Open Peer Review on Qeios

Covid-19: the angiotensin II pro-inflammatory response, the Mas receptor downregulation, pulmonary artery and nitric oxide involvement

Dimitris Labrou

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes the disease covid-19, is characterized by high mortality among the elderly. The main manifestation that separates this virus from other beta-coronaviruses, is associated with the increased risk of pneumonia, that leads to acute respiratory distress syndrome (ARDS). Any tissue damage in the periphery, is triggered by the excess of cytokines, that are released in the bloodstream, after the initiation of ARDS. Moreover, the virus appears to have the RNAemia trait, a condition that is also witnessed in the case of the human immunodeficiency virus (HIV), but the difference lies in the inability of the former to be transmitted through blood. The angiotensin-converting enzyme 2 receptor (ACE2R) downregulation leads to increased renin-angiotensin system (RAS) activation, and also decreased activity of the Mas receptor, a well-known GPCR, which is the substrate for the ligand angiotensin 1-7, which is produced by the conversion of angiotensin II, by the ACE2R. Last but not least, since pneumonia is one of the main causes of acute lung injury (ALI), the latter, present due to severe damage to the main pulmonary artery, we hence claim that medication used for the treatment of pulmonary hypertension could decrease the fatality risk of pneumonia, and in combination with the standard approach of corticosteroids, antiviral agents, and NO administration, could alleviate, or even eradicate pneumonia symptoms.

Introduction

1. Covid-19 pathophysiology and mechanisms of infection

Covid-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The entry receptor for the virus is the ACE2R, whereas other coronaviruses with the same target receptor include the beta-coronavirus SARS-CoV, the alpha-coronavirus HCoV-NL63, alpha-coronavirus, HCoV-229E, and beta-coronaviruses HCoV-OC43 and HCoV-HKU1. The cleavage of spike protein into S1 and S2 subunits takes place during their formulation in the infected host cell. The same subunits are essential for binding to ACE2(S2) and cell entry (S1), respectively. There is some acclaimed involvement of proteases like TMPRSS2 and FURIN assisting with the functions of the S trimer (spike), since the cleavage site of TMPRSS2 lies in the S2' subunit of the spike, whereas the FURIN cleavage site is located between the S1 and S2

subunits. [1] The symptoms of the virus are embedded by heterogeneity, that is exacerbated with older age and increased viral load. In most patients the main ailments include symptoms that resemble that of the common cold virus and that of Influenza, but in some cases, there is a need for immediate hospitalization, for patients to be stabilized, and the symptoms tend to be more severe in nature, with pneumonia and ARDS, considered the most imminent threat. [2] A lower threshold for developing pneumonia and ARDS brings about a high mortality rate. Other classes of coronaviruses, that pose the same risk, include the severe respiratory distress syndrome coronavirus (SARS-CoV) [3] and the middle eastern respiratory syndrome coronavirus (MERS-CoV) [4]. The main localization of all three coronaviruses described is mainly the lungs and the nasopharynx, hence the high chance of causing pneumonia. Initial estimates of fatality were approximately in the range of 1.5-2% and an overall 31.7% of covid-19 patients required hospitalization. Of course, the spread of the disease to the general population diversified those estimates, but frequent hospitalization of elderly was still evident. [5] The uniqueness of SARS-CoV-2, compared to the rest, is based on the dependence on comorbidities, to fully lead to a deteriorated state, given that most covid-19 victims previously had diseases of either the cardiovascular or the respiratory system. [6] This liability possibly entails the importance of the entry receptor, in those conditions, which, in turn, amplifies health complications that lead to the patient's 'departure'.

2. The nicotine hypothesis

Any potential discussion, concerning the interaction of the virus with secondary receptor subtypes, mainly those of the nicotinic cholinergic system, the most prominent being the alpha 7 nicotinic receptor (a7nAchR) is lacking. First of all, the authors that had previously supported this statement, including the author of this manuscript, claimed that the virus affects the function of nicotinic receptors (nAchRs). [7] This is supposed to take place through binding to the a7nAchR of local epithelial cells of the lungs, that are directly projected by the vagus nerve. [8] The value of this approach scolds behind the idea that all the ligands that possess the same mechanism of action, such as various neurotoxins, neuromuscular blocking agents (NMBA), as well as bupropion, should cause the same toxicity, but this is not materialized. [9][10][11] The vagus nerve is part of the inflammatory reflex. The inflammatory reflex consists of the brain, the immune system, and the vagus nerve, the latter being the main operator. Even more, the medication that enhances the function of the vagus nerve, mainly most anti-epileptics, should have been empowered as a potential treatment for covid-19, which is not the case, for patients who have already been administered this treatment for the relative neurological disorder. [12] The therapeutics of nicotine, are questionable, since it might encourage the public to turn to smoking, or those who are willing to enter smoking cessation, to essentially discontinue their effort. [13] Of course, the authors quoted, do encourage the use of patches and nicotine gums, but the most likely scenario for the common folk is to turn to the cheapest alternative. Moreover, the addictive nature of this alkaloid, will, in the long-term, cause dependence on the substance, thereby sliding backward any effort of the anti-smoking campaigns. Apart from that, no matter the drug formulation, nicotine, which is thought to upregulate ACE2R, [14] cannot help with the alleviation of symptoms, taking into consideration that the expression of ACE2R, either widespread, or minimized, does not affect the membrane's action potential, since it does not have an intracellular pathway. [15] The idea that either the reduced or the increased expression of the enzyme can make symptoms milder, is based on the observation that minors and generally younger people, experienced more subtle

symptomatology, whereas less ACE2R means fewer points of entry. Both assumptions are irrelevant, since the ACE2R is widespread across the whole body, so there cannot be a limited expression, [16] and younger people do have fewer symptoms, due to a lack of comorbidities, though there are some comorbidities with increased risk for covid-19, even in minors, which explain some rare cases of deaths in that age group. [17]

3. The Mas receptor

Therefore, how can the expression of ACE2R affect in any way possible, the patient and the general symptoms experienced? It is more likely, that the binding of the spike to ACE2R, downregulates the ACE2R, or at least keeps more copies of the receptor occupied by the spike, and this in turn, leads to decreased conversion rates of angiotensin II into angiotensin 1-7, [18] which is the active ligand for the Mas receptor, a well-known GPCR, that has many properties, among which are included angiogenic and hypertension regulation ones. [19] The gene of the Mas receptor is not one, but two, and the point is that one of those genes, is a proto-oncogene, suggesting that overstimulation of the receptor can potentially lead to tumor-genesis. The design of a novel agonist for the Mas receptor or even the external administration of angiotensin 1-7 is a likely solution, according to the quoted citation, especially taking into account the cardio-protective role of this peptide agonist. [20] However, we ought to proceed with caution, despite the conflicting evidence debating the anti-tumor versus the tumor-genic nature of the Mas receptor. It should be clarified that the type of tumor expressed, is either indifferent or vital in its dependence on the Mas receptor. Chances are, that a lot of the symptoms of covid-19, are strongly aggregated by the downregulation of the Mas receptor and generally, by the overall comorbidities of the cardiovascular system, due to the cell entry enzyme.

To better examine the phenomenon, we have to address the issue of the angiotensin-converting enzyme inhibitors (ACEI), that are used for cases of hypertension, as well as heart failure. These agents, up to a point do affect the ACE2R, as well as the Mas receptor, via upregulation, and the entire RAS system in general, via downregulation, that is manifested through the host's ability to resist the effects of those agents. However, ACEI medication does not provide any prophylactic or compromising traits, concerning covid-19. The referenced article suggests that there is a reduced risk for hospitalization, but it is ethnic-dependent, and generally, the literature based on the matter is contradictory, so any potential conclusion on the matter seems vague, for the time being. [21][22]

4. ARDS, cytokine storm, and RNAemia intrerperspective

Studying the hospitalized patients, we observe a high rate of pneumonia and ARDS.[23] Those patients, at the same time, do express cytokine storm. [24] Moreover, they have increased chances of experiencing RNAemia, which leads to a worse prognosis. [25] RNAemia cannot cause infection of another individual, through blood transfusion,[26] hence why it might be simply, commonplace, among patients having ARDS and/or pneumonia. To verify the solidity of the last sentence, we searched for data on pneumonia/ARDS, that were caused by other viruses, or even bacteria, in order to ascertain whether the RNAemia trait and the excess of cytokines, are common ground among patients with the same condition.

In detail, the influenza virus can cause RNAemia, during the acute phase of the infection, which pinpoints the exact cause,

as diffusion of the virus, through the capillaries of the lungs, with RNAemia potentially deteriorating the prognosis of the patient. There are some indications of distal virus incubation in various tissues, but it is disputable whether the latter is actually the case, having considered that every virus requires a virion to force cell entry. [27] Another candidate for viremia, is the human immunodeficiency virus (HIV), though the same conditions of RNAemia, are less common among patients with the disease, since the viremia trait is much more predominant. [28] Despite data that are supporting viremia, being mostly restricted to certain viruses, the same can be said for bacterial-acquired pneumonia, which may eventually lead to sepsis, with a high mortality rate of 51%. [29] This condition can be reached both through infections, most commonly that of the lungs, as well as minor injuries, such as excessive tooth brushing. [30] Sepsis, much like ARDS, causes an overload of cytokine release across the whole body, with the body's inability to suppress systemic inflammation, leading to a phenotype much similar to ARDS. Although, lung infection is the major etiology of sepsis, other tissues' vulnerability can lead to the same condition, such as infections of the urinary tract, as well as of the gastrointestinal tract. [31]

Taking into account the similarities between sepsis and ARDS, as well as the common ground of viremia, between different viruses, it is best to quantify the cytokine response of the cytokine storm, compared to that of sepsis, to verify whether those two conditions are related, or even intertwined. This test revealed case reports of patients developing cytokine storm, early on, after abdominal surgery. At the same time, the diagnosis also mentioned the pre-existence of sepsis, and possibly a faulty surgery might be to blame for the acquirement of both ailments. The co-existence of those major pro-inflammatory conditions in the same individual, suggests that one can interfere or even lead to the development, of the other. [32] Another case that should be heed, concerns ARDS versus cytokine storm. Data from reviews mention that cytokine storm is linked to ARDS, and the cytokine storm can lead to ARDS and vice versa. [33] Other references mention that the cause of ARDS is an immune system overreaction to the infection, which leads to ample release of cytokines in the lungs, that in turn, causes extensive tissue damage. The same effect can be triggered by the cytokine storm, with the localization of inflammation being systemic versus localized. [34] The cytokines that are overproduced during the cytokine storm, are interleukin-4(IL-4), IL-5, IL-1, IL-6, IL-17, tumor necrosis factor alpha (TNF-a), and IL-13. From the pool of patients with pneumonia, 15% of them eventually develop ARDS, as well, hence pneumonia and cytokine storm, is more prevalent than ARDS, in the covid-19 infection. The cytokine storm is characterized by major cell apoptosis, as well as distal tissue sustained damage, due to the unleashed and of course, uncontrolled, actions of pro-inflammatory cytokines, whose effects, can lead to multiple organ failure. Apart from that, most patients with covid-19, regardless of the viral load, and severity of symptoms, do suffer from lymphocytopenia, mostly related to a decreased title of CD4+ and CD8+ T cells. T cells do not express the ACE2 receptor, thus it is unlikely that this condition is reached via direct T cell infection. According to the overall evidence, it is palpable, that lymphocytopenia is triggered by the regulation of T cell production, via cytokine signaling. The first candidate is IL-6, which possesses both pro-inflammatory and anti-inflammatory roles, depending on the quantity released in the serum. The over-stimulation of the IL-6R, the receptor of IL-6, leads to pro-inflammatory responses and is linked to ARDS as well as severe symptoms of covid-19, which led to the hypothesis that IL-6 and IL-6R neutralizing antibodies can improve prognosis. We would also add, that the binary profile of action of IL-6 depending on extracellular concentration, might indicate the pharmacodynamics of a partial agonist, which is commonplace among ligands that have contradictory effects, depending on dose availability, although this is mere speculation, that we use to imply that IL-6R blockers, might be more beneficial

than IL-6 neutralizing antibodies. Another ligand of potential interest is IL-1, which has a distinct pro-inflammatory role and is released from infected cells. The signaling pathway of IL-1 activates basic pro-inflammatory agents, such as the NF-kB superfamily, pinpointing the exacerbation of inflammation through this response. IL-17 seems to help in the maturation of T cells, into Th17 cells, while, at the same time, it halts the immune system mobilization, prolonging the infection, via a long-term decrease of adaptive immune system cell recruitment. Moreover, IL-17 has been evaluated as a biomarker in lung pathology of viral infections. Lastly, TNF-a, apart from its direct role in cell apoptosis, is also responsible for bronchoconstriction and breathing difficulties. Treatment of patients with TNF-a blockers led to recovery without the need for hospitalization. [35]

5. Mas receptor, ACE2 receptor, and acute lung injury

Having established the connection between the Mas receptor and the RAS system, in general, it is high time we discuss the properties of the Mas receptor in detail. The Mas receptor, angiotensin 1-7, angiotensin 1-9, the ACE2, and the angiotensin II receptor (AT2R), pose the major counterweight in the actions of the RAS system. ACE2R converts angiotensin II, to angiotensin 1-7 and angiotensin I, to angiotensin 1-9. The activation of the Mas receptor by angiotensin 1-7, promotes blood pressure reduction, noradrenaline decreased release, vasodilation, NO generation and release, an increase in parasympathetic tone, and baroreflex sensitivity. The angiotensin 1-9, also binds to the AT2R and promotes natriuresis and NO release. Interestingly enough, the cardioprotective role of the Mas receptor is attributed to the antagonism of the angiotensin II signaling. The AT1R and AT2R have opposing effects, which are contributed to their signaling, with angiotensin II binding to both, whereas angiotensin 1-7, binding to AT2R, but most likely not Mas. The AT1R can interact with the MasR to form heterodimers, whose function is to halt the AT1R activity. The same ability to form heterodimers with the MasR is also a tendency of the AT2R. While MasR potential agonist angiotensin 1-7, does not bind to the receptor, an antagonist of the AT2R, also known as PD123319, can also bind to the MasR, suggesting that a modification of the structure of the angiotensin 1-7 might produce an agonist for both. Studying the potential benefits of ACE2R agonists, in terms of pulmonary arterial hypertension, those ligands may face resistance to their effects, due to the cleaving of the ACE2R, which is a membrane enzyme, and at the same time, substrate, to various proteases. That is why analyzed experiments with recombinant ACE2R gave better results, with a good safety profile, with the process still ongoing, and in need of further investigation. However, soluble ACE2Rs can enhance the counter-balancing actions of the RAS system, which is the main theme of this experiment. The MasR theoretical agonist angiotensin 1-7, due to a limited half-life of 10 seconds, cannot provide a viable solution. As suggested before, the Mas-ACE2-angiotensin 1-7 Axis can regulate the actions of the RAS system, and promote cardio-protective effects, as well as anti-inflammatory responses. In terms of any cardiovascular disease, it is emphasized that the developed ligands, either synthetic, or endogenous, do not provide enough data, to enter the market just yet. [36] However, this article gives us enough details about the importance of the MasR, as well as the angiotensin 1-7. As said before, those components are being tested for the treatment of pulmonary arterial hypertension, and we believe that the same artery is involved in the acute lung injury, sustained due to covid-19.

Studying cases of ARDS, patients with etiology other than covid-19, do suffer from gas partial pressure abnormalities, in a

range of 10-12%, whereas covid-19 ARDS has this feature much more common, approximately 40-50%. The inequity in the frequency of this complication, can be limited to two parameters, anatomic intact tissues and gas exchange incapacities. All in all, it seems that in other cases, some tissues are left with some component of aerial regeneration, whereas in covid-19, some areas are completely starved out of oxygen, hence making the hypoxemia more severe, increasing the need for mechanical ventilation. The areas without oxygen (dead space) are more likely to suffer from vasoconstriction, as well as immuno-thrombosis. The phenomenon of thrombosis is relative to severe vascular damage, sustained, likely by the increased release of Angiotensin II, as well as the cytokines of ARDS. [37]

The comorbidity of pulmonary arterial hypertension (PAH) seems to be accompanied, most often by atrial fibrillation (AF)/atrial arrhythmias. The key manifestations are hypoxemia and PAH, which distort the autonomic sympathetic tone, and eventually bring about AF, with most of those cases having a poor prognosis. [38] Therefore, the treatment of both might potentially decrease the risk of heart arrhythmias. A meta-analysis of PAH acquired due to covid-19 showed an increased mortality rate. [39] As for the causes, most likely they are summed up to lung and vascular tissue damage. [40] As said before, the lead cause behind vascular and alveolar damage in the lungs, has to do with the gas exchange of O2/CO2, relative of course, to hypoxemia, because this deficiency leads to dead space in the lungs, thereby altering blood supply in those areas. In the meantime, the other endogenous gas in the lungs, nitric oxide (NO) in particular, can pose a buffer in the abnormalities of the other two gasses and many researchers have described the therapeutic potential of this agent. Though the researchers mention the ability of NO to inhibit SARS-CoV-2 replication, this is highly unlikely, but the most plausible case scenario, involves the chance to restore the imbalance between the O2/CO2 and decrease dyspnea [41] As described, by the previous references, one of the functions of the MasR, is to increase the release of NO and to try stimulating this pathway, which may as well provide a potential treatment, in combination with the administration of NO via inhalation.

To connect the pieces of the puzzle, it seems that, at first, patients experience pneumonia, due to covid-19, followed by hypoxia, which is the first sign of pO2/pCO2 imbalance. Then, considering the delay between diagnosis and the patient's transfer to the ICUs, pneumonia deteriorates with excessive release of pro-inflammatory cytokines, that cause damage to the tissue, that is already labeled as anatomic dead space, meaning that it does not receive enough blood and oxygen supply from the pulmonary artery, due to alveolar and pulmonary artery sustained damage. At that point, there is a high chance of development of PAH, that is often accompanied by AF or other cardiac arrhythmias. If the latter is not treated sufficiently, there is a high chance of acute lung injury (ALI). Data from the literature, pinpoint that PAH is more common than thought, in covid-19 patients, and only their transfer to specialized centers treating PAH, could save their lives, especially considering that from a sample of patients, approximately 63.6% required transfer to ICU, of which 45.45% died, and only a minimum 36% of those submitted to ICUs, eventually received treatment for PAH, and survived. [42] Meanwhile, patients admitted to ICUs, experienced AF, at a rate of 4.2% among a sample of 3435 patients overall, and those that did have a higher risk of passing away, with the overall ratio being 37.2% versus 16.9%, having compared the development of AF within the ICU, with the incident AF admission, respectively. [43] Studying the incidence of PAH and right ventricular dysfunction (RVD), the latter being a liability for developing AF, researchers found that in a sample of hospitalized non-ICU patients, RVD was not a liability for higher mortality, but the same cannot be said for PAH,

and the study did not even consider having both abnormalities at the same time. [44] Another article quoted mentions that the co-existence of PAH and AF, causes severe impairment in daily activities, and this poses a deterrent to any chances of improved prognosis. [45]

Discussion

Having taken into account the different parameters of covid-19 complications, it seems that the first issue that needs to be addressed is the gas exchange imbalance, which needs mechanical ventilation, along with the administration of NO, to help with the hypoxemia. Moreover, extreme inflammation, albeit it is ARDS or cytokine storm, though both are interconnected, must be dealt with anti-inflammatory agents, one of which is TNF-a blockers, an example of which is ananikra. Also, the administration of corticosteroids, most commonly methylprednisolone is crucial for any chances of halting inflammation, especially the one linked to specific interleukins, that we analyzed above. But the bigger issue is to restore blood supply to the lungs to avoid ALI, so this involves medications used against PAH, such as sildenafil. As for the case of AF, one needs to treat it, simultaneously with PAH, to get better results. RNAemia accurately used as a biomarker for prognosis, is an indication of multiple organ failure, and also might be triggered by severe alveolar damage, having considered that most patients with covid-19 suffer from alveolar edema, which can at the same time lead to RNAemia, and we believe that this is caused by severe lung damage due to hypoxemia and cytokine release, that would eventually disturb the alveoli's ability to control which components pass from the lungs to the blood and which not. [46] Given the importance of increased angiotensin II release, due to ACE2 downregulation, and the counter-intuitive role of MasR-ACE2-angiotensin 1-7, to the RAS system, we believe that if we promote the increased action of ACE2R, angiotensin 1-7, angiotensin 1-9, and the MasR, either directly, or indirectly, we could effectively reduce the actions of angiotensin II. This in turn, could potentially decrease the cytokine storm, which is mainly triggered by the pro-inflammatory actions of angiotensin II on the AT1R, and the decreased activity of the MasR, [47][48] and in turn reverse and prevent the chance of ALI.

Conclusion

All in all, covid-19 is a multiparameter disease. First, the lung edema, then the cytokine storm, the PAH, and AF-in other words too many factors to take into account. However, one can easily observe, that one is the result of a dysregulation of the other. We thereby, note that, the turning point in a patient's prognosis begins with the accumulation of pus in the lungs, which leads to lung edema, and subsequently PAH and ARDS. The initial cause for this is the development of pneumonia and hypoxemia, which might not be as early diagnosed, as needed, but could still be reversed. That is why, it is vital to provide auxiliary treatment for PAH, and AF/cardiac diseases, and at the same time to the point that it is feasible, to offer mechanical ventilation, not just with oxygen, but NO as well. In the end, restoring and counter-balancing the RAS system's excessive stimulation, can in turn, reduce the severe inflammation sustained. The latter is based on the restoration of the MasR-angiotensin 1-7-ACE2R Axis.

References

1. ^*Jackson, C.B., Farzan, M., Chen, B. et al. Mechanisms of SARS-CoV-2 entry into cells. Nat Rev Mol Cell Biol 23, 3-20 (2022). https://doi.org/10.1038/s41580-021-00418-x*
2. ^*Chen, YY., Assefa, Y. The heterogeneity of the COVID-19 pandemic and national responses: an explanatory mixed-methods study. BMC Public Health 21, 835 (2021). https://doi.org/10.1186/s12889-021-10885-8*
3. ^*Demmler GJ, Ligon BL. Severe acute respiratory syndrome (SARS): a review of the history, epidemiology, prevention, and concerns for the future. Semin Pediatr Infect Dis. 2003 Jul;14(3):240-4. doi: 10.1016/s1045-1870(03)00056-6. PMID: 12913837; PMCID: PMC7128384.*
4. ^*Baharoon S, Memish ZA. MERS-CoV as an emerging respiratory illness: A review of prevention methods. Travel Med Infect Dis. 2019 Nov 12;32:101520. doi: 10.1016/j.tmaid.2019.101520. Epub ahead of print. PMID: 31730910; PMCID: PMC7110694.*
5. ^*Wen-Lin Su, Kuo-Cheng Lu, Chih-Yu Chan, You-Chen Chao, COVID-19 and the lungs: A review, Journal of Infection and Public Health, Volume 14, Issue 11,2021, Pages 1708-1714, ISSN 1876-0341, https://doi.org/10.1016/j.jiph.2021.09.024.*
6. ^*Russell, C.D., Lone, N.I. & Baillie, J.K. Comorbidities, multimorbidity and COVID-19. Nat Med 29, 334-343 (2023). https://doi.org/10.1038/s41591-022-02156-9*
7. ^*Dormoy V, Perotin JM, Gosset P, Maskos U, Polette M, Deslée G. Nicotinic receptors as SARS-CoV-2 spike co-receptors? Med Hypotheses. 2022 Jan;158:110741. doi: 10.1016/j.mehy.2021.110741. Epub 2021 Dec 14. PMID: 34924680; PMCID: PMC8669939.*
8. ^*Tracey, K. The inflammatory reflex. Nature 420, 853-859 (2002). https://doi.org/10.1038/nature01321*
9. ^*Ferraz CR, Arrahman A, Xie C, Casewell NR, Lewis RJ, Kool J and Cardoso FC (2019) Multifunctional Toxins in Snake Venoms and Therapeutic Implications: From Pain to Hemorrhage and Necrosis. Front. Ecol. Evol. 7:218. doi: 10.3389/fevo.2019.00218*
10. ^*Naguib M, Magboul MM. Adverse effects of neuromuscular blockers and their antagonists. Middle East J Anaesthesiol. 1998 Jun;14(5):341-73. PMID: 9785339.*
11. ^*Vázquez-Gómez E, Arias HR, Feuerbach D, Miranda-Morales M, Mihailescu S, Targowska-Duda KM, Jozwiak K, García-Colunga J. Bupropion-induced inhibition of α7 nicotinic acetylcholine receptors expressed in heterologous cells and neurons from dorsal raphe nucleus and hippocampus. Eur J Pharmacol. 2014 Oct 5;740:103-11. doi: 10.1016/j.ejphar.2014.06.059. Epub 2014 Jul 9. PMID: 25016090.*
12. ^*Kuroda N. Epilepsy and COVID-19: Updated evidence and narrative review. Epilepsy Behav. 2021 Mar;116:107785. doi: 10.1016/j.yebeh.2021.107785. Epub 2021 Jan 13. PMID: 33515934; PMCID: PMC7805398.*
13. ^*Korzeniowska A, Ręka G, Bilska M, Piecewicz-Szczęsna H. The smoker's paradox during the COVID-19 pandemic? The influence of smoking and vaping on the incidence and course of SARS-CoV-2 virus infection as well as possibility of using nicotine in the treatment of COVID-19 - Review of the literature. Przegl Epidemiol. 2021;75(1):27-44. doi: 10.32394/pe.75.03. PMID: 34328284.*
14. ^*Farsalinos, K., Bagos, P.G., Giannouchos, T. et al. Smoking prevalence among hospitalized COVID-19 patients and*

its association with disease severity and mortality: an expanded re-analysis of a recent publication. Harm Reduct J 18, 9 (2021). https://doi.org/10.1186/s12954-020-00437-5

15. ^*Sodhi, P.V.; Sidime, F.; Tarazona, D.D.; Valdivia, F.; Levano, K.S. A Closer Look at ACE2 Signaling Pathway and Processing during COVID-19 Infection: Identifying Possible Targets. Vaccines 2023, 11, 13. https://doi.org/10.3390/vaccines11010013*
16. ^*Li, MY., Li, L., Zhang, Y. et al. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. Infect Dis Poverty 9, 45 (2020). https://doi.org/10.1186/s40249-020-00662-x*
17. ^*Mann EA, Rompicherla S, Gallagher MP, Alonso GT, Fogel NR, Simmons J, Wood JR, Wong JC, Noor N, Gomez P, Daniels M, Ebekozien O. Comorbidities increase COVID-19 hospitalization in young people with type 1 diabetes. Pediatr Diabetes. 2022 Nov;23(7):968-975. doi: 10.1111/pedi.13402. Epub 2022 Aug 28. PMID: 36054578; PMCID: PMC9538459.*
18. ^*Patel VB, Zhong JC, Grant MB, Oudit GY. Role of the ACE2/Angiotensin 1-7 Axis of the Renin-Angiotensin System in Heart Failure. Circ Res. 2016 Apr 15;118(8):1313-26. doi: 10.1161/CIRCRESAHA.116.307708. PMID: 27081112; PMCID: PMC4939482.*
19. ^*Xu J, Fan J, Wu F, Huang Q, Guo M, Lv Z, Han J, Duan L, Hu G, Chen L, Liao T, Ma W, Tao X and Jin Y (2017) The ACE2/Angiotensin-(1-7)/Mas Receptor Axis: Pleiotropic Roles in Cancer. Front. Physiol. 8:276. doi: 10.3389/fphys.2017.00276*
20. ^*Savergnini SQ, Beiman M, Lautner RQ, de Paula-Carvalho V, Allahdadi K, Pessoa DC, Costa-Fraga FP, Fraga-Silva RA, Cojocaru G, Cohen Y, Bader M, de Almeida AP, Rotman G, Santos RA. Vascular relaxation, antihypertensive effect, and cardioprotection of a novel peptide agonist of the MAS receptor. Hypertension. 2010 Jul;56(1):112-20. doi: 10.1161/HYPERTENSIONAHA.110.152942. Epub 2010 May 17. PMID: 20479330.*
21. ^*Parit R, Jayavel S. Association of ACE inhibitors and angiotensin type II blockers with ACE2 overexpression in COVID-19 comorbidities: A pathway-based analytical study. Eur J Pharmacol. 2021 Apr 5;896:173899. doi: 10.1016/j.ejphar.2021.173899. Epub 2021 Jan 27. PMID: 33508281; PMCID: PMC7839513.*
22. ^*Hippisley-Cox J, Young D, Coupland C, Channon KM, Tan PS, Harrison DA, Rowan K, Aveyard P, Pavord ID, Watkinson PJ. Risk of severe COVID-19 disease with ACE inhibitors and angiotensin receptor blockers: cohort study including 8.3 million people. Heart. 2020 Oct;106(19):1503-1511. doi: 10.1136/heartjnl-2020-317393. Epub 2020 Jul 31. PMID: 32737124; PMCID: PMC7509391.*
23. ^*Weidmann MD, Berry GJ, Zucker JE, Huang S, Sobieszczyk ME, Green DA. Bacterial Pneumonia and Respiratory Culture Utilization among Hospitalized Patients with and without COVID-19 in a New York City Hospital. J Clin Microbiol. 2022 Jul 20;60(7):e0017422. doi: 10.1128/jcm.00174-22. Epub 2022 Jun 1. PMID: 35642519; PMCID: PMC9297819.*
24. ^*Shcherbak SG, Anisenkova AY, Mosenko SV, Glotov OS, Chernov AN, Apalko SV, Urazov SP, Garbuzov EY, Khobotnikov DN, Klitsenko OA, Minina EM and Asaulenko ZP (2021) Basic Predictive Risk Factors for Cytokine Storms in COVID-19 Patients. Front. Immunol. 12:745515. doi: 10.3389/fimmu.2021.745515*
25. ^*RT Journal Article, A1 Jacobs, Jana L, A1 Bain, William, A1 Naqvi, Asma, A1 Staines, Brittany, A1 Castanha, Priscila M S, A1 Yang, Haopu, A1 Boltz, Valerie F, A1 Barratt-Boyes, Simon, A1 Marques, Ernesto T A, A1 Mitchell, Stephanie*

L, A1 Methé, Barbara, A1 Olonisakin, Tolani F, A1 Haidar, Ghady, A1 Burke, Thomas W, A1 Petzold, Elizabeth, A1 Denny, Thomas,, A1 Woods, Chris WA1 McVerry, Bryan J, A1 Lee, Janet S, A1 Watkins, Simon C, A1 St Croix, Claudette M, A1 Morris, Alison, A1 Kearney, Mary F, A1 Ladinsky, Mark S, A1 Bjorkman, Pamela J, A1 Kitsios, Georgios D, A1 Mellors, John W, T1 Severe Acute Respiratory Syndrome Coronavirus 2 Viremia Is Associated With Coronavirus Disease 2019 Severity and Predicts Clinical Outcomes https://doi.org/10.1093/cid/ciab686

26. ^*Bassil J, Rassy E, Kattan J. Is blood transfusion safe during the COVID-19 pandemic? Future Sci OA. 2020 Sep 17;6(9):FSO626. doi: 10.2144/fsoa-2020-0116. PMID: 33230421; PMCID: PMC7505015.*
27. ^*Mori I, Komatsu T, Takeuchi K, Nakakuki K, Sudo M, Kimura Y. Viremia induced by influenza virus. Microb Pathog. 1995 Oct;19(4):237-44. doi: 10.1016/s0882-4010(95)90290-2. PMID: 8825911.*
28. ^*Ortíz, D.W., Roberts-Sano, O., Marroquin, H.E. et al. Factors associated with viremia in people living with HIV on antiretroviral therapy in Guatemala. AIDS Res Ther 18, 79 (2021). https://doi.org/10.1186/s12981-021-00400-9*
29. ^*Speiser, J.L., Karvellas, C.J., Shumilak, G. et al. Predicting in-hospital mortality in pneumonia-associated septic shock patients using a classification and regression tree: a nested cohort study. j intensive care 6, 66 (2018). https://doi.org/10.1186/s40560-018-0335-3*
30. ^*Oisin Skinnader, Scott Nguyen, Helina Marshall, Caroline Meharg, Séamus Fanning, Enterobacter Species☆, Editor (s): Paul L.H. McSweeney, John P. McNamara, Encyclopedia of Dairy Sciences (Third Edition), Academic Press,2022, Pages 469-481, ISBN 9780128187678, https://doi.org/10.1016/B978-0-08-100596-5.23002-3.*
31. ^*Bone RC. The sepsis syndrome. Definition and general approach to management. Clin Chest Med. 1996 Jun;17(2):175-81. doi: 10.1016/s0272-5231(05)70307-5. PMID: 8792059.*
32. ^*Chao J, Cui S, Liu C, Liu S, Liu S, Han Y, Gao Y, Ge D, Yu A, Yang R. Detection of Early Cytokine Storm in Patients with Septic Shock After Abdominal Surgery. J Transl Int Med. 2020 Jun 30;8(2):91-98. doi: 10.2478/jtim-2020-0014. PMID: 32983931; PMCID: PMC7500114.*
33. ^*Wang, J., Yang, X., Li, Y. et al. Specific cytokines in the inflammatory cytokine storm of patients with COVID-19-associated acute respiratory distress syndrome and extrapulmonary multiple-organ dysfunction. Virol J 18, 117 (2021). https://doi.org/10.1186/s12985-021-01588-y*
34. ^*Chen R, Lan Z, Ye J, Pang L, Liu Y, Wu W, Qin X, Guo Y and Zhang P (2021) Cytokine Storm: The Primary Determinant for the Pathophysiological Evolution of COVID-19 Deterioration. Front. Immunol. 12:589095. doi: 10.3389/fimmu.2021.589095*
35. ^*Montazersaheb, S., Hosseiniyan Khatibi, S.M., Hejazi, M.S. et al. COVID-19 infection: an overview on cytokine storm and related interventions. Virol J 19, 92 (2022). https://doi.org/10.1186/s12985-022-01814-1*
36. ^*Paz Ocaranza, M., Riquelme, J.A., García, L. et al. Counter-regulatory renin–angiotensin system in cardiovascular disease. Nat Rev Cardiol 17, 116-129 (2020). https://doi.org/10.1038/s41569-019-0244-8*
37. ^*Camporota L, Cronin JN, Busana M, Gattinoni L, Formenti F. Pathophysiology of coronavirus-19 disease acute lung injury. Curr Opin Crit Care. 2022 Feb 1;28(1):9-16. doi: 10.1097/MCC.0000000000000911. PMID: 34907979; PMCID: PMC8711311.*
38. ^*Wanamaker B, Cascino T, McLaughlin V, Oral H, Latchamsetty R, Siontis KC. Atrial Arrhythmias in Pulmonary Hypertension: Pathogenesis, Prognosis and Management. Arrhythm Electrophysiol Rev. 2018 Mar;7(1):43-48. doi:*

10.15420/aer.2018.3.2. PMID: 29636972; PMCID: PMC5889803.

39. ^*Mamzer A, Waligora M, Kopec G, Ptaszynska-Kopczynska K, Kurzyna M, Darocha S, Florczyk M, Mroczek E, Mularek-Kubzdela T, Smukowska-Gorynia A, Wrotynski M, Chrzanowski L, Dzikowska-Diduch O, Perzanowska-Brzeszkiewicz K, Pruszczyk P, Skoczylas I, Lewicka E, Blaszczak P, Karasek D, Kusmierczyk-Droszcz B, Mizia-Stec K, Kaminski K, Jachec W, Peregud-Pogorzelska M, Doboszynska A, Gasior Z, Tomaszewski M, Pawlak A, Zablocka W, Ryczek R, Widejko-Pietkiewicz K, Kasprzak JD. Impact of the COVID-19 Pandemic on Pulmonary Hypertension Patients: Insights from the BNP-PL National Database. Int J Environ Res Public Health. 2022 Jul 10;19(14):8423. doi: 10.3390/ijerph19148423. PMID: 35886278; PMCID: PMC9316841.*
40. ^*Smith, B., Genuardi, M.V., Koczo, A., Zou, R.H., Thoma, F.W., Handen, A., Craig, E., Hogan, C.M., Girard, T., Althouse, A.D. and Chan, S.Y. (2018), Atrial arrhythmias are associated with increased mortality in pulmonary arterial hypertension. Pulmonary Circulation, 8: 1-9 2045894018790316. https://doi.org/10.1177/2045894018790316*
41. ^*Safaee Fakhr B, Di Fenza R, Gianni S, Wiegand SB, Miyazaki Y, Araujo Morais CC, Gibson LE, Chang MG, Mueller AL, Rodriguez-Lopez JM, Ackman JB, Arora P, Scott LK, Bloch DB, Zapol WM, Carroll RW, Ichinose F, Berra L; Nitric Oxide Study Investigators. Inhaled high dose nitric oxide is a safe and effective respiratory treatment in spontaneous breathing hospitalized patients with COVID-19 pneumonia. Nitric Oxide. 2021 Nov 1;116:7-13. doi: 10.1016/j.niox.2021.08.003. Epub 2021 Aug 13. PMID: 34400339; PMCID: PMC8361002.*
42. ^*Sulica R, Cefali F, Motschwiller C, Fenton R, Barroso A, Sterman D. COVID-19 in Pulmonary Artery Hypertension (PAH) Patients: Observations from a Large PAH Center in New York City. Diagnostics (Basel). 2021 Jan 15;11(1):128. doi: 10.3390/diagnostics11010128. PMID: 33467533; PMCID: PMC7829711.*
43. ^*Maloberti A, Giannattasio C, Rebora P, Occhino G, Ughi N, Biolcati M, Gualini E, Rizzi JG, Algeri M, Giani V, Rossetti C, Epis OM, Molon G, Beltrame A, Bonfanti P, Valsecchi MG, Genovesi S. Incident Atrial Fibrillation and In-Hospital Mortality in SARS-CoV-2 Patients. Biomedicines. 2022 Aug 10;10(8):1940. doi: 10.3390/biomedicines10081940. PMID: 36009487; PMCID: PMC9406191.*
44. ^*Pagnesi M, Baldetti L, Beneduce A, et al, Pulmonary hypertension and right ventricular involvement in hospitalised patients with COVID-19, Heart 2020;106: 1324-1331.*
45. ^*Rottlaender D, Motloch LJ, Schmidt D, Reda S, Larbig R, Wolny M, Dumitrescu D, Rosenkranz S, Erdmann E, Hoppe UC. Clinical impact of atrial fibrillation in patients with pulmonary hypertension. PLoS One. 2012;7(3):e33902. doi: 10.1371/journal.pone.0033902. Epub 2012 Mar 16. PMID: 22439013; PMCID: PMC3306317.*
46. ^*Yuan S, Jiang SC, Zhang ZW, Fu YF, Hu J, Li ZL. The Role of Alveolar Edema in COVID-19. Cells. 2021 Jul 26;10(8):1897. doi: 10.3390/cells10081897. PMID: 34440665; PMCID: PMC8391241.*
47. ^*Rodrigues Prestes TR, Rocha NP, Miranda AS, Teixeira AL, Simoes-E-Silva AC. The Anti-Inflammatory Potential of ACE2/Angiotensin-(1-7)/Mas Receptor Axis: Evidence from Basic and Clinical Research. Curr Drug Targets. 2017;18(11):1301-1313. doi: 10.2174/1389450117666160727142401. PMID: 27469342.*
48. ^*Dandona P, Dhindsa S, Ghanim H, Chaudhuri A. Angiotensin II and inflammation: the effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockade. J Hum Hypertens. 2007 Jan;21(1):20-7. doi: 10.1038/sj.jhh.1002101. Epub 2006 Nov 9. PMID: 17096009.*