Review Article

Hypoalbuminemia in COVID-19: Molecular and Mechanistic Approach

Ali Afzal[1#], Sara Shahzaman[1#], Arwa Azam[1#], Usman Ghani[1#], Muhammad Babar Khawar[2#*], Nimra Afzal[3], Muhammad Idnan[4], Ume Habiba[1], Muhammad Abu Talha Safdar Hashmi[1], Syeda Eisha Hamid[1], Rimsha Naseem[1]

[1]Molecular Medicine and Cancer Therapeutics Lab, Department of Zoology, Faculty of Sciences, University of Central Punjab, Lahore, Pakistan.
[2]Applied Molecular Biology and Biomedicine Lab, Department of Zoology, University of Narowal, Narowal, Pakistan.
[3]Environmental Health and Wildlife, Department of Zoology, Faculty of Science and Technology, University of Central Punjab, Lahore, Pakistan.
[4]Department of Wildlife & Ecology, University of Okara, Okara, Pakistan.

Received: 03 Dec 2022 | Revised: 16 May 2023 | Accepted: 30 May 2023 |Published Online: 06 Jun 2023

*babarkhawar@yahoo.com [#]These authors have contributed equally.

ISSN 2816-8119

Open Access

Citation
Afzal, A., Shahzaman, S., Azam, A., Ghani, U., Khawar, M. B., Afzal, N., Idnan, M., Habiba, U., Hashmi, M. A. T. S., Hamid, S. E., & Naseem, R. (2023). Hypoalbuminemia in COVID-19: Molecular and Mechanistic Approach. *Albus Scientia*, *2023*, Article ID e230606, 1-11.

DOI
http://doi.org/10.56512/AS.2023.1.e230606

Copyright
Copyright © 2023 [Afzal et al.]. This is an open access article distributed under the terms of the Creative Commons Attribution 4.0 International License, (CC BY-NC) which permits reusers to distribute, remix, adapt, and build upon the material in any medium or format for non-commercial purposes only, and only so long as Attribution is given to the creator.

Competing interests
The authors have declared that no competing interests exist.

Abstract

Hypoalbuminemia is a clinical feature of COVID-19 which is caused by a multitude of processes in COVID-19, including acute liver damage (ALI), oxidative burst, viral-albumin binding, dysregulated immunological responses, and viral genome interference in the host cell, all of which lead to organ failure and patient mortality. We used a mechanistic approach to discuss number of potential molecular mechanisms that cause hypoalbuminemia, as well as some effective treatment methods. As this study employs molecular approaches to characterize hypoalbuminemia, this work is promising in molecular medicine and drug development.

Key words: *COVID-19, Hypoalbuminemia, Hospitalization, Mortality rate.*

Introduction

In December 2019, the first incidence of COVID-19 emerged as a series of Acute Respiratory Distress Syndrome (ARDs) in Wuhan, China (Tabibzadeh et al., 2021; Yuki et al., 2020), followed by a worldwide pandemic that quickly swept throughout the globe by April 6, 2020 (Sheam et al., 2020). The Severe Acute Respiratory Syndrome Corona Virus-19 (SARS-CoV-2) is a spherical, positive sense RNA virus with a ssRNA (27-32 kb long) that encodes ORF1 a/b, club-shaped glycoprotein (Kumar et al., 2020) or spikes, envelope, nucleocapsid, hemagglutinin-esterase, and other proteins (Tabibzadeh et al., 2021). SARS-CoV-2 is classified in the genus β-coronavirus in the order Nidovirales in the subfamily Coronavirinae in the family Coronaviridae, according to the International Committee on Virus Taxonomy (Cui et al., 2019). Two independently published findings from 2005 show that the natural host (Figure 1) is the horse-shoe bat (*Rhinolophus affinis*) (Cui et al., 2019; Lau et al., 2005; Sheam et al., 2020) since the coronavirus isolated from the bat had 96 percent genomic uniqueness with SARS-CoV-2. However, the genetic distance implies an intermediate host, which is thought to be the Malayan pangolin (*Manis javanica*) (Sheam et al., 2020) but not confirmed yet.

Early COVID-19 research revealed symptoms of infection in the lower respiratory tract, such as fever with chills, pneumonia, dyspnea (Huang et al., 2020; Kumar et al., 2020; Yuki et al., 2020), dry cough, shortness of breath, muscle pain, and loss of taste and smell (Sheam et al., 2020), but patients later developed headaches, dizziness, sputum production, and diarrhoea (Kumar et al., 2020; Sheam et al., 2020; Shi et al., 2020). Based on clinical examination, a research team led by Guan et al. (2020) found the lowest percentage of conjunctival congestion (Guan et al., 2020; Sheam et al., 2020). COVID-19, on the other hand, has been found to have a wide range of symptoms, ranging from moderate to severe hypoxia (Huang et al., 2020; Kumar et al., 2020) and acute respiratory distress syndrome (Yuki et al., 2020). According to a survey of 2,134 pediatric COVID-19 patients in China, newborns and the elderly are more susceptible, while pediatric patients have a lower prevalence (Dong et al., 2020; Yuki et al., 2020).

We have previously reviewed the psychological impacts of COVID-19 (Khawar et al., 2021), nutraceuticals in relation to vitamin D and COVID infection (Farooq et al., 2022; Sohail et al., 2023), risk assessment in health workers during the pandemic (Amaan et al., 2020), and the second wave scenario and combating strategies (Khawar et al., 2022). In this review, our focus is on exploring the molecular pathways that are primarily affected in relation to hypoalbuminemia.

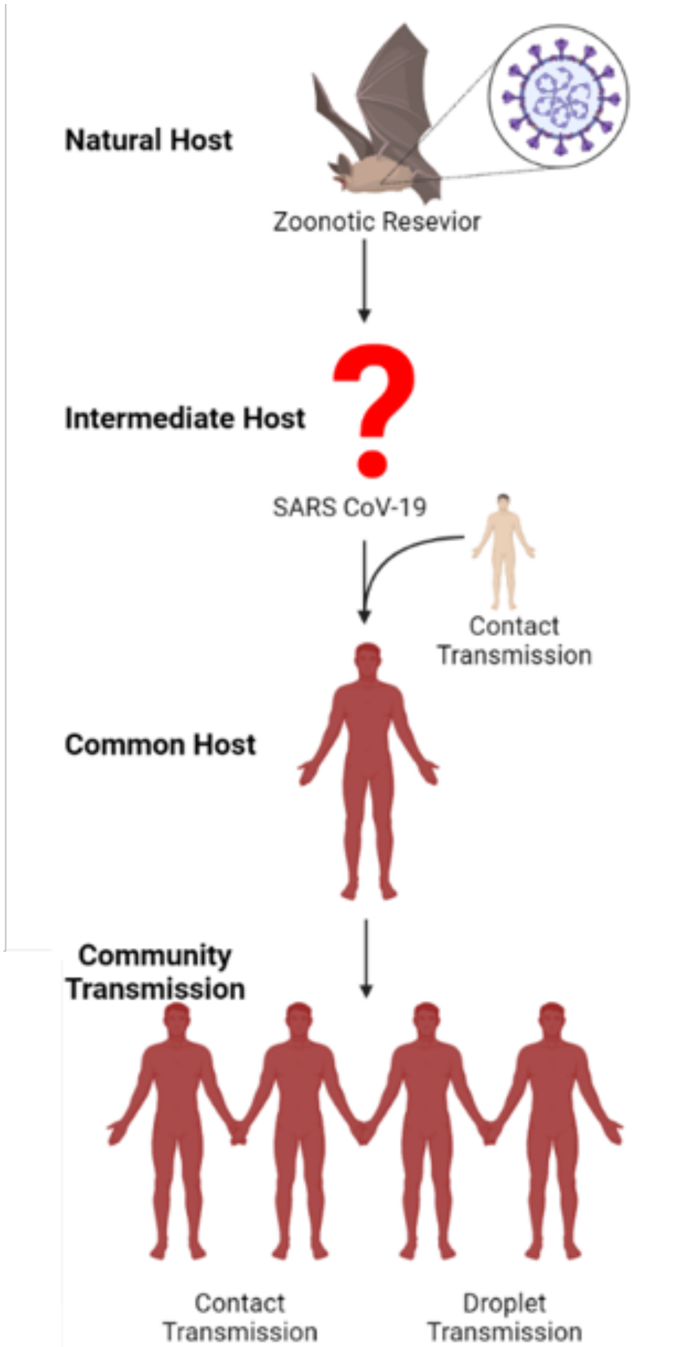

Figure 1: SARS-CoV-2 transmitted from its natural host Rhinolophus affinis to human through an undiscovered intermediate host. Community transmission is then triggered by close contact and airborne zoonotic droplets which include cough and sneezing.

Albumin

Hepatocytes in liver produce human serum albumin (HSA), one of the most essential proteins present in our blood, weighing 66.5 kDA. Albumin levels are usually consistent between the ages of 20 and 60, and albumin concentration in hepatocytes varies between 200 and 500 g/grams of liver. Serum albumin content has long been utilized as a health and disease indicator. Albumin is made up of 585 amino acids, with arginine, lysine, glutamate, and aspartate accounting for the majority of the charged amino acids (Moman et al., 2017). HSA's tertiary structure is heart-shaped and comprises two domains that are crucial for molecule transport and binding (He & Carter, 1992). Albumin may be found in both oxidized and reduced forms (Moman et al., 2017). The cystine-34 (Cys-34) residue in HSA serves as the primary and most significant extracellular antioxidant (Evans, 2002). The 16 imidazole histidine residues in albumin with a pH of 6.75 are crucial for performing buffer function relative to the ambient pH (King, 1961). Albumin serves antioxidant functions, endothelium stability, antithrombotic activity, and immunomodulation. Cysteine residue, domain I and II, and imidazole residue are the three major structural characteristics of albumin (Evans, 2002).

Within the hepatocytes, there is a unique manufacturing assembly line for albumin synthesis. In the nucleus, the blueprints for albumin production are transcribed from DNA. These mRNAs subsequently go to ribosomes, where they are translated into a 585-amino-acid-residue long albumin polypeptide. Albumin, like other secretory proteins, is not poured directly into the cytoplasm; instead, it follows an intracellular transit route. After translation, albumin polypeptide is transported from the endoplasmic reticulum to the Golgi apparatus, and subsequently to blood serum through intravascular spaces (Spinella et al., 2016). The concentration of potassium ions (K^+) in hepatocytes has a big impact on this transport route (Rothschild et al., 1977). Albumin release is slowed down when potassium levels are low. Hepatocytes have a well-defined complex cytoplasm that serves as a highway for protein-containing vesicles to be transported outside the cell and discharged into liver lymph and eventually blood plasma.

Albumin and COVID-19

The aim of this review is to focus on the suggested processes that cause hypoalbuminemia in COVID-19 patients, which, according to numerous studies, is independent of gender. Different research investigations on COVID-19 patients' serology have found indications of decreased HSA. We tried to compile most of the research that showed low HSA levels and compared albumin levels in COVID-19 individuals with severe and non-severe COVID-19, as indicated in the Table 1.

The average level of albumin in human blood is 34-35 g/L, but in severe COVID-19 patients, the level drops to as low as 20.3 g/L. At this level, many patients end up in the ICU and die, whereas non-severe patients show a few mild signs and symptoms.

SARS-CoV-2 targets ciliated bronchial epithelium and type-II pneumocytes through ACE-II, (Cui et al., 2019; Li et al., 2003; Qian et al., 2013), and its expressions are also found in numerous organs (Singhal, 2020), including the oral mucosa, kidney, brain, and thymus (Velasco et al., 2020). Hepatic endothelium contains high levels of ACE-II expression, and SARS-CoV-2 has been shown to cause hepatocyte lysis, leading to Acute Liver Injury (ALI) (Xu et al., 2020), making the liver a potential target for SARS-CoV-2 infection (Hamming et al., 2004; Hoffmann et al., 2020; Singhal, 2020; Tang et al., 2020; Velasco et al., 2020; Xu et al., 2020). Albumin, is important for binding and transporting endogenous and exogenous molecules, antithrombic functions, and antioxidant functions due to the presence of a free sulfhydryl group (Rahmani-Kukia et al., 2020) at the Cys-34 free end amino acid residue (Spinella et al., 2016). Chemically, albumin's structure is susceptible to reversible or irreversible oxidation, thiolation, and nitrosylation via enzymatic or non-enzymatic reactions at residue Cys-34 (Spinella et al., 2016), resulting in

Table 1: Summary of COVID-19 patients with respect to rate of albumin in severe and non-severe patients

Sr. #	Study period	No. of Patients	Albumin (g/L)		References
			Severe	Non-Severe	
1	25th January – 24th March 2020	299	30.5	37.6	(J. Huang et al., 2020)
2	13th January -28th January	274	30.1	36.3	(Chen et al., 2020)
3	25th December 2019 - 26th January 2020	201	30.4	33.7	(Wu et al., 2020)
4	1st January 2019 – 5th February 2019	155	36.0	39.0	(Mo et al., 2020)
5	23rd January 2020 - 8th February 2020	135	36.0	49.9	(Wan et al., 2020)
6	18th January 2020 – 22nd February 2020.	115	34.4	40.4	(Zhang et al.)
7	15th March 2020 and 31st March 2020	48	29.0	39.2	(de la Rica et al., 2020)
8	16th December 2019 -2nd January2020	41	27.9	34.7	(Yang et al., 2020)
9	27th January 2020	21	29.6	37.2	(Chen et al., 2012)
10	23rd January 2020 -8th February 2020	32	35.5	40.5	(C. Liu et al., 2020)
11	11th January 2020 – 21st January 2020	12	37.7	44.3	(Y. Liu et al., 2020)
12	27th January 2020	21	30.2	37.3	(Chen et al., 2012)
13	10th January 2020 -31st January 2020	30	35.0	42.0	(M. Liu et al., 2020)
14	30th December 2019 – 15th January 2020	78	36.6	41.3	(Li et al., 2019)
15	28th January 2020 – 6th February 2020	17	46.0	44.9	(Chow et al., 2016)
16	21st February 2020 – 31st March 2020	427	20.3	28.3	(Aloisio et al., 2020)
17	13th March 2020- 30th April 2020	191	35.8	47.5	(Bastug et al., 2020)
18	23rd January 2020 – 4th February 2020	113	38.8	41.3	(Bi et al., 2020)
19	1st March 2020 – 30th March 2020	144	34.1	36.5	(Bonetti et al., 2020)
20	21st January 2020 – 12 February 2020	80	32.8	36.8	(Cao et al., 2020)
21	1st January 2020 – 20th March 2020	456	37.9	40.2	(B. Cheng et al., 2020)
22	3rd January 2020 – 26 February 2020	89	34.0	39.2	(L. Cheng et al., 2020)
23	15th March 2020 – 31st March 2020	48	29.0	39.2	(de la Rica et al., 2020)
24	13th March 2020 – 12th April 2020	65	40.9	42.0	(Deng et al., 2020)
25	23rd January 2020 – 22nd February 2020	114	29.9	35.6	(Feng et al., 2020)
26	5th February 2020 – 8th March 2020	95	30.5	34.9	(Gan et al., 2020)
27	28th January 2020 – 9th February 2020	210	30.8	36.2	(Gao et al., 2020)
28	March 2020 – April 2020	66	25.0	29.0	(Ghweil et al., 2020)
29	20th January 2020 – 2nd March 2020	189	34.2	39.7	(Gong et al., 2020)
30	28th January 2020 – 29th February 2020	74	26.5	29.4	(Guo et al., 2020)
31	1st February 2020	53	31.7	41	(He et al., 2020)
32	20th February 2020 and 30th April 2020	61	31.0	39.5	(Hirashima et al., 2021)
33	21st January 2020 – 9th March 2020	101	32.3	36.5	(Hou et al., 2020)
34	24th January 2020- 26th March 2020	40	35.6	41.6	(H. Hu et al., 2020)
35	6th February 2020 – 1st March 2020	182	27.2	31.4	(J. Hu et al., 2020)
36	2nd February 2020 – 31st March 2020	469	31.4	32.7	(Hua et al., 2020)
37	2nd January 2020	41	28.4	33.8	(C. Huang et al., 2020)
38	25th January 2020 – 24th March 2020	299	30.5	37.6	(J. Huang et al., 2020)
39	29th January 2020- 6th March 2020	2623	32.0	36.7	(W. Huang et al., 2020)
40	14th March 2020 – 23rd April 2020	1827	31.0	34.0	(Hundt et al., 2020)
41	21st February 2020 – 2nd April 2020	694	35.3	41.2	(Hong et al., 2020)
42	24th January 2020 -17th February 2020	115	33.2	35.5	(Lei et al., 2020)
43	January 2020 – 20th February 2020	65	35.0	40.0	(W. Liu et al., 2020)
44	2nd January 2020 – 15th February 2020	523	36.3	40.7	(Li et al., 2021)
45	1st January 2020 – 20th February 2020	134	36.0	40.4	(Q. Liu et al., 2020)
46	17th January 2020-13th April 2020	232	35.2	38.4	(Lian, 2020)
47	20th February 2020 – 17th March 2020	1590	32.6	33.9	(Liang et al., 2020)
48	13th January 2020-24th February 2020	61	41.8	44.0	(J. Liu et al., 2020)
49	1st February 2020 – 13th March 2020	336	27.6	35.8	(Q. Liu et al., 2020)
50	10th January 2020 -15th March 2020	625	38.4	41.9	(S. Liu et al., 2020)
51	30th December 2019 – 15th January 2020	78	36.6	41.3	(D. Li et al., 2020)
52	16th February 2020	523	38.9	40.7	(Ma et al., 2020)
53	12th January 2020 – 26th February 2020	118	33.1	33.6	(J. Zhou et al., 2020)
54	10th March 2020- 2nd June 2020	45	25.0	34.7	(Mori et al., 2020)

55	27th January 2020 – 19th March 2020	124	28.1	29.1	(Pan et al., 2020)
56	20th February 2020 – 2nd April 2020	570	30.0	34.7	(Toutkaboni et al., 2020)
57	30th March 2020 – 15 May 2020	109	27.0	31.9	(Recinella et al., 2020)
58	29th December 2019 - 1st February 2020	191	29.0	33.5	(F. Zhou et al., 2020)
59	31st January 2020 – 29th March 2020	87	29.3	36.2	(Paliogiannis et al., 2021)
60	15th March 2020 – 15th May 2020	105	32.3	34.7	(Zinellu et al., 2021)
61	6th April 2020 – 6th May 2020	61	26.0	33.0	(Tsibouris et al., 2020)
62	1st April 2020 – 31st May 2020	144	29.8	33.3	(Varim et al., 2020)
63	March 2020 – April 2020	319	30.3	33.9	(F Violi et al., 2020)
64	10th January 2020 – 28th February 2020	85	33.2	37.6	(Gao et al., 2020)
65	15th January 2020 – 28th February 2020	143	32.0	38.6	(D. Wang et al., 2020)
66	29th January 2020 – 10th February 2020	28	30.5	35.0	(Feng et al., 2020)
67	28th January 2020 – 4th March 2020	199	31.6	34.9	(Deng et al., 2020)
68	12th January 2020- 17th March 2020	105	37.7	42.1	(Q. Wang et al., 2020)
69	20th January 2020 – 10th February 2020	275	34.3	41.0	(Y. Wang et al., 2020)
70	25th December 2019 – 13th February 2020	201	30.3	33.7	(Wu et al., 2020)
71	10th February 2020 – 7th March 2020	114	28.0	34.8	(Xue et al., 2020)
72	30th January 2020 – 11th February 2020	108	31.1	39.3	(Cieślik-Guerra et al., 2014)
73	14th January 2020 – 28th February 2020	1663	34.5	35.7	(Yu et al., 2020)
74	22nd January 2020 – 14th March 2020	461	35.6	40.3	(Zeng et al., 2021)
75	January 2020 – April 2020	80	32.8	37.5	(C. Zhang et al., 2020)
76	17th January 2020 – 8th February 2020	645	41.0	42.5	(X. Zhang et al., 2020)
77	18th January 2020 – 22nd February 2020	115	34.4	40.4	(Y. Liu et al., 2020)
78	19th February 2020 – 15th April 2020	123	40.4	42.4	(C. Zhou et al., 2020)

free thiol groups that acts as an effective hunter for reactive oxidant species (ROS) such as H_2O_2, O^{2-}, OH, and others (Inoue et al., 2018; Spinella et al., 2016; Francesco Violi et al., 2020).

Hypoalbuminemia in COVID-19

In a study (Mardani et al., 2020), increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values were seen in 70 out of 200 COVID-19 patients, indicating ALI. Another research by Xu et al. (Chen et al., 2020) suggests that hepatotoxicity caused by viruses, as well as liver damage caused by immunological activation or inflammation, may result in increased levels of aminotransferases such ALT and AST. When such an abnormal state occurs, followed by high oxidative stress due to an innate immune response, ROS are released, which permanently oxidize Cys-34, destroying or decreasing its antioxidant function and causing tissue and organ damage (Inoue et al., 2018; Spinella et al., 2016; Violi et al., 2020) (Figure 2). By secreting cytokines, the endothelium, as one of the primary bodily defense lines, regulates innate and adaptive immune responses (Loganathan et al., 2021). Furthermore, infection raises inflammatory markers like as C-reactive protein, tumor necrosis factor, and others in COVID patients. The production of these acute phase proteins necessitates albumin consumption, resulting in hypoalbuminemia (T. Li et al., 2020). Binding and transport of particles is one of albumin's most essential functions. It is possible for the binding to be competitive or non-competitive. SARS-CoV-2 binds non-specifically and irreversibly to albumin; therefore, the equilibrium is determined by the relative HSA concentration and the free virus particle. As the infection progresses, the balance is disrupted, resulting in an increase in virus-albumin complexes (Figure 3). This causes a breakdown in albumin-mediated nutrient transportation, resulting in decreased cell nutrition and a cell's vulnerability to lysis, ultimately leading to organ failure. As a result, viral -albumin binding in the blood inhibits albumin from transporting nutrients (Johnson et al., 2020).

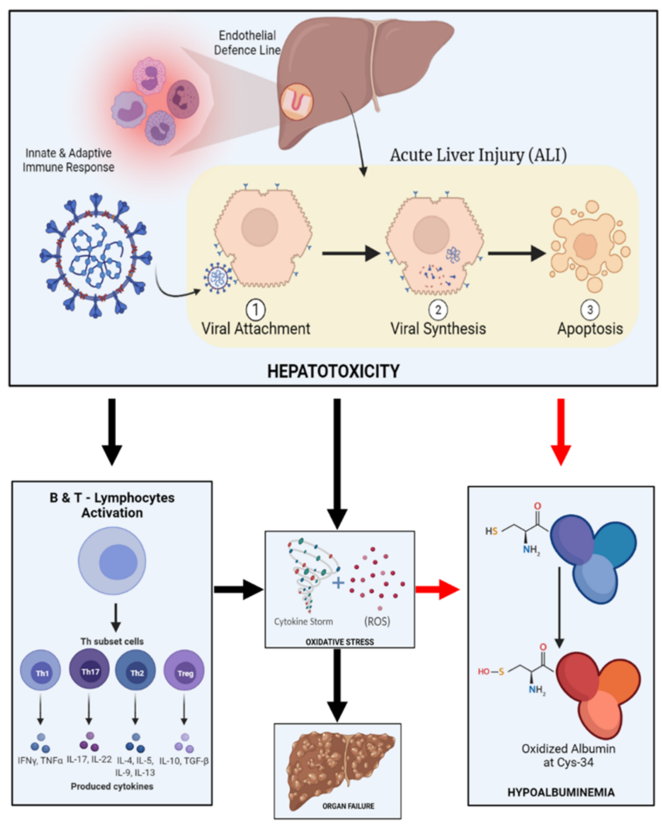

Figure 2: Various molecular mechanisms are responsible for organ dysfunction. These mechanisms include release of ROS by liver cells, immune cells and endothelium shown by black arrows cause overall organ damage. High oxidative stress and acute liver injury (ALI) shown by red arrows cause albumin oxidation which results in hypoalbuminemia.

Under stress, the immune system also releases proinflammatory and anti-inflammatory cytokines (Figure 2). T-subset cells such as Th1, Th2, and Th17 release cytokines such as IL-6, IL-7, IL-

10, G-CSF, TNF-α, and IP-10 in response to lymphocyte activation (Loganathan et al., 2021), resulting in a cytokine storm (Kouhpayeh et al., 2020) that causes significant oxidative stress (Loganathan et al., 2021) and hepatotoxicity in the liver (W. Huang et al., 2020). When albumin distribution is changed in intra and extravascular spaces owing to excess leakage via capillaries, the cytokine storm by immune response causes dysregulation of the inflammatory response, which is directly related with hypoalbuminemia in severe cases. In COVID-19 patients, inflammatory dysregulation and, indirectly, hypoalbuminemia have been related to increased mortality and long-term hospitalisation in severe instances (Viana-Llamas et al., 2021)

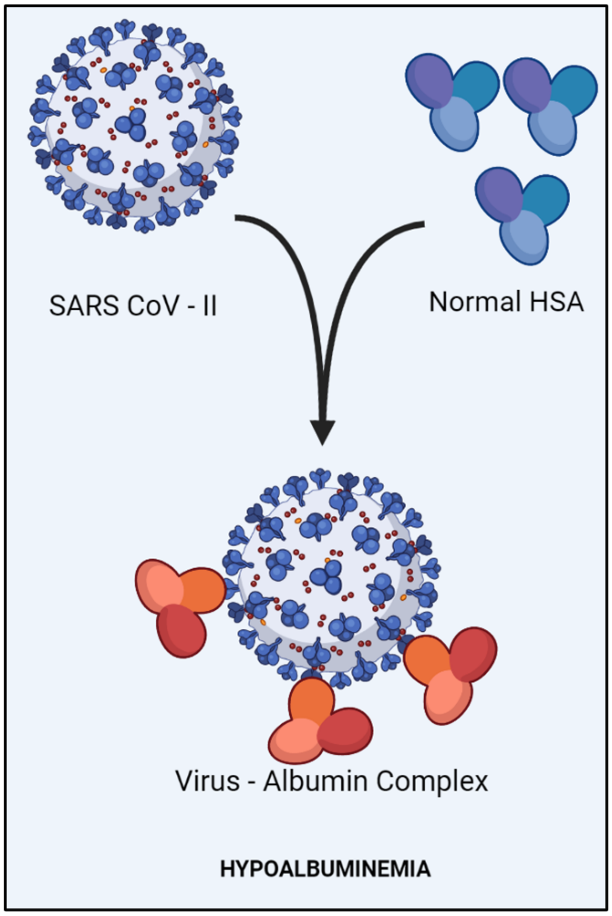

Figure 3: HSA (shown in blue) binds with viral particles resulting in viral – albumin complexes in serum. This binding diminishes the vital functions of albumin (shown in red) leading to hypoalbuminemia.

Hypoalbuminemia is linked to unfavourable outcomes including acute heart failure, sepsis, acute renal damage, and acute respiratory dysfunction syndrome (ARDS)., according to a retrospective observational research (Viana-Llamas et al. 2021). In hypoalbuminemic conditions, cardiovascular and cardiac problems are more likely to arise due to a lack of physiological activities such as antioxidant, anti-coagulant, and anti-platelet characteristics, as well as colloidal osmotic functions (Viana-Llamas et al., 2021). It is possible that the viral genome instructs the host cell to release type-I interferons and proinflammatory cytokines, resulting in higher levels of IL-6, C-reactive proteins, and tumour necrosis factor. In COVID-19 patients, elevated levels of proinflammatory cytokines such as IL-6, IL-7, IL-10, G-CSF, TNF-α, and IP-10 have been found in several investigations. On the one hand, these cytokines increase ROS, which accelerates ATP and NAD^+ depletion (Kouhpayeh et al., 2020) and, on the other hand, cell lysis (apoptosis or necrosis). This condition eventually leads to organ malfunction (Loganathan et al., 2021).

Therapeutic Strategies

It has recently been shown that there should be an etiological therapy eliminating the underlying cause, rather than a symptomatic treatment, based on the concept that "hypoalbuminemia is not a disease but a symptom" (Sitges-Serra, 2001). In this work, we attempted to determine the processes underlying low HSA, which has resulted in higher mortality and hospitalization in COVID-19 patients, suggesting that 1) oxidative stress and 2) viral load are the primary causes of hypoalbuminemia. There is a potential that the normal HSA can be restored if oxidative stress and viral load are both lowered by medicines.

Furthermore, minimal benefit can be obtained when it is treated symptomatically, i.e., by administering salt-poor exogenous albumin, but this feature is disputed and currently under research, according to current evidence. A short comparative analysis of 17 non-COVID-19 patients found that recurrent albumin infusions improved liver cirrhosis (Tarao & Iwamura, 1983), and another unblinded and randomised trial of 100 cirrhotic and ascitic patients found the same findings (Romanelli et al., 2006). Some studies also show that albumin has some therapeutic effectiveness in cirrhosis, acting as a regulator of inflammation and oxidative stress, as well as better oxygenation in ARDS (Soeters et al., 2019). Several investigations and trials in severe liver injury have indicated that albumin infusion reduces the incidence of circulatory dysfunction, mortality, and morbidity, although albumin infusion is not the ultimate step in COVID-19 patients (Gatta et al., 2012). Another approach is albumin dialysis, which involves adapting some extracorporeal liver support systems, such as the Prometheus system and single pass albumin dialysis, to replace non-functional albumin with functional albumin. Despite this, clinical dietitians can assess with a proper diet plan for the patients that includes all raw amino acid residue for increasing albumin synthesis rate (Xu et al., 2020), and thus clinical dietitians can assess with a proper diet plan for the patients that includes all raw amino acid residue for increasing albumin synthesis rate. As a result, in order to eliminate the cause, COVID-19 patients should be treated with medicines that may protect the damaged organ, mostly the liver, while also preventing oxidative stress in general, such as ammonium glycyrrhizinate, which can speed up the disease recovery process (Xu et al., 2020).

Conclusion

SARS-CoV-2 has infected people in every country on the planet since its discovery, causing numerous complications, organ failure, and death. Hypoalbuminemia, one of its clinical manifestations, has been linked to COVID-19 and has been used as a predictor of death and extended hospitalization. Low HSA is most likely caused by oxidative stress, viral attachment to albumin, capillary leakage, and a variety of other factors such as an overly controlled immune system, viral interference in the host genome, and minor problems. Most of the aforementioned factors enhance oxidative stress by secreting cytokines and chemokines, resulting in a cytokine storm in the body, which leads to hypoalbuminemia. Hypoalbuminemia causes HSA essential characteristics to malfunction, resulting in extended hospitalization or even death of patients. To avoid this condition, a symptomatic strategy may be used to decrease the negative consequences of hypoalbuminemia, which includes dietary evaluations, albumin infusion, and eventually the use of an organ support system such as albumin dialysis. The pathogenic root-mechanisms should be eliminated by medicines when treated etiologically to reduce total oxidative stress. COVID-19 patients' mortality and hospitalization may be decreased because of this strategy.

Future Perspectives

There is a lot of information about nearly every element of SARS-CoV-2, but it isn't comprehensive yet. Hypoalbuminemia, being one of the primary symptoms of COVID-19, necessitates additional research into some of its features, such as treatment methods based on genetic control or advancements in albumin infusion, which is still contentious, to reduce total hospitalization and death.

References

Aloisio, E., Chibireva, M., Serafini, L., Pasqualetti, S., Falvella, F. S., Dolci, A., & Panteghini, M. (2020). A Comprehensive Appraisal of Laboratory Biochemistry Tests as Major Predictors of COVID-19 Severity. *Archives of Pathology & Laboratory Medicine*, *144*(12), 1457–1464. https://doi.org/10.5858/arpa.2020-0389-SA

Amaan, H. N., Khawar, M. B., Abbasi, M. H., & Sheikh, N. (2020). Risk assessment in Pakistani health workers during COVID-19 pandemic. *RADS Journal of Pharmacy and Pharmaceutical Sciences, 8*(2), 126-128. https://doi.org/10.37962/jpps.v8i2.422

Bastug, A., Bodur, H., Erdogan, S., Gokcinar, D., Kazancioglu, S., Kosovali, B. D., Ozbay, B. O., Gok, G., Turan, I. O., Yilmaz, G., Gonen, C. C., & Yilmaz, F. M. (2020). Clinical and laboratory features of COVID-19: Predictors of severe prognosis. *International Immunopharmacology*, *88*, 106950. https://doi.org/10.1016/j.intimp.2020.106950

Bi, X., Su, Z., Yan, H., Du, J., Wang, J., Chen, L., Peng, M., Chen, S., Shen, B., & Li, J. (2020). Prediction of severe illness due to COVID-19 based on an analysis of initial Fibrinogen to Albumin Ratio and Platelet count. *Platelets*, *31*(5), 674–679. https://doi.org/10.1080/09537104.2020.1760230

Bonetti, G., Manelli, F., Patroni, A., Bettinardi, A., Borrelli, G., Fiordalisi, G., Marino, A., Menolfi, A., Saggini, S., Volpi, R., Anesi, A., & Lippi, G. (2020). Laboratory predictors of death from coronavirus disease 2019 (COVID-19) in the area of Valcamonica, Italy. *Clinical Chemistry and Laboratory medicine*, *58*(7), 1100–1105. https://doi.org/10.1515/cclm-2020-0459

Cao, Z., Li, T., Liang, L., Wang, H., Wei, F., Meng, S., Cai, M., Zhang, Y., Xu, H., Zhang, J., & Jin, R. (2020). Clinical characteristics of Coronavirus Disease 2019 patients in Beijing, China. *PloS One*, *15*(6), e0234764. https://doi.org/10.1371/journal.pone.0234764

Chen, Z., McCrosky, S., Guo, W., Li, H., & Gerton, J. L. (2012). A genetic screen to discover pathways affecting cohesin function in Schizosaccharomyces pombe identifies chromatin effectors. *G3 (Bethesda, Md.)*, *2*(10), 1161–1168. https://doi.org/10.1534/g3.112.003327

Cheng, B., Hu, J., Zuo, X., Chen, J., Li, X., Chen, Y., Yang, G., Shi, X., & Deng, A. (2020). Predictors of progression from moderate to severe coronavirus disease 2019: a retrospective cohort. *Clinical Microbiology and Infection*, *26*(10), 1400–1405. https://doi.org/10.1016/j.cmi.2020.06.033

Cheng, L., Yang, J. Z., Bai, W. H., Li, Z. Y., Sun, L. F., Yan, J. J., Zhou, C. L., & Tang, B. P. (2020). Prognostic value of serum amyloid A in patients with COVID-19. *Infection*, *48*(5), 715–722. https://doi.org/10.1007/s15010-020-01468-7

Chow, R., Chiu, N., Bruera, E., Krishnan, M., Chiu, L., Lam, H., DeAngelis, C., Pulenzas, N., Vuong, S., & Chow, E. (2016). Inter-rater reliability in performance status assessment among health care professionals: a systematic review. *Annals of Palliative Medicine*, *5*(2), 83–92. https://doi.org/10.21037/apm.2016.03.02

Cieślik-Guerra, U. I., Fila, M., Kamiński, M., Kotas, R., Wróblewski, J., Trzos, E., Uznańska-Loch, B., Rechciński, T., Wierzbowska-Drabik, K., Kasprzak, J. D., & Kurpesa, M. (2014). Correlation between the activity of the autonomic nervous system and endothelial function in patients with acute coronary syndrome. *Polskie Archiwum Medycyny Wewnetrznej*, *124*(10), 509–515. https://doi.org/10.20452/pamw.2456

Cui, J., Li, F., & Shi, Z. L. (2019). Origin and evolution of pathogenic coronaviruses. *Nature Reviews. Microbiology*, *17*(3), 181–192. https://doi.org/10.1038/s41579-018-0118-9

de la Rica, R., Borges, M., Aranda, M., Del Castillo, A., Socias, A., Payeras, A., Rialp, G., Socias, L., Masmiquel, L., & Gonzalez-Freire, M. (2020). Low Albumin Levels Are Associated with Poorer Outcomes in a Case Series of COVID-19 Patients in Spain: A Retrospective Cohort Study. *Microorganisms*, *8*(8), 1106. https://doi.org/10.3390/microorganisms8081106

Deng, M., Qi, Y., Deng, L., Wang, H., Xu, Y., Li, Z., Meng, Z., Tang, J., & Dai, Z. (2020). Obesity as a Potential Predictor of Disease Severity in Young COVID-19 Patients: A Retrospective Study. *Obesity (Silver Spring, Md.)*, *28*(10), 1815–1825. https://doi.org/10.1002/oby.22943

Dong, Y., Mo, X., Hu, Y., Qi, X., Jiang, F., Jiang, Z., & Tong, S. (2020). Epidemiology of COVID-19 Among Children in China. *Pediatrics*, *145*(6), e20200702. https://doi.org/10.1542/peds.2020-0702

Evans T. W. (2002). Review article: albumin as a drug--biological effects of albumin unrelated to oncotic pressure. *Alimentary Pharmacology & Therapeutics*, *16 Suppl 5*, 6–11. https://doi.org/10.1046/j.1365-2036.16.s5.2.x

Farooq, A., Abbasi, M. H., Khawar, M. B., & Sheikh, N. (2022). A Recent Update on the Role of Nutraceuticals in COVID-19 Infection. *Asian Journal of Health Sciences, 8*(2), ID41. https://doi.org/https://doi.org/10.15419/ajhs.v8i2.512

Feng, X., Li, P., Ma, L., Liang, H., Lei, J., Li, W., Wang, K., Song, Y., Li, S., Yang, W., & Yang, C. (2020). Clinical Characteristics and Short-Term Outcomes of Severe Patients

With COVID-19 in Wuhan, China. *Frontiers in Medicine*, *7*, 491. https://doi.org/10.3389/fmed.2020.00491

Gan, J., Li, J., Li, S., & Yang, C. (2020). Leucocyte Subsets Effectively Predict the Clinical Outcome of Patients With COVID-19 Pneumonia: A Retrospective Case-Control Study. *Frontiers in Public Health*, *8*, 299. https://doi.org/10.3389/fpubh.2020.00299

Gao, S., Jiang, F., Jin, W., Shi, Y., Yang, L., Xia, Y., Jia, L., Wang, B., Lin, H., Cai, Y., Xia, Z., & Peng, J. (2020). Risk factors influencing the prognosis of elderly patients infected with COVID-19: a clinical retrospective study in Wuhan, China. *Aging*, *12*(13), 12504–12516. https://doi.org/10.18632/aging.103631

Gatta, A., Verardo, A., & Bolognesi, M. (2012). Hypoalbuminemia. *Internal and Eemergency Medicine*, *7 Suppl 3*, S193–S199. https://doi.org/10.1007/s11739-012-0802-0

Ghweil, A. A., Hassan, M. H., Khodeary, A., Mohamed, A. O., Mohammed, H. M., Abdelazez, A. A., Osman, H. A., & Bazeed, S. E. S. (2020). Characteristics, Outcomes and Indicators of Severity for COVID-19 Among Sample of ESNA Quarantine Hospital's Patients, Egypt: A Retrospective Study. *Infection and Drug Resistance*, *13*, 2375–2383. https://doi.org/10.2147/IDR.S263489

Gong, J., Ou, J., Qiu, X., Jie, Y., Chen, Y., Yuan, L., Cao, J., Tan, M., Xu, W., Zheng, F., Shi, Y., & Hu, B. (2020). A Tool for Early Prediction of Severe Coronavirus Disease 2019 (COVID-19): A Multicenter Study Using the Risk Nomogram in Wuhan and Guangdong, China. *Clinical infectious diseases*, *71*(15), 833–840. https://doi.org/10.1093/cid/ciaa443

Guan, W. J., Ni, Z. Y., Hu, Y., Liang, W. H., Ou, C. Q., He, J. X., Liu, L., Shan, H., Lei, C. L., Hui, D. S. C., Du, B., Li, L. J., Zeng, G., Yuen, K. Y., Chen, R. C., Tang, C. L., Wang, T., Chen, P. Y., Xiang, J., Li, S. Y., … China Medical Treatment Expert Group for Covid-19 (2020). Clinical Characteristics of Coronavirus Disease 2019 in China. *The New England Journal of Medicine*, *382*(18), 1708–1720. https://doi.org/10.1056/NEJMoa2002032

Guo, J., Zhou, B., Zhu, M., Yuan, Y., Wang, Q., Zhou, H., Wang, X., Lv, T., Li, S., Liu, P., Yang, Y., He, P., & Zhang, P. (2020). CURB-65 may serve as a useful prognostic marker in COVID-19 patients within Wuhan, China: a retrospective cohort study. *Epidemiology and Infection*, *148*, e241. https://doi.org/10.1017/S0950268820002368

Hamming, I., Timens, W., Bulthuis, M. L., Lely, A. T., Navis, G., & van Goor, H. (2004). Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *The Journal of Pathology*, *203*(2), 631–637. https://doi.org/10.1002/path.1570

He, B., Wang, J., Wang, Y., Zhao, J., Huang, J., Tian, Y., Yang, C., Zhang, H., Zhang, M., Gu, L., Zhou, X., & Zhou, J. (2020). The Metabolic Changes and Immune Profiles in Patients With COVID-19. *Frontiers in Immunology*, *11*, 2075. https://doi.org/10.3389/fimmu.2020.02075

He, X. M., & Carter, D. C. (1992). Atomic structure and chemistry of human serum albumin. *Nature*, *358*(6383), 209–215. https://doi.org/10.1038/358209a0

Hirashima, T., Arai, T., Kitajima, H., Tamura, Y., Yamada, T., Hashimoto, S., Morishita, H., Minamoto, S., Kawashima, K., Kashiwa, Y., Kameda, M., Takeshita, T., Suzuki, H., Matsuoka, H., Yamaguchi, S., Tanaka, T., & Nagai, T. (2021). Factors significantly associated with COVID-19 severity in symptomatic patients: A retrospective single-center study. *Journal of infection and chemotherapy, 27*(1), 76–82. https://doi.org/10.1016/j.jiac.2020.09.022

Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Schiergens, T. S., Herrler, G., Wu, N. H., Nitsche, A., Müller, M. A., Drosten, C., & Pöhlmann, S. (2020). SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*, *181*(2), 271–280.e8. https://doi.org/10.1016/j.cell.2020.02.052

Hong, K. H., Lee, S. W., Kim, T. S., Huh, H. J., Lee, J., Kim, S. Y., Park, J. S., Kim, G. J., Sung, H., Roh, K. H., Kim, J. S., Kim, H. S., Lee, S. T., Seong, M. W., Ryoo, N., Lee, H., Kwon, K. C., & Yoo, C. K. (2020). Guidelines for Laboratory Diagnosis of Coronavirus Disease 2019 (COVID-19) in Korea. *Annals of Laboratory Medicine*, *40*(5), 351–360. https://doi.org/10.3343/alm.2020.40.5.351

Hou, W., Zhang, W., Jin, R., Liang, L., Xu, B., & Hu, Z. (2020). Risk factors for disease progression in hospitalized patients with COVID-19: a retrospective cohort study. *Infectious diseases, 52*(7), 498–505. https://doi.org/10.1080/23744235.2020.1759817

Hu, H., Du, H., Li, J., Wang, Y., Wu, X., Wang, C., Zhang, Y., Zhang, G., Zhao, Y., Kang, W., & Lian, J. (2020). Early prediction and identification for severe patients during the pandemic of COVID-19: A severe COVID-19 risk model constructed by multivariate logistic regression analysis. *Journal of Global Health*, *10*(2), 020510. https://doi.org/10.7189/jogh.10.020510

Hu, J., Zhou, J., Dong, F., Tan, J., Wang, S., Li, Z., Zhang, X., Zhang, H., Ming, J., & Huang, T. (2020). Combination of serum lactate dehydrogenase and sex is predictive of severe disease in patients with COVID-19. *Medicine*, *99*(42), e22774. https://doi.org/10.1097/MD.0000000000022774

Hua, J., Qian, C., Luo, Z., Li, Q., & Wang, F. (2020). Invasive mechanical ventilation in COVID-19 patient management: the experience with 469 patients in Wuhan. *Critical Care*, *24*(1), 348. https://doi.org/10.1186/s13054-020-03044-9

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., Xiao, Y., … Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*, *395*(10223), 497–506. https://doi.org/10.1016/S0140-6736(20)30183-5

Huang, J., Cheng, A., Kumar, R., Fang, Y., Chen, G., Zhu, Y., & Lin, S. (2020). Hypoalbuminemia predicts the outcome of COVID-19 independent of age and co-morbidity. *Journal of Medical Virology*, *92*(10), 2152–2158. https://doi.org/10.1002/jmv.26003

Huang, W., Li, C., Wang, Z., Wang, H., Zhou, N., Jiang, J., Ni, L., Zhang, X. A., & Wang, D. W. (2020). Decreased serum albumin level indicates poor prognosis of COVID-19 patients:

hepatic injury analysis from 2,623 hospitalized cases. *Science China. Life Sciences*, *63*(11), 1678–1687. https://doi.org/10.1007/s11427-020-1733-4

Hundt, M. A., Deng, Y., Ciarleglio, M. M., Nathanson, M. H., & Lim, J. K. (2020). Abnormal Liver Tests in COVID-19: A Retrospective Observational Cohort Study of 1,827 Patients in a Major U.S. Hospital Network. *Hepatology*, *72*(4), 1169–1176. https://doi.org/10.1002/hep.31487

Inoue, M., Nakashima, R., Enomoto, M., Koike, Y., Zhao, X., Yip, K., Huang, S. H., Waldron, J. N., Ikura, M., Liu, F. F., & Bratman, S. V. (2018). Plasma redox imbalance caused by albumin oxidation promotes lung-predominant NETosis and pulmonary cancer metastasis. *Nature Communications*, *9*(1), 5116. https://doi.org/10.1038/s41467-018-07550-x

Johnson, A. S., Fatemi, R., & Winlow, W. (2020). SARS-CoV-2 Bound Human Serum Albumin and Systemic Septic Shock. *Frontiers in Cardiovascular Medicine*, *7*, 153.

https://doi.org/10.3389/fcvm.2020.00153

Khawar, M. B., Abbasi, M. H., Hussain, S., Riaz, M., Rafiq, M., Mehmood, R., Sheikh, N., Amaan, H. N., Fatima, S., Jabeen, F., Ahmad, Z., & Farooq, A. (2021). Psychological impacts of COVID-19 and satisfaction from online classes: disturbance in daily routine and prevalence of depression, stress, and anxiety among students of Pakistan. *Heliyon*, *7*(5), e07030. https://doi.org/10.1016/j.heliyon.2021.e07030

Khawar, M. B., Abbasi, M. H., Sheikh, N., Riaz, M., Rafiq, M., Farooq, A., Ahmad, Z., Fatima, S., & Amaan, H. N. (2022). Second Wave Scenario of COVID-19 in Pakistan and Combating Strategies. *Albus Scientia, 2022*(1), e220430. https://doi.org/10.56512/AS.2022.1.e220430

King T. P. (1961). On the sulfhydryl group of human plasma albumin. *The Journal of Biological Chemistry*, *236*, PC5.

Kouhpayeh, S.; Shariati, L.; Boshtam, M.; Rahimmanesh, I.; Mirian, M.; Zeinalian, M.; Salari-jazi, A.; Khanahmad, N.; Damavandi, M.S.; Sadeghi, P.; Khanahmad, H. The Molecular Story of COVID-19; NAD^+ Depletion Addresses All Questions in this Infection. *Preprints.org 2020*, 2020030346. https://doi.org/10.20944/preprints202003.0346.v1

Kumar, D., Malviya, R., & Sharma, P. K. (2020). Corona virus: a review of COVID-19. *Eurasian Journal of Medicine and Oncology*, *4*(1), 8-25. https://doi.org/10.14744/ejmo.2020.51418

Lau, S. K., Woo, P. C., Li, K. S., Huang, Y., Tsoi, H. W., Wong, B. H., Wong, S. S., Leung, S. Y., Chan, K. H., & Yuen, K. Y. (2005). Severe acute respiratory syndrome coronavirus-like virus in Chinese horseshoe bats. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(39), 14040–14045. https://doi.org/10.1073/pnas.0506735102

Lei, P., Zhang, L., Han, P., Zheng, C., Tong, Q., Shang, H., Yang, F., Hu, Y., Li, X., & Song, Y. (2020). Liver injury in patients with COVID-19: clinical profiles, CT findings, the correlation of the severity with liver injury. *Hepatology International*, *14*(5), 733–742. https://doi.org/10.1007/s12072-020-10087-1

Li, C. X., Shen, C. B., Xue, K., Shen, X., Jing, Y., Wang, Z. Y., Xu, F., Meng, R. S., Yu, J. B., & Cui, Y. (2019). Artificial intelligence in dermatology: past, present, and future. *Chinese Medical Journal*, *132*(17), 2017–2020. https://doi.org/10.1097/CM9.0000000000000372

Li, D., Liu, C., Liu, J., Hu, J., Yang, Y., & Zhou, Y. (2020). Analysis of risk factors for 24 patients with COVID-19 developing from moderate to severe condition. *Frontiers in Cellular and Infection Microbiology*, *10*, 548582. https://doi.org/10.3389/fcimb.2020.548582

Li, G., Zhou, C. L., Ba, Y. M., Wang, Y. M., Song, B., Cheng, X. B., Dong, Q. F., Wang, L. L., & You, S. S. (2021). Nutritional risk and therapy for severe and critical COVID-19 patients: A multicenter retrospective observational study. *Clinical Nutrition, 40*(4), 2154–2161. https://doi.org/10.1016/j.clnu.2020.09.040

Li, T., Zhang, Y., Gong, C., Wang, J., Liu, B., Shi, L., & Duan, J. (2020). Prevalence of malnutrition and analysis of related factors in elderly patients with COVID-19 in Wuhan, China. *European journal of clinical nutrition*, *74*(6), 871–875. https://doi.org/10.1038/s41430-020-0642-3

Li, W., Moore, M. J., Vasilieva, N., Sui, J., Wong, S. K., Berne, M. A., Somasundaran, M., Sullivan, J. L., Luzuriaga, K., Greenough, T. C., Choe, H., & Farzan, M. (2003). Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature*, *426*(6965), 450–454. https://doi.org/10.1038/nature02145

Lian, J., Jin, C., Hao, S., Zhang, X., Yang, M., Jin, X., Lu, Y., Hu, J., Zhang, S., Zheng, L., Jia, H., Cai, H., Zhang, Y., Yu, G., Wang, X., Gu, J., Ye, C., Yu, X., Gao, J., Yang, Y., … Sheng, J. (2020). High neutrophil-to-lymphocyte ratio associated with progression to critical illness in older patients with COVID-19: a multicenter retrospective study. *Aging*, *12*(14), 13849–13859. https://doi.org/10.18632/aging.103582

Liang, W., Liang, H., Ou, L., Chen, B., Chen, A., Li, C., Li, Y., Guan, W., Sang, L., Lu, J., Xu, Y., Chen, G., Guo, H., Guo, J., Chen, Z., Zhao, Y., Li, S., Zhang, N., Zhong, N., He, J., … China Medical Treatment Expert Group for COVID-19 (2020). Development and validation of a clinical risk score to predict the occurrence of critical illness in hospitalized patients with COVID-19. *JAMA Internal Medicine*, *180*(8), 1081–1089. https://doi.org/10.1001/jamainternmed.2020.2033

Liu, C., Jiang, Z. C., Shao, C. X., Zhang, H. G., Yue, H. M., Chen, Z. H., Ma, B. Y., Liu, W. Y., Huang, H. H., Yang, J., Wang, Y., Liu, H. Y., Xu, D., Wang, J. T., Yang, J. Y., Pan, H Q., Zou, S. Q., Li, F. J., Lei, J. Q., Li, X., … Qi, X. L. (2020). [Preliminary study of the relationship between novel coronavirus pneumonia and liver function damage: a multicenter study]. *Chinese Journal of Hepatology*, *28*(2), 107–111. https://doi.org/10.3760/cma.j.issn.1007-3418.2020.02.003

Liu, J., Liu, Y., Xiang, P., Pu, L., Xiong, H., Li, C., Zhang, M., Tan, J., Xu, Y., Song, R., Song, M., Wang, L., Zhang, W., Han, B., Yang, L., Wang, X., Zhou, G., Zhang, T., Li, B., Wang, Y., … Wang, X. (2020). Neutrophil-to-lymphocyte ratio predicts critical illness patients with 2019 coronavirus disease in the early stage. *Journal of Translational Medicine*, *18*(1), 206. https://doi.org/10.1186/s12967-020-02374-0

Liu, M., He, P., Liu, H. G., Wang, X. J., Li, F. J., Chen, S., Lin, J., Chen, P., Liu, J. H., & Li, C. H. (2020). [Clinical characteristics of 30 medical workers infected with new coronavirus pneumonia]. *Chinese Journal of Tuberculosis and Respiratory Diseases*, *43*(3), 209–214. https://doi.org/10.3760/cma.j.issn.1001-0939.2020.03.014

Liu, Q., Song, N. C., Zheng, Z. K., Li, J. S., & Li, S. K. (2020). Laboratory findings and a combined multifactorial approach to predict death in critically ill patients with COVID-19: a retrospective study. *Epidemiology and Infection*, *148*, e129. https://doi.org/10.1017/S0950268820001442

Liu, S., Luo, H., Wang, Y., Cuevas, L. E., Wang, D., Ju, S., & Yang, Y. (2020). Clinical characteristics and risk factors of patients with severe COVID-19 in Jiangsu province, China: a retrospective multicentre cohort study. *BMC Infectious Diseases*, *20*(1), 584. https://doi.org/10.1186/s12879-020-05314-x

Liu, W., Tao, Z. W., Wang, L., Yuan, M. L., Liu, K., Zhou, L., Wei, S., Deng, Y., Liu, J., Liu, H. G., Yang, M., & Hu, Y. (2020). Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. *Chinese Medical Journal*, *133*(9), 1032–1038. https://doi.org/10.1097/CM9.0000000000000775

Liu, Y., Yang, Y., Zhang, C., Huang, F., Wang, F., Yuan, J., Wang, Z., Li, J., Li, J., Feng, C., Zhang, Z., Wang, L., Peng, L., Chen, L., Qin, Y., Zhao, D., Tan, S., Yin, L., Xu, J., Zhou, C., … Liu, L. (2020). Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Science China. Life Sciences*, *63*(3), 364–374. https://doi.org/10.1007/s11427-020-1643-8

Ma, X., Li, A., Jiao, M., Shi, Q., An, X., Feng, Y., Xing, L., Liang, H., Chen, J., Li, H., Li, J., Ren, Z., Sun, R., Cui, G., Zhou, Y., Cheng, M., Jiao, P., Wang, Y., Xing, J., Shen, S., … Yu, Z. (2020). Characteristic of 523 COVID-19 in Henan province and a death prediction model. *Frontiers in Public Health*, *8*, 475. https://doi.org/10.3389/fpubh.2020.00475

Loganathan, S., Kuppusamy, M., Wankhar, W., Gurugubelli, K. R., Mahadevappa, V. H., Lepcha, L., & Choudhary, A. K. (2021). Angiotensin-converting enzyme 2 (ACE2): COVID 19 gate way to multiple organ failure syndromes. *Respiratory Physiology & Neurobiology*, *283*, 103548. https://doi.org/10.1016/j.resp.2020.103548

Mardani, R., Ahmadi Vasmehjani, A., Zali, F., Gholami, A., Mousavi Nasab, S. D., Kaghazian, H., Kaviani, M., & Ahmadi, N. (2020). Laboratory Parameters in Detection of COVID-19 Patients with Positive RT-PCR; a Diagnostic Accuracy Study. *Archives of Academic Emergency Medicine*, *8*(1), e43.

Mo, P., Xing, Y., Xiao, Y., Deng, L., Zhao, Q., Wang, H., Xiong, Y., Cheng, Z., Gao, S., Liang, K., Luo, M., Chen, T., Song, S., Ma, Z., Chen, X., Zheng, R., Cao, Q., Wang, F., & Zhang, Y. (2021). Clinical Characteristics of Refractory Coronavirus Disease 2019 in Wuhan, China. *Clinical Infectious Diseases*, *73*(11), e4208–e4213. https://doi.org/10.1093/cid/ciaa270

Moman, R. N., Gupta, N., & Varacallo, M. (2017). Physiology, Albumin. In *StatPearls*. StatPearls Publishing.

Mori, S., Ai, T., & Otomo, Y. (2020). Characteristics, laboratories, and prognosis of severe COVID-19 in the Tokyo metropolitan area: A retrospective case series. *PloS One*, *15*(9), e0239644. https://doi.org/10.1371/journal.pone.0239644

Paliogiannis, P., Mangoni, A. A., Cangemi, M., Fois, A. G., Carru, C., & Zinellu, A. (2021). Serum albumin concentrations are associated with disease severity and outcomes in coronavirus 19 disease (COVID-19): a systematic review and meta-analysis. *Clinical and Experimental Medicine*, *21*(3), 343–354. https://doi.org/10.1007/s10238-021-00686-z

Pan, F., Yang, L., Li, Y., Liang, B., Li, L., Ye, T., Li, L., Liu, D., Gui, S., Hu, Y., & Zheng, C. (2020). Factors associated with death outcome in patients with severe coronavirus disease-19 (COVID-19): a case-control study. *International Journal of Medical Sciences*, *17*(9), 1281–1292. https://doi.org/10.7150/ijms.46614

Qian, Z., Travanty, E. A., Oko, L., Edeen, K., Berglund, A., Wang, J., Ito, Y., Holmes, K. V., & Mason, R. J. (2013). Innate immune response of human alveolar type II cells infected with severe acute respiratory syndrome-coronavirus. *American Journal of Respiratory Cell and Molecular Biology*, *48*(6), 742–748. https://doi.org/10.1165/rcmb.2012-0339OC

Rahmani-Kukia, N., Abbasi, A., Pakravan, N., & Hassan, Z. M. (2020). Measurement of oxidized albumin: An opportunity for diagnoses or treatment of COVID-19. *Bioorganic Chemistry*, *105*, 104429. https://doi.org/10.1016/j.bioorg.2020.104429

Recinella, G., Marasco, G., Serafini, G., Maestri, L., Bianchi, G., Forti, P., & Zoli, M. (2020). Prognostic role of nutritional status in elderly patients hospitalized for COVID-19: a monocentric study. *Aging Clinical and Experimental Research*, *32*(12), 2695–2701. https://doi.org/10.1007/s40520-020-01727-5

Romanelli, R. G., La Villa, G., Barletta, G., Vizzutti, F., Lanini, F., Arena, U., Boddi, V., Tarquini, R., Pantaleo, P., Gentilini, P., & Laffi, G. (2006). Long-term albumin infusion improves survival in patients with cirrhosis and ascites: an unblinded randomized trial. *World Journal of Gastroenterology*, *12*(9), 1403–1407. https://doi.org/10.3748/wjg.v12.i9.1403

Rothschild, M. A., Oratz, M., & SCHREIBER, S. S. (1977). Albumin Synthesis. *Albumin: Structure, Function Uses*, 227-253.

Sheam, M. M., Syed, S., Barman, S., Hasan, M. R., Paul, D., & Islam, R. (2020). COVID-19: the catastrophe of our time. *Journal of Advanced Biotechnology and Experimental Therapeutics. 3*(4), 1-13. https://doi.org/10.5455/jabet.2020.d150

Shi, H., Han, X., Jiang, N., Cao, Y., Alwalid, O., Gu, J., Fan, Y., & Zheng, C. (2020). Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *The Lancet. Infectious Diseases*, *20*(4), 425–434. https://doi.org/10.1016/S1473-3099(20)30086-4

Singhal T. (2020). A Review of Coronavirus Disease-2019 (COVID-19). *Indian Journal of Pediatrics*, *87*(4), 281–286. https://doi.org/10.1007/s12098-020-03263-6

Sitges-Serra, A. (2001). Introduction to the Symposium. *Clinical Nutrition*, *3*(20), 263-264.

Soeters, P. B., Wolfe, R. R., & Shenkin, A. (2019). Hypoalbuminemia: Pathogenesis and Clinical Significance. *JPEN. Journal of Parenteral and Enteral Nutrition*, *43*(2), 181–193. https://doi.org/10.1002/jpen.1451

Sohail, A.M., Khawar, M.B., Afzal A., Idnan, M., Arshad, S., Habiba, U., Hamid, S.E., Shahzaman S., Shahid N., Ashraf M.A., & Ramzan, M. (2023). Vitamin D: A ray of hope in combating COVID-19. *Albus Scientia,* 2(1), 1-7. https://doi.org/10.56512/AS.2023.1.e230318

Spinella, R., Sawhney, R., & Jalan, R. (2016). Albumin in chronic liver disease: structure, functions and therapeutic implications. *Hepatology International*, *10*(1), 124–132. https://doi.org/10.1007/s12072-015-9665-6

Tabibzadeh, A., Esghaei, M., Soltani, S., Yousefi, P., Taherizadeh, M., Safarnezhad Tameshkel, F., Golahdooz, M., Panahi, M., Ajdarkosh, H., Zamani, F., & Karbalaie Niya, M. H. (2021). Evolutionary study of COVID-19, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as an emerging coronavirus: Phylogenetic analysis and literature review. *Veterinary Medicine and Science*, *7*(2), 559–571. https://doi.org/10.1002/vms3.394

Tang, X., Wu, C., Li, X., Song, Y., Yao, X., Wu, X., Duan, Y., Zhang, H., Wang, Y., Qian, Z., Cui, J., & Lu, J. (2020). On the origin and continuing evolution of SARS-CoV-2. *National Science Review*, *7*(6), 1012–1023. https://doi.org/10.1093/nsr/nwaa036

Tarao, K., & Iwamura, K. (1983). Influence of long-term administration of serum albumin on the prognosis of liver cirrhosis in man. *The Tokai Journal of Experimental and Clinical Medicine*, *8*(1), 71–78.

Toutkaboni, M. P., Askari, E., Khalili, N., Tabarsi, P., Jamaati, H., Velayati, A. A., Dorudinia, A., Rezaei, M., Nadji, S. A., Mohamadnia, A., & Khalili, N. (2020). Demographics, laboratory parameters and outcomes of 1061 patients with coronavirus disease 2019: a report from Tehran, Iran. *New Microbes and New Infections*, *38*, 100777. https://doi.org/10.1016/j.nmni.2020.100777

Tsibouris, P., Ekmektzoglou, K., Agorogianni, A., Kalantzis, C., Theofanopoulou, A., Toumbelis, K., Petrogiannopoulos, L., Poutakidis, C., Goggaki, S., Braimakis, I., Vlachou, E., Pouliakis, A., & Apostolopoulos, P. (2020). Gastrointestinal involvement in COVID-19 patients: a retrospective study from a Greek COVID-19 referral hospital. *Annals of Gastroenterology*, *33*(5), 465–472. https://doi.org/10.20524/aog.2020.0514

Varim, C., Yaylaci, S., Demirci, T., Kaya, T., Nalbant, A., Dheir, H., Senocak, D., Kurt, R., Cengiz, H., & Karacaer, C. (2020). Neutrophil count to albumin ratio as a new predictor of mortality in patients with COVID-19 infection. *Revista da Associacao Medica Brasileira (1992)*, *66Suppl 2*(Suppl 2), 77–81. https://doi.org/10.1590/1806-9282.66.S2.77

Velarde-Ruiz Velasco, J. A., García-Jiménez, E. S., & Remes-Troche, J. M. (2020). Hepatic manifestations and impact of COVID-19 on the cirrhotic patient. Manifestaciones hepáticas y repercusión en el paciente cirrótico de COVID-19. *Revista de Gastroenterologia de Mexico (English)*, *85*(3), 303–311. https://doi.org/10.1016/j.rgmx.2020.05.002

Viana-Llamas, M. C., Arroyo-Espliguero, R., Silva-Obregón, J. A., Uribe-Heredia, G., Núñez-Gil, I., García-Magallón, B., Torán-Martínez, C. G., Castillo-Sandoval, A., Díaz-Caraballo, E., Rodríguez-Guinea, I., & Domínguez-López, J. (2021). Hypoalbuminemia on admission in COVID-19 infection: An early predictor of mortality and adverse events. A retrospective observational study. *Medicina Clinica*, *156*(9), 428–436. https://doi.org/10.1016/j.medcli.2020.12.018

Violi, F., Cangemi, R., Romiti, G. F., Ceccarelli, G., Oliva, A., Alessandri, F., Pirro, M., Pignatelli, P., Lichtner, M., Carraro, A., Cipollone, F., D'ardes, D., Pugliese, F., & Mastroianni, C. M. (2021). Is Albumin Predictor of Mortality in COVID-19? *Antioxidants & Redox Signaling*, *35*(2), 139–142. https://doi.org/10.1089/ars.2020.8142

Wan, S., Xiang, Y., Fang, W., Zheng, Y., Li, B., Hu, Y., Lang, C., Huang, D., Sun, Q., Xiong, Y., Huang, X., Lv, J., Luo, Y., Shen, L., Yang, H., Huang, G., & Yang, R. (2020). Clinical features and treatment of COVID-19 patients in northeast Chongqing. *Journal of Medical Virology*, *92*(7), 797–806. https://doi.org/10.1002/jmv.25783

Wang, D., Li, R., Wang, J., Jiang, Q., Gao, C., Yang, J., Ge, L., & Hu, Q. (2020). Correlation analysis between disease severity and clinical and biochemical characteristics of 143 cases of COVID-19 in Wuhan, China: a descriptive study. *BMC Infectious Diseases*, *20*(1), 519. https://doi.org/10.1186/s12879-020-05242-w

Wang, Q., Zhao, H., Liu, L. G., Wang, Y. B., Zhang, T., Li, M. H., Xu, Y. L., Gao, G. J., Xiong, H. F., Fan, Y., Cao, Y., Ding, R., Wang, J. J., Cheng, C., & Xie, W. (2020). Pattern of liver injury in adult patients with COVID-19: a retrospective analysis of 105 patients. *Military Medical Research*, *7*(1), 28. https://doi.org/10.1186/s40779-020-00256-6

Wang, Y., Liao, B., Guo, Y., Li, F., Lei, C., Zhang, F., Cai, W., Hong, W., Zeng, Y., Qiu, S., Wang, J., Li, Y., Deng, X., Li, J., Xiao, G., Guo, F., Lai, X., Liang, Z., Wen, X., Li, P., … Guan, Y. (2020). Clinical Characteristics of patients infected with the novel 2019 coronavirus (SARS-Cov-2) in Guangzhou, China. *Open Forum Infectious Diseases*, *7*(6), 187. https://doi.org/10.1093/ofid/ofaa187

Wu, C., Chen, X., Cai, Y., Xia, J., Zhou, X., Xu, S., Huang, H., Zhang, L., Zhou, X., Du, C., Zhang, Y., Song, J., Wang, S., Chao, Y., Yang, Z., Xu, J., Zhou, X., Chen, D., Xiong, W., Xu, L., … 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. https://doi.org/10.1001/jamainternmed.2020.0994

Xu, L., Liu, J., Lu, M., Yang, D., & Zheng, X. (2020). Liver injury during highly pathogenic human coronavirus infections. *Liver international*, *40*(5), 998–1004. https://doi.org/10.1111/liv.14435

Xue, G., Gan, X., Wu, Z., Xie, D., Xiong, Y., Hua, L., Zhou, B., Zhou, N., Xiang, J., & Li, J. (2020). Novel serological biomarkers for inflammation in predicting disease severity in patients with COVID-19. *International Immunopharmacology*, *89*, 107065. https://doi.org/10.1016/j.intimp.2020.107065

Yang, X., Yu, Y., Xu, J., Shu, H., Xia, J., Liu, H., Wu, Y., Zhang, L., Yu, Z., Fang, M., Yu, T., Wang, Y., Pan, S., Zou, X., Yuan, S., & Shang, Y. (2020). Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *The Lancet. Respiratory Medicine*, *8*(5), 475–481. https://doi.org/10.1016/S2213-2600(20)30079-5

Yu, C., Lei, Q., Li, W., Wang, X., Li, W., & Liu, W. (2020). Epidemiological and clinical characteristics of 1663 hospitalized patients infected with COVID-19 in Wuhan, China: a single-center experience. *Journal of Infection and Public Health*, *13*(9), 1202–1209. https://doi.org/10.1016/j.jiph.2020.07.002

Yuki, K., Fujiogi, M., & Koutsogiannaki, S. (2020). COVID-19 pathophysiology: A review. *Clinical immunology, 215*, 108427. https://doi.org/10.1016/j.clim.2020.108427

Zeng, Z., Ma, Y., Zeng, H., Huang, P., Liu, W., Jiang, M., Xiang, X., Deng, D., Liao, X., Chen, P., & Chen, Y. (2021). Simple nomogram based on initial laboratory data for predicting the probability of ICU transfer of COVID-19 patients: Multicenter retrospective study. *Journal of Medical Virology*, *93*(1), 434–440. https://doi.org/10.1002/jmv.26244

Zhang, C., Qin, L., Li, K., Wang, Q., Zhao, Y., Xu, B., Liang, L., Dai, Y., Feng, Y., Sun, J., Li, X., Hu, Z., Xiang, H., Dong, T., Jin, R., & Zhang, Y. (2020). A Novel Scoring System for Prediction of Disease Severity in COVID-19. *Frontiers in Cellular and Infection Microbiology*, *10*, 318. https://doi.org/10.3389/fcimb.2020.00318

Zhang, X., Cai, H., Hu, J., Lian, J., Gu, J., Zhang, S., Ye, C., Lu, Y., Jin, C., Yu, G., Jia, H., Zhang, Y., Sheng, J., Li, L., & Yang, Y. (2020). Epidemiological, clinical characteristics of cases of SARS-CoV-2 infection with abnormal imaging findings. *International journal of infectious diseases*, *94*, 81–87. https://doi.org/10.1016/j.ijid.2020.03.040

Zhang, Y., Zheng, L., Liu, L., Zhao, M., Xiao, J., & Zhao, Q. (2020). Liver impairment in COVID-19 patients: A retrospective analysis of 115 cases from a single centre in Wuhan city, China. *Liver International*, *40*(9), 2095–2103. https://doi.org/10.1111/liv.14455

Zhou, C., Huang, Z., Tan, W., Li, X., Yin, W., Xiao, Y., Tao, Z., Geng, S., & Hu, Y. (2020). Predictive factors of severe coronavirus disease 2019 in previously healthy young adults: a single-center, retrospective study. *Respiratory Research*, *21*(1), 157. https://doi.org/10.1186/s12931-020-01412-1

Zhou, F., Fan, G., Liu, Z., & Cao, B. (2020). SARS-CoV-2 shedding and infectivity - Authors' reply. *Lancet*, *395*(10233), 1340. https://doi.org/10.1016/S0140-6736(20)30869-2

Zhou, J., Huang, L., Chen, J., Yuan, X., Shen, Q., Dong, S., Cheng, B., & Guo, T. M. (2020). Clinical features predicting mortality risk in older patients with COVID-19. *Current Medical Research and Opinion*, *36*(11), 1753–1759. https://doi.org/10.1080/03007995.2020.1825365

Zinellu, A., Arru, F., De Vito, A., Sassu, A., Valdes, G., Scano, V., Zinellu, E., Perra, R., Madeddu, G., Carru, C., Pirina, P., Mangoni, A. A., Babudieri, S., & Fois, A. G. (2021). The De Ritis ratio as prognostic biomarker of in-hospital mortality in COVID-19 patients. *European Journal of Clinical Investigation*, *51*(1), e13427. https://doi.org/10.1111/eci.13427