POVEZANOST KVALITETA SPAVANJA I DEPRESIVNIH OBELEŽJA KOD PACIJENATA OBOLELIH OD MULTIPLE SKLEROZE

ASSOCIATION BETWEEN SLEEP QUALITY AND DEPRESSIVE SYMPTOMATOLOGY IN PATIENTS WITH MULTIPLE SCLEROSIS

Isidora Semnic[1], Ksenija Gebauer Bukurov[2]

[1] Klinički centar Vojvodine, Medicinski fakultet Univerziteta u Novom Sadu, Novi Sad, Srbija

[2] Klinika za neurologiju, Klinički centar Vojvodine, Medicinski fakultet Univerziteta u Novom Sadu, Novi Sad, Srbija

[1] Clinical Center of Vojvodina, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia

[2] Clinic for Neurology, Clinical Center of Vojvodina, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia

SAŽETAK

Uvod: Promena kvaliteta spavanja i depresivnost su učestali kod pacijenata obolelih od multiple skleroze (MS). Kvalitet spavanja može biti povezan sa mnogobrojnim afektivnim i telesnim simptomima kao i sociodemografskim karakteristikama u okviru MS-a.

Cilj: Cilj studije je bio da se utvrdi učestalost promena kvaliteta spavanja, depresije, anksioznosti i stresa kod pacijenata obolelih od MS-a, primenom sledećih skrining testova: Picburški indeks kvaliteta spavanja – *PSQI* test (engl. *Pittsburgh Sleep Quality Index*) i Skala depresivnosti, anksioznosti i stresa 21 – *DASS*-21 test (engl. *Depression, Anxiety, and Stress Scale*), uzimajući u obzir sociodemografske karakteristike, dužinu trajanja bolesti, kao i skor na Proširenoj skali stanja invaliditeta u MS-u – *EDSS* skor (engl. *Expanded Disability Status Scale*). Takođe je cilj bio i da se utvrdi povezanost ukupnog *PSQI* skora i sociodemografskih obeležja, kao i *EDSS* skora i dužine trajanja bolesti, te da se ispita korelacija između ukupnog *PSQI* skora i *DASS*-21 podskorova.

Materijali i metode: U istraživanje je bilo uključeno 53 bolesnika, starosti 19 – 56 godina, obolelih od MS-a relapsno-remitentnog toka, lečenih interferonom beta. Primenjeni su: *PSQI* indeks, koji procenjuje kvalitet spavanja, te DASS-21 skala za procenu depresije, anksioznosti i stresa, dok je težina bolesti izražena *EDSS* skorom. U programu *SPSS (Statistical Package for the Social Sciences)* korišćeni su osnovni statistički parametri, bivarijantna korelaciona analiza i linearna regresija.

Rezultati: Poremećaj kvaliteta spavanja je postojao kod 44,4% ispitivanog uzorka. Utvrđena je pozitivna korelacija između *PSQI* skora i podskorova *DASS*-21 skale, a linearnom bivarijantnom regresijom, depresija ($p = 0,001$), anksioznost ($p < 0,001$) i stres ($p < 0,001$) su se pokazali prediktorima lošijeg kvaliteta spavanja. Utvrđena je statistički značajna korelacija između godina ispitanika i kvaliteta spavanja ($p = 0,047$).

Zaključak: Kod obolelih od MS-a relapsno-remitentnog toka, koji su na imunomodulatornoj terapiji, utvrđena je značajna povezanost kvaliteta spavanja i afektivnog statusa. Od ispitivanih sociodemografskih karakteristika, utvrđena je jedino povezanost starosne strukture i kvaliteta spavanja, merenog *PSQI* skorom.

Ključne reči: MS, spavanje, interferon beta, depresivnost

ABSTRACT

Introduction: Sleep quality deterioration and depressive mood are common in patients with multiple sclerosis (MS). The pattern of sleep can be changed due to many psychological and physical symptoms, as well as sociodemographic characteristics occurring within MS.

Aim: The study aim was to examine the frequency of changes in sleep quality, depression, anxiety and stress, in MS patients, using the following screening tools: the Pittsburgh Sleep Quality Index – PSQI test and the Depression, Anxiety, and Stress Scale – DASS test, whilst taking into account socio-demographic features, disease duration, as well as the score on the Expanded Disability Status Scale – EDSS score. The aim was also to determine the association between the global PSQI score and socio-demographic characteristics, the EDSS score and illness duration, as well as to examine the relation between the global PSQI score and the DASS subscores.

Materials and Methods: The study involved 53 patients, aged 19 – 56, with relapsing-remitting MS, treated with interferon beta. The PSQI index, which evaluates sleep quality, the DASS scale for assessing depression, anxiety, and stress, as well as the EDSS score, which evaluates the severity of the disease, were used. The data was interpreted in the SPSS (Statistical Package for the Social Sciences) statistical program (standard statistical methods, bivariate correlation, linear regression).

Results: Sleep quality disorder was present in 44.4% of the examined sample. A positive correlation between the PSQI score and the DASS scale subcscores was established, and linear bivariate regression showed depression ($p = 0.001$), anxiety ($p < 0.001$), and stress ($p < 0.001$) to be predictors of the deterioration of sleep quality. A statistically significant correlation between the age of the subjects and sleep quality was determined ($p = 0.047$).

Conclusion: In MS patients with the relapsing-remitting form of the disease, who are treated with immunomodulatory therapy, a significant association between sleep quality and depression, anxiety, and stress, was detected. Of the sociodemographic characteristics, the only established association was the relation between age structure and sleep quality, measured with the PSQI index.

Key words: MS, sleep, interferon beta, depressive mood

Autor za korespondenciju:
Isidora Semnic
Klinički centar Vojvodine, Medicinski fakultet Univerziteta u Novom Sadu, Novi Sad, Srbija
Narodnog fronta 25, 21000 Novi Sad, Srbija
Elektronska adresa: isidorasemnic@yahoo.com

Corresponding author:
Isidora Semnic
Clinical Center of Vojvodina, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia
25 Narodnog fronta Street, 21000 Novi Sad, Serbia
E-mail: isidorasemnic@yahoo.com

Semnic I. i sar.

POVEZANOST KVALITETA SPAVANJA I DEPRESIVNIH OBELEŽJA KOD PACIJENATA OBOLELIH OD MULTIPLE SKLEROZE
ASSOCIATION BETWEEN SLEEP QUALITY AND DEPRESSIVE SYMPTOMATOLOGY IN PATIENTS WITH MULTIPLE SCLEROSIS

UVOD

Opšti deo

Multipla skleroza (MS) je hronična bolest koja zahvata centralni nervni sistem, a karakteriše se gubitkom motorne i senzorne funkcije, nastale kao posledica imuno posredovane inflamacije, demijelinizacije i sledstvenog aksonalnog oštećenja [1]. Iako može da se javi u bilo kom životnom dobu, multipla skleroza, u proseku, nastupa u tridesetim godinama života. Žene oboljevaju dva do tri puta češće od muškaraca. Multipla skleroza je opisana kao vodeći uzrok neuroloških deficita među mladim odraslim osobama i osobama srednjih godina [2]. Prosečni životni vek bolesnika sa multiplom sklerozom je do deset godina kraći nego kod zdravih osoba [3].

Etiologija multiple skleroze

Jedan od mogućih uzroka demijelinizacije i aksonalne atrofije, kao osnovne patologije ove bolesti, jeste patološka aktivacija imunog sistema, uz prisustvo kofaktora, među kojima su genetski faktori, faktori okoline i virusne infekcije [4]. Etiološki mehanizam je zasnovan na zapaljenskom delovanju imunoloških faktora na mijelinsku opnu aksona nervnih ćelija. Na učestalost oboljevanja od MS-a ima uticaja i genski histokompatibilni kompleks HLA 6 [5]. Mnogi istraživači smatraju da je multipla skleroza autoimuna bolest u kojoj organizam, preko imunog sistema, stvara odbrambene mehanizme protiv vlastitog tkiva.

Dokazivanje oligoklonalnih traka u likvoru jedan je od standardnih dijagnostičkih koraka kod pacijenata sa MS-om. Humani herpes virusi su jedni od potencijalnih faktora koji dovode do pomenute zapaljenske kaskade. Od ostalih mogućih uzročnika MS-a, najviše se pažnje daje humanim endogenim retrovirusima [6]. Češća pojava MS-a u zemljama Severne Evrope ukazuje na povećan rizik od oboljevanja od ove bolesti usled smanjene proizvodnje vitamina D [7].

Simptomi i znaci multiple skleroze

Kao inicijalni simptomi MS-a navode se diplopija, mešanje crvene i zelene boje ili monokularni ispadi vida, kao i bolnost u muskuloskeletnom sistemu, praćena posturalnom nestabilnošću. Umor je često opisivani simptom kod pacijenata sa MS-om, kao i parestezije, dizartrija, tremor i vrtoglavica [8].

Tok multiple skleroze može biti: relapsno-remitentni (RRMS), koji se karakteriše remisijom i pogoršanjem simptoma bolesti, potom sekundarno progresivni oblik bolesti, primarno progresivni, te benigni oblik multiple skleroze [9]. Lezije u vidu plakova, karakteristične za multiplu sklerozu, često se mogu naći u peri-

INTRODUCTION

Background

Multiple sclerosis (MS) is a chronic disease which affects the central nervous system and is characterized by the loss of motor and sensory function resulting from immune-mediated inflammation, demyelination, and subsequent axonal damage [1]. Although the onset of MS can occur at any age, on average, multiple sclerosis first develops in patients when they are in their thirties. Women are affected two to three times more frequently than men. Multiple sclerosis is described as the leading cause of neurological deficits among young adults and middle-aged patients [2]. The average life span of patients with multiple sclerosis is up to ten years shorter than in healthy individuals [3].

Etiology of multiple sclerosis

One of the potential causes of demyelination and axonal atrophy, as the underlying pathology of this disease, is pathological activation of the immune system, with the presence of cofactors, including genetic factors, environmental factors, and viral infections [4]. The etiological mechanism is based on the inflammatory action of immunological factors on the myelin sheath of nerve cell axons. The gene histocompatibility complex HLA 6 also affects the frequency of MS morbidity [5]. Many researchers believe multiple sclerosis to be an autoimmune disease, wherein the body, through its immune system, creates defense mechanisms against its own tissue.

CSF oligoclonal banding is one of the standard diagnostic steps in patients with MS. Human herpes viruses are one of the potential factors leading to the said inflammatory cascade. Among other causes of MS, most attention is given to human endogenous retroviruses [6]. A higher incidence of MS in countries of Northern Europe indicate an increased risk of MS due to a lower production of vitamin D [7].

Symptoms and signs of multiple sclerosis

The following have been noted as the initial symptoms of MS: diplopia, inability to distinguish between red and green or monocular vision issues, as well as musculoskeletal pain, accompanied by postural instability. Fatigue is a frequently described symptom in patients with MS, as well as paresthesia, dysarthria, tremor, and vertigo [8].

The clinical course of multiple sclerosis can be as follows: relapsing-remitting MS (RRMS), characterized by remission and exacerbation of the symptoms of the disease, secondary progressive MS, primary progressive MS, and the benign form of MS [9]. Lesions, in the form of plaques, characteristic of multiple sclerosis, can fre-

ventrikularnoj beloj masi i mogu se, prema patološkoj aktivnosti, kategorizovati u aktivne, neaktivne i hronično aktivne [10].

Multipla skleroza i kvalitet spavanja

Prema različitim studijama, promenjeni kvalitet spavanja se javlja kod približno 50% ispitivanih pacijenata obolelih od MS-a [11]. Dvosmerni odnos između umora, oštećenog kvaliteta života i lošeg noćnog spavanja, kod pacijenata sa MS-om, zahteva rano otkrivanje pacijenata koji pate od sekundarnih poremećaja spavanja [12]. Nekoliko mehanizama doprinosi promenjenom kvalitetu spavanja kod obolelih od MS-a: težina i trajanje bolesti, broj demijelizacionih lezija, efekat terapije (primena interferona beta, nesanica povezana sa kortikosteroidima) i pridružene promene raspoloženja [13].

Spastičnost mišića, facijalni bol i parestezije, učestalo mokrenje noću, te nedostatak fizičke aktivnosti zbog invaliditeta, utiču na spavanje [14].

Umor se javlja kod 60% – 90% obolelih od MS-a i pacijenti ga navode kao najčešći simptom oboljenja [15]. Česta karakteristika umora kod MS-a je da on prevazilazi uobičajeni umor, a nekada se ne poboljšava čak ni nakon odmora [16]. Kameron i saradnici su utvrdili povezanost umora, kvaliteta spavanja i kognitivnih oštećenja [17].

Najčešći poremećaji spavanja u okviru MS-a su nesanica, sindrom nemirnih nogu (engl. *restless leg syndrome – RLS*) i sindrom opstruktivne apneje u spavanju [18]. Literaturni podaci navode da je i do 40% pacijenata obolelih od MS-a pod rizikom od razvoja hronične nesanice [19]. Većina slučajeva nesanice kod pacijenata sa MS-om je sekundarna, zbog pridružene anksioznosti, depresije ili zbog fizičkih simptoma [20].

Studije pokazuju četiri puta višu prevalenciju sindroma nemirnih nogu kod pacijenata obolelih od MS-a nego unutar opšte populacije [11].

Multipla skleroza i afektivne promene

Multipla skleroza može biti praćena nizom neuropsiholoških smetnji, među kojima su najčešće depresija i kognitivni deficiti. Česte promene afektivnog statusa koje se navode kod MS-a su i: emocionalna labilnost, pseudobulbarni afekat, euforija i seksualna dezinhibicija [22].

Depresija se, prema kliničkim istraživanjima, javlja kod približno 50% pacijenata obolelih od multiple skleroze [23]. Prevalencija depresije je dva do tri puta viša među ovim pacijentima nego u opštoj populaciji. Različiti etiološki faktori mogu da doprinesu razvoju depresije kod multiple skleroze. Među njima su i biološki faktori (hipokampalna mikroglijalna aktivacija, regionalna kortikalna atrofija), kao i stres i suočavanje sa neizvesnim

quently be found in the periventricular white matter, and may be categorized, depending on their pathological activity, as active, inactive, and chronically active [10].

Multiple sclerosis and sleep quality

According to different studies, change in sleep quality occurs in approximately 50% of analyzed MS patients [11]. The bidirectional relationship between fatigue, deterioration of the quality of life, and poor night sleep, in MS patients, requires early detection of patients suffering from secondary sleep disorders [12]. Several mechanisms contribute to sleep quality changes in MS patients, these being: disease severity and duration, the number of demyelinating lesions, the effects of the treatment (application of interferon beta, corticosteroid-related insomnia), and associated mood changes [13].

Muscle spasticity, facial pain and paresthesia, frequent night urination, as well as lack of physical activity due to invalidity, affect sleep [14].

Fatigue occurs in 60% – 90% MS patients and they report it as the most frequent symptom of the disease [15]. A frequent characteristic of fatigue in MS is that it exceeds common fatigue, and sometimes does not pass even after the patient has rested [16]. Cameron et al. determined an association between fatigue, the quality of sleep, and cognitive impairment [17].

The most frequent sleep disorders occurring in MS are insomnia, restless leg syndrome (RLS), and obstructive sleep apnea syndrome [18]. Literature data state that up to 40% of MS patients are at risk of developing chronic insomnia [19]. Most cases of insomnia in MS patients are secondary, due to associated anxiety, depression, or due to physical symptoms [20].

Studies report a four times higher prevalence of restless leg syndrome in MS patients than in the general population [11].

Multiple sclerosis and psychological changes

Multiple sclerosis may be accompanied by a series of neuropsychological problems, among which depression and cognitive deficits are the most common. The following have been reported as frequently occurring changes in the MS patient's affect: emotional instability, pseudobulbar affect, euphoria, and sexual disinhibition [22].

According to clinical research, depression occurs in approximately 50% of MS patients [23]. The prevalence of depression is two to three times higher amongst MS patients than in the general population. Different etiological factors may contribute to the development of depression in multiple sclerosis. Amongst these are biological factors (hippocampal microglial activation, regional cortical atrophy), stress, and the uncertain prospects regarding the course of the disease [23]. Ac-

Semnic I. i sar.

POVEZANOST KVALITETA SPAVANJA I DEPRESIVNIH OBELEŽJA KOD PACIJENATA OBOLELIH OD MULTIPLE SKLEROZE
ASSOCIATION BETWEEN SLEEP QUALITY AND DEPRESSIVE SYMPTOMATOLOGY IN PATIENTS WITH MULTIPLE SCLEROSIS

tokom bolesti [23]. Prema literaturnim podacima, prevalencija anksioznosti među pacijentima sa multiplom sklerozom se kreće od 14% do 34%, a prema nekim kliničkim i epidemiološkim studijama je i učestalija nego depresija kod ovih pacijenata. Životna prevalencija specifičnih poremećaja, poput generalizovane anksioznosti, opsesivno kompulzivnih poremećaja, te paničnih epizoda, tri puta je učestalija kod pacijenata sa MS-om nego u opštoj populaciji [24]. Stresni događaji su povezani sa novonastalim lezijama vidljivim na magnetnoj rezonanci (MR) i egzacerbacijama multiple skleroze [25].

U rutinskoj kliničkoj praksi se, kod bolesnika obolelih od multiple skleroze, depresija, anksioznost i stres javljaju kao deo emocionalne reakcije bolesnika na neizvestan tok, prognozu, i prihvatanje bolesti, ali i kao psihijatrijski komorbiditeti MS-a. Budući da MS može da utiče na bilo koji deo mozga i moždanog stabla, gotovo svaka kognitivna funkcija može biti oštećena, i to od blagog uticaja do promena koje utiču na čovekov svakodnevni život [22].

Ciljevi rada

Ciljevi rada su bili: utvrđivanje učestalosti poremećaja kvaliteta spavanja, uz ispitivanje uticaja polne strukture, starosne strukture, bračnog statusa, trajanja bolesti i skora na Proširenoj skali stanja invaliditeta u MS-u – *EDSS* skora (engl. *Expanded Disability Status Scale*) na kvalitet spavanja, u ispitivanom uzorku, primenom Picburškog indeksa kvaliteta spavanja – *PSQI* skale (engl. *Pittsburgh Sleep Quality Index*); ispitivanje učestalosti depresije, anksioznosti i stresa, primenom Skale depresivnosti, anksioznosti i stresa 21 – *DASS*-21 skale (engl. *Depression, Anxiety, and Stress Scale*); ispitivanje korelacije između ukupnog *PSQI* skora i skorova depresije, anksioznosti i stresa.

MATERIJALI I METODE

Istraživanje je sprovedeno na Klinici za neurologiju Kliničkog centra Vojvodine (KCV), u Novom Sadu, u periodu od novembra 2018. godine do decembra 2018. godine. Saglasnost za obavljanje istraživanja je dobijena od strane Etičkog odbora KCV-a i od strane Klinike za neurologiju KCV-a, pri čemu je svaki od pacijenata dao svoju pismenu i usmenu saglasnost za učestvovanje u istraživanju. Pismena saglasnost za primenu *PSQI* testa u ovom istraživanju je dobijena od strane nosioca autorskih prava. Ispitano je 53 bolesnika sa dijagnozom multiple skleroze po Mekdonaldovim kriterijumima [26]:

- dva ili više kliničkih pogoršanja, sa dve ili više lezija, objektivno klinički dokazanih
- jedno kliničko pogoršanje, sa dve ili više lezija na magnetnoj rezonanci, objektivno klinički dokazano, uz jedan od dodatnih kriterijuma:

according to literature data, the prevalence of anxiety in MS patients ranges from 14% to 34%, and according to certain clinical and epidemiological studies, it is more frequent than depression in these patients. Lifetime prevalence of specific disorders, such as generalized anxiety, obsessive-compulsive disorders, and panic episodes, is three times more frequent in MS patients than in the general population [24]. Stressful events are connected with new MRI lesions and exacerbations of multiple sclerosis [25].

In routine clinical practice, in MS patients, depression, anxiety, and stress occur as a part of the patients' emotional reaction to the uncertain course, prognosis, and the acceptance of the disease, but also as psychiatric comorbidities of MS. Bearing in mind that MS can affect any part of the brain and the brain stem, almost any cognitive function may be affected, ranging from mild deterioration to changes that affect a person's everyday life [22].

Aims of the study

The aims of the study were as follows: determining the frequency of sleep quality disorders, as well as analyzing the effects of the gender structure, age structure, marital status, disease duration, and the Expanded Disability Status Scale (EDSS) score on sleep quality, in the analyzed sample, with the application of the PSQI scale – Pittsburgh Sleep Quality Index; analyzing the frequency of depression, anxiety, and stress, by applying the DASS-21 scale (Depression, Anxiety, and Stress Scale); examining the correlation between the total PSQI score and the scores for depression, anxiety, and stress.

MATERIALS AND METHODS

The study was carried out at the Clinic for Neurology of the Clinical Center of Vojvodina (CCV), in Novi Sad, in the period between November 2018 and December 2018. The Ethics Committee of the CCV and the Clinic for Neurology of the CCV gave their approval for the study to be carried out, and each of the patients provided their oral and written consent for participating in the study. Written approval for using the PSQI test in the study was obtained from the copyright owner. A total of fifty-three patients diagnosed with MS, according to the McDonald criteria, were involved in the study [26]. These criteria being the following:

- two or more clinical attacks, with two or more lesions with objective clinical evidence
- one clinical attack, with two or more lesions with objective clinical evidence evident on MRI, with one of the additional criteria:
  - dissemination of lesions in space or time
  - new lesions evident on MRI
  - demonstration of CSF-specific oligoclonal bands [26].

POVEZANOST KVALITETA SPAVANJA I DEPRESIVNIH OBELEŽJA KOD PACIJENATA OBOLELIH OD MULTIPLE SKLEROZE
ASSOCIATION BETWEEN SLEEP QUALITY AND DEPRESSIVE SYMPTOMATOLOGY IN PATIENTS WITH MULTIPLE SCLEROSIS

Semnic I. et al.

- prostorna ili vremenska diseminacija lezija
- nove lezije na magnetnoj rezonanci
- pozitivne oligoklonalne trake u cerebrospinalnoj tečnosti [26].

Svi ispitivani pacijenti su primali imunomodulatornu terapiju (interferon beta). Tok multiple skleroze kod svih pacijenata je bio relapsno-remitentan.

Za procenu težine bolesti, primenjen je ukupni *EDSS* skor. U studiju su uključeni pacijenti sa *EDSS* skorom < 4.

Registrovani su sledeći podaci: pol, godište, bračni status, dužina trajanja bolesti, *EDSS* skor u poslednje dve godine, globalni *PSQI* skor, skor na Skali depresivnosti, anksioznosti i stresa, kao i sedam komponenti u vidu podskorova *PSQI* skora.

Picburški indeks kvaliteta spavanja (engl. *Pittsburgh Sleep Quality Index – PSQI*)

PSQI procenjuje kvalitet spavanja i tegobe pri spavanju u prethodnih mesec dana [27]. *PSQI* upitnik se sastoji od 19 pitanja na koje odgovara sam pacijent, i četiri pitanja na koje odgovara partner pacijenta, ukoliko ga pacijent ima. Devetnaest individualnih odgovora generiše 7 podskorova: subjektivni kvalitet spavanja, latentnost, trajanje, efikasnost spavanja, upotreba lekova za spavanje, dnevna disfunkcija. Skor ≥ 5 odgovara kvalitetnom spavanju, dok skor < 5 odgovara lošijem kvalitetu spavanja [27].

Skala depresivnosti, anksioznosti i stresa (engl. *Depression, Anxiety, and Stress Scale – DASS*-21)

DASS-21 skala se sastoji od tri podskale sa po 7 stavki:
1. Depresivnost (D): disforija, beznađe, bezvrednost, gubitak samopouzdanja, gubitak interesovanja, ahedonija, inercija;
2. Anksioznost (A): vegetativno ispoljavanje, podrhtavanje skeletne muskulature, situaciona anksioznost, subjektivni osećaj anksioznog afekta;
3. Stres (S): poteškoća relaksacije, nervna napetost, agitacija, iritabilnost, preterana reaktivnost, nestrpljivost.

Ispitanici su na četvorostepenoj skali Likertovog tipa (raspona od 0 – nimalo do 3 – uglavnom ili skoro uvek) procenjivali kako su se osećali u poslednjih mesec dana. Skorovi *DASS*-21 su izračunavani kao zbir skorova relevantnih stavki a potom su gradirani od blage do ekstremno izražene depresivnosti, anksioznosti i stresa.

Osnovne metode statističke obrade podataka

Statistička obrada je vršena u programu *SPSS 23 for Windows*. Korelacija podataka je ispitivana bivarijantnom korelacijom varijabli i Spirmanovim *(rs)* koeficijentom. Za analizu podataka, u cilju određivanja prediktivnih faktora, korišćena je regresiona linearna analiza. Statistička značajnost je bila na nivou *p* < 0,05.

All the patients included in the study received immunomodulatory therapy (interferon beta). They all had relapsing-remitting MS.

The total EDSS score was used to assess disease severity. Patients with an EDSS score < 4 were included in the study.

The following data were registered: sex, age, marital status, disease duration, EDSS score in the preceding two years, the global PSQI score, the score on the Depression, Anxiety, and Stress Scale, as well as seven components in the form of subscores of the PSQI score.

Pittsburgh Sleep Quality Index (PSQI)

The PSQI assesses sleep quality and sleep disturbances over the preceding one-month period [27]. The PSQI questionnaire consists of nineteen questions which the patient answers himself/herself, and four questions that are answered by the patient's partner – if the patient has a partner. The nineteen individual answers generate seven subscores: subjective sleep quality, latency, duration, efficiency of sleep, use of sleeping pills, daily dysfunction. A score of ≥ 5 indicates good sleepers, while a score of < 5 is equivalent to poor sleep quality [27].

Depression, Anxiety, and Stress Scale – DASS-21

The DASS-21 scale consists of three subscales with seven items each:
1. Depression (D): dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest/involvement, anhedonia and inertia;
2. Anxiety (A): autonomic arousal, skeletal muscle effects, situational anxiety, and subjective experience of anxious affect;
3. Stress (S): difficulty relaxing, nervous arousal, being easily upset/agitated, irritable/over-reactive and impatient.

On a four-point Likert scale (range: 0 = not at all; 3 = very much or most of the time), the respondents assessed how they had felt during the preceding month. The DASS-21 scores were calculated as the sum of scores for relevant items and were then graded from mild to extremely pronounced depressive mood, anxiety, and stress.

Basic methods of statistical data processing

Statistical processing was performed in SPSS 23 for Windows. The correlation between data was tested with bivariate correlation of variables and the Spearman correlation coefficient *(rs)*. Linear regression analysis was used for data analysis, with the aim of determining predictive factors. Statistical significance was set at $p < 0.05$.

Semnic I. i sar.

POVEZANOST KVALITETA SPAVANJA I DEPRESIVNIH OBELEŽJA KOD PACIJENATA OBOLELIH OD MULTIPLE SKLEROZE
ASSOCIATION BETWEEN SLEEP QUALITY AND DEPRESSIVE SYMPTOMATOLOGY IN PATIENTS WITH MULTIPLE SCLEROSIS

REZULTATI

Osnovne sociodemografske karakteristike ispitivane grupe

U analiziranoj populaciji od 53 obolela pacijenta, najviše je bio zastupljen ženski pol (60,4%), zatim starosna grupa od 30 do 40 godina (51,1%) i bračni status (66% pacijenata je imalo partnera). Prosečna starost ispitanika je bila 37,7 godina (raspon: 19 – 56 godina). Druga po učestalosti je bila starosna grupa od 41 do 50 godina (25%).

1. Poremećaj kvaliteta spavanja u ispitivanom uzorku meren *PSQI* skorom

Više od pola ispitivanih pacijenata (56,6%) je imalo *PSQI* skor < 5, što ovu grupu bolesnika svrstava u kategoriju onih sa kvalitetnim snom (engl. *good sleepers*). Sa druge strane, 44,4% pacijenata je imalo *PSQI* skor viši od 5, te su oni spadali u kategoriju onih sa poremećajem kvaliteta spavanja (engl. *bad sleepers*).

Radi lakšeg poređenja, skorovi su svrstani u sledeće kategorije:
1. Nema poremećaja kvaliteta spavanja (*PSQI* = 0);
2. Blagi poremećaj kvaliteta spavanja (*PSQI* = 1 – 4);
3. Umereni poremećaj kvaliteta spavanja (*PSQI* = 5 – 9);
4. Teški poremećaj kvaliteta spavanja (*PSQI* =10 – 15)
5. Ekstremno teški poremećaj kvaliteta spavanja (*PSQI* = 16).

Najviše je bio zastupljen blagi poremećaj spavanja (67,9 %), praćen umerenim poremećajem spavanja (18,9%). Kod 90,6% svih ispitanika, na testu se izdvojila komponenta C5, koja objedinjuje smetnje koje prekidaju kontinuitet spavanja: buđenje u toku noći, bolovi, odlazak u kupatilo, naleti hladnoće ili toplote, poteškoće pri disanju, kašalj, košmari i hrkanje. Druga po učestalosti je bila teškoća usnivanja.

2. Poremećaj kvaliteta spavanja i sociodemografske karakteristike

Postojala je veća zastupljenost poremećaja kvaliteta spavanja kod ženske populacije (Grafikon 1). Od 36 ispitanika koji su imali blagi poremećaj spavanja, 22 osobe su bile ženskog pola (41,5% ukupnog broja ispitanika). Teži poremećaj spavanja je bio češći kod muškaraca u ispitivanoj grupi.

Bila je prisutna veća zastupljenost poremećaja kvaliteta spavanja kod osoba starosti od 30 do 50 godina (Grafikon 2). Od 31 ispitanika sa blagim poremećajem spavanja, 23 osobe su bile starosti od 30 do 50 godina (48,9% ukupnog broja ispitanika), dok je od 10 ispitanika sa umerenim poremećajem spavanja, 9 osoba bilo starosti od 30 do 50 godina (19,1% ukupnog broja ispitanika).

RESULTS

Basic sociodemographic characteristics of the examined group

In the analyzed population of 53 patients, the female sex was the most prevalent (60.4%), followed by the 30 – 40 age group (51.1%) and the status of being married (66% of the patients had a partner). The average age of the respondents was 37.7 years (range: 19 – 56 years). The second most frequent group was the 41 – 50 age group (25%).

1. Sleep quality disorders in the observed sample measured with the PSQI score

More than half of the analyzed patients (56.6%) had a PSQI score of < 5, placing this group of patients in the category of good sleepers. On the other hand, 44.4% of patients had a PSQI score of > 5, placing them in the category of those with sleep quality disorder – bad sleepers.

For easier comparison, the scores were divided into the following categories:
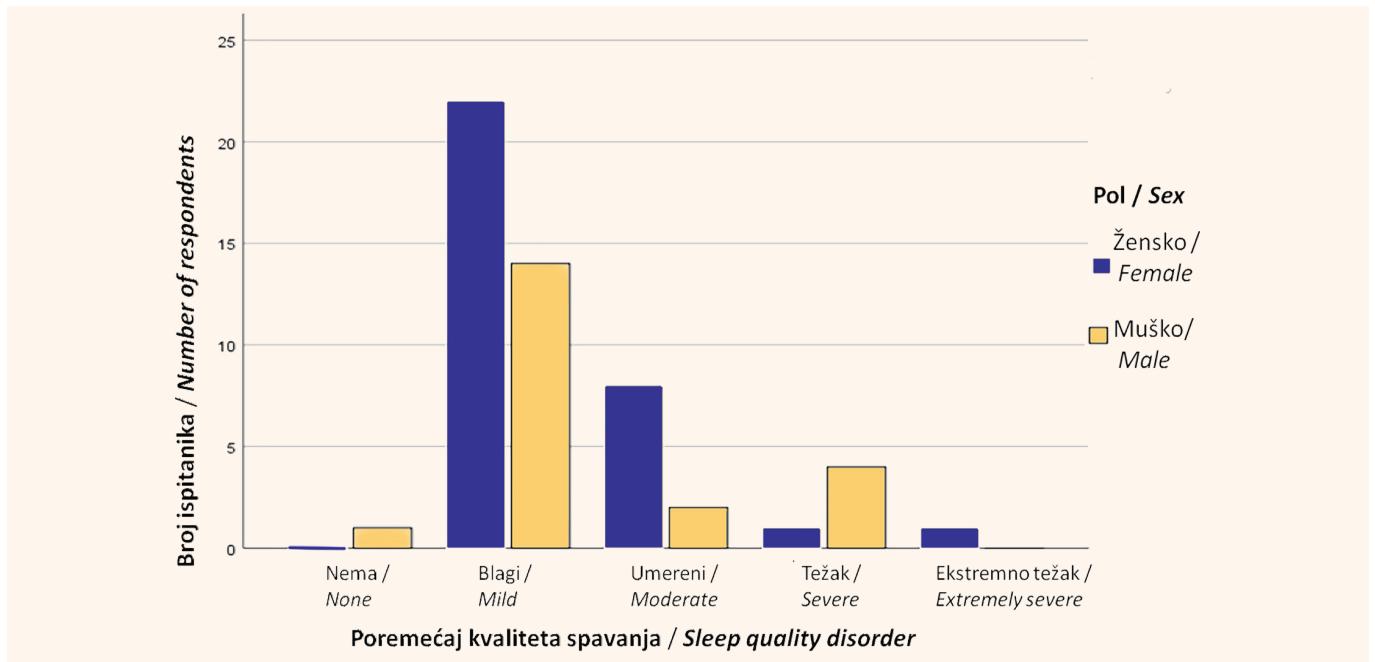1. No sleep quality disorder (PSQI = 0);
2. Mild sleep quality disorder (PSQI = 1 – 4);
3. Moderate sleep quality disorder (PSQI = 5 – 9);
4. Severe sleep quality disorder (PSQI =10 – 15)
5. Extremely severe sleep quality disorder (PSQI = 16).

Mild sleep quality disorder was the most prevalent (67.9 %), followed by moderate sleep quality disorder (18.9%). In 90.6% of all respondents, the C5 component stood out on the test. This component incorporates disturbances that interrupt sleep continuity: waking up during the night, pain, visits to the bathroom, hot or cold flashes, trouble breathing, coughing, nightmares, and snoring. The second most prevalent component was difficulty falling asleep.

2. Sleep quality disorder and sociodemographic characteristics

There was a higher prevalence of sleep quality disorder in the female population (Graph 1). Of the 36 respondents with mild sleep disorder, 22 were female (41.5% of the total number of respondents). In the analyzed group, severe sleep disorder was more frequent in men.

A higher prevalence of sleep quality disorder was registered in the 30 – 50 age group (Graph 2). Of the 31 respondents with mild sleep disorder, 23 individuals were aged between 30 and 50 years (48.9% of the total number of respondents), while of the 10 respondents with moderate sleep disorder, 9 persons were aged 30 to 50 years (19.1% of the total number of respondents).
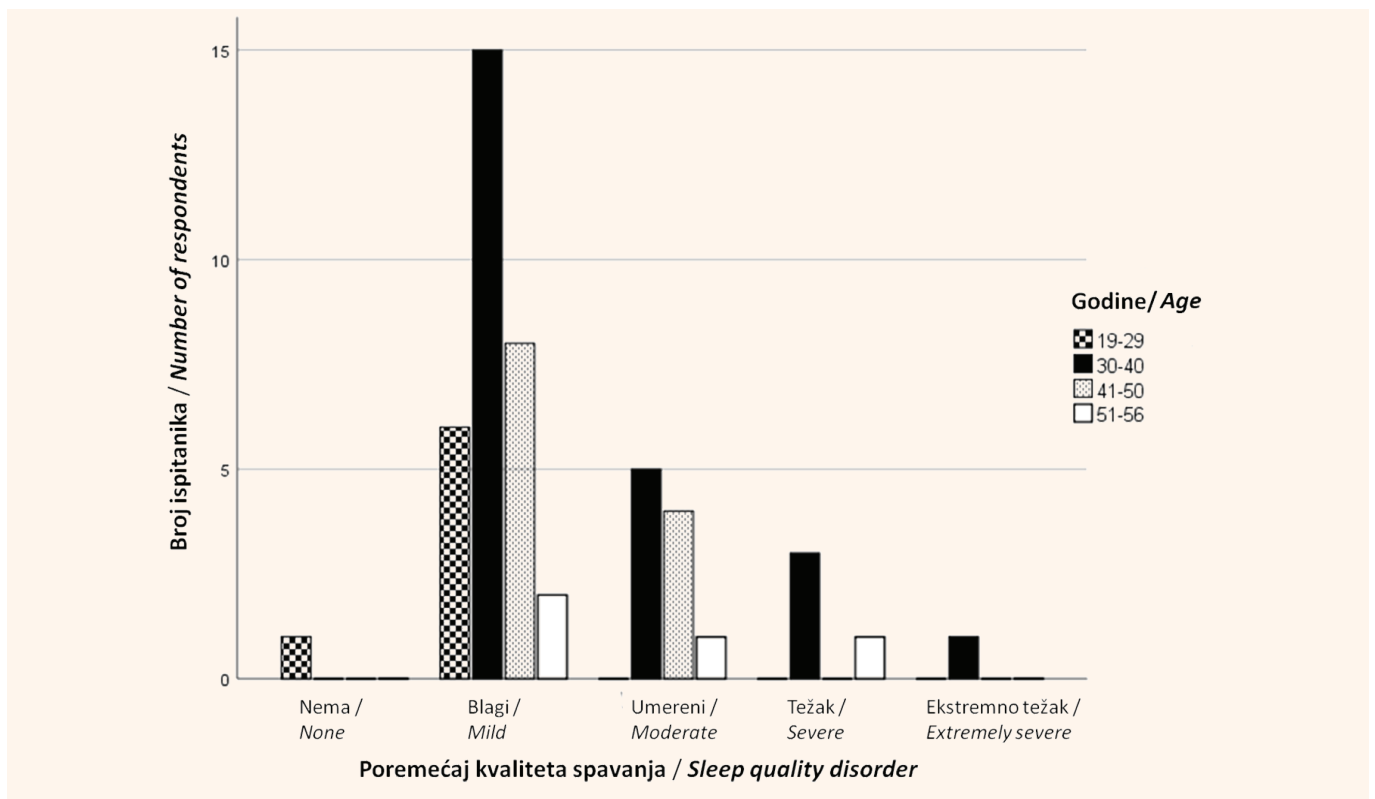
Grafikon 1. Težina poremećaja kvaliteta spavanja u odnosu na pol

Figure 1. Severity of sleep quality disorder in relation to sex

Primenom Spirmanovog koeficijenta, utvrđena je korelacija između godina starosti ispitanika i *PSQI* skora ($rs = 0{,}291$; $p = 0{,}047$). Iako je postojala statistički značajna korelacija između godina i *PSQI* skora, linearne regresije su ukazale na to da broj godina života nije bio dobar prediktivni faktor *PSQI* skora ($p = 0{,}079$), iako se približio statističkoj značajnosti.

The Spearman correlation coefficient established a correlation between the age of the respondents and the PSQI score ($rs = 0.291$; $p = 0.047$). Although there was a statistically significant correlation between age and the PSQI score, linear regression analyses indicated that age was not a good predictive factor of the PSQI score ($p = 0.079$), although it approached statistical significance.

Grafikon 2. Težina poremećaja kvaliteta spavanja u odnosu na godine

Figure 2. Severity of sleep quality disorder in relation to age

Semnic I. i sar.

POVEZANOST KVALITETA SPAVANJA I DEPRESIVNIH OBELEŽJA KOD PACIJENATA OBOLELIH OD MULTIPLE SKLEROZE
ASSOCIATION BETWEEN SLEEP QUALITY AND DEPRESSIVE SYMPTOMATOLOGY IN PATIENTS WITH MULTIPLE SCLEROSIS

Postojala je veća zastupljenost poremećaja kvaliteta spavanja kod osoba koje su navele da imaju partnera – od 36 ispitanika sa blagim poremećajem spavanja, 24 osobe su imale partnera (45,3% ukupnog broja ispitanika). Izuzetak je bio teški poremećaj spavanja u kome je dominirao udeo ispitanika bez partnera (četiri ispitanika od pet nije imalo partnera).

Primenom Spirmanovog koeficijenta nije utvrđen uticaj pola kao ni bračnog statusa na *PSQI* skor. U ispitivanoj grupi, najviše je bio izražen uticaj starijeg životnog doba na kvalitet spavanja ($p = 0,079$).

3. Poremećaj kvaliteta spavanja i klinička obeležja multiple skleroze u ispitivanoj grupi

EDSS skor od jedan je imao najveću učestalost i javio se kod 26,4% ispitanika, dok je najveća zastupljenost dužine trajanja bolesti bila 5 godina (17,3% ispitanika). Primenom Spirmanovog koeficijenta nije utvrđena statistički značajna povezanost *EDSS* skora i kvaliteta spavanja ($p = 0,18$; $rs = 0,187$), kao ni između dužine trajanja bolesti i kvaliteta spavanja ($p = 0,364$; $rs = 0,128$).

4. Učestalost depresije, anksioznosti i stresa u ispitivanoj grupi

Depresija se javila kod 36,8% ukupnog broja pacijenata. Najviše je bila zastupljena blaga depresivnost, koja se javila kod 17% ispitanika, a sledila ju je umerena depresivnost sa učestalošću od 13,2%. Anksioznost se javila kod 37,8% ukupnog broja pacijenata. Najviše je bila zastupljena blaga anksioznost, koja se javila kod 11,3% ispitanika. Ekstremno izražena anksioznost je u ispitivanom uzorku bila učestalija od izražene anksio-

There was a higher prevalence of sleep quality disorder in persons stating that they had a partner – of the 36 respondents with mild sleep disorder, 24 persons had a partner (45.3% of the total number of respondents). The exception was severe sleep disorder where the ratio of respondents without a partner was predominant (four out of five respondents did not have a partner).

The Spearman correlation coefficient established no effect of sex or marital status on the PSQI score. In the examined group, the impact of older age on the quality of sleep was the most prominent ($p = 0.079$).

3. Sleep quality disorder and clinical markers of multiple sclerosis in the examined group

The EDSS = 1 score was the most frequent and occurred in 26.4% of respondents, while the highest prevalence of disease duration was five years (17.3% of respondents). No statistically significant association between the EDSS score and sleep quality was determined ($p = 0.18$; $rs = 0.187$). In the same way, no statistically significant association was established between disease duration and sleep quality ($p = 0.364$; $rs = 0.128$).

4. Frequency of depression, anxiety, and stress in the examined group

Depression occurred in 36.8% of the total number of patients. Mild depressive mood was the most common, occurring in 17% of respondents, followed by moderate depressive mood, with a frequency of 13.2%. Anxiety occurred in 37.8% of the total number of patients. Mild anxiety was the most frequent, occurring in
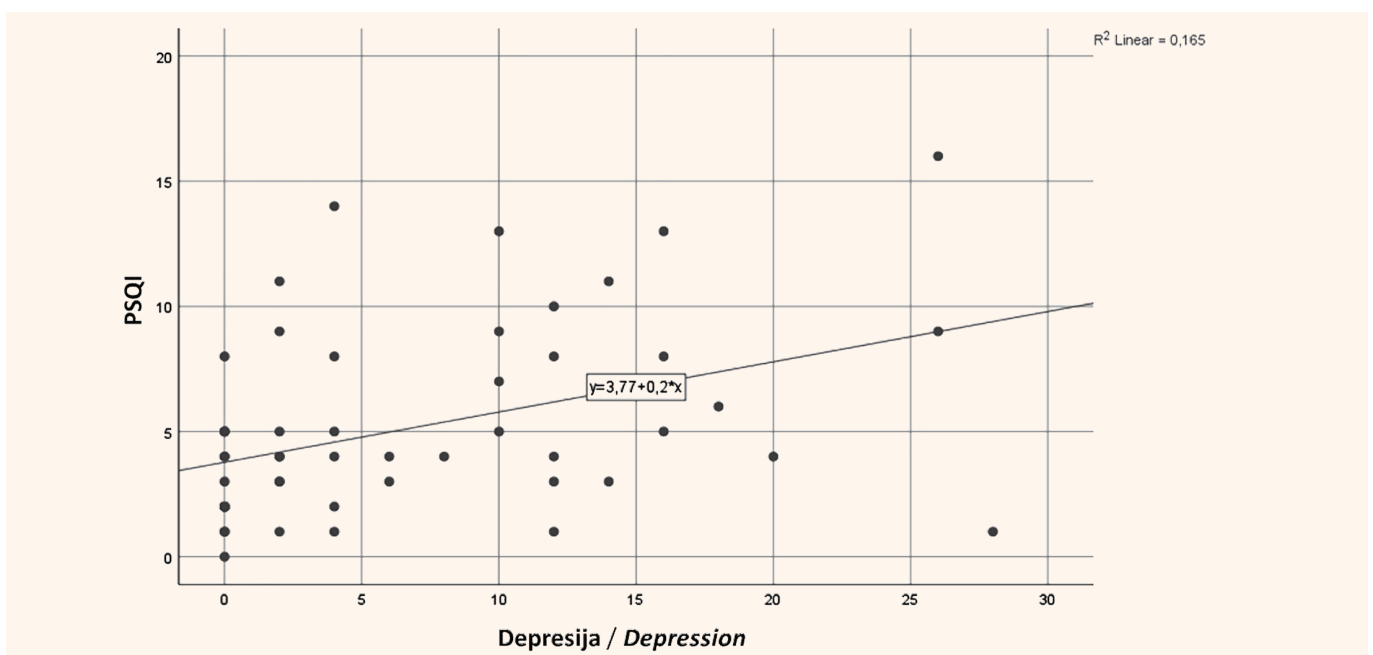
Grafikon 3. Povezanost depresivnosti i *PSQI* skora

Figure 3. Association between depression and the PSQI score

POVEZANOST KVALITETA SPAVANJA I DEPRESIVNIH OBELEŽJA KOD PACIJENATA OBOLELIH OD MULTIPLE SKLEROZE
ASSOCIATION BETWEEN SLEEP QUALITY AND DEPRESSIVE SYMPTOMATOLOGY IN PATIENTS WITH MULTIPLE SCLEROSIS

Semnic I. et al.

znosti. Stres se javio kod 26,4% ukupnog broja pacijenata. Najviše je bio zastupljen umereni stres, koji se javio kod 6 od 14 pacijenata (11,3 %), za kojim sledi blagi stres, sa učestalošću od 9,4% (5 od 14 pacijenata).

5.1. Povezanost depresivnosti i kvaliteta spavanja

Depresivnost se pokazala kao dobar prediktor *PSQI* skora ($p = 0,003$; $rs = 0,406$). Spirmanovim koeficijentom je pokazana statistički značajna korelacija između depresivnosti i *PSQI* skora ($p = 0,001$; $rs = 0,427$), (Grafikon 3).

5.2. Povezanost anksioznosti i kvaliteta spavanja

Spirmanovim koeficijentom je utvrđena statistički značajna korelacija između anksioznosti i *PSQI* skora ($p < 0,001$; $rs = 0,543$). U ispitivanom uzorku, anksioznost je bila dobar pokazatelj *PSQI* skora ($p < 0,001$; $rs = 0,537$), što je prikazano u grafikonu bivarijantne linearne regresije (Grafikon 4).

5.3. Povezanost stresa i kvaliteta spavanja

Spirmanovim koeficijentom je utvrđena statistički značajna povezanost stresa i *PSQI* skora ($p = 0,004$; $rs = 0,391$). U ispitivanom uzorku, stres je bio dobar pokazatelj *PSQI* skora ($p < 0,001$; $rs = 0,481$), što je prikazano u grafikonu bivarijantne linearne regresije, (Grafikon 5).

DISKUSIJA

Sociodemografska obeležja ispitivane grupe pacijenata obolelih od MS-a bila su veća zastupljenost osoba ženskog pola (41,5%) i veća zastupljenost starosne gru-

11.3% of the respondents. Extreme anxiety was more frequent in the analyzed sample than severe anxiety. Stress occurred in 26.4% of the total number of patients. Moderate stress was most common, occurring in 6 out of 14 patients (11.3 %), followed by mild stress, with a frequency of 9.4% (5 out of 14 patients).

## 5.1. Association between depressive mood and sleep quality

Depressive mood proved to be a good predictor of the PSQI score ($p = 0.003$; $rs = 0.406$). The Spearman correlation coefficient showed a statistically significant correlation between depressive mood and the PSQI score ($p = 0.001$; $rs = 0.427$), (Graph 3).

5.2. Association between anxiety and sleep quality

The Spearman correlation coefficient showed a statistically significant correlation between anxiety and the PSQI score ($p < 0.001$; $rs = 0.543$). In the analyzed sample, anxiety was a good indicator of the PDQI score ($p < 0.001$; $rs = 0.537$), as presented in the bivariate linear regression graph (Graph 4).

5.3. Association between stress and sleep quality

The Spearman correlation coefficient found a statistically significant association between stress and the PSQI score ($p = 0.004$; $rs = 0.391$). In the examined sample, stress was a good indicator of the PSQI score ($p < 0.001$; $rs = 0.481$), as presented in the bivariate linear regression graph (Graph 5).
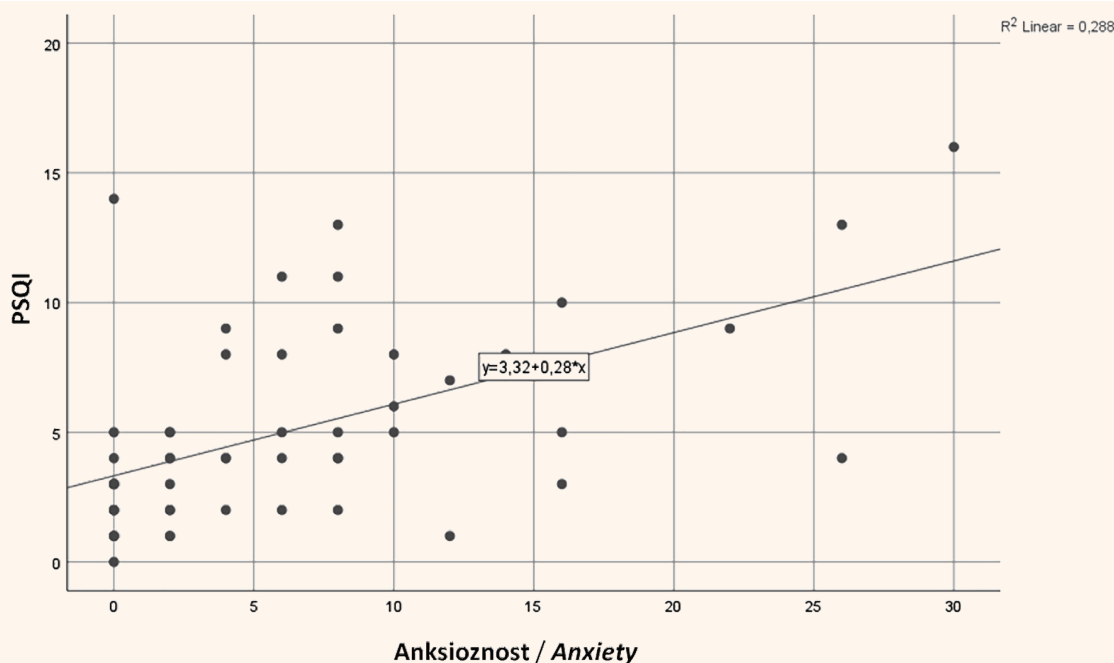
Grafikon 4. Povezanost anksioznosti i *PSQI* skora

Figure 4. Association between anxiety and the PSQI score
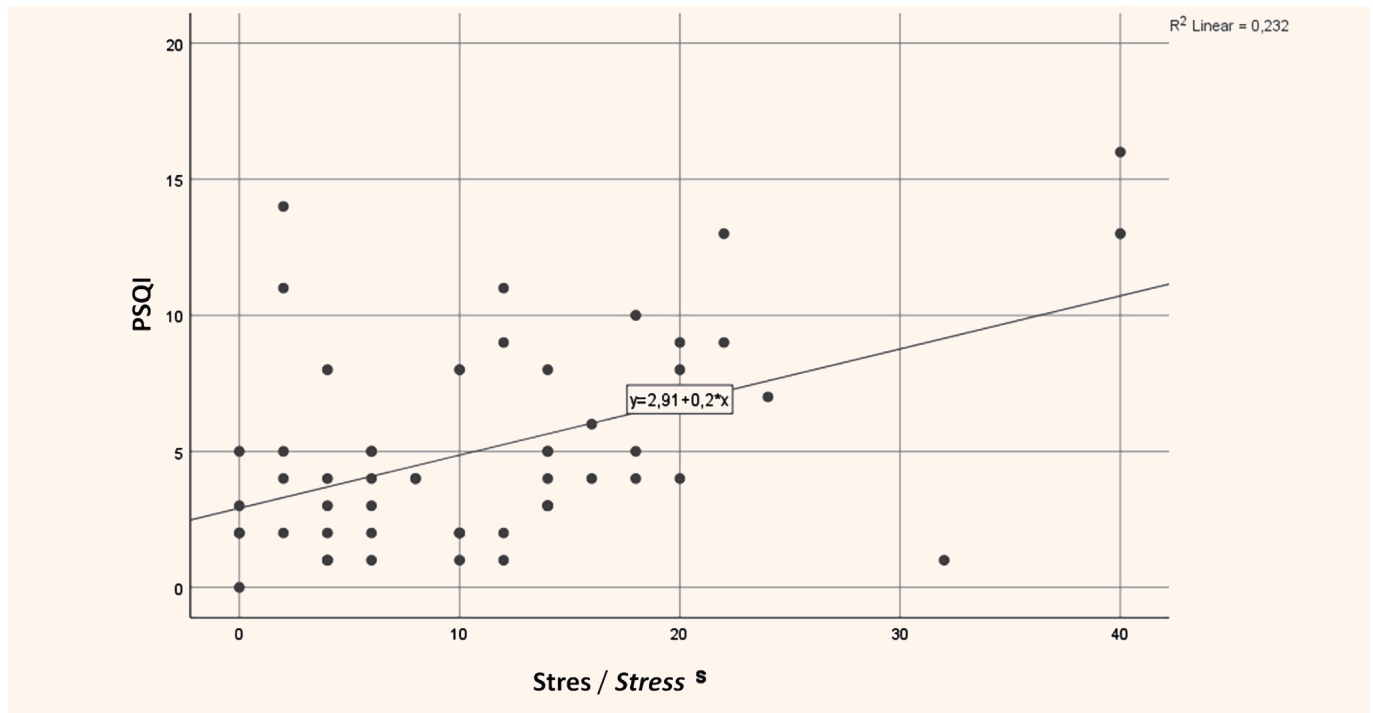
Grafikon 5. Povezanost stresa i *PSQI* skora

Figure 5. Association between anxiety and the PSQI score

pe od 30 do 40 godina (51,1%), što je u skladu sa podacima iz literature [2]. Tok multiple skleroze kod svih ispitivanih pacijenata u ovoj studiji je bio relapsno-remitentan. Dugotrajna praćenja ispitanika ukazuju na to da na početku bolesti, 85% - 90% bolesnika ima relapsno-remitentnu formu bolesti, dok preostalih 10% - 15% bolesnika ima primarno progresivni tok. Ovo je razlog zašto su našim istraživanjem obuhvaćeni pacijenti sa relapsno-remitentnim tokom.

Kvalitet spavanja kod obolelih od multiple skleroze

Loš kvalitet spavanja je čest nalaz kod pacijenata obolelih od MS-a. U istraživanju koje su sproveli Mankoni i saradnici, 2008. godine, prevalencija lošeg kvaliteta spavanja je bila 47,5% [11], dok su naši rezultati pokazali da je 44,4% pacijenata ispitivane grupe imalo loš kvalitet spavanja, odnosno *PSQI* skor viši od 5. U odnosu na aspekte poremećaja kvaliteta spavanja u našem istraživanju, kod 90,6% svih ispitanika se izdvaja komponenta koja objedinjuje smetnje koje prekidaju kontinuitet spavanja (buđenje u toku noći, hronični bolovi, smena naleta toplote i hladnoće, dizestezije). Literaturni podaci navode da je i do 40% pacijenata obolelih od MS-a pod rizikom od razvoja hronične nesanice [19]. Autori ističu značaj inicijalne nesanice kao najvažniju i najučestaliju subjektivnu tegobu pacijenata [28, 29]. I u našem istraživanju je postojala značajna učestalost poteškoće usnivanja, koja se javila kod 58,5% pacijenata. U literaturi je utvrđena veza između nesanice, depre-

DISCUSSION

The sociodemographic markers of the analyzed group of MS patients were a higher prevalence of female subjects (41.5%) and a higher prevalence of the 30 – 40 age group (51.1%), which is in keeping with data found in literature [2]. All the analyzed patients had the relapsing-remitting form of multiple sclerosis. Long-term follow-up indicates that, at the onset of disease, 85% - 90% of MS patients have the relapsing-remitting form of the disease, while the remaining 10% - 15% of patients have the primary progressive form of MS. This is the reason why our study included patients with the relapsing-remitting course of MS.

Sleep quality in patients suffering from multiple sclerosis

Poor sleep quality is a common finding in MS patients. In a study carried out by Manconi et al., in 2008, the prevalence of poor sleep quality was 47.5% [11], while our results showed that 44.4% of patients in the examined group had poor sleep quality, i.e., a PSQI score higher than 5. In relation to the aspects of sleep quality disorder in our study, in 90.6% of all respondents the component integrating disturbances interfering with sleep continuity (waking up during the night, chronic pain, alternating hot and cold flashes, dysesthesia) was most prominent. Literature data state that up to 40% of MS patients are at risk of developing chronic insomnia [19]. Authors stress the significance of initial insomnia

sije i bola, kao i činjenica da lečenje nesanice može da ublaži ove simptome [30]. Prema istraživanjima, većina slučajeva nesanice kod pacijenata sa MS-om je sekundarna, zbog pridružene anksioznosti/depresije ili zbog fizičkih simptoma koji uzrokuju noćnu nelagodu, poput neurogene mokraćne bešike [20].

U našoj studiji, učestalost poremećaja spavanja je bila veća kod ženskog pola, ali nije bila povezana sa višim *PSQI* skorom (*p* = 0,914), što se razlikuje od rezultata pojedinih studija u kojima je dokazana značajna povezanost pola i *PSQI* skora (*p* = 0,040) [30]. Najveća učestalost lošeg spavanja je bila kod pacijenata u starosnoj grupi od 30 do 50 godina, a dokazana je i statistički značajna povezanost godina starosti ispitanika i *PSQI* skora (*p* = 0,047; *rs* = 0,291). Međutim, starost nije bila prediktivni faktor višeg skora. Merlino i saradnici su, 2009. godine, takođe pokazali da je starost povezana sa *PSQI* skorom (*p* = 0,001) ali ne i bračni status (*p* = 0,080) [28]. I našim istraživanjem je potvrđeno da ne postoji korelacija između bračnog statusa i lošeg kvaliteta spavanja.

U pogledu povezanosti težine bolesti i poremećaja kvaliteta spavanja, izveštaji literature nisu konzistentni. U našem istraživanju nije pronađena povezanost težine bolesti, procenjene *EDSS* skorom, i kvaliteta spavanja, što ne odgovara podacima iz literature. Merlino i saradnici su pokazali znatno viši *EDSS* skor kod obolelih sa lošijim kvalitetom spavanja i dokazali značajnu povezanost navedenih varijabli (*p* = 0,009) [28]. Za razliku od navedenog istraživanja, Stanton i saradnici su, 2006. godine, pokazali da *PSQI* skor nije zavisan od *EDSS* skora, što su rezultati našeg istraživanja i potvrdili (*p* = 0,180) [29]. Našim istraživanjem nije utvrđena povezanost dužine trajanja bolesti i *PSQI* skora (*p* = 0,364), što je u saglasnosti sa drugim istraživanjima [28].

Promene ponašanja kod pacijenata obolelih od multiple skleroze

Depresija se javila kod 35,8% pacijenata sa MS-om u našem istraživanju. Studije sugerišu da je klinička depresija, kao najteži oblik, češća među obolelima od MS-a nego u opštoj populaciji ili kod mnogih drugih hroničnih bolesti, kao i da je rizik od samoubistva veći kod pacijenata sa MS-om [31]. Štaviše, depresija je važna odrednica kvaliteta života u MS-u i možda je najvažniji faktor koji ga određuje [23]. Studija sprovedena 2015. godine je otkrila da je skoro polovina učesnika sa multiplom sklerozom imala emocionalne promene (poput zaravnjenog emocionalnog afekta ili smanjene emocionalne kontrole), koje su bile suptilnije i teže ih je bilo otkriti od depresije ili anksioznosti. Kako čak i suptilne emocionalne promene takođe utiču na kvalitet života, istraživači ukazuju na važnost njihovog prepoznavanja [32].

as the most important and most frequent subjective patient complaint [28,29]. In our study, as well, there was a significant frequency of difficulty falling asleep, occurring in 58.5% of patients. Literature has established an association between insomnia, depression, and pain, as well as the fact that treating insomnia can alleviate these symptoms [30]. According to research data, most cases of insomnia in MS patients are secondary, due to associated anxiety/depression or due to physical symptoms causing nighttime discomfort, such as neurogenic bladder [20].

In our study, the frequency of sleep disorder was higher in female subjects but was not associated with a higher PSQI score (*p* = 0.914), which is different from the results of certain studies wherein a significant association between sex and the PSQI score was proven (*p* = 0.040) [30]. The highest frequency of poor sleep was in patients belonging to the 30 – 50 age group, and a statistically significant association was proven between respondent age and the PSQI score, as well (*p* = 0.047; *rs* = 0.291). However, age was not a predictive factor of a higher score. In 2009, Merlino et al. also showed an association between age and the PSQI score (*p* = 0.001), but no association between marital status and PSQI (*p* = 0.080) [28]. Our study also confirmed that there was no correlation between marital status and poor sleep quality.

With regards to the association between disease severity and sleep quality disorder, literature data are not consistent. In our study, no association was found between disease severity, assessed with the EDSS score, and sleep quality, which does not correspond to literature data. Merlino et al. reported a significantly higher EDSS score in patients with poorer sleep quality and proved a significant association between the said variables (*p* = 0.009) [28]. As opposed to the aforementioned study, Stanton et al. showed, in 2006, that the PSQI score was not dependent on the EDSS score, which was also confirmed by the results of our study (*p* = 0.180) [29]. Our study did not find an association between disease duration and the PSQI score (*p* = 0.364), which is in keeping with other studies [28].

Behavioral changes in patients suffering from multiple sclerosis

Depression occurred in 35.8% of MS patients included in our study. Studies suggest that clinical depression, as the most severe from, is more frequent amongst MS patients than in the general population or in patients suffering from many other chronic diseases, as well as that the risk of suicide is higher in MS patients [31]. In fact, depression is an important determinant of the quality of life in MS and maybe the most important factor defining it [23]. A study carried out in 2015 discov-

U istraživanju Galeazija i saradnika, anksioznost se javila kod 36% pacijenata u okviru ispitivane grupe [33], dok je u našem istraživanju anksioznost bila zastupljena kod 37,8% obolelih, i učestalija od depresije. Smit i Jang su procenili prevalenciju anksioznosti i depresije na uzorku od 88 pacijenata koji su pohađali savetovalište za MS, koristeći Bolničku skalu za anksioznost i depresiju (engl. *Hospital Anxiety and Depression Scale - HADS*), gde su rezultati pokazali prevalenciju od 34% pacijenata obolelih od MS-a i 40% njihovih partnera [34].

Indikatori stresa su se u našoj grupi javili sa učestalošću od 26,4%. Voren i saradnici su, 1982. godine, prikazali značajno višu prevalenciju stresa kod ispitivane grupe (79%) nego kod kontrolne grupe (54%) [35].

Interferon i depresija kod obolelih od multiple skleroze

Pojavom interferona beta kao terapije relapsno-remitentne multiple skleroze, javila se zabrinutost u vezi sa potencijalom ovog leka da izazove ili pogorša depresiju. U studiji engleske istraživačke grupe, zabeležena je znatno veća stopa depresije (20%) među 193 pacijenta lečenih interferonom nego među 190 kontrola, koje su dobile samo placebo (13%) [36]. Promene ponašanja treba posebno proceniti kao deo holističkog pristupa u terapiji MS-a, s obzirom na širok spektar mera koje se koriste za dijagnostikovanje i kvantifikovanje težine psiholoških fenomena. Postoji malo ili nimalo slaganja među istraživačima o kliničkom zlatnom standardu za dijagnostikovanje depresije kod pacijenata sa MS-om. Ovome se pridružuje rizik da somatski simptomi, kao što je umor, mogu uticati na procenu prevalencije depresije u multiploj sklerozi.

Povezanost spavanja sa depresivnošću, anksioznošću i stresom kod obolelih od multiple skleroze

U našem ispitivanju, Spirmanovim koeficijentom je utvrđena statistički značajna povezanost depresivnosti i *PSQI* skora (*p* = 0,001; *rs* = 0,427). U ispitivanom uzorku, depresivnost je bila dobar pokazatelj *PSQI* skora (*p* = 0,003; *rs* = 0,406). Ovo potvrđuje rezultate prethodnih istraživanja koja ubrajaju depresiju u jedan od najvažnijih faktora koji doprinosi lošem kvalitetu spavanja kod pacijenata obolelih od MS-a [30]. Rezultati istraživanja dokazuju dvosmernu relaciju između depresije i kvaliteta spavanja, odnosno depresija se pokazala kao dobar prediktor lošeg kvaliteta spavanja i obrnuto [28].

Spirmanovim koeficijentom utvrđena je statistički značajna povezanost anksioznosti i *PSQI* skora (*p* < 0,001; *rs* = 0,543). U ispitivanom uzorku, anksioznost je bila dobar pokazatelj *PSQI* skora (*p* < 0,001;

ered that almost half of the participants with multiple sclerosis experienced emotional changes (such as flat emotional affect or reduced emotional control), which were more subtle and more difficult to detect than depression or anxiety. Since even subtle emotional changes also affect the quality of life, researchrs point out the importance of their detection [32].

In a study by Galeazzi et al., anxiety occurred in 36% of the patients within the analyzed group [33], while in our study anxiety was present in 37.8% of the patients and was more frequent than depression. Smith and Young assessed the prevalence of anxiety and depression in a sample of 88 patients attending an MS clinic, using the Hospital Anxiety and Depression Scale (HADS), with the results indicating a prevalence of 34% of MS patients and 40% of their partners [34].

Indicators of stress occurred in our study with a frequency of 26.4%. In 1982, Warren et al. demonstrated a significantly higher prevalence of stress in the analyzed group of patients (79%), as compared to the control group (54%) [35].

Interferon and depression in patients suffering from multiple sclerosis

With the advent of interferon beta as the treatment for relapsing-remitting multiple sclerosis, concern arose regarding the potential of this drug to cause or exacerbate depression. In a study carried out by an English group of researchers, a significantly higher depression rate (20%) was registered among 193 patients treated with interferon than among 190 controls, who received only placebo (13%) [36]. Behavioral changes should be especially assessed as a part of the holistic approach to the treatment of MS, bearing in mind the wide array of measures applied in the diagnostics and quantification of the severity of the psychological phenomena. There is little or no consensus among researchers on the clinical standard for diagnosing depression in patients with MS. Additionally, there is a risk that somatic symptoms, such as fatigue, may affect the assessment of the prevalence of depression in multiple sclerosis.

Association between sleep and depressive mood, anxiety and stress in patients suffering from multiple sclerosis

In our study, with the use of the Spearman correlation coefficient, it was found that there was a statistically significant association between depressive mood and the PSQI score (*p* = 0.001; *rs* = 0.427). In the analyzed sample, depressive mood was a good indicator of the PSQI score (*p* = 0.003; *rs* = 0.406). This confirms the results of previous studies which include depression amongst the most important factors contributing to

POVEZANOST KVALITETA SPAVANJA I DEPRESIVNIH OBELEŽJA KOD PACIJENATA OBOLELIH OD MULTIPLE SKLEROZE
ASSOCIATION BETWEEN SLEEP QUALITY AND DEPRESSIVE SYMPTOMATOLOGY IN PATIENTS WITH MULTIPLE SCLEROSIS

Semnic I. et al.

rs= 0,5). Rezultat potvrđuje prethodna istraživanja po kojima je anksioznost i uzrok i posledica lošeg kvaliteta spavanja, i da je, uz depresiju, najviše povezana sa lošim spavanjem, u odnosu na ostale varijable (pol, trajanje bolesti, ozbiljnost bolesti, terapija) [13]. Merlino i saradnici su, 2009. godine, dobili drugačiji rezultat, u kome je kvalitet spavanja bio striktno zavisan od depresije, ali ne i od anksioznosti [28]. Ovim istraživanjem je pokazano da se i primenom skrining skale, kao što je *DASS*-21, može potvrditi postojanje afektivnih smetnji, kao i njihova povezanost sa promenjenim kvalitetom spavanja. *DASS*-21 skala spada u orijentacione metode, te su za suptilne promene afektivnog statusa neophodne dodatne i specifične procene. Ograničenje datog istraživanja je mali uzorak. Pravci budućeg istraživanja na ovom području mogu biti poređenje kvaliteta spavanja pacijenata lečenih imunomodulatornom terapijom u odnosu na druge terapijske modalitete.

Kvalitet spavanja i afektivni status kod pacijenata obolelih od multiple skleroze tokom pandemije KOVID-19 oboljenja

Mali broj istraživanja se bavio problematikom lošijeg kvaliteta spavanja kod pacijenata sa MS-om, pre i tokom pandemije KOVID-19 oboljenja. Stojanov i saradnici su dokazali da je *PSQI* skor bio znatno viši kod obolelih od MS-a relapsno-remitentnog toka, tokom pandemije KOVID-19 oboljenja, u odnosu na zdravu kontrolnu grupu, kao i u odnosu na period pre izbijanja pandemije [37]. Dokazano je da je *PSQI* skor korelirao sa ženskim polom, nižim nivoom obrazovanja i partnerskim statusom kod pacijenata sa MS-om, u većoj meri tokom pandemije nego u standardnim životnim okolnostima. Rezultati ove studije ukazali su na neophodnost skriniga i monitoringa umora i kvaliteta spavanja u populaciji pacijenata sa MS-om, naročito tokom pandemija [37]. Uzevši u obzir etiologiju multiple skleroze, gde virusna infekcija može biti jedan od ključnih faktora pogoršanja bolesti, koja doprinosi lošijem kvalitetu sna i života, dalja istraživanja u ovom pravcu su ključna [37].

Istraživanja su pokazala da je pandemija KOVID-19 oboljenja takođe imala značajni uticaj na psihološki status pacijenata obolelih od MS-a sa relapsno-remitentnim oblikom bolesti (RRMS) [38]. U studiji koja je uključila 95 pacijenata sa relapsno-remitentnim oblikom bolesti, kao najčešća briga pacijenata navodi se strah od mogućnosti zaraze i nedostatka specifičnog tretmana u slučaju egzacerbacije hronične bolesti i povećanja broja relapsa. U istoj studiji dokazano je da je nivo anksioznosti tokom pandemije KOVID-19 oboljenja bio značajno viši u grupi pacijenata sa MS-om nego u zdravoj kontrolnoj grupi [38]. U ovom istraživa-

poor sleep quality in MS patients [30]. The study results prove a bidirectional relationship between depression and sleep quality, i.e., depression proved to be a good predictor of poor sleep quality and vice versa [28].

The Spearman correlation coefficient found a statistically significant association between anxiety and the PSQI score ($p < 0.001$; $rs = 0.543$). In the analyzed sample, anxiety was a good indicator of the PSQI score ($p < 0.001$; $rs = 0.5$). The result confirms the results of previous studies, according to which anxiety is both the cause and effect of poor sleep quality and, along with depression, has the highest association with poor sleep quality, as compared to other variables (sex, disease duration, disease severity, therapy) [13]. In 2009, Merlino et al. arrived at a different result, wherein sleep quality was strictly dependent on depression, but not on anxiety [28]. This study showed that by applying a screening scale, such as the DASS-21, the presence of psychological problems can be confirmed, as well as their association with change in sleep quality. The DASS-21 scale belongs to the category of approximative methods, which is why additional specific assessments are necessary for subtle changes in psychological status. A limitation of the study is the small size of the sample. Possible directions of future research in this area may be aimed at comparing the sleep quality of patients treated with immunomodulatory therapy and other therapeutic modalities.

Sleep quality and the psychological status of patients suffering from multiple sclerosis during the COVID-19 pandemic

Few studies have been focused on poor sleep quality in MS patients, before and during the COVID-19 pandemic. Stojanov et al. proved that the PSQI score was considerably higher in patients suffering from relapsing-remitting MS, during the COVID-19 pandemic, in comparison with the healthy control group, as well as in comparison with the period prior to the outbreak of the pandemic [37]. It was proven that the PSQI score correlated with the female sex, a lower education level, and the partnership status in MS patients, to a greater extent during the pandemic than in standard life circumstances. The results of this study indicated the necessity of screening and monitoring fatigue and sleep quality in the population of MS patients, especially during pandemics [37]. Bearing in mind the etiology of multiple sclerosis, where viral infection may be one of the key factors in disease exacerbation, contributing to poorer sleep quality and quality of life, further research in this direction is crucial [37].

Studies have shown that the COVID-19 pandemic also had significant impact on the psychological sta-

nju, jedan od uzroka anksioznosti bila je nemogućnost odlaska u bolnicu zbog epidemiološke situacije [38]. Pretpostavku da je psihološka patnja tokom i nakon pandemije KOVID-19 oboljenja bila izraženija kod ljudi sa hroničnim bolestima, poput MS-a, potvrdila je i velika studija kineske populacije [39]. Studijom srpske, ali i drugih istraživačkih grupa, pokazano je da su restriktivne mere za vreme pandemije, uprkos njihovom pozitivnom učinku sa epidemiološkog aspekta, doprinele lošijem kvalitetu života i većoj incidenciji depresivnosti i stresa kod pacijenata sa MS-om [38].

ZAKLJUČAK

Prema skali za procenu kvaliteta spavanja – *Pittsburgh Sleep Quality Index* (*PSQI*), utvrđeno je da je 44,4% pacijenata obolelih od multiple skleroze imalo lošiji kvalitet spavanja (*PSQI* > 5). Iako je postojala veća zastupljenost promena kvaliteta spavanja kod ženskog pola i starosne grupe od 30 do 50 godina, nije utvrđena statistički značajna povezanost ženske populacije, starijeg životnog doba i partnerskog statusa, sa jedne strane, i lošijeg kvaliteta spavanja, sa druge. Primenom *Expanded Disability Status Scale* (*EDSS*) skora nije dokazan uticaj dužine trajanja bolesti na kvalitet spavanja. Depresivnost se u ispitivanoj grupi javila sa učestalošću od 35,8%, anksioznost sa 37,8%, a stres sa 26,4%. Afektivni simptomi su imali negativni uticaj na kvalitet spavanja. Pacijenti oboleli od multiple skleroze koji su bili na imunomodulatornoj terapiji, imali su lošiji kvalitet spavanja ukoliko su imali viši skor na Skali depresije, anksioznosti i stresa (engl. *Depression, Anxiety, and Stress Scale – DASS*-21). Pandemija KOVID-19 oboljenja je imala značajni uticaj na kvalitet spavanja i na psihološki status pacijenata obolelih od MS-a, što implicira potrebu za adekvatnim tretmanom i psihološkom podrškom.

Sukob interesa: Nije prijavljen.

LITERATURA / *REFERENCES*

1. Compston A, Coles A. Multiple sclerosis. Lancet. 2008 Oct 25;372(9648):1502-17. doi: 10.1016/S0140-6736(08)61620-7.

2. World Health Organization and Multiple Sclerosis International Federation. Atlas: multiple sclerosis resources in the world 2008. [Internet]. 2008. Dostupno: https://apps.who.int/iris/handle/10665/43968.

3. Poser S, Poser W, Schlaf G, Firnhaber W, Lauer K, Wolter M, et al. Prognostic indicators in multiple sclerosis. Acta Neurol Scand. 1986 Nov;74(5):387-92. doi: 10.1111/j.1600-0404.1986.tb03531.x.

4. Kostić V, Apostolski S, Bulat P, Bumbaširević L, Cerovac N, Dragašević N, et al. Neurologija za studente medicine. Drugo izdanje. Beograd: Medicinski fakultet u Beogradu; 2016. p397.

5. Dyment DA, Ebers GC, Sadovnick AD. Genetics of multiple sclerosis. Lancet Neurol. 2004 Feb;3(2):104-10. doi: 10.1016/s1474-4422(03)00663-x.

tus of patients suffering from relapsing-remitting MS (RRMS) [38]. In a study involving 95 patients with relapsing-remitting MS, as the greatest patient concern, the fear of possible infection and of the lack of specific treatment in case of chronic disease exacerbation and the increase in the number of relapses, was reported. In the same study, it was proven that the anxiety level during the COVID-19 pandemic was significantly higher in the group of MS patients than in the healthy control group [38]. In this study, one of the causes of anxiety was the impossibility of going to hospital due to the epidemiological situation [38]. The assumption that psychological suffering during and after the COVID-19 pandemic was more pronounced in individuals with chronic diseases, such as MS, was confirmed by a large study in the Chinese population [39]. A study carried out by a Serbian research group, but also studies carried out by other researchers, have shown that the restrictive measures during the pandemic, despite their positive effect from the epidemiological point of view, have contributed to a poorer quality of life and a higher incidence of depressive mood and stress in MS patients [38].

CONCLUSION

According to the scale for assessing sleep quality – the Pittsburgh Sleep Quality Index (PSQI), it was found that 44.4% of patients suffering from multiple sclerosis had poor sleep quality (PSQI > 5). Although there was a higher prevalence of changes in sleep quality in the group of female patients and the 30 – 50 age group, statistically significant association between the female population, older age, and partnership status, on one hand, and poor sleep quality, on the other, was not established. The application of the score on the Expanded Disability Status Scale (EDSS) did not prove the effect of disease duration on sleep quality. Depressive mood occurred in the analyzed group with a frequency of 35.8%, anxiety with a frequency of 37.8%, and stress with a frequency of 26.4%. Psychological symptoms had a negative effect on sleep quality. MS patients treated with immunomodulatory therapy had poorer sleep quality if they had a higher score on the Depression, Anxiety, and Stress Scale – DASS-21. The COVID-19 pandemic had significant impact on sleep quality and on the psychological status of MS patients, which implies the need for appropriate treatment and psychological support.

Conflict of interest: None declared.

6. Sotelo J, Martínez-Palomo A, Ordoñez G, Pineda B. Varicella-zoster virus in cerebrospinal fluid at relapses of multiple sclerosis. Ann Neurol. 2008 Mar;63(3):303-11. doi: 10.1002/ana.21316.

7. Marrie RA. Environmental risk factors in multiple sclerosis aetiology. Lancet Neurol. 2004 Dec;3(12):709-18. doi: 10.1016/S1474-4422(04)00933-0.

8. Ford H. Clinical presentation and diagnosis of multiple sclerosis. Clin Med (Lond). 2020 Jul;20(4):380-383. doi: 10.7861/clinmed.2020-0292.

9. Hubert H. Ultimate review for the neurology boards. New York: Demos Medical Publishing; 2006. p496.

10. Kutzelnigg A, Lucchinetti CF, Stadelmann C, Brück W, Rauschka H, Bergmann M, et al. Cortical demyelination and diffuse white matter injury in multiple sclerosis. Brain. 2005 Nov;128(Pt 11):2705-12. doi: 10.1093/brain/awh641.

11. Manconi M, Rocca MA, Ferini-Strambi L, Tortorella P, Agosta F, Comi G, et al. Restless legs syndrome is a common finding in multiple sclerosis and correlates with cervical cord damage. Mult Scler. 2008 Jan;14(1):86-93. doi: 10.1177/1352458507080734.

12. Braley TJ, Boudreau EA. Sleep Disorders in Multiple Sclerosis. Curr Neurol Neurosci Rep. 2016 May;16(5):50. doi: 10.1007/s11910-016-0649-2.

13. Nociti V, Losavio FA, Gnoni V, Losurdo A, Testani E, Vollono C, et al. Sleep and fatigue in multiple sclerosis: A questionnaire-based, cross-sectional, cohort study. J Neurol Sci. 2017 Jan 15;372:387-392. doi: 10.1016/j.jns.2016.10.040.

14. Wallin MT, Culpepper WJ, Campbell JD, Nelson LM, Langer-Gould A, Marrie RA, et al.; US Multiple Sclerosis Prevalence Workgroup. The prevalence of MS in the United States: A population-based estimate using health claims data. Neurology. 2019 Mar 5;92(10):e1029-e1040. doi: 10.1212/WNL.0000000000007035.

15. Krupp L. Fatigue is intrinsic to multiple sclerosis (MS) and is the most commonly reported symptom of the disease. Mult Scler. 2006 Aug;12(4):367-8. doi: 10.1191/135248506ms1373ed.

16. Berger JR, Pocoski J, Preblick R, Boklage S. Fatigue heralding multiple sclerosis. Mult Scler. 2013 Oct;19(11):1526-32. doi: 10.1177/1352458513477924.

17. Cameron MH, Peterson V, Boudreau EA, Downs A, Lovera J, Kim E, et al. Fatigue is associated with poor sleep in people with multiple sclerosis and cognitive impairment. Mult Scler Int. 2014;2014:872732. doi: 10.1155/2014/872732.

18. Veauthier C. Sleep disorders in multiple sclerosis. Review. Curr Neurol Neurosci Rep. 2015 May;15(5):21. doi: 10.1007/s11910-015-0546-0.

19. Braley TJ, Segal BM, Chervin RD. Obstructive sleep apnea and fatigue in patients with multiple sclerosis. J Clin Sleep Med. 2014 Feb 15;10(2):155-62. doi: 10.5664/jcsm.3442.

20. Foschi M, Rizzo G, Liguori R, Avoni P, Mancinelli L, Lugaresi A, et al. Sleep-related disorders and their relationship with MRI findings in multiple sclerosis. Sleep Med. 2019 Apr;56:90-97. doi: 10.1016/j.sleep.2019.01.010.

21. Patten SB, Marrie RA, Carta MG. Depression in multiple sclerosis. Int Rev Psychiatry. 2017 Oct;29(5):463-472. doi: 10.1080/09540261.2017.1322555.

22. Lamargue Hamel D, Deloire M, Ruet A, Charré-Morin J, Saubusse A, Ouallet JC, et al. Deciphering Depressive Mood in Relapsing-Remitting and Progressive Multiple Sclerosis and Its Consequence on Quality of Life. PLoS One. 2015 Nov 10;10(11):e0142152. doi: 10.1371/journal.pone.0142152.

23. Minden SL, Orav J, Reich P. Depression in multiple sclerosis. Gen Hosp Psychiatry. 1987 Nov;9(6):426-34. doi: 10.1016/0163-8343(87)90052-1.

24. Korostil M, Feinstein A. Anxiety disorders and their clinical correlates in multiple sclerosis patients. Mult Scler. 2007 Jan;13(1):67-72. doi: 10.1177/1352458506071161.

25. Mohr DC, Goodkin DE, Bacchetti P, Boudewyn AC, Huang L, Marrietta P, et al. Psychological stress and the subsequent appearance of new brain MRI lesions in MS. Neurology. 2000 Jul 12;55(1):55-61. doi: 10.1212/wnl.55.1.55.

26. Carroll WM. 2017 McDonald MS diagnostic criteria: Evidence-based revisions. Mult Scler. 2018 Feb;24(2):92-95. doi: 10.1177/1352458517751861.

27. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989 May;28(2):193-213. doi: 10.1016/0165-1781(89)90047-4.

28. Merlino G, Fratticci L, Lenchig C, Valente M, Cargnelutti D, Picello M, et al. Prevalence of 'poor sleep' among patients with multiple sclerosis: an independent predictor of mental and physical status. Sleep Med. 2009 Jan;10(1):26-34. doi: 10.1016/j.sleep.2007.11.004.

29. Stanton BR, Barnes F, Silber E. Sleep and fatigue in multiple sclerosis. Mult Scler. 2006 Aug;12(4):481-6. doi: 10.1191/135248506ms1320oa.

30. Bøe Lunde HM, Aae TF, Indrevåg W, Aarseth J, Bjorvatn B, Myhr KM, et al. Poor sleep in patients with multiple sclerosis. PLoS One. 2012;7(11):e49996. doi: 10.1371/journal.pone.0049996.

31. Feinstein A. Multiple sclerosis and depression. Mult Scler. 2011 Nov;17(11):1276-81. doi: 10.1177/1352458511417835.

32. Lamargue Hamel D, Deloire M, Ruet A, Charré-Morin J, Saubusse A, Ouallet JC, et al. Deciphering Depressive Mood in Relapsing-Remitting and Progressive Multiple Sclerosis and Its Consequence on Quality of Life. PLoS One. 2015 Nov 10;10(11):e0142152. doi: 10.1371/journal.pone.0142152.

33. Galeazzi GM, Ferrari S, Giaroli G, Mackinnon A, Merelli E, Motti L, et al. Psychiatric disorders and depression in multiple sclerosis outpatients: impact of disability and interferon beta therapy. Neurol Sci. 2005 Oct;26(4):255-62. doi: 10.1007/s10072-005-0468-8.

34. Smith SJ, Young CA. The role of affect on the perception of disability in multiple sclerosis. Clin Rehabil. 2000 Feb;14(1):50-4. doi: 10.1191/026921500676724210.

35. Warren S, Greenhill S, Warren KG. Emotional stress and the development of multiple sclerosis: case-control evidence of a relationship. J Chronic Dis. 1982;35(11):821-31. doi: 10.1016/0021-9681(82)90047-9.

36. Feinstein A. Multiple sclerosis, disease modifying treatments and depression: a critical methodological review. Mult Scler. 2000 Oct;6(5):343-8. doi: 10.1177/135245850000600509.

37. Stojanov A, Vojinovic S, Stojanov J, Malobabic M, Stevic M, Milosevic V, et al. Quality of sleep and fatigue in patients with the relapsing-remitting multiple sclerosis during the coronavirus disease-2019 pandemic. Clin Neurol Neurosurg. 2021 Apr 14;205:106640. doi: 10.1016/j.clineuro.2021.106640.

38. Stojanov A, Malobabic M, Milosevic V, Stojanov J, Vojinovic S, Stanojevic G, et al. Psychological status of patients with relapsing-remitting multiple sclerosis during coronavirus disease-2019 outbreak. Mult Scler Relat Disord. 2020 Oct;45:102407. doi: 10.1016/j.msard.2020.102407.

39. Qiu J, Shen B, Zhao M, Wang Z, Xie B, Xu Y. A nationwide survey of psychological distress among Chinese people in the COVID-19 epidemic: implications and policy recommendations. Gen Psychiatr. 2020 Mar 6;33(2):e100213. doi: 10.1136/gpsych-2020-100213.