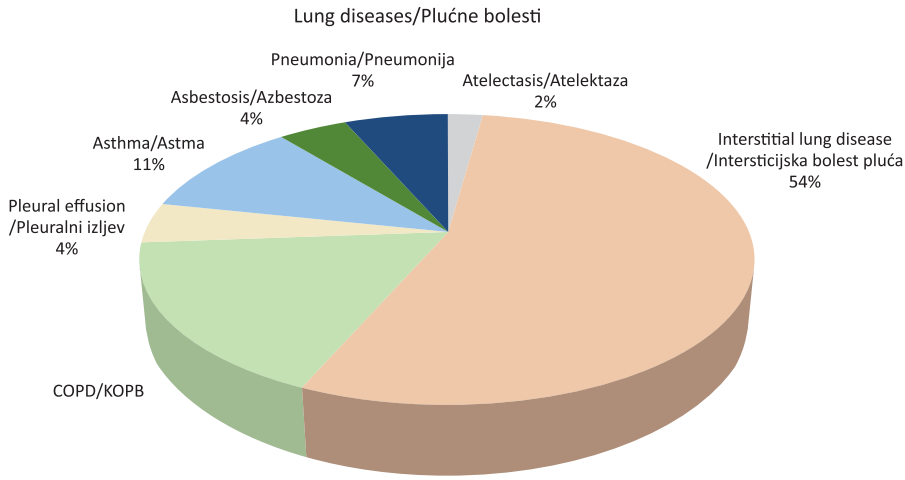
The frequency of lung diseases is 2.7 times higher in men than in women. Figure 2 shows the share of different lung diseases, of which we single out interstitial lung disease as the most represented entity. It should be emphasized that pulmonary fibrosis was the most common form of ILD with a 40% incidence, 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).

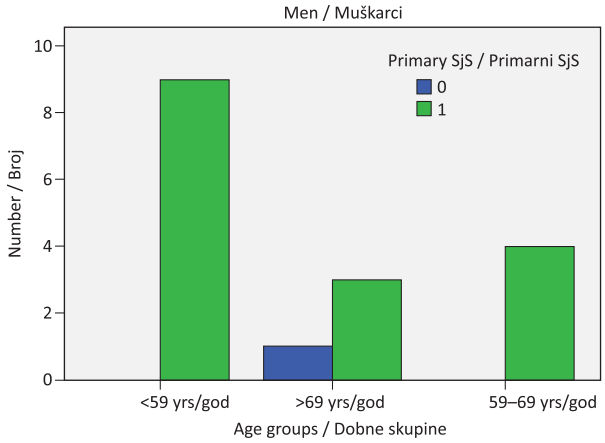
Iako nije bilo statistički značajne povezanosti u prevalenciji bubrežnih bolesti sa spolom (tablica 1) i među promatranim dobnim skupinama, svakako je važno istaknuti da smo u istraživanju ukupno imali 41 (12,9%) pacijenta s jednom od dijagnosticiranih bubrežnih bolesti, od čega je jedan (5,9%) bio muškarac, 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

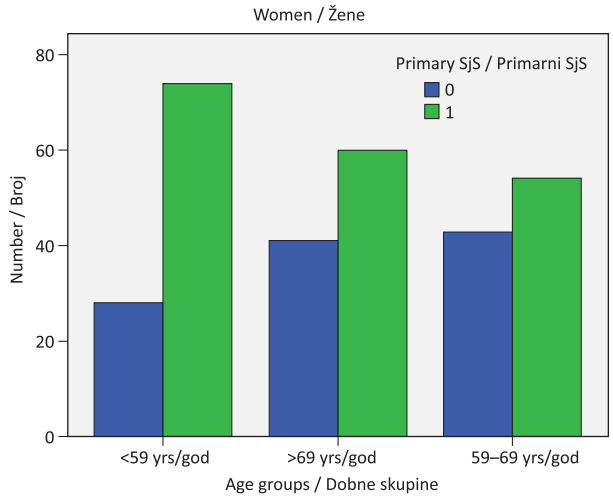
Dependent variable / Zavisna varijabla	Independent variable / Nezavisne varijable	OR (95% CI)	P**
Primary SS/ Primarni SS	Gender/ Spol (women / žene*)	8.7 (1.1–66.9)	**0.038**
	Age groups / Dobne skupine (59–69 years of age / godina*)	2.1 (1.2–3.8)***	**0.013**

*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.

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