

## DIJAGNOSTIČKI I TERAPIJSKI IZAZOVI U LEČENJU PACIJENATA TOKOM KOVID-19 EPIDEMIJE

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### SAŽETAK

**Uvod:** Početak decembra 2019. godine se smatra periodom početka infekcije novim korona virusom (engl. *Severe Acute Respiratory Syndrome Coronavirus 2* - SARS-CoV-2), u Vuhanu, u Kini, koja je stručnoj javnosti poznatija kao Kovid-19 (engl. *Coronavirus Disease 2019* - COVID-19).

**Prikaz slučaja:** Pacijent muškog pola, starosti 42 godine, upućen je na pregled zbog sumnje na Kovid-19. Prema rečima pacijenta, simptomi su počeli četiri dana ranije pojavom mučnine i kašlja, a potom otežanog disanja i povišene temperature. Tokom pregleda, pacijent je bio bled, otežanog disanja, subfebrilan, tahikardičan i normotenzivan. Radiološkim pregledom verifikovan je težak oblik Kovid-19 pneumonije. Laboratorijski parametri ukazivali su na infektivni sindrom i srčanu slabost. Prvog dana hospitalizacije došlo je do pogoršanja opšteg stanja: pojavom aritmije, potom respiratornog pogoršanja. Obezbeđena je terapijska potpora prema Kovid-19 protokolu. Drugog dana hospitalizacije pacijent je intubiran, sprovedena je trodnevna mehanička ventilatorna potpora, vazopresorna potpora hemodinamike, dvojnja stimulacija diureze, nakon koje dolazi do stabilizacije vitalnih parametara. Ponavljano *Polymerase Chain Reaction* (PCR) testiranje i testiranje iz bronho-alveolarnog lavata (BAL) bilo je negativno. Ponovljeni rendgenski snimak ukazao je na značajnu regresiju nalaza na plućima. Urađen je ultrazvučni pregled srca koji je ukazao na značajno redukovanu funkciju leve komore, u poređenju sa prethodnim pregledom. Konsultovan je kardiohirurg koji je potvrdio neophodnost operativnog lečenja valvularne mane na aortnoj i mitralnoj poziciji uz prethodnu sanaciju infekcije i kardiološku pripremu. Dva meseca nakon ove hospitalizacije, urađen je rekonstruktivni kardiohirurški zahvat.

**Zaključak:** Prikazom kliničkog toka bolesti, dijagnostičkog i terapijskog pristupa kod pacijenta sa kardiovaskularnim komorbiditetom hteli smo da ukažemo i na poteškoće u prepoznavanju kliničke slike i dijagnostikovanju Kovida-19.

**Cljučne reči:** Kovid-19, pneumonija, mehanička ventilacija, prikaz slučaja

### Uvod

Početak decembra 2019. godine se smatra periodom početka infekcije novim koronavirusom (engl. *Severe Acute Respiratory Syndrome Coronavirus 2* - SARS-CoV-2), u Vuhanu, u Kini, koja je stručnoj populaciji poznatija kao Kovid-19 (engl. *Coronavirus Disease 2019* - COVID-19) (1). Prema izveštaju Svetske zdravstvene organizacije (SZO) na dan 21.09.2020. od decembra 2019. godine do 21.09.2020. je u celom svetu, od Kovid-19 infekcije obolelo više od 31 milion ljudi, a preminulo 959.116 osoba, sa letalitetom od 3,1% (2). Prema dnevnom izveštaju Instituta

za javno zdravlje Republike Srbije „Dr Milan Jovanović Batut”, na dan 21.09.2020. godine, od početka epidemije u Republici Srbiji je od Kovid-19 obolelo 32.938 osoba, dok su 743 preminule od posledica infekcije, sa letalitetom od 2,3% (3).

### Prikaz slučaja

Pacijent muškog pola, starosti 42 godine, upućen je na pregled na Kliniku za infektivne i tropske bolesti Kliničkog centra Srbije (KCS) zbog sumnje na Kovid-19. Prema rečima pacijenta, simptomi su počeli četiri dana ranije pojavom mučnine i kašlja, potom otežanog

**CASE REPORT****DIAGNOSTIC AND THERAPEUTIC CHALLENGES IN THE TREATMENT OF PATIENTS DURING THE COVID-19 EPIDEMIC****Jelena Jovicic<sup>1</sup>, Natasa Petrovic<sup>1</sup>, Nikola Ladjevic<sup>2</sup>, Andjela Magdelinic<sup>3</sup>, Nebojsa Ladjevic<sup>1,4</sup>**<sup>1</sup> Department of Anaesthesiology, Urology Hospital, Clinical Center of Serbia, Belgrade, Serbia<sup>2</sup> Urology Hospital, Clinical Centre of Serbia, Belgrade, Serbia<sup>3</sup> Clinic for Gynecology and Obstetrics, Clinical Centre of Serbia, Belgrade, Serbia<sup>4</sup> Faculty of Medicine, University of Belgrade, Belgrade, Serbia**SUMMARY**

**Introduction:** The beginning of December 2019 is considered to be the beginning of infection with the new coronavirus (Severe Acute Respiratory Syndrome Coronavirus 2 - SARS-CoV-2), in Wuhan, China, better known among professionals as COVID-19 (Coronavirus Disease 2019 -COVID-19).

**Case report:** A 42-year-old male was referred for examination due to suspicion of COVID-19. According to the patient, the symptoms started four days ago with nausea and cough, heavy breathing, and fever. During the examination, the patient was pale, breathed with difficulty, subfebrile, tachycardic, normotensive. A severe form of COVID 19 pneumonia was verified by the radiological examination. Laboratory parameters indicated the infectious syndrome and heart failure. On the first day of hospitalization, the general condition worsened: with the appearance of arrhythmia, then respiratory deterioration. The therapeutic support was provided according to the COVID-19 protocol. On the second day of hospitalization, the patient was intubated, followed by three-day mechanical ventilatory support, vasopressor stimulation of hemodynamics, double stimulation of diuresis. All steps provided vital parameter stabilization. Repeated Polymerase Chain Reaction (PCR) testing and bronchoalveolar lavage (BAL) testing were negative. Repeated chest x-ray indicated the significant regression of findings. A heart ultrasound was performed, which indicated a significantly reduced function of the left ventricle in comparison to the previous examination. The patient had previous cardiac co-morbidities and the cardiac surgeon gave an opinion and confirmed the need for surgical correction of aortic and mitral valves disease with the previous treatment of the infection. Two months later, reconstructive cardiac surgery was performed.

**Conclusion:** By presenting the clinical course of the disease, diagnostic, and therapeutic approach in a patient with cardiovascular comorbidity, we wanted to point out the difficulties in recognizing the clinical picture and diagnosing COVID-19.

**Key words:** COVID-19, pneumonia, mechanic ventilatory support, case report

**Introduction**

The beginning of December 2019 is considered to be the beginning of the infection with the novel coronavirus (Severe Acute Respiratory Syndrome Coronavirus 2 - SARS-CoV-2,) in Wuhan, in China, which is known as COVID-19 among professionals (1). According to the report of the World Health Organization from December 2019 to September 21st, 2020 more than 31 million people were infected by the COVID-19, while 959.116 died, with the lethality of 3.1% (2). According to the daily

report of the Public Health Institute of Serbia "Dr Milan Jovanovic Batut" on September 21st, 2020, 32,938 people got infected with COVID-19 in the Republic of Serbia from the beginning of the epidemic, while 743 died of the consequences of this infection, with the lethality of 2.4% (3).

**A Case Report**

A 42 year old male patient was referred to the Clinic for Infectious and Tropical Diseases of the Clinical Centre of Serbia due to the suspicion of Covid-19. According to him, symptoms started

disanja i povišene temperature. Za to vreme, koristio je simptomatsku terapiju. Pacijent negira prisustvo alergija na lekove i ranije operativne zahvate. Navodi da zna za oštećenje jednog srčanog zaliska i da se nalazi na listi čekanja za kardiohirurški operativni zahvat. Kako navodi, zbog čestih ekstrasistola, redovno koristi tablete bisoprolola 2,5 mg. Strastveni je pušač 14 godina unazad. Socio-epidemiološka anamneza bila je uredna.

Uvidom u medicinsku dokumentaciju, na ultrazvučnom pregledu srca urađenom prethodne godine, uočene su značajno dilatirane leve srčane šupljine uredne kinetike (leva komora 7,9/4,3 cm; leva pretkomora 5,1 × 5,4 × 5,6 cm), uz očuvanu ejectionu frakciju (EF) leve komore od 75%, masivni prolaps zadnjeg mitralnog kuspisa i degenerativno izmenjenu aortnu valvulu. U dostavljenim laboratorijskim analizama krvi izdvaja se leukocitoza 16,3 hiljada leukocita (granična vrednost 10 hiljada) sa limfocitopenijom od 5,8% (granična vrednost 15%), C - reaktivnim proteinom (CRP) 75,8 mg/l (granična vrednost 0-3 mg/l), laktat-dehidrogenazom (LDH) 420 U/l (granična vrednost 85-227 U/l), d-dimerom 8,5 mg/l FEU (granična vrednost <0,5 mg/l FEU). Na radiografskom snimku pluća zapažaju se masivne mrljaste konfluentne konsolidacije obostrano, skoro zbrisanih ivičnih kontura srca, koje je značajno uvećano.

Kliničkim pregledom uočeno je da je pacijent astenične konstitucije, normalne uhranjenosti, blede prebojene kože, blago lividnih usana i akralnih završetaka, dispnoičan, tahikardičan (104 otkucaja/min), normotenzivan (krvni pritisak (TA) 110/56 mmHg), subfebrilan (37,4°C), saturacije arterijske krvi (SpO<sub>2</sub> 94%) na sobnom vazduhu, određeno pulsnom oksimetrijom. Auskultacijom je utvrđen difuzno oslabljen disajni šum i prisutvo sistolno-dijastolnog šuma nad celim prekordijumom.

Nakon razgovora sa pacijentom i obavljenog kliničkog pregleda, uzet je uzorak venske krvi za određivanje krvne slike, biohemisjskih i hemostatskih parametara, vrednosti CRP, troponina i feritina, prema protokolu. Takođe, uzet je i nazofaringealni bris (NFB) za PCR (engl. *Polomerase Chain Reaction*) dijagnostiku Kovid-19. Predložena je hospitalizacija pacijenta na kliničkom odeljenju uz protokolom propisanu

terapiju: ceftriakson 2 g × 2 intravenski (i.v.), hlorokin 500 mg × 2 oralno (p.o.), clexane 0,6 ml × 2 subkutano (s.c.), vitaminsku terapija i.v. (vitamin C 2 g, α-D3 2 mcg), kiseonična potpora 6 l/min.

Na urađenoj kompjuterizovanoj tomografiji (engl. *Computed Tomography* - CT) grudnog koša prvog dana hospitalizacije, u parenhimu pluća utvrđene su radiološke karakteristike specifične za uznapredovali stadijum Kovid-19 infekcije, dok se u desnoj pleuri uočava izliv 13 mm i perikardni izliv oko desnog srca od 12 mm. Nakon urađenog CT pregleda, verifikovan je paroksizam supraventrikularne tahikardije (PSVT) sa srčanom frekvencijom 180 otkucaja/min (engl. *Heart Rate* - HR). Srčani ritam konvertovan je intravenskom (i.v) primenom verapamila.

Odlučeno je se da se zbog radiografskog nalaza i ritmološke nestabilnosti pacijenta dalje lečenje nastavi u jedinici intenzivnog lečenja (JIL). Na prijemu u JIL pacijent je budan, komunikativan, dispnoičan i ortopnoičan, preznojen, blede prebojene kože, cijanotičnih akrosa, HR 110/min, TA 115/60 mmHg, SpO<sub>2</sub> 92% uz kiseoničnu potporu preko maske. Bez perifernih edema. Vene vrata nisu nabrekli. U postojeću terapiju uključen je furosemid i.v. 20 mg/12h, nastavljena je kiseonična potpora 5 l/min preko maske uz postignutu SpO<sub>2</sub> 92-98%. U arterijskim gasnim analizama (ABG), parcijalni pritisak kiseonika (pO<sub>2</sub>) 8,6 kPa, uz fiziološki pH, normokarbiju i zadovoljavajući metabolički status, ali blagu hiperlaktatemiju od 2,4. Rezultat PCR testiranja na Kovid-19 iz prijemne ambulante klinike bio je negativan. Odmah je ponovljen NFB. U laboratorijskim analizama i dalje je prisutna leukocitoza 16,8 hiljada (limfocitopenija 9,3%), LDH 480 U/l, fibrinogen 6,5 g/l (granična vrednost 1,8-3,5 g/l), d-dimer 8,1 mg/l FEU, troponin 18 ng/ml (granična vrednost 14 ng/ml), proBNP 1300 µg (granična vrednost <300 µg/ml), CRP 75,3 mg/l, interleukin 6 (Il-6) 50,0 pg/ml (granična vrednost 0-7 pg/ml). Ponovljena radiografija pluća ukazuje na prisustvo mrljastih konsolidacija obostrano, što klinički u komparaciji sa laboratorijskim nalazima ukazuje na infekciju koronavirusom (Slika 1). Konsultovan je kardiolog koji je predložio dvojni diuretsku terapiju (furosemid 20 mg/2 h i.v., spironolacton 50 mg/24h p.o.).

four days before with nausea and cough, and then heavy breathing and high temperature. During that time, he used the symptomatic therapy. He negated the existence of allergies to drugs and previous surgical procedures. He stated that he knew about the damage of one heart valve and that he was on the list and waited for the cardio surgical procedure. As he stated, due to frequent extrasystoles, he regularly used bisoprolol tablets 2.5 mg. He has been a passionate smoker for 14 years. Socio-epidemiological anamnesis was neat.

According to the medical documentation, the ultrasound heart examination from the previous year showed the significantly dilated left heart ventricle of neat kinetics (left ventricle 7.9/4.3 cm; left auricle 5.1 × 5.4 × 5.6 cm), with the preserved ejection fraction (EF) of the left ventricle of 75%, massive prolapse of the anterior mitral cusp and degeneratively changed aortic valve. In the laboratory blood findings, leukocytosis of 16.3 thousand leucocytes was found (cut-off 10 thousand) with lymphocytopenia of 5.8% (cut-off 15%), C-reactive protein (CRP) 75.8 mg/l (cut-off 0-3 mg/l), lactate dehydrogenase (LDH) 420 U/l (cut-off 85-227 U/l), d-dimer 8.5 mg/l FEU (cut-off <0.5 mg/l FEU). Massive stained confluent configurations were found on both sides of the lungs on the radiograph image, with almost erased edge contours of the heart, which was significantly enlarged.

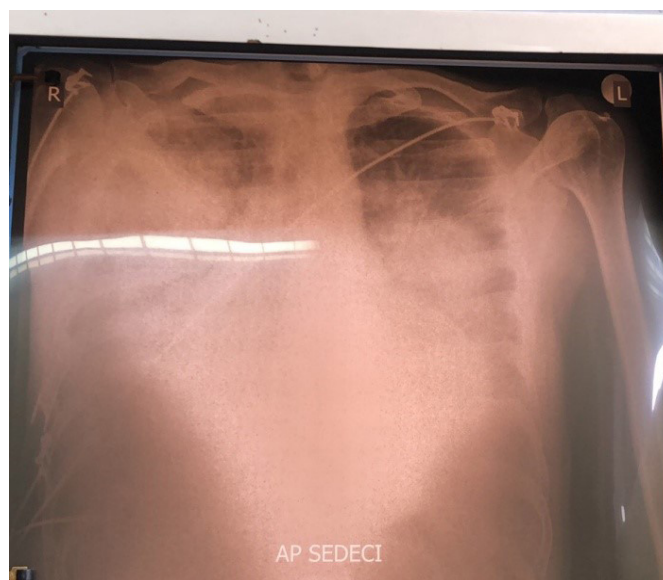
During the clinical examination it was noticed that the patient had an asthenic constitution, normal weight, his skin was pale, with mildly livid lips and acral endings, he was dyspnoic, tachycardic 104/min, normotensive 110/56 mmHg, subfebrile 37.4°C, with the saturation of arterial blood (SpO<sub>2</sub>) 94% at room temperature, determined by pulse oximetry. Diffusely decreased breath murmur and the presence of systolic-diastolic murmur over the whole precordium were determined by auscultation.

After clinical examination and conversation with the patient, the blood sample was taken from the venous blood in order to determine the biochemical and hemostatic parameters, CRP values, troponin, ferritin, according to the protocol. Also, the nasopharyngeal swab was taken for the PCR diagnostics of Covid-19. The

hospitalization of this patient was proposed at the clinic together with the therapy according to the protocol: ceftriaxone 2g × 2 intravenously (i.v., chloroquine 500 mg × 2 orally (p.o.), clexane 0.6 ml × 2 subcutaneously (s.c.), vitamin therapy iv (vitamin C 2 g, α-D3 2 mcg), oxygen support 6 l/min (O<sub>2</sub> support).

The computed tomography (CT) of the chest during the first day of hospitalization, radiological characteristics specific for the late stadium of Covid-19 infection were found in the lung parenchyma, while the right-sided pleural effusion of 13 mm was noticed, as well as the pericardial effusion of 12 mm around the right heart. After CT had been done, paroxysmal supraventricular tachycardia (PSVT) with the heart rate 180/min was verified. Heart rate was treated by the administration of verapamil iv.

The decision was made that the patient should be treated in the intensive care unit due to the radiographic findings and rhythmic instability of the patient. During the admission to the intensive care unit, the patient was awake, communicative, dyspnoic, orthopnoic, sweaty, pale, with acrocyanosis, HR 110/min, TA 115/60 mmHg, SpO<sub>2</sub> 92% with oxygen support with the help of a mask. He was without peripheral edema. The neck veins were not swollen. Furosemide i.v. 20 mg/12h was introduced into the existing therapy; he continued to get oxygen support 5 l/min with the help of a mask and SpO<sub>2</sub> was 92-98%. In arterial blood gas analyses (ABG), partial oxygen pressure (pO<sub>2</sub>) was 8.6 kPa, with physiological pH, normocarbica, and satisfying metabolic status, but mild hyperlactatemia 2.4. The result of PCR testing for Covid-19 from the infirmary was negative. NFS was immediately repeated. Leukocytosis 16.8 thousand (lymphocytopenia 9.3%), LDH 480 U/l, fibrinogen 6.5 g/l, d-dimer 8.1 mg/l FEU, troponin 18 ng/ml (cut-off 14 ng/ml) proBNP 1300 µg (cut-off < 300 µg/ml), CRP 75.3 mg/l, interleukin 6 (Il-6) 50.0 pg/ml (cut-off 0-7 pg/ml) were still present in the laboratory findings. The repeated lung radiography pointed to the presence of stained bilateral consolidations, which clinically in combination with laboratory findings pointed to the infection of coronavirus (Picture 1). We consulted a cardiologist who proposed a double diuretic therapy (furosemide 20 mg/12h iv, spironolactone 50 mg/24h p.o.).



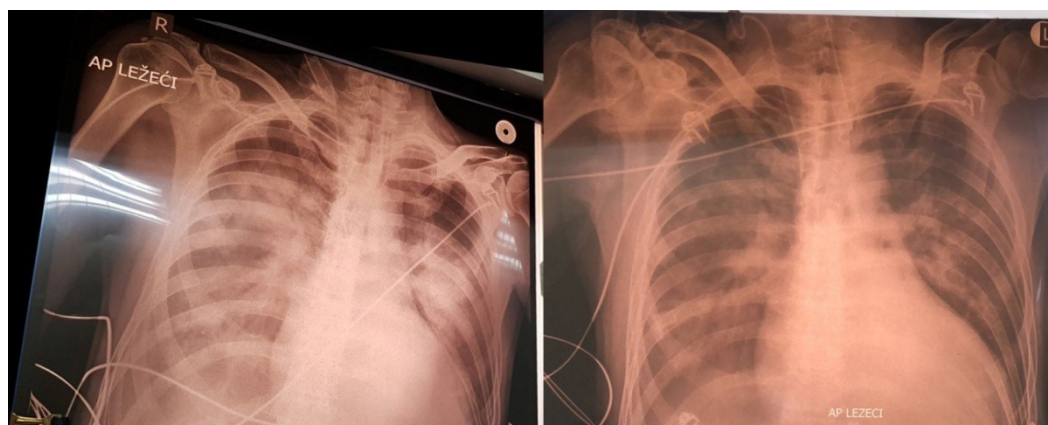
**Slika 1.** Radiografski snimak pluća na prijemu u jedinicu intenzivnog lečenja

Savetovao je da se dodatna kontrola srčanog ritma sprovodi amiodaronom i presololom uz tablete bisoprolola, uz praćenje dužine QT intervala. U načinjenom EKG zapisu u momentu kardiološkog pregleda, nije bilo poremećaja srčanog ritma, ali su viđeni znaci rane repolarizacije u dijafragmalnim odvodima.

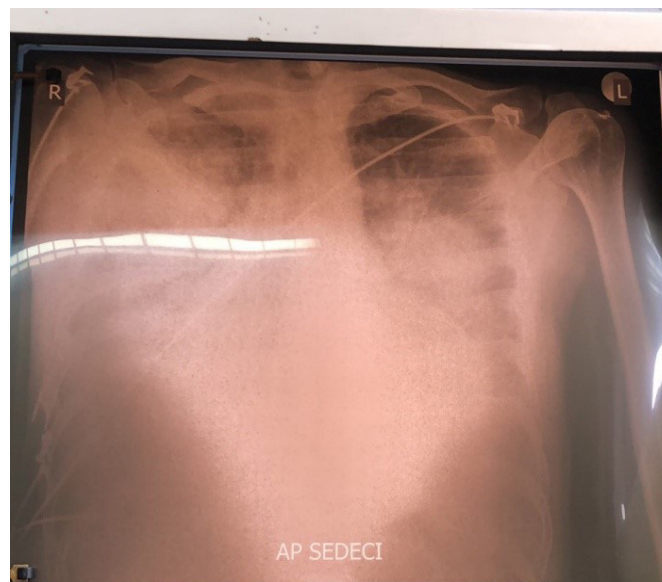
Narednog dana hospitalizacije, pacijent postaje izrazitije dispnoičan, povremeno uznemiren uz osećaj nedostatka vazduha,  $SpO_2$  85% uprkos kiseoničnoj potpori preko maske od 12 l/min, uz očuvanu stabilnost hemodinamike i srčanog ritma. Kiseonična potpora preko maske zamenjena je uređajem sa visokim protokom kiseonika, HFNC (engl. *High Flow Nasal Cannula*). Parametri na HFNC podešeni su na inspiratornu frakciju kiseonika ( $FiO_2$  60%), protok 40 l/min,

čime se  $SpO_2$  koriguje na 90-95%. Pristigao je rezultat ponovljenog PCR testiranja koji je opet negativan. U toku večernjih sati, ponovo PSVT 180/min, kupirana primenom verapamila i.v. Iz terapije je isključen hlorokin. Tokom noći, pacijent je bio respiratorno i kardiovaskularno stabilan.

Narednog dana, u jutranjim satima, pacijent je psihomotorno uznemiren, dezorijentisan, otežano kooperativan, hiposaturisan ( $SpO_2$  90%) uprkos intenzivnoj kiseoničnoj potpori, očuvanih hemodinamskih parametara. Odlučuje se da se kod pacijenta primeni neinvazivna ventilatorna potpora (NIMV): CPAP-PS mod ( $FiO_2$  60%, PEEP 5  $cmH_2O$ , PS 12  $cmH_2O$ ), sa *full face* maskom. Promenjeni režim potpore je poboljšao oksigenaciju, ali je pacijent kratkotrajno toleriše,



**Slika 2.** Radiografski snimak pluća tokom perioda primene invazivne ventilatorne potpore (levo - 4h nakon intubacije, desno - neposredno pre ekstubacije)



**Picture 1.** Radiographic image of lungs during admission at the intensive care unit

He advised controlling the cardiac rhythm additionally with amiodarone and presolol together with tablets of bisoprolol, and observation of length of QT intervals. The ECG recording during the cardiological examination did not show disorders of heart rhythm, but signs of early repolarization in diaphragm drains were noticed.

During the next day of hospitalization the patient became more dyspnoic, and at times anxious and lacking air,  $SpO_2$  85%, in spite of oxygen support using a mask of 12 l/min, with preserved stability of hemodynamics and heart rate. Oxygen support with the help of a mask was replaced by the high flow nasal cannula (HFNC). Parameters on the HFNC were adjusted for the fraction of inspired oxygen ( $FiO_2$  60%), the flow

40 l/min, by which  $SpO_2$  was 90-95%. The result of the repeated PCR testing was negative again. During evening hours, PSVT was 180/min and decreased by verapamil iv. Chloroquine was eliminated from the therapy. During the night, the patient's respiratory and cardiovascular state was stable.

The next day, in the morning hours, psychomotor agitation was present, he was disoriented, cooperated with difficulty, hyposaturated ( $SpO_2$  90%) in spite of intensive oxygen support, with preserved hemodynamic parameters. The decision was made to administer the non-invasive ventilatory support: CPAP-PS mod ( $FiO_2$  60%, PEEP 5  $cmH_2O$ , PS 12  $cmH_2O$ ) with the full face mask. The changed regime of support improved oxygenation, but the patient tolerated



**Picture 2.** Radiographic image of lungs during the period of application of invasive ventilatory support (left – 4h after intubation, right – immediately before extubation)

zbog čega je odlučeno da se pacijent intubira. U nastavku, za potrebe intubacije, pacijent je sediran midazolamom 10 mg i.v., propofolom 50 mg i.v., esmeronom 80 mg (1 mg/kg) i.v., intubiran, nakon čega je obezbeđena mehanička ventilatorna potpora - MVP (*BiLevel mod*: FiO<sub>2</sub> 50%, *Flow* 5 cm H<sub>2</sub>O, *Phigh* 15 cmH<sub>2</sub>O, RR 12/min, I:E- 1:2). Plasiran je centralni venski kateter preko desne jugularne vene, arterijska kanila preko *a. radialis dex.* i obezbeđeno invazivno merenje arterijskog krvnog pritiska. Naknadno je obezbeđena kontinuirana sedacija midazolamom (0,1 mg/kg/h i.v.) i vazopresorna potpora cirkulacije noradrenalinom (0,03 mcg/kg/min i.v.) uz postojeću dvojni diuretsku terapiju. Plasirana je nazogastrična sonda zbog ishrane i primene oralne terapije. Urađene ABG ukazuju na dobru gasnu razmenu i uredan metabolički status (pH 7,42/ pO<sub>2</sub> 10,2 kPa/ pCO<sub>2</sub> 5,3kPa/ sO<sub>2</sub> 95%/ HCO<sub>3</sub> 22,3/ BEecf-1,2/ Lac 1,4). Urađena je radiografija pluća četiri sata nakon intubacije (Slika 2, levo) koja ukazuje na

značajno manju konsolidaciju sa desne strane uz održavanje konsolidacije sa leve strane u srednjem plućnom polju, u poređenju sa grafijom od prethodnog dana. Pacijent je i dalje subfebrilan (37,3°C), te zamenjena antibiotska terapija: isključen ceftriakson, uključen cefepim 1 g/12h i.v., levofloxacin 500 mg/24h i.v., fluconazol 400 mg/24h. Kako je NFB dvostruko negativan, odlučuje se da se NFB ponovi za Kovid-19 i uzorkuje bronho-alveolarni lavat (BAL) i uradi PCR testiranje na proširenu paletu respiratornih virusa i Kovid-19, koji bi mogli dati sliku intersticijalne pneumonije i akutnog respiratornog distres sindroma (engl. *Acute Respiratory Distress Syndrome* - ARDS). Uzeti su uzorci krvi za hemokulturu (iz plasiranog centralnog venskog katetera i iz periferne vene) i uzorak urina za urinokulturu.

Narednog dana, pacijent je i dalje kontinuirano sediran midazolamom, na poziv otvara oči i izvršava jednostavne naloge. Intubiran, na MVP (CPAP-PS: FiO<sub>2</sub> 50%, PEEP

**Tabela 1.** Paleta mogućih prouzrokovača respiratornog distresa (rezultat)

<b>Vrsta uzorka:</b> <b>Nazofaringealni bris</b>	<b>Lab. broj protokola:</b> <b>XXXX</b>	<b>Uzorkovan: 20.04.2020.</b> <b>Primljen: 20.04.2020. 01:08</b>
Napomena	PCR respiratorni panel:	
Adenovirus	Nije detektovana DNK	
Coronavirus 229E	Nije detektovana RNK	
Coronavirus HKU1	Nije detektovana RNK	
Coronavirus NL63	Nije detektovana RNK	
Coronavirus OC43	Nije detektovana RNK	
Coronavirus (MERS-CoV)	Nije detektovana RNK	
Metapneumovirus-humani	Nije detektovana RNK	
Rhinovirus-humani/Enterovirus	Nije detektovana RNK	
Influenza A	Nije detektovana RNK	
Influenza B	Nije detektovana RNK	
Parainfluenza virus 1	Nije detektovana RNK	
Parainfluenza virus 2	Nije detektovana RNK	
Parainfluenza virus 3	Nije detektovana RNK	
Parainfluenza virus 4	Nije detektovana RNK	
Parainfluenza virus 1	Nije detektovana RNK	
Resiratorni sincicijalni virus	Nije detektovana RNK	
Bordatella pertussis	Nije detektovana DNK	
Bordatella parapertussis	Nije detektovana DNK	
Chlamydomphila pneumoniae	Nije detektovana DNK	
Mycoplasma pneumoniae	Nije detektovana DNK	

it for a short time, and therefore, the decision was made to intubate him. For the needs of intubation, the patient was sedated with midazolam 10 mg i.v., propofol 50 mg i.v., Esmeron 80 mg (1 mg/kg), intubated, and then mechanical ventilatory support was provided – MVS (BiLevel mod: FiO<sub>2</sub> 50%, P<sub>low</sub> 5 cmH<sub>2</sub>O, RR 12/min, I:E-1:2). The central venous catheter was placed via the right jugular vein, arterial cannula via *a. radialis. dex.* and invasive measuring of arterial blood pressure was provided. Continuous sedation with midazolam was provided (0.1 mg/kg/h i.v.) as well as vasopressor support of circulation with noradrenaline (0.03 mcg/kg/min i.v.) with the existing double diuretic therapy. A nasogastric tube was placed for oral therapy and food. ABG pointed to the good gas exchange and neat metabolic status (pH 7.42/pO<sub>2</sub> 10.2kPa/pCO<sub>2</sub> 5.3kPa/sO<sub>2</sub> 95%/HCO<sub>3</sub> 22.3/BE<sub>ecf</sub>-1.2/Lac 1.4). The lung radiography was done 4 hours after the intubation (Picture 2, on the left), which pointed to the significantly

decreased consolidation on the right side with the consolidation on the left side in the mid-lung, in comparison to radiography from the previous day. The patient was still subfebrile (37.3°C), and therefore antibiotic therapy was changed: ceftriaxone was not administered, and cefepime was introduced 1 g/12h i.v., levofloxacin 500 mg/24h i.v., fluconazole 400 mg/24h. As NFS was negative two times, the decision was made to take the NFS for Covid-19 again and to take a sample for broncho-alveolar lavage (BAL) and do the PCR test for the expanded range of respiratory viruses and Covid-19, as well, which would give a picture of interstitial pneumonia and acute respiratory distress syndrome. Blood samples were taken for hemoculture (from the placed central venous catheter and from the peripheral vein) and the sample of urine for urine culture.

The next day, the patient was continuously sedated by midazolam, he opened eyes when he was asked to and reacted to simple orders.

**Table 1.** A list of possible causes of respiratory distress (result)

Type of sample: Nasopharyngeal swab	Laboratory protocol number: XXXX	Sampled: 20.04.2020. Received: 20.04.2020. 01:08
Note	PCR respiratory panel:	
Adenovirus	No DNA was detected	
Coronavirus 229E	No RNA was detected	
Coronavirus HKU1	No RNA was detected	
Coronavirus NL63	No RNA was detected	
Coronavirus OC43	No RNA was detected	
Coronavirus (MERS-CoV)	No RNA was detected	
Human metapneumovirus	No RNA was detected	
Rhinovirus-human/Enterovirus	No RNA was detected	
Influenza A	No RNA was detected	
Influenza B	No RNA was detected	
Parainfluenza virus 1	No RNA was detected	
Parainfluenza virus 2	No RNA was detected	
Parainfluenza virus 3	No RNA was detected	
Parainfluenza virus 4	No RNA was detected	
Parainfluenza virus 1	No RNA was detected	
Respiratory syncytial virus	No RNA was detected	
Bordatella pertussis	No DNA was detected	
Bordatella parapertussis	No DNA was detected	
Chlamydomphila pneumoniae	No DNA was detected	
Mycoplasma pneumoniae	No DNA was detected	



5, PS 10), uredne gasne razmene i metaboličkog statusa, afebrilan. Hemodinamika je održavana minimalnom dozom noradrenalina (0,01 mcg/kg/min), a diureza je stimulirana dvojnomo diuretskom terapijom u istoj dozi. Srčana frekvencija održavana je tabletama bisoprolola. Doza cleksana kontrolisana je merenjem vrednosti anti Xa (0,45-0,62). Laboratorijski, blaga leukocitoza bez odstupanja u leukocitarnoj formuli (leukociti 10,2 hiljade), CRP 5,6 mg/l, Il-6 15,8 pg/ml, LDH 260 U/l, troponin 11 ng/ml, proBNP 980 µg. Tokom večeri, isključena je sedacija midazolamom.

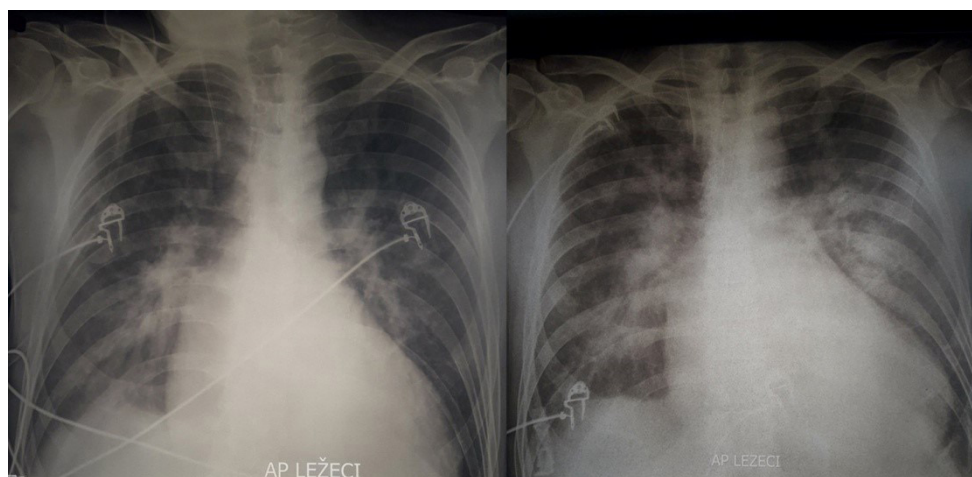
Narednog jutra, ponovljena je radiografija pluća (Slika 2, desno) i kako je nalaz u značajnoj regresiji, a pacijent u potpunosti kooperativan, laboratorijski parametri korektni, uz minimalnu vazopresornu potporu dobro kontrolisana hemodinamika, odlučuje se da se pacijent ekstubira. Nakon ekstubacije, uklonjena je nazogastrična sonda, obezbeđena je kiseonična potpora kiseoničnom maskom (protok 12 l/min), zadržana je vazopresorna potpora cirkulacije i sva prethodna terapija u već postojećim dozama.

Narednog dana, pristigao je rezultat PCR testiranja koji je bio negativan na sve ispitivane viruse (Slika 3). Takođe, sterilni su bili i uzorci za hemokulturu i urinokulturu. Ponovljena grafija pluća koja je opisana da je bez bitnijih promena u odnosu na prethodnu (Slika 4, levo). Urađen je ultrazvučni pregled srca koji je u odnosu na prethodni ukazao na značajno redukovanu funkciju leve komore, sa EF 35% uz hipokontraktinost svih zidova

leve komore. Konsultovan je kardiohirurg koji je potvrdio neophodnost operativnog lečenja valvularne mane na aortnoj i mitralnoj poziciji, uz prethodnu sanaciju infekcije i kardiološku pripremu. U trenutku pregleda, pacijent je bez indikacija za hitnim operativnim kardiohirurškim lečenjem. Isključena je vazopresorna potpora noradrenalinom, ostala terapija sprovedena je kao prethodnog dana. Kako je pacijent eupnoičan, aktivan u postelji, urednih parametra iz ABG, postepeno je redukovana kiseonična potpora (maska, 6 l/min). Svi parametri zapaljenskog sindroma bili su u referentnom opsegu.

Narednog dana (9. dana lečenja u JIL), odlučeno je da pacijent nastavi lečenje na Odeljenju kardiologije za lečenje srčane insuficijencije KCS. Neposredno pre otpusta iz JIL, urađen je kontrolni RTG snimak pluća koji je opisan kao stacionaran (Slika 4, desno). Na otpustu, pacijent je eupnoičan, na kiseoničnoj potpori preko maske, SpO<sub>2</sub> 98%, hemodinamksi i ritmološki stabilan, afebrilan i bez perifernih otoka.

Nakon jednomesečne kardiološke pripreme i optimizacije kadiovaskularnog statusa, započete su pripreme za kardiohiruršku proceduru. Serološki test na SARS-CoV-2 bio je negativan, kao i ostale mikrobiološke pretrage. Koronarografija nije ukazala na postojanje koronarne bolesti. Dva meseca nakon hospitalizacije na Infektivnoj klinici KCS pacijent je preveden na kardiohirurgiju gde je urađen rekonstruktivni kardiohirurški zahvat (zamena oštećenog zaliska veštačkim na mitralnoj i



**Slika 3.** Radiografski snimak pluća posle ekstubacije (levo) i na otpustu sa lečenja (desno)

He was intubated, on MVS (CPAP-PS: FiO<sub>2</sub> 50%, PEEP 5, PS 10), with regular gas exchange and metabolic status, afebrile. Hemodynamics was regulated by the minimal dose of noradrenaline (0.01 mcg/kg/min), while diuresis was stimulated by double diuretic therapy in the same dose. Heart rate was maintained by tablets of bisoprolol. The dose of clexane was controlled by the measurement of anti-Xa values (0.45-0.62). Laboratory findings showed mild leukocytosis without deviations in leukocyte formula (leukocyte 10.2 thousand), CRP 5.6 mg/l, Il-6 15.8 pg/ml, LDH 260 U/l, troponin 11 ng/ml, proBNP 980 µg. During the evening, sedation with midazolam was stopped.

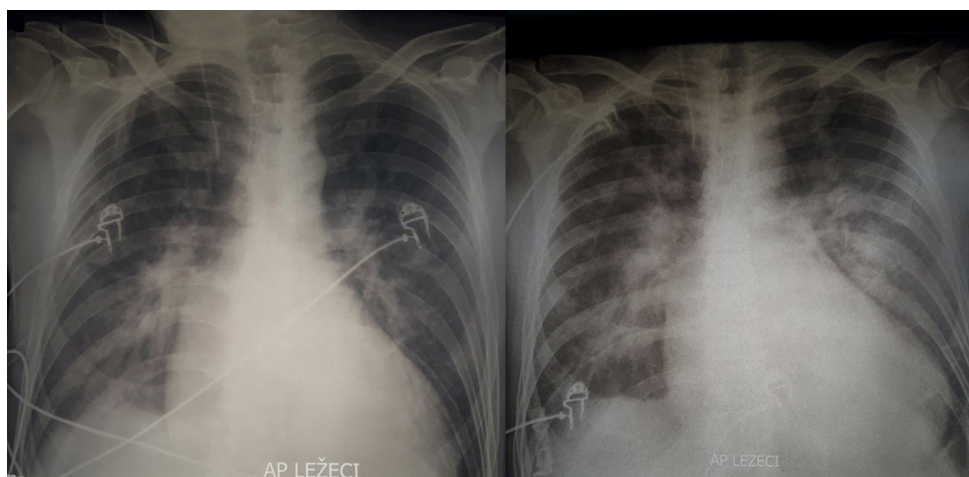
The next morning, chest radiography was done (Picture 2, on the right) and since the findings showed significant regression and the patient was completely cooperative, laboratory findings were correct, hemodynamics controlled with minimal vasopressor support, the decision was made to extubate the patient. After the extubation, the nasogastric tube was removed and oxygen support was provided via the oxygen mask (flow 12 l/min), vasopressor support of circulation was kept and all the previous therapy in the current doses. The next day, the PCR testing result was negative for all the examined viruses (Picture 3). Also, samples for hemoculture and urine culture were sterile.

The repeated lung radiography was without significant changes in comparison to the previous one (Picture 4, on the left). The ultrasound examination of the heart pointed

to the significantly reduced function of the left ventricle, with EF 35% with hypercontractility of all walls of the left ventricle. The cardiac surgeon confirmed that it was necessary to treat surgically the valvular defect on the aortic and mitral position with the previous curing of infection and cardiac surgery preparation. During the examination, there were no indications for urgent cardiac surgery. The vasopressor support with noradrenaline was canceled, while the therapy was the same as the previous day. As the patient was eupneic, active in bed, with regular parameters from ABG, the oxygen support was gradually reduced (mask 6 l/min). All parameters of the inflammatory syndrome were within the reference range.

The next day (9th day at the intensive care unit), the decision was made that the patient should be treated at the Department for Cardiology for the treatment of cardiac insufficiency at the Clinical Centre of Serbia. Before he was discharged from the intensive care unit, the control lung radiography was described as stationary (Picture 4, on the right). At the moment of discharge from the hospital, the patient was eupneic, on the oxygen support via a mask, SpO<sub>2</sub> 98%, with stable hemodynamics and rhythm, afebrile, without peripheral edema.

After the cardiac surgery preparation that lasted one month and the organization of cardiovascular status, the preparations for the cardiac surgical procedure were made. The serology testing for SARS-CoV-2 was negative, as well as other microbiological findings.



**Picture 3.** Radiographic image of lungs after extubation (left) and during discharge from the hospital (right)

aortnoj poziciji). Celokupan perioperativni period je protekao bez komplikacija. Mesec dana nakon izvršenog operativnog zahvata, redovna ultrazvučna kontrola ukazuje na EF 35% i dobro funkcionalne veštačke zaliske na mitralnoj i aortnoj poziciji.

### Diskusija

Komorbiditet predstavlja nezavistan faktor rizika za razvoj teške kliničke slike Kovida-19 (4). Kako navode Jordan i saradnici (5), najčešći i najzastupljeniji zajednički faktori rizika su starost, pol, gojaznost, dijabetes melitus, hipertenzija, bolest kardiovaskularnog sistema i hronična bolest pluća (astma i hronični opstruktivni bronhitis). Liang navodi da nije dokazana jasna korelacija između postojanja maligniteta i težine kliničke slike Kovid-19 oboljenja (6). Međutim, Livingston i saradnici ukazuju da značajno mesto imaju faktori rizika kao što su muški pol i pušenje cigareta (7). U studiji koju su ovi autori sprovedeli među italijanskom populacijom, navodi se da pušenje cigareta posledično utiče na obolevanje kardiovaskularnog i respiratornog sistema, potom i na značajno veću mogućnost formiranja teške kliničke slike bolesti. Isti autori navode da je korelacija komorbiditeta i težine kliničke slike Kovid-19 uslovljena i ažurnošću zdravstvenog sistema jedne države i njenih građana da blagovremeno registruju komorbiditete, kako bi se preciznije moglo zaključivati o komorbiditet - klinička slika intereakciji u momentu transmisije virusa.

U opisanom prikazu slučaja, pacijent je imao vrlo ozbiljne faktore rizika za razvoj teškog oblika Kovid-19: muški pol, pušenje cigareta i kardiovaskularni komorbiditet u fazi akutizacije. Međutim, srčana insuficijencija koja je nastupila u fazi epidemije novog korona virusa je najpre posledica prisustva dugogodišnjih valvularnih mana, strukturnih i funkcionalnih promena na miokardu. Intereakcija između Kovida-19 i komorbiditeta je dvosmerna. Kako navode Clerkin i saradnici (8), princip ulaska SARS-CoV- 2 u organizam je vezivanje serinproteaze 2 virusa za receptor angiotenzin-konvertujućeg enzima 2 (ACE2) čoveka. Ekspresija ACE2 je najveća u plućima (tip 2 alveolarnih ćelija), u vaskularnom endotelu, bubrezima, gastrointestinalnom sistemu i u srcu. Što je

veća aktivnost ACE2, to je veća transmisija virusa u organizmu i teža klinička slika. Opisani mehanizam za nastanak bolesti se dešava u stanjima kod kojih postoji pojačana aktivnost ACE2, odnosno povećana aktivnost renin-angiotenzin sistema: ateroskleroza, hipertenzija (naročito kod upotrebe ACE inhibitora zbog ushodne regulacije broja receptora za ACE2), srčana insuficijencija.

Kako navode Shi i saradnici (9,10), u nekoliko studija sprovedenih na velikom uzorku pacijenata, dokazan je uticaj infekcije koronavirusom na kardiovaskularni sistem: direktno oštećenje miokarda, akutni koronarni sindrom, aritmije, arterijski i venski tromboembolizam. Prikazani pacijent je bolovao od srčane insuficijencije sa očuvanom EF, na šta ukazuje ultrazvučni pregled urađen 2019. godine kada je zabeležena EF leve komore 75% uz značajnu dilataciju levih srčanih šupljina. Pacijent nije koristio lekove iz grupe ACE inhibitora u hroničnoj terapiji srčane insuficijencije. Međutim, značajno povišena vrednost proBNP uz vrednosti troponina u referentnom opsegu ukazuje na izostanak akutnog koronarnog sindroma, ali na prisutnu slabost leve komore.

Od samog početka hospitalizacije pacijenta razmatrana je mogućnost pogoršanja srčane funkcije sa ili bez prisustva virusa, zbog čega je urađen CT pregled grudnog koša koji je jasno ukazao na razvijeni oblik Kovid-19 pneumonije. Pravilnim i blagovremenim uzorkovanjem nismo uspeli da dokažemo prisustvo korona virusa (ponavljano PCR testiranje, BAL uzorkovanje) niti prisustvo nekog drugog infektivnog agensa u uzorku urina i krvi, iako laboratorijski parametri ukazuju na postojanje infektivnog procesa (leukocitoza uz tipičnu leukocitarnu formulu, povišen CRP i Il-6, subfebrilnost). Tan i saradnici navode jasnu korelaciju između CT nalaza i vrednosti CRP u stratifikovanju kliničke slike Kovid-19 (11). Isti autori navode nedovoljno dobru korelaciju između CT nalaza i vrednosti limfocita, ističući veliku dijagnostičku senzitivnost CT pregleda. Kako navode Stojadinović i saradnici (12), prema preporukama ekspertskeg panela Naučnog odbora časopisa *Radiology* (13), smatra se da je senzitivnost CT pregleda grudnog koša za dijagnozu Kovid-19 pneumonije 80-90%,

Coronarography did not point to the existence of a coronary disease. Two months after the hospitalization at the Clinic for Infectious Diseases of the Clinical Centre of Serbia, the patient was moved to cardiac surgery, where the reconstructive cardiac surgical procedure was done (replacement of the damaged heart valve with the artificial one on the mitral and aortic position). The whole perioperative period passed without complications. One month after the surgical procedure, regular ultrasound check-up showed that EF was 35% and that artificial valves on mitral and aortic positions functioned well.

## Discussion

Comorbidity presents an independent risk factor for the development of a severe clinical picture of Covid-19 (4). According to Jordan and associates (5), the most frequent and most common risk factors are age, gender, obesity, diabetes mellitus, hypertension, diseases of the cardiovascular system, and chronic lung diseases (asthma and chronic obstructive bronchitis). Liang states that the clear correlation between the existence of malignancy and the severity of the clinical picture of Covid-19 has not been proved (6). However, Livingston and associates state that significant risk factors are male gender and smoking cigarettes (7). In the study conducted by these authors in the Italian population, they state how smoking consequently induces cardiovascular and respiratory diseases, and then the possibility of severe forms of the disease. The same authors state that the correlation of comorbidities and the severity of clinical picture of Covid-19 is conditioned by the agility of the health care system of one state and its citizens to register the comorbidities on time so that conclusions could be made on the comorbidities, that is, the interaction between the comorbidities and clinical picture at the moment of virus transmission.

In the described case report, the patient had very pronounced risk factors for the development of severe forms of Covid-19: male gender, smoking and cardiovascular comorbidity in the acute phase. However, cardiac insufficiency, which appeared during the epidemic of the novel coronavirus, is the consequence of valve

deficiencies of many years, structural and functional changes of the myocardium. The interaction between Covid-19 and comorbidities is a two-way relationship. As Clerkin and associates (8) state, the principle of entry of SARS-CoV-2 into the organism is the binding of serin-protease 2 virus to the receptor of the angiotensin-converting enzyme 2 (ACE2). The expression of ACE2 is greatest in the lungs (type 2 alveolar cells), in the vascular endothelium, kidneys, gastrointestinal system, and heart. When the activity of ACE2 is greater, the virus transmission in the organism is bigger and the clinical picture is more severe. The described mechanism for the appearance of this disease happens when the activity of ACE2 increases, that is, the activity of the rennin-angiotensin system: atherosclerosis, hypertension (especially when ACE inhibitors are used due to the rising regulation of the number of receptors for ACE2), cardiac insufficiency.

According to Shi (9,10), in a few studies conducted on a large sample of patients, the influence of novel coronavirus on the cardiovascular system has been proven: direct damage of myocardium, acute coronary syndrome, arrhythmias, arterial and venous thromboembolism. The patient, who we presented, suffered from cardiac insufficiency with the preserved EF, to which the ultrasound examination from December 2019 pointed, when EF of the left ventricle was 75% with significant dilatation of left heart cavities. The patient did not use drugs from the group of ACE inhibitors in the chronic therapy of cardiac insufficiency. However, a significantly increased level of proBNP in addition to troponin values in the reference range pointed to the absence of acute coronary syndrome, but to the present weakness of the left ventricle.

From the very beginning of the patient's hospitalization, the possibility of worsening of the cardiac function was considered with or without the virus, and therefore CT of the chest was done and it pointed clearly to the developed form of Covid-19 pneumonia. Timely and correct sampling did not prove the presence of coronavirus (repeated PCR testing, BAL sampling) or some other infectious agents in the blood and urine samples, although laboratory parameters pointed to the presence

a specifičnost 60-70%. Oni preporučuju CT pregled u situacijama ukada treba doneti odluku o daljem lečenju ili kada je neophodno razlikovanje Kovid-19 pneumonije od pneumonije druge etiologije.

I dalje ostaje nejasno zašto nismo uspeli da dobijemo pozitivan PCR test za ovog bolesnika iako smo uzorak uzeli i iz BAL-a, a celokupna klinička slika i laboratorijski parametri su govorili u prilog postojanja korona virus infekcije i posledičnog srčanog popuštanja. Ovaj prikaz pokazuje svu komplikovanost u lečenju i dijagnostici pacijenata sa potencijalnom Kovid-19 infekcijom, a posebno kod pacijenata sa pratećim oboljenjima.

### Zaključak

Prikazom kliničkog toka bolesti, dijagnostičkog i terapijskog pristupa kod pacijenta sa kardiovaskularnim komorbiditetom hteli smo da ukažemo i na poteškoće u prepoznavanju kliničke slike i dijagnostikovanju Kovid-19. Ovaj prikaz slučaja sugerise na neophodnu organizacionu i dijagnostičku stratifikaciju pacijenata sa komorbiditetima koji se manifestuju kliničkom i laboratorijskom slikom koja je slična Kovidu-19. Kako bismo smanjili rizik da pacijent sa pogoršanjem hronične bolesti bude dodatno životno ugrožen, neophodno je pacijente sa komorbiditetima primarno hospitalno lečiti na formiranim odeljenjima za izolaciju u okviru ne-kovid bolnica.

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of infectious process (leukocytosis for the typical leukocyte formula, increased CRP and Il-6, subfebrile state). Tan and associates state the clear correlation between CT findings and CRP values in the stratification of the clinical picture of Covid-19 infection (11). The same authors state that the correlation between CT findings and lymphocyte values is not sufficient, emphasizing the great diagnostic sensitivity of CT findings. As Stojadinovic and associates state (12), according to the recommendations of the panel of experts from the scientific board of Radiology journal (13), the sensitivity of CT chest examination for the diagnosis of Covid-19 pneumonia is considered to be 80-90%, while specificity is 60-70%. They recommend the CT examination in situations, in which it will influence the decision on further treatment, as well as when it is necessary to differentiate Covid-19 pneumonia from pneumonia of different etiology.

It is still not clear why we did not get the positive PCR test for this patient although we took the sample from the BAL as well, and the whole clinical picture and laboratory findings spoke in favor of coronavirus infection and resulting cardiac insufficiency. This report presents all the complexities in relation to the treatment and diagnostics of patients with potential Covid-19, and especially in patients with comorbidities.

## Conclusion

The aim of this presentation of the clinical course of this disease, diagnostic and therapeutic approach in the patient with cardiovascular comorbidities was to point to the difficulties in recognizing the clinical picture in Covid-19 diagnostics. This case report suggests that the organizational and diagnostic stratification of patients with comorbidities, which are manifested as clinical and laboratory picture similar to Covid-19, is necessary. In order to diminish the risk that is additionally life-threatening to patients with the worsening of chronic diseases, it is necessary to treat patients with comorbidities primarily at hospitals within specially created departments for isolation in non-Covid hospitals.

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