

FAKTORI POVEZANI SA SUBJEKTIVNIM OSEĆAJEM UMORA TRI MESECA NAKON PRELEŽANE KOVID-19 INFEKCIJE

ORIGINALNI RAD

ORIGINAL ARTICLE

FACTORS ASSOCIATED WITH THE SUBJECTIVE FEELING OF FATIGUE THREE MONTHS AFTER COVID-19

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SAŽETAK

Uvod: Subjektivni osećaj umora je jedna od najčešćih post-KOVID-19 manifestacija. Karakteriše ga netolerancija na fizički i kognitivni napor, koji je pojedinac prethodno dobro podnosio, praćena malaksalošću i drugim simptomima.

Cilj: Cilj rada je bio da se ispita učestalost subjektivnog osećaja umora, tri meseca nakon izlečenja, kod pacijenata koji su preležali KOVID-19 infekciju, kao i da se ispituju povezani faktori.

Metode: Studijom preseka obuhvaćeno je 110 pacijenata koji su preležali KOVID-19 infekciju, a koji su se javili na redovni kontrolni pregled u Zdravstveni centar „Kosovska Mitrovica“, tri meseca nakon izlečenja od akutne infekcije. Korišćen je specijalno konstruisani upitnik, koji se sastojao od dela sa sociodemografskim podacima, dela sa podacima o zdravstvenom stanju i KOVID-19 infekciji kod pacijenta, kao i dela upitnika o samoproceni zdravstvenog stanja nakon KOVID-19 infekcije.

Rezultati: U našem uzorku, od 110 ispitanika, čak 52 su osećala umor. Faktori koji su bili statistički značajno povezani sa subjektivnim osećajem umora, tri meseca nakon izlečenja od KOVID-19 infekcije, su starost ispitanika i hronične bolesti ($p < 0,05$). Prisustvo povišene telesne temperature i pneumonije tokom bolovanja od KOVID-19 infekcije bili su statistički značajno povezani sa subjektivnim osećajem umora, tri meseca nakon izlečenja ($p < 0,05$). Hospitalizovani pacijenti i oni koji su bili duže hospitalizovani su takođe češće osećali umor tri meseca nakon izlečenja ($p < 0,05$).

Zaključak: Subjektivni osećaj umora, tri meseca nakon izlečenja, kao jedna od post-KOVID-19 manifestacija, kao i sledstvena nemogućnost pacijenta da se vrati poslovnim i privatnim obavezama, može predstavljati ozbiljan lični i javno-zdravstveni problem, zbog čega je potrebno njegovo adekvatno prepoznavanje i tretiranje.

Cljučne reči: umor, KOVID-19, post-KOVID-19, samoprocena

ABSTRACT

Introduction: The subjective feeling of fatigue is one of the most common post-COVID-19 manifestations. It is characterized by intolerance to physical and cognitive effort that the individual previously tolerated well, accompanied by weakness and other symptoms.

Aim: The aim of this study was to examine the frequency of the subjective feeling of fatigue, three months after recovery from the infection, amongst patients who had been infected with COVID-19, as well as to analyze correlated factors.

Methods: This cross-sectional study included 110 patients who had previously contracted COVID-19, and who came for a regular follow-up examination at the Health Center Kosovska Mitrovica, 3 months after recovery from acute infection. A specially designed questionnaire was used, which consisted of the segment with sociodemographic data, the segment with the data on the patient's health status and the course of their COVID-19 infection, as well as the segment of the questionnaire related to self-assessment of the patient's health status after the COVID-19 infection.

Results: In our sample, out of 110 respondents, as many as 52 felt fatigue. Factors that were statistically significantly associated with the subjective feeling of fatigue, three months after treatment, were the age of the subject and the presence of chronic disease ($p < 0.05$). The presence of fever and pneumonia during infection were statistically significantly associated with the presence of the subjective feeling of fatigue, three months after treatment ($p < 0.05$). Hospitalized patients and those who were hospitalized for a longer period of time were also more likely to feel fatigue three months after recovering from the infection ($p < 0.05$).

Conclusion: The subjective feeling of fatigue, as one of post-COVID manifestations, as well as the consequent inability of the patient to resume work-related and personal tasks and responsibilities, can be a serious individual and public health problem, which is why it is necessary to appropriately recognize and treat it.

Key words: fatigue, COVID-19, post-COVID-19, self-assessment

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UVOD

Decembra 2019. godine, u gradu Vuhanu u Kini, pojavio se novi soj korona virusa nazvan SARS-CoV-2 (engl. SARS-CoV-2) koji se velikom brzinom proširio na veći deo planete [1]. Pojava ovog virusa dovela je svet u stanje nove pandemije izazvane virusom o kome se jako malo znalo [2]. U početku, KOVID-19 infekcija se delila na blagu, umerenu, tešku i kritične slučajeve, a kasnije su u ovu podelu dodati i asimptomatski pacijenti, koji su pokazali veliki značaj u širenju virusa [3].

Kako je vreme prolazilo, tako se i simptomatologija ovoga virusa menjala, ali simptomi koji su ostali karakteristični za ovu infekciju jesu: povišena telesna temperatura, slabost, malaksalost, kašalj, mialgija, kao i gubitak čula mirisa i ukusa. Od nespecifičnih, uglavnom su prisutni gastrointestinalni simptomi [4]. Pneumonija je bila najčešći uzrok hospitalizacije, zbog svog nepredvidivog toka [5].

Za pojedine pacijente, preležana akutna KOVID-19 infekcija je bila samo jedan korak u izlečenju. Svedoci smo koliko postoji mogućih komplikacija, upravo zbog heterogenosti kliničke slike. Iz ovog razloga, uveden je termin post-KOVID-19 sindrom (engl. post-COVID-19 syndrome) ili produženi KOVID (engl. long COVID), koji podrazumeva klaster fizičkih i psiholoških simptoma [6]. Smatra se da u patogenezi neuroloških, kognitivnih, ali i mnogih drugih simptoma, značajnu ulogu ima prolongirana inflamacija [7].

Kao česta komplikacija u sklopu produženog KOVID-a, ali i drugih virusnih infekcija, izdvaja se umor. Umor karakterišu netolerancija na napor, uz prisustvo patološkog umora koji ne prolazi nakon odmora, malaksalost, i drugi simptomi, pogoršani fizičkim ili kognitivnim naporima, pri intenzitetima koje je pojedinac prethodno dobro podnosio [8]. Etiopatogeneza hroničnog umora još uvek nije dovoljno razjašnjena. Pretpostavlja se da veliku ulogu imaju proinflamatorni citokini – interleukin-1 i interferon alfa [9,10].

Ono što je sigurno jeste da subjektivni osećaj umora u velikoj meri utiče na svakodnevni život pojedinca, do te mere da osoba može veći deo dana provesti u krevetu, nefunkcionalna [11,12].

Cilj rada je da se ispita učestalost subjektivnog osećaja umora, tri meseca nakon akutne infekcije, kod pacijenata koji su preležali KOVID-19 infekciju, kao i da se ispituju povezani faktori.

MATERIJAL I METODE

Istraživanje je urađeno kao studija preseka, u periodu od maja do juna 2021. godine. U studiju su uključeni pacijenti koji su se javili na redovni kontrolini pregled u Zdravstveni centar „Kosovska Mitrovica“, tri meseca nakon preležane KOVID-19 infekcije. Kontrolni pregledi

INTRODUCTION

In December 2019, in the city of Wuhan, in China, a new coronavirus strain emerged. It was named SARS-CoV-2, and it spread very quickly to almost all parts of the globe [1]. The emergence of this virus brought the world into the state of a new pandemic, caused by a virus of which little was known [2]. At the beginning, COVID-19 was categorized as: mild, moderate, severe, and critical cases, and later, asymptomatic patients were added to this categorization, and they have proven to be of great significance in virus transmission [3].

As time went by, the symptomatology of the virus changed, but the symptoms that remain characteristic of this infection are as follows: elevated body temperature, weakness, malaise, cough, myalgia, as well as loss of the sense of smell and taste. Amongst nonspecific symptoms, the ones most commonly present are gastrointestinal symptoms [4]. Pneumonia was the most common cause of hospitalization; due to the unpredictable course it may take [5].

For certain patients, recovering from acute COVID-19 infection was just one step towards complete recovery. We have witnessed a variety of possible complications, precisely due to the heterogenous clinical presentation of the disease. This is why the term post-COVID-19 syndrome, or long COVID, which entails a cluster of physical and psychological symptoms, was introduced [6]. It is believed that prolonged inflammation plays a significant role in the pathogenesis of neurological, cognitive and many other symptoms [7].

Fatigue occurs as a frequent complication within long COVID, but also in other viral infections. Fatigue is characterized by intolerance to effort, with the presence of pathological fatigue which does not pass after rest, weakness, and other symptoms, exacerbated by physical or mental strain, at intensities previously well tolerated by the individual [8]. Etiopathogenesis of chronic fatigue has as yet not been sufficiently elucidated. It is believed that proinflammatory cytokines – interleukin-1 and interferon alpha, play a significant role [9,10].

What is certain is that the subjective feeling of fatigue greatly impacts the everyday life of the individual to such an extent that the person may spend most of their day in bed, unable to function normally [11,12].

The aim of the paper is to analyze the frequency of the subjective feeling of fatigue, three months after acute infection, in patients who had had COVID-19, as well as to examine correlated factors.

MATERIALS AND METHODS

The research was carried out as a cross-sectional study, in the period between May and June 2021. The study included patients who came in for a regular follow-up

su bili zakazani po proceni lekara koji su lečili pacijente u toku infekcije, na osnovu kliničke slike u akutnoj fazi bolesti. S obzirom na to da je u našem regionu period sa najvećim brojem obolelih bio februar – mart 2021. godine, istraživanje je sprovedeno tri meseca od akutne infekcije, na zakazanoj redovnoj kontroli.

Kriterijumi za uključivanje u studiju su bili:

1. Punoletni ispitanici
2. Postavljena dijagnoza KOVID-19 infekcije na osnovu pozitivnog PCR testa u toku akutne faze
3. Zakazan kontrolni pregled od strane ordinirajućeg lekara u toku lečenja KOVID-19 infekcije.

Kriterijumi za isključivanje iz studije:

1. Navođenje pacijenta da je u periodu februar – mart 2021. godine imao/la simptome KOVID-19 infekcije koja nije potvrđena PCR testom
2. Pacijenti koji se imali KOVID-19 infekciju posle 31. marta 2021. godine
3. Odbijanje pacijenta da učestvuje u istraživanju. (Nije bilo onih koji su odbili).

Svi pacijenti su bili obavešteni da će rezultati ispitivanja biti korišćeni isključivo u istraživačke svrhe i da, u svakom trenutku, u slučaju da žele, mogu i da odustanu. Nakon dobijanja informacija u vezi sa upitnikom, svi pacijenti su dali potpisani pristanak da budu uključeni u istraživački proces. Nakon završenog pregleda, pacijenti su samostalno popunjavali upitnik.

Korišćen je specijalno osmišljen upitnik za potrebe ove studije, koji se sastojao od 18 pitanja podeljenih na tri dela. Prvi deo je bio sastavljen od 7 pitanja, koja su se odnosila na sociodemografske podatke (godine starosti, pol, mesto stanovanja, nivo obrazovanja, radni status, pušački status, navike u vezi sa konzumiranjem alkohola). Drugi deo upitnika o zdravstvenom stanju ispitanika činilo je 4 pitanja, koja su se odnosila na sledeće: da li pacijent ima hronične bolesti; ako ih ima, koje su; da li koristi lekove i koje. Treći deo upitnika je činilo 5 pitanja o KOVID-19 infekciji, u okviru kojih su ispitanici pitani koje su simptome KOVID-19 infekcije imali; da li su imali pneumoniju; da li su bili hospitalizovani; i ako jesu, koliko dana kao i koju terapiju su koristili za lečenje.

Poslednji deo upitnika su činila dva pitanja u vezi sa umorom.

1. Da li ste u poslednja tri meseca osećali umor koji nije prolazio nakon sna i odmora?
2. Da li vas je umor sprečavao u obavljanju svakodnevnih aktivnosti?

Studija je odobrena od strane direktora i Etičkog odbora ustanove (broj odluke 4866/21).

Za analizu podataka korišćene su deskriptivne statističke metode i metode za testiranje statističkih

examination to the Health Center Kosovska Mitrovica, three months after recovering from acute COVID-19 infection. The follow-up examinations had been scheduled according to the assessment made by the physicians treating the patients during the infection, based on clinical presentation in the acute phase of the disease. Bearing in mind that, in our region, the period with the highest incidence of the infection was between February and March 2021, the study was performed three months after acute infection, at scheduled follow-up examinations.

The inclusion criteria for the study were the following:

1. Adult respondents
2. COVID-19 diagnosis confirmed with a positive PCR test during the acute phase of infection
3. Follow-up examination scheduled by attending physician during treatment of the COVID-19 infection.

The exclusion criteria for the study were the following:

1. Testimony of the patient that in the period of February – May 2021 they had had symptoms of the COVID-19 infection, which was not confirmed with a PCR test
2. Patients who had COVID-19 after March 31, 2021
3. Patients declining to enter the study. (There were no such patients).

All patients were informed that the results of the study would be used exclusively for research purposes and that, at any moment, if they chose to do so, the patients could withdraw from participating in the study. After receiving information related to the questionnaire, all of the patients gave their written consent to be included in the research process. After the follow-up examination had been completed, the patients filled out the questionnaire on their own.

A questionnaire specially designed for this study was used. It consisted of 18 questions divided into three sections. The first section consisted of 7 questions, which related to sociodemographic data (age, sex, place of residence, education level, employment status, smoker status, alcohol intake). The second section of the questionnaire related to the health status of the respondent and consisted of 4 questions, which were in relation to the following: whether the patient suffered from any chronic illness; if they did, which diseases these were; whether the patient was on any drugs and which ones. The third section of the questionnaire consisted of 5 questions on COVID-19. Within this section, the respondents were asked to state the COVID-19 symptoms they had experienced; whether they had had pneumonia; whether they had been hospitalized; and if so, what was their length of stay, as well as which therapy they had been treated with.

hipoteza. Od deskriptivnih statističkih metoda korišćeni su: aritmetička sredina, medijana, opseg (min - max), apsolutni i relativni brojevi.

Za testiranje hipoteze o razlici učestalosti korišćen je hi-kvadrat test. Od neparametrijskih metoda za podatke koji odstupaju od normalne raspodele, korišćen je Man-Vitnijev U test, odnosno test sume rangova. Kriterijum za statističku značajnost je bio $p < 0,05$.

Za statističku obradu rezultata korišćen je softverski program SPSS Statistics 22.

REZULTATI

Studijom je obuhvaćeno 110 pacijenata, starosti od 21 do 72 godine. Prosečna starost je iznosila $48,2 \pm 14,1$ godinu. Od ukupnog broja pacijenata, njih 54 (49,1%) je bilo muškog, a 56 (50,0%) ženskog pola.

Subjektivni osećaj umora, tri meseca posle izlečenja KOVID-19 infekcije, osećalo je čak 52 ispitanika što čini gotovo polovinu uzorka (48,0%) (Grafikon 1).

Sociodemografske varijable kao što su: pol, mesto stanovanja, bračni, radni i pušački status, navike u vezi sa konzumiranjem alkohola, nisu pokazale statistički značajnu povezanost sa prisustvom subjektivnog osećaja umora, tri meseca nakon izlečenja, što je prikazano u Tabeli 1.

Od sociodemografskih varijabli, jedino je starost ispitanika pokazala statističku značajnost u odnosu na osećaj hroničnog umora. Medijana starosti ispitanika koji su osećali umor iznosila je 59 godina (opseg 34 – 76 godina), a onih koji ga nisu osećali 42 godine (opseg

The last section of the questionnaire was made up of two questions related to fatigue.

1. In the previous three months have you felt fatigue that did not pass after sleep and rest?
2. Has the fatigue prevented you from performing everyday duties?

The study was approved by the Chair of the Hospital Ethics Committee (Decision No. 4866/21). Descriptive statistical methods were used for data analysis, as were methods for testing statistical hypotheses. The following descriptive statistical methods were applied: arithmetic mean, median, range (min - max), absolute and relative numbers.

The chi-square test was used for testing the hypothesis on the difference in frequency. Of the non-parametric methods for data deviating from the normal distribution, the Mann-Whitney U test, i.e., Rank Sum Test, was used. The criterion of statistical significance was $p < 0.05$.

The SPSS Statistics 22 software was used for statistical processing of the results.

RESULTS

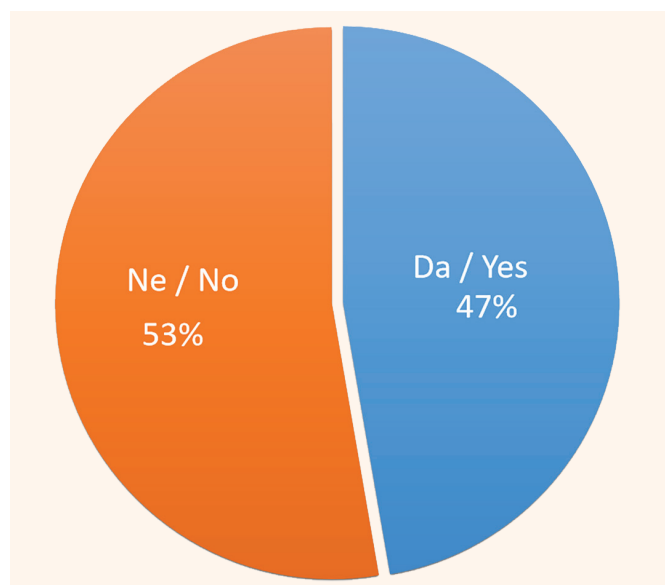
The study included 110 patients, aged 21 – 72 years. The average age was 48.2 ± 14.1 years. Of the total number of patients, 54 (49.1%) were male, while 56 (50.0%) were female.

The subjective feeling of fatigue, three months after recovery from acute COVID-19 infection, was felt by as many as 52 respondents, which makes up for almost half of the sample (48,0%) (Figure 1).

Sociodemographic variables, such as: sex, place of residence, marital, employment, and smoker status, alcohol intake, did not show statistically significant association to the occurrence of the subjective feeling of fatigue, three months after recovery from acute COVID-19 infection, which is shown in Table 1.

Of the sociodemographic variables, only the respondent age demonstrated statistical significance in relation to the feeling of chronic fatigue. The median age of the respondents experiencing fatigue was 59 years (range 34 – 76 years), while, for those who did not experience fatigue, the median age was 42 years (range 21 – 78 years). Subjects experiencing fatigue were statistically significantly older than those who did not experience fatigue ($p = 0.004$) (Figure 2).

In the second section of the questionnaire, which contained questions related to health status and data on the COVID-19 infection, the factors that were statistically significantly associated with the feeling of fatigue were the following: chronic diseases, elevated body temperature as a symptom of acute infection, pneumonia, hospitalization, as well as the length of hospital stay.



Grafikon 1. Učestalost subjektivnog osećaja umora kod pacijenata koji su preležali KOVID-19 infekciju

Figure 1. Frequency of the subjective feeling of fatigue in patients who had had COVID-19

Tabela 1. Uticaj sociodemografskih varijabli na prisustvo subjektivnog osećaja umora

	Osećaj umora / Feeling of fatigue		p
	Ne / No	Da / Yes	
Ukupan broj, n (%) / Total number, n(%)	58 (53.0%)	52 (47.0%)	
Pol, n(%) / Sex, n(%)			
Muški / Male	28 (48.3%)	20 (38.5%)	0.464
Ženski / Female	30 (51.7%)	32 (61.5%)	
Mesto stanovanja, n(%) / Residence, n(%)			
Selo / Rural	24 (41.4%)	14 (26.9%)	0.260
Grad / Urban	34 (58.6%)	38 (73.1%)	
Bračni status, n(%) / Marital status, n(%)			
Oženjen/udata / Married	38 (65.5%)	42 (80.8%)	0.208
Neoženjen/neudata / Single	16 (27.6%)	4 (7.7%)	
Razveden/razvedena / Divorced	4 (6.9%)	4 (7.7%)	
Udovac/udovica / Widowed	0 (0.0%)	2 (3.9%)	
Radni status, n(%) / Work status, n(%)			
Zaposlen/zaposlena / Employed	42 (72.4%)	34 (65.4%)	0.879
Nezaposlen/nezaposlena / Unemployed	10 (17.2%)	12 (23.1%)	
Penzioner/penzionerka / Retired	6 (10.3%)	6 (11.5%)	
Pušački status, n (%) / Smoker status, n (%)			
Pušač / Smoker	28 (48.3%)	28 (53.9%)	0.241
Nepušač / Nonsmoker	30 (51.7%)	24 (46.2%)	
Konzumacija alkohola, n (%) / Alcohol intake, n (%)	20 (34.5%)	30 (57.7%)	0.106

Table 1. The effect of sociodemographic variables on the occurrence of the subjective feeling of fatigue

21 – 78 godina). Ispitanici koji su osećali umor su bili statistički značajno starijeg životnog doba u odnosu na one bez njega ($p = 0,004$) (Grafikon 2).

U drugom delu upitnika, koji je sadržao pitanja u vezi sa zdravstvenim stanjem i podatke o KOVID-19 infekciji, faktori koji su bili statistički značajno povezani sa osećajem umora bili su: hronične bolesti, povišena telesna temperatura kao simptom akutne infekcije, pneumonija, hospitalizacija, kao i dužina hospitalizacije.

Učestalost hroničnih bolesti kod pacijenata koji su osećali umor je iznosila 38 slučajeva (73,1%), dok je u grupi pacijenata koji nisu osećali umor iznosila 20 slučajeva (34,5%).

Subjektivni osećaj umora, tri meseca posle izlečenja, bio je statistički značajno češće prisutan kod ispitanika sa hroničnim bolestima ($p = 0,004$) (Tabela 2).

U grupi pacijenata sa subjektivnim osećajem umora tri meseca posle izlečenja, čak 40 (76,9%) njih je u toku akutne infekcije imalo povišenu telesnu temperaturu, dok je u grupi pacijenata bez osećaja umora, njih 28 (48,3%) imalo isti simptom. Povišena telesna temperatura u akutnoj fazi KOVID-19 infekcije je bila statistički značajno učestalija u kategoriji pacijenata koji

The frequency of chronic diseases in patients who experienced fatigue was 38 cases (73.1%), while it was 20 cases (34.5%) in the group of patients who did not experience fatigue.

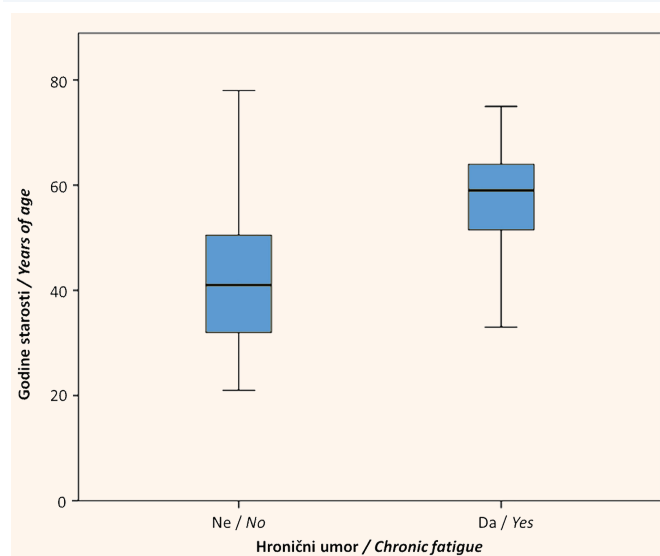
**Grafikon 2.** Uticaj godina starosti na subjektivni osećaj umora**Figure 2.** Effect of age on the subjective feeling of fatigue

Tabela 2. Uticaj zdravstvenog stanja i karakteristika KOVID-19 infekcije na prisustvo subjektivnog osećaja umora

Table 2. The effect of health status and the characteristics of the COVID-19 infection on the occurrence of the subjective feeling of fatigue

	Osećaj umora / Feeling of fatigue		p
	Ne / No	Da / Yes	
Ukupan broj, n (%) / Total number, n (%)	58 (53.0%)	52 (47.0%)	
Hronična bolest, n (%) / Chronic disease, n (%)	20 (34.5%)	38 (73.1%)	0.004
Suplementacija vitaminima, n (%) / Vitamin supplementation, n (%)	20 (34.5%)	24 (46.2%)	0.378
Povišena telesna temperatura, n (%) / Elevated body temperature, n (%)	28 (48.3%)	40 (76.9%)	0.029
Gubitak čula mirisa i ukusa, n (%) / Loss of sense of smell and taste, n (%)	20 (34.5%)	12 (23.1%)	0.352
Pneumonija, n (%) / Pneumonia, n (%)	10 (17.2%)	26 (50.0%)	0.010
Hospitalizacija, n (%) / Hospitalization, n (%)	8 (13.8%)	24 (46.2%)	0.008

su osećali umor tri meseca posle izlečenja ($p = 0,029$) (Tabela 2).

U akutnoj fazi bolesti, 26 (50%) pacijenata sa subjektivnim osećajem umora tri meseca posle izlečenja je imalo pneumoniju, dok je u grupi pacijenata bez osećaja umora njih 10 (17,2%) imalo pneumoniju.

Subjektivni osećaj umora tri meseca posle izlečenja se statistički značajno češće javljao u kategoriji pacijenata koji su imali pneumoniju u akutnoj fazi bolesti ($p = 0,010$) (Tabela 2).

U grupi pacijenata sa subjektivnim osećajem umora tri meseca posle izlečenja, njih 24 (46,2%) je bilo hospitalizovano, dok je u grupi bez ovog simptoma bilo hospitalizovano samo njih 8 (13,8%).

The subjective feeling of fatigue, three months after recovering from the infection, was statistically significantly more frequently present in subjects with chronic diseases ($p = 0.004$) (Table 2).

In the group of patients with the subjective feeling of fatigue, three months after COVID-19, as many as 40 (76.9%) of them had elevated body temperature during the acute infection, while in the group of patients who did not experience fatigue, 28 (48.3%) of them had the same symptom. Elevated body temperature in the acute phase of COVID-19 was statistically significantly more frequent in the category of patients experiencing fatigue three months after recovering from acute COVID-19 ($p = 0.029$) (Table 2).

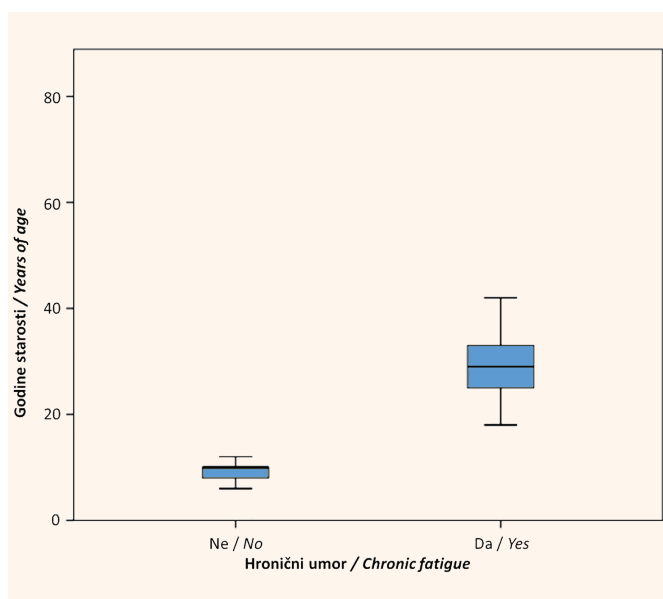
In the acute phase of disease, 26 (50%) patients with the subjective feeling of fatigue, three months after recovering from acute COVID-19, had had pneumonia, while in the group of patients not experiencing fatigue, 10 (17.2%) patients had had pneumonia.

The subjective feeling of fatigue, three months after recovering from acute COVID-19, occurred statistically significantly more often in the category of patients who had had pneumonia in the acute phase of the disease ($p = 0.010$) (Table 2).

In the group of patients with the subjective feeling of fatigue three months after recovery from acute COVID-19, 24 (46.2%) patients had been hospitalized, while in the group of patients without this symptom, only 8 (13.8%) patients had been hospitalized.

The subjective feeling of fatigue occurred statistically significantly more often in the category of patients who had been hospitalized during acute COVID-19 infection ($p < 0.008$) (Table 2).

In patients who experienced fatigue, the median length of hospital stay during acute COVID-19 infection was 15 days (range 9 – 21), while in patients who did not experience fatigue, the median hospital stay was 5 days



Grafikon 3. Ispitivanje uticaja dužine hospitalizacije na prisustvo subjektivnog osećaja umora

Figure 3. Analysis of the effect of the length of hospital stay on the occurrence of the subjective feeling of fatigue

Subjektivni osećaj umora se statistički značajno češće javljao u kategoriji pacijenata koji su bili hospitalizovani tokom akutne KOVID-19 infekcije ($p < 0,008$) (Tabela 2).

Medijana broja dana hospitalizacije u akutnoj KOVID-19 infekciji kod pacijenata koji su osećali umor je iznosila 15 dana (opseg 9 – 21), a kod pacijenata koji ga nisu osećali je iznosila 5 dana (opseg, 3 – 6). Subjektivni osećaj umora, tri meseca posle izlečenja, statistički se značajno češće javljao kod ispitanika koji su bili duže hospitalizovani ($p = 0,012$) (Grafikon 3).

Statistički značajna povezanost osećaja umora sa suplementacijom vitaminima ($p = 0,378$) i sa gubitkom čula mirisa i ukusa ($p = 0,352$) nije nađena (Tabela 2).

DISKUSIJA

Prema podacima iz literature, oko 10% – 30 % pacijenata širom sveta, nakon preležane KOVID-19 infekcije, ima znake produžene bolesti, dugo nakon negativnog testa [13]. Kao što je u rezultatima navedeno, umor je osećala gotovo polovina ispitanika. Rezultati incidencije hroničnog umora se razlikuju od istraživanja do istraživanja i kreću se od 35% u američkoj, preko 53% u irskoj, do čak 87% u italijanskoj multicentričnoj studiji, sprovedenoj dva meseca nakon akutne faze bolesti [14,15,16].

Najveća studija praćenja, koju su sproveli Huang i saradnici, sa više od 2.000 ispitanika, pokazala je da je umor osećalo oko 63% ispitanika [17], što je nešto više nego u našoj studiji. U istoj studiji [17], godine starosti, kao i prisutne hronične bolesti, pokazale su značajnu povezanost sa pojavom subjektivnog osećaja umora, što je u skladu sa našim rezultatima. Rezultati američke multicentrične studije, na populaciji 582 ispitanika, pokazali su da je umor kao simptom najviše bio prisutan u starosnoj grupi od 35 do 49 godina, dok je u našem istraživanju, incidencija umora rasla sa godinama starosti. Prema našim rezultatima, povišena telesna temperatura, pneumonija, hospitalizacija i dužina hospitalizacije su bili značajno povezani sa prisustvom ovog simptoma, tri meseca nakon izlečenja od akutne infekcije.

U svojoj studiji sprovedenoj telefonskim upitnikom sa pacijentima, 30 i 60 dana nakon inicijalne infekcije, Kahvaljo-Šnajder i saradnici su došli do rezultata da su auskultatorni nalaz koji ukazuje na pneumoniju i hospitalizacija povezani sa prisustvom osećaja umora, 60 dana nakon inicijalne infekcije [18]. Takođe, prošlogodišnja norveška studija preseka je multivarijantnom regresijom došla do rezultata da je brojnija simptomatologija za vreme akutne infekcije pozitivan prediktor nastanka umora [19]. Sistematska meta-analiza, u kojoj je obrađeno oko 40 studija, takođe ukazuje na slične rezultate, ali u isto vreme ukazuje i na heterogenost

(range 3 – 6). The subjective feeling of fatigue, three months after recovery from acute COVID-19, occurred statistically significantly more often in respondents who had been hospitalized longer ($p = 0.012$) (Figure 3).

Statistically significant association was not found between the feeling of fatigue and vitamin supplementation ($p = 0.378$), nor was it established between the feeling of fatigue and the loss of the sense of smell and taste ($p = 0.352$) (Table 2).

DISCUSSION

According to data found in literature, around 10% – 30 % of patients worldwide exhibit signs of prolonged illness after acute COVID-19 infection and long after a negative COVID-19 test [13]. As stated in the results, fatigue was experienced by almost half of the respondents. The results related to the incidence of chronic fatigue are different from study to study, and range from 35% in the American study, to 53% in the Irish study, to as many as 87% in the Italian multicentric study, carried out two months after the acute phase of the disease [14,15,16].

The largest follow-up study, carried out by Huang et al., which included more than 2,000 subjects, showed that 63% of the respondents felt fatigue [17], which is somewhat more than in our study. In the same study [17], age, as well as existing chronic diseases, showed significant association to the occurrence of the subjective feeling of fatigue, which is in keeping with our results. The results of an American multicentric study, involving a population of 582 subjects, showed fatigue to be the symptom that was most commonly present in the 35 – 49 age group, while, in our study, the incidence of fatigue rose with age. According to our results, elevated body temperature, pneumonia, hospitalization, and length of hospital stay were significantly associated to the occurrence of this symptom, three months after recovery from acute infection.

In their study carried out by telephone conversations with patients, 30 and 60 days after initial infection, Carvalho-Schneider et al. obtained results that an auscultatory finding indicating pneumonia as well as hospitalization were associated with the presence of the feeling of fatigue, 60 days after initial infection [18]. Also, through multivariate regression, a cross-sectional study conducted last year in Norway obtained results indicating that the presence of a greater number of symptoms during acute infection was a positive predictor of the occurrence of fatigue [19]. A systematic meta-analysis, which included around 40 studies, also indicated similar results, but, at the same time, it showed the heterogeneity of results, due to the differing study designs, different samples in different time intervals, and different modes of obtaining results

rezultata, usled različitog načina na koji su studije osmišljene, različitog uzorka u različitim vremenskim intervalima i dobijanja rezultata različitim putem (putem upitnika, uvidom u istorije bolesti, telefonskim putem). Heterogenost je takođe prisutna zbog upotrebe raznovrsnih validiranih i nevalidiranih upitnika [20].

Ograničenje našeg istraživanja ogleda se u kratkom periodu praćenja, što ne dozvoljava generalizaciju podataka na sve pacijente koji su bolovali od KOVID-19 infekcije. U budućim istraživanjima potrebno je produžiti period izvođenja studije, a samim tim i povećati broj ispitanika, kako bismo nalaze dobijene u ovom istraživanju potvrdili ili dopunili. Najbolje bi bilo sprovesti metodološki dobro osmišljenu kohortnu studiju kojom bi se utvrdili i ostali simptomi u post-KOVID periodu, ali i prevazišla ograničenja karakteristična za studije preseka.

I ova studija, kao i druge studije preseka, nisu u mogućnosti da pokažu uzročnu posledičnu povezanost, već korelaciju. Nalazi iz ovog istraživanja mogu poslužiti samo kao orijentir za buduća slična istraživanja. U nastavku istraživanja, drugi faktori potencijalno povezani sa umorom, moraju se isključiti, odnosno, njihov pridruženi efekat se mora uračunati pre donošenja zaključka.

Takođe, vrlo često ograničenje kod istraživanja zasnovanih na upitniku, jeste razumevanje pitanja i motivacija za davanje iskrenog odgovora, stoga je moguće da postoji pristrasnost (engl. bias), u smislu preuveličanog odnosno nedovoljnog izveštavanja. Upitnik iz naše studije nije standardizovan, jer je ovo bilo pilot istraživanje, koje je poslužilo da se isprave mane i slabosti pitanja i samog načina sprovođenja upitnika. Bez obzira na to, visok procenat pacijenata sa subjektivnim osećajem umora tri meseca posle izlečenja od KOVID-19 infekcije, govori o značaju ovog istraživanja.

ZAKLJUČAK

Subjektivni osećaj umora je prisutan u velikom procentu ispitanika, kako u našoj, tako i u drugim studijama. Povezan je sa godinama starosti, hroničnim bolestima, visokom telesnom temperaturom, pneumonijom, hospitalizacijom, kao i dužinom hospitalizacije u akutnoj fazi infekcije. Subjektivni osećaj umora, tri meseca posle izlečenja, kao česta post-KOVID manifestacija, kao i posledična nemogućnost pacijenta da se vrati poslovnim i privatnim obavezama, mogu predstavljati ozbiljan javnozdravstveni problem, te je potrebno adekvatno prepoznavanje i tretiranje subjektivnog osećaja umora.

Sukob interesa: Nije prijavljen.

(through questionnaires, insight into patient histories, and through telephone conversations). Heterogeneity is also present due to the use of various validated and non-validated questionnaires [20].

The limitation of our study is reflected in the short follow-up period, which does not allow for generalization of data so as to apply to all patients who had suffered from COVID-19. In future research, it is necessary to lengthen the time of research and consequently increase the number of subjects, in order to confirm or supplement the findings from this study. The best solution would be to carry out a methodologically well-designed cohort study which would determine other symptoms in the post-COVID period, but also overcome the limitations typical of cross-sectional studies.

Just like other cross-sectional studies, this study also lacks the capacity to demonstrate cause-and-effect relationships, merely correlation. The findings from this study may be used merely as a reference for future similar studies. In further research, other factors potentially associated with fatigue need to be excluded, i.e., their confounding effect must be taken into consideration before conclusions are drawn.

Also, a very frequent limitation in questionnaire-based studies is the issue of understanding the questions, as well as the issue of motivation for providing candid answers, which is why there is a possibility of bias, in the sense of exaggerated or insufficient feedback. The questionnaire in our study was not standardized, as this was a pilot study, whose purpose was to correct the flaws and weaknesses of the items themselves, as well as the method of questionnaire distribution. Nevertheless, a high percentage of patients experiencing a subjective feeling of fatigue, three months after recovery from acute COVID-19 infection, is a testimony of the significance of this study.

CONCLUSION

The subjective feeling of fatigue is present in a high percentage of subjects, not only in our study, but in other studies as well. This symptom is connected to age, chronic diseases, elevated body temperature, pneumonia, hospitalization, as well as to the length of hospital stay, during the acute phase of the infection. The subjective feeling of fatigue, three months after recovery from acute COVID-19, as a frequent post-COVID manifestation, as well as the consequent inability of the patient to return to their work-related and personal tasks and responsibilities, may represent a serious public health problem, which is why it is necessary to appropriately recognize and treat the subjective feeling of fatigue.

Conflict of interest: None declared

LITERATURA / REFERENCES

- Ahn DG, Shin HJ, Kim MH, Lee S, Kim HS, Myoung J, et al. Current Status of Epidemiology, Diagnosis, Therapeutics, and Vaccines for Novel Coronavirus Disease 2019 (COVID-19). *J Microbiol Biotechnol*. 2020 Mar 28;30(3):313-24. doi: 10.4014/jmb.2003.03011.
- Atzrodt CL, Maknojia I, McCarthy RDP, Oldfield TM, Po J, Ta KTL, et al. A Guide to COVID-19: a global pandemic caused by the novel coronavirus SARS-CoV-2. *FEBS J*. 2020 Sep;287(17):3633-50. doi: 10.1111/febs.15375.
- Gao Z, Xu Y, Sun C, Wang X, Guo Y, Qiu S, et al. A systematic review of asymptomatic infections with COVID-19. *J Microbiol Immunol Infect*. 2021 Feb;54(1):12-6. doi: 10.1016/j.jmii.2020.05.001.
- Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. *JAMA*. 2020 Aug 25;324(8):782-793. doi: 10.1001/jama.2020.12839.
- Attaway AH, Scheraga RG, Bhimraj A, Biehl M, Hatipoğlu U. Severe covid-19 pneumonia: pathogenesis and clinical management. *BMJ*. 2021 Mar 10;372:n436. doi: 10.1136/bmj.n436.
- Lamprecht B. Gibt es ein Post-COVID-Syndrom? [Is there a post-COVID syndrome?]. *Pneumologe (Berl)*. 2020;17(6):398-405. German. doi: 10.1007/s10405-020-00347-0.
- Maltezou HC, Pavli A, Tsakris A. Post-COVID Syndrome: An Insight on Its Pathogenesis. *Vaccines (Basel)*. 2021 May 12;9(5):497. doi: 10.3390/vaccines9050497.
- Nacul L, Authier FJ, Scheibenbogen C, Lorusso L, Helland IB, Martin JA, et al. European Network on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (EUROMENE): Expert Consensus on the Diagnosis, Service Provision, and Care of People with ME/CFS in Europe. *Medicina (Kaunas)*. 2021 May 19;57(5):510. doi: 10.3390/medicina57050510.
- Roerink ME, van der Schaaf ME, Dinarello CA, Knoop H, van der Meer JW. Interleukin-1 as a mediator of fatigue in disease: a narrative review. *J Neuroinflammation*. 2017 Jan 21;14(1):16. doi: 10.1186/s12974-017-0796-7.
- Russell A, Hepgul N, Nikkheslat N, Borsini A, Zajkowska Z, Moll N, et al. Persistent fatigue induced by interferon-alpha: a novel, inflammation-based, proxy model of chronic fatigue syndrome. *Psychoneuroendocrinology*. 2019 Feb;100:276-85. doi: 10.1016/j.psyneuen.2018.11.032.
- Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A: The International Chronic Fatigue Syndrome Study Group. The chronic fatigue syndrome: A comprehensive approach to its definition and study. *Annals of Internal Medicine*. 1994, 121 (12): 953-959. <https://doi.org/10.7326/0003-4819-121-12-199412150-00009>
- Ross SD, Estok RP, Frame D, Stone LR, Ludensky V, Levine CB. Disability and chronic fatigue syndrome: a focus on function. *Arch Intern Med*. 2004 May 24;164(10):1098-107. doi: 10.1001/archinte.164.10.1098.
- Mackay A. A Paradigm for Post-Covid-19 Fatigue Syndrome Analogous to ME/CFS. *Front Neurol*. 2021 Aug 2;12:701419. doi: 10.3389/fneur.2021.701419.
- Tenforde MW, Kim SS, Lindsell CJ, Billig Rose E, Shapiro NI, Files DC, et al.; IVY Network Investigators; CDC COVID-19 Response Team; IVY Network Investigators. Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network - United States, March-June 2020. *MMWR Morb Mortal Wkly Rep*. 2020 Jul 31;69(30):993-8. doi: 10.15585/mmwr.mm6930e1.
- Carfi A, Bernabei R, Landi F; Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent Symptoms in Patients After Acute COVID-19. *JAMA*. 2020 Aug 11;324(6):603-5. doi: 10.1001/jama.2020.12603.
- Townsend L, Dyer AH, Jones K, Dunne J, Mooney A, Gaffney F, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. *PLoS One*. 2020 Nov 9;15(11):e0240784. doi: 10.1371/journal.pone.0240784.
- Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*. 2021 Jan 16;397(10270):220-232. doi: 10.1016/S0140-6736(20)32656-8.
- Carvalho-Schneider C, Laurent E, Lemaignen A, Beaufile E, Bourbao-Tournois C, Laribi S, et al. Follow-up of adults with noncritical COVID-19 two months after symptom onset. *Clin Microbiol Infect*. 2021 Feb;27(2):258-63. doi: 10.1016/j.cmi.2020.09.052.
- Stavem K, Ghanima W, Olsen MK, Gilboe HM, Einvik G. Prevalence and Determinants of Fatigue after COVID-19 in Non-Hospitalized Subjects: A Population-Based Study. *Int J Environ Res Public Health*. 2021 Feb 19;18(4):2030. doi: 10.3390/ijerph18042030.
- Iqbal FM, Lam K, Sounderajah V, Clarke JM, Ashrafiyan H, Darzi A. Characteristics and predictors of acute and chronic post-COVID syndrome: A systematic review and meta-analysis. *EClinicalMedicine*. 2021 May 24;36:100899. doi: 10.1016/j.eclinm.2021.100899.