ORIGINALNI RAD

OTKRIVANJE PROGNOSTIČKE MOĆI RANE SIMPTOMATOLOGIJE UMERENO TEŠKIH DO TEŠKIH OBLIKA COVID-19 BOLESTI

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SAŽETAK

Uvod/Cilj: Nije u potpunosti jasno koji početni simptomi mogu biti prediktori loših ishoda COVID-19 bolesti. Cilj ove studije je bio da identifikuje početne simptome i znake COVID-19 bolesti povezane sa potrebom lečenja u jedinici intenzivne nege (JIN) i smrtnim ishodom.

Metode: Sprovedena je retrospektivna analiza pacijenata koji su hospitalizovani u dve zdravstvene ustanove (u Beogradu i Somboru) od marta 2021. do aprila 2022. godine. Podaci su prikupljeni iz elektronske medicinske dokumentacije. Glavni ishodi bili su lečenje i umiranje u JIN. Korišćen je Koksov proporcionalni regresioni model kako bi se identifikovali početni simptomi i znaci COVID-19 povezani sa lečenjem i umiranjem u JIN.

Rezultati: U ovom istraživanju učestvovalo je 457 pacijenata. Prosečna starost pacijenata iznosila je 63,77±13,75 godina. Najčešći početni simptomi i znaci COVID-19 bili su febrilnost (85,1%), kašalj (77,2%) i malaksalost (54,5%). Najređi početni simptomi bili su promuklost (2,8%), teškoće pri gutanju (2,8%) i svrab očiju (1,7%). Model korigovan na relevantne faktore pokazao je da su stariji uzrast i bol u grudima nezavisno povezani sa potrebom za lečenjem u JIN. Takođe, stariji urast, otežano disanje, glavobolja i dijareja, kao i odsustvo nazalne kongestije, bili su nezavisni prediktori smrtnog ishoda.

Zaključak: Rezultati ove studije ukazuju na važnost pažljivog praćenja i brze intervencije kod pacijenata koji se javljaju sa bolom u grudima, otežanim disanjem, glavoboljom, dijarejom, posebno ako se radi o starijim osobama.

Ključne reči: COVID-19, prognoza, jedinica intezivne nege, smrtni ishod, simptomi.

Uvod

Iako većina ljudi koji se zaraze koronavirus-nom bolešću 2019 (COVID-19) imaju blagu kliničku sliku, pojedini pacijenti, posebno oni koji već imaju hronične bolesti, mogu razviti teške komplikacije, kao što su respiratorna insuficijencija, aritmije, septički šok, bubrežnu insuficijenciju, kardiova-skularno oštećenje, ili disfunkcija jetre (1,2). Iako je nazofarinks primarno mesto ulaska prouzrokovača COVID-19, nedavna studija je pokazala da osobe koje su zaražene koronavirusom 2 izazivačem teškog akutnog respiratornog sindroma (SARS-

CoV-2) retko imaju simptome u nivou gornjih disa-jnih puteva na samom početku kliničke faze bolesti (3). Najčešći početni simptomi COVID-19 podra-zumevaju febrilnost, kašalj, mijalgiju ili umor, gubi-tak čula ukusa i mirisa (4,5), koji se javljaju prilikom infekcije svim varijantama SARS-CoV-2.

Međutim, teško je razlikovati koji od ovih simp-toma bi mogao biti najjači prediktor loših ishoda COVID-19. Prethodno istraživanje je pokazalo da ljudi koji imaju otežano disanje i bol u grudima imaju veće šanse za razvoj teške forme infekcije

ORIGINAL ARTICLE

UNVEILING THE PROGNOSTIC POWER OF EARLY SYMPTOMOLOGY IN MODERATE TO SEVERE FORM OF COVID-19 DISEASE

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SUMMARY

Introduction/Aim: It is not entirely clear what initial symptoms could predict poorer COVID-19 outcomes. The purpose of this study was to identify the initial COVID-19 symptoms associated with the need for an intensive care unit (ICU) treatment and having fatal outcomes of COVID-19.

Methods: A retrospective analysis was conducted on patients who were hospitalized in two health care facilities (in Belgrade and Sombor) from March 2021 to April 2022. Data were collected from the electronic medical records. The main outcomes were treatment in the ICU and ICU mortality. The Cox proportional hazard model was used to identify the initial COVID-19 symptoms associated with the ICU treatment and mortality.

Results: This research included 457 patients. The average age of patients was 63.77±13.75 years. The most common initial symptoms of COVID-19 were fever (85.1%), cough (77.2%), and fatigue (54.5%). The least common initial symptoms were hoarseness (2.8%), difficulty swallowing (2.8%), and eye itching (1.7%). The adjusted model showed that being older and having chest pain were independently associated with needing the ICU treatment. Furthermore, being older, having shortness of breath, headache and diarrhea, but absence of nasal congestion, were independently associated with poorer survival.

Conclusion: The results of this study emphasize the importance of vigilant monitoring and swift intervention in patients presenting with chest pain, shortness of breath, headache, and diarrhea, particularly among older people.

Keywords: COVID-19, prognosis, intensive care unit, fatal outcome, symptoms.

Introduction

Even though most people who catch coronavirus disease 2019 (COVID-19) have mild illness, certain individuals, particularly those who have preexisting chronic health conditions, may develop severe complications, such as such as respiratory failure, arrhythmias, septic shock, renal failure, cardiovascular damage, or liver dysfunction (1, 2). Although the nasopharynx is the primary portal of entry for causative agent of COVID-19, a recent study has shown that individuals who are infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) seldom present upper respiratory symptoms at the very beginning of the clinical phase of the disease (3). Most common initial symptoms of COVID-19 include fever, cough, myalgia or fatigue, loss of sense of taste and smell (4, 5), and they are consistent across all variants of the SARS-CoV-2.

However, it might be difficult to distinguish which of those symptoms could be the strongest predictor of poorer COVID-19 outcomes. Previous research found that people who present

COVID-19, jer ovi simptomi odgovaraju početnoj manifestaciji pneumonije (5). Početni simptomi COVID-19 mogu varirati u zavisnosti od vremena posmatranja što može dovesti do širokog spektra heterogenih nalaza (6). Ova varijabilnost je značajna kako bi se definisali ključni početni simptomi povezani sa lošijim ishodima COVID-19 (6).

Imajući u vidu sve prethodno navedeno, cilj ove studije je bio da se utvrde početni simptomi i znaci COVID-19 bolesti koji su povezani sa potrebom za lečenjem u jedinici intenzivne nege (JIN) i fatalnim ishodima kod osoba sa umereno do teškom COVID-19 bolešću.

Metod

Ova retrospektivna studija sprovedena je u dve zdravstvene ustanove: na Klinici za infektivne i tropske bolesti, Univerzitetskog Kliničkog Centra Srbije (UKCS) u Beogradu i u Opštoj bolnici „Dr Radivoj Simonović" u Somboru. Ovo istraživanje je obuhvatilo pacijenate koji su primljeni na bolničko lečenje između 1. marta 2021. i 7. aprila 2022. Da bi bili uključeni u studiju, pacijenti su morali da ispune sledeće kriterijume: 1) potvrđena infekcija SARS-CoV-2 metodom kvantitative polimerazne lančane reakcije (RT-PCR) ili antigenskim testom, 2) uzrast od 18 i više godina, 3) postojanje umerene do teške kliničke slike bolesti COVID-19, 4) postojanje detaljne evidenciju početnih simptoma u istoriji bolesti koja je dokumentovana prilikom prijema na bolničko lečenje, 5) imaju detaljnu evidenciju ishoda bolesti COVID-19 (prijem u JIN, smrtni ishod ili vreme otpusta).

Umereno teška klinička slika karakteriše se teškom hipoksijom koja zahteva: primenu kiseoničke terapije, prisustvom povišene telesne temperature, pojavom višestrukih opacifikacija na rendgenskom snimku pluća ili specifičnim promenama na plućima koje su uočljive na skeneru grudnog koša, kao i znacima citokinske oluje koja dovodi do pogoršanja opšteg stanja pacijenta uz nagli porast vrednosti bilo CRP, fibrinogena, D-dimera ili IL-6 (2). Teška klinička slika podrazumeva dalje napredovanje citokinske oluje koja dovodi do nastanka akutnog respiratornog distres sindroma (2).

Određivanje veličine uzorka studije zasnivalo se na: 1) veličini populacije gradskog područja Beograda (procenjeno na oko 1,4 miliona stanovnika) i veličini populacije Zapadnobačkog okruga (procenjeno na oko 0,18 miliona stanovnika); 2) očekiva-

noj prevalenciji COVID-19 pozitivnih osoba kojima je potrebno bolničko lečenje (9% prema literaturi (7)), 3) intervalu poverenja od 95% i 4) verovatnoći alfa greške od 5%. Primenom ovih parametara, minimalna izračunata veličina uzorka je bila 126 (https://www.calculator.net/sample-size-calculator.html).

Ovo istraživanje je sprovedeno u skladu sa odredbama Helsinške deklaracije. Studiju je odobrio etički odbor UKCS (odobrenje br. 82/3-2023) i etički odbor Opšte bolnice „Dr Radivoj Simonović" u Somboru (odobrenje br. 23-2171/2023-2).

Demografski i klinički podaci su prikupljeni iz elektronske medicinske dokumentacije putem zdravstvenog informacionog sistema Heliant Health iz obe zdravstvene institucije. Demografski podaci uključivali su: pol, uzrast, glavne tegobe i fizikalni nalaz na prijemu, početne simptome bolesti COVID-19, kao i vakcinalni status protiv SARS-CoV-2. Početni simptomi COVID-19 infekcije koji su razmatrani u studiji bili su febrilnost, malaksalost, otežano disanje (dispneju), artalgiju, bol u grudima, gubitak apetita, glavobolju, dijareju, anosmiju, kvantitativne poremećaje svesti, povraćanje, bol u leđima, kvantitativne poremećaje svesti, nazalnu kongestiju, promuklost, svrab oka i otežano gutanje. Kvantitativni poremećaji svesti odnosili su se na smanjenje nivoa svesti kada je osoba budna, ali ima smanjenu reaktivnost na draži. S druge strane, kvalitativni poremećaji svesti uključivali su promene u stanju svesti, koje utiču na sadržaj tako i na jasnoću svesti (kao što su zbunjenost, uznemirenost i nemir).

Pacijenti su bili podeljeni u dve grupe u zavisnosti od toga da li su bili lečeni u JIN-e. U okviru podgrupe pacijenata lečenih u JIN-e, dalja klasifikacija je izvršena na osnovu ishoda lečenja, pri čemu su podeljeni dodatno i na pacijente koji su preživeli i na one koji nisu preživeli do kraja hospitalizacije. Ove podgrupe su označene kao: 2a) preživeli iz JIN-e i 2b) pacijenti iz JIN-e koji nisu preživeli.

Statističke analize su sprovedene korišćenjem IBM SPSS verzije 17 (IBM Corp). Vrednost verovatnoće p manja od 0,05 je smatrana statistički značajnom. Deskriptivne karakteristike su prikazane korišćenjem srednjih vrednosti i standardnih devijacija za kontinualne varijable, dok su frekvencije i procenti korišćeni za kategoričke vaijable.

Normalnost raspodele kontinualnih varijabli je procenjena pomoću Kolmogorov-Smirnov testa. Za proceni razlike normalno raspoređenih kon-

with shortness of breath and chest pain have higher chances of developing severe COVID-19 because these symptoms correspond to the initial presentation of pneumonia (5). The initial symptoms of COVID-19 may vary depending on the time of observation, and therefore generate a wide array of heterogeneous findings (6). This variability is relevant in efforts to define key symptoms associated with poorer COVID-19 outcomes (6).

Bearing in mind all mentioned above, the purpose of this study was to identify the initial COVID-19 symptoms associated with the need for the intensive care unit (ICU) treatment and fatal outcomes of COVID-19.

Methods

This retrospective study was conducted at two healthcare facilities: the Clinic for Infectious and Tropical Diseases, University Clinical Center of Serbia (UCCS) in Belgrade and the General Hospital "Dr Radivoj Simonovic" situated in Sombor. This research included patients admitted to hospital between March 1, 2021, and April 7, 2022. To be eligible for study participation, the patients had to meet the following criteria: 1) confirmed SARS-CoV-2 infection by real-time reverse-transcription polymerase chain reaction (RT-PCR) or antigen testing, 2) being 18 years of age or older, 3) exhibit moderate to severe clinical forms of COVID-19 disease, 4) have a detailed record of the initial symptoms in their medical history upon hospital admission 5) have a detailed record of COVID-19 disease outcomes (ICU admission, vital status during hospital stay or time of discharge).

A moderately severe clinical presentation is characterized by severe hypoxia requiring: oxygen therapy, elevated body temperature, presence of multiple opacities on chest X-ray or specific lung changes visible on chest CT scan, signs of cytokine storm leading to worsening of patient's general health status with a sudden increase in either C-reactive protein (CRP), fibrinogen, D-dimer, or interleukin 6 (IL-6) levels (2). A severe clinical presentation includes further progression of the cytokine storm and possible acute respiratory distress syndrome (2).

The calculation of the sample size was based on 1) the size population of the Belgrade metropolitan area (approximately 1.4 million inhabitants) and the population of the West Bačka District (estimated at around 0.18 million inhabitants); 2)

the prevalence of people severe COVID-19 who require hospitalization (9% as per literature (7));3) a 95% confidence interval, and 4) an alpha error of 5%. Using these parameters, the minimum sample size was 126 participants (https://www.calculator.net/sample-size-calculator.html).

This study was conducted in line with the Helsinki Declaration. Ethical approval was granted by both the Ethics Committee of UCCS (approval no. 82/3-2023) and the Ethics Committee of the "Dr. Radivoj Simonovic" General Hospital in Sombor (approval no. 23-2171/2023-2).

Demographic and clinical data were collected from electronic medical records using the Heliant Health information system from both health care institutions. The demographic data included: gender, age, chief complaints and physical findings upon admission as the initial COVID-19 symptoms and SARS-CoV-2 vaccination status. The initial symptoms of COVID-19 infection considered in the study were fatigue, shortness of breath, arthralgia, chest pain, loss of appetite, headache, diarrhea, anosmia, qualitative disturbance of consciousness, vomiting, back pain, quantitative disturbance of consciousness, nasal congestion, hoarseness, itching of the eye, and difficulty swallowing. Quantitative disturbances of consciousness referred to a decrease in consciousness levels when a person is awake, but has a diminished responsiveness. On the other hand, qualitative disturbances of consciousness involve changes in the state of consciousness, affecting both the content and clarity of consciousness (such as confusion, agitation and restlessness).

Patients were divided into two groups based on whether they received the ICU treatment or not. Within the subgroup of patients treated in the ICU, a further classification was performed based on the treatment outcome, distinguishing between patients who survived the ICU treatment and those who did not. These subgroups were labeled as: 2a) ICU survivors and 2b) ICU non-survivors.

Statistical analyses were conducted using the IBM SPSS version 17 (IBM Corp). A p-value of less than 0.05 was considered statistically significant. Descriptive characteristics were reported using means and standard deviations for continuous variables, while frequencies and percentages were used for categorical variables.

The normality of distribution of parametric variables was assessed by the Kolmogorov-Smirnov

tinuiranih varijabli je korišćen t-test za dva nezavisna uzorka, dok je za kontinuirane varijable koje nisu imale normalnu raspodelu korišćen dvostrani Man-Vitnijev test. Procena razlike za kategoričke varijable je izvršena uz pomoć Fišerovog testa tačne verovatnoće i hi-kvadrat testom.
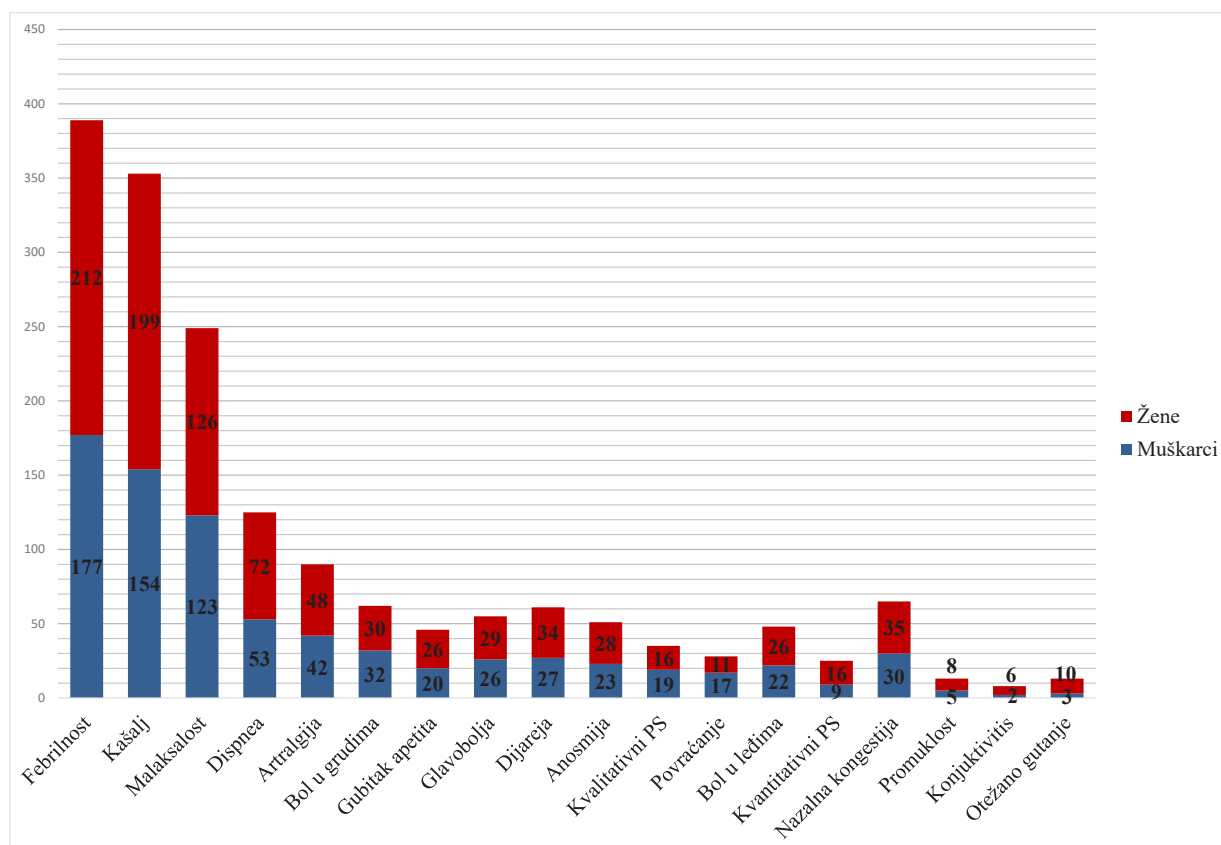
Koksov proporcijalni prediktivni model je korišćen za procenu faktora povezanih sa potrebom za lečenjem u JIN-u i smrtnim ishodom. Dimenzija vremena je obuhvatila dane od pojave prvih simptoma do analiziranih ishoda (lečenje u intenzivnoj nezi, smrt ili otpust iz bolnice). Najpre su analizirane sve demografske i kliničke varijable u univarijantnom modelu. Nakon testiranja nekoliko različitih pristupa multivarijantnom modelu, utvrđeno je da je optimalni multivarijantni model bio standardni opšti model u kojem su sve demografske i kliničke karakteristike analizirane zajedno.

Rezultati

U studiju je uključeno 457 pacijenata. U uzorku je bilo nešto više žena u odnosu na muškarce (260; 56,9%). Prosečna starost ispitanika bila je 63,77±13,75 godine. Većina pacijenata nije bila

vakcinisana (332; 74,6%). Najčešći početni simptomi su bili febrilnost (85,1%), kašalj (77,2%) i malaksalost (54,5%). Nešto ređi simptomi uključivali su otežano disanje (27,4%), artalgiju (19,7%), nazalnu kongestiju (14,2%), bol u grudima (13,6%) i dijareju (13,3%). Glavobolja (12,0%), gubitak apetita (12,0%), anosmija (11,1%) i bol u leđima (10,.5%) je navelo malo pacijenata. Najređi početni simptomi bili su kvalitativni (7,6%) i kvantitativni (5,4%) poremećaji svesti, povraćanje (6,1%), promuklost (2,8%), otežano gutanje (2,8%) i svrab oka (1,7%). Distribucija simptoma prema polu prikazana je na slici 1. U proseku, pacijenti su primljeni u bolnicu 5,2±1,9 dana od pojave simptoma. Takođe, srednje vreme od pojave simptoma do smrti bilo je 9,2±2,5 dana.

Pacijenti koji su lečeni u JIN-e češće su bili stariji (p=0,001) i češće nisu bili vakcinisani (p=0,005), češće su prijavljivali otežano disanje (p=0,018), bol u grudima (p=0,001) i anosmiju (p=0,019) kao početne simptome COVID-19, za razliku od pacijenata koji nisu bili lečeni u JIN-e. Ipak, značajne razlike u distribuciji ostalih početnih simptoma infekcije SARS-CoV-2 nisu zabeležene (Tabela 1).

Legenda: PS - poremećaj svesti

Grafikon 1. Broj ispitanika sa početnim simptomima infekcije uzrokovane virusom SARS-CoV2 u trenutku prijema u bolnicu

test. For normally distributed continuous variables, differences were assessed by the independent samples t-test, whereas non-normally distributed variables were analyzed using the nonparametric two-tailed Mann-Whitney test. Differences in categorical variables were evaluated using the Fisher's exact test and the Chi-square test.
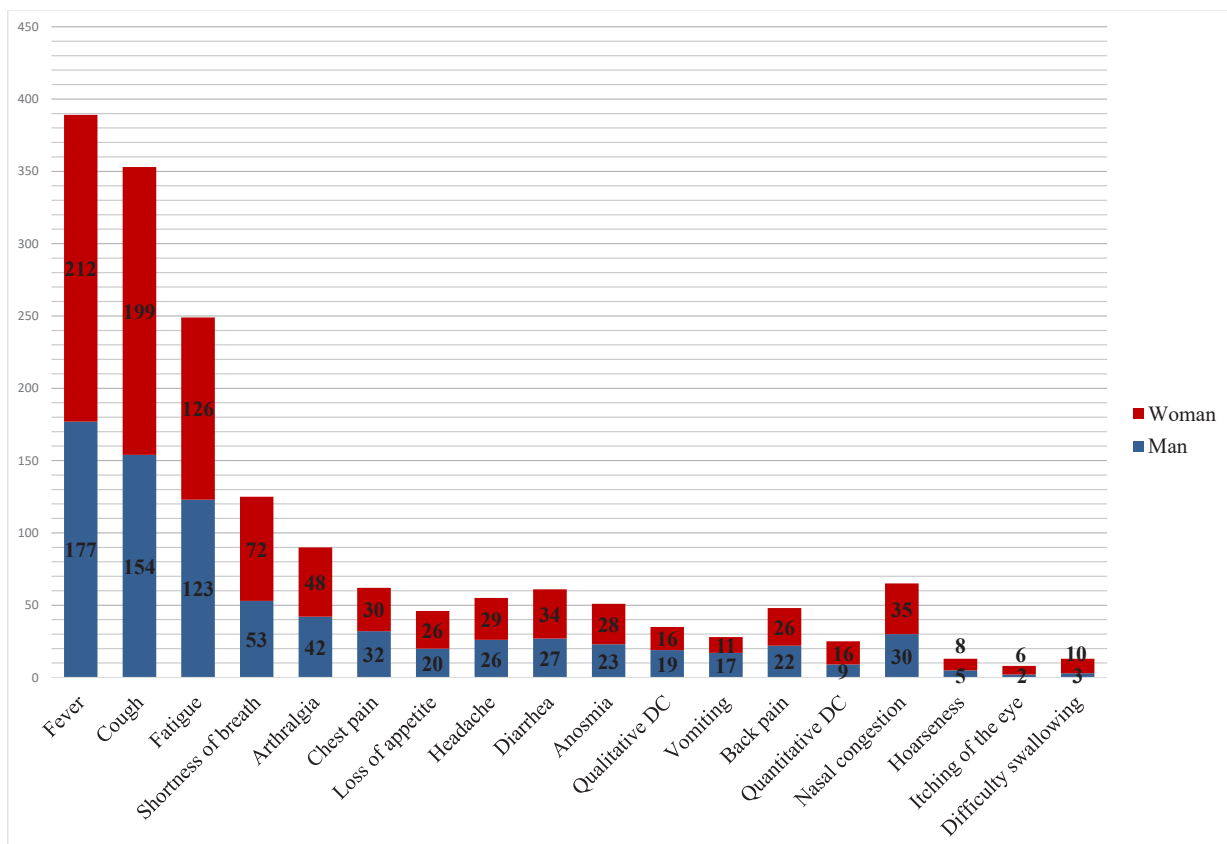
The Cox proportional hazard model was applied to identify factors associated with the need for ICU treatment and ICU mortality. The timeline included days from the first symptom onset until the observed outcomes (ICU treatment, death or hospital discharge). First, we tested all demographic and clinical parameters a univariate model. After testing several different approaches to a selective multivariate model, we determined that the optimum adjusted model was the overall model when all demographic and clinical characteristics (symptoms) were analyzed together.

Results

A total of 457 patients were included in the study. There were slightly more women than men (260; 56.9%). The average age of the study patients was 63.77±13.75 years. Most patients were not vaccinated (332;72.6%). The most frequent initial symptoms of COVID-19 were fever (85.1%), cough (77.2%), and fatigue (54.5%). Slightly less common symptoms included dyspnea (27.4%), arthralgia (19.7%), nasal congestion (14.2%), chest pain (13.6%) and diarrhea (13.3%). Headache (12.0%), loss of appetite (12.0%), anosmia (11.1%), and back pain (10.5%) were reported by few patients. The least frequent symptoms were qualitative (7.6%) and quantitative (5.4%) disturbances of consciousness, vomiting (6.1%), hoarseness (2.8%), swallowing difficulty (2.8%), and eye itching (1.7%). Distribution of symptoms according to gender is presented in Figure 1. On average, patients were admitted to hospital 5.2±1.9 days since the onset of symptoms. Also, mean time from the onset of symptoms until death was 9.2±2.5 days.

Patients treated in the ICU were older (p=0.001) and more often unvaccinated (p=0.005) compared to patients not needing the ICU treatment. Patients undergoing the ICU treatment more commonly reported shortness of breath (p=0.018), chest pain

Legend: DC - disturbance of consciousness

Figure 1. Number of patients with initial symptoms of SARS-CoV-2 infection upon hospital admission

Tabela 1. Demografske i kliničke karakteristike ispitanika u odnosu na potrebu za nastavkom lečenja u jedinici intenzivne nege

Varijable	Potreba za nastavkom lečenja u JIN		
	Ne N=332 n (%)	Da N=125 n (%)	p vrednost
Pol			
Muški	145 (43,7)	52 (41,6)	0,223*
Ženski	187 (56,3)	73 (58,4)	
Uzrast, medijana (IKO)	61,0 (19,7)	74,0 (17,5)	**0,001†**
COVID-19 vakcinacija			
Da	96 (28,9)	20 (16,0)	**0,005***
Ne	236 (71,7)	105 (84,0)	
Febrilnost	284 (85,5)	105 (84,0)	0,840*
Kašalj	259 (78,0)	94 (75,2)	0,643*
Malaksalost	167 (50,3)	66 (52,8)	0,554*
Dispneja	53 (42,4)	72 (57,6)	**0,018***
Artalgija	63 (19,0)	27 (21,6)	0,529*
Bol u grudima	25 (7,5)	37 (29,6)	**0,001***
Gubitak apetita	33 (9,9)	13 (10,4)	0,884*
Glavobolja	42 (12,7)	13 (10,4)	0,510*
Dijareja	45 (13,6)	16 (12,8)	0,833*
Anosmija	30 (9,0)	21 (16,8)	**0,019***
Kvalitativni poremećaj svesti	26 (7,8)	9 (7,2)	0,821*
Povraćanje	23 (6,9)	5 (4,0)	0,245*
Bol u leđima	33 (9,9)	15 (12,0)	0,522*
Kvantitativni poremećaj sveti	15 (4,5)	10 (8,0)	0,145*
Nazalna kongestija	45 (13,6)	20 (16,0)	0,505*
Promuklost	9 (2,7)	3 (2,4)	0,487*
Konjunktivitis	7 (2,1)	1 (0,8)	0,456*
Otežano gutanje	9 (2,7)	4 (3,2)	0,779*

JIN-jedinica intenzivne nege; IKO - interkvartilni opseg;*prema Hi kvadrat testu ili Fišerovom testu tačne verovatnoće, † Man Vitnijev test; Podebljane vrednosti su statistički značajne

Pacijenti koji su preminuli u JIN-e češće su prijavljivali otežano disanje (p=0,001), dijareju (p=0,010) i anosmiju (p=0,001) u poređenju sa preživelim pacijentima u JIN-e. Pacijenti koji su se oporavili češće su imali febrilnost (p=0,005) i nazalnu kongestiju kao početne simptome COVID-19 u poređenju sa pacijentima koji su preminuli u JIN-e. Ostale razlike u distribuciji početnih simptoma nisu bile značajne (Tabela 2).

Tokom bolničkog lečenja 125 (27,3%) pacijenata sa COVID-19-om prevedeno je u JIN, dok je preostalih 332 (72,7%) pacijenata zbrinuto na opštim odeljenjima. Utvrđeno je da su stariji uzrast i bol u grudima kao početni simptom COVID-19 bili znača-jno povezani sa potrebom za lečenjem u JIN-e, prema rezultatu univarijantne analize. U multivarijantnoj analizi, stariji uzrast i bol u grudima, kao početni simptom COVID-19, ostali su značajno nezavisno povezani sa potrebom za lečenjem u JIN-e (Tabela 3).

Od 125 pacijenata koji su imali potrebu za nastavkom lečenja u JIN-e, 64 je umrlo, što je predstavlja letalitet u JIN-u od 51,2%. Na osnovu univarijantnog Koksovog proporcionalnog prediktivnog modela, stariji uzrast, dispneja, anosmija, kao i odsustvo temperature i nazalne kongestije, bili su značajno povezani sa smrtnošću u JIN-e. U multivarijantnom Koksovom proporcionalnom modelu,

Table 1. Demographic and clinical characteristics of the subjects in relation to the need for continued treatment in the intensive care unit

| Variable | Need for treatment in ICU | | p value |
	No N=332 n (85.6%)	Yes N=125 n (27.3%)	
Gender			
Male	145 (43.7)	52 (41.6)	0.223*
Female	187 (56.3)	73 (58.4)	
Age, median	61.0 (19.7)	74.0 (17.5)	**0.001†**
COVID-19 vaccination			
Yes	96 (28.9)	20 (16.0)	**0.005***
No	236 (71.7)	105 (84.0)	
Fever	284 (85.5)	105 (84.0)	0.840*
Cough	259 (78.0)	94 (75.2)	0.643*
Fatigue	167 (50.3)	66 (52.8)	0.554*
Shortness of breath	53 (42.4)	72 (57.6)	**0.018***
Arthralgia	63 (19.0)	27 (21.6)	0.529*
Chest pain	25 (7.5)	37 (29.6)	**0.001***
Loss of appetite	33 (9.9)	13 (10.4)	0.884*
Headache	42 (12.7)	13 (10.4)	0.510*
Diarrhea	45 (13.6)	16 (12.8)	0.833*
Anosmia	30 (9.0)	21 (16.8)	**0.019***
Qualitative disturbance of consciousness	26 (7.8)	9 (7.2)	0.821*
Vomiting	23 (6.9)	5 (4.0)	0.245*
Back pain	33 (9.9)	15 (12.0)	0.522*
Quantitative disturbance of consciousness	15 (4.5)	10 (8.0)	0.145*
Nasal congestion	45 (13.6)	20 (16.0)	0.505*
Hoarseness	9 (2.7)	3 (2.4)	0.487*
Itching of the eye	7 (2.1)	1 (0.8)	0.456*
Difficulty swallowing	9 (2.7)	4 (3.2)	0.779*

ICU-intensive care unit; IQR - interquartile range; *by Chi square test or Fisher's exact test, † Mann Whitney test; Bolded values denote statistical significance.

(p=0.001), and anosmia (p=0.019) as the initial COVID-19 symptoms, unlike patients who were not in need of the ICU. However, differences in the distribution of other initial symptoms of SARS-CoV-2 infection were not observed (Table 1).

Patients who died in the ICU more often reported shortness of breath (p=0.001), diarrhea (p=0.010), anosmia (p=0.001), and nasal congestion (p=0.011) compared to the surviving patients. Patients who recovered more often had fever (p=0.005) as the initial COVID-19 symptom compared to patients who died. Other differences in the distribution of initial symptoms were not recorded (Table 2).

During hospital stay, 125 (27.3%) COVID-19-infected patients were transferred to the ICU, while the remaining 332 (72.7%) patients were treated on the floor. It was found that being older and having chest pain as the initial COVID-19 symptoms were univariately associated with needing the ICU care. In the multivariate analysis, being older and having chest pain as the initial COVID-19 symptoms remained independently associated with needing the intensive care (Table 3).

Of 125 patients requiring ICU treatment, a total of 64 deaths occurred, resulting in an ICU case-fatality rate of 51.2%. Based on the univariate Cox

Tabela 2. Demografske i kliničke karakteristike ispitanika u odnosu na smrtni ishod u jedinici intenzivne nege

Varijable	Smrtni ishod u JIN		p vrednost
	Ne N=61 n (%)	Da N=64 n (%)	
Pol			
Muški	27 (44,3)	25 (39,1)	0,555*
Ženski	34 (55,7)	39 (60,9)	
Uzrast, medijana (IKO)	74,0 (16,5)	73,5 (18,7)	0,919†
COVID-19 vakcinacija			
Da	12 (19,7)	8 (12,5)	0,274*
Ne	49 (80,3)	56 (87,5)	
Febrilnost	57 (93,4)	48 (75,0)	**0,005***
Kašalj	45 (73,8)	49 (76,6)	0,718*
Malaksalost	27 (44,3)	39 (60,9)	0,062*
Dispneja	23 (37,7)	49 (76,6)	**0,001***
Artalgija	16 (26,2)	11 (17,2)	0,219*
Bol u grudima	18 (29,5)	19 (29,7)	0,982*
Gubitak apetita	7 (11,5)	6 (9,4)	0,701*
Glavobolja	4 (6,6)	9 (14,1)	0,169*
Dijareja	3 (4,9)	13 (20,3)	**0,010***
Anosmija	2 (3,3)	19 (29,7)	**0,001***
Kvalitativni poremećaj svesti	3 (4,9)	6 (9,4)	0,335*
Povraćanje	1 (1,6)	4 (6,3)	0,189*
Bol u leđima	9 (14,8)	6 (9,4)	0,355*
Kvantitativni poremećaj sveti	3 (4,9)	7 (10,9)	0,215*
Nazalna kongestija	15 (24,6)	5 (7,8)	**0,011***
Promuklost	2 (3,3)	1 (1,6)	0,487*
Konjunktivitis	0 (0,0)	1 (1,6)	0,327*
Otežano gutanje	2 (3,3)	2 (3,1)	0,961*

JIN-jedinica intenzivne nege; IKO - interkvartilni opseg; *prema χ2 testu ili Fišerovom testu tačne verovatnoće, † Man Vitnijev test; Podebljane vrednosti su statistički značajne

stariji uzrast, otežano disanje, glavobolja i dijareja, ali i odsustvo nazalne kongestije, kao početni simptomi COVID-19, bili su značajno nezavisno povezani sa smrtnim ishodom u JIN-e (Tabela 4).

Diskusija

Ova studija je zabeležila da su dominantni početni simptomi i znaci COVID-19 kod pacijenata iz ove studijske populacije bili febrilnost, kašalj i umor. Na osnovu multivarijantnih modela, nezavisni prediktori potrebe za lečenjem u JIN-u bili su stariji uzrast i prisustvo bola u grudima. Dodatno, nezavisni prediktori fatalnog ishoda bili su stariji uzrast, otežano disanje, glavobolja, dijareja, ali i odsustvo nazale kongestije kao početni simptomi

i znaci COVID-19. Iako su febrilnost, kašalj i umor česti, nisu bili povezani sa potrebom za lečenjem u JIN-u niti sa smrtnim ishodom usled bolesti COVID-19. Stoga, ova studija ističe specifične simptome i znake na početku COVID-19 koji mogu biti ključni za prognozu COVID-19 prilikom prijema u bolnicu.

U našoj studiji primećeno je da je stariji uzrast bio jedini zajednički prediktor potrebe za lečenjem u JIN-e i smrtnog ishoda usled COVID-19 u JIN-e. Stariji uzrast je očigledan i očekivan faktor udružen sa lošim ishodima COVID-19, zbog smanjene funkcionalne rezerve organa i višeg opšteg rizika od smrti. U studijama koje su ispitivale izolovani efekat uzrasta na ishode COVID-19, zabeležen je do porast rizika za bolničko lečenje za 3,4% i

Table 2. Demographic and clinical characteristics of subjects in relation to death in the intensive care unit

Variable	Fatal outcome in ICU		p value
	No N=61 n (%)	Yes N=64 n (%)	
Gender			
Male	27 (44.3)	25 (39.1)	0.555*
Female	34 (55.7)	39 (60.9)	
Age, median (IQR)	74.0 (16.5)	73.5 (18.7)	0.919†
COVID-19 vaccination			
Yes	12 (19.7)	8 (12.5)	0.274*
No	49 (80.3)	56 (87.5)	
Fever	57 (93.4)	48 (75.0)	**0.005***
Cough	45 (73.8)	49 (76.6)	0.718*
Fatigue	27 (44.3)	39 (60.9)	0.062*
Shortness of breath	23 (37.7)	49 (76.6)	**0.001***
Arthralgia	16 (26.2)	11 (17.2)	0.219*
Chest pain	18 (29.5)	19 (29.7)	0.982*
Loss of appetite	7 (11.5)	6 (9.4)	0.701*
Headache	4 (6.6)	9 (14.1)	0.169*
Diarrhea	3 (4.9)	13 (20.3)	**0.010***
Anosmia	2 (3.3)	19 (29.7)	**0.001***
Qualitative disturbance of consciousness	3 (4.9)	6 (9.4)	0.335*
Vomiting	1 (1.6)	4 (6.3)	0.189*
Back pain	9 (14.8)	6 (9.4)	0.355*
Quantitative disturbance of consciousness	3 (4.9)	7 (10.9)	0.215*
Nasal congestion	15 (24.6)	5 (7.8)	**0.011***
Hoarseness	2 (3.3)	1 (1.6)	0.487*
Itching of the eye	0 (0.0)	1 (1.6)	0.327*
Difficulty swallowing	2 (3.3)	2 (3.1)	0.961*

ICU-intensive care unit; IQR - interquartile range; *by Chi square test or Fisher's exact test, † Mann Whitney test; Bolded values denote statistical significance.

proportional hazard model, being older, having shortness of breath and anosmia, but absence of fever and nasal congestion were associated with the ICU mortality. In the multivariate Cox hazard model, being older, having shortness of breath, headache and diarrhea, but absence of nasal congestion as the initial symptoms of COVID-19 were independently associated with the ICU mortality in this population (Table 4).

Discussion

This study reports that predominant initial symptoms of COVID-19 in our patients were fever, cough, and fatigue. Based on the multivariate models, the independent predictors of needing the ICU treatment were older age and having chest pain. Furthermore, the independent predictors of having fatal COVID-19 outcome were being older, having shortness of breath, headache, diarrhea, but no nasal congestion, as the initial symptoms of COVID-19. Despite being common, neither fever, nor cough nor fatigue was associated with receiving the ICU treatment and poor COVID-19 outcomes. Therefore, this study highlights specific symptoms at the beginning of clinically manifested COVID-19, which may be crucial for COVID-19 prognosis upon hospital admission.

Tabela 3. Rezultati univarijatnog i multivarijatnog Koksovog proporcionalnog prediktivnog modela: faktori povezani sa nastavkom lečenja u jedinici intenzivne nege

Varijable	Univarijantni model*			Multivarijantni model*		
	HR	95% CI	p	HR	95% CI	p
Muški pol	0,79	0,55-1,14	0,206	0,75	0,51-1,11	0,153
Stariji uzrast	1,03	1,02-1,05	**0,001**	1,03	1,02- 1,05	**0,001**
COVID-19 vakcinacija	0,68	0,42-1,10	0,119	0,74	0,45-1,23	0,251
Febrilnost	0,91	0,56-1,47	0,702	0,89	0,53-1,50	0,668
Kašalj	1,01	0,67-1,52	0,959	0,95	0,62-1,47	0,843
Malaksalost	1,02	0,72-1,45	0,910	1,03	0,71-1,51	0,875
Dispneja	1,31	0,92-1,88	0,134	1,39	0,95-2,04	0,093
Artalgija	1,08	0,71-1,66	0,714	1,20	0,77-1,88	0,409
Bol u grudima	1,66	1,11-2,47	**0,013**	1,62	1,04-2,53	**0,032**
Gubitak apetita	1,06	0,59-1,88	0,851	1,24	0,67-2,30	0,487
Glavobolja	1,11	0,62-1,97	0,731	1,63	0,87-3,04	0,124
Dijareja	1,01	0,59-1,71	0,980	1,27	0,73-2,21	0,395
Anosmija	1,08	0,66-1,75	0,768	0,70	0,39-1,23	0,213
Kvalitativni poremećaj svesti	0,83	0,42-1,63	0,583	0,98	0,48-2,00	0,965
Povraćanje	0,51	0,21-1,25	0,145	0,60	0,24-1,52	0,280
Bol u leđima	0,89	0,52-1,54	0,685	0,8	0,50-1,55	0,649
Kvantitativni poremećaj sveti	0,15	0,81-2,45	0,192	1,65	0,79-3,42	0,182
Nazalna kongestija	0,97	0,59-1,60	0,974	1,08	0,64-1,81	0,766
Promuklost	0,66	0,21-2,08	0,480	0,39	0,11-1,30	0,124
Konjunktivitis	0,44	0,06-3,19	0,420	0,29	0,04-2,19	0,232
Otežano gutanje	1,38	0,51-3,74	0,528	1,38	0,49-3,91	0,546

JIN – jedinica intenzivne nege; HR-hazard ratio; CI-interval poverenja; Podebljane vrednosti su statistički značajne.

porast rizika za smrtni ishod u bolnici za 5,7% za svaku stariju godinu uzrasta (8, 9). Međutim, nema dokaza o postojanju praga starosti posle kojeg rizik za težu formu bolesti raste, pa je efekat starosti utvrđen kao linearan (9). U studiji koja je ispitivala prediktore respiratorne insuficijencije, primećeno je da je uzrast preko 60 godina značajan faktor povezan sa pojavom respiratorne insuficijencije i potrebom za mehaničkom ventilacijom (10). Stoga su naši rezultati u skladu sa prethodnim studijama.

Bol u grudima kao početni simptom je bio značajan prediktor nastavka lečenja u JIN-e u ovoj studijskoj grupi. Osnovni mehanizmi bola u grudima kao početnog simptoma u bolesti COVID-19 se mogu objasniti na nekoliko načina. Direktan uticaj virusa na tkiva pluća, koji rezultira inflamacijom i naknadnom aktivacijom nociceptivnih receptora u pleuri ili zidu grudnog koša, može dovesti do per-

cepcije bola (11). Pored toga, neregulisani imunski odgovor izazvan SARS-CoV-2 karakteriše intenzivno oslobađanje proinflamatornih citokina kao što su IL-6 i faktor nekroze tumora alfa (TNF-α). Ovi medijatori doprinose patogenezi bola u grudima (12). Nadalje, potencijalni razvoj komplikacija povezanih sa bolešću COVID-19, poput pneumonije i akutnog respiratornog distres sindroma, može dodatno pogoršati neprijatne senzacije u nivou pluća i povećati nivo subjektivnog osećaja bola u grudnom košu (13).

Otežano disanje na početku bolesti COVID-19 kod pacijenata sa umerenom do teškom kliničkom slikom je zapažen kao prediktor fatalne forme COVID-19. Klinička slika dispneje, , kao rani simptom infekcije COVID-19 može se pripisati složenoj reakciji patofizioloških mehanizama koji uključuju virusom izazvanu bolest pluća, inflamatorne odgo-

Table 3. Univariate and multivariate Cox proportional predictive model results: factors associated with continuation of treatment in the intensive care unit

Variable	Univariate model			Multivariate model		
	HR	95% CI	p	HR	95% CI	p
Male gender	0.79	0.55-1.14	0.206	0.75	0.51-1.11	0.153
Older age	1.03	1.02-1.05	**0.001**	1.03	1.02- 1.05	**0.001**
COVID-19 vaccination	0.68	0.42-1.10	0.119	0.74	0.45-1.23	0.251
Fever	0.91	0.56-1.47	0.702	0.89	0.53-1.50	0.668
Cough	1.01	0.67-1.52	0.959	0.95	0.62-1.47	0.843
Fatigue	1.02	0.72-1.45	0.910	1.03	0.71-1.51	0.875
Shortness of breath	1.31	0.92-1.88	0.134	1.39	0.95-2.04	0.093
Arthralgia	1.08	0.71-1.66	0.714	1.20	0.77-1.88	0.409
Chest pain	1.66	1.11-2.47	**0.013**	1.62	1.04-2.53	**0.032**
Loss of appetite	1.06	0.59-1.88	0.851	1.24	0.67-2.30	0.487
Headache	1.11	0.62-1.97	0.731	1.63	0.87-3.04	0.124
Diarrhea	1.01	0.59-1.71	0.980	1.27	0.73-2.21	0.395
Anosmia	1.08	0.66-1.75	0.768	0.70	0.39-1.23	0.213
Qualitative disturbance of consciousness	0.83	0.42-1.63	0.583	0.98	0.48-2.00	0.965
Vomiting	0.51	0.21-1.25	0.145	0.60	0.24-1.52	0.280
Back pain	0.89	0.52-1.54	0.685	0.8	0.50-1.55	0.649
Quantitative disturbance of consciousness	0.15	0.81-2.45	0.192	1.65	0.79-3.42	0.182
Nasal congestion	0.97	0.59-1.60	0.974	1.08	0.64-1.81	0.766
Hoarseness	0.66	0.21-2.08	0.480	0.39	0.11-1.30	0.124
Itching of the eye	0.44	0.06-3.19	0.420	0.29	0.04-2.19	0.232
Difficulty swallowing	1.38	0.51-3.74	0.528	1.38	0.49-3.91	0.546

HR-hazard ratio; CI-confidence interval; Bolded values are statistically significant, DC - disturbance of consciousness.

In our study, it was observed that older age was the only common predictor of both needing the ICU treatment and of fatal COVID-19 outcomes. Age is an obvious and expected contributor to poorer COVID-19 outcomes, due to the reduced organ reserve and higher risk of mortality in general. In studies examining the isolated effect of age on COVID-19 outcomes, there was a 3.4% increase in risk for hospital treatment and 5.7% increase in risk of hospital mortality per each year of age (8, 9). Furthermore, there was no evidence of an age threshold at which the risk of disease severity increases, because the effect of age on poorer COVID-19 outcomes was identified as linear (9). In a study focusing on predictors of respiratory failure, it was observed that age above 60 years is a contributor to respiratory failure and needing mechanical ventilation (10). Thus, our results are in line with previous studies.

Chest pain emerged as an initial symptom predictive of needing the ICU treatment in this study. The underlying mechanisms of chest pain as an initial symptom in COVID-19 infection can be explained through several pathways. The direct viral impact on lung tissues resulting in the inflammation and subsequent activation of nociceptive receptors in the pleura or chest wall can lead to a subjective perception of pain (11). Additionally, the dysregulated immune response in COVID-19 includes an abundant release of pro-inflammatory cytokines, such as the IL-6 and tumor necrosis factor-alpha (TNF-α). These mediators have been found to facilitate the onset of chest pain (12). Furthermore, potential development of COVID-19-related complications, such as pneumonia and acute respiratory distress

Tabela 4. Rezultati univarijantnog i multivarijantnog Koksovog proporcionalnog prediktivnog modela: faktori povezani sa smrtnim ishodom u jedinici intenzivne nege

Varijable	Univarijantni model*			Multivarijantni model*		
	HR	95% CI	p	HR	95% CI	p
Muški pol	0,14	0,41-1,14	0,145	0,78	0,44-1,37	0,385
Godine	1,03	1,01-1,05	**0,004**	1,04	1,01-1,06	**0,001**
COVID-19 vakcinacija	0,52	0,25-1,09	0,084	0,62	0,28-1,34	0,228
Febrilnost	0,53	0,30-0,93	**0,027**	0,70	0,35-1,36	0,292
Kašalj	1,07	0,59-1,91	0,830	1,03	0,54-1,94	0,935
Malaksalost	1,39	0,84-2,32	0,199	1,19	0,67-2,10	0,541
Dispneja	3,10	1,73-5,57	**0,001**	3,02	1,62-5,62	**0,001**
Artalgija	0,82	0,43-1,57	0,549	0,99	0,50-1,96	0,980
Bol u grudima	1,59	0,91-2,78	0,130	1,53	0,78-2,96	0,208
Gubitak apetita	0,95	0,41-2,21	0,907	1,40	0,56-3,45	0,470
Glavobolja	1,67	0,81-3,33	0,174	2,51	1,10-5,66	**0,027**
Dijareja	1,76	0,95-3,24	0,072	2,43	1,21-4,83	**0,012**
Anosmija	2,27	1,28-3,88	**0,005**	1,35	0,67-2,71	0,393
Kvalitativni poremećaj svesti	1,11	0,48-2,58	0,807	1,20	0,48-3,01	0,692
Povraćanje	0,81	0,30-2,26	0,697	0,93	0,31-2,78	0,901
Bol u leđima	0,67	0,29-1,56	0,353	0,78	0,32-1,89	0,583
Kvantitativni poremećaj sveti	2,16	0,98-4,78	0,056	1,18	0,41-3,31	0,757
Nazalna kongestija	0,35	0,13-0,97	**0,045**	0,32	0,10-0,93	**0,037**
Promuklost	0,39	0,05-2,83	0,622	0,28	0,03-2,16	0,221
Konjunktivitis	0,95	0,13-6,89	0,961	0,52	0,06-4,19	0,547
Otežano gutanje	1,33	0,32-4,46	0,692	1,29	0,28-5,92	0,739

JIN – jedinica intenzivne nege; HR-hazard ratio; CI-interval poverenja; Podebljane vrednosti su statistički značajne

vore i disregulaciju sistema renin-angiotenzin-aldosteron (14-16). SARS-CoV-2 izaziva kaskadu inflamatornih procesa preko receptora angiotenzin-konvertujućeg enzima 2 (ACE2) eksprimiranih pretežno u respiratornom epitelu (15). To dovodi do aktivacije imunih ćelija, kao što su makrofagi i limfociti (15). Aktivacija puteva koagulacije i formiranje mikrotromba u plućnoj vaskulaturnoj mreži dalje doprinosi narušavanju razmene gasova i nastanku respiratornog distresa u teškim slučajevima infekcije (16). Multifaktorska priroda otežanog disanja kod COVID-19 naglašava složenu interakciju između patogeneze virusa, imunoloških odgovora i kardiovaskularne dinamike (15).

Refleks kašlja kod COVID-19 oboljenja je prvenstveno odgovor na iritaciju respiratorne sluzokože zbog inflamatornog odgovora koji je virus izazvao, što dovodi do povećane proizvodnje sluzi i hiperreaktivnosti disajnih puteva (16). Štaviše, neurogena inflamacija povezana sa aktivacijom senzornih nerava u epitelu disajnih puteva može doprineti upornom kašlju koji je primećen kod nekih pacijenata (15). Svi ovi faktori, dakle, mogu predisponirati osobu za razvoj sistemskih efekata zapaljenja, posledično, respiratorne insuficijencije.

U ovoj studiji zabeleženo je da je glavobolja kao početni simptom povezana sa smrtnim ishodom COVID-19 bolesti. Naši nalazi su u suprotnosti sa prethodno objavljenom meta-analizom koja je sugerisala da pacijenti koji prijavljuju glavobolju kao početni simptom COVID-19 imaju veće šanse za preživljavanje u poređenju sa osobama koje nemaju glavobolju (17). Postoje oprečni rezultati o vezi između glavobolje i nivoa proinflamatornih citokina. Naime, nivoi IL-6 su viši kod osoba koje prijavljuju glavobolju kao početni simptom COVID-

Table 4. Univariate and multivariate Cox proportional predictive model results: factors associated with fatal outcome in the intensive care unit

Variable	Univariate model			Multivariate model		
	HR	95% CI	p	HR	95% CI	p
Male gander	0.14	0.41-1.14	0.145	0.78	0.44-1.37	0.385
Age	1.03	1.01-1.05	**0.004**	1.04	1.01-1.06	**0.001**
COVID-19 vaccination	0.52	0.25-1.09	0.084	0.62	0.28-1.34	0.228
Fever	0.53	0.30-0.93	**0.027**	0.70	0.35-1.36	0.292
Cough	1.07	0.59-1.91	0.830	1.03	0.54-1.94	0.935
Fatigue	1.39	0.84-2.32	0.199	1.19	0.67-2.10	0.541
Shortness of breath	3.10	1.73-5.57	**0.001**	3.02	1.62-5.62	**0.001**
Arthralgia	0.82	0.43-1.57	0.549	0.99	0.50-1.96	0.980
Chest pain	1.59	0.91-2.78	0.130	1.53	0.78-2.96	0.208
Loss of appetite	0.95	0.41-2.21	0.907	1.40	0.56-3.45	0.470
Headache	1.67	0.81-3.33	0.174	2.51	1.10-5.66	**0.027**
Diarrhea	1.76	0.95-3.24	0.072	2.43	1.21-4.83	**0.012**
Anosmia	2.27	1.28-3.88	**0.005**	1.35	0.67-2.71	0.393
Qualitative disturbance of consciousness	1.11	0.48-2.58	0.807	1.20	0.48-3.01	0.692
Vomiting	0.81	0.30-2.26	0.697	0.93	0.31-2.78	0.901
Back pain	0.67	0.29-1.56	0.353	0.78	0.32-1.89	0.583
Quantitative disturbance of consciousness	2.16	0.98-4.78	0.056	1.18	0.41-3.31	0.757
Nasal congestion	0.35	0.13-0.97	**0.045**	0.32	0.10-0.93	**0.037**
Hoarseness	0.39	0.05-2.83	0.622	0.28	0.03-2.16	0.221
Itching of the eye	0.95	0.13-6.89	0.961	0.52	0.06-4.19	0.547
Difficulty swallowing	1.33	0.32-4.46	0.692	1.29	0.28-5.92	0.739

HR-hazard ratio; CI-confidence interval; Bolded values are statistically significant.

syndrome, can further exacerbate chest discomfort and increase the level of subjective pain (13).

Shortness of breath, as an initial symptom of COVID-19 in patients with moderate to severe clinical form, has been identified as the predictor of fatal COVID-19. The onset of dyspnea, commonly known as shortness of breath, as an early symptom of COVID-19, can be attributed to a complex interplay of pathophysiological mechanisms involving viral-induced lung injury, inflammatory responses, and dysregulation of the renin-angiotensin-aldosterone system (RAAS) (14-16). The SARS-CoV-2 induces a cascade of inflammatory processes through angiotensin-converting enzyme 2 (ACE2) receptors expressed predominantly in the respiratory epithelium (15). This leads to the activation of immune cells, such as macrophages and lymphocytes (15). The activation of coagulation

pathways and the formation of microthrombi within the pulmonary vasculature further contribute to the impairment of gas exchange and the onset of respiratory distress in severe cases of the infection (16). The multifactorial nature of dyspnea in COVID-19 suggests that there is interplay between viral pathogenesis, immunological responses, and cardiovascular dynamics (15).

The cough reflex in COVID-19 is primarily a result of irritation of the respiratory mucosa due to the inflammatory response to SARS-CoV-2 (16). Hence, there is an increased mucus production and airway hyperresponsiveness (16). Furthermore, the neurogenic inflammation associated with the activation of sensory nerves in the respiratory epithelium could contribute to the persistent cough observed in some patients (15). All these factors can, therefore, predispose an individual to

19, ali nema daljih nepovoljnih efekata u kasnijim fazama infekcije (18). Druga studija je zabeležila da su nivoi IL-6 viši kod osoba sa glavoboljom tokom COVID-19, ali da kasnije vrednosti IL-6 dostižu plato koji odsustvuje kod onih pacijenata koji ne prijavljuju glavobolju (19). Studije koje su ispitivale pacijente koji su prethodno imali glavobolje takođe beleže nešto više stope preživljavanja u poređenju sa opštom populacijom obolelom od COVID-19 bolesti, što se pripisuje modifikovanoj funkciji sistema renin-angiotenzin-aldosteron tokom lečenja glavobolje i ranijom suplementacijom vitaminom D (20, 21). Ova razlika u našim rezulatatima i podacima iz literature ukazuje na potrebu za daljim istraživanjima o uticaju glavobolje kao početnog simptoma COVID-19 na ishode bolesti.

U našoj studiji, dijareja kao početni simptom infekcije je bila povezana sa smrtnim ishodom COVID-19 infekcije. Prethodna studija je pokazala da je potrebno duže vreme za prijem u bolnicu kad pacijenti sa COVID-19 oboljenjem a koji imaju gastrointestinalne smetnje u poređenju sa onima bez njih (22). Ovo se pripisuje odsustvu tipičnih respiratornih simptoma u početku, što usporava pravovremenu dijagnozu i lečenje (22). Noviji podaci sugerišu da je dijareja povezana sa težim oblicima COVID-19 i ukazuju na to da bi njeno prisustvo moglo biti pouzdaniji indikator razvoja teškog oblika COVID-19 (23). U drugim studijama, dijareja je bila povezana sa težom formom bolesti COVID-19 (24). Međutim, postoje podaci o inicijalnoj manifestaciji COVID-19 infekcije sa dijarejom i glavoboljom istovremeno, gde je ovaj način početka infekcije bio povezan sa boljim preživljavanjem pacijenata (25). Zbog razlika u rezultatima, potrebna su dalja istraživanja kako bi se bolje razumeli ovi simptomi i njihova veza sa lakom do teškom formom COVID-19 bolesti praćenom dijarejom.

U ovoj studiji, odsustvo nazalne kongestije bilo je povezano sa smrtnim ishodom COVID-19. Slične studije su zabeležile da odsustvo nazalne kongestije, u kombinaciji sa anosmijom, može biti povezan sa ozbiljnijim ispoljavanjem COVID-19 (26, 27). Međutim, nedostaju detaljni patofiziološki mehanizmi koji objašnjavaju ovaj nalaz. U ovoj studiji, sistemski simptomi, poput glavobolje, dijareje i otežanog disanja, bili su udruženi sa lošim ishodom COVID-19 bolesti. Iako se COVID-19 klasifikuje kao respiratorna infekcija, koja se prenosi kapljičnim putem, nema sumnje da se radi o sistemskoj infekciji koja zahvata praktično sve sisteme organa. Iz tog razloga, potrebna je pažljiva evaluacija pacijenata primljenih u bolnicu u vezi sa njihovim simptomima kako bi se precizno predvideo dalje lečenje u JIN-e i ishod lečenja.

Ograničenja ove studije odnose se na činjenicu da je analiza sprovedena u dve medicinske ustanove. Zato potencijalna pristrasnosti izbora u selekciji ispitanika može onemogućiti generalizaciju rezultata ove studije na celokupnu populaciju obolelih od infekcije COVID-19. Dodatno, ova studija nije istraživala uticaj pojedinačnih varianti SARS-CoV-2, iako mogu postojati razlike u njihovim ishodima. Budući da su uzeti u obzir samo simptomi i znaci, a ne i drugi relevantni podaci, poput laboratorijskih parametara, moguće je da postoji i rezidualna pristrasnost usled pridruženosti (konfaunding).

Zaključak

Rezultati ove studije ističu važnost pažljivog praćenja i brze intervencije kod pacijenata koji imaju bol u grudima, otežano disanje, glavobolju i dijareju, posebno kod starijih osoba. Dalja istraživanja sa različitim kohortama pacijenata i dužim periodom praćenja su neophodna kako bi se potvrdili ovi prediktori. Razumevanje početnih simptoma COVID-19 i njihove povezanosti sa lošim ishodima infekcije mogu pomoći u definisanju odgovarajućih pristupa lečenju sa ciljem optimizacije ishoda COVID-19.

Konflikt interesa

Autori su izjavili da nema konflikta interesa.

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detrimental systemic effects of the inflammation and, subsequently, respiratory failure.

In this study, we observed that headache as the initial symptom is associated with fatal outcomes of COVID-19. Our findings contradict the previously published meta-analysis which suggested that patients reporting headache atthe onset of COVID-19 have higher chances of survival compared to those people without headache (17). There are inconsistent findings regarding the association between headache and proinflammatory cytokine levels. Specifically, IL-6 levels are higher in individuals reporting headache at the onset of COVID-19, but they do not sustain further detrimental effects in later stages of the infection (18). Another study found that IL-6 levels are elevated in individuals with headache during COVID-19, but later, IL-6 values reach a plateau, which is absent in those patients not reporting headache (19). Studies focusing on patients with pre-existing headaches also reported slightly higher survival rates compared to the general population with COVID-19. This is attributed to a modified RAAS system function during headache treatment and earlier vitamin D supplementation (20, 21). This discrepancy with our findings underscores the necessity for more research focusing on the impact of headache as an initial symptom of COVID-19 on disease outcomes.

In our study, diarrhea as an initial symptom of the infection was associated with fatal COVID-19 outcomes. A previous study reported that patients with gastrointestinal disturbances took longer time to be admitted to hospital compared to those without them (22). This was attributed to the absence of typical respiratory symptoms initially, thus delaying timely diagnosis and treatment (22). Emerging data suggest that diarrhea is linked to severe forms of COVID-19 and indicate that it could serve as a reliable indicator of risk of developing severe COVID-19 form (23). In other studies, diarrhea has been associated with an increase in severity of COVID-19-related pathology (24). However, there are data on the simultaneous initial presentation of COVID-19 infection with diarrhea and headache, where this combination of symptoms is associated with better survival (25). Due to disparities in results, further research is needed to better understand these characteristics and their association with severe COVID-19 accompanied by diarrhea.

In the present study, the absence of nasal congestion was associated with poor COVID-19 outcome. Related studies have identified the absence of nasal congestion, combined with anosmia, may potentially be associated with a more severe presentation of COVID-19 (26, 27). However, detailed pathophysiological mechanisms explaining this finding are lacking. In this set of patients, systemic symptoms, such as headache, gastrointestinal presentation and shortness of breath were the key symptoms at the onset of COVID-19 predictive of poorer infection outcomes. While COVID-19 is classified as a respiratory infection, transmitted via droplet spread, there is no doubt that it is a systemic infection which affects virtually all organ systems. For this reason, careful assessment of patients admitted to hospital is needed with regards to their symptoms to accurately predict further ICU treatment and outcomes.

Limitations of this study are related to the notion that this analysis was conducted at two medical centers. This potential selection bias may restrict generalization of study findings to the entire population who were affected by COVID-19. Additionally, this study did not investigate the impact of individual SARS-CoV-2 variants, as there may be differences in outcomes. Because only symptoms were taken into account and not other relevant data, such as serum parameters, this analysis is open to potential unobserved confounding.

Conclusion

The results of this study emphasize the importance of vigilant monitoring and swift intervention in patients presenting with chest pain, shortness of breath, headache, and diarrhea, particularly among older people. Further research with diverse patient cohorts and an extended follow-up period is essential to validate these findings. Understanding initial COVID-19 symptoms and their association with poor infection outcomes can help to design tailored approaches to treatment with the goal to optimize COVID-19 outcomes.

Competing interests

The authors declared no competing interests.

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