Biopsihosocijalne odrednice post-COVID sindroma

/ Biopsychosocial Determinants of Post-COVID Syndrome

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Post-COVID sindrom je kompleksno stanje koje obuhvaća brojne posljedice oporavka od akutne faze infekcije COVID-19. Cilj ovog preglednog rada je biopsihosocijalnim modelom analizirati tjelesne, psihološke, kognitivne i socijalne teškoće koje pacijenti mogu doživjeti nakon otpuštanja iz bolnice, kao i njihov utjecaj na kvalitetu života pacijenata. Posebno su naglašene dugoročne posljedice liječenja u jedinicama intenzivnog liječenja (JIL) izvan konteksta pandemije COVID-19 s fokusom na sindrom postintenzivne njege (engl. *post-intensive care syndrome*, PICS) te povezanost tih posljedica s post-COVID sindromom. Pregledom literature istražena je prevalencija i priroda post-COVID simptoma te njihova sličnost sa simptomima PICS-a. Dugotrajni COVID uključuje simptome poput umora, depresije, anksioznosti i kognitivne teškoće. Psihičke smetnje često utječu na smanjenje kvalitete života, a faktori rizika uključuju dob, spol i komorbiditete. Hospitalizacija povećava rizik za post-COVID simptome, dok cjepiva smanjuju rizik od teških oblika bolesti. Dugoročne posljedice liječenja u JIL-u povezane su s PICS-om. Preživjeli pacijenti često doživljavaju post-COVID simptome i psihološke teškoće. U radu se razmatra važnost interdisciplinarnosti u liječenju ovih sindroma te ističe potreba za daljnjim istraživanjima kako bi se razvile strategije prevencije i intervencije. Nalazi ukazuju na preklapanje post-COVID sindroma i PICS-a te potrebu individualiziranih terapijskih pristupa koji uključuju medicinsku i psihološku podršku.

***/** Post-COVID syndrome is a complex condition encompassing various consequences of recovering from the acute phase of COVID-19 infection. The aim of this review article is to use the biopsychosocial model in order to analyze the physical, psychological, cognitive, and social difficulties that patients may experience after hospital discharge, as well as their impact on the patients' quality of life. Particular emphasis is placed on the long-term consequences of treatment in intensive care units (ICUs) outside the context of the COVID-19 pandemic, focusing on post-intensive care syndrome (PICS), and the association of these consequences with post-COVID syndrome. A literature review was conducted to examine the prevalence and nature of post-COVID symptoms, and their similarity to PICS symptoms. Long COVID includes symptoms such as fatigue, depression, anxiety, and cognitive difficulties. Psychological disturbances often reduce the quality of life, while the risk factors include age, sex, and comorbidities. Hospitalization increases the risk of post-COVID symptoms, while vaccination reduces the likelihood of severe disease outcomes. The long-term consequences of ICU treatment are associated with PICS. Survivors frequently experience post-COVID symptoms and psychological difficulties. This article highlights the importance of an interdisciplinary approach in treating these syndromes, and underscores the need for further research to develop prevention and intervention strategies. In conclusion, the findings indicate an overlap between post-COVID syndrome and PICS, emphasizing the need for individualized therapeutic approaches that would include medical and psychological support.*

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KLJUČNE RIJEČI / *KEY WORDS:*
Post-COVID / *Post-COVID*
Dugotrajni COVID / *Long COVID*
Mentalno zdravlje / *Mental Health*
Sindrom postintenzivne njege / Post-intensive care syndrome - *PICS*

TO LINK TO THIS ARTICLE: https://doi.org/10.24869/spsih.2025.99

UVOD

Kliničke manifestacije koronavirusa (engl. *Coronavirus Disease 2019*, COVID-19) variraju od asimptomatskih stanja do teških kliničkih slika koje su respiratorne i višeorganske (1-6). Epidemiološki podatci pokazuju da do 20 % pacijenata s COVID-19 napreduje do teškog stanja koje zahtijeva bolničko liječenje (7). Jednoj četvrtini hospitaliziranih potrebno je liječenje u jedinici intenzivnog liječenja (JIL), što u njih češće dovodi do sekundarne upale pluća, kardiovaskularnih teškoća, sepse, oštećenja bubrega, i neuroloških poremećaja (8). Stopa smrtnosti takvih bolesnika varira u rasponu od 20 do 40 % (9).

Na početku pandemije COVID-19 prevladavalo je široko rasprostranjeno mišljenje da je COVID-19 akutna infekcija koja kod većine ljudi završava oporavkom nakon 2 tjedna, a kod jednog manjeg broja, uglavnom starijih ili imunokompromitiranih ljudi, ima fatalan ishod.

Međutim, protokom vremena i sve većim brojem osoba koje su preboljele COVID-19 uvidjelo se da su mnogi tjednima ili mjesecima nakon prebolijevanja osjećali širok spektar fluktuirajućih simptoma. Potencijalni dugoročni učinci mogu uključivati višeorganske komplikacije koji se odnose na simptome središnjeg živčanog sustava, kardiovaskularne, pulmološke, hematološke, bubrežne i gastrointestinalne simptome kao i psihosocijalne posljedice, a često su prijavljivani dugotrajni umor, dispneja,

INTRODUCTION

The clinical manifestations of coronavirus disease (COVID-19) range from asymptomatic conditions to severe clinical presentations affecting the respiratory system and multiple organs (1-6). Epidemiological data indicate that up to 20% of COVID-19 patients progress to a severe condition requiring hospitalization (7). Among hospitalized patients, one-quarter require treatment in the intensive care unit (ICU), making them more vulnerable to secondary pneumonia, cardiovascular complications, sepsis, kidney damage, and neurological disorders (8). Mortality rates among these patients range from 20% to 40% (9).

At the beginning of the COVID-19 pandemic, the prevailing belief was that COVID-19 was an acute infection that, in most cases, resolved within two weeks, while in a smaller subset of patients, mainly older adults or immunocompromised individuals, it led to fatal outcomes.

However, over time and as more people recovered from COVID-19, it became evident that many experienced a wide range of fluctuating symptoms for weeks or months after recovering from the acute phase. Potential long-term effects can include multi-organ complications affecting the central nervous system, including cardiovascular, pulmonary, hematological, renal, and gastrointestinal symptoms, as well as psychosocial consequences. Frequently reported symptoms include persistent fatigue, dys-

te bol u zglobovima i bol u prsima (10,11). Ove komplikacije manifestiraju se kao široki niz tjelesnih (npr. umor, glavobolja, dispneja, bol u mišićima, srčane abnormalnosti i anosmija) i neuroloških simptoma (npr. poremećaji spavanja, problemi s koncentracijom, kognitivno oštećenje) (1,11,12).

Osim tjelesnih, COVID je sa sobom donio i niz psiholoških posljedica uključujući depresiju, anksioznost, stres i poremećaje prilagodbe, lošiji san, povećanu uporabu psihoaktivnih tvari i povećanu uporabu antidepresiva i opioida (13-15).

Uobičajeno se za opisivanje posljedica i simptoma koji traju nakon akutnog preboljenja bolesti koriste termini dugotrajni COVID ili post-COVID. U listopadu 2021. Svjetska zdravstvena organizacija (SZO) definirala je dugotrajni COVID (engl. *long COVID*) kao stanje koje se javlja kod pojedinaca s potvrđenom ili vjerojatnom infekcijom. Teškim akutnim respiratornim sindromom koronavirus 2 (engl. *severe acute respiratory syndrome coronavirus 2,* SARS-CoV-2), obično tri mjeseca nakon pojave simptoma bolesti, traje najmanje dva mjeseca i ne može se objasniti bilo kojom alternativnom dijagnozom (16). Do sada nije postignut univerzalni konsenzus oko definicije ovog kliničkog stanja, a kao sinonimi koriste se i drugi izrazi, kao što su post-akutni COVID-19, kronični COVID-19, post-COVID-19 sindrom, dugotrajni COVID-19 sindrom i dugotrajni COVID-19. Tako smjernice Nacionalnog instituta za zdravlje i izvrsnost skrbi (NICE) navode da se termin post-COVID-19 sindrom odnosi na znakove i simptome koji se razvijaju tijekom ili nakon infekcije COVID-19, traju dulje od 12 tjedana (tri mjeseca) i nisu objašnjeni alternativnom dijagnozom (17), dakle na ono što Svjetska zdravstvena organizacija naziva dugotrajnim COVID-om. Ponekad se termin dugotrajni COVID koristi za dugotrajnu bolest koja traje od 4 do 12 tjedana nakon akutne bolesti i tijekom oporavka (npr. 18,19). U daljnjem tekstu ovog

pnea, joint pain, and chest pain (10, 11). These complications manifest as a broad spectrum of physical symptoms (e.g., fatigue, headache, dyspnea, muscle pain, cardiac abnormalities, anosmia) and neurological symptoms (e.g., sleep disturbances, concentration problems, cognitive impairment) (1, 11, 12).

Beyond physical symptoms, COVID-19 has also led to a range of psychological consequences, including depression, anxiety, stress, and adjustment disorders, poorer sleep quality, increased use of psychoactive substances, and higher consumption of antidepressants and opioids (13-15).

The terms "long COVID" or "post-COVID" are commonly used to describe the lingering consequences and symptoms following acute COVID-19 infection. In October 2021, the World Health Organization (WHO) defined long COVID as a condition occurring in individuals with confirmed or probable infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), typically three months after symptom onset, persisting for at least two months, and not attributable to any alternative diagnosis (16). However, a universal consensus on the definition of this clinical condition has yet to be reached, and various terms such as post-acute COVID-19, chronic COVID-19, post-COVID-19 syndrome, long COVID-19 syndrome and long COVID-19 are used interchangeably. The guidelines of the National Institute for Health and Care Excellence (NICE) thus define post-COVID-19 syndrome as the signs and symptoms that develop during or after a COVID-19 infection, persist for more than 12 weeks (three months), and cannot be explained by an alternative diagnosis (17), which aligns with what the WHO refers to as long COVID. The term long COVID is sometimes used to describe an extended illness lasting between 4 and 12 weeks after the acute infection and during recovery (e.g., 18, 19). In this article, the term post-COVID will be used,

rada korist ćemo termin post-COVID, a odnosi se na smetnje koje se javljaju kao posljedica preboljenja COVID-a.

Na početku se smatralo da se post-COVID odnosi na osobe koje su bile hospitalizirane, uključujući i one pacijente koji su bili liječeni na JIL-u, međutim novija istraživanja jasno pokazuju da ga je moguće prepoznati i kod osoba koje nisu bile hospitalizirane ili koje nisu odmah potražile liječničku skrb (20).

Dosadašnja istraživanja daju različite podatke o učestalosti i kliničkoj slici post-COVID-a.

Najčešće prijavljeni simptomi, koji se pojavljuju i kod osoba koje nisu bolovale od teških oblika COVID-19 (21,22) su umor (npr. 23-25), slabost mišića (npr. 26,27), dispnej (npr.. 28,29), teškoće spavanja (npr. 26,30), anksioznost ili depresija (npr. 21,27), smanjen kapacitet pluća (npr 24,31), teškoće pamćenja/kognitivne teškoće ("magla u mozgu") (npr. 25,27), hiposmija/anosmija (npr. 30), te nemogućnost potpune tjelesne aktivnosti ili rada. Najčešći simptom post-COVID-a je umor, neovisan o težini akutne bolesti ili prisutnosti respiratornih problema (npr. 31,32).

Jedna od ranijih meta-analiza utvrdila je da je jedan od četiri pacijenta imao neuropsihijatrijske simptome koji uključuju poremećaje spavanja, umor, anksioznost i posttraumatski stres (PTSP) nakon početka COVID-19 s približnim trajanjem praćenja od 77 dana (33). Druga meta-analiza 39 studija, uključujući preko 10 000 oboljelih, otkrila je da je 19 % ljudi s post-COVID-om prijavilo anksioznost i 8 % depresiju kao jedan od simptoma (34). Međutim, rezultati pojedinačnih istraživanja u nekim zemljama izvještavaju o puno većoj prevalenciji (npr. 42 % za tjeskobu i 41 % za loše raspoloženje u Velikoj Britaniji) (35).

Post-COVID je povezan s češćim pojavljivanjem depresije, anksioznosti, PTSP-a i smanjenog zadovoljstva životom (36), što bi se moglo djelomično pripisati dugotrajnim tjelesnim simptomima

referring to the complications arising as a consequence of recovering from COVID-19.

Post-COVID was initially thought to affect only the patients who had been hospitalized, including ICU patients. However, recent studies clearly indicate that it can also be identified in individuals who were never hospitalized or who did not seek immediate medical care (20).

The existing studies report varying prevalence rates and clinical presentations of post-COVID. The most frequently reported symptoms, found even among individuals who did not experience severe COVID-19 (21, 22), include fatigue (e.g., 23-25), muscle weakness (e.g., 26, 27), dyspnea (e.g., 28, 29), sleep disturbances (e.g., 26, 30), anxiety or depression (e.g., 21, 27), reduced lung capacity (e.g., 24, 31), memory difficulties/cognitive impairments ("brain fog") (e.g., 25, 27), hyposmia/anosmia (e.g., 30), and an inability to fully engage in physical activity or work. The most common post-COVID symptom is fatigue, regardless of the severity of the acute infection or the presence of respiratory issues (e.g., 31, 32).

One of the early meta-analyses found that one in four patients experienced neuropsychiatric symptoms such as sleep disorders, fatigue, anxiety, and post-traumatic stress disorder (PTSD) following the onset of COVID-19, with an average follow-up duration of 77 days (33). Another meta-analysis of 39 studies involving over 10 000 patients found that 19% of individuals with post-COVID reported feeling anxiety, while 8% reported depression as one of the symptoms (34). However, findings from individual studies in some countries suggested much higher prevalence rates (e.g., 42% for anxiety and 41% for low mood in Great Britain) (35).

Post-COVID has been linked to increased rates of depression, anxiety, PTSD, and reduced life satisfaction (36), which may be partially attributed to persistent physical symptoms of post-COVID (37). A study by Zhao et al. (38)

post-COVID-a (37). Istraživanje Zhaoa i suradnika (38) otkrilo je da je približno 9,6 % hospitaliziranih pacijenata koji pate od umjerene onesposobljenosti prijavljivalo probleme psihičkog zdravlja i kognitivne simptome 20 mjeseci nakon izlaska iz bolnice. Nekoliko čimbenika predviđa dugoročne tjelesne i kognitivne simptome, a uključuju dob, boravak u bolnici, spol i komorbiditete. Osobe ženskog spola, starije dobi, s više komorbiditeta i dužim boravkom u bolnici imat će viši rizik za razvoj post-COVID sindroma (4).

Iako se psihološki simptomi općenito poboljšavaju tijekom vremena, neki se mogu zadržati znatno dulje (i dulje od jedne godine) bez puno poboljšanja ili čak može doći do pogoršanja tijekom vremena (21,39). Do danas su zabilježeni dugotrajni simptomi i do dvije godine nakon infekcije (2,4).

Važno je osvrnuti se na ulogu cjepiva protiv COVID-19 u razvoju post-COVID-a. Iako cjepiva sprječavaju smrt i tešku bolest, još nije jasno mogu li spriječiti i pojavu post-COVID-a (40). Manja istraživanja pokazuju da su cjepiva AstraZeneca i Pfizer-BioNTech povezana s općenitim poboljšanjima simptoma post-COVID-a (41). Antonelli i suradnici (42) navode da su izgledi za zadržavanje simptoma 28 dana ili više nakon razvijene infekcije, iako je osoba primila cjepivo, bili otprilike dva puta manji uzimanjem dviju doza cjepiva.

Cilj ovog preglednog rada bio je analizirati tjelesne, psihološke, kognitivne i socijalne teškoće koje pacijenti koji su oboljeli od teškog COVID-19 mogu doživjeti nakon otpuštanja iz bolnice, kao i njihov utjecaj na kvalitetu života pacijenata i njihovih obitelji.

METODOLOGIJA PRETRAŽIVANJA RADOVA

Pretraživanje literature provedeno je u bazama podataka *PubMed, Scopus* i *PsycINFO* korištenjem ključnih pojmova *post-COVID syndrome*,

found that approximately 9.6% of hospitalized patients experiencing moderate disability reported mental health problems and cognitive symptoms 20 months after being discharged from the hospital. Several factors predict long-term physical and cognitive symptoms, and they include age, hospitalization, sex, and comorbidities. Women, older adults, individuals with multiple comorbidities, and those with prolonged hospital stays are at a higher risk of developing post-COVID syndrome (4).

Although psychological symptoms generally improve over time, some may persist significantly longer (over a year) with little improvement, or may even worsen over time (21, 39). Long-term symptoms have so far been observed to last up to two years after infection (2, 4).

It is also important to consider the role of COVID-19 vaccines in the development of post-COVID. While vaccines prevent death and severe illness, it remains unclear whether they can also prevent post-COVID (40). Smaller studies suggested that the AstraZeneca and Pfizer-BioNTech vaccines are associated with overall improvements in post-COVID symptoms (41). Antonelli et al. (42) reported that the likelihood of experiencing symptoms persisting for 28 days or longer after infection, despite vaccination, was approximately halved in individuals who received two vaccine doses.

The aim of this review article was to analyze the physical, psychological, cognitive, and social difficulties that patients with severe COVID-19 may experience after hospital discharge, as well as their impact on the quality of life of the patients and their families.

METHODOLOGY OF LITERATURE SEARCH

The literature search was conducted using the PubMed, Scopus, and PsycINFO databases, employing key terms such as *post-COVID syndrome*,

long COVID, *post-intensive care syndrome (PICS)*, *COVID-19 recovery*, *mental health* i *quality of life*. Obuhvaćeni su radovi objavljeni u razdoblju od 2020. do 2024. kako bi se osigurao pregled recentnih saznanja o posljedicama COVID-19 infekcije. Dvije autorice su neovisno pregledavale sažetke i naslove identificiranih radova te su na temelju relevantnosti za biopsihosocijalni model post-COVID sindroma odabrale one koji su uključeni u daljnju analizu. Posebno su naglašeni radovi koji ispituju fizičke, psihološke, kognitivne i socijalne aspekte post-COVID sindroma te njihovu povezanost sa sindromom postintenzivne njege (PICS).

Čimbenici koji pridonose pojavi psihičkih smetnji bit će prikazani iz biopsihosocijalne perspektive s fokusom na psihološke čimbenike ranjivosti. Kao jedan od čimbenika koji se posebno izdvaja jest hospitalizacija u JIL-u kao potencijalni traumatski događaj, te će biti prikazani rezultati istraživanja o psihičkim posljedicama intenzivnog liječenja pri čemu će se rezultati staviti u kontekst spoznaja o reakcijama na liječenje drugih zaraznih bolesti.

ETIOLOŠKI ČIMBENICI PSIHIČKIH SMETNJI U POST-COVID SINDROMU

Suočavanje s COVID-om, kao i s bilo kojim drugim zdravstvenim stanjem, uključuje sve dimenzije postojanja osobe – onu biološku, potom socijalnu, te vrlo važnu psihološku dimenziju koja je u slučaju liječenja bolesti bila dodatno obilježena traumatskim situacijama hospitalizacije i boravka u JIL-u. Psihološke posljedice mogle bi se odnositi i na one osobe zaražene virusom koje su zabrinute zbog stigme (43), ishoda bolesti (44), traumatskih sjećanja na teške bolesti ili amnezije (45), psiholoških reakcija nakon zaraze COVID-19 i povezanih medicinskih intervencija (46). Međutim, na sve osobe, bez obzira jesu li zaražene virusom ili nisu, mogu utjecati iskustva povezana

long COVID, *post-intensive care syndrome (PICS)*, *COVID-19 recovery*, *mental health*, and *quality of life*. The review included studies published between 2020 and 2024 so as to ensure an overview of recent findings on the consequences of COVID-19 infection. Two authors independently screened the abstracts and titles of the identified studies, and selected those relevant to the biopsychosocial model of post-COVID syndrome for further analysis. Special emphasis was placed on studies examining the physical, psychological, cognitive, and social aspects of post-COVID syndrome, and their association with post-intensive care syndrome (PICS).

The factors contributing to the development of psychological difficulties will be presented from a biopsychosocial perspective, with a focus on psychological vulnerability factors. One factor that particularly stands out is hospitalization in an intensive care unit (ICU) as a potentially traumatic event. Research findings on the psychological consequences of intensive care treatment will be presented, whereby the results will be viewed in the context of the existing knowledge about responses to treatment for other infectious diseases.

ETIOLOGICAL FACTORS OF PSYCHOLOGICAL DISTURBANCES IN POST-COVID SYNDROME

Coping with COVID-19, as with any other health condition, involves all dimensions of a person's existence – the biological, the social, and the very important psychological dimension. In the case of COVID-19 treatment, the psychological aspect was further marked by traumatic experiences of hospitalization and ICU stays. Psychological consequences may also affect individuals infected with the virus who are concerned about the stigma (43), disease outcomes (44), traumatic memories of severe illness or amnesia (45), psychological reactions after contracting COVID-19, and related medical interventions

s pandemijom uključujući socijalnu izolaciju (47), tjeskobu (48), te financijske teškoće i nezaposlenost (49). Psihički poremećaji povezani s COVID-19 vjerojatno su višefaktorski zbog kombinacije okolinskih, psihosocijalnih i bioloških čimbenika koji su rezultat ove globalne pandemije.

Biološki čimbenici

Pretpostavlja se da je patogeneza neuropsihijatrijskih manifestacija COVID-19 uglavnom rezultat neizravnog imunološkog upalnog oštećenja središnjeg živčanog sustava (SŽS) i, hipotetski, potencijalna posljedica izravne virusne neuroinvazije (50,51). Koronavirusi, uključujući SARS-CoV-2, imaju sposobnost inficiranja SŽS-a hematogeno ili neuronski retrogradnim neuroinvazivnim putevima. Ovaj mehanizam ulaska i naknadna infekcija SŽS-a mogu objasniti visoku učestalost neuroupale koja se vidi kod pacijenata s COVID-19 (52). Ova neuroupala može rezultirati štetnim dugoročnim posljedicama, koje su povezane s neurodegenerativnim i psihijatrijskim poremećajima. Kod nekih oboljelih s post-COVID-om virus je prisutan u različitim tjelesnim organima i mjesecima nakon akutne infekcije (53,54). Također, SARS-CoV-2 može utjecati na propusnost krvno-moždane barijere što omogućuje perifernim citokinima i drugim tvarima iz krvi da prodru u SŽS i potaknu neuroupalu. Tromboembolični putevi mogu biti uzrok povećane prevalencije moždanog udara kod COVID-19, dok se "moždana magla" može razviti iz PTSP-a (51).

Dostupni dokazi ukazuju da izravni virusni encefalitis, sustavna upala, disfunkcija perifernih organa, mitohondrijska disfunkcija izazvana hipoksijom i cerebrovaskularne promjene mogu doprinijeti razvoju dugotrajnih posljedica nakon COVID-19 (55-57). Što se tiče moguće etiologije neuropsiholoških simptoma post-COVID-a, jedno objašnjenje vezano je uz

(46). However, pandemic-related experiences, including social isolation (47), anxiety (48), financial difficulties and unemployment (49), can impact all individuals regardless of whether they have contracted the virus. Psychological disorders associated with COVID-19 are likely multifactorial due to the combination of environmental, psychosocial, and biological factors resulting from this global pandemic.

Biological factors

It is hypothesized that the pathogenesis of neuropsychiatric manifestations of COVID-19 is primarily the result of indirect immune-inflammatory damage to the central nervous system (CNS) and, hypothetically, a potential consequence of direct viral neuroinvasion (50, 51). Coronaviruses, including SARS-CoV-2, have the ability to infect the CNS via hematogenous or neuronal pathways, through retrograde neuroinvasive routes. This mechanism of entry and subsequent CNS infection may explain the high prevalence of neuroinflammation observed in COVID-19 patients (52). Such neuroinflammation can lead to harmful long-term consequences associated with neurodegenerative and psychiatric disorders. In some individuals with post-COVID syndrome, the virus remains present in various body organs for months after the acute infection (53, 54). Additionally, SARS-CoV-2 can impact the permeability of the blood-brain barrier, allowing peripheral cytokines and other blood-borne substances to enter the CNS and trigger neuroinflammation. Thromboembolic pathways may contribute to the increased prevalence of stroke in COVID-19, while "brain fog" may develop as a result of PTSD (51).

Available evidence suggests that direct viral encephalitis, systemic inflammation, peripheral organ dysfunction, hypoxia-induced mitochondrial dysfunction, and cerebrovascular changes may contribute to the development of long-term consequences after COVID-19 (55-57).

upalne procese u mozgu - cirkulirajući citokini prodiru kroz krvno-moždanu barijeru što za posljedicu može imati sniženo raspoloženje i teškoće koncentracije i pamćenja. Istraživanja ukazuju na poremećaj GABA-receptora, što se može povezati sa simptomima tjelesnog i kognitivnog umora (58).

Još je jedan važan aspekt koji treba istaknuti - mogućnost da tjelesni simptomi kao što su zaduhe i mialgija utječu na psihičko stanje oboljelih od dugotrajnih posljedica COVID-19. Ova interakcija može biti dvosmjerna: tjelesne smetnje mogu rezultirati psihičkim simptomima, dok se psihički simptomi depresije, anksioznosti i PTSP-a mogu manifestirati kao tjelesni simptomi (59).

Fernández-de-las-Peñas i suradnici (4) navode da je najznačajniji faktor rizika za razvoj post-COVID-a broj simptoma pri prijmu u bolnicu. To podupire ideju da veći teret simptoma tijekom akutne faze bolesti povećava vjerojatnost pojave post-COVID stanja (5).

Istraživanja pokazuju da žene imaju značajno veću vjerojatnost da će imati simptome post-COVID-a od muškaraca (4,6), ali samo do dobi od 60 godina nakon koje omjer postaje podjednak (60). Umor, dispneja, problemi s psihičkim zdravljem, poremećaji spavanja češće su prijavljivani kod žena (4,6), što je posljedično povezano i s nižom kvalitetom života povezanom sa zdravljem. Ostali čimbenici rizika uključuju postojeću astmu (ali nisu na nju ograničeni), prisutne komorbiditete i stariju dob (5,61).

Socijalni čimbenici

Razmjeri patnje od kroničnih bolesti nisu jednostavno određeni težinom same bolesti, već su moderirani vanjskim i individualnim čimbenicima (62). Kako Teorija tereta liječenja postulira, nošenje s kroničnim stanjima uključuje svakodnevnu skrb s ciljem kontrole bolesti. Kako se tereti liječenja gomilaju, neki

Regarding the possible etiology of neuropsychological symptoms in post-COVID syndrome, one explanation relates to inflammatory processes in the brain – circulating cytokines penetrate the blood-brain barrier, potentially leading to low mood, concentration difficulties, and memory impairments. Research also indicates that GABA receptor dysfunction may be linked to symptoms of physical and cognitive fatigue (58).

Another important aspect to highlight is the possibility that physical symptoms, such as shortness of breath and myalgia, affect the psychological state of individuals suffering from long-term COVID-19 consequences. This interaction can be bidirectional: physical ailments may lead to psychological symptoms, while psychological symptoms such as depression, anxiety, and PTSD may manifest as physical complaints (59).

Fernández-de-las-Peñas et al. (4) observed that the most significant risk factor for developing post-COVID syndrome is the number of symptoms experienced at the time of hospital admission. This supports the idea that a higher symptom burden during the acute phase of illness increases the likelihood of developing post-COVID conditions (5).

Studies have shown that women are significantly more likely than men to experience post-COVID symptoms (4, 6), but this difference disappears after the age of 60, when the ratio becomes fairly equal (60). Symptoms such as fatigue, dyspnea, mental health issues, and sleep disturbances are more commonly reported among women (4, 6), which is consequently associated with lower health-related quality of life. Other risk factors include (but are not limited to) pre-existing asthma, as well as existing comorbidities and older age (5, 61).

Social factors

The extent of suffering from chronic illnesses is not solely determined by the severity of the disease itself, but is also moderated by exter-

pacijenti postaju preopterećeni što dovodi do lošijih ishoda, stresa za njihove njegovatelje, i povećanja troškova zdravstvene zaštite (63). Percipirani teret post-COVID-a ukazuje na jasnu povezanost bolesti s psihičkim zdravljem pacijenata. Velik je broj čimbenika kojima se pripisuju međuodnos između stvarne težine tjelesne bolesti, zahtjeva liječenja i percepcije sposobnosti pojedinca da se prilagodi post-COVID-u (64). Prema Teoriji o teretu liječenja (63) percipirano opterećenje bolešću bolesnika s post-COVID-om može biti pojačano teškoćama u upravljanju simptomima. Medicinski troškovi (65) i financijske teškoće (66) kao posljedice pandemije COVID-19 mogu rezultirati pokušajima pacijenata da se što brže vrate na posao ignorirajući simptome post-COVID-a, čime posljedično usporavaju oporavak i dodaju teret liječenju.

Veliki je broj istraživanja usmjeren na povezanost javnozdravstvenih mjera tijekom pandemije COVID-om (kao što su karantena, socijalna izolacija i druga ograničenja osobnih sloboda) s psihičkim zdravljem utvrdila su povezanost sa simptomima depresije, tjeskobe, usamljenosti, psihosocijalnog stresa i trajne uznemirenosti (67,68). To je moguće alternativno objašnjenje za veću prevalenciju psihijatrijskih simptoma među pacijentima s post-COVID-om. Upravo veća prevalencija može biti više posljedica nametnute karantene i drugih ograničenja u smislu tjeskobe, straha, ljutnje i drugih neugodnih emocija, bez obzira na specifične aspekte infekcije COVID-19 kao što je neuroupala ili sistemska upala. Istraživanja su jasno pokazala da su oboljeli od COVID-a bili stigmatizirani i da je stigma negativno utjecala na njihovu kvalitetu života te razvijanje psihičkih smetnji (69,70). Novija istraživanja pokazuju da se slično ponavlja i s post-COVID sindromom. Oboljeli koji doživljavaju vanjsku stigmatizaciju, zabrinutost zbog razotkrivanja i internaliziranu stigmu imaju više depresivnih i anksioznih smetnji, što dodatno intenzivira

nal and individual factors (62). According to the Burden of Treatment Theory, coping with chronic conditions involves daily care aimed at disease management. As treatment burdens accumulate, some patients become overwhelmed, leading to poorer outcomes, stress for their caregivers, and increased healthcare costs (63). The perceived burden of post-COVID indicates a clear connection between the illness and the patients' mental health. Numerous factors contribute to the interplay between the actual severity of physical illness, treatment demands, and the individuals' perceived ability to adapt to post-COVID (64). Based on the Burden of Treatment Theory (63), the perceived burden of illness in post-COVID patients may be exacerbated by difficulties in managing symptoms. Medical costs (65) and financial hardships (66) resulting from the COVID-19 pandemic may lead patients to rush back to work while ignoring post-COVID symptoms, thus slowing their recovery and adding to the burden of treatment.

A large body of research has focused on the relationship between public health measures during the COVID-19 pandemic (such as quarantine, social isolation, and other restrictions on personal freedoms) and mental health. These studies have identified associations with the symptoms of depression, anxiety, loneliness, psychosocial stress, and persistent distress (67, 68). This presents an alternative explanation for the higher prevalence of psychiatric symptoms among post-COVID patients. Increased prevalence itself may be more attributable to imposed quarantine and other restrictions leading to anxiety, fear, anger, and other distressing emotions, rather than to specific aspects of COVID-19 infection, such as neuro- or systemic inflammation. Studies have clearly shown that COVID-19 patients were stigmatized, which negatively affected their quality of life and contributed to the development of mental health difficulties (69, 70). Recent studies indicate that a similar pattern is

smetnje koje sam post-COVID donosi sa sobom (71).

Za odnos post-COVID-a i psihičkog zdravlja odgovorne mogu biti i promjene koje su se dogodile zbog pandemije kao što su financijska nestabilnost, socijalna distanca i nošenje maski (72-74).

Psihološki čimbenici

Individualni čimbenici imaju važnu ulogu u određivanju nošenja s bolešću. Prema Leventhalovom modelu samoregulacije reprezentacije bolesti pacijenta (uvjerenja o uzroku, vremenskoj liniji, posljedicama, itd.), odražavaju njihov percipirani teret i time utječu na samoregulacijska ponašanja, psihološku prilagodbu i psihičko zdravlje (75). Stoga teret bolesti koji percipiraju oboljeli od post-COVID-a, kao i od bilo koje druge kronične bolesti, može imati izravan utjecaj na njihovo psihičko zdravlje. Vjerojatno bi se izražena tjeskoba i depresija mogle pojaviti ubrzo nakon infekcije SARS-CoV-2. Međutim, prisutna je i povećana socijalna izolacija zbog dugotrajnog COVID-a i tjeskoba povezana s trajnim simptomima što može značiti da se psihološki simptomi zapravo pojavljuju tijekom i povećavaju nakon akutnog stanja infekcije među pacijentima s post-COVID-om (76,77).

Kvalitativna istraživanja pokazuju da je proživljeno iskustvo post-COVID-a vrlo različito i percipira se kao da je u suprotnosti s javnom percepcijom i službenim smjernicama za COVID-19 (78). Oboljeli opisuju niz pozitivnih i negativnih zdravstvenih iskustava.

Simptomi koje doživljavaju pacijenti s post-COVID-om variraju u težini od relativno blagih simptoma do simptoma potencijalno opasnih za život koji su zahtijevali bolničko liječenje (32). Također, takvi se simptomi izmjenjuju tijekom vremena s novim simptomima i to u različitim dijelovima tijela. Svaki je pojedinačni simptom trajao različito vrijeme,

emerging with post-COVID syndrome. Patients who experience external stigmatization, concern about disclosure, and internalized stigma, report more depressive and anxiety symptoms, further intensifying the distress already associated with post-COVID (71).

Changes brought about by the pandemic, such as financial instability, social distancing, and mask-wearing, may also play a role in the relationship between post-COVID and mental health (72-74).

Psychological factors

Individual factors play an important role in determining how individuals cope with illness. According to Leventhal's Self-Regulation Model, patients' illness representations (beliefs about the cause, timeline, consequences, etc.) reflect their perceived burden and consequently influence their self-regulatory behaviors, psychological adjustment, and mental health (75). The burden of illness perceived by individuals with post-COVID, as with any other chronic illness, can therefore have a direct impact on their mental well-being. It is likely that pronounced anxiety and depression may emerge soon after SARS-CoV-2 infection. However, increased social isolation due to long COVID and anxiety related to persistent symptoms may indicate that psychological symptoms actually appear during and intensify after the acute phase of infection among post-COVID patients (76, 77).

Qualitative studies suggest that the experience of post-COVID varies significantly and is often perceived as being at odds with the public perception and official COVID-19 guidelines (78). Patients describe a range of both positive and negative health experiences.

The symptoms experienced by post-COVID patients range in severity, from relatively mild to potentially life-threatening symptoms requiring hospitalization (32). Additionally, such symptoms fluctuate over time, with new symptoms

ali u mnogim je slučajevima postojao kumulativni učinak. Oboljeli su opisivali kako su doživljavali sebe prije i poslije bolesti, i to unutar konteksta obitelji i posla. Navode da se često uspoređuju s osobom koja su bili prije bolesti, što neki autori objašnjavaju konceptom „uništenog identiteta", jer se identitet kakav je prije bio (zdrav, neovisan i uspješan) zbog post-COVID-a doživljava ugroženim (79).

Oboljeli su vjerovali da oporavak zahtijeva kratko razdoblje i da će se na posao vratiti u razdoblju od dva tjedna, a to su uvjerenje imali i njihovi poslodavci i okolina (79,80). Taj nesklad između očekivanja i iskustva imao je izravan učinak na psihičko i emocionalno stanje osoba s post-COVID-om i osjećaj neizvjesnosti o tome što učiniti u vezi sa svojim simptomima. Opisivali su potrebu da prilagode svoj životni stil uključujući vođenje vlastitog tempa i postavljanje realnih ciljeva kako bi sami upravljali svojim simptomima.

Osim opisanog, oboljeli su imali osjećaj stigme povezan s post-COVID-om, doživljavaju osjećaj srama i samookrivljavanje zbog simptoma i onesposobljenosti njima i izražavaju strah da bi ih poslodavci i drugi u okolini mogli stigmatizirati zbog post-COVID-a.

Ako se psihološki simptomi pojavljuju već tijekom infekcije, postavlja se pitanje utječe li njihova razina izraženosti u toj fazi na pojavu post-COVID-a, odnosno razlikuje li se među osobama koje će imati kratki oporavak od bolesti od onih s post-COVID-om.

Među istraživanjima koja se bave dugoročnim posljedicama COVID-19 tek ih je manji broj koja se bave posljedicama kod osoba koje su tijekom i zbog bolesti bile hospitalizirane s teškim ili kritičnim kliničkim slikama i liječene u jedinicama JIL-a. Unatoč sve većem znanju o COVID-19 i njegovim posljedicama još uvijek se relativno malo zna o dugotrajnim posljedicama kod osoba koje su preživjele li-

emerging in different parts of the body. Each individual symptom persists for varying durations, but in many cases, there is a cumulative effect. Patients described how they perceived themselves before and after the illness within the context of their families and work. They often compared themselves to the person they were before falling ill, which some authors explain through the concept of a "shattered identity", where their previous identity (healthy, independent, and successful) is perceived as being threatened due to post-COVID (79).

Patients believed that recovery would take only a short time and that they would return to work within two weeks, an expectation shared by their employers and social environment (79, 80). The mismatch between expectations and actual experience had a direct impact on the psychological and emotional state of individuals with post-COVID, contributing to the feeling of uncertainty about how to manage their symptoms. Many reported a need to adjust their lifestyle, including pacing themselves and setting realistic goals in order to self-manage their symptoms.

In addition to the aforementioned, individuals with post-COVID experienced stigma, feelings of shame, and self-blame related to their symptoms and disability. They also expressed fear that employers and others in their environment might stigmatize them due to their post-COVID condition.

If psychological symptoms appear during the infection itself, the question arises as to whether their severity at this stage influences the development of post-COVID, i.e. whether it is different among those who recover quickly and those who experience post-COVID.

Among studies investigating the long-term consequences of COVID-19, only few focus on the consequences among the individuals who were hospitalized with severe or critical clinical conditions and treated in intensive care units (ICUs) during the infection or due to the infection.

ječenje na JIL-u i kakve su one u odnosu na istraživanja koja se odnose na ne-COVID-19 hospitalizacije.

Iako je činjenica da osobe koje su liječene u jedinicama intenzivne skrbi često imaju simptome koji traju i nakon otpuštanja iz bolnice i koji se povezuju sa samim iskustvom hospitalizacije (81,82), pandemija COVID-19 i pojava post-COVID sindroma ponovno je u fokus vratila sindrom postintenzivne njege (engl. *post-intenzive care syndrome,* PICS).

Liječenje u JIL-u nosi sa sobom sve elemente traumatskog iskustva, no hoće li se nakon njega razviti PTSP ovisi o interakciji osobina ličnosti, vrsti traumatskih iskustava i podrške koju je osoba primala tijekom i nakon liječenja.

DUGOROČNE POSLJEDICE LIJEČENJA U JIL-u (NEVEZANO UZ PANDEMIJU COVID-19)

Liječenje i preživljavanje pacijenata (što se podrazumijeva kao otpuštanje živih iz jedinice intenzivne njege) koji su se liječili u intenzivnim jedinicama tradicionalno se smatra mjerom uspjeha liječenja (83). Sve veća prevalencija teških i kritičnih bolesti u kombinaciji s napretkom u medicini intenzivne skrbi rezultirala je sve većim brojem pacijenata (~80-90 %) koji su preživjeli do otpusta iz bolnice (84-86). Međutim, odmicanjem od samo tradicionalnih pogleda sve je veći interes za dugoročne zdravstvene ishode osoba koje su preživjele intenzivnu njegu, što je rezultiralo pomicanjem cilja intenzivne skrbi s preživljavanja na povratak u svakodnevni život nakon kritične bolesti (87).

Prijam na intenzivno liječenje ima potencijalno dugotrajne posljedice za osobe koje su ga preživjele i njihove članove obitelji. Osobe koje su preživjele liječenje u JIL-u mogu razviti tjelesne, psihološke i/ili kognitivne teškoće koje se nazivaju i sindromom postintenzivne njege (PICS) (88-91). Tjelesni simptomi su umor i

Despite increasing knowledge about COVID-19 and its consequences, relatively little is still known about the long-term effects in survivors of ICU treatment and how these compare to the research on non-COVID-19 hospitalizations.

Although it is well established that individuals treated in intensive care units often experience persistent symptoms after hospital discharge and symptoms linked to the hospitalization experience itself (81, 82), the COVID-19 pandemic and the emergence of post-COVID syndrome have brought about a renewed attention to Post-Intensive Care Syndrome (PICS).

ICU treatment involves all elements of a traumatic experience, but whether an individual develops PTSD depends on the interaction between personality traits, the nature of the traumatic experiences, and the support received during and after treatment.

LONG-TERM CONSEQUENCES OF ICU TREATMENT (UNRELATED TO THE COVID-19 PANDEMIC)

The treatment and survival of patients (defined as being discharged alive from the intensive care unit) who were treated in intensive care units (ICUs) have traditionally been considered a measure of treatment success (83). The increasing prevalence of severe and critical illnesses, combined with advancements in intensive care medicine, has resulted in a growing number of patients (~80–90%) surviving until hospital discharge (84–86). However, moving beyond the mere traditional perspectives, there is growing interest in the long-term health outcomes of ICU survivors, leading to a shift in the focus of intensive care from mere survival to returning to daily life after experiencing a critical illness (87).

Admission to intensive care has potentially long-term consequences for both survivors and their family members. ICU survivors may develop physical, psychological, and/or cog-

nesanica, dok kognitivni i psihijatrijski simptomi uključuju anksioznost, depresiju, teškoće pažnje i pamćenja i PTSP.

Raznolikost i ozbiljnost posljedica značajno varira u istraživanjima. Istraživanja pokazuju da 70 % osoba koje su liječene u JIL-u razvije jedan ili više simptoma PICS-a jednu godinu nakon otpusta s liječenja (92), ali i da PICS može trajati čak i 5 godina nakon izlaska iz bolnice (93-96). Šest mjeseci nakon otpusta 25 % preživjelih pati od teške onesposobljenosti, a samo se oko 55 % vratilo na posao (97). Psihološki poremećaji uključujući depresiju, anksioznost i PTSP su česti, pogađaju 55 % osoba u prvoj godini nakon otpuštanja iz JIL-a (98-100).

I za osobe koje su preživjele liječenje u JIL-a i za članove njihovih obitelji simptomi mogu imati negativan utjecaj na socijalne aspekte njihovog svakodnevnog života, kao što su povratak na posao, uloge i odgovornosti unutar obitelji i kvalitetu života (engl. *Quality of Life*, QoL) (101-103). Osim toga, iskustvo osobe koja je liječena na JIL-u razlikuje se od iskustva članova njegove obitelji, što naknadno može utjecati na njihove odnose i načine suočavanja (104).

Sve opisane posljedice PICS-a na oboljele i članove njihovih obitelji rezultiraju povećanim troškovima zdravstvene skrbi, ponovnim hospitalizacijama, nezaposlenosti, češćim posjetima liječnicima u primarnoj zdravstvenoj zaštiti i smanjenjem kvalitete života povezane sa zdravljem (105-110).

Čimbenici rizika za pojavu PICS-a nisu jasno definirani i razlikuju se u različitim studijama, no općenito su odvojeni u dvije kategorije: oni koji se odnose na već postojeće čimbenike (postojeće bolesti te komorbiditete ili psihijatrijsku anamnezu) i oni koji su povezani s JIL-om, uključujući prisutnost delirija, dozu primijenjenih sedativa, prisutnost sindroma akutnog respiratornog distresa (ARDS-a) ili sepse (111).

nitive difficulties, collectively referred to as post-intensive care syndrome (PICS) (88–91). Physical symptoms include fatigue and insomnia, while cognitive and psychiatric symptoms encompass anxiety, depression, attention and memory difficulties, and post-traumatic stress disorder (PTSD).

The variety and severity of these consequences vary significantly across studies. Research indicates that 70% of ICU-treated individuals develop one or more PICS symptoms within a year after discharge (92), and PICS can persist for up to five years post-hospitalization (93–96). Six months after discharge, 25% of survivors suffer from severe disability, and only about 55% return to work (97). Psychological disorders, including depression, anxiety, and PTSD, are common and affect 55% of individuals in the first year after ICU discharge (98–100).

For both ICU survivors and their family members, these symptoms can have a negative impact on the social aspects of daily life, such as returning to work, family roles and responsibilities, and overall quality of life (QoL) (101–103). Additionally, the experience of an ICU patient differs from that of their family members, which can subsequently affect their relationships and coping strategies (104).

The described consequences of PICS for both patients and their families result in increased healthcare costs, rehospitalizations, unemployment, more frequent visits to primary care physicians, and reduced health-related quality of life (105–110).

Risk factors for PICS have not been clearly defined and vary across studies, but they are generally categorized into two groups: those referring to pre-existing factors (such as existing illnesses, comorbidities, or a history of psychiatric disorders) and ICU-related factors, including the presence of delirium, dosage of administered sedatives, the presence of acute respiratory distress syndrome (ARDS), or sepsis (111).

PICS I POST-COVID

Daljnjim poboljšanjem skrbi za pacijente na intenzivnoj njezi tijekom pandemije COVID 19 došlo je do povećanja broja preživjelih što je pomaknulo fokus na pitanja vezana uz dugoročne ishode. Osobe koje su preživjele teški ili kritični COVID-19 zbog kojeg su bile hospitalizirane izložene su velikom riziku razvoja PICS-a (112-115). Post-COVID simptomi, koji traju dugo nakon otpuštanja iz JIL-a, pokazuju značajno preklapanje s PICS-om i mogu pogoršati njegove simptome (116,117) (slika 1).

Kod više od 90 % pacijenata prijavljeni su simptomi koji pogađaju barem jednu glavnu PICS domenu (114).

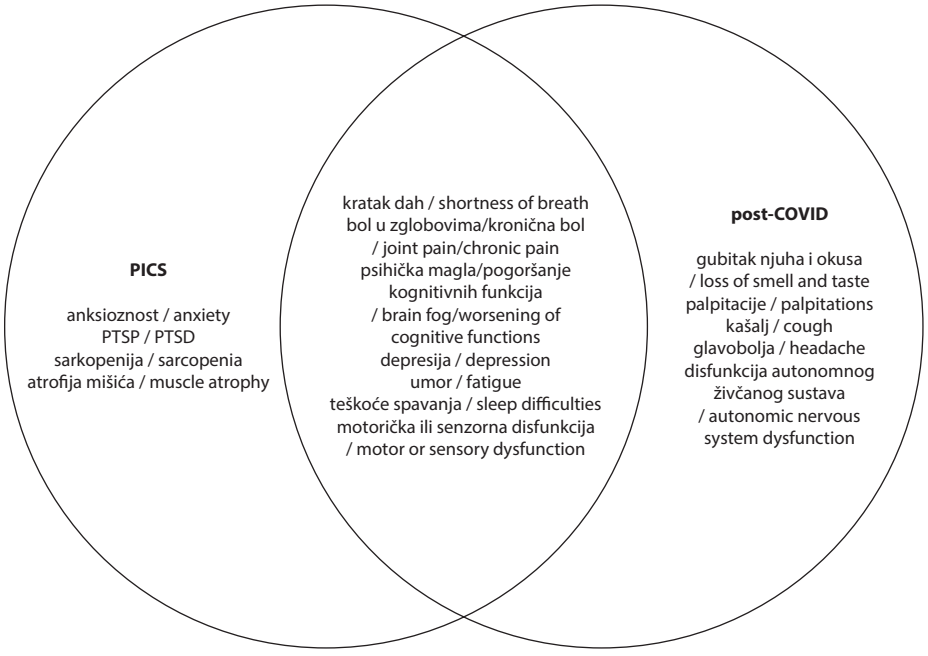
U nizozemskoj prospektivnoj kohortnoj studiji koja je uključivala procjenu 246 pacijenata jednu godinu nakon liječenja COVID-19 na intenzivnoj njezi, 74,3 % je prijavilo tjelesne simptome, 26,2 % psihičke smetnje, a 16,2 % kognitivne simptome (118). Jedan od prvih sustavnih pregleda istraživanja upućivao je na visoku prevalenciju kognitivnih poremećaja kod osoba koje su preživjele intenzivnu njegu: oko

PICS AND POST-COVID

With further improvements in intensive care for patients during the COVID-19 pandemic, the number of survivors has increased, shifting the focus to long-term outcomes. Individuals who survived severe or critical COVID-19 that required hospitalization are at a high risk of developing PICS (112-115). Post-COVID symptoms, which persist long after discharge from the ICU, significantly overlap with PICS and may exacerbate its symptoms (116, 117) (Figure 1).

More than 90% of patients have reported symptoms affecting at least one major PICS domain (114).

In a Dutch prospective cohort study that examined 246 patients one year after ICU treatment due to COVID-19, 74.3% reported physical symptoms, 26.2% reported psychological distress, and 16.2% reported cognitive symptoms (118). One of the first systematic reviews of research pointed to a high prevalence of cognitive impairments among ICU survivors: approximately 50% to 80% of ICU survivors had



SLIKA 1. Preklapanje simptoma PICS-a i post-COVID-a
FIGURE 1. Overlapping symptoms of PICS and post-COVID

50 % do 80 % osoba koje su preživjele intenzivnu njegu imalo je kognitivna oštećenja (119). Prevalencija je bila veća kod ARDS-a preživjelih u usporedbi s mješovitim pacijentima na intenzivnoj njezi, a bila je veća i kada su se koristile objektivne mjere procjene u usporedbi sa subjektivnim samoprocjenama. Istraživanje koje se bavilo 12-mjesečnim ishodima pacijenata nakon prijmova u bolnicu zbog bolesti COVID-19 (120) utvrdilo je smanjenje kvalitete života povezane sa zdravljem (engl. *health-related quality of life*, HRQoL) nakon jedne godine i blaga do umjerena tjelesna ograničenja kod 29 % sudionika. U drugoj studiji (121) sudionici su izjavili da je umor (27 %) najizraženiji simptom 12 mjeseci nakon otpusta iz bolnice. Osobe koje su preživjele intenzivnu njegu također su prijavljivale bol kao važan simptom, a najistaknutije vrste boli su bol u zglobovima, bol u mišićima i bol u živcima (122). Sahoo i suradnici (123) izvijestili su da pacijenti smatraju liječenje u JIL-u bolnim iskustvom i kao jednu od najgorih faza svog života. Tijekom bolničkog liječenja imali su izražen strah od smrti zbog neizvjesnosti ishoda liječenja, a nakon otpusta bili su uznemireni zbog dugotrajnosti bolesti i niza psihosocijalnih negativnih posljedica (124).

U velikoj kohorti pacijenata koji su proveli u prosjeku 10 dana u JIL-u poremećaji spavanja i kognitivni poremećaji bili su dvije najčešće posljedice koje su oboljeli prijavljivali i četiri mjeseca nakon otpusta (125). Otprilike mjesec dana nakon otpusta više je od jedne trećine pacijenata prijavilo simptome akutnog stresnog poremećaja (126) ili kognitivnu disfunkciju (127), a tri mjeseca nakon akutne bolesti preživjeli su još uvijek imali narušenu kvalitetu života povezanu sa zdravljem (125,128). Šest mjeseci nakon kritičnog COVID-19 bol, nelagoda, tjeskoba ili depresija i dalje su prevladavali, za razliku od problema s pokretljivošću. Istraživanja pokazuju da je broj oboljelih koji su potpuno bez simptoma nakon liječenja u JIL-u iznimno mali. Manje od 10 % pacijenata

cognitive impairments (119). The prevalence was higher among ARDS survivors compared to mixed ICU patients, and was also higher when objective assessment measures were used compared to subjective self-assessments. A study examining 12-month outcomes in patients after COVID-19 hospitalization (120) found a decline in the health-related quality of life (HRQoL) after one year, and mild to moderate physical limitations in 29% of participants. In another study (121), participants reported fatigue (27%) as the most prominent symptom 12 months after hospital discharge. ICU survivors also reported pain as a significant symptom, with joint pain, muscle pain, and nerve pain being the most common (122). Sahoo et al. (123) reported that patients perceived ICU treatment as a painful experience and one of the worst phases of their lives. During hospitalization, they experienced intense fear of death due to uncertainty about treatment outcomes, and after discharge, they were distressed by the prolonged illness and various psychosocial negative consequences (124).

In a large cohort of patients who spent an average of 10 days in the ICU, sleep disorders and cognitive impairments were the two most common consequences, reported by the patients even four months after discharge (125). Approximately one month after discharge, more than one-third of patients reported symptoms of acute stress disorder (126) or cognitive dysfunction (127), while three months after acute illness, survivors still reported impaired health-related quality of life (125, 128). Six months after critical COVID-19, pain, discomfort, anxiety, or depression remained prevalent, as opposed to mobility problems. Studies indicate that the number of patients completely symptom-free after ICU treatment is exceptionally low. Less than 10% of patients had no PICS symptoms and were fully recovered after three months (129), suggesting a very slow clinical improvement without active and continuous post-ICU

nije imalo simptome PICS-a i bili su potpuno oporavljeni nakon tri mjeseca (129) što ukazuje na vrlo sporo poboljšanje kliničkog statusa bez aktivne i kontinuirane skrbi nakon intenzivne njege. Stvarne posljedice mogu biti podcijenjene s obzirom na kontinuiranu pristranost odabira sudionika jer manje onesposobljeni pacijenti prihvaćaju ili mogu prisustvovati u istraživanjima i dugotrajnim praćenjima.

Nekoliko istraživanja utvrdilo je da je nezaposlenost povezana s depresijom, anksioznošću i lošom kvalitetom života. Nakon povratka na posao utvrđeno je poboljšanje psihičkog zdravlja i kvalitete života, te su sudionici povratak na posao doživjeli kao znak oporavka (122). Takva koherentnost između posla i življenja smislenog života opisana je u nekoliko studija (130-132). Međutim, osobe koje su preživjele intenzivnu njegu u kvalitativnoj studiji izvještavaju da im posao više nije glavni životni prioritet i da su im socijalni odnosi postali važniji (122).

Čini se da je hospitalizacija jedan od ključnih čimbenika za prisutnost i ozbiljnost post-COVID-a. Zabilježeno je da je hospitalizacija dovela do većih ograničenja svakodnevnih životnih aktivnosti imala veći utjecaj na povratak na posao (5) i povećala rizik od dispneje, tjeskobe, mialgije i gubitka kose (7). U nekoliko sustavnih pregleda, meta-analiza i studija uspoređivano je stanje između hospitaliziranih i nehospitaliziranih pojedinaca. U takvim se studijama pokazalo da prethodno hospitalizirani pacijenti imaju veći rizik od post-COVID-19 stanja i češće pate od težih simptoma nego osobe koje nisu hospitalizirane (5,7,133-135). U jednoj od objavljenih meta-analiza prijavljena je značajna (ukupna) prevalencija post-COVID-a pri čemu je prevalencija u hospitaliziranih pacijenata bila veća (54 % (95 % CI 44-63 %)) nego u nehospitaliziranih (34 % (95 % CI 29-37 %)) (3).

Houben-Wilke i suradnici (136) proveli su *online* anketu među članovima Facebook grupe COVID pacijenata sa stalnim tegobama. Šest mjeseci nakon infekcije, depresija i anksioznost

care. The true consequences may be underestimated due to continuous selection bias, as less disabled patients accept to or can participate in research and long-term follow-ups.

Several studies have found that unemployment is associated with depression, anxiety, and poor quality of life. Returning to work was linked to improved mental health and quality of life, and participants perceived work resumption as a sign of recovery (122). Such coherence between work and living a meaningful life has been described in several studies (130-132). However, in a qualitative study, ICU survivors reported that work was no longer their main life priority and that social relationships had become more important to them (122).

Hospitalization appears to be one of the key factors for the presence and severity of post-COVID symptoms. It has been observed that hospitalization led to greater restrictions in daily life activities, had a greater impact on returning to work (5), and increased the risk of dyspnea, anxiety, myalgia, and hair loss (7). Several systematic reviews, meta-analyses, and studies have compared the conditions of hospitalized and non-hospitalized individuals. These studies have shown that previously hospitalized patients have a higher risk of post-COVID-19 syndrome and often suffer from more severe symptoms than those who were not hospitalized (5, 7, 133-135). One of the published meta-analyses reported a significant (overall) prevalence of post-COVID symptoms, whereby there was a higher prevalence in hospitalized patients (54% (95% CI 44–63%)) compared to non-hospitalized patients (34% (95% CI 29–37%)) (3).

Houben-Wilke et al. (136) conducted an online survey among members of a Facebook group for COVID patients with persistent symptoms. Six months after infection, depression and anxiety were reported in 42% and 29% of hospitalized individuals, respectively, and in 40% and 37% of non-hospitalized individuals, respectively.

zabilježene su kod 42 % i 29 % hospitaliziranih osoba te kod 40 % i 37 % nehospitaliziranih. Johnsen i suradnici (137) istraživali su pacijente s COVID-19 tri mjeseca nakon otpusta iz bolnice i pacijente koje je njihov liječnik opće prakse uputio u respiratornu ambulantu zbog postojanih simptoma post-COVID-a. Kvaliteta života povezana sa zdravljem bila je slična u obje skupine, iako je postojala tendencija nižih vrijednosti u nehospitaliziranih. Perrot i suradnici (138) usporedili su simptome post-COVID-a u tri skupine pacijenata koji su primljeni u svoju jedinicu za rehabilitaciju post-COVID-a (prosječno trajanje od 110 dana od otpusta iz bolnice): pacijenti koji nisu bili hospitalizirani, pacijenti primljeni na opći odjel i pacijenti primljeni u JIL. Utvrđeno je da je anksioznost značajno rjeđa kod pacijenata na intenzivnoj njezi (18,7 % prema 40,7-46,7 %), a depresija je bila značajno češća kod pacijenata koji nisu bili primljeni u bolnicu (37,0 % prema 17,6-26,7 %). Sukladno s time psihička komponenta upitnika o zdravstvenoj kvaliteti života SF-36 bila je niža kod pacijenata koji nisu bili liječeni u JIL-u. Međutim, tjelesna komponenta upitnika nije se razlikovala između triju skupina, a dispneja je bila podjednako učestala. Ukupno gledajući, zdravstvena kvaliteta života značajno je pogoršana kod svih oboljelih od post-COVID-a.

Veći teret samoprijavljenih simptoma kod nehospitaliziranih pojedinaca mogao bi biti posljedica njihovih različitih gledišta. Nehospitalizirane osobe smatrale su se zdravima prije i tijekom infekcije, a nakon infekcije pate od simptoma. Nasuprot tome, hospitalizirani pacijenti potencijalno su doživjeli olakšanje simptoma u vrijeme istraživanja, npr. mogli su disati samostalno i ponovno živjeti kod kuće sa svojim obiteljima. Osim toga, bili su pod strogim nadzorom, intenzivnim praćenjem i rehabilitacijom tijekom razdoblja hospitalizacije. Stoga bi stajalište hospitaliziranih pacijenata moglo biti pozitivnije, dok bi stajalište nehospitaliziranih pacijenata moglo biti negativnije.

Johnsen et al. (137) researched COVID-19 patients three months after hospital discharge, as well as patients referred by their general practitioners to a respiratory clinic due to persistent post-COVID symptoms. Health-related quality of life was similar in both groups, although there was a tendency toward lower values in non-hospitalized individuals. Perrot et al. (138) compared post-COVID symptoms in three groups of patients admitted to their post-COVID rehabilitation unit (average duration of 110 days from hospital discharge): non-hospitalized patients, patients admitted to a general ward, and ICU patients. Anxiety was significantly less common in ICU patients (18.7% vs. 40.7–46.7%), whereas depression was significantly more common in non-hospitalized patients (37.0% vs. 17.6–26.7%). Accordingly, the mental component of the SF-36 health-related quality of life questionnaire was lower in non-ICU patients. However, the physical component of the questionnaire did not differ between the three groups, and dyspnea was equally prevalent. Overall, health-related quality of life was significantly impaired in all post-COVID patients.

A higher burden of self-reported symptoms among non-hospitalized individuals could be due to their different perspectives. Non-hospitalized individuals considered themselves healthy before and during the infection, but suffered from symptoms afterward. In contrast, hospitalized patients may have experienced symptom relief by the time of the study, e.g., they were able to breathe independently and live at home with their families again. Additionally, they were under strict supervision, intensive monitoring, and rehabilitation during hospitalization. Hospitalized patients may, therefore, have had a more positive outlook, whereas non-hospitalized patients may have had a more negative perception.

Beyond ICU treatment itself, the COVID-19 pandemic had additional factors that could

Uz samo liječenje u JIL-u pandemija COVID-19 imala je i druge čimbenike koji mogu povećati psihičke smetnje, kao što su ograničenja posjeta i nedostatak direktnog kontakta i vidljivosti zdravstvenog osoblja zbog nošenja zaštitne odjeće (139).

POVEZANOST POST-COVID-a I DRUGIH INFEKCIJA

COVID-19 je zapravo samo najnovija od mnogih drugih zaraznih bolesti koje su povezane s kroničnim posljedicama nakon oporavka od akutne faze infekcije (140). Choutk i suradnici (140) istraživali su zajedničke karakteristike između post-COVID-19-a i drugih kroničnih infektivnih sindroma i utvrdili veću prevalenciju sljedećih simptoma: netolerancija na tjelesni napor, neurokognitivno i senzorno oštećenje, perzistentni simptomi nalik gripi, poremećaj sna, mialgije i artralgije. Najveće sličnosti su s post-akutnim učincima opisanim u SARS epidemiji 2002–2004 (141) i bliskoistočnim respiratornim sindromom (engl. *Middle East Respiratory Syndrome,* MERS) koje su obje povezane s dugoročnim neuropsihijatrijskim implikacijama (142). Jedna meta-analiza pokazuje da otprilike jedna trećina preživjelih SARS-a i MERS-a ima dugotrajne psihološke posljedice kao što su anksioznost, depresija i PTSP koji traju 6 mjeseci nakon otpusta iz bolnice (143). Tijekom ranijeg izbijanja SARS-a prethodni su podatci pokazali da oboljenje od koronavirusa može rezultirati produljenim psihičkim poremećajima s dugotrajnim neuropsihijatrijskim posljedicama (144,145). Psihijatrijski simptomi koje su prijavili preživjeli od SARS-a uključuju depresiju, PTSP, opsesivno-kompulzivni poremećaj (OKP) i panični poremećaj nakon praćenja od 1 do 50 mjeseci (3,144,146).

Preklapanje kliničkih obilježja post-COVID-a s drugim postinfektivnim sindromima ukazivalo bi na uključenost zajedničkih patofizioloških

have increased psychological distress, such as visitor restrictions and the lack of direct contact and visibility of healthcare staff due to protective clothing (139).

CONNECTION BETWEEN POST-COVID AND OTHER INFECTIONS

COVID-19 is, in fact, only the latest in a series of numerous infectious diseases associated with chronic consequences after recovery from the acute phase of infection (140). Choutk et al. (140) explored the common features between post-COVID-19 and other chronic infectious syndromes, finding a higher prevalence of the following symptoms: intolerance to physical exertion, neurocognitive and sensory impairments, persistent flu-like symptoms, sleep disturbances, myalgias, and arthralgias. The greatest similarities were observed in terms of the post-acute effects described in the SARS epidemic of 2002–2004 (141) and the Middle East Respiratory Syndrome (MERS), both of which are linked to long-term neuropsychiatric implications (142). One meta-analysis showed that approximately one-third of SARS and MERS survivors experienced long-term psychological consequences such as anxiety, depression, and PTSD, lasting six months after discharge from the hospital (143). During the earlier SARS outbreak, previous data indicated that coronavirus infection could result in prolonged psychological disorders with long-lasting neuropsychiatric consequences (144, 145). Psychiatric symptoms reported by SARS survivors include depression, PTSD, obsessive-compulsive disorder (OCD), and panic disorder after follow-ups ranging from 1 to 50 months (3, 144, 146).

The overlap of clinical features of post-COVID with other post-infectious syndromes suggests an involvement of shared pathophysiological pathways. Identifying a unique etiological model would facilitate the planning of diagnostic

kih puteva. Otkrivanje jedinstvenog etiološkog modela olakšao bi planiranje dijagnostičkih postupaka i prilagođenih tretmana (140). Trenutno je, nažalost, naše razumijevanje temeljnih patofizioloških mehanizama i etioloških čimbenika nedostatno, iako se provode obećavajuće studije (147-149).

ISTRAŽIVANJA U HRVATSKOM KONTEKSTU

Tijekom pandemije COVID-19 u Hrvatskoj veliki su istraživački napori bili usmjereni na ispitivanje utjecaja pandemije na psihičko zdravlje različitih skupina sudionika iz opće populacije. Međutim, prema našim spoznajama broj objavljenih istraživačkih radova koji se odnose na post-COVID simptome, a provedeni su na hrvatskim pacijentima, je neznatan. Istraživački tim Klinike za plućne bolesti Jordanovac bavio se u prvom redu tjelesnim i pulmološkim simptomima post-COVID-a (150,151) . U jednom istraživanju provedenom na uzorku osoba s akutnim i post-COVID simptomima koji su uključeni u rehabilitacijski program utvrdili su da su tijekom akutne faze bolesti simptomi emocionalne uznemirenosti i anksioznosti bili povišeni, te da je došlo do pada simptoma u post-COVID fazi bolesti (151).

U jednom istraživanju provedenom na uzorku od 227 sudionika s neurološkim post-COVID-19 simptomima rezultati su pokazali da je većina oboljelih imala više simptoma, a najčešći simptomi bili su glavobolja (30 %), kognitivne tegobe (29 %), poremećaji mirisa (17 %), parestezije (16 %), kronični umor (15 %), vrtoglavica s mučninom i povraćanjem (15 %) i nesanica (11 %) (152).

U istraživanju koje je provedeno u svrhu završetka magistarskog studija, a provedeno je na 266 sudionika u pulmološkoj post–COVID ambulanti OB Dubrovnik, dobiveno je da se pacijenti najčešće žale na zaduhu (37,2 %), kašalj

procedures and tailored treatments (140). Unfortunately, our understanding of the underlying pathophysiological mechanisms and etiological factors remains insufficient, although promising studies are underway (147-149).

RESEARCH IN THE CROATIAN CONTEXT

During the COVID-19 pandemic, significant research efforts in Croatia were focused on examining the impact of the pandemic on the mental health of various participant groups from the general population. However, to our knowledge, the number of published research papers related to post-COVID symptoms conducted on Croatian patients is insignificant. The research team at the Clinic for Pulmonary Diseases Jordanovac primarily focused on the physical and pulmonary symptoms of post-COVID (150, 151). One study conducted on a group of individuals with acute and post-COVID symptoms enrolled in a rehabilitation program found that during the acute phase of the illness, symptoms of emotional distress and anxiety were elevated, but these symptoms decreased in the post-COVID phase (151).

In a study conducted on a sample of 227 participants with neurological post-COVID-19 symptoms, the results showed that most patients had multiple symptoms, with the most common being headaches (30%), cognitive difficulties (29%), smell disorders (17%), paresthesias (16%), chronic fatigue (15%), dizziness with nausea and vomiting (15%), and insomnia (11%) (152).

In a study conducted for the completion of a master's thesis, which involved 266 participants at the post-COVID pulmonary clinic in Dubrovnik General Hospital, it was found that patients most commonly complained of shortness of breath (37.2%), cough (34.2%), muscle weakness (16.9%), and fever (15.8%) (153).

(34,2 %), mišićnu slabost (16,9 %) i febrilitet (15,8 %) (153).

ZAKLJUČAK

Post-COVID sindrom je složeno stanje koje je praćeno tjelesnim i psihičkim smetnjama, ali i socijalnom ugroženošću u svim elementima stigmatizacije. Kako je uključena i socijalna dimenzija potrebno je provoditi istraživanja u hrvatskim uvjetima jer su naše društvene okolnosti različite u odnosu na velike zemlje iz kojih uglavnom dolaze nalazi istraživanja. No, iz svega opisanog vrlo je jasno da upravljanje post-COVID-om zahtijeva interdisciplinarnost uključujući liječnike različitih specijalnosti (opća medicina, pulmologija, kardiologija i infektologija), fizijatre, stručnjake za psihičko zdravlje, fizioterapeute, radne terapeute i socijalne radnike koji će se baviti kliničkim i psihološkim aspektima bolesti. Uz praćenje i liječenje pacijenata s post-COVID-om potrebno je osigurati rehabilitaciju i oporavak općih funkcija. Uzroci post-COVID-a su još uvijek nejasni, ali istraživanja već pokazuju da poboljšanje psihičkog stanja svakako dovodi i do boljih tjelesnih funkcija preko složenih psihoneuroimunoloških mehanizama (154,155).

CONCLUSION

Post-COVID syndrome is a complex condition characterized by both physical and psychological disturbances, as well as social vulnerability due to all the elements of stigmatization. Considering that the social dimension is involved, it is necessary to conduct research in Croatian conditions, as our societal circumstances differ from those of large countries, where research findings mainly originate from. However, it is very clear from the above that managing post-COVID requires interdisciplinarity, involving physicians from various specialties (general medicine, pulmonology, cardiology, and infectology), physiatrists, mental health professionals, physical therapists, occupational therapists, and social workers, who must address the clinical and psychological aspects of the disease. In addition to monitoring and treating patients with post-COVID, rehabilitation and recovery of general functions must be ensured. The causes of post-COVID remain unclear, however studies have already shown that improving the psychological condition certainly leads to better physical functions through complex psychoneuroimmunological mechanisms (154, 155).

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