THE VIEW OF THE CLINICIAN ON THE PROBLEM OF COVID-19

Yeryomenko G., Bezditko T., Ospanova T.

Kharkiv National Medical University

https://doi.org/10.35339/ic.8.4.217-225

Abstract

The review article features the peculiarities in the epidemiological and clinical picture of a new coronavirus infection, COVID-19. The purpose of the review was to analyze the issues of the management. Pathogenetic relationships between SARS-CoV-2 virus, COVID-19 and angiotensin-converting enzyme 2 (ACE2) are assessed. Predisposing factors, which result in development of pneumonia and endothelial dysfunction, disorders in microcirculation, vasoconstriction, work of the renin-angiotensin system with subsequent development of ischemia in certain organs, inflammation and edema of tissues, are analyzed. Lung damage causes development of interstitial pneumonia, activation of the process of formation of fibrosis and decreased pulmonary function. Accumulation of anti-inflammatory cytokines, which break the blood-brain barrier, in the CNS can cause dysregulation of central structures, autonomic dysfunction and severe asthenic syndrome, which can maintain low-grade inflammation for a long time. Opportune diagnosis and treatment of concomitant diseases in post-COVID-19 patients are of paramount significance for achieving a positive clinical outcome. The plan of rehabilitation treatment should be individualized according to the patient's needs. In order to assess remote consequences of COVID-19 all patients require further follow-ups.

***Keywords**: SARS-CoV-2, post COVID-19, ACE2, cytokines.*

At the end of 2019 an outbreak of a new coronavirus infection took place in the People's Republic of China with its epicentre in the City of Wuhan. On February 11, 2020 the World Health Organization gave an official name, COVID-19 (CoronaVirus Disease 2019), to the infection caused by the new coronavirus [1]. The International Committee on Taxonomy of Viruses named the causative agent of this infection as SARS-CoV-2. The peculiar epidemiological and clinical picture of the new coronavirus infection, COVID-19, necessitates the analysis of the information about the pathogenesis of the above infection that is important because of absence of any etiotropic therapy at present and forced use of pathogenetic treatment [2]. Similar to other respiratory coronaviruses, the primary transmission of COVID-19 is via droplet spread, the fecal-oral route is not excluded [3].

SARS-CoV-2 is an RNA-containing virus, which together with SARS-CoV and MERS-CoV belong to β-coronaviruses. Angiotensin-converting enzyme 2 (ACE2), which participates in the functioning of the heart muscle and regulation of blood pressure, is the receptor of SARS-CoV-2 in people. In cases of COVID-19 the spike protein (protein S) with the crown-like form of the viral membrane is bound with the ACE2 receptor, and after that the viral RNA enters the cell [4, 5]. A number of researches and observations have demonstrated absence of any general consensus concerning the role of ACE2 receptors in the pathogenesis of this disease. ACE2 receptors are present on the cells of the respiratory tract, kidneys, esophagus, bladder, intestines, heart and central nervous system [6, 7].

In order to penetrate into a cell the virus cooperates with an ACE2 receptor and membrane-bound serine protease 2 (TMPRSS2), which is necessary for priming protein S. The binding of protein S with ACE2 is followed by direct fusion of the viral and cellular membranes; after that the protein is subjected to partial breakdown and becomes active. Viral RNA enters the cytoplasm, where translation is followed by an active replication of the viral genome; their cooperation with the Golgi apparatus makes it possible for viral particles to release themselves into the plasma, thereby continuing the cycle of the virus spread in the

Corresponding Author:
Galyna Yeryomenko, MD, DMedSci, Department of Propedeutic of internal medicine №2 and Nursing care, Kharkiv National Medical University, Ukraine.E-mail:hvyeromenko.po19@knmu.edu.ua

organism [8, 9]. Taking into consideration a decreased expression of ACE2 against a background of COVID-19, we may suppose a subsequent violation in the work of the renin-angiotensin system that can affect regulation of blood pressure and hydroelectrolytic balance [10]. Meanwhile, we cannot exclude that this change in the expression of ACE2 receptors plays an important role in the pathogenesis of COVID-19 itself. Statistical analysis of COVID-19 cases in individuals, who lived in high lands, revealed a milder course of disease versus inhabitants from even lands. The authors believe that the above fact can be caused by both a reduced period of life of the virus in conditions of a decreased atmospheric pressure and an induced decline of the ACE2 level against a background of hypoxia [11, 12]. Experimental data in mice, mutant by ACE2, revealed lower viral load and replication; on the other hand, proceeding from similar lung damages in COVID-19 and "avian influenza" virus H5N1, we may suppose a protective effect of exogenous introduction of ACE2 on the development of acute respiratory distress syndrome (ARDS) [13,14].

For a long time the ability to bind the human ACE2 receptor as well as some peculiarities in the structure of ORF3 and ORF8 genes, which are supposed to play a certain part in the pathogenesis of the virus, were regarded to be unique properties of SARS-CoV. Large-scale studies of Chinese populations of bats resulted in isolation of several viruses, which are similar to SARS-CoV by the structure of their receptor-binding domain. It has been shown that in order to penetrate into a cell these strains are able to use receptors of both people, bats and civets. A number of other strains had a similar structure of ORF3 and ORF8 genes [15]. Hence, among the viruses that circulate in colonies of bats there are variants, which already have the required tropism and ability to infect people without any necessity for an additional adaptation in an intermediate host [16, 17].

Type II alveolocytes are the main and rapidly achieved target for ACE2 receptors; their lesion with the virus results in diffuse alveolar damage that manifests clinically with development of ARDS in 41.8% of patients with lethal outcome in more than 50% of cases [18].

It is well known that in order to penetrate into a cell the virus uses ACE2 receptors, expressed on alveolar pneumocytes, thereby causing lung damages. However, ACE2 receptors are also widely expressed on endotheliocytes, which line the vessels of many organs. It has been proven that SARS-CoV-2 can directly infect epitheliocytes of human blood vessels in vitro. Vascular endothelium is an active paracrine, endocrine and autocrine organ, which participates in the regulation of vascular tone and maintaining of vascular homeostasis [19, 20]. By now there is evidence for direct contamination of endothelial cells with SARS-CoV-2 virus and resultant diffuse endothelial inflammation [21, 22]. Studies of molecular markers, which characterize the functional state of the vascular endothelium, reveal that endothelitis is one of key syndromes in COVID-19 and later a trigger for post-COVID syndrome. Direct lesion of endotheliocytes with the virus or their indirect damage with immune cells, cytokines and free radicals can result in significant endothelial dysfunction. The latter, which develops in COVID-19, causes disorders in microcirculation and vasoconstriction with subsequent development of ischemia of organs, inflammation and edema of tissues, procoagulation [23, 24]. Endothelitis can explain systemic impairments of microcirculatory function in different vascular beds and their clinical consequences in patients with COVID-19.

Oxidative stress plays a significant role in the pathogenesis of COVID-19, aggravating the consequences of cytokine storm, blood coagulation and hypoxia that cause damages of tissues and organ failure. It is hypothesized that there is a cross connection between cytokine storm and oxidative stress. These disorders can play an important role in the severity of signs and symptoms in patients with COVID-19 [25, 26]. Hence it is quite logical to present a model of the pathogenesis of coronavirus infection with a primary lung damage and late hematological tissue hypoxemia (cytopathic hypoxemia) and mitochondrial dysfunction caused by participation of oxidative stress. This fact is confirmed with reliable experimental data [27].

Dysregulatory activation of monocytic phagocytes, development of generalized thrombosis in the microcirculatory bed and interstitial pneumonia in COVID-19 [28]. In response to penetration of SARS-CoV-2 virus,

T-cell immune reactions prevail during the exudative and proliferative stages. In the fibrotic stage, the total amount of T lymphocytes is sharply reduced, whereas cells of humoral immunity are not revealed. The prevalence of CD8+ T suppressor lymphocytes over CD4+ T helper lymphocytes may be associated with mechanisms of autoimmune damage [29].

Lung damage as consequence of the direct injury of the vascular endothelium and alveolar complex (alveolocytes and interalveolar septa, when the radiological sign of "clouded glass" develops) with the coronavirus and cytokines causes development of interstitial pneumonia, activation of the process of formation of fibrosis as well as decreased pulmonary function [30].

Different aspects of patho- and morphogenesis of coronavirus infection are thoroughly studied; in particular, morphological changes in the pulmonary tissue of patients, who died within different time periods after appearance of the first clinical signs of the disease, are comparatively analyzed [31]. Analysis of macro- and microscopic changes in the respiratory tract with use of immunohistochemical studies has made it possible to assess the state of their lungs in patients with COVID-19 in 80 cases of lethal outcome [32]. The peculiarities of diffuse alveolar damage have been revealed and therefore make it possible to distinguish 3 phases in the pathomorphogenesis of interstitial pneumonia in COVID-19: fulminant (up to 10 days; it corresponds to the exudative and proliferative stages of ARDS), persisting (11-20 days; it corresponds to the proliferative stage of ARDS) and fibrotic (revealed in patients, who died on the 21st-45th days; it corresponds to the stage of organization of ARDS) [33].

An evidence base for a relation of ACE2 gene with sex dimorphism of mortality in COVID-19 (a lower death rate was detected in women) is presented. This fact may be caused by either genetic dimorphism, as ACE2 gene is located on X chromosome, or different immunoregulatory effects of estrogens and testosterone [34].

Accordingly, development and progression of the disease most frequently occur in two directions: lung damages and coagulation disorders, which often remain undetected. Coagulation disorders both result in the appearance of clinically significant thrombotic complications and play the role in the pathogenesis of coronavirus infection, including cases with lung damage. Disorders of microcirculation resulting from microthromboses can significantly aggravate the course of acute respiratory failure in patients with COVID-19 [35].

Many patients, who survived acute manifestations of COVID-19, are only in the beginning of their way to recovery. What consequences should be expected after the acute stage of coronavirus infection? It depends upon the spread and severity of viral damages in different types of cells and organs. Despite a vast number of scientific publications, the picture of long-term consequences of COVID-19 remains unclear. Without large-scale prospective observational studies, which are only in the beginning of their performance, clinicians cannot obtain any certain information about cases of post-COVID complications or small studies [36, 37].

Within the framework of the study with participation of 150 noncritical patients with COVID-19, conducted by researchers from the University of Tours (France), it was revealed that on the 30th or 60th days after appearance of signs and symptoms of COVID-19 the patients, who had survived a noncritical stage of the disease, still had the following signs and symptoms (at least one of them): loss of body weight (≥5%), severe dyspnea or asthenia, pain in the chest, palpitation, anosmia/ageusia, headache, skin manifestations, arthralgia, myalgia, digestive disorders, elevation of body temperature. At least one symptom was present in 68% of cases (n=103/150) on the 30th day and in 66% (n=86/130) on the 60th day. The commonest signs and symptoms were as follows:

• anosmia/ageusia: in 59% at the onset of the disease, in 28% on the 30th day and in 23% on the 60th day;

• dyspnoea: in 36.7% on the 30th day and in 30% on the 60th day;

• asthenia: in 50% on the 30th day and in 40% on the 60th day;

• persistent signs and symptoms on the 60th day were most frequently observed in individuals aged 40-60, they were associated with hospitalization and changes in the auscultation picture at the onset of the disease; a severe

course of COVID-19 and dyspnea at the onset of the disease were associated with presence of persistent signs and symptoms on the 30th day [38].

According to the information from the World Health Organization in February of 2020 (on the basis of preliminary data), the period from the onset to clinical recovery in mild cases of COVID-19 is approximately 2 weeks, in severe or critical cases it lasts from 3 to 6 weeks. But many patients have certain signs and symptoms for much more weeks and even months. Persistent damages of many organs and systems (lungs, heart, brain, kidneys, vascular system, etc.) have been documented in post-COVID-19 patients [39].

Different mechanisms in the development of these states are under investigation. Such damages may be caused by severe inflammatory reactions, thrombotic microangiopathy, venous thromboembolism, oxygen deficiency, autoimmune processes, pathological consequences after the acute period (pneumofibrosis) or persistence of the causative agent [40, 41].

The diagnosis, monitoring of the patient's state, prognostic criteria and treatment have been insufficiently studied and require improvement [42].

Clinical guidelines of the National Institute for Health and Care Excellence of Great Britain "COVID-19 rapid guideline: managing the long-term effects of COVID-19" (NG188) use the following clinical definitions for the primary disease and duration of COVID-19 depending upon the time when they appeared and during which they exist:

- acute COVID-19 – signs and symptoms of the disease are present up to 4 weeks;
- ongoing symptomatic COVID-19 – signs and symptoms of the disease are present from 4 to 12 weeks;
- post-COVID-19-syndrome – signs and symptoms develop during or after the infectious disease, which corresponds to COVID-19, are present longer than 12 weeks and not explained by an alternative diagnosis.

In turn, the Infectious Diseases Society of America (IDSA) distinguishes "long-lasting COVID-19", "post-COVID syndrome" and "post-acute COVID syndrome". Harvard Medical School uses such a definition as "long haulers". The concept "chronic" or "long-lasting" course of an infectious disease takes into consideration persistence of the causative agent. It is known that other coronaviruses have a potential to persist in the nervous system for a long period of time; it is possible, SARS-CoV-2 as well [43, 44]. If the pathological state after the survived disease remains, but the causative agent is not revealed, these facts point out consequences of the disease that can be rightfully termed post-COVID syndrome [30]. Post-COVID long-hauler is any patient with COVID-19 caused by SARS-CoV-2, who has not returned to his/her level of health and functioning in 6 months after the survived disease. According to different data, from 10 to 50% of post-COVID-19 cases become long-haulers [45]. Two groups of such patients are isolated: cases with irreversible damages in the lungs, heart, kidneys or brain that affect their ability to function; patients who go on suffering from devastating symptoms despite absence of any visible damages of their organs. No matter how natural the changes caused by long-term persistence of clinical manifestations or appearance of new signs and symptoms after survival of acute disease are, their presence necessitate rehabilitation of such cases [46].

Many patients develop severe asthenic syndrome, which significantly aggravates their quality of life and appreciably decreases capacity for work. For a long period of time such cases may preserve low-grade inflammation in the brain, reduced blood flow to it, its autoimmune damage or a combination of these abnormalities. Accumulation of pro-inflammatory cytokines, which penetrate the blood-brain barrier, in the CNS can cause dysregulation of central structures and cause autonomic dysfunction (elevated body temperature, sleep cycle disorders, cognitive disorders, rapid fatigue) [47].

Post-COVID asthenic syndrome most frequently manifests with mental problems and general exhaustion of the patient. The commonest manifestations of asthenia in post-COVID syndrome are as follows: rapid fatigue, irritable weakness (hyperexcitability, which rapidly changes into exhaustion), affective lability with traits of capriciousness and discontent, increased tears, memory defects. Possible causes for the development of asthenia in post-COVID syndrome include: massive drug load during therapy for COVID-19 (in particular, administration of dexamethasone,

which has the catabolic direction of its effect), long and devastating course of the disease with respiratory failure and hydroelectrolytic disorders, concomitant severe and/or uncompensated systemic diseases such as diabetes mellitus [48].

Important directions in rehabilitation treatment, for example for post-COVID-19 patients, were pointed out by a group of experts from the Defence Medical Rehabilitation Centre in Stanford Hall (Great Britain), who developed a relevant document, the Stanford Hall consensus statement, which contains the following general recommendations after COVID-19 for a target population of active individuals:

- rehabilitation treatment plans should be individualized according to the patient's needs, taking into consideration his/her comorbidities;
- in patients with COVID-19, rehabilitation should be aimed at relieving symptoms (dyspnea), improving psychological state, physical function and quality of life;
- patients should be periodically examined during their rehabilitation;
- patients should receive information about their condition and strategies of recovery after COVID-19.

Nevertheless, these are primarily general recommendations, which describe examination of patients with post-COVID syndrome and care for them. These guidelines do not elucidate drug treatment for such patients. In order to understand more clearly the direction of rehabilitation measures and their possible drug supplementation it is reasonable to examine the morphology and pathogenesis of post-COVID changes in more detail.

The main directions of treatment in post-COVID asthenic syndrome are as follows:

- optimization of drug treatment and early withdrawal of drugs with the catabolic effect (dexamethasone);
- organization of the diet, which should be optimum in amount and balanced by its components;
- psychological support in family and at work;
- revealing and control of hydroelectrolytic and metabolic disorders;
- monitoring and correction of disorders in presence of concomitant diseases (diabetes mellitus, arterial hypertension);
- prevention of metabolic disorders (fasting ketoacidosis and diabetic ketoacidosis);
- compensation for intracellular energy deficit.

According to the Stanford Hall consensus statement, the principles of pulmonary rehabilitation in post-COVID-19 patients are as follows:

- respiratory complications after COVID-19 may present with some degree of impairment and functional limitation, including (but not exclusively) due to decreased respiratory function;
- initial assessment of the patient's state is recommended in a timely manner, depending on the degree of dysfunction, normocapnic respiratory failure and the patient's physical and mental status;
- low intensity exercises should be considered initially particularly for patients who require oxygen therapy, while concurrently monitoring vital signs (heart rate, pulse oximetry and blood pressure). Gradual increase in the exercise should be based on severity of the patient's symptoms.

Respiratory rehabilitation in post-COVID-19 patients is aimed at decreasing manifestations of dyspnea, relieving anxiety and depression, preventing respiratory dysfunction, reducing disability rate, preserving the maximum volume of the respiratory function as well as improving the quality of life.

Recommendations for respiratory rehabilitation contain the following physical exercises:

- aerobic: walking, brisk walking, slow jogging, swimming, etc., beginning at a low intensity before progressively increasing in intensity and duration;
- training of strength: progressive trainings with load bearings;
- training of breathing: in presence of dyspnea, wheezing and difficult discharge of sputum it is necessary to use respiratory training techniques for improving sputum discharge and mode of breathing, including adjustment of breathing rhythm, thoracic activity training and mobilization of certain muscle groups.

Common signs and symptoms in hospitalized patients with COVID-19 include respiratory failure, dry cough, dyspnea and lung abnormalities on computerized tomography (opacity and/or thickening in the form of "clouded glass").

During the acute phase, physical exercise tolerance cannot be assessed with help of standard tests (e.g., 6-minute walking). Some patients still need oxygen therapy or have respiratory symptoms on discharge from hospital [49]. Follow-up of the respiratory system state is crucially important for assessing the pulmonary function, alveolar-arterial gas exchange and tolerance of physical exercise in patients, who recovered after COVID-19. At present, nothing is known about remote respiratory complications in post-COVID-19 patients.

Accordingly, a number of problems remain, which necessitate further study for developing methods of early diagnosis and more thorough prevention and effective rehabilitation of post-COVID-19 patients on the basis of innovation researches. Hence, having raised a huge number of fundamental questions concerning the pathogenesis of pneumonia, interactions of the virus with the lung microbiome and human immune system, heterogeneity and unpredictable severity of its course, the problem of SARS-CoV-2 virus-caused coronavirus infection of 2019, unprecedented in the human history, remains the main subject of the present-day life. Etiotropic and pathogenetic therapy of COVID-19 patients is now at the stage of development. Priority directions of research include development of a vaccine against COVID-19. The medical-organizational crisis,caused by the outbreak of COVID-19, also necessitates improvement of antiepidemic measures at the level of a medical establishment, a country and the world, modernization of health care systems and revision of their financing. Today a great army of specialists works tirelessly over solution of this difficult problem, thereby contributing to continuous updating and supplementing information about the above disease [50]. It is still urgent to develop comprehensive strategies for responding COVID-19 pandemic in order to decide in what way pathological states, caused by this infection, should be effectively controlled.

Declarations

Statement of Ethics

The author has no ethical conflicts to disclosure.

Consent for publication

The author gives her consent to publication.

Disclosure Statement

The author has no potential conflicts of interest to disclosure.

Funding Sources

There are no external sources of funding.

Data Transparency

The data can be requested from the author.

References

1. Zhao, Y., Zhao, Z., Wang, Y., Zhou, Y., Ma, Y., & Zuo W. (2020). Single-cell RNA expression profiling of ACE2, the receptor of SARS-CoV-2. American Journal of Respiratory and Critical Care Medicine, 202(5), 756–759 doi: 10.1164/rccm.202001-0179LE

2. Feshchenko, Yu. I., Holubovska, O. A., Dziublyk, O. Ya., Havrysiuk, V. K., Dziublyk, Ya. O., & Liskina, I. V. (2021). Osoblyvosti urazhennia lehen pry COVID-19 [Pulmonary disease in COVID-19]. Ukr. pulmonol. journal, (1), 5-14. [In Ukranian] doi: 10.31215/2306-4927-2021-29-1-5-14.

3. Uddin, M., Mustafa, F., Rizvi, T. A., Loney, T., Suwaidi, H. A., Al-Marzouqi, …& Senok, A. C. (2020). SARS-CoV-2/COVID-19: Viral Genomics, Epidemiology, Vaccines, and Therapeutic Interventions. Viruses, 12(5), 526. doi: 10.3390/v12050526.

4. Ortega, J. T., Serrano, M. L., Pujol, F. H., & Rangel, H. R. (2020). Role of changes in SARS-CoV-2 spike protein in the interaction with the human ACE2 receptor: An in silico analysis. EXCLI journal, 19, 410–417. doi: 10.17179/excli2020-1167.

5. Bonetti, P. O., Lerman, L. O., & Lerman, A. (2003). Endothelial dysfunction: a marker of atherosclerotic risk. Arteriosclerosis, thrombosis, and vascular biology, 23(2), 168–175. doi: 10.1161/01.atv.0000051384.43104.fc.

6. Kopcha, V.S., Bondarenko, A.M., & Sai, I.V. (2020). Patohenetychna terapiia koronavirusnoi pnevmonii pry COVID-19 [Pathogenetic therapy of COVID-19 associated pneumonia]. Klinichna immunolohiia. Alerholohiia. Infektolohiia, 6(127), 5-13. [in Ukrainian] Retrieved from: https://is.gd/9GJfKw.

7. South, A. M., Diz, D. I., & Chappell, M. C. (2020). COVID-19, ACE2, and the cardiovascular consequences. American journal of physiology. Heart and circulatory physiology, 318(5), H1084–H1090. doi: 10.1152/ajpheart.00217.2020.

8. Kai, H., & Kai, M. (2020). Interactions of coronaviruses with ACE2, angiotensin II, and RAS inhibitors-lessons from available evidence and insights into COVID-19. Hypertension research : official journal of the Japanese Society of Hypertension, 43(7), 648–654. doi: 10.1038/s41440-020-0455-8.
9. Ahmadian, E., Hosseiniyan Khatibi, S. M., Razi Soofiyani, S., Abediazar, S., Shoja, M. M., Ardalan, M., & Zununi Vahed, S. (2021). Covid-19 and kidney injury: Pathophysiology and molecular mechanisms. Reviews in medical virology, 31(3), e2176. doi: 10.1002/rmv.2176.
10. Yaqinuddin, A., & Kashir, J. (2020). Innate immunity in COVID-19 patients mediated by NKG2A receptors, and potential treatment using Monalizumab, Cholroquine, and antiviral agents. Medical hypotheses, 140, 109777. Advance online publication. doi: 10.1016/j.mehy.2020.109777.
11. Bhatia, K. S., Sritharan, H. P., Chia, J., Ciofani, J., Nour, D., Chui, K. … & Bhindi, R. (2021). Cardiac Complications in Patients Hospitalised With COVID-19 in Australia. Heart, lung & circulation, 30(12), 1834–1840. doi: 10.1016/j.hlc.2021.08.001.
12. Arias-Reyes, C., Zubieta-DeUrioste, N., Poma-Machicao, L., Aliaga-Raduan, F., Carvajal-Rodriguez, F., Dutschmann, M., & Soliz, J. (2020). Does the pathogenesis of SARS-CoV-2 virus decrease at high-altitude? Respiratory physiology & neurobiology, 277, 103443. doi: 10.1016/j.resp.2020.103443.
13. Lindsay, P. J., Rosovsky, R., Bittner, E. A., & Chang, M. G. (2021). Nuts and bolts of COVID-19 associated coagulopathy: the essentials for management and treatment. Postgraduate medicine, 133(8), 899–911. doi: 10.1080/00325481.2021.1974212.
14. Egilmezer, E., & Rawlinson, W. D. (2021). Review of studies of severe acute respiratory syndrome related coronavirus-2 pathogenesis in human organoid models. Reviews in medical virology, 31(6), e2227. doi: 10.1002/rmv.2227.
15. Wu, C., Chen, X., Cai, Y., Xia, J., Zhou, X., Xu, S., … &Song, Y. (2020). Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA internal medicine, 180(7), 934–943. doi: 10.1001/jamainternmed.2020.0994.
16. Flammer, A. J., Anderson, T., Celermajer, D. S., Creager, M. A., Deanfield, J., Ganz, P., … & Lerman, A. (2012). The assessment of endothelial function: from research into clinical practice. Circulation, 126(6), 753–767. doi: 10.1161/CIRCULATIONAHA.112.093245.
17. Varga, Z., Flammer, A. J., Steiger, P., Haberecker, M., Andermatt, R., Zinkernagel, A. S., … & Moch, H. (2020). Endothelial cell infection and endotheliitis in COVID-19. Lancet, 395(10234), 1417–1418. doi: 10.1016/S0140-6736(20)30937-5.
18. Ferrario, C. M., Jessup, J., Chappell, M. C., Averill, D. B., Brosnihan, K. B., Tallant, E. A., … & Gallagher, P. E. (2005). Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation, 111(20), 2605–2610. doi: 10.1161/CIRCULATIONAHA.104.510461.
19. Leon, A. S., Franklin, B. A., Costa, F., Balady, G. J., Berra, K. A., Stewart, K. J. … & Lauer, M. S. (2005). Cardiac rehabilitation and secondary prevention of coronary heart disease. Circulation , 111(3), 369-376. doi: 10.1161/01.CIR.0000151788.08740.5C.
20. Monteil, V., Kwon, H., Prado, P., Hagelkrüys, A., Wimmer, R. A., Stahl, M., … & Penninger, J. M. (2020). Inhibition of SARS-CoV-2 Infections in Engineered Human Tissues Using Clinical-Grade Soluble Human ACE2. Cell, 181(4), 905–913.e7. doi: 10.1016/j.cell.2020.04.004
21. Marongiu, F., Grandone, E., & Barcellona, D. (2020). Pulmonary thrombosis in 2019-nCoV pneumonia? Journal of thrombosis and haemostasis : JTH, 18(6), 1511–1513. doi: 10.1111/jth.14818.
22. Cecchini, R., & Cecchini, A. L. (2020). SARS-CoV-2 infection pathogenesis is related to oxidative stress as a response to aggression. Medical hypotheses, 143, 110102. doi: 10.1016/j.mehy.2020.110102.
23. Tay, M. Z., Poh, C. M., Rénia, L., MacAry, P. A., & Ng, L. (2020). The trinity of COVID-19: immunity, inflammation and intervention. Nature reviews. Immunology, 20(6), 363–374. doi: 10.1038/s41577-020-0311-8.
24. Gemelli Against COVID-19 Post-Acute Care Study Group (2020). Post-COVID-19 global health strategies: the need for an interdisciplinary approach. Aging clinical and experimental research, 32(8), 1613–1620. doi: 10.1007/s40520-020-01616-x.

25. Mechi, A., Al-Khalidi, A., Al-Darraji, R., Al-Dujaili, M. N., Al-Buthabhak, K., Alareedh, M., … & Nafakhi, H. (2021). Long-term persistent symptoms of COVID-19 infection in patients with diabetes mellitus. International journal of diabetes in developing countries, 1–4. Advance online publication. doi: 10.1007/s13410-021-00994-w.
26. Goërtz, Y., Van Herck, M., Delbressine, J. M., Vaes, A. W., Meys, R., Machado, F. … & Spruit, M. A. (2020). Persistent symptoms 3-months after a SARS-CoV-2 infection: the post-COVID-19 syndrome? ERJ open research, 6(4), 00542-2020. doi: 10.1183/23120541.00542-2020.
27. Baj, J., Ciesielka, M., Buszewicz, G., Maciejewski, R., Budzyńska, B., Listos, P., & Teresiński, G. (2021). COVID-19 in the autopsy room-requirements, safety, recommendations and pathological findings. Forensic science, medicine, and pathology, 17(1), 101–113. doi: 10.1007/s12024-020-00341-1.
28. Hasichaolu, Zhang, X., Li, X., Li, X., & Li, D. (2020). Circulating Cytokines and Lymphocyte Subsets in Patients Who Have Recovered from COVID-19. BioMed research international, 2020, 7570981. doi: 10.1155/2020/7570981.
29. COVID-19 rapid guideline: managing the long-term effects of COVID-19. (2020). National Institute for Health and Care Excellence (NICE). Retrieved from: www.nice.org.uk/guidance/ng188
30. Feshchenko, Y. I., Dziublyk, O. Y., Dziublyk, Y. O., Pylypenko, M. M., & Bororova, O. L. (2020). Nehospitalna pnevmoniia, asotsiiovana z COVID-19: pohliad na likuvannia. [Community-acquired pneumonia associated with COVID-19: the treatment perspectives]. Ukr. pulmonol. journal, (2), 5-12. [In Ukrainian]. doi: 10.31215/2306-4927-2021-29-1-5-14
31. Rosca, E. C., Heneghan, C., Spencer, E. A., Brassey, J., Plüddemann, A., Onakpoya, I. J. … & Jefferson, T. (2021). Transmission of SARS-CoV-2 associated with aircraft travel: a systematic review. Journal of travel medicine, 28(7), taab133. doi: 10.1093/jtm/taab133.
32. Atique, M., Ghafoor, A., Javed, R., Fatima, N., Yousaf, A., & Zahra, S. (2021). Correlation of Viral Load With the Clinical and Biochemical Profiles of COVID-19 Patients. Cureus, 13(7), e16655. doi: 10.7759/cureus.16655.
33. Alba, G. A., Ziehr, D. R., Rouvina, J. N., Hariri, L. P., Knipe, R. S., Medoff, B. D. … & Hardin, C. C. (2021). Exercise performance in patients with post-acute sequelae of SARS-CoV-2 infection compared to patients with unexplained dyspnea. EClinicalMedicine, 39, 101066. doi: 10.1016/j.eclinm.2021.101066.
34. Pertseva, T. A., Kireyeva, T. V., Bielosludtseva, K. O., & Kryhtina M. A. (2017). Klinichni, zahalni, hemokoahuliatsiini ta patolohoanatomichni osoblyvosti patsiientiv z pomirnoiu ta vazhkoiu vnutrishnoiu nabutoiu pnevmoniieiu za danymy retrospektyvnoho analizu. [Clinical, general, hemocoagulation and pathologicanatomical features of patients with moderate and severe community acquired pneumonia by the data of retrospective analysis]. Medicni Perspektivi, 22(3), 17–24. [In Ukrainian]. doi:10.26641/2307-0404.2017.3.111858.
35. Hu, B., Zeng, L. P., Yang, X. L., Ge, X. Y., Zhang, W., Li, B. ... & Shi, Z. L. (2017). Discovery of a rich gene pool of bat SARS-related coronaviruses provides new insights into the origin of SARS coronavirus. PLoS pathogens, 13(11), e1006698. doi: 10.1371/journal.ppat.1006698
36. Arbour, N., Côté, G., Lachance, C., Tardieu, M., Cashman, N. R., & Talbot, P. J. (1999). Acute and persistent infection of human neural cell lines by human coronavirus OC43. Journal of virology, 73(4), 3338–3350. doi: 10.1128/JVI.73.4.3338-3350.1999.
37. Arbour, N., Ekandé, S., Côté, G., Lachance, C., Chagnon, F., Tardieu, M., … & Talbot, P. J. (1999). Persistent infection of human oligodendrocytic and neuroglial cell lines by human coronavirus 229E. Journal of virology, 73(4), 3326–3337. doi: 10.1128/JVI.73.4.3326-3337.1999.\
38. Carvalho-Schneider, C., Lauren,t E., Lemaignen, A., Beaufils, E., Bourbao-Tournois, C., Laribi, S., …& Bernard L. (2021) Follow-up of adults with noncritical COVID-19 two months after symptom onset. Clin Microbiol Infect. 27(2), 258-263. doi: 10.1016/j.cmi.2020.09.052.
39. Çomoğlu, Ş., Öztürk, S., Topçu, A., Kulalı, F., Kant, A., Sobay, R., … & Yilmaz, G. (2021). The Role of CO-RADS Scoring System in the Diagnosis of COVID-19 Infection and its Correlation with Clinical Signs. Current medical imaging. Advance online publication. 27. doi: 10.2174/1573405617666210827150937.
40. Robinson, P. (2021). Long COVID and breathlessness: an overview. British journal of community nursing, 26(9), 438–443. doi: 10.12968/bjcn.2021.26.9.438.

41. Wynberg, E., van Willigen, H., Dijkstra, M., Boyd, A., Kootstra, N. A., van den Aardweg, J. G. … & RECoVERED Study Group (2021). Evolution of COVID-19 symptoms during the first 12 months after illness onset. Clinical infectious diseases, ciab759. doi: 10.1093/cid/ciab759. Online ahead of print.
42. Basanets, A. V., Yermakova, O. V., Kriukova, L. B., Gvozdetsky, V. A., & Zhurahovskaya, N. V. (2021). Acute respiratory disease COVID-19 as occupational disease. Ukrainian Pulmonology Journal, 29(2), 25–29. doi:10.31215/2306-4927-2021-29-2-25-29
43. Levison M.E. Commentary: what we know so far about post-COVID syndrome. Retrieved from: https://www.msdmanuals.com/professional/news/editorial/2020/09/23/20/17/post-covid-syndrome
44. Komaroff, A. (2020). The tragedy of long COVID. Health Alerts from Harvard Medical School, Harvard Health Publishing, Retrieved from: https://www.health.harvard.edu/blog/the-tragedy-of-the-post-covid-long-haulers-2020101521173
45. Wijeratne, T., & Crewther, S. (2020). Post-COVID 19 Neurological Syndrome (PCNS); a novel syndrome with challenges for the global neurology community. Journal of the neurological sciences, 419, 117179. doi: 10.1016/j.jns.2020.117179.
46. Dinh, A., Jaulmes, L., Dechartres, A., Duran, C., Mascitti, H., Lescure, X., … AP-HP/Universities/INSERM COVID-19 research collaboration, Data-sciences committee, Scientific committee, & Covidom regional centre steering commitee (2021). Time to resolution of respiratory and systemic coronavirus disease 2019 symptoms in community setting. Clinical microbiology and infection, 27(12), 1862.e1–1862.e4. doi: 10.1016/j.cmi.2021.08.021.
47. Zhao, H.M., Xie, Y.X., Wang, C.; Chinese Association of Rehabilitation Medicine; Respiratory Rehabilitation Committee of Chinese Association of Rehabilitation Medicine; Cardiopulmonary Rehabilitation Group of Chinese Society of Physical Medicine and Rehabilitation. (2020) Recommendations for respiratory rehabilitation in adults with coronavirus disease. Chin Med J (Engl), 133, 13, 1595-1602. doi: 10.1097/CM9.0000000000000848.
48. Wade, D.T. (2020). Rehabilitation after COVID-19: an evidence-based approach. Clin Med (Lond), 20(4), 359–365. doi: 10.7861/clinmed.2020-0353
49. Barker-Davies, R. M., O'Sullivan, O., Senaratne, K., Baker, P., Cranley, M., Dharm-Datta, S. … &Bahadur, S. (2020). The Stanford Hall consensus statement for post-COVID-19 rehabilitation. British journal of sports medicine, 54(16), 949–959. doi: 10.1136/bjsports-2020-102596.
50. Mylvaganam, R. J., Bailey, J. I., Sznajder, J. I., Sala, M. A., & Northwestern Comprehensive COVID Center Consortium (2021). Recovering from a pandemic: pulmonary fibrosis after SARS-CoV-2 infection. European respiratory review, 15, 30(162), 210194. doi: 10.1183/16000617.0194-2021.

Received: 17-Sep-2021
Accepted: 13-Dec-2021