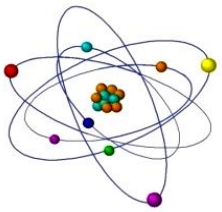
SOME OF THE SIMILARITIES BETWEEN MULTIORGAN DAMAGES CAUSED BY COVID-19 AND HIGH DOSES OF RADIATION



(Brief Review)

Sujashvili R.Sh.
Laboratory of Biophysics, I.Beritashvili Center of Experimental Biomedicine, Georgia

ABSTRACT: *The modern world has a number of challenges. Climate change, rising radiation backgrounds, cancer, cardiovascular diseases, infections threaten the sustainable development of humanity. Today, as never before, it is time for scientists to work together to overcome these challenges. The spread of SARS-COV-2 virus has completely changed the biomedical research agenda. Multi-organ lesions caused by the virus require the analysis of knowledge and experience accumulated in various fields. One of the most serious factors causing multi-organ injuries is radiation. As studies show, pathologies obtained with covid-19 and high-dose radiation are very similar to each other. Determining the advantages of many years of experience and methods of radiation disease management for treatment of similar disorders caused by the SARS-COV-2 virus creates an excellent prospect for rescuing patients with moderate to severe symptoms.*

Inflammation is a major common player in COVID-19 and ARS (Acute Radiation Syndrome) and causes multiple systemic damage. Both cause cytokine storms, the number of pro-inflammatory cytokines increases, and the number of anti-inflammatory cytokines decreases. Both COVID-19 and radiation exposure result in systemic damage of the vascular system, lungs, heart, kidneys, liver, intestines, eyes, and brain. Regardless of the target organ, the management of immunogenic pathway hyperactivity is a major target for overcoming COVID-19and acute radiation exposure.

The goal of presented review is to underline some ofthe similarities of multisystem damages caused by Covid-19 infection and ARS. A long-term and diversified study of ARS has identified the main targets of radiation exposure and developed ARS medical management strategies that can be successfully adapted to manage systemic lesions in patients with COVID-19.

Key words: acute radiation disease, covid-19, inflammation, cytokine storm

INTRODUCTION

Acute Radiation Syndrome (ARS), the same radiation sickness develops in people whoselarge part of the body is exposed to high doses in a short period. The result is damage to the hematopoiesis, gastrointestinal tract, skin, neurovascular systems, and immune dysfunction as part of the damage to the hematopoietic system [1,10,28].

COVID-19 affects virtually every organ. It causes inflammation, endotheliitis, vasoconstriction, hypercoagulation and edema. Lymphocytopenia, elevated D-dimer, elevated fibrin degradation products, and widespread intravascular coagulation have been reported. Regardless of which organ or system is damaged, hyperactivity of the immune system is an acute reaction to withstand to both SARS-CoV-2 and acute radiation exposure [18, 29].

Physiological and pathological processes in different tissues can initiate production of Cytokines by eg. macrophages, mast cells, endothelial cells, and Schwann cells [8, 45]. Under normal conditions, cytokines have a short half-life and act as mediators. A complex communication network gives a healthy immune system the proper signals to respond in a proportionate response against an infectious agent or inflammatory stimulus [38]. A dramatic increase in cytokine levels triggers a cytokine storm, to which the body responds with acute systemic inflammation [39, 46]. The cytokine storm is common effect of SARS-CoV-2 infection and radiation exposure [37]; the result in both cases is the systemic

inflammation that injures numerous tissues and organs [24, 27, 31]. Further, inthe review we will discuss some of pathologies resulting from Covid-19 and RAS diseases.

HEMATOPOIETIC DISORDERS

Hematology studies were found to be a valuable tool for assessing the status of COVID-19 patients. Assessment of neutrophils, lymphocytes, and platelets reveals a strong correlation between neutrophil-lymphocyte-platelet (NLP) and progression of COVID-19 disease [22]. Moreover, lymphocyte depletion is associated with COVID-19 severity. In addition, the number of T cells, eosinophils and platelets is significantly reduced in particularly critical and fatal patients [48]. Studies have shown that an increase in the neutrophil-lymphocyte ratio (NLR) is an early warning sign for severe COVID-19 [16, 19]. Lymphopenia and thrombocytopenia are commonly observed in hospitalized COVID-19 patients, and low platelet counts are associated with higher mortality [4, 44]. SARS-CoV-2 is thought to damage both bone marrow cells and platelets via the CD13 receptor, leading to cell growth inhibition and apoptosis. Another cause of thrombocytopenia is platelet activation, aggregation, and thrombus formation at the site of lung injury [9, 33].

As in COVID-19 patients, radiation exposure also causes profound hematologic disorders in humans characterized by granulocytopenia, lymphopenia, and thrombocytopenia [14, 25].

Unlike COVID-19, in addition to other cytopenias, a significant decrease in neutrophils is a hallmark of ARS [6]. The kinetics of lymphocyte decline is directly related to the dose of absorbed radiation from 0.5 to 10 Gy. In additions, a change in the ratio of neutrophils to lymphocytes was used to determine radiation dose exposure [32]. Thrombocytopenia is directly related to radiation dose [14].

VASCULAR DYSFUNCTION

Histological analysis of COVID-19 showed that SARS-CoV-2 infection causes endothelitis throughout the human body, leading to systemic macro- and microcirculatory dysfunction. VEGF-D (vascular endothelial growth factor –D involved in formation of lymphatic vasculature around lung bronchioles) is used as a procoagulant biomarker of COVID-19 progression [23], and angiopoietin-2 (marker of endothelial activation) is a marker of microvascular dysfunction. Disorders such as vascular thickening are also characteristic of COVID-19 disease [20].

Vascular dysfunction due to radiation exposure is also known. The main target of vascular radiation damage is the endothelial cell. The acute phase of the lesion occurs from the moment of irradiation to several weeks and is characterized by endothelial edema, decreased vascular permeability, lymphocyte adhesion and infiltration, and apoptosis [11].

Interestingly, many of the symptoms as well as the underlying pathogenesis in multi-organ damage caused by SARS-CoV-2 are similar to the multifaceted damage caused by exposure to acute ionizing radiation. In a nuclear incident, the entire human body can be damaged by large doses of ionizing radiation, and SARS-CoV-2 can cause multiorgan damage by interacting with cells whose membranes express angiotensin-converting enzyme 2- ACE2 and Type 2 transmembrane serine protease TMPRSS2 [3, 5]. Viruses reach cells as soon as viral spike protein binds to the ACE2. The virus uses endocytosis or fusion with the membrane to enter cells [17]. In both cases, it is necessary to cleave the ACE2-associated Spike protein with specific proteases in order for the Spike fusion domains to act. In endosomes, the spike is cleaved by cathepsin L, and then the viral membrane fuses with the endocytic membrane [21, 43]. On the cell surface, to ensure fusion of the virus and the host cell membrane, the spike digs into other proteases, mainly

TMPRSS2, after fusion, SARS-CoV-2 is transferred to the cytosol and the virus begins a replication cycle [40].

These proteins are expressed to varying degrees in airway and alveolar epithelial cells, pulmonary macrophages and vascular endothelial cells, ileum and large intestinal enterocytes. Systemic inflammation and coagulopathy, intravascular coagulation (DIC) and extracellular neutrophil counts are both signs of COVID-19 and signs of acute radiation damage. Injuries found in both COVID-19 and ARS can cause similar distant side effects in many organ systems [35].

OTHER COMPLICATIONS

Acute respiratory syndrome is the most common complication of COVID-19 and is the most common cause of death, while in irradiated patients it is a late effect, which often progresses to pulmonary fibrosis [7, 12, 15].Although pulmonary symptoms are most common in COVID-19 patients, GI symptoms are also common [2, 47]. Nausea, vomiting and diarrhea are all common symptoms for both COVID-19 and irradiated patients [30, 36].

Another organ of concern is the heart. Although coagulopathy, seen in both COVID-19 and ARS, may contribute to cardiomyopathy and circulatory failure, direct remodeling of heart tissue is also seen in both disease processes [10, 42]. Cardiac ischemia, inflammation, fibrosis, and wall thickening have been reported in COVID-19 patients [41] and after irradiation, although dose-dependent and post-irradiation time. SARS-CoV-2 infection and radiation both increase myocardial infarction and most likely have long-term effects.

Central nervous system damage has been reported in patients with COVID-19 and ARS. Headache, disorientation, cognitive dysfunction, ataxia, seizures, unconsciousness, as well as other symptoms have been reported in patients receiving high-dose lethal radiation and in adult and juvenile COVID-19 patients [13].

In addition, there is some evidence that radiation exposure can cause long-term psychological problems [26] and given that, there are similarities between radiation and COVID-19-induced central nervous system inflammation and coagulopathy, SARC-2 may cause long-term neurological and psychological effects [34]. Comparison of systemic damages caused by Covid-19 and acute radiation exposure Fig. 1 and Fig. 2.

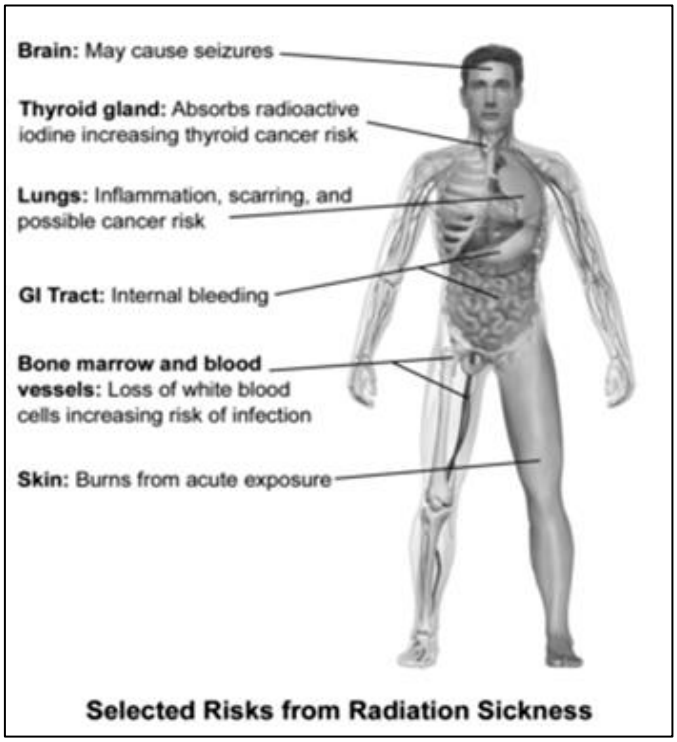


Fig. 1. Organs targeted by radiation: brain, thyroid gland, lungs, GI tract, bone marrow, blood vessels, skin. https://commons.wikimedia.org/wiki/File: Radiation_Sickness.png

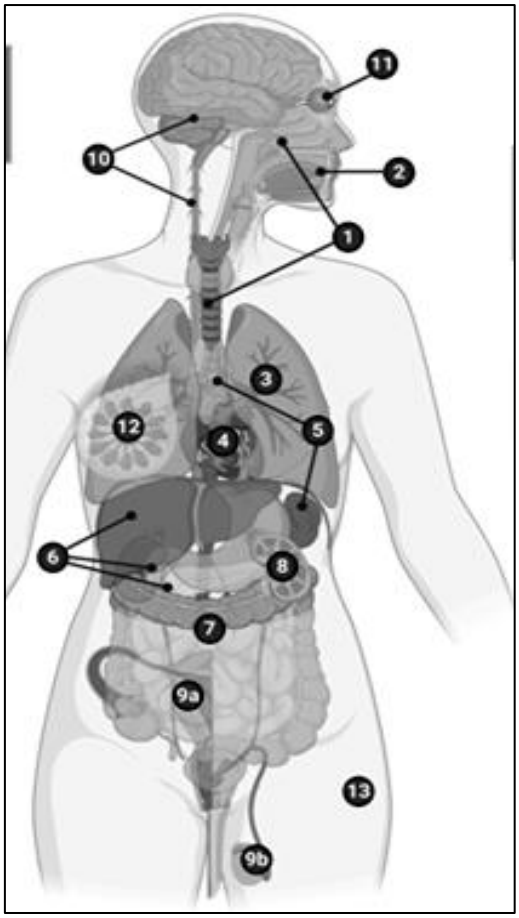


Fig 2. Organs targeted by of SARS-CoV-2: brain, thyroid gland, lungs, cardiovascular system, immune system, bone marrow etc. This figure was created with
BioRender.com.
https://doi.org/10.1371/journal.ppat.1009037.g003

1-Upper airways, Mucus, Nasopharynx, Trachea ciliated epithelial cells; 2-Mouth, Sputum, Oropharynx; 3-Lungs, Bronchoalveolar lavage, Ciliated and secretory epithelial cells, Type I and II pneumocytes, Alveolar macrophages; 4-Cardiovascular system, Heart interstitial fibroblasts, Vessel endothelial cells; 5-Immune system, Blood, Lymph nodes, spleen; 6-Liver, gallbladder, Pancreas; 7-Gastrointestinal tract (GI), Stool, Stomach, Enterocytes; 8-Urinary system, Urine, Kidney tubular epithelial cells, podocytes; 9-9a. Female reproductive tract; 9b. Male reproductive tract, Testicular spermatogenic, Sertoli and Leyding cells; 10-Nervous system, Brain, Cerebrospinal fluid; 11-Eye, Tears, Conjunctiva; 12-Mammary glands, Breast milk; 13-Skin and adipose tissue

CONCLUSION

Presented review underlined some of the similarities of multisystem damages caused by Covid-19 infection and ARS. Mechanisms of immune dysregulation, disease progression, and organ damage during COVID-19 are similar to the biological reactions to high doses of ionizing radiation. A long-term and diversified study of ARS has identified the main targets of radiation exposure and developed ARS medical management strategies that can be successfully adapted to manage systemic lesions in patients with COVID-19.There is extensive experience in radiation biology for treatment of inflammation, pulmonary fibrosis, and vascular damage, and due to the symptomatic similarity between the two diseases (Covid-19 and RAS) the use of same methods for treatment may be appropriate. Moreover, versus, new treatment achievements considered for COVID-19 infections may be used for anti-radiation therapy.

REFERENCES

1. Azizova, T. V., Osovets, S. V., Day, R. D., Druzhinina, M. B., Sumina, M. V., Pesternikova, V. S., Teplyakov, I. I., Zhang, A., Kuniak, M., Vasilenko, E. K., Wald, N., Slaughter, D. M., Okladnikova, N. D., &Schall, L. C. (2008). PREDICTABILITY OF ACUTE RADIATION INJURY SEVERITY. Health Physics, 94(3), 255–263. https://doi.org/10.1097/01.hp.0000290833.66789.df
2. Bösmüller, H., Traxler, S., Bitzer, M., Häberle, H., Raiser, W., Nann, D., Frauenfeld, L., Vogelsberg, A., Klingel, K., & Fend, F. (2020). The evolution of pulmonary pathology in fatal COVID-19 disease: an autopsy study with clinical correlation. VirchowsArchiv, 477(3), 349–357. https://doi.org/10.1007/s00428-020-02881-x

3. Busse, L. W., Chow, J. H., McCurdy, M. T., & Khanna, A. K. (2020). COVID-19 and the RAAS—a potential role for angiotensin II? Critical Care, 24(1). https://doi.org/10.1186/s13054-020-02862-1
4. Devreese, K. M. J. (2021). COVID-19–related laboratory coagulation findings. International Journal of Laboratory Hematology, 43(S1), 36–42. https://doi.org/10.1111/ijlh.13547
5. Djomkam, A. L. Z., Olwal, C. O., Sala, T. B., &Paemka, L. (2020). Commentary: SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Frontiers in Oncology, 10. https://doi.org/10.3389/fonc.2020.01448
6. Fliedner, T. M., Graessle, D., Meineke, V., &Dörr, H. (2007). Pathophysiological principles underlying the blood cell concentration responses used to assess the severity of effect after accidental whole-body radiation exposure: An essential basis for an evidence-based clinical triage. Experimental Hematology, 35(4), 8–16. https://doi.org/10.1016/j.exphem.2007.01.006
7. Gao, J., Peng, S., Shan, X., Deng, G., Shen, L., Sun, J., Jiang, C., Yang, X., Chang, Z., Sun, X., Feng, F., Kong, L., Gu, Y., Guo, W., Xu, Q., & Sun, Y. (2019). Inhibition of AIM2 inflammasome-mediated pyroptosis by Andrographolide contributes to amelioration of radiation-induced lung inflammation and fibrosis. Cell Death & Disease, 10(12). https://doi.org/10.1038/s41419-019-2195-8
8. Gebremeskel, S., Schanin, J., Coyle, K. M., Butuci, M., Luu, T., Brock, E. C., Xu, A., Wong, A., Leung, J., Korver, W., Morin, R. D., Schleimer, R. P., Bochner, B. S., & Youngblood, B. A. (2021). Mast Cell and Eosinophil Activation Are Associated With COVID-19 and TLR-Mediated Viral Inflammation: Implications for an Anti-Siglec-8 Antibody. Frontiers in Immunology, 12. https://doi.org/10.3389/fimmu.2021.650331
9. Giannis, D., Ziogas, I. A., & Gianni, P. (2020). Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. Journal of Clinical Virology, 127, 104362. https://doi.org/10.1016/j.jcv.2020.104362
10. Goans, R. E., Holloway, E. C., Berger, M. E., & Ricks, R. C. (2001). Early Dose Assessment In Criticality Accidents. Health Physics, 81(4), 446–449. https://doi.org/10.1097/00004032-200110000-00009
11. Gustafson, D., Raju, S., Wu, R., Ching, C., Veitch, S., Rathnakumar, K., Boudreau, E., Howe, K. L., & Fish, J. E. (2020). Overcoming Barriers. Arteriosclerosis, Thrombosis, and Vascular Biology, 40(8), 1818–1829. https://doi.org/10.1161/atvbaha.120.314558
12. Hanania, A. N., Mainwaring, W., Ghebre, Y. T., Hanania, N. A., & Ludwig, M. (2019). Radiation-Induced Lung Injury. Chest, 156(1), 150–162. https://doi.org/10.1016/j.chest.2019.03.033
13. Helms, J., Kremer, S., Merdji, H., Clere-Jehl, R., Schenck, M., Kummerlen, C., Collange, O., Boulay, C., Fafi-Kremer, S., Ohana, M., Anheim, M., &Meziani, F. (2020). Neurologic Features in Severe SARS-CoV-2 Infection. New England Journal of Medicine, 382(23), 2268–2270. https://doi.org/10.1056/nejmc2008597
14. Henry, B. M., de Oliveira, M. H. S., Benoit, S., Plebani, M., & Lippi, G. (2020). Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clinical Chemistry and Laboratory Medicine (CCLM), 58(7), 1021–1028. https://doi.org/10.1515/cclm-2020-0369
15. Huang, Y., Zhang, W., Yu, F., &Gao, F. (2017). The Cellular and Molecular Mechanism of Radiation-Induced Lung Injury. Medical Science Monitor, 23, 3446–3450. https://doi.org/10.12659/msm.902353
16. Huyut, M. T., &İLkbahar, F. (2021). The effectiveness of blood routine parameters and some biomarkers as a potential diagnostic tool in the diagnosis and prognosis of Covid-19 disease. International Immunopharmacology, 98, 107838. https://doi.org/10.1016/j.intimp.2021.107838
17. Imai, Y., Kuba, K., Rao, S., Huan, Y., Guo, F., Guan, B., Yang, P., Sarao, R., Wada, T., Leong-Poi, H., Crackower, M. A., Fukamizu, A., Hui, C. C., Hein, L., Uhlig, S., Slutsky, A. S., Jiang, C., &Penninger, J. M. (2005). Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature, 436(7047), 112–116. https://doi.org/10.1038/nature03712
18. Jain, U. (2020). Effect of COVID-19 on the Organs. Cureus. Published. https://doi.org/10.7759/cureus.9540

19. Kermali, M., Khalsa, R. K., Pillai, K., Ismail, Z., &Harky, A. (2020). The role of biomarkers in diagnosis of COVID-19 – A systematic review. Life Sciences, 254, 117788. https://doi.org/10.1016/j.lfs.2020.117788
20. Krigsfeld, G. S., & Kennedy, A. R. (2013). Is Disseminated Intravascular Coagulation the Major Cause of Mortality from Radiation at Relatively Low Whole Body Doses? Radiation Research, 180(3), 231–234. https://doi.org/10.1667/rr3321.1
21. Kuba, K., Imai, Y., Rao, S., Gao, H., Guo, F., Guan, B., Huan, Y., Yang, P., Zhang, Y., Deng, W., Bao, L., Zhang, B., Liu, G., Wang, Z., Chappell, M., Liu, Y., Zheng, D., Leibbrandt, A., Wada, T., . . . Penninger, J. M. (2005). A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus–induced lung injury. Nature Medicine, 11(8), 875–879. https://doi.org/10.1038/nm1267
22. Lagunas-Rangel, F. A. (2020). Neutrophil-to-lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. Journal of Medical Virology, 92(10), 1733–1734. https://doi.org/10.1002/jmv.25819
23. Léonard-Lorant, I., Delabranche, X., Séverac, F., Helms, J., Pauzet, C., Collange, O., Schneider, F., Labani, A., Bilbault, P., Molière, S., Leyendecker, P., Roy, C., &Ohana, M. (2020). Acute Pulmonary Embolism in Patients with COVID-19 at CT Angiography and Relationship to d-Dimer Levels. Radiology, 296(3), E189–E191. https://doi.org/10.1148/radiol.2020201561
24. Lierova, A., Jelicova, M., Nemcova, M., Proksova, M., Pejchal, J., Zarybnicka, L., &Sinkorova, Z. (2018). Cytokines and radiation-induced pulmonary injuries. Journal of Radiation Research. Published. https://doi.org/10.1093/jrr/rry067
25. Lippi, G., Plebani, M., & Henry, B. M. (2020). Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. ClinicaChimicaActa, 506, 145–148. https://doi.org/10.1016/j.cca.2020.03.022
26. Loganovsky, K. N., &Loganovskaja, T. K. (2000). Schizophrenia Spectrum Disorders in Persons Exposed to Ionizing Radiation as a Result of the Chernobyl Accident. Schizophrenia Bulletin, 26(4), 751–773. https://doi.org/10.1093/oxfordjournals.schbul.a033492
27. Müller, K., &Meineke, V. (2007). Radiation-induced alterations in cytokine production by skin cells. Experimental Hematology, 35(4), 96–104. https://doi.org/10.1016/j.exphem.2007.01.017
28. Osovets, S. V., Azizova, T. V., Day, R. D., Wald, N., &Druzhinina, M. B. (2011). ASSESSMENT OF RISKS AND DOSE THRESHOLDS FOR SOME EFFECTS OF ACUTE EXPOSURE. Health Physics, 100(2), 176–184. https://doi.org/10.1097/hp.0b013e3181ebd123
29. Pan, L., Mu, M., Yang, P., Sun, Y., Wang, R., Yan, J., Li, P., Hu, B., Wang, J., Hu, C., Jin, Y., Niu, X., Ping, R., Du, Y., Li, T., Xu, G., Hu, Q., &Tu, L. (2020). Clinical Characteristics of COVID-19 Patients With Digestive Symptoms in Hubei, China: A Descriptive, Cross-Sectional, Multicenter Study. American Journal of Gastroenterology, 115(5), 766–773. https://doi.org/10.14309/ajg.0000000000000620
30. Paris, F. (2001). Endothelial Apoptosis as the Primary Lesion Initiating Intestinal Radiation Damage in Mice. Science, 293(5528), 293–297. https://doi.org/10.1126/science.1060191
31. Ponti, G., Maccaferri, M., Ruini, C., Tomasi, A., &Ozben, T. (2020). Biomarkers associated with COVID-19 disease progression. Critical Reviews in Clinical Laboratory Sciences, 57(6), 389–399. https://doi.org/10.1080/10408363.2020.1770685
32. Prabhakarpandian, B., Goetz, D. J., Swerlick, R. A., Chen, x., & Kiani, M. F. (2001). Expression and Functional Significance of Adhesion Molecules on Cultured Endothelial Cells in Response to Ionizing Radiation. Microcirculation, 8(5), 355–364. https://doi.org/10.1111/j.1549-8719.2001.tb00182.x
33. Price, L. C., McCabe, C., Garfield, B., &Wort, S. J. (2020). Thrombosis and COVID-19 pneumonia: the clot thickens! European Respiratory Journal, 56(1), 2001608. https://doi.org/10.1183/13993003.01608-2020
34. Rogers, J. P., Chesney, E., Oliver, D., Pollak, T. A., McGuire, P., Fusar-Poli, P., Zandi, M. S., Lewis, G., & David, A. S. (2020). Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. The Lancet Psychiatry, 7(7), 611–627. https://doi.org/10.1016/s2215-0366(20)30203-0

35. Shimazawa, R., & Ikeda, M. (2011). Medical Management of the Acute Radiation Syndrome. Annals of Internal Medicine, 155(2), 135. https://doi.org/10.7326/0003-4819-155-2-201107190-00017
36. Spagnolo, P., Balestro, E., Aliberti, S., Cocconcelli, E., Biondini, D., Casa, G. D., Sverzellati, N., & Maher, T. M. (2020). Pulmonary fibrosis secondary to COVID-19: a call to arms? The Lancet Respiratory Medicine, 8(8), 750–752. https://doi.org/10.1016/s2213-2600(20)30222-8
37. Stoecklein, V. M., Osuka, A., Ishikawa, S., Lederer, M. R., Wanke-Jellinek, L., &Lederer, J. A. (2014). Radiation Exposure Induces Inflammasome Pathway Activation in Immune Cells. The Journal of Immunology, 194(3), 1178–1189. https://doi.org/10.4049/jimmunol.1303051
38. Subscription and Copyright Information. (2021). Trends in Biochemical Sciences, 46(10), e1. https://doi.org/10.1016/s0968-0004(21)00176-6
39. Sun, X., Wang, T., Cai, D., Hu, Z., Chen, J., Liao, H., Zhi, L., Wei, H., Zhang, Z., Qiu, Y., Wang, J., & Wang, A. (2020). Cytokine storm intervention in the early stages of COVID-19 pneumonia. Cytokine & Growth Factor Reviews, 53, 38–42. https://doi.org/10.1016/j.cytogfr.2020.04.002
40. Tay, M. Z., Poh, C. M., Rénia, L., MacAry, P. A., & Ng, L. F. P. (2020). The trinity of COVID-19: immunity, inflammation and intervention. Nature Reviews Immunology, 20(6), 363–374. https://doi.org/10.1038/s41577-020-0311-8
41. Trejo Gabriel Y Galán, J. (2020). Stroke as a complication and prognostic factor of COVID-19. Neurología (English Edition), 35(5), 318–322. https://doi.org/10.1016/j
42. Venkatesulu, B. P., Mahadevan, L. S., Aliru, M. L., Yang, X., Bodd, M. H., Singh, P. K., Yusuf, S. W., Abe, J. I., & Krishnan, S. (2018). Radiation-Induced Endothelial Vascular Injury. JACC: Basic to Translational Science, 3(4), 563–572. https://doi.org/10.1016/j.jacbts.2018.01.014
43. Walls, A. C., Park, Y. J., Tortorici, M. A., Wall, A., McGuire, A. T., &Veesler, D. (2020). Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell, 181(2), 281–292.e6. https://doi.org/10.1016/j.cell.2020.02.058
44. Wang, H., Ding, Y., Li, N., Wu, L., Gao, Y., Xiao, C., Jiang, H., Zheng, Y., Mao, C., Deng, J., Wang, H., & Xu, N. (2020). Prognostic Value of Neutrophil–Lymphocyte Ratio, Platelet–Lymphocyte Ratio, and Combined Neutrophil–Lymphocyte Ratio and Platelet–Lymphocyte Ratio in Stage IV Advanced Gastric Cancer. Frontiers in Oncology, 10. https://doi.org/10.3389/fonc.2020.00841
45. Wang, J., Jiang, M., Chen, X., &Montaner, L. J. (2020). Cytokine storm and leukocyte changes in mild versus severe SARS-CoV-2 infection: Review of 3939 COVID-19 patients in China and emerging pathogenesis and therapy concepts. Journal of Leukocyte Biology, 108(1), 17–41. https://doi.org/10.1002/jlb.3covr0520-272r
46. Xu, G., Qi, F., Li, H., Yang, Q., Wang, H., Wang, X., Liu, X., Zhao, J., Liao, X., Liu, Y., Liu, L., Zhang, S., & Zhang, Z. (2020). The differential immune responses to COVID-19 in peripheral and lung revealed by single-cell RNA sequencing. Cell Discovery, 6(1). https://doi.org/10.1038/s41421-020-00225-2
47. Zhang, K., Yin, L., Zhang, M., Parker, M. D., Binder, H. J., Salzman, P., Zhang, L., Okunieff, P., &Vidyasagar, S. (2011). Radiation decreases murine small intestinal HCO3−secretion. International Journal of Radiation Biology, 87(8), 878–888. https://doi.org/10.3109/09553002.2011.583314
48. Zhou, Y., Fu, B., Zheng, X., Wang, D., Zhao, C., Qi, Y., Sun, R., Tian, Z., Xu, X., & Wei, H. (2020). Pathogenic T-cells and inflammatory monocytes incite inflammatory storms in severe COVID-19 patients. National Science Review, 7(6), 998–1002. https://doi.org/10.1093/nsr/nwaa041