COVID-19, PNEUMONIA & INFLAMMASOMES – THE MELATONIN CONNECTION

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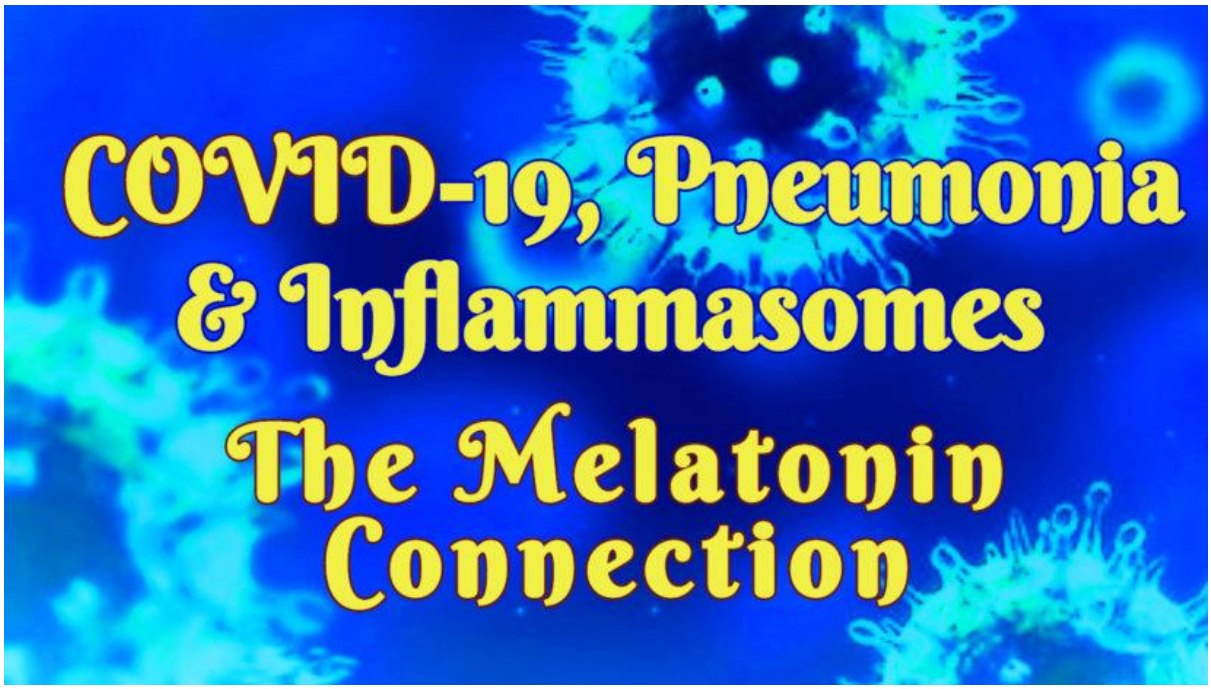

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By Doris Loh

On March 11th, 2020 during a media briefing, the World Health Organizati\aon (WHO) declared COVID-19 a pandemic as confirmed COVID-19 cases outside of China increased 13-fold and the number of countries affected tripled. On that

day, 126,000 people around the world contracted COVID-19, while 122 countries around the world reported COVID-19 infections [3].

Even though cases in China and South Korea have declined dramatically, those in Italy and Iran have been rising relentlessly. Italy has the most cases outside China with roughly 12,462 infections, followed by Iran with 9,000 infections and South Korea with 7,775 (March 11th, 2020). COVID-19 patients in Italy also have the highest case fatality rate, currently at 6.6% [3].

Unofficial reports from doctors and healthcare workers from COVID-19 frontlines in Italy described most patients displayed symptoms of bilateral interstitial pneumonia that required intubation (invasive ventilation) to assist difficulty in breathing. Even young patients without comorbidities have been observed with severe pneumonia that required intensive care in ICUs [4, 5].

These dramatic and shocking accounts of severe pneumonia in Italians infected by COVID-19 strongly support similar evidence presented by scientists and doctors in China where mortality of critically ill patients with SARS-CoV-2 pneumonia is extremely high. In one study, 86% of ICU patients requiring invasive mechanical ventilation did not survive [6].

In general, patients above 65 years of age with comorbidities and ARDS are at a much higher risk of death. Acute respiratory distress syndrome (ARDS), or acute lung injury (ALI), is a condition when severe lung failure is marked by acute onset of respiratory failure, accompanied by low arterial oxygen levels. Most often than not, bilateral opacities in the lungs are also observed in ARDS patients [7].

In one recent cohort study from China, 86% of patients with COVID-19 pneumonia showed typical imaging features of ground-glass opacities (GGO) in their lungs [8]; and 64% had mixed GGO and consolidation [9]. Most shocking of all, 70.2% of patients examined in the study were between the ages of 21 to 50 years [8]. Thus, young patients stricken with bilateral interstitial pneumonia in Italy is not inconsistent with the results of COVID-19 patients observed in China.

Why does SARS-CoV-2, the coronavirus responsible for COVID-19 infection, induce pneumonia in adult patients regardless of age?

COVID-19 Infectiousness & Increased Incidences of Pneumonia

A review of COVID-19 patients between January 12, 2020 to February 6, 2020 who managed to recover from COVID-19 pneumonia, all showed greatest severity of lung disease at approximately 10 days after initial onset of symptoms. The chart below excluded patients with severe pneumonia with symptoms of respiratory distress together with breath rates under 30 per minute, as well as patients who required mechanical ventilation assistance [14].

Distribution and frequency of the major of lung lesions on CT in different stages defined by the time of onset of symptoms.

	Stage-1 (n=24)	Stage-2 (n=17)	Stage-3 (n=21)	Stage-4 (n=20)
Distribution of pulmonary lesions				
No lesion	4 (17%)	0 (0%)	0 (0%)	0 (0%)
Peripheral	13 (54%)	10 (59%)	13 (62%)	14 (70%)
Random	7 (29%)	6 (35%)	7 (33%)	5 (25%)
Diffuse	0 (0%)	1 (5.9%)	1 (4.8%)	1 (5.0%)
Involvement of the lesions				
No involvement	4 (17%)	0 (0%)	0 (0%)	0 (0%)
Single lobe	10 (42%)	4 (24%)	3 (14%)	4 (20%)
Bilateral multilobe	10 (42%)	13 (77%)	18 (86%)	16 (80%)

[Source: Feng Pan, Tianhe Ye et al. Time Course of Lung Changes On Chest CT During Recovery From 2019 Novel Coronavirus (COVID-19) Pneumonia, Radiology RSNA.org Feb 13 2020 doi.org/10.1148/radiol.2020200370]

By Stage 3, which is day 9 to day 13 after onset of symptoms, 86% of patients with non-severe pneumonia all showed lesions in both lungs (bilateral). 17% of these patients showed no lesions during Stage 1, from onset of symptoms to the 4th day [14].

However, 81% of critically ill COVID-19 patients would progress to develop life-threatening Acute Respiratory Distress Syndrome (ARDS) [10]. Bilateral interstitial pneumonia will cause progressive scarring of lung tissues in both lungs, eventually reducing the capacity to breathe and the ability to circulate adequate oxygen in the bloodstream [11]. Once ARDS develops, mechanical ventilation assistance is required to facilitate breathing [15].

Coronaviruses are known for causing respiratory diseases with symptoms ranging from common colds to pneumonia [12]. The SARS-CoV or Severe Acute Respiratory Syndrome epidemic of 2003 infected over 8000 people worldwide, with a 10% mortality rate [13]. The closely related MERS-CoV of 2012, also induced acute pneumonia similar to the one caused by SARS-CoV [14].
The current SARS-CoV-2, with 79% similarity to SARS-CoV, also induces pneumonia of varying severity in adult patients regardless of age. However, unlike SARS-CoV that only infected 8,000 people worldwide in 8 months [16], the current SARS-CoV-2, which has been estimated to be up to 1,000 times more infectious than SARS-CoV or other coronaviruses [17, 18], has already infected over 120,000 people worldwide in under three months.

COVID-19 Upper Respiratory Tract Viral Load is 1000 Times HIGHER Than SARS (2003)

Due to the high mutation rate of the spike protein in SARS-CoV-2 [19], the virus is showing a pattern of higher infectiousness. A study released by scientists in Germany on March 8th, 2020 found that this coronavirus is not only infecting lower respiratory tracts as seen in early January when COVID-19 patients in China examined displayed no obvious symptoms of rhinorrhoea (runny nose), sneezing, or sore throat, but all had pneumonia with abnormal chest CTs and 29% of those early patients examined developed ARDS (acute respiratory distress syndrome) [20].
The subjects from the German study were all young to middle-aged professionals without significant underlying disease, some had no comorbidity. All cases were tested when symptoms were still mild, including fever, cough, rhinitis, sinusitis diarrhea. One subject had no symptoms at all. Upon taking throat swabs from these patients upon onset of symptoms, all results from day 1 to day 5 tested positive for COVID-19. The high viral load from these early throat swabs indicated potential viral replication in upper respiratory tract tissues. This means that there is actually ACTIVE VIRAL replication of SARS-CoV-2 in the throat during the first 5 days after symptoms onset [21].
The positive early throat swabs contrasts starkly to SARS, where only 39% of nasal or nasopharyngeal swab samples tested positive in patients infected by SARS in 2003, Hong Kong [22]. The difference in viral loads detected between these two coronavirus ‘cousins’ are quite staggering. In Sars-CoV, it took 7 to 10 days after onet to reach peak RNA concentration. Whereas SARS-CoV-2 reached

peak RNA concentration by only the 5th day. In addition, the **number of SARS-CoV-2 viral copies obtained per swab was ONE THOUSAND TIMES higher than those of SARS-CoV in 2003!** [22. 23, 24]

SARS-CoV-2 Spike Protein Furin Cleavage Site – The Reason For COVID-19 High Infectivity and Pathogenicity?

On March 11th, 2020, Wenling Wang et al. released an alarming paper detailing the results of 1070 specimens collected from 205 COVID-10 patients. The mean age of patients was 44 years, between the ages of 5 to 67 years. 68% of the patients were male. The study specimens were collected from three hospitals in the Hubei and Shandong provinces and Beijing, China, during the period from January 1 through February 17, 2020 [25].

The team led by Wang collected pharyngeal (throat) swabs from patients 1 to 3 days after hospital admission. Other samples from blood, sputum, feces, urine and nose were collected throughout the illness. 19% of the patients were in critical condition and required mechanical ventilation. These patients were sampled by bronchoalveolar lavage fluid and fibrobronchoscope brush biopsy [25]. What Wenling Wang et al. discovered supported the findings of the German team, led by Roman Wölfel [21].

The highest viral load was found in specimens from bronchoalveolar lavage fluid (93%), followed by sputum (72%), nasal (63%) fibrobronchoscope brush biopsy (46%), pharyngeal swabs (32%), feces (29%), and blood (1%). Interestingly, none of the 72 urine specimens tested positive for the coronavirus [25].

The team of German scientists led by Wölfel et al. proposed the hypothesis that the extension of tropism of the coronavirus is due to the furin cleavage site in the spike protein of SARS-CoV-2. This cleavage site is not present in SARS-CoV [17, 18] The presence of furins on almost all cell surfaces allow a dramatically increased ability to fuse to host cells, facilitating viral entry even in cells that have low expressions of the ACE2 receptor [26].

The furin cleavage allows efficient virus entry into basically all cell types, making the COVID-19 easily transmissible at rates up to **1,000 times greater than the virulent SARS coronavirus** [18]. This is possibly the reason why SARS (2003) infected only 8,000 people worldwide and COVID-19 infected over 120,000

people in one third of the time, even though both coronaviruses cause pneumonia of varying severity.

Cleavage specificity can dictate the tropism and virulence of the virus. The fact that COVID-19 has cleavage sites for furin enzymes renders this virus to be highly pathogenic, with the capacity to replicate in MULTIPLE tissues and organs due to how furins are utilized and distributed in the human body [27].

Furin-like cleavage in human coronaviruses have been associated with the development of neurological diseases where the invasiveness and efficient establishment of lower pathogenicity can result in persistent infection of the central nervous system [28]. Thus it was not a surprise when in early March of 2020, doctors from Beijing Ditan Hospital affiliated to Capital Medical University, a designated institution for COVID-19 treatment, showed for the first time that COVID-19 can attack the human central nervous system, causing symptoms of encephalitis [29].

The presence of furin enzymes on all cell surfaces cleaves and activates the SARS-CoV-2 in a wide range of tissues and organs. Activated SARS-CoV-2 then unleashes NLRP3 inflammasomes, initiating a flurry of immune reactions that can result in deadly cytokine storms.

ARDS/ALI, Cytokine Storms & NLRP3 Inflammasomes – The COVID-19 Viroporin Connection

Critically ill COVID-19 patients often develop acute respiratory distress syndrome and acute lung injury (ARDS/ALI). The uncontrolled progressive inflammation in the lungs causes acute diffuse alveolar damage recognized as areas with ground-glass opacities, and other areas with increased density but without any recognizable vessels (consolidation) [30].

When ARDS progress to the acute phase, alveolar flooding (edema), interstitial inflammation and compression atelectasis, as well as increase in lung tissue and reduction in lung gas volume are observed [31,32, 41]. COVID-19 patients suffering from ARDS/ALI often require intubation and invasive mechanical ventilation to assist difficulty in breathing because the increasing hypoxemic respiratory failure results in acute diffuse alveolar damage [42, 7].

Acute respiratory distress syndrome and acute lung injury (ARDS/ALI) are often characterized by the accumulation of neutrophils in the lungs and the increased

production of inflammatory cytokines, chemokines, proteases and oxidants. The initiation and development of ARDS/ALI is dependent upon the activation of inflammasomes.

Inflammasomes are an integral part of our innate immune system. Inflammasomes sense pathogens, danger associated molecular patterns (DAMPs) as well as biological crystals including urate and cholesterol. The activation of inflammasomes releases proinflammatory cytokines interleukin (IL)-1β and IL-18.

Recently, the NLRP3 inflammasome has been identified as key to the induction of ADRS/ALI [33, 40]. Interleukin 1 beta (IL-1β) is a potent proinflammatory cytokine that is implicated in the pathogenesis of acute respiratory distress syndrome because the initiation of hypoxemia (below normal oxygen levels in blood) is induced by IL-1β signaling [38]. The production of IL-1β is tightly controlled and is dependent upon NLRP3 inflammasome activation [39] .

A study published in June 2019 demonstrated that high level activation of NLRP3 inflammasome is essential for the induction and development of cytokine storms and multi-organ dysfunctions in a streptococcal toxic shock-like syndrome model [34]. How are NLRP3 inflammasomes connected to the SARS-CoV-2 coronavirus?

All viruses encode proteins that can interfere with the innate immune system. The interferences can either inhibit or enhance host immune responses. Some viruses would disrupt the immune system to promote evasion and pathogenicity, while others modulate cellular factors that would also disrupt immune responses [35, 36, 37].

Coronaviruses like SARS-CoV-2 use viroporins to STIMULATE immune responses as part of their pathogenicity.

Viroporins are ion channel proteins encoded by viruses. Viroporins ORF3a and E protein play critical roles in virus replication and pathogenesis. A virus lacking both E and ORF3a proteins would not be viable. Maximal replication and virulence of the SARS-CoV coronavirus has been shown to be the direct result of viroporin proteins E and ORF3a [43]. This means that how quickly a virus like SARS-CoV replicates, the infectiousness and damage it can cause is totally dependent upon the functionality of its viroporins. How do viroporins work? Scientists have known for a few years that viroporin envelope (E) protein is responsible for the virulence of SARS-CoV. Studies have been able to associate the E protein ion channel (IC) activities in SARS-CoV to enhanced pulmonary

damage, edema accumulation and death. Edema is the major determinant of ARDS that could result in death. Whenever E protein ion channel activities were observed, both edema and IL-1β mediated proinflammatory response were elevated. Deletion of the E protein in SARS-CoV resulted in significantly reduced IL-1β activity in lung airways of infected animal models lacking E protein ion conductivity [44].

SARS-CoV viroporin E proteins form protein-lipid channels in cell membranes that allow passage of calcium ions. These ion channel movements involving calcium are specific triggers in the activation of NLRP3 inflammasomes, resulting in the overproduction of pro-inflammatory IL-1β cytokines. Calcium transport through these E protein ion channels initiates the cascade of cytokine production that may eventually result in uncontrollable cytokine storms, and ARDS/ALI in bilateral interstitial pneumonia.

Ionic disturbances at the cell level is the reason why coronaviruses like SARS-CoV can have such immense impact on causing severe immunopathological consequences and disease progression that spiral out of control in infected patients [45].

Why do coronaviruses activate inflammasomes to enhance the production of pro-inflammatory cytokine like IL-1β?

Cytokines – Dangerous Double-Edged Swords Exploited by Coronaviruses

Proinflammatory cytokines defend host cells from invading pathogens, but they are also capable of driving pathological inflammation [46]. During viral infections, inflammation can act in dynamically opposing antiviral and proviral roles. Inflammatory responses can inhibit viral replication and lower infection, but inflammation also has the capacity to release a large number of virions, further disseminating viral infection to cells like macrophages which will spread the virus to various other tissues and organs in the host [46].

SARS-CoV coronaviruses encode viroporin proteins to activate inflammasomes in order to facilitate viral dissemination. The recent discovery of the ORF3a viroporin further deepens understanding as to why SARS-CoV can exert so much damage when infecting hosts.

Like E proteins, ORF3a also activates NLRP3 inflammasome. It is widely accepted that both E and ORF3a proteins are required for viral replication and virulence

[44, 45]. The lack of these two proteins renders the virus nonviable. ORF3a is HIGHLY expressed in infected cells. This viroporin also conducts calcium or sodium ions in membranes like the E protein [59]. Viruses deficient in viroporin ORF3a remain viable but showed reduced pathogenicity in rodent models [60], but the lack of both viroporin E and 3a would completely disable virus from replication [43].

What distinguishes viroporin ORF3a from E protein is its unique ability to induce NF-κB activation, chemokine production, Golgi fragmentation, endoplasmic reticulum stress, and accumulation of intracellular vesicles. ORF3a ion channel activity has been clearly demonstrated to be responsible for initiating pro-apoptotic cell deaths [61, 62, 63, 64].

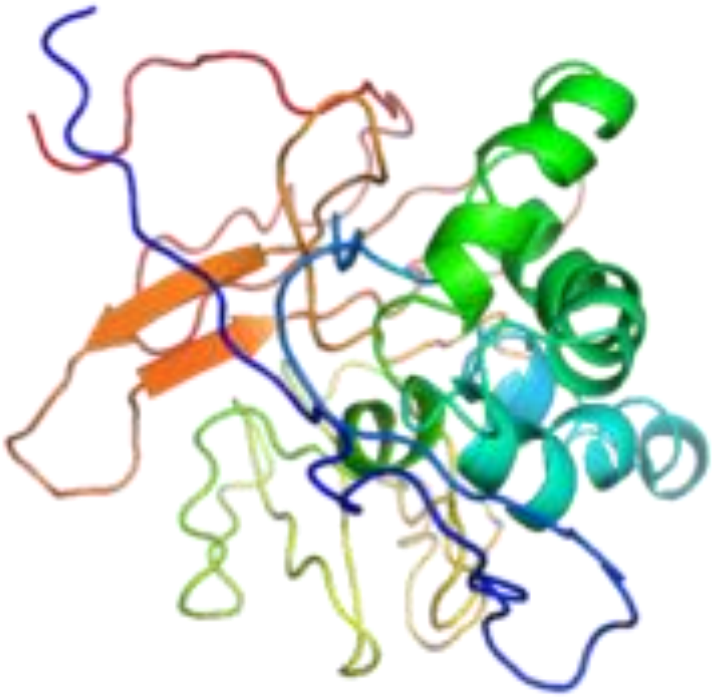
The viroporin E protein activates NLRP3 inflammasomes through its ion channel activities. What surprised Siu et al. (April 2019) was that the ability of ORF3a to activate NLRP3 inflammasomes to induce cytokine storms that eventually result in severe lung damage is INDEPENDENT of its ion channel activities [65].

ORF3a can induce pro–IL-1β gene transcription and IL-1β protein secretion by facilitating ubiquitination processes that induce gene transcriptions that provide signals required for activation of NLRP3 inflammasomes [66]. The activation of NLRP3 inflammasomes in macrophages of mice infected with SARS-CoV have also been observed by Chen et al. (Jan 2019) [67].

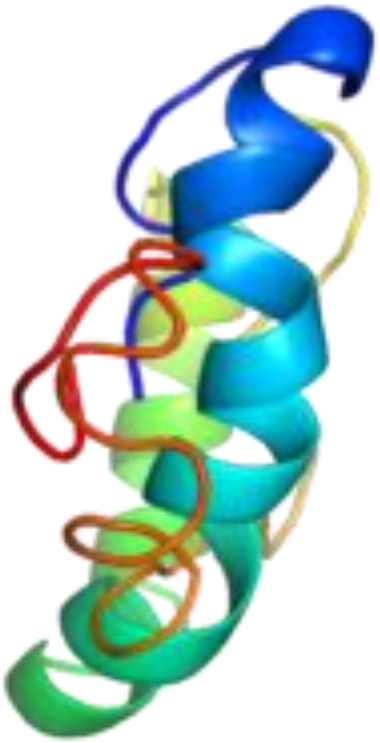
SARS-CoV encodes both viroporin ORF3a and E protein. That is the reason for their high virulence and pathogenicity. Does SARS-CoV-2 encode these two viroporins also?

The most current structure models of all mature peptides of SARS-CoV-2 generated by the C-I-TASSER pipeline [68] clearly shows that SARS-CoV-2, responsible for the COVID-19 disease encodes **BOTH ORF3a AND E protein viroporins** [69]**!**

ORF3a Viroporin of SARS-CoV-2



E protein Viroporin of SARS-CoV-2



This is the reason why SARS-CoV-2 is significantly more infectious and pathogenic than SARS-CoV.
One question that has not been truly answered is why infants and children under the age of nine do not seem to suffer any severe symptoms upon COVID-19 infection. It is understandable why older patients may be more susceptible to higher risks, but what spares young children? Why are young adults without comorbidities also suffering from pneumonia as a result of COVID-19 infections?

Take a look at the following chart showing the fatality rate according to age groups:

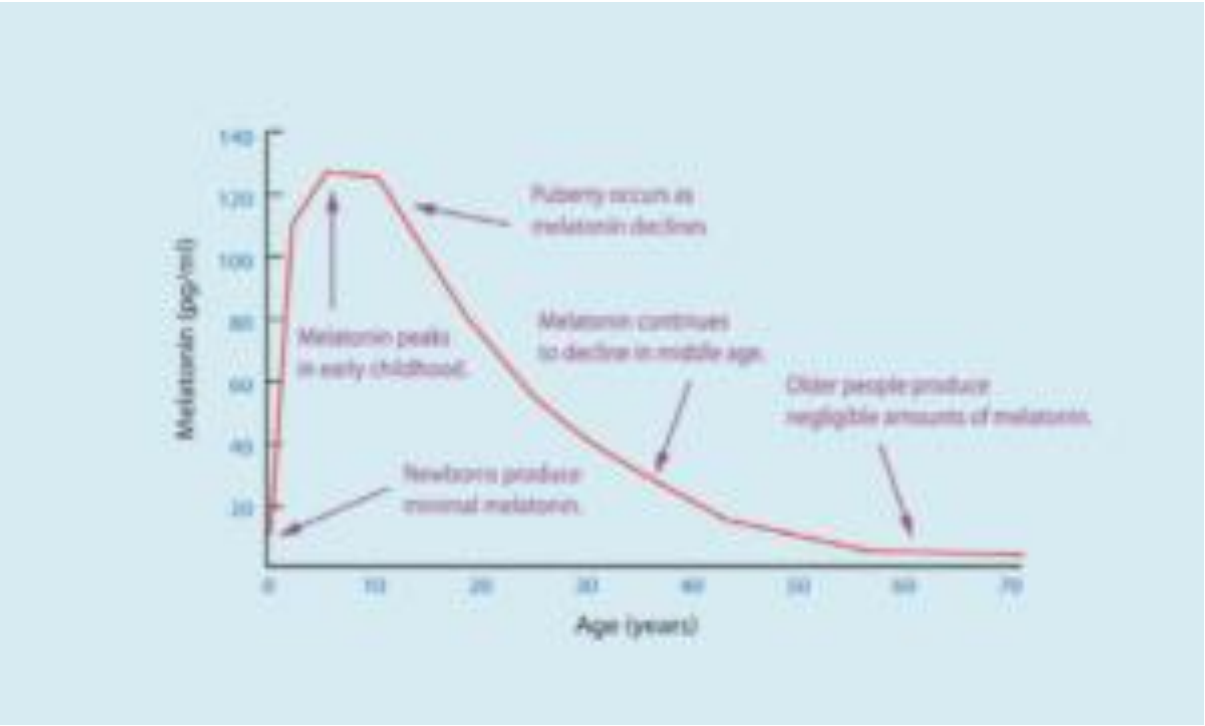
COVID-19 fatality rate by age

AGE	DEATH RATE*
80+ years old	14.8%
70-79 years old	8.0%
60-69 years old	3.6%
50-59 years old	1.3%
40-49 years old	0.4%
30-39 years old	0.2%
20-29 years old	0.2%
10-19 years old	0.2%
0-9 years old	no fatalities

{Source: https://www.worldometers.info/coronavirus/coronavirus-age-sex-demographics/]

There are no fatalities recorded for infected COVID-19 patients under the age of nine. The fatality rate increases linearly with age. The highest rate of fatality is seen in patients aged 80 and above [71]. Experts have yet to answer the question as to why COVID-19 is sparing young children [72].

While you ponder over this puzzle, take a look at this chart, which mirrors the above table but in REVERSE:



[Source: Grivas TB, Savvidou OD. Melatonin the "light of night" in human biology and adolescent idiopathic scoliosis. Scoliosis. 2007;2:6. Published 2007 Apr 4. doi:10.1186/1748-7161-2-6]

What does this chart measure? An ancient and powerful molecule that everyone is familiar with – melatonin. What does melatonin have to do with SARS-CoV-2?

Melatonin Inhibits NLRP3 Inflammasomes

Melatonin is well known for its chronobiotic effects, regulating biological functions tied to circadian rhythms. Numerous studies have revealed that melatonin exerts effects beyond the control of circadian oscillators. The NLRP3 inflammasome is now recognized as a target for melatonin!

The fact that the pro-inflammatory cytokine storm effects are induced by the activation of NLRP3 inflammasomes, the ability of melatonin to INHIBIT NLRP3 inflammasome elevates this powerful molecule to a truly unique position in the fight against COVID-19. This also means that if a patient, regardless of age, has adequate melatonin, the infectiousness of COVID-19 will be greatly reduced, and the chances of developing ARDS/ALI significantly diminished.

Melatonin is the reason why children under the age of 9 seldom exhibit severe symptoms. In fact, children may exhibit mild or even no symptoms at all, even

though they have been infected by SARS-CoV-2 [73]. How significant is the difference in melatonin production between children, adults and the elderly?
For most people, peak melatonin production is between the hours of 2 am to 3 am. The maximum melatonin levels measured in healthy adults between the ages of 65 to 70 years appeared to be around 49.3 picograms/ml (pg/ml). Adults more than 75 years of age only have maximum production levels of 27.8 pg/ml [74].
Young children, on the other hand, have extremely high melatonin levels, compared to adults. The maximum levels recorded for children showed a decline as age increased. Children between the ages of 1 to 5 had peak melatonin at 325 pg/ml, while those between the ages of 5 to 11 already declined to 133 pg/ml [76].
Compared to healthy adult seniors, a young child can easily have TEN TIMES the amount of peak melatonin levels. But even then, the actual physiological concentration is extremely low. How much is one picogram, exactly?
To give you some perspective, most melatonin supplements are around 3 to 5 mg per capsule or tablet. One milligram equals 1,000,000,000 picograms. That is why the physiological dosage generally recommended for melatonin supplementation is around 0.3 milligram [75].
The fact that young children have such high melatonin levels explains why they show very mild symptoms after COVID-19 infections.

Melatonin is a potent inhibitor of NLRP3 inflammasomes.

Generally referred to as the "hormone of darkness", the ability of melatonin to regulate both pro- as well as anti-inflammatory cytokines in different pathophysiological conditions has only been extensively studied in the past several years.
Controlling cytokine storms is one of the major challenges in the treatment of sepsis [82]. The NLRP3 inflammasome has an interesting nickname of "Pandora's Box for Sepsis" [83]. Yet nature provides all the solutions to difficult health challenges.
NLRP3 inflammasomes is a direct target of melatonin. Animal models of sepsis showed melatonin's ability to maintain mitochondrial homeostasis, reduce reactive oxygen species and lower production of proinflammatory cytokines.

Melatonin was shown to inhibit NLRP3 inflammasomes in mice with myocardial septic conditions, transforming severe myocardial inflammation into milder symptoms, preventing cardiac failure, and significantly enhanced survival rates of septic mice [77, 78].

An excellent study by Volt et al (2016) showed that chronic low doses of melatonin in aged mice could prevent increase in inflammation, ROS and mitochondria impairments reflective of inflammaging [79, 80]. Volt et al. also showed that acute administration of melatonin could counteract severe inflammatory responses [81].

It is therefore not surprising to find that melatonin is able to prevent ARDS/ALI through suppression of NLRP3 inflammasomes.

In rodent acute lung injury (ALI) models, melatonin was found to markedly reduce pulmonary injury, lower infiltration of macrophages and neutrophils into lungs. Melatonin protected mice from acute lung injuries by inhibiting the activation of NLRP3 inflammasomes through the suppression of extracellular release of histones and blocking histone-induced NLRP3 inflammasome activation [84].

In rodent models of acute respiratory distress syndrome (ARDS), combined treatment of melatonin and mitochondria significantly attenuated progression of ARDS [85].

Melatonin Protects Lung Injury from Mechanical Ventilation Interventions

COVID-19 patients with ARDS/ALI often require intubation with mechanical ventilation. Even though the intervention may help patients, in many instances, patients develop ventilator-induced lung injury as a result of mechanical ventilation [86]. In particular, high ventilation pressures and high tidal volumes required to maintain proper oxygenation and CO2 elimination can cause lung damage and impair gas exchange.

A study released on March 6, 2020 by Geng-Chin Wu et al. demonstrated that by increasing melatonin with the use of a melatonin receptor agonist, damaging effects of ventilator-induced lung injury could be prevented in rodent models [87].

The full therapeutic potential of melatonin in its ability to modulate the immune system, especially the critical function of suppressing cytokine storms to prevent progression of acute respiratory distress syndrome (ARDS) and respiratory

failure in infected patients was clearly demonstrated in a study by Huan]g et al. (2019). Huang et al. infected rodents with the highly lethal and infectious H1N1 influenza A virus. Co-treatment of these infected rodents with melatonin and an antiviral drug significantly increased their survival rates compared to mice treated only with antivirals alone [88]!

It is no wonder that none of the pregnant mothers infected by COVID-19 admitted to Zhongnan Hospital of Wuhan University, Wuhan, China, developed severe pneumonia or died; nor were their babies infected by COVID-19 [89]. Why?

Melatonin secretion in the third trimester of pregnancy is more than doubled compared to the first trimester.

Serum melatonin in pregnant and non-pregnant women

Serum melatonin in the first semester (pmol/l)	29.7 +/- 9.9
Serum melatonin in the second semester (pmol/l)	39.1 +/- 11.2
Serum melatonin in the third semester (pmol/l)	76.5 +/- 38.3
Non-pregnant(pmol/l)	41.7 +/- 15.5

[Source: Voiculescu SE, Zygouropoulos N, Zahiu CD, Zagrean AM. Role of melatonin in embryo fetal development. J Med Life. 2014;7(4):488–492.]

However, if you noticed in the earlier chart showing melatonin levels during various ages, you will notice that infants younger than three months have very little melatonin [76]. Yet studies from China showed that infants under one year of age who were infected by COVID-19 did not exhibit any severe symptoms [90]. Why?

Nitric Oxide and Ascorbic Acid Inhibits NLRP3 Inflammasomes

Nitric oxide produced in nasal passages is possibly part of the defense system against bacterial and viral infections [91]. Newborns have been found to have an extremely high level of nitric oxide in their barely developed paranasal sinuses.

The levels of nitric oxide in nasal passages of infants matched those found in adults [92].

In rodent sepsis models, nitric oxide was demonstrated to inhibit NLRP3 activation [93]. Ascorbic acid, in addition to supporting the production of nitric oxide [97], can act on multiple levels, reducing oxidative stress, regulating hypoxia signaling, mitochondrial membrane potential, furin expression, and modulation of immune defenses to stem the progression of cytokine storms [94, 95, 96].

Ascorbic acid can dose-dependently inhibit NLRP3 Inflammasomes both in vitro and in vivo, decreasing IL-1β secretion, without inducing any cytotoxic effects nor cell death [98].

Thus, the combined use of melatonin and ascorbic acid may prove to be most effective in the treatment for COVID-19 patients, especially those with cardiovascular and hypertension comorbidities.

ACE Inhibitors & COVID-19 – The Connection to CVD, Hypertension & Diabetes

Inflammasomes multiprotein complexes formed in macrophages aggravate pulmonary systemic inflammation. Melatonin has recently been shown to reduce IL-1β secretion and attenuate inflammasome-associated vascular disorders by improving endothelial leakage and suppressing NLRP3 inflammasomes [99]. Patients with underlying CVD conditions may greatly benefit from the use of melatonin in the treatment of COVID-19.

Selenium is a strong scavenger of free radicals. Selenium is believed to be effective against viruses such as Ebola, HIV and influenza A virus [47, 48]. However, selenium may also be an effective inhibitor of angiotensin-converting enzyme (ACE) [49, 102]. Patients suffering from cardiovascular diseases, hypertension and diabetes are often prescribed drugs that either inhibit ACE or block angiotensin II type-I receptor (ARB). **Both types of drugs increase the expression of ACE2** [51].

The use of selenium during COVID-19 infections therefore, can be problematic. ACE inhibitors actually INCREASE expression of ACE2, and SARS-CoV-2 infects host cells through binding with ACE2 receptors [50]. ACE2 receptors are found on lung epithelial cells, intestines, kidneys and blood vessels. Thus using ACE

inhibitors either through medication or supplements risk elevating COVID-19 infection and developing severe or even fatal disease complications [51].

Long-term Effects of COVID-19 Infections – The ACE2 Connection

It is true most people will recover from COVID-19 infections. However, because SARS-CoV-2 binds to ACE2, we need to find out if there are any longer term effects of COVID-19. The manner in which SARS-CoV-2 infects host cells by binding to ACE2 receptors makes this coronavirus especially dangerous for patients with underlying cardiovascular diseases, increasing their risk of death [52]. It is not unreasonable to assume that there can be substantial damage to the cardiovascular system over the long term as a result of COVID-19 infections.
From reports taken by the National Health Commission of China (NHC), some patients initially went to see their physicians due to cardiovascular symptoms such as heart palpitations and chest tightness, rather than respiratory distress, fever and cough. These patients were later diagnosed with COVID-19. NIH data also showed that 11.8% of patients who died from COVID-19 **WITHOUT** underlying CVD showed **SUBSTANTIAL HEART DAMAGE,** with cardiac arrest during hospitalization [53].
The binding of SARS-CoV-2 to ACE2 exposes patients with CVD to higher risk for pneumonia and increased severity of symptoms. Reports showed that in China, among COVID-19 patients with severe symptoms, 58% had hypertension, 25% had heart disease and 44% had arrhythmia [55]. Fatality data released by China's NHC showed 35% of patients who died from SARS-CoV-2 infection had a history of hypertension, while 17% had a history of coronary heart disease [56].
NLRP3 inflammasomes are also one of the primary reasons why COVID-19 causes cardiovascular complications. The increased production of pro-inflammatory cytokines interleukin-1β and interleukin-18 from the activation of inflammasomes can induce a signal transduction cascade of strong immune responses that speeds disease progression in CVD. Inflammasomes are now definitively associated with the progression of atherosclerosis, myocardial infarction and heart failure [70].
Even more disturbing is a 12-year follow-up survey of 25 patients who recovered from SARS-CoV infection from 2003 [54].
68% had hyperlipidaemia, 44% had cardiovascular system abnormalities and 60% had glucose metabolism disorders.

Compared to individuals without a history of SARS infection, patients who recovered from SARS-CoV exhibited significant dysregulation in lipid metabolism [54].

It is now clear as crystal why authorities and medical experts, scientists around the world are deeply concerned over the spread of COVID-19. SARS-CoV-2 is a coronavirus that uses the same deadly mechanisms as SARS-CoV to activate NLRP3 inflammasomes to initiate cytokine storms that can result in fatal acute respiratory distress syndrome and acute lung injury (ARDS/ALI).

SARS-CoV-2 may also be 1,000 times more infectious and virulent than SAR-CoV due to the furin cleavage site [57], which basically allows this coronavirus to be activated anywhere in host tissues and organs. Activation of SARS-CoV-2 allows it bind effectively to ACE2, causing more damage and destruction in the vital cardiovascular system and other critical pathways involving angiotensin-converting enzyme 2.

One important aspect that has not been elucidated is the importance of ACE2 in the progression of ARDS. Melatonin, nitric oxide and ascorbic acid (vitamin C) are all inextricably intertwined and deeply involved with ACE2. Melatonin, nitric oxide and ascorbic acid can reduce COVID-19 virulence by inhibiting NLRP3 inflammasomes to stop the perpetuation of cytokine storms. Their critical roles in biochemical reactions and biological pathways that involve ACE2 must be fully explored as part of our fight against COVID-19…….. To Be Continued ……..

As part of my contribution to support the dedication and selfless efforts undertaken by men and women around the globe in the battle against COVID-19, I humbly offer to you the following Appendix:

Supplementing with Melatonin & Ascorbic Acid for COVID-19 – A Simple Guide

Please understand the following is NOT MEDICAL ADVICE. Please consult your trusted physician regarding COVID-19 treatment, especially if you have comorbidities like CVD, hypertension, diabetes, respiratory diseases and cancer.

Maintenance Dosages During COVID-19 Pandemic

MELATONIN

Exogenous intake during COVID-19 is recommended only because normal endogenous production for adults may not be adequate for protection against COVID-19. Children under nine are protected from COVID-19 because they have up to TEN TIMES the 'normal' amount of adults. Our high tech environment, light pollution at night have already vastly diminished the normally low level of melatonin in adults. Supplementing with a minimum physiological dose during COVID-19 pandemic can provide additional protection against infections.
If you are an adult without major health challenges, you should take no more than the physiological dosage recommended below.
The following dosage is a range. The higher end of the range applies to people who are older or have slightly weaker health. So if you are a young healthy adult, you may require no more than the lowest physiological dose of 0.2 mg.
Physiological dose: 0.2 milligram to 0.5 milligram per day

Please take melatonin at night, about 1 to 2 hours before sleep and 2 to 3 hours AFTER your last meal. You should ideally finish eating before it is dark.
It is also extremely helpful if you can lower your ambient lighting at night, as the lowest amount of light will disrupt melatonin production. Melatonin is produced in all cells, including mitochondria, not just in pineal glands [100].

Ascorbic Acid

Again, your age matters because of the level of endogenous melatonin. If you are older or more susceptible to COVID-19 for various reasons, your maintenance dose should be one gram per hour, to total 10-18 grams per day, depending on your tolerance level. You will experience loose stools, or what is known as hitting Bowel Tolerance if you have saturated your system with ascorbic acid.

Dosage During COVID-19 Infection

If you suspect infection, notify authorities in charge and your physician immediately. If you are self-quarantined at home, the following dosage applies.

MELATONIN

Melatonin COVID-19 Infection Dosage: 5 milligrams to 50 milligrams

The lower range is for people with mild or no symptoms. The higher range is for older people or those with more severe symptoms.

IF you are taking ACE inhibitors, have cardiac conditions, hypertension, you need to consult your physician before taking high doses of melatonin. Melatonin may lower blood pressure and cause hypotension at higher dosages.

The Infection dose should ideally be divided into DAYTIME and NIGHTTIME doses.

DAYTIME – 40% of total daily dose, divided into small equal portions to be taken every TWO HOURS.

NIGHTTIME – 60% of total daily dose, divided into two portions taken 2-3 hours after dinner. The final dose at night should be completed by 10 pm (latest).

IF you are diabetic, or have insulin resistance, DO NOT TAKE MELATONIN before 3 pm. Melatonin is able to suppress insulin.

Please remember that oral dosage higher than physiological concentration is applicable during infections only. Supplementation of high dose melatonin MUST BE SUPPORTED by ascorbic acid. You may not experience full benefits of melatonin in the absence of ascorbic acid.

Ascorbic Acid

Ascorbic Acid COVID-19 Infection Dosage: 1 gram every 15 to 30 minutes, depending on severity of symptoms. Increase to 2 grams every 15 to 30 minutes if symptoms are not reversed within 12-24 hours.

IF you are infected, you will essentially have an 'unlimited' tolerance for ascorbic acid. Your tolerance may increase above 100 grams or more. That is normal.

During infection, rest, drink plenty of purified water. You may lose your appetite.

Do not force yourself to eat if you are not hungry. Calorie restriction initiates mitophagy and autophagy, which will facilitate healing [101].
The journey ahead for everyone in every corner of the world will prove to be challenging. During this time of darkness, we must keep absolute faith that Nature has protected our ancestors for millions of years, even under extinction conditions. Nature will NOT fail us with COVID-19, as long as we stay true to her intentions. Blessings to all.

This article is part of the ongoing COVID-19 series. For further understanding on the beneficial effects of ascorbic acid, and how it is able to protect you from COVID-19, please read:

COVID-19 Mutations, Vaccines & Nitric Oxide – The Vitamin C Connection – EvolutaMente.it https://www.evolutamente.it/covid-19-mutations-vaccines-nitric-oxide-the-vitamin-c-connection/
COVID-19, Furins & Hypoxia – The Vitamin C Connection – EvolutaMente.it https://www.evolutamente.it/covid-19-pneumonia-inflammasomes-the-melatonin-connection/

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DORIS LOH
Doris Loh is an independent researcher and writer specializing in the investigation of familiar and innovative health topics using unique perspectives in traditional and quantum biology. Her training as a classical pianist allows her the freedom to explore concepts and theories with a curiosity that often results in distinctive conclusions. Recent works by Doris are focused on how health and disease are greatly affected by electromagnetic radiation that surround us everywhere we go. Her works on EMF offer insight and solutions to the challenges humans and other living organisms face during this era of change. Major works by Doris include an in-depth series on deuterium, as well as a startling series on the birefringent quantum properties of the major REDOX balancer, Vitamin C (ascorbic acid). The ongoing series on COVID-19 is recognized around the world for the in-depth coverage of the disease and discussion on holistic alternatives for prevention and treatment.