

Odbor za kardiovaskularnu patologiju Srpske akademije nauka i umetnosti<sup>1</sup>  
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## SARS-CoV-2 → COVID-19

### ULOGA I DOPRINOS PATOLOGA U ISTRAŽIVANJU ETIO-PATOGENEZE I PATO-MORFOLOŠKOG SUPSTRATA BOLESTI (OBDUKCIJA, HISTOPATOLOGIJA I ELEKTRONSKA MIKROSKOPIJA)

(X interaktivni edukativni kviz)

## SARS-CoV-2 → COVID-19

### THE ROLE AND CONTRIBUTION OF PATHOLOGISTS IN THE RESEARCH OF ETIO-PATHOGENESIS AND PATHO-MORPHOLOGICAL SUBSTRATE OF DISEASE (AUTOPSY, HISTO-PATHOLOGY AND ELECTRON MICROSCOPY)

(X interactive educational quiz)

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Pitanja su označena brojevima i odvojeno su napisana od odgovarajućih odgovora (označenih istim brojevima) kako bi čitaoci mogli sami sebi da testiraju znanje.

*The questions are numbered and written separately from the corresponding answers (marked with the same numbers) so that readers can test their knowledge on their own.*

## PITANJA: QUESTIONS:

1. Kakva je to grupa virusa “Viridae Corona” koja deluje i na ljudsku vrstu?

*What is the group of viruses “Viridae Corona” that affects also the human species?*

2. Kakvo je poreklo SARS-CoV-2 prema stavu kineskih naučnika iz Wuhan-a?

*What is the origin of the SARS-CoV-2 according to Chinese scientists from Wuhan?*

3. Koji virusolog je otkrio virus HIV i za to dobio Nobelovu nagradu i šta on misli o poreklu virusa SARS-CoV-2?

*Which virologist discovered the HIV virus and won the Nobel Prize for that 2008, and what he thinks about the origin of the SARS-CoV-2?*

4. Šta o poreklu SARS-CoV-2 misli ostala relevantna naučna zajednica?

*What does the rest of the relevant scientific community think about the origin of SARS-CoV-2?*

5. Na koji način SARS-CoV-2 ulazi u ljudsku ćeliju?

*How does SARS-CoV-2 enter the human cell?*

6. Koji su početni simptomi COVID-19?

*What are the initial symptoms of COVID-19?*

7. Kako se dalje razvija COVID-19 i koji organi su pogođeni?  
*How does COVID-19 develop further and which organs are affected?*

8. Kakva je uloga i doprinos patologa (obdukcija + histopatologija + elektronska mikroskopija) u istraživanju etiopatogeneze i morfoloških lezija kod COVID-19?

*What is the role and contribution of pathologists (autopsy + histo-pathology + electron microscopy) in the investigation of the etio-pathogenesis and morphological lesions of COVID-19?*

9. Kakvi su makroskopski (obdukcijski) i mikroskopski (histopatologija + elektronska mikroskopija) nalazi na plućima kod COVID-19?

*What are macroscopic (autopsy) and microscopic (histo-pathology + electron microscopy) found on the lungs in COVID - 19?*

10. Kako kod COVID-19 dolazi do blokade oksigenacije krvi u plućima, sa sledejućom hipoksijom, tj. nedostatkom kiseonika za sve ćelije organizma?

*How does in COVID-19 the blockage of blood oxygenation in the lungs occur; with the following hypoxia, ie. lack of oxygen for all cells in the body?*

11. Kakve su lezije kardiovaskularnog sistema kod COVID-19?  
*What are the lesions of the cardiovascular system in COVID-19?*

12. Koje su najteže i najvažnije patološke lezije kod COVID-19?

*Which are the most dangerous and important pathological lesions in COVID-19?*

13. Kakav je društveno-psihološki odgovor čovečanstva na COVID-19 (pozitivni i negativni stavovi)?

*What is the social - psychological response of humanity to COVID-19 (positive and negative attitudes)?*

14. Ko je među prvima u Kini upozorio na epidemiju COVID-19, izdržao zbog toga policijske pritiske, umro od COVID-19 i bio posthumno rehabilitovan?

*Who was among the first in China to warn of the COVID-19 epidemic, withstand police pressure because of it, died of COVID-19 and, was posthumously rehabilitated?*

15. Kako bi se čuvena rečenica Marka Miljanova o junaštvu i čojstvu u Srbiji i Srpskoj mogla primeniti na zdravstvene radnike i građane u dosadašnjoj borbi protiv COVID-19?

*How would the famous sentence Marko Miljanov's about heroism and chivarily could be applied in Serbia and the Republic of Srpska to health workers and citizens in the struggle so far the fight against COVID-19?*

## ODGOVORI: ANSWERS:

**1. Grupa virusa „Viridae Corona“<sup>1-5</sup>** (Sl. 1,2) poznata je od 1965. Dobila je ime „Corona“ zbog svojih šiljaka na površini koji podsećaju na krunu (lat. Corona). Od ove grupe virusa, sedam napada i ljude i to: 229E; NL63; OC43; HKU1, koji izazivaju blage zapaljenjske smetnje gornjih respiratornih puteva – nalez i SARS-CoV; MERS-CoV i SARS-CoV-2, koji izazivaju težak akutni respiratorni sindrom (SARS = Severe Acute Respiratory Syndrome) i mogu dovesti do letalnog ishoda. Svi postoje kod slepih miševa sa koji su prešli, preko životinja posrednika na ljude (Sl.3). Radi se o RNK virusima, koji ne mogu da se „pritaje“ u organizmu kao DNK virusi. Genomi su im pročitani, utvrđeni i poznati. Genom SARS-CoV-2 su kineski naučnici iz Wuhan-a odmah obznanili, pokazali i publikovali za svetsku naučnu javnost.

**SARS-CoV** (Svere Acute Respiratory Syndrome–SARS), pojavio se 2002. u Kini (provincija Guangdong) i proširio se na tridesetak zemalja. Obolelo je 8000 ljudi. Epidemije su suzbijene i nestao je 2004. Kod 20% zaraženih dovodi do teškog zapaljenja pluća sa progresivnom respiratornom insuficijencijom. Smrtnost je bila 12% a kod starijih 50%.

Nosilac virusa je slepi miš, koji se preko kineske civet mačke ili svinje, preneo na čoveka.

**MERS-CoV** (Middle East Respiratory Syndrome), pojavio se 2013. u Saudijskoj Arabiji. Smrtnost je bila 30%. Nosilac virusa je slepi miš i preko kamile preneo se na čoveka.

Prenosivost na čoveka je mala, tako da sada tek poneko od ovog virusa oboli.

**SARS-CoV-2** u svom genomu ima i delove genoma SARS-CoV i MERS-CoV. On izaziva bolest **COVID-19** (Sl.4), koja je počela 2019. u Wuhan-u (Kina) i rasprostranila se po celom svetu, tako da je Svetska zdravstvena organizacija (WHO) proglasila pandemiju 11. marta 2020. Postoje vironoše; blagi i teški oblici, sa razvojem difuznog alveolarnog oštećenja (**Diffuse Alveolar Damage = DAD**). Bolest je blaža od prethodne dve, ali je zaraznost daleko veća – pandemijska (ali, ipak, manja nego kod virusa malih boginja). U Kini je smrtnost bila 0,2% u populaciji do 40 godina ali 15% za 80-godišnjake. Ukupna stopa umiranja bila je 2,8 za muškarce i 1,7 za žene. Što se smrtnosti, dakle, tiče sezonski grip je ubojitiji od COVID-19.

*The group of viruses “Viridae Corona”<sup>1-5</sup> (Fig. 1,2) has been known since 1965. It was named “Corona” because of its spikes on the surface that resemble a crown (Latin: Corona). Of this group of viruses, seven attacks humans: 229E; NL63; OC43; HKU1, which cause mild inflammatory disorders of the upper respiratory tract - common colds and SARS-*

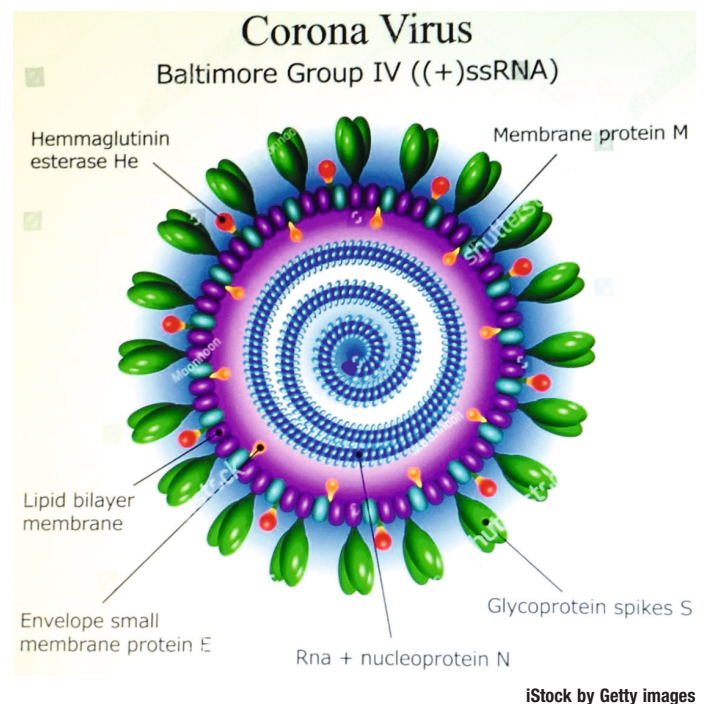
*CoV; MERS-CoV and SARS-CoV-2, which cause Severe Acute Respiratory Syndrome-SARS and can be fatal. They all exist in bat from which they through different animals passed on to humans (Fig. 3). These are RNA viruses, which cannot “hide” in the body like DNA viruses. Their genomes have been read, identified and known. The SARS-CoV-2 genome was immediately announced and published to the world scientific community by Chinese scientists from Wuhan.*

**SARS-CoV**, appeared in 2002 in China (Guangdong Province) and expanded to about thirty countries. 8000 people became ill. The epidemics were suppressed and disappeared in 2004. In 20% of those infected, it leads to severe pneumonia with progressive respiratory insufficiency with a mortality rate of 12%, and in the elderly 50%. The carrier of the virus is a bat, which was transmitted to humans through a Chinese cat or pig.

**MERS-CoV** (Middle East Respiratory Syndrome), appeared in 2013 in Saudi Arabia.

Mortality was 30%. The carrier of the virus is a bat and it was transmitted to humans through a camel. Human transmission is small, so now only there are a few persons with this illness.

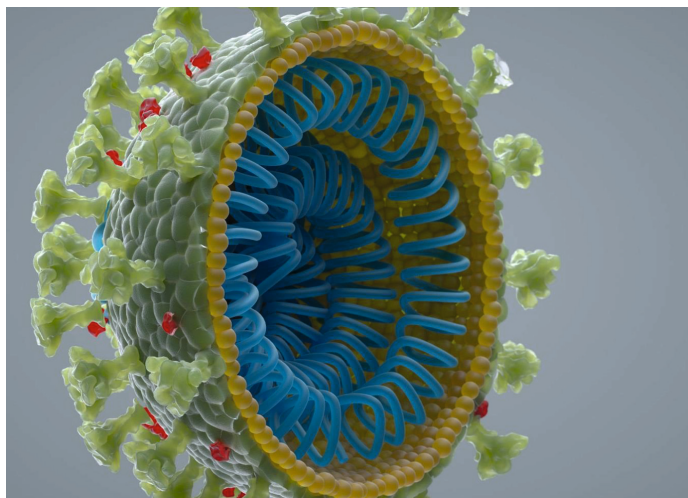
**SARS-CoV-2** also has parts of SARS-CoV and MERS-CoV genome in its genome. It causes the disease **COVID-19** (Fig. 4), which started in 2019 in Wuhan (China) and spread all over the world, so that the World Health Organization (WHO) declared a pandemic on March 11, 2020. There are people who only carry the virus; mild and severe cases, with the development of **Diffuse Alveolar Damage (DAD)**. The disease is milder than the previous two, but the contagion is much higher - pandemic (but no such contagious as the virus of morbilli). In China, the mortality rate was 0.2% in the under-40 population but 15% for 80-year-olds. The overall mortality rate was 2.8 for men and 1.7 for women. In terms of mortality, then, seasonal flu is more deadly than COVID-19.



Sl./Fig. 1. SARS-CoV-2

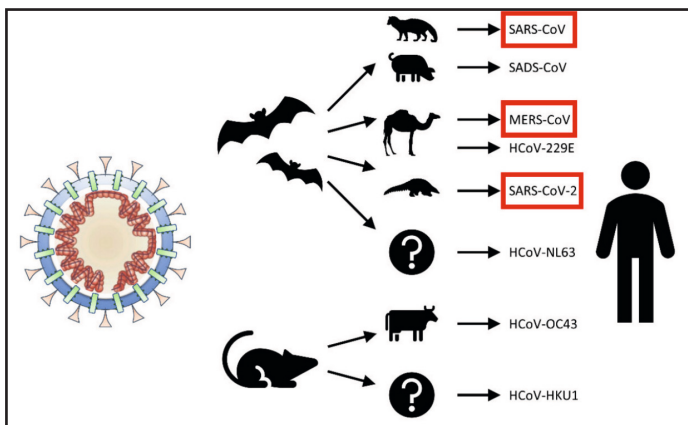
iStock by Getty images





Bryner J. Live Science 2020. Author of fig.: A.Onufryenco. Getty images

Sl./Fig. 2. Omotač SARS-CoV-2 koji čuva lanac RNK. The SARS-CoV-2 envelope that guards the RNA chain.

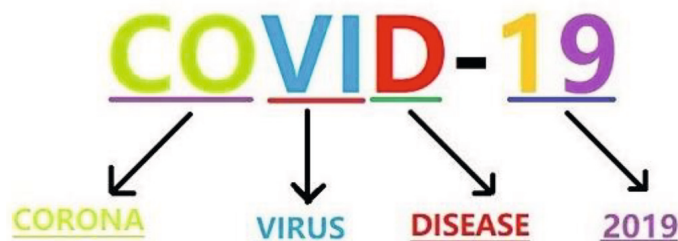


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Sl./Fig. 3. Životinjsko poreklo ljudskih koronavirusa<sup>6,7</sup>. SARS-CoV i MERS-CoV preneseni su ljudima sa slepih miševa preko kineskih civet mačaka, svinja i dvogrbne kamile. SARS-CoV-2 verovatno se 2019. preneo na ljude od slepog miša putem pangolina, koji se ilegalno prodaju na kineskim pijacama.

*Animal origins of human coronaviruses<sup>6-7</sup>. SARS-CoV and MERS-CoV were transmitted to humans from bats by civet cats, pig, and dromedary camels. The SARS-CoV-2 was likely transmitted to humans 2019 from bats through pangolins that are illegally sold in Chinese markets.*

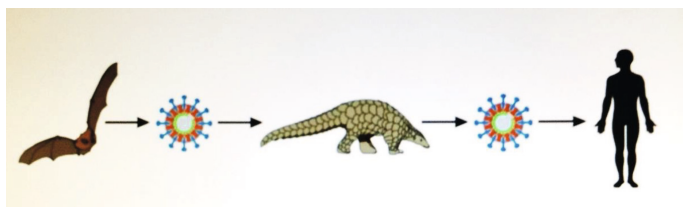
Domaće životinje (pas i druge) pokazuju malu susceptibilnost prema SARS-CoV-2, ali je velika kod feretke (priprtomljeni afrički tvor) i mačke. Mačke se mogu i eksperimentalno kapljicama zaraziti virusom. Domestic animals (dogs and others) have little susceptibility to the virus SARS-CoV-2 but it is great in ferrets, and cats. Cats can also be infected experimentally with a droplet viral infection.



Sl/ Fig. 4. Bolest uzrokovana SARS-CoV-2, koja se pojavila u Vuhanu (Kina) 2019. godine. Disease caused by SARS-CoV-2, which appeared in Wuhan (China) in 2019.

## 2 Kineski naučnici iz Vuhana smatraju da je SARS-CoV-2 nastao prirodnom selekcijom (a ne u laboratoriji) i da je od slepih miševa preko pangolina prenet na čoveka (Sl./Fig.5-8).

Chinese scientists from Wuhan believe that SARS-CoV-2 was created by natural selection (not in the laboratory) and that it was transmitted to humans from bats via pangolins.



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Sl./Fig. 5. Zaraženi slepi miš SARS-CoV-2, preneo je ovaj virus pangolinu, a ovaj čoveku na Pijaci za hranu, uključujući morske plodove i žive divlje životinje u Vuhanu.

*An infected bat with the SARS-CoV-2 transmitted this virus to pangolin and this one to a man in the Wholefood market including seafood and live wild animals in Wuhan.*



Alamy Stock Photo. The Guardian 2020.

Sl./Fig. 6. Slep miš (*Rhinolophus affinis*) je jedini sisar koji leti i zahvaljujući svom „ultrazvuku“ ne sudara se sa preprekama. Kinezi jedu supu od njega.

*The bat (Rhinolophus affinis) is the only mammal that flies and thanks to its “ultrasound” it does not collides with obstacles. The Chinese eat soup from it.*



(Image: © Shutterstock)

Sl./Fig. 7. Slep miševi izlaze noću iz pećina, love insekte i piju krv najčešće domaćim životinjama. Pokazuju veliku međusobnu solidarnost! Ako neko nije našao da se napije krvi, drugi slepi miš mu povрати deo svoje popijene krvi u usta (a ovaj mu u sličnoj situaciji vraća „pozajmicu“)<sup>7</sup>. Bats come out of caves at night, hunting insects and drink the blood of domestic animals. They show great mutual solidarity! If someone didn't find blood to drink, another bat, by vomiting, give some blood in his mouth (and this one returns “loan” to him in a similar situation)<sup>7</sup>.



Google 2020.

**Sl./Fig. 8.** Malajski pangolin (*Manis javanica*) je sisar, mravojed sa dugom njuškom, koji se ilegalno prodaje u Kini (i na wuhanskoj pijaci) za potrebe tradicionalne kineske medicine.

*The Malayan pangolin (*Manis javanica*) is a mammal, an ant-eater, with a long snout, which is sold illegally in China (also at Wuhan Market) for needs of traditional Chinese medicine.*

**3.** Otkrio virus HIV-a i za to dobio 2008. Nobelovu nagradu. Za poreklo SARS-CoV-2 tvrdi da je napravljen u laboratoriji. Naime, u njegovoj RNK postoji segment genoma virusa HIV-a. Neko je to uradio u laboratoriji nastojeći da napravi vakcinu protiv HIV-a, ali mu je greškom virus pobjegao iz laboratorije. Kaže da su i indijski virusolozi pre njega to otkrili, ali su se povukli zbog raznih pritisaka. On je nobelovac i zbog toga se ne boji takvih pritisaka. Međutim, u svetskoj naučnoj javnosti smatraju da je postao kontroverzan, pogrešio je i ne slažu se s njim!?

*French virologist prof. Luc Montagnier discovered the HIV virus and got in 2008. the Nobel Prize. For the origin of SARS-CoV-2, he claims that this virus has a segment of RNA of HIV virus. Someone did it in the laboratory trying to make a vaccine against HIV, but the virus escaped from the laboratory by mistake. He says that Indian virologists before him did the same discovery but withdrew it due to various pressures. He is a Nobel laureate and that is why he is not afraid of such pressures. However, the world scientific community thinks that he made mistake and has become controversial and they do not agree with him!?*



Sl./Fig. 9. Prof. Luc Montagnier na (on) TV.

**4.** Relevantna naučna zajednica većinom smatra da je SARS-CoV-2 nastao prirodnom selekcijom (i daje dokaze da nije genetskim inženjeringom napravljen u laboratoriji) ali, ipak, u ovom momentu još se ne mogu sa sigurnošću isključiti druge mogućnosti.<sup>8-10</sup>

*The relevant scientific community mostly believes that SARS-CoV-2 was created by natural selection (and gives evidence that it*

*was not made by genetic engineering in the laboratory), but at this moment, other possibilities cannot be ruled out with certainty.<sup>8-10</sup>*

O SARS-CoV-2 postoje, naročito u sredstvima javnog informisanja, mnoge netačne informacije, teorije zavere – da je napravljen kao biološko oružje ili da je greškom pobjegao iz neke laboratorije. Vlada SAD je 16. aprila 2020. objavila da preduzima istraživanja o mogućnosti da je virus napravljen genetskim inženjeringom ili nekako pobjegao iz laboratorije u Wuhan-u.

Međutim, mnogi naučni timovi smatraju da je virus nastao spontanom evolucijom.<sup>8-10</sup>

- Ubrzo posle početka epidemije COVID-19, Kinezi su sekvencirali ceo genom SARS-CoV-2 i obznanili ga celom svetu.
- Mutirani molekularni mehanizam kojim virus ulazi u ćeliju (Sl.10) nije napravljen u laboratoriji jer postoji i kod slepih miševa i pangolina.
- Upoređivanjem genoma SARS-CoV-2 sa ostalih šest Corona virusa koji deluju na čoveka ukazuje da nije stvoren u laboratoriji jer je više sličan virusima kod slepih miševa i pangolina nego drugim ljudskim Corona virusima. Molekularna struktura kojom se virus SARS-CoV-2 prikačinje za humanu ćeliju je slična kao kod pangolina.
- SARS-CoV-2 su međusobno slični u 99,98% što govori za skori skok virusa u čoveka. Da nije tako, zbog česte mutacije virusa, razlika bi morala biti veća.

*There are many inaccuracies about SARS-CoV-2, especially in the media information, and conspiracy theories - that it was made as a biological weapon or escaped from some laboratory. On April 16, 2020, the US government announced that it was taking investigation for the possibility that the virus was made by genetic engineering or somehow escaped from a Laboratory in Wuhan.*

*However, many scientific teams consider that a virus is formed by spontaneous evolution<sup>8-10</sup>.*

- Shortly after the onset of the COVID-19 epidemic, the Chinese sequenced the entire SARS-CoV-2 genome and made it known to the world.
- The mutated molecular mechanism by which the virus enters the human cell (Fig.10) was not made in the laboratory because it also exists in bats and pangolins.
- Comparing the SARS-CoV-2 genome with the other 6 human-acting Corona viruses indicates that it was not created in the laboratory because it is more similar to bat and pangolin viruses than other human Corona viruses. The molecular structure by which the SARS-CoV-2 virus attaches to a human cell is similar to that of pangolin.
- SARS-CoV-2 are 99.98% similar to each other, which indicates a recent jump of the virus to humans. If not, due to the frequent mutation of the virus, the difference would have to be greater.

**5.** SARS-CoV-2 ulazi u ljudsku ćeliju na način prikazan na Slici 10.:

*SARS-CoV-2 enters the human cell as shown in Figure 10:*





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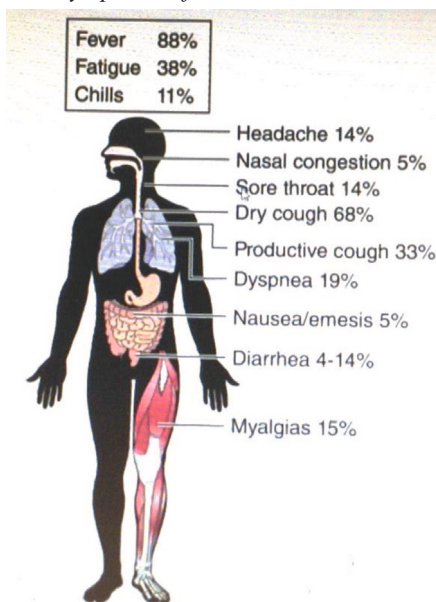
SI/Fig. 10. (A) Proteini šiljaka na površini korona virusa vežu se na receptore angiotenzin-konvertujućeg enzima 2 (ACE-2) na površini ljudske ćelije; (B) Transmembranska serinska proteaza tipa II veže se i cepa ACE-2 receptor. U procesu se aktivira protein šiljka; (C) Rascepljeni ACE-2 i aktivirani protein šiljka olakšavaju ulazak virusa. Ekspresija TMPRSS2 povećava ćelijski unos korona virusa.

(A) Spike proteins on the surface of the coronavirus bind to angiotensin-converting enzyme 2 (ACE-2) receptors on the surface of the human cell; (B) The type II transmembrane serine protease (TMPRSS2) binds to and cleaves the ACE-2 receptor. In the process, the spike protein is activated; (C) Cleaved ACE-2 and activated spike protein facilitate viral entry. TMPRSS2 expression increases cellular uptake of the coronavirus.

Protein šiljka ima domen (The Receptor Binding Domain = RBD) koji se vezuje za ACE2- receptor ćelije („ključ šiljka za bravu receptora“). Izvesne aminokiseline ovog „ključa“ su genetski izmenjene i to omogućava bolju penetraciju virusa u ćeliju. Isto to čini i ekstrasekvencija genoma virusa koja kodira izmenjeni glycan virusa.

The spike protein has a domain (The Receptor Binding Domain = RBD) that binds to the ACE2-receptor of human cell (“key of the spike for the receptor lock”). Certain amino acids of this “key” are genetically modified, which enables better penetration of the virus into the cell. The same is done by the extra sequence of the virus genome encoding the altered glycan of the virus.

## 6. Početni simptomi COVID-19 prikazani su na Sl. 11. The initial symptoms of COVID-19 are shown in Fig. 11



Al-Mallah MH. Circulation 2020. Methodist leading Medicine

SI/Fig. 11. Početni simptomi COVID-19. The initial symptoms of COVID-19.

## 7. Posle zaražavanja čoveka SARS-CoV-2, COVID-19 se razvija na sledeći način:

After human infection by SARS-CoV-2, COVID-19 develops as follows:

SARS-CoV-2 zaražava čoveka time što dospeva u njegov nazofarings odakle se spušta naniže i preko larinksa, traheje i bronhija (sve ove strukture su u zapaljenju) dospeva do pluća i pogađa pneumocite I i II. Razvija se teško zapaljenje pluća (SARS= Severe Acute Respiratory Syndrome) sa hiperimunom reakcijom organizma i nekad bakterijskom ili gljivičnom superinfekcijom. Plućne alveole su multifokalno opustošene i pružaju sliku difuznog alveolarnog oštećenja (DAD = Diffuse Alveolar Damage). Razvija se progresivna respiratorna insuficijencija i blokada oksigenacije krvi u plućima sa hipoksijom i nekad smrtni ishod.

Virus prelazi u krv i viremijom može da dospe u sve delove organizma. Ulazi u humane ćelije koje imaju ACE2 receptor: Srce, endotel<sup>11</sup>, bubrezi, jetra, skeletni mišići, centralni nervni sistem<sup>12</sup>, testisi<sup>13</sup> (otvara se mogućnost zaražavanja preko sperme<sup>13?</sup>), creva<sup>14</sup>, placenta<sup>15</sup>, itd.

U literaturi su učestali radovi koji govore da se kod dece pozitivne na SARS-CoV-2 pojavljuje „Multisistemski imuni odgovor“, koji nalikuje Kawasaki sindromu.

Kawasaki sindrom<sup>16,17</sup> je opisao Japanac dr Tomisaku Kawasaki 1967. izveštavajući o svojih 50 slučajeva. Radi se o mukokutanom, febrilnom limfonodularnom sindromu sa vaskulitisom (pokreću ga, izgleda, korona virusi), koji pogađa i koronarne arterije, stvarajući na njima aneurizme, a nekad i infarkt miokarda. Pri tome, radi se o jakoj, po organizam štetnoj, autoimunoj reakciji. Oboljenje pogađa jedno od hiljadu dece sa SARS-CoV-2.

SARS-CoV-2 infects a person by reaching his naso-pharynx, from where it descends downwards and through the larynx, trachea and bronchi (all these structures are inflamed), reaches the lungs and affects pneumocytes I and II. Severe pneumonia (SARS = Severe Acute Respiratory Syndrome) develops with a hyperimmune reaction of the organism and, sometimes, bacterial or fungal superinfection. Pulmonary alveoli are multifocally devastated and provide a picture of diffuse alveolar damage (DAD = Diffuse Alveolar Damage). Progressive respiratory failure and blockage of blood oxygenation in the lungs with hypoxia occur, causing sometimes fatal outcome.

The virus enters the blood (viremia) and can reach all parts of the body. It is entering human cells that have the ACE2 receptor: Heart, endothelium<sup>11</sup>, kidneys, liver, skeletal muscles, central nervous system<sup>12</sup>, testicles<sup>13</sup> (opens the possibility of infection through sperm<sup>13?</sup>), gut<sup>14</sup>, placenta<sup>15</sup>, etc.

There have been frequent reports in the literature that SARS-CoV-2-positive children develop “a Multisystem immune response” that resembles Kawasaki syndrome.

Kawasaki syndrome<sup>16,17</sup> was described by Japanese Tomisaku

*Kawasaki, MD in 1967 reporting his 50 cases. It is a muco-cutaneous, febrile lymphonodular syndrome with vasculitis (triggered, it seems, by corona viruses), which also affects the coronary arteries, creating aneurysms and sometimes myocardial infarction. This is a strong, harmful to the body, autoimmune reaction. The disease affects one of a thousand children with SARS-CoV-2.*

## 8. Uloga patologa u COVID-19.<sup>18-22</sup> The role of pathologists in COVID-19.

U početku epidemije, izvesni zdravstveni rukovodioci na Zapadu su smatrali da ne treba vršiti obdukcije „da se ne bi povećao broj zaraženih i zbog delatnosti patologa (obducenta) i njihovih saradnika“.

Međutim, nemački patolozi su odmah bili protiv toga i zahtevali da se vrše obdukcije. To je rezultovalo i naredbom u Hamburgu (Nemačka) da **svi umrli zbog ili sa COVID-19 moraju biti obdukovani**.

Na obdukciji, naravno, leš ne može da kašlje u lice obducentu (kao što bolesnik može kliničaru) ali obducent se može ubosti ili poseći skalpelom, a postupcima obdukcije podižu se sitne čestice sa virusom vazduhom uvis, a izlivenne telesne tečnosti mogu biti prepune virusa – što je sve opasnost za obducenta kao i njegove saradnike koji manipulišu lešom.

Odmah je ustanovljen princip da se razlikuje: Da li je bolesnik **umro zbog COVID-19**, tj. da li je COVID-19 osnovno oboljenje i uzrok smrti ili je **umro sa COVID-19**, a osnovno oboljenje je uzrok smrti je neko drugo oboljenje (koje je COVID-19 samo pospešio).

Budući da najviše umiru stariji ljudi, oni, naravno, obično imaju različite komorbiditete.

Patolozi su obdukcijom, histopatologijom, specijalnim bojenjima, imunohistohemijom, citologijom, elektronskom mikroskopijom uz dijagnostiku samog virusa veoma mnogo doprineli i doprinose istraživanju etiopatogeneze i patološko-morfološkog supstrata kod COVID-19. Naročito u sagledavanju plućnih lezija, tromboze i tromboembolija (često klinički neotkrivenih), lezija na skeletnim mišićima i srcu, otkrivanju multiorganske bolesti i elektronskom mikroskopijom dokazivanje virusa u tkivima i ćelijama, itd.

*At the beginning of the epidemic, certain health leaders in the West believed that autopsies should not be performed “in order not to increase the number of infected people due to the activities of pathologists and their associates.”*

*However, German pathologists were immediately against it and demanded that autopsies be performed. This resulted in an order in Hamburg (Germany) that all those who died because of or with COVID-19 must be autopsied.*

*At the autopsy, of course, the cadaver cannot cough in the face of the pathologists (as the patient can in the clinician), but pathologist may be stabbed or cut with a scalpel and the autopsy procedures raise in the air small particles with the virus, and spilled body fluids can be full of virus - which is a danger to the pathologists and his associates who manipulate with cadaver.*

*The principle of differentiation was immediately established: Did the patient die due to COVID-19, ie. whether COVID-19 is the main disease and the cause of death or died with COVID-19 and the main disease and cause of death is some other disease (which COVID-19 only accelerated).*

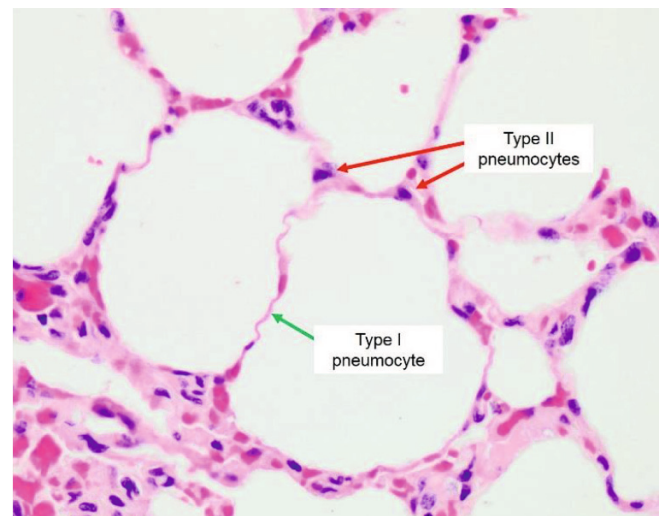
*Since older people die the most, they, of course, usually have different comorbidities.*

*Pathologists have contributed a lot to the research of etiopathogenesis and patho-morphological substrate in COVID-19 with autopsy, histo-pathology, special staining, immunohistochem-*

*istry, cytology, electron microscopy and diagnostics of the virus itself. This is especially true in lung lesions, thrombosis and thromboembolism (often clinically undetected), lesions of skeletal muscles and heart, detection of multi-organic diseases and by electron microscopy diagnostics of viruses in tissues and cells, etc.*

## 9. Plućne lezije kod COVID-19 Pulmonary lesion in COVID-19

**Plućne lezije zbog virusnog zapaljenja i hiperreaktivne imune reakcije organizma (uključujući i plućni trombní embolizam) su najteže i najsmrtonosnije kod COVID-19.** Na Slici 12. je histologija normalnih plućnih alveola, a na Slici 13. pustoš u plućnim alveolama sa oblepljivanjem („tapaciranjem“) njihovih zidova, što onemogućava oksigenaciju krvi, sa sledejućom hipoksijom zbog koje pate sve ćelije organizma. Kontrast između ove dve slike je već na prvi pogled očigledan i laicima te ukazuje na teško oboljenje pluća: SARS (Severe Acute Respiratory Syndrome) i DAD (Diffuse Alveolar Damage).



Google 2020.

**Sl./Fig. 12.** Normalne plućne alveole, ispunjene vazduhom. Uporedi sa Sl.13 kada su alveole ispunjene zapaljenjskim sadržajem, koji oblepljuje njihove zidove vršeći blokadu oksigenacije krvi.

*Normal air-filled lung alveoli. Compare with Fig.13 when the alveoli are filled with inflammatory contents, which plastered their walls and blocking blood oxygenation.*

Značajni doprinos istraživanju plućnih lezija kod 38 obdukovanih bolesnika zbog COVID-19 dali su L. Carsana<sup>20</sup> i 14 saradnika iz bolnice *L.Saceo* u Milanu i bolnice *Papa Giovanni XXIII* u Bergamu u Lombardiji (Italija) najsmrtonosnijem centru COVIDA-19 (odakle se većinom zaraza prenela u Srbiju i Republiku Srpsku).

MAKROSKOPSKI, plućna krila su **uvećana i teža**. Težina pluća na obdukciji je 840 g za muškarce i 639 g za žene. Kod COVID-19 prosečna težina pluća je 1,988 g! Kod jednog 85-godišnjaka muškarca bila je čak 3.420 g, tj. četiri puta veća od normalnog proseka!

U plućima postoji **kongestija i edem, multifokalna ognjišta konsolidacije – (bronho)pneumonija**, nekad i **pleuritis**.

MIKROSKOPSKI (histopatološki<sup>20</sup>) postoje teške promene u plućnim alveolama, a nekad i endotelitis u njihovim kapilarima. Postoje tri faze ovih promena: eksudativna, proliferativna i fibrozna. Prve dve se nekad preklapaju a treća je retka, jer bolesnici do sada nisu praćeni na duže staze.



**Eksudativna faza:** Kapilarna kongestija, intersticijalni i alveolarni edem, alveolarna proteinoza, alveolarna hemoragija, hijaline membrane, kolaps alveola sa ili bez proširenja alveolarnih duktusa, prisutni limfociti, granulociti i megakariociti, gubitak pneumocita i fibrinski trombi.

**Proliferativna faza:** Hiperplazija pneumocita 2, skvamozna metaplazija sa atipijom, intersticijalna miofibroblastična reakcija, alveolarno granulaciono tkivo, alveolarna okluzivna fibroza - kompletna ili „prstenasta“, deponovanje kolagena u pregradama, fibroza alveolarnih duktusa, umnožavanje kapilara, bronhiolitis obliterans, organizovane alveole sa proširenim alveolarnim duktusima.

**Fibrozna faza:** Zahvaćenost pleure, ožiljci, fibrozne mikrociste, klasterovani mikrocistični vazdušni prostori, arterijska hiperplazija.

**Druge udružene lezije:** Intersticijalni zapaljenjski infiltrati, alveolarni zapaljenjski infiltrati (makrofagi), alveolarne mnogojezarne džinovske ćelije, nakalemljena bakterijska ili gljivična infekcija, bronhopneumonija, trombocitno-fibrinski trombi u malim ograncima (< 1mm u prečniku) plućne arterije, infarkti. Elektron-ska mikroskopija otkriva virusne čestice u citoplazmi pneumocita.

*Pulmonary lesions due to viral inflammation and hyperreactive immune response of the organism (including pulmonary thrombotic embolism) are the most severe and deadly in COVID-19. Figure 12 shows the histology of normal pulmonary alveoli, and Figure 13 shows the devastation in the pulmonary alveoli with the lining (“upholstery”) of its walls, which prevents blood oxygenation (with subsequent hypoxia that causes all cells in the body to suffer). The contrast between these two images is obvious to laymen at first glance and indicates severe lung disease: SARS (Severe Acute Respiratory Syndrome) and DAD (Diffuse Alveolar Damage).*

*A significant contribution to the study of lung lesions in 38 autopsied patients due to COVID-19 was made by L. Carsana<sup>20</sup> with his 14 associates from L. Sacco Hospital in Milan and Papa Giovanni XXIII Hospital in Bergamo in Lombardy (Italy) – the most lethal COVID-19 center (from which the infection has been transmitted to Serbia and Republic of Srpska).*

*MACROSCOPICALLY the lungs are enlarged and heavier. The weight of the lungs at the autopsy is 840 gr. for men and 639 gr. for women. With COVID-19, the average lungs weight is 1,988 gr. In an 85-year-old man, it was as much as 3,420 grams, that is four times the normal average.*

*Then, congestion and edema in the lungs, multifocal foci of consolidation - (broncho) pneumonia, sometimes pleurisy.*

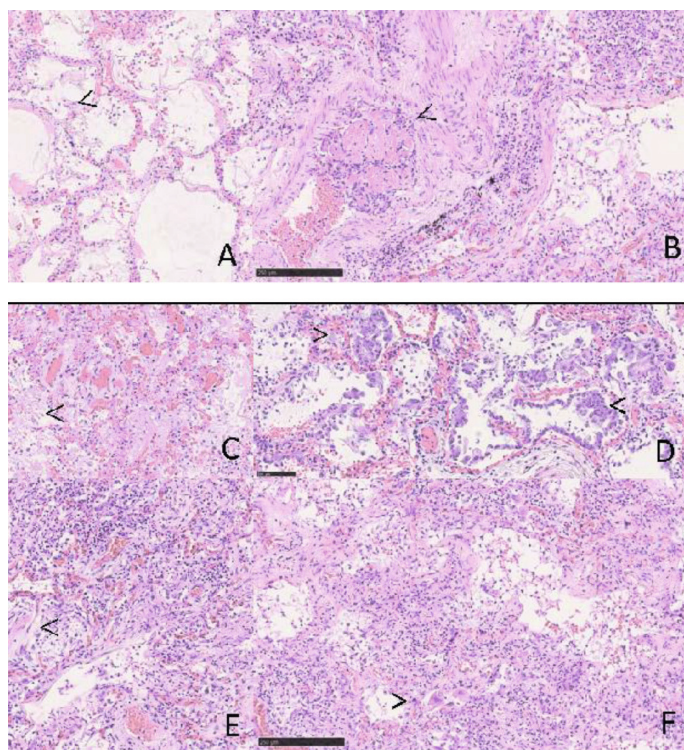
*MICROSCOPIC (histo-pathologically<sup>20</sup>) there are severe changes in the pulmonary alveoli and sometimes endotheliitis in their capillaries. There are three phases of these changes: exudative, proliferative, and fibrous. The first two sometimes overlap and the third one is rare because patients have not been followed in the long run so far.*

**Exudative phase:** Capillary congestion, interstitial and alveolar edema, alveolar proteinosis, alveolar hemorrhage, hyaline membranes, alveolar collapse with or without dilation of alveolar ducts, lymphocytes, granulocytes, and megakaryocytes present, pneumocyte loss, fibrin thrombi.

**Proliferative phase:** Pneumocyte 2 hyperplasia, squamous metaplasia with atypia, interstitial myofibroblastic reaction, alveolar granulation tissue, alveolar occlusive fibrosis- complete or “annular”, collagen deposition in septa, bronhiolitis obliterans, alveolar duct fibrosis.

**Fibrous phase:** Pleural involvement, scarring, clustered fibrous microcysts air spaces, arterial hypermuscularization.

**Other associated lesions:** Interstitial inflammatory infiltrates, alveolar inflammatory infiltrates (macrophages), alveolar multinucleated giant cells, superimposed bacterial or fungal infections, bronchopneumonia, platelet-fibrin thrombi in small branches (> 1mm in diameter) of pulmonary artery, infarction. Electron microscopy revealed viral particles in the cytoplasm of pneumocytes.



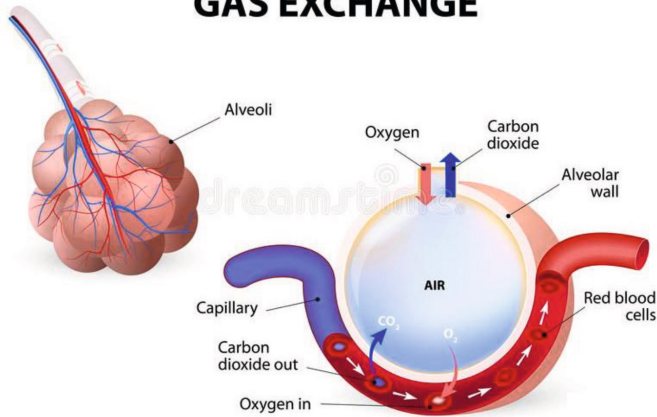
**Sl./Fig. 13.** Plućni parenhim sa difuznim alveolarnim oštećenjem<sup>20</sup>: A – Eksudativna faza sa hijalnim membranama (strelica); B – Mikrotrombus u organizaciji (strelica); C – Megakariociti u alveolarnim kapilarima (strelica); D – Rana proliferativna faza sa mnogo hiperplastičnih, retko atipičnih pneumocita tipa 2 (strelice); E – Intermedijalna faza sa luminalnom fibrozom (strelica); F – Odmakla proliferativna faza sa intersticijalnom miofibroblastičnom reakcijom i rezidualnim razbacanim hiperplastičnim pneumocitima tipa 2 (strelica). Hematoxylin-Eozin, OM 10x.

*Lung parenchyma with diffuse alveolar damage<sup>20</sup>: A - Exudative phase with hyaline membranes (arrow); B - Organising microthrombus (arrow); C - Entrapped megakaryocytes in alveolar capillaries (arrow); D - Early proliferative phase with many hyperplastic, seldom atypical, type II pneumocytes (arrows); E - Intermediate phase with luminal organizing fibrosis (arrow); F - Advanced proliferative phase, with interstitial myofibroblastic reaction and residual scattered hyperplastic type II pneumocytes (arrow). Hematoxylin-Eosin, OM 10x.*

## 10. Normalna izmena gasova i oksigenacija venske krvi u plućima<sup>23</sup> (koje kompromituje COVID-19) prikazani su na slikama 14. i 15.:

*Gas exchange and venous blood oxygenation in the lungs<sup>23</sup> (which compromises COVID-19) are shown in Figures 14 and 15:*

## ALVEOLUS GAS EXCHANGE

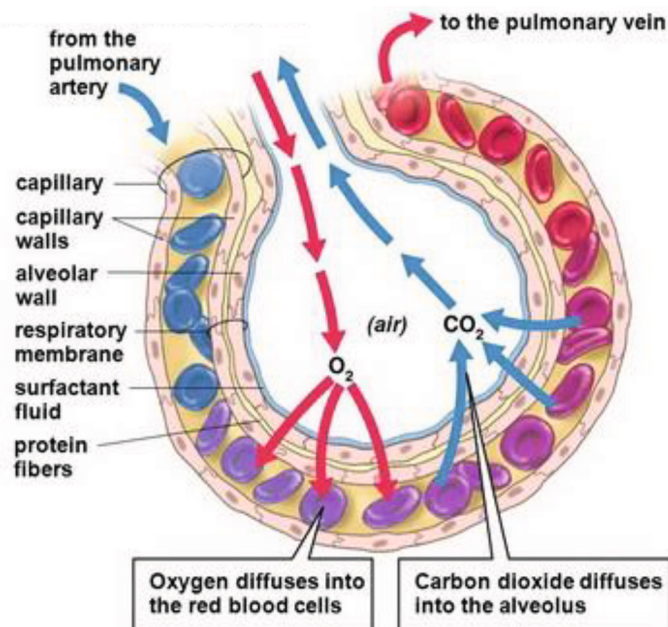


Google 2020.

Sl./Fig. 14.<sup>23</sup> Gore – levo: bronhiola kojom se dovodi i odvodi vazduh iz alveola. Dovodna arteriola i odvodna venula koja nosi oksigenisanu krv preko plućnih vena u levu pretkomoru.

Dole – desno: alveola sa vazduhom i kapilar. Kroz njihove zidove se vrši razmena gasova i oksigenacija krvi u plućima za potrebe celog organizma. **Above - left:** bronchiole which brings and takes air out of the alveoli. Supply arteriole and a draining venule that carries oxygenated blood via pulmonary veins to the left atrium.

**Bottom - right:** alveoli with air and capillaries. Gases are exchanged through their walls. Oxygenation of the blood in the lungs for the needs of the whole organism.



Google 2020.

Sl./Fig. 15. Razmena kiseonika i ugljen-dioksida između alveole i njenog kapilara i oksigenacija krvi u plućima.

Exchange of oxygen and carbon dioxide between the alveolus and its capillary and oxygenation of the blood in the lungs.

## 11. U kardiovaskularnom sistemu otkrivene su sledeće lezije kod COVID-19:

The following lesions were detected in the cardiovascular system in COVID - 19:

SARS-CoV-2 deluje na srce na tri načina: (1) Zbog hiperinflamacije i imune reakcije; (2) direktno na miokard i (3) posredno, preko respiratorne insuficijencije i hipoksije. Dolazi do: Mi-

okarditisa, aritmija, perikarditisa, akutnog koronarnog sindroma, srčane insuficijencije.

Zbog hiperkoagulabilnosti krvi (**koagulopatije**), nastaju **lokalne tromboze i trombni embolizam**<sup>21,24,25</sup>. Klinički su često neotkrivene tromboze dubokih vena nogu bez ili sa plućnim tromboembolijama kao i tromboze paraprostaticnog venskog spleta.

Postoji rasprostranjeni **endotheliitis**<sup>11</sup>.

*SARS-CoV-2 acts on the heart in three ways: (1) Due to hyperinflammation and immune response; (2) directly to the myocardium, and (3) indirectly, through respiratory failure and hypoxia. There are: Myocarditis, arrhythmia, pericarditis, acute coronary syndrome, heart failure.*

*Due to the hypercoagulability of the blood (coagulopathy), local thrombosis and thrombotic embolism<sup>21,24,25</sup> occur. Deep vein thrombosis of the legs without or with pulmonary thromboembolism as well as paraprostatic venous plexus thrombosis (often clinically undetected).*

*There is widespread endotheliitis<sup>11</sup>.*

## 12. Najteže i najvažnije patološke lezije kod COVID-19: The most severe and important pathological lesions in COVID-19:

- Teško virusno i hiperimuno zapaljenje pluća – teški akutni respiratorni sindrom (Severe Acute Respiratory Syndrome – SARS) i difuzno alveolarno oštećenje (Diffuse Alveolar Damage - DAD) sa progresivnom respiratornom insuficijencijom i hipoksijom.

*Severe viral and hyperimmune pneumonia - Severe Acute Respiratory Syndrome - SARS) and Diffuse Alveolar Damage – DAD with progressive respiratory failure and hypoxia.*

- Blokada oksigenacije krvi u plućima – hipoksija (od koje pate sve ćelije organizma).

*Blockade of blood oxygenation in the lungs - hypoxia (from which all cells of the organism suffer).*

- Hiperkoagulabilnost - koagulopatija – lokalne tromboze i trombni embolusi

*Hypercoagulability - coagulopathy - local thrombosis and thrombus emboli*

- Viremija – virus preko krvi može da dođe na svako mesto u organizmu.

*Viremia - the virus can reach any place in the body through the blood.*

- Rasprostranjeni endotheliitis.

*Widespread endotheliitis.*

- Multiorganska bolest (miokard, bubrezi, itd.)

*Multiorgan disease (myocardium, kidneys, etc.)*

- Nakalemjene bakterijske ili gljivične infekcije.

*Grafted bacterial or fungal infections.*

Najviše obolevaju **stariji ljudi** zbog uzrastno smanjenog imuniteta (produkuje se manje antitela i, važnije, produkuje se manje T ćelija, koje prepoznaju nove antigene i ubijaju ćelije zaražene virusom). Stariji imaju i više komorbiditeta (kardiovaskularna i plućna oboljenja, gojaznost, dijabetes melitus tipa 2, itd.).

*Older people get sick the most due to age-reduced immunity (fewer antibodies are produced and, more importantly, fewer T cells*



are produced, which recognize new antigens and kill cells infected with the virus). They have more comorbidity (cardiovascular and pulmonary diseases, obesity, diabetes mellitus type 2, etc.).

**13. Društveno-psihološki odgovori čovečanstva na COVID-19 su dvojaki.** To je najbolje objasnio Juval Noa Harari<sup>26</sup>, izraelski istoričar, u jednom intervjuu:

*Socio-psychological responses of humanity to COVID-19 are twofold. This was best explained by Juval Noah Harari<sup>26</sup>, an Israeli historian, in an interview:*

“Mislim da najveća opasnost nije sam virus. Čovečanstvo ima sva naučna saznanja i tehnološke alate za prevladavanje virusa. Veliki problem su naši vlastiti unutrašnji demoni, naša vlastita mržnja, pohlepa i neznanje. Bojim se da ljudi reaguju na ovu krizu ne globalnom solidarnošću, već mržnjom, optužujući druge zemlje, optužujući etničke i verske manjine.

Ali, nadam se da ćemo uspeti razviti saosećanje, a ne mržnju, da reagujemo globalnom solidarnošću, koja će razviti našu velikodušnost za pomoć ljudima u nevolji. I da razvijamo svoju sposobnost razaznavanje istine i ne verujemo u sve te teorije zavere. Ako to učinimo, ne sumnjam da ovu krizu možemo lako prevladati”.

*“I think the biggest danger is not the virus itself. Humanity has all the scientific knowledge and technological tools to overcome the virus. The really big problem is our own inner demons, our own hatred, greed and ignorance. I’m afraid that people are reacting to this crisis not with global solidarity, but with hatred, blaming other countries, blaming ethnic and religious minorities.*

*But I hope that we will be able to develop our compassion, and not our hatred, to react with global solidarity, which will develop our generosity to help people in need. And that we develop our ability to discern the truth and not believe all these conspiracy theories. If we do that, I have no doubt that we can easily overcome this crisis”.*

**Profesor Yuval Noa Harari** (Sl./Fig.16) je autor knjiga *Sapiens: Kratka istorija čovečanstva; Homo Deus; i 21 lekcija za 21. vek*, koje su u Srbiji prevedene. Njegova Fondacija za socijalni uticaj *Sapienship* donirala je milion dolara Svetskoj zdravstvenoj organizaciji (WHO) posle odluke američkog predsednika da obustavi finansiranje.

*Professor Yuval Noa Harari is the author of the books Sapiens: A Brief History of Humankind; Homo Deus; and 21 Lessons for the 21st Century, which were translated in Serbia. His social impact Foundation Sapienship donated \$1 million to the World Health Organization (WHO) following the US president’s decision to hold back funding.*



Sl./Fig. 16. Prof. Juval Noa Harari

**14. Kineski oftalmolog iz Wuhan-a Li Wenliang<sup>27</sup> je među prvima ukazao da postoji epidemija misterioznih pneumonija u Wuhan-u (koje su kasnije dijagnostikovane kao COVID-19).** Policija je izvršila pritisak na njega zato što je na internetu objavio da “postoji pojava nekontrolisanog SARS-a”. Umro je od pneumonije COVID-19. Komunistička partija Kine dala je “Svečano izvinjenje” njegovoj porodici i odbacila optužbe protiv njega.

*Chinese ophthalmologist from Wuhan Li Wenliang<sup>27</sup> was among the first to point out that there is an epidemic of mysterious pneumonias in Wuhan (which were later diagnosed as COVID-19). Police put pressure on him because he announced on the Internet that “there was an uncontrolled SARS”. He died of pneumonia from COVID 19. The Communist Party of China issued a “Solemn apology” to his family and dismissed the charges against him.*



Sl./Fig. 17. Li Wenliang, (Beizhen, Liaoning, China, 12.X 1986. – Wuhan, Hubei, China 7.II 2020. IN MEMORIAM

**15.**



Sl./Fig. 17. Vojvoda Marko Miljanov  
Duke Marko Miljanov

(Medun, 25.IV 1833. – Herceg Novi, 2.II 1901)

„Junaštvo je kada sebe braniš od drugoga,  
Čojstvo je kada drugoga braniš od sebe.“

*“Heroism is when you defend yourself from another;  
Chivalry is when you defend another from yourself.”*

U Srbiji i Republici Srpskoj su u borbi protiv COVID-19 pokazali **JUNAŠTVO** zdravstveni radnici, a **ČOJSTVO** građani koji su nosili maske i time čuvali druge od sebe.

*In Serbia and the Republic of Srpska, in the fight against COVID-19, **HEROISM** was shown by health workers and **CHIVALRY** by citizens who wore masks and thus kept others from themselves.*

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