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PREDIKTORI TEŽINE BOLESTI KOD BOLESNIKA SA COVID-19 BOLEŠĆU

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SAŽETAK

Uvod/Cilj: U kliničkoj slici COVID-19 dominira respiratorna simptomatologija, ali se u osnovi radi o multisistemskom poremećaju. Cilj ove studije je bio da se identifikuju prediktori teških oblika COVID-19 definisanih kao potreba za potpomognutom ventilacijom (neinvazivna ili invazivna mehanička ventilacija).
Metode: Sprovedena je retrospektivna kohortna studija u Opštoj bolnici „Laza K. Lazarević" u Šapcu u periodu od 1.4.2020. do 15.11.2020. godine. Odnos između demografskih i kliničkih parametara pacijenata i potrebe za asistiranom ventilacijom ispitan je logističkom regresionom analizom.
Rezultati: Studijom je obuhvaćeno 516 pacijenata, 334 ispitanika muškog pola (64,7%), starosti 60 i više godina (52,7%). Najčešći prijavljeni simptomi bili su groznica (89%) i generalizovana slabost (68,8%). Mehanička ventilacija je bila potrebna za 44 pacijenta, od kojih su većina bili muškarci (64,7%). Dominantni komorbiditeti u grupi sa mehaničkom ventilacijom bili su hipertenzija (63,6%) i dijabetes (22,7%). Prema multivarijantnoj analizi, nezavisni faktori rizika za potpomognutu ventilaciju bili su: febrilnost (p=0,022), trajanje bolesti više od sedam dana pre hospitalizacije (p=0,023), oksigena saturacija (sO_2) na prijemu <90% (p=0,002), aritmija (p=0,001), leukocitoza (p=0,034), i CRP>50 mg/l (p=0,002).
Zaključak: Rizik od potpomognute ventilacije je bio veći kod febrilnih pacijenata, sa oksigenom saturacijom manje od 90% na prijemu u bolnicu, trajanjem bolesti više od sedam dana pre hospitalizacije, aritmijama, leukocitozom, i CRP većim od 50 mg/l.

Ključne reči: COVID-19, komorbiditeti, faktori rzika, težina bolesti, potpomognuta ventilacija strategije, etički kodeks

Uvod

Korona virusi su jednolančani RNK virusi koji pogađaju ljude i mnoge životinjske vrste i poznati su od 1960. godine. Njihov potencijal otkriven je u novembru 2002. godine sa pojavom teškog akutnog respiratornog sindroma (engl. *Severe acute respiratory syndrome*, SARS). U međuvremenu, 2009. godine čovečanstvo je preživelo još jednu pandemiju gripa H1N1, a u junu 2012. godine ponovo je upozoreno na značaj korona virusa sa epidemijama bliskoistočnog respiratornog sindroma (engl. *Middle East Respiratory Syndrome*, MERS). Kompetentan, brz i odlučan odgovor nadležnih u slučaju SARS i MERS sindroma ograničio je broj obolelih i umrlih, ali je takođe ukazao na neke karakteristike koje će obeležiti pandemiju Koronavirusne bolesti 2019 (engl. *Coronavirus disease 2019* - COVID-19), poput visokog stepena straha od novih zaraznih bolesti među stanovništvom (SARS), potencijala za nozokomijalno širenje i čestih asimptomatskih slučajeva (MERS) (1).

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PREDICTORS OF DISEASE SEVERITY IN COVID-19 PATIENTS

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SUMMARY

Background/Aim: In the clinical picture of COVID-19 respiratory symptomatology dominates, but it is basically a multisystemic disorder. The aim of this study was to identify predictors of severe forms of COVID-19 defined as the need for assisted ventilation (non-invasive or invasive mechanical ventilation).
Methods: The research was conducted as a retrospective cohort study at the General hospital "Laza K. Lazarević" in Šabac for the period from1.4.2020. to 14.11.2020. The relationship between demographic and clinical parameters of patients and the need for assisted ventilation was examined by logistic regression analysis.
Results: The study included 516 patients, 334 male subjects (64.7%), with the age of60 and over (52.7%). The most commonly reported symptoms were fever (89%) and generalized weakness (68.8%). Mechanical ventilation was required by 44 patients, majority of whom were male (64.7%). The dominant comorbidities in mechanically ventilated group were hypertension (63.6%) and diabetes (22.7%). According to multivariate analysis independent risk factors for assisted ventilation were: fever (p=0.016), duration of illness more than seven days before hospitalization (p=0.023), oxygen saturation (sO2) <90% (p=0.002), arrhythmia(p=0.001), leukocytosis(p=0.034), and CRP≥50 mg/l (p=0.002).
Conclusion: The risk of assisted ventilation was higher in patients with fever, sO2<90% on admission to hospital, duration of illness more than seven days before hospitalization, arrhythmia, leukocytosis, lymphopenia<1.0x109 and CRP>50 mg/l.

Keywords: COVID-19, comorbidities, risk factors, disease severity, assisted ventilation

Introduction

Coronaviruses are single-stranded RNA viruses that affect humans and a wide variety of animal species and have been known since 1960. Their emerging potential was discovered in November 2002 with severe acute respiratory syndrome (SARS). Meanwhile, in 2009, humanity survived another pandemic of H1N1 influenza and in June 2012, it was again warned about the significance of the coronavirus with the Middle East Respiratory Syndrome (MERS) epidemics. The competent, rapid and decisive response of the authorities in SARS as well as in MERS limited the number of diseased and mortality, but also pointed out to some features that will mark the COVID-19 pandemic, such as high level of fear of new infectious diseases in population (SARS), potential for nosocomial spread and prevalent asymptomatic cases (MERS) (1).

At the end of 2019, a large number of patients with similar forms of acute pneumonias were

Krajem 2019. godine, otkriven je veliki broj pacijenata sa sličnim oblicima akutnih pneumonija u Vuhanu, u Kini. Do tada nepoznati korona virus SARS-CoV-2 ubrzo je identifikovan kao uzročnik uz pomoć molekularnih metoda, a bolest je nazvana COVID-19. Usledilo je brzo širenje SARS-CoV-2 infekcije u Kini, a potom i širom sveta. Svetska zdravstvena organizacija je 11. marta 2020. proglasila pandemiju COVID-19 bolesti. U ovoj trećoj epidemiji korona virusa dominirao je broj obolelih i umrlih i potpuno je razotkrivena globalna nespremnost za borbu protiv pandemije (1). Do 09.10.2024. COVID-19 bolest je dovela do preko 776 miliona dijagnostifikovanih slučajeva i više od sedam miliona smrtnih slučajeva širom sveta. Istog dana registrovano je 270.000 novih slučajeva COVID-19 bolesti širom sveta (2).

Kliničke manifestacije infekcije uzrokovane SARS-CoV-2 su različite, od blagih simptoma do akutne respiratorne insuficijencije i multiorganske disfunkcije. Kod većine obolelih od COVID-19 bolesti, prisutni su znaci blage respiratorne infekcije, ali bolest je zapravo multisistemski poremećaj i 14% pacijenata zahteva lečenje u jedinici intenzivne nege (3,4). Veća učestalost teških oblika bolesti i posledične hospitalizacije utvrđena je kod starijih osoba sa komorbiditetima – demencijom, dijabetesom tipa 2, hroničnom opstruktivnom bolešću pluća (HOBP), pneumonijom, depresijom, atrijalnom fibrilacijom, i hipertenzijom (5). Najteži oblici bolesti lečeni su u jedinicama intenzivne nege, a starije osobe, dijabetičari, osobe sa hiperholesterolemijom i HOBP bile su u većem riziku od smrtnog ishoda (6).

Rana identifikacija faktora rizika za teške oblike COVID-19 bolesti može biti od pomoći u upravljanju bolničkim prijemima. U ovom istraživanju identifikovani su prediktori teških oblika COVID-19 bolesti. Težak oblik COVID-19 je definisan kao potreba za asistiranom ventilacijom (neinvazivnom ili invazivnom mehaničkom ventilacijom).

Metode

U ovoj retrospektivnoj kohortnoj studiji podaci su prikupljeni iz elektronske dokumentacije Opšte bolnice „Laza K. Lazarević“ u Šapcu, Srbiji, u periodu od 1.4.2020. do 15.11.2020. Analiza je uključila sve obolele koji su potvrđeni metodom reverzne transkripcije lančane reakcije polimeraze (RT-PCR).

Istorije bolesti pacijenata sa COVID-19 oboljenjem su popunjavane nakon kliničkog pregleda. Pacijenti su davali informacije o trajanju i simptomima bolesti, komorbiditetima i istoriji pušenja. Uzimanje krvi za analizu i rendgensko snimanje grudnog koša rađeni su u roku od 24 sata od prijema u bolnicu, osim uzorkovanja d-dimera, koje je zbog organizacionih poteškoća urađeno u periodu od 72 sata od prijema. Lekar je procenjivao gojaznost tokom kliničkog pregleda.

Podaci o pacijentima su sadržali demografske karakteristike (pol, starost, mesto stanovanja), bihejvioralne rizike (gojaznost, pušački status), simptome i znake bolesti na prijemu (povišena temperatura, opšta slabost, kašalj i prisustvo sputuma, dijareja, hemoptiza, teškoće sa disanjem, mijalgija, vrtoglavica, sinkopa, gubitak svesti i trajanje bolesti od početka bolesti do prijema u bolnicu), rendgensi snimak grudnog koša i laboratorijske parametre (oksigena saturacija - sO_2, leukociti, limfociti, neutrofili, eritrociti i trombociti, hemoglobin, CRP, transaminaze u serumu - alanin i aspartat transaminase, ALT i AST, urea, kreatinin, bilirubin, laktat dehidrogenaza, LDH, d dimer), komorbiditete (hipertenzija, dijabetes, ishemijska bolest srca, vaskularna oboljenja, srčana insuficijencija, kardiomiopatija, hronični bronhitis, emfizem, astma, bubrežna insuficijencija, terapija zamene bubrežne funkcije – RRT tj. renalna dijaliza, prethodni moždani udar ili cerebralno krvarenje, demencija, Parkinsonova bolest, demijelinizirajuće bolesti nervnog sistema, maligne bolesti, epilepsija, autoimune bolesti, insuficijencija jetre, aritmije, sarkoidoza) i potreba za neinvazivnom ili invazivnom mehaničkom ventilacijom.

Da bi se identifikovali faktori povezani sa mehaničkom ventilacijom među pacijentima sa COVID-19 bolešću korišćena je logistička regresiona analiza. Izlazna varijabla bila je prijem u jedinicu intenzivnog lečenja koji je zahtevao neinvazivnu ili invazivnu mehaničku ventilaciju. Prediktorske varijable uključivale su demografske karakteristike, bihejvioralne rizike, simptome i znake bolesti na prijemu, laboratorijske parametre, radiološke nalaze grudnog koša i podatke o komorbiditetima. Varijable $p<0,10$, zasnovane na univarijantnoj logističkoj regresionoj analizi, uključene su u multivarijantnu logističku regresionu analizu. Efekat uree u serumu i vrednosti kreatinina procenjivani su u univarijantnoj i multivarijantnoj analizi samo kod ispitanika koji nisu bili zavisni od RRT.

Statistički paket za društvene nauke SPSS 20.0 korišćen je za obradu podataka.

detected in the Wuhan, China. The previously unknown corona virus SARS-CoV-2 was soon identified by molecular methods as a causative agent and the disease was named as Coronavirus disease 2019, abbreviated COVID-19. This was followed by rapid spread of SARS-CoV-2 in China and then worldwide. On March 11, 2020, the World Health Organization declared COVID-19 pandemic. This third coronavirus epidemic dominated with the number of patients and deaths and completely unmasked the global unpreparedness to fight the pandemic(1).As of 09.10.2024. COVID-19 has led to over 776 million diagnosed cases and more than seven million COVID-19 related deaths worldwide. On the same day 270,000 new cases were registered worldwide (2).

The clinical manifestations of COVID-19 infection are variable, ranging from mild symptoms to acute respiratory failure and multiorgan dysfunction. Majority of COVID-19 have signs of a mild respiratory infection, but disease is in fact a multisystem disorder and 14% of patients require treatment in intensive care unit (3, 4). A higher frequency of severe forms of the disease, and consequent hospitalization, has been observed in older people with comorbidities - dementia, type 2 diabetes, chronic obstructive pulmonary disease (COPD), pneumonia, depression, atrial fibrillation, hypertension (5). The most severe forms of the disease were treated in intensive care units, the elderly and diabetics, hypercholesterolemia, COPD were at higher risk of death (6).

Early identification of the risk factors for severe COVID-19 disease could be helpful in managing hospital admissions. In this research predictors of severe COVID19 disease were identified. The severe COVID-19 disease was defined as the need for assisted ventilation (non-invasive or invasive mechanical ventilation).

Methods

In this retrospective cohort study data were collected from electronic documentation at the General Hospital "Laza K. Lazarević" in Šabac, Serbia in period from 1.4.2020. to 15.11.2020. The analysis included allreverse transcriptasepolymerase chain reaction (RT–PCR) confirmed cases.

Case histories of COVID-19 patients were completed after the clinical examination. Patients provided information on the duration and symptoms of the disease, comorbidities, smoking history. Blood sampling and chest X-ray were performed within 24 hours of admission, except for the d-dimer sampling, which was performed within 72 hours of admission because of organizational difficulties. Obesity was assessed by the physician on clinical examination.

Patient data included demographic characteristics (sex, age, place of residence), behavioral risks (obesity, smoking status), symptoms and signs of the disease on admission (fever, generalized weakness, cough and sputum production, diarrhea, hemoptysis, breathing difficulty, musculoskeletal pain, dizziness, syncope, loss of consciousness and duration of illness from onset of disease to hospital admission), chest X-ray findings and laboratory parameters (oxygen saturation - sO_2, blood leukocytes, lymphocytes, neutrophils, erythrocyte and platelet count, hemoglobin, CRP, serum transaminases - alanine and aspartate transaminases, ALT and AST, urea, creatinine, bilirubin, lactate dehydrogenase - LDH, d dimer), comorbidities (hypertension, diabetes, ischemic heart disease, vascular disease, heart failure, cardiomyopathy, chronic bronchitis, emphysema, asthma, renal failure, renal replacement therapy – RRT or renal dialysis, previous stroke or cerebral hemorrhage, dementia, parkinsonism, demyelinating diseases of central nervous system, malignancy, epilepsy, autoimmune diseases, liver failure, arrhythmias, sarcoidosis) and demand for noninvasive or invasive mechanical ventilation.

Logistic regression analysis was performed to identify factors associated with mechanical ventilation among COVID-19 cases. The outcome variable was ICU admission requiring noninvasive or invasive mechanical ventilation. The predictor variables included demographic characteristics, behavioral risks, symptoms and signs of the disease on admission, laboratory parameters, chest X-ray findings and comorbidities data. Variables with $p \leq 0.10$, based on univariate logistical regression analysis were included in the multivariate logistic regression analysis. The effect of serum urea and creatinine levels in both univariate and multivariate analyses was assessed only in subjects who were not dependent on RRT.

The Statistical Package for Social Science, SPSS 20.0, was used in data processing.

Rezultati

U studiji je učestvovalo ukupno 516 pacijenata kod kojih je SARS-CoV-2 infekcija potvrđena uz pomoć RT-PCR testa. Srednja vrednost starosne dobi bila je 61 godina, dok je najveći procenat slučajeva bio kod osoba starih 60 i više godina (52,7%). Od ovih pacijenata, 334 su bili muškarci (64,7%), pretežno iz urbanih sredina (52,7%).

Najčešći simptomi su bili povišena telesna temperatura (89,0%) i opšta slabost (68,8%), samo 0,4% je imalo poremećaje svesti, a 1,4% hemoptizu. Srednja vrednost trajanja bolesti pre prijema u bolnicu bila je 7 dana. Radiološki nalazi bilateralne pneumonije bili su prisutni kod 313 pacijenata (65,6%). Najčešće prijavljivani komorbiditeti su bili hipertenzija (48,3%) i dijabetes (15,7%).

Od 516 hospitalizovanih pacijenata, bilo je 54 smrtna ishoda, dok je srednja vrednost starosne dobi iznosila 69,5 godina, a većina su bili muškarci (81,5%).

Mehanička ventilacija je bila neophodna kod 44 pacijenta (ukupno 27 intubiranih), a većina intubiranih pacijenata bili su muškarci (64,7%). Srednja vrednost trajanja bolesti od početka do prijema u jedinicu intenzivne nege (JIN) bila je 9 dana. Dominantni komorbiditeti u grupi pacijenata koji su bili na mehaničkoj ventilaciji bili su hipertenzija (63,3%) i dijabetes (22,7%). Ukupno 6 pacijenata je preživelo nakon neinvazivne ventilacije.

Univarijantna logistička regresiona analiza je pokazala da su pol, starost, gojaznost, istorija pušenja, visoka temperatura, kratak dah, trajanje bolesti pre prijema u bolnicu, sO_2, leukociti u krvi, limfociti, neutrofili, trombociti, urea, kreatinin, CRP, AST, LDH, hipertenzija, ishemijska bolest srca, periferna vaskularna bolest, bubrežna insuficijencija, RRT, epilepsija i aritmije značajni prediktori teških oblika COVID-19 bolesti, koji su uključeni u model multivarijantne logističke regresione analize (Tabele 1-3).

Rezultati multivarijantne logističke regresione analize su pokazali da je rizik od asistirane ventilacije značajno češći kod pacijenata koji su imali febrilnost na prijemu (p=0,016), duže trajanje bolesti pre hospitalizacije (p=0,023), sa oksigenom saturacijom <90% (p=0,002), leukocitozom (p=0,034), CRP>50 mg/l (p=0,002) i poremećajem srčanog ritma (p=0,001) (Tabela 4).

Diskusija

U ovoj studiji, prosečna starost pacijenata je bila slična starosti pacijenata u studijama sprovedenim u Lombardiji (63,9 godina) (7), Vuhanu (60 godina) (8) i Sjedinjenim Američkim Državama (61 i 63 godine) (9,10), ali niža u odnosu na studije sprovedene u Nemačkoj i Ujedinjenom Kraljevstvu (73 godine) (11,12). U svim navedenim studijama, učesnici su dominantno bili muškarci (50,9-70,7%).

Većina hospitalizovanih pacijenata imala je povišenu telesnu temperaturu, što je u skladu sa nalazima drugih studija, a to je bilo praćeno opštom slabošću (68,8%), i kašljem kao trećim najčešćim simptomom (66,7%). U većini drugih istraživanja kašalj je bio drugi najčešći simptom (8, 10-14), osim u studijama sprovedenim u Lombardiji i Mičigenu, u kojima je kašalj bio prvi simptom (77,8%) (7).

Kao i u drugim studijama, najčešći komorbiditeti su bili hipertenzija i dijabetes (8, 11-13). Hipertenzija i dijabetes tipa 2 su česti komorbiditeti u slučaju SARS i MERS infekcija, a ozbiljne forme bolesti se mogu povezati sa stanjem metaboličke inflamacije koja podstiče oslobađanje citokina u infekcijama (14,15).

Proporcija pacijenata koji su zahtevali intubaciju tokom hospitalizacije (5,2%) u Šapcu bila je niža nego za Sjedinjene Američke Države (12,2-15,3%) (9,10), Ujedinjeno Kraljevstvo (10%) (12) i Nemačku (14%) (11), a viša u poređenju sa podacima iz Kine (0,2-4,6%) (8,13) tokom 2020. godine. Takođe, uočene su razlike kada su u pitanju podaci o umiranju (ukupan mortalitet 10,5%; 86,4% kod pacijenata na mehaničkoj ventilaciji; 3,6% kod pacijenata bez asistirane ventilacije) u poređenju sa rezultatima studija iz SAD-a (ukupan mortalitet 21%; 81,1% za mehaničku ventilaciju) (10), Nemačke (16,6%; 33% za mehaničku ventilaciju) (11) i Kine (ukupan mortalitet 16,5%) (8), dok se podaci studija sprovedenih u Britaniji i Lombardiji ne mogu uporediti (nije bilo prijavljenih ishoda kod ovih pacijenata) (7,12). Ove razlike se mogu objasniti različitim kriterijumima za hospitalizaciju, preporukama za intubiranje pacijenata, kao i brojem dostupnih ležaja u jedinicama intenzivne nege i različitim nivoima opreme u JIN.

Starija životna dob i prateći komorbiditeti su prediktori teških ishoda kod većine virusnih infekcija (16). U studiji iz Nemačke, pacijenti stariji od 79 godina bili su u najvećem riziku od smrtnog

Results

A total of 516 patients with RT-PCR confirmed SARS-CoV-2 infection were enrolled. The median age of population was 61 years, and highest percent of cases were in people aged 60 and over (52.7%). Of these patients, 334 participants were male (64.7%), predominantly from urban areas (52.7%).

The most common symptoms were fever (89%) and generalized weakness (68.8%), only 0.4% had impaired consciousness and 1.4% had hemoptysis. The median duration of illness spreadmission was 7 days. X-ray findings of bilateral pneumonia were present in 313 patients (65.6%). The most commonly reported comorbidities were hypertension (48.3%) and diabetes (15.7%).

Of the 516 patients who were hospitalized 54 died, median age of deceased were 69.5 years and majority were male (81.5%).

Mechanical ventilation was required by 44 patients (a total of 27 was intubated), majority of patients were male (64.7%). The median duration of illness from onset to Intensive Care Unit (ICU) admission was 9 days. The dominant comorbidities in mechanically ventilated group were hypertension (63.6%) and diabetes (22.7%). In total 6 patients survived after non-invasive ventilation.

The univariate logistical regression analysis demonstrated that gender, age, obesity, smoking history, fever, shortness of breath, preadmission illness duration, sO_2, blood leukocytes, lymphocytes, neutrophils and platelets count, urea, creatinine, CRP, AST, LDH, hypertension, ischemic heart/peripheral vascular disease, renal failure, RRT, epilepsy and arrhythmias were significant predictor variables which were used for multivariate logistical regression analysis (Tables 1 -3).

The multivariate logistical regression analysis revealed that the risk for assisted ventilation was higher in patients who were febrile on admission (p=0.016), had longer preadmission illness duration (p=0.023), sO_2<90% (p=0.002), leukocytosis (p=0.034), CRP≥50 mg/l (p=0.002) and heart rhythm disorders (p=0.001) (Table 4).

Discussion

In this study median age of the patients was similar to the patients from the studies in Lombardy (63.9 years) (7), Wuhan (60 years) (8), USA (61 and 63 years) (9, 10) but lower than in German and UK studies (73 years) (11,12). In all mentioned researches participants were dominantly males (50.9-70.7%).

The majority of hospitalized patients had fever, which is consistent with findings of other studies, followed by generalized weakness (68.8%) while cough is the third (66.7%) and in most other researches the second most common symptom(8,10-14), except in the Lombard and Michigan studies where it was the first symptom (77.8%) (7).

As in other researches the most common comorbidities were hypertension and diabetes (8,11-13). Hypertension and type II diabetes are common comorbidities in both SARS and MERS infections and severe form of the disease may be related to a state of metabolic inflammation that potentiates the release of cytokines in infections (15).

The proportion of patients who required intubation during hospitalization (5.2%) in Šabac differed from US data (12.2-15.3%) (9, 10), UK (10%) (12) and Germany (14%)(11)but it was higher compared to China (0.2-4.6%) (8,13)during 2020. There were also differences in mortality (10.5%; 86.4% in patients with mechanical ventilation; 3.6% in patients without assisted ventilation) compared to results from the USA (21%; 81.1%for mechanical ventilation) (10), Germany (16.6%; 33% for mechanical ventilation)(11), China (total mortality 16.5%;) (8), while the data for the British and Lombard studies are not comparable (there were patients with no recorded outcome) (7,12). The differences could be explained with different hospitalization criteria, recommendations for intubation of patients as well as the number of ICU beds available and different ICU equipment levels.

Older age and underlying comorbidities are predictors of severe outcomes in most viral infections(16). In the German study patients older than 79 years were at highest risk of death but risk of mechanical ventilation was lower because of strict implementation of "do not intubate" recommendations (11).

Symptoms and signs of COVID-19 present on admission may predict a more severe course of the disease. The regression model showed that the odds of requiring noninvasive/invasive mechanical

Tabela 1. Demografske karakterteristike i prikaz simptoma kod pacijenata sa COVID-19

	Broj pacijenata		Neasistirana ventilacija		Asistirana ventilacija		
Varijabla	**n (516)**	**%**	**n (472)**	**%**	**n (44)**	**%**	**p**
Pol							
Muško	334	64,7	297	62,9	37	84,1	0,007
Žensko	182	35,3	175	37,1	7	15,9	
Starost (godine)							
<60	244	47,3	235	49,8	9	20,5	0,001
≥ 60	272	52,7	237	50,2	35	79,5	
Vrsta naselja							
Grad	272	52,7	250	53,0	22	50,0	0,706
Selo	244	47,3	222	47,0	22	50,0	
Gojaznost							
Da	125	24,2	108	22,9	17	38,6	0,022
Ne	391	75,8	364	77,1	27	61,4	
Istorija pušenja							
Pušač, bivši pušač	81	15,7	68	14,4	13	29,5	0,010
Nepušač	435	84,3	404	85,6	31	70,5	
Telesna temperatura (°C)							
≤ 38,5	351	68,0	331	70,1	20	45,5	0,001
> 38,5	165	32,0	141	29,9	24	54,5	
Opštaslabost							
Da	355	68,8	325	68,9	30	68,2	0,926
Ne	161	31,2	147	31,1	14	31,8	
Kašalj							
Da	344	66,7	317	67,2	27	6,4	0,436
Ne	172	33,3	155	32,8	17	3,6	
Prisustvo sputuma							
Da	65	12,6	57	12,1	8	18,2	0,247
Ne	451	87,4	415	87,9	36	81,8	
Hemoptiza							
Da	7	1,4	6	1,3	1	2,3	0,588
Ne	509	98,6	466	98,7	43	97,7	
Kratkoća daha							
Da	108	20,9	89	18,9	19	43,2	0,001
Ne	408	79,1	383	81,1	25	56,8	
Dijareja							
Da	94	18,2	86	18,2	8	18,2	0,995
Ne	422	81,8	386	81,8	36	81,8	
Mijalgija							
Da	173	33,5	162	34,3	11	25,0	0,213
Ne	343	66,5	310	65,7	33	75,0	
Sinkopa							
Da	16	3,1	13	2,8	3	6,8	0,151
Ne	500	96,9	459	97,2	41	93,2	
Trajanje bolesti (dani)							
≤ 7	211	40,9	202	42,8	9	20,5	0,006
> 7	305	59,1	270	57,2	35	79,5	
sO_2 (%)							
<90	80	15,5	55	11,7	25	5,8	0,001
≥90	436	84,5	417	88,3	19	43,2	

Table 1. Demographic characteristics and presenting symptomsof COVID-19 patients

	Number of patients		No assisted ventilation		Assisted ventilation		
Variable	**n (516)**	**%**	**n (472)**	**%**	**n (44)**	**%**	**p**
Gender							
Male	334	64.7	297	62.9	37	84.1	0.007
Female	182	35.3	175	37.1	7	15.9	
Age (years)							
<60	244	47.3	235	49.8	9	20.5	0.001
≥ 60	272	52.7	237	50.2	35	79.5	
Settlement type							
Urban	272	52.7	250	53.0	22	50.0	0.706
Rural	244	47.3	222	47.0	22	50.0	
Obesity							
Yes	125	24.2	108	22.9	17	38.6	0.022
No	391	75.8	364	77.1	27	61.4	
Smoking history							
Smoker, ex-smoker	81	15.7	68	14.4	13	29.5	0.010
Non-smoker	435	84.3	404	85.6	31	70.5	
Body temperature (°C)							
≤ 38,5	351	68.0	331	70.1	20	45.5	0.001
> 38,5	165	32.0	141	29.9	24	54.5	
Generalized weakness							
Yes	355	68.8	325	68.9	30	68.2	0.926
No	161	31.2	147	31.1	14	31.8	
Cough							
Yes	344	66.7	317	67.2	27	6.4	0.436
No	172	33.3	155	32.8	17	3.6	
Presence of sputum							
Yes	65	12.6	57	12.1	8	18.2	0.247
No	451	87.4	415	87.9	36	81.8	
Hemoptysis							
Yes	7	1.4	6	1.3	1	2.3	0.588
No	509	98.6	466	98.7	43	97.7	
Shortness of breath							
Yes	108	20.9	89	18.9	19	43.2	0.001
No	408	79.1	383	81.1	25	56.8	
Diarrhea							
Yes	94	18.2	86	18.2	8	18.2	0.995
No	422	81.8	386	81.8	36	81.8	
Myalgia							
Yes	173	33.5	162	34.3	11	25.0	0.213
No	343	66.5	310	65.7	33	75.0	
Syncope							
Yes	16	3.1	13	2.8	3	6.8	0.151
No	500	96.9	459	97.2	41	93.2	
Duration of illness (days)							
Yes	211	40.9	202	42.8	9	20.5	0.006
No	305	59.1	270	57.2	35	79.5	
sO_2 (%)							
Yes	80	15.5	55	11.7	25	5.8	0.001
No	436	84.5	417	88.3	19	43.2	

Tabela 2. Radiološki laboratorijski nalazi kod pacijenata sa COVID-19

	Broj pacijenata		Neasistirana ventilacija		Asistirana ventilacija		
Varijabla	**n**	**%**	**n**	**%**	**n**	**%**	**p**
Pneumonija	(473)		(430)		(43)		
Unilateralna	135	28,5	127	29,5	8	18,6	0,135
Bilateralna	338	71,5	303	70,5	35	8,4	
Pleuralni izliv	(473)		(430)		(43)		
Da	12	2,3	10	2,1	2	4,5	0,320
Ne	503	97,7	461	97,9	42	95,5	
Leukociti (10^9/l)	(516)		(472)		(44)		
≤ 9,7	456	88,4	425	90,0	31	70,5	0,001
> 9,7	60	11,6	47	10,0	13	29,5	
Limfociti (10^9/l)	(516)		(472)		(44)		
< 1,0	184	35,7	158	33,5	18	59,1	0,001
≥ 1,0	332	64,3	314	66,5	44	40,9	
Granulociti (10^9/l)	(516)		(472)		(44)		
≤ 6,5	428	82,9	402	85,2	26	59,1	0,001
>6,5	88	17,1	70	14,8	18	40,9	
Hemoglobin (g/l)	(516)		(472)		(44)		
< 100	25	4,8	21	4,4	4	9,1	0,180
≥ 100	491	95,2	451	95,6	40	90,9	
Trombociti (10^9/l)	(516)		(472)		(44)		
< 158	145	28,1	126	26,7	19	43,2	0,022
≥ 158	371	71,9	346	73,3	25	56,8	
CRP (mg/l)	(512)		(468)		(44)		
< 50,0	270	52,7	264	56,4	6	13,6	0,001
≥ 50,0	242	47,3	204	43,6	38	86,4	
ALT (U/l)	(460)		(420)		(40)		
≤ 55	344	74,8	314	74,8	30	75,0	0,974
> 55	116	25,2	106	25,2	10	25,0	
AST (U/l)	(459)		(419)		(40)		
≤ 34	189	41,2	181	43,2	8	20,0	0,006
> 34	270	58,8	238	56,8	32	80,0	
LDH (U/l)	(409)		(372)		(37)		
≤ 246	192	46,9	188	50,5	4	10,8	0,001
> 246	217	53,1	184	49,5	33	89,2	
Urea (mmol/l)	(507)		(464)		(43)		
≤ 8,2	425	87,4	401	89,7	24	61,5	0,001
> 8,2	61	12,6	46	10,3	15	38,5	
Kreatinin (umol/l)	(506)		(464)		(42)		
≤ 110,5	446	91,8	421	94,0	25	65,8	0,001
> 110,5	60	8,2	43	6,0	17	34,2	
D dimer (ug/ml)	(128)		(110)		(18)		
≤ 0,5	57	44,5	51	46,4	6	33,3	0,306
> 0,5	71	55,5	59	53,6	12	66,7	

p vrednost za χ^2 test

Table 2. Radiographic and laboratory findings of patients with COVID-19

	Number of patients		No assisted ventilation		Assisted ventilation		
Variable	**n**	**%**	**n**	**%**	**n**	**%**	**p**
Pneumonia	(473)		(430)		(43)		
Unilateral	135	28.5	127	29.5	8	18.6	0.135
Bilateral	338	71.5	303	70.5	35	8.4	
Pleuraln effusion	(473)		(430)		(43)		
Yes	12	2.3	10	2.1	2	4.5	0.320
No	503	97.7	461	97.9	42	95.5	
Leukocytes (10^9/l)	(516)		(472)		(44)		
≤ 9.7	456	88.4	425	90.0	31	70.5	0.001
> 9.7	60	11.6	47	10.0	13	29.5	
Lymphocytes (10^9/l)	(516)		(472)		(44)		
< 1.0	184	35.7	158	33.5	18	59.1	0.001
≥ 1.0	332	64.3	314	66.5	44	40.9	
Granulocytes (10^9/l)	(516)		(472)		(44)		
≤ 6.5	428	82.9	402	85.2	26	59.1	0.001
>6.5	88	17.1	70	14.8	18	40.9	
Hemoglobin (g/l)	(516)		(472)		(44)		
< 100	25	4.8	21	4.4	4	9.1	0.180
≥ 100	491	95.2	451	95.6	40	90.9	
Platelets (10^9/l)	(516)		(472)		(44)		
< 158	145	28.1	126	26.7	19	43.2	0.022
≥ 158	371	71.9	346	73.3	25	56.8	
CRP (mg/l)	(512)		(468)		(44)		
< 50.0	270	52.7	264	56.4	6	13.6	0.001
≥ 50.0	242	47.3	204	43.6	38	86.4	
ALT (U/l)	(460)		(420)		(40)		
≤ 55	344	74.8	314	74.8	30	75.0	0.974
> 55	116	25.2	106	25.2	10	25.0	
AST (U/l)	(459)		(419)		(40)		
≤ 34	189	41.2	181	43.2	8	20.0	0.006
> 34	270	58.8	238	56.8	32	80.0	
LDH (U/l)	(409)		(372)		(37)		
≤ 246	192	46.9	188	50.5	4	10.8	0.001
> 246	217	53.1	184	49.5	33	89.2	
Urea (mmol/l)	(507)		(464)		(43)		
≤ 8.2	425	87.4	401	89.7	24	61.5	0.001
> 8.2	61	12.6	46	10.3	15	38.5	
Creatinine (umol/l)	(506)		(464)		(42)		
≤ 110.5	446	91.8	421	94.0	25	65.8	0.001
> 110.5	60	8.2	43	6.0	17	34.2	
D dimer (ug/ml)	(128)		(110)		(18)		
≤ 0.5	57	44.5	51	46.4	6	33.3	0.306
> 0.5	71	55.5	59	53.6	12	66.7	

p value for χ^2 test

Tabela 3. Komorbiditeti pacijenata sa COVID-19

	Broj pacijenata		Neasistirana ventilacija		Asistirana ventilacija		
Varijabla	**n (516)**	**%**	**n (472)**	**%**	**n (44)**	**%**	**p**
Hipertenzija							
Da	249	48,3	221	46,8	28	63,6	
Ne	267	51,7	251	53,2	16	36,4	0,035
Šećerna bolest							
Da	81	15,7	71	15,0	10	22,7	
Ne	435	84,3	401	85,0	44	77,3	0,184
Ishemična srčana bolest							
Da	32	6,2	25	5,3	7	15,9	
Ne	484	93,8	447	94,7	37	84,1	0,008
Kardiomiopatija							
Da	16	3,1	14	3,0	2	4,5	
Ne	500	96,9	458	97,0	42	95,5	0,566
Hronični bronhitis							
Da	9	1,7	7	1,5	2	4,5	
Ne	507	98,3	465	98,5	42	95,5	0,159
Astma							
Da	39	7,6	37	7,8	2	4,5	
Ne	477	92,4	435	92,2	42	95,5	0,435
Bubrežna insuficijencija							
Da	29	5,6	22	4,7	7	15,9	
Ne	487	94,4	450	95,3	37	84,1	0,004
Dijaliza							
Da	21	4,1	17	3,6	4	9,1	
Ne	495	95,9	455	96,4	44	90,9	0,089
Cerebrovaskularna bolest							
Da	12	2,3	11	2,3	1	2,3	
Ne	504	97,7	461	97,7	43	97,7	0,981
Parkinsonova bolest							
Da	5	1,0	4	0,8	1	2,3	
Ne	511	99,0	468	99,2	43	97,7	0,375
Maligna oboljenja							
Da	23	4,5	22	4,7	1	2,3	
Ne	493	95,5	450	95,3	43	97,7	0,473
Epilepsija							
Da	2	0,4	1	0,2	1	2,3	
Ne	514	99,6	471	99,8	43	97,7	0,093
Aritmija							
Da	25	4,8	18	3,8	7	15,9	
Ne	491	95,2	454	96,2	37	84,1	0,001

p vrednost za χ^2 test

Table 3. Comorbidities of COVID-19 patients

	Number of patients		No assisted ventilation		Assisted ventilation		
Variable	**n (516)**	**%**	**n (472)**	**%**	**n (44)**	**%**	**p**
Hypertension							
Yes	249	48.3	221	46.8	28	63.6	
No	267	51.7	251	53.2	16	36.4	0.035
Diabetes							
Yes	81	15.7	71	15.0	10	22.7	
No	435	84.3	401	85.0	44	77.3	0.184
Ischemic heart disease							
Yes	32	6.2	25	5.3	7	15.9	
No	484	93.8	447	94.7	37	84.1	0.008
Cardiomyopathy							
Yes	16	3.1	14	3.0	2	4.5	
No	500	96.9	458	97.0	42	95.5	0.566
Chronic bronchitis							
Yes	9	1.7	7	1.5	2	4.5	
No	507	98.3	465	98.5	42	95.5	0.159
Asthma							
Yes	39	7.6	37	7.8	2	4.5	
No	477	92.4	435	92.2	42	95.5	0.435
Renal failure							
Yes	29	5.6	22	4.7	7	15.9	
No	487	94.4	450	95.3	37	84.1	0.004
Dialysis							
Yes	21	4.1	17	3.6	4	9.1	
No	495	95.9	455	96.4	44	90.9	0.089
Cerebrovascular disease							
Yes	12	2.3	11	2.3	1	2.3	
No	504	97.7	461	97.7	43	97.7	0.981
Parkinsonism							
Yes	5	1.0	4	0.8	1	2.3	
No	511	99.0	468	99.2	43	97.7	0.375
Malignancies							
Yes	23	4.5	22	4.7	1	2.3	
No	493	95.5	450	95.3	43	97.7	0.473
Epilepsy							
Yes	2	0.4	1	0.2	1	2.3	
No	514	99.6	471	99.8	43	97.7	0.093
Arrhythmia							
Yes	25	4.8	18	3.8	7	15.9	
No	491	95.2	454	96.2	37	84.1	0.001

p value for χ^2 test

Tabela 4. Faktori koji se odnose na potrebu za asistiranom ventilacijom prema rezultatima multivarijantne logističke regresione analize

Varijabla	RR	(95%IP)	p
Telesna temperatura >38,5°C	2,9	(1,2 – 7,1)	0,016
Trajanje bolesti >7 dana	3,1	(1,2– 8,3)	0,023
sO_2 <90%	4,0	(1,7 – 9,1)	0,002
Leukociti >9,7 10^9/l	2,9	(1,1 – 8,0)	0,034
CRP ≥ 50,0 mg/l	7,5	(2,1 – 26,9)	0,002
Aritmija	14,3	(3,6– 50,0)	0,001

RR-relativnirizik; IP-interval poverenja

ishoda, ali je rizik od mehaničke ventilacije bio manji zbog striktne primene preporuka da se ne intubiraju (11).

Simptomi i znaci COVID-19 bolesti na prijemu mogu predvideti teži tok bolesti. Regresioni model je pokazao da su šanse da će biti potrebna neinvazivna/invazivna mehanička ventilacija bile 2,9 puta veće za febrilne pacijente (telesna temperatura > 38,5°C). Podaci iz Nemačke (11) takođe ukazuju na vezu između povišene telesne temperature i potrebe za asistiranom mehaničkom ventilacijom, ali slična veza nije primećena u studijama iz Kine (8) ili Italije (7). Zanimljivo je da su u Nemačkoj ispitanici sa rinorejom bili pod većim rizikom od mehaničke ventilacije (11), što nije potvrđeno u istraživanju Imama i saradnika (9), dok u našoj studiji rinoreja nije registrovana kao simptom.

Naši nalazi sugerišu da je saturacija kiseonikom periferne krvi statistički visoko značajan prognostički parametar. Pacijenti koji su na prijemu imali sO_2<90% imali su značajnu veći rizik za upotrebu mehaničke ventilacije. Povezanost vrednosti sO_2 na prijemu i teških formi bolesti nije potvrđena u Vuhanu (8). Zanimljivo je da vrednosti parcijalnog pritiska kiseonika u krvi tokom hospitalizacije nisu imale prognostički značaj kod pacijenata u Italiji, dok je nizak odnos parcijalnog pritiska arterijskog kiseonika (engl. *Partial pressure of arterial oxygen*, PaO_2) i frakcije udahnutog kiseonika (engl. *Fractional inspired oxygen*, FiO_2) bio značajan indikator nastajanja akutne respiratorne insuficijencije prema definiciji akutnog respiratornog sindroma (7).

Pacijenti sa CRP > 50 mg/l su imali 7,5 puta veći rizik od mehaničke ventilacije, a rizik je takođe bio skoro utrostručen u prisustvu leukocitoze. Kod pacijenata u Kini, pored nivoa CRP, prediktori progresije u teške oblike COVID-19 bili su trombocitopenija i povišene transaminaze u serumu, ali nije bilo kontrole na konfaunding faktore (13). Značaj povišenih nivoa AST i trombocitopenije otkriven je u našem istraživanju u univarijantnoj logističkoj regresionoj analizi, ali nije potvrđen u modelu multivarijantne logističke regresione analize. U drugoj studiji iz Kine, u multivarijantnoj analizi, značajni prediktori su bili leukocitoza, povišeni nivoi LDH i d dimera > 1 mg/l (8). Povezanost nivoa d dimera i teških oblika COVID-19 je potvrđena u nekoliko istraživanja (17), ali naši rezultati nisu bili u skladu sa njihovim nalazima, što se može dovesti u vezu sa relativno malim brojem pacijenata sa dostupnim nalazom d dimera (128 pacijenata; 24,8%). Pored vrednosti CRP-a među ispitanicima u Lombardiji, značajan parametar za progresiju u teške forme bolesti bile su povišene vrednosti kreatinina u serumu (7).

Podaci iz više studija pokazuju da su odrasli sa teškim osnovnim zdravstvenim stanjima u većem riziku od bolesti i smrti usled teške forme COVID-19 bolesti (7,11,18). U našoj studiji, 34,3% pacijenata nije imalo pridružene bolesti, 35,9% je imalo jednu, 21,1% dve, 5,8% tri, 2,1% četiri, 0,4% pet, 0,2% (1 osoba) šest i 0,2% osam komorbiditeta. U multivarijantnoj analizi značajan prediktor mehaničke ventilacije je bio poremećaj srčanog ritma, što je u skladu sa rezultatima drugih studija (7,8,11). Među pacijentima u Lombardiji, prisustvo koronarne bolesti je identifikovan kao prediktor progresije SARS-CoV infekcije u teži oblik COVID-19 bolesti (7). Značaj kardiovaskularnih oboljenja i hroničnih bolesti donjeg respiratornog trakta za mehaničku ventilaciju potvrđen je u studiji sprovedenoj u Nemačkoj, u kojoj je dijabetes bio značajan prediktor mehaničke ventilacije (11) i kod pacijenata iz Vuhana hipertenzija je bila značajan faktor za razvoj invazivne ventilacije (8).

Table 4. Factors related to the requirement for the assisted ventilation according to the results of multivariate logistic regression analysis

Varijabla	HR	(95%IP)	p
Body temperature >38.5°C	2.9	(1.2 – 7.1)	0.016
Duration of illness >7 days	3.1	(1.2– 8.3)	0.023
sO_2 <90%	4.0	(1.7 – 9.1)	0.002
Leucocytes >9,7 10^9/l	2.9	(1.1 – 8.0)	0.034
CRP ≥ 50,0 mg/l	7.5	(2.1 – 26.9)	0.002
Arrhythmia	14.3	(3.6– 50.0)	0.001

HR-hazard ratio; CI-confidence interval

ventilation were 2.94 times higher for febrile patients (body temperature >38.5 °C). Data from Germany (11) also indicate an association between fever and the need for assisted ventilation, but a similar relationship was not observed in the Chinese (8) or Italian study (7). Interestingly, German subjects with rhinorrhea were at higher risk for mechanical ventilation (11), a fact that wasn't confirmed in Imam et al research (9) and in our subjects rhinorrhea wasn't registered as a symptom.

Our findings suggest that peripheral blood oxygen saturation a statistically highly significant prognostic parameter. Patients with admission sO_2<90% had a significantly higher risk of requiring assisted ventilation. The association of admission sO_2 and severe disease forms has not been confirmed in Wuhan (8). Interestingly the values of blood oxygen partial pressure during hospitalization had no prognostic significance in Italian patients and low PaO_2/ FiO_2 ratio was a significant indicator of emerging acute respiratory failure as per acute respiratory syndrome definition (7).

Patients with CRP≥50mg/l had 7.5 times higher risk for mechanical ventilation, the risk was also almost tripled in presence of leukocytosis. In patients in China, beside CRP levels, predictors of progression to severe COVID-19 forms were thrombocytopenia and elevated serum transaminases but there was no control of confounding factors (13). Significance of elevated AST levels and thrombocytopenia was detected in our research in univariate logistical regression analysis but wasn't confirmed in multivariate logistics. regression model. In another Chinese study in multivariate analysis, important predictors were leukocytosis, elevated LDH and d dimer levels > 1mg/l (8). Association of d dimer levels and severe forms of COVID-19 was confirmed in several researches (17) but our results were not consistent with their findings, fact that could be related with the relatively small number of patients with available d dimer result (128 patients; 24.8%). In addition to CRP in subjects in Lombardy, a significant parameter for progression to severe disease was serum creatinine (7).

Data from multiple studies indicate that adults with severe underlying health conditions are at higher risk for severe COVID-19-associated illness and death (7,11,18). In our research 34.3% patients had no associated diseases, 35.9% had one, 21.1% two, 5.8% three, 2.1% four, 0.4% five, 0, 2% (one person) six and 0.2% eight comorbidities. In the multivariate analysis of mechanical ventilation predictors, heart rhythm disorders were highly statistically significant risk factor, which is consistent with results of other studies (7,8,11). In patients in Lombardy, the presence of coronary heart disease was a predictor of progression to a more severe form of COVID-19 (7). The importance of cardiovascular diseases and chronic diseases of the lower respiratory tract for the mechanical ventilation was confirmed in a German study in which diabetes was an important predictor of mechanical ventilation (11)and in Wuhan patients in whom hypertension was associated with higher invasive ventilation risk (8).

Our research had some notable limitations. The number of cases requiring assisted ventilation was small (44 patients, 8.5%), the data were collected from single hospital in Serbia and may not represent the national population. Hospitalization criteria were variable and resource dependent.

Naše istraživanje je imalo neka značajna ograničenja. Broj slučajeva koji zahtevaju asistiranu ventilaciju je bio mali (44 pacijenta, 8,5%), podaci su prikupljeni iz jedne bolnice u Srbiji i ne odnose se na ukupno stanovništvo. Kriterijumi za hospitalizaciju su bili promenljivi i zavisili su od resursa.

Zaključak

Slučajevi COVID-19 sa temperaturom, dužim trajanjem bolesti pre prijema, sO_2<90%, leukocitozom, CRP≥50 mg/l i sa aritmijom imali su značajno veći rizik od razvoja teške forme bolesti, koja je zahtevala neinvazivnu/invazivnu mehaničku ventilaciju.

Konflikt interesa

Autori su izjavili da nema konflikta interesa.

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Conclusion

COVID-19 cases with fever, longer preadmission illness duration, sO_2<90%, leukocytosis, CRP≥50 mg/l and having arrhythmia had significantly higher risk of developing severe disease, which required non-invasive/invasive mechanical ventilation.

Competing interests

The author declared no competing interests.

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