Review

Could Pulmonary Inflammation of COVID-19 ARDS Patients Worsen Due to an Excessive Repetition of Follow up Radiological Studies?

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Abstract: The 2006 report of the United Nations Scientific Committee on the Effects of Atomic Radiation Sources was the first document published by an international organisation to abandon the classical paradigm that ionising radiation (IR) was purely immunosuppressive, considering the idea that at low doses it enhances the appearance of anti-inflammatory biomarkers [72]. It considers radiation as an immune modulating agent due to the multitude of opposing ways in which it can influence the innate immune system, depending on various parameters such as dose, dose rate, age, health status, comorbidity, genetic background, lifestyle and environmental co-stressors like air pollution [48]. Background radiation is the most dangerous source of IR for public health, closely followed by medical imaging. Naturally occurring radionuclides attach to particles and continue to disintegrate after inhalation and deposition in the lungs. This article links the inflammation by natural radiation to inflammatory issues related to SARS-CoV-2 viral infection. To that end, we have conducted an extensive *review* focusing on common anti-inflammatory biomarkers found both in acute respiratory distress syndrome (ARDS) elderly COVID-19 patients and those found in healthy subjects exposed to natural low-level ionising radiation, in places on the planet with higher natural background values due to geographical particularities. Therefore, we have hypothesised that radioactivity increases biomarkers of inflammation, which surprisingly turn out to be the same as those caused by the virus, boosting its adverse effects. If this fact could be confirmed by further clinical studies beyond this paper, could artificial radiation from medical X-ray imaging cause the same effects on the immune system at low doses? Our search strategy involved the use of PubMed databases, using numerous terms, e.g., dose-response, hormesis, *J-shaped*, NLRP3 inflammasome, natural radioactivity, LNT model, etc.

Keywords: Acute Respiratory Distress Syndrome; ARDS; COVID-19; Computed Tomography; Hormesis; Ionizing radiation; NLRP3 inflammasome

1. Introduction

On the one hand, human beings are continuously exposed to small doses of ionizing radiation from natural sources, in particular cosmic radiation, mainly from the Sun and

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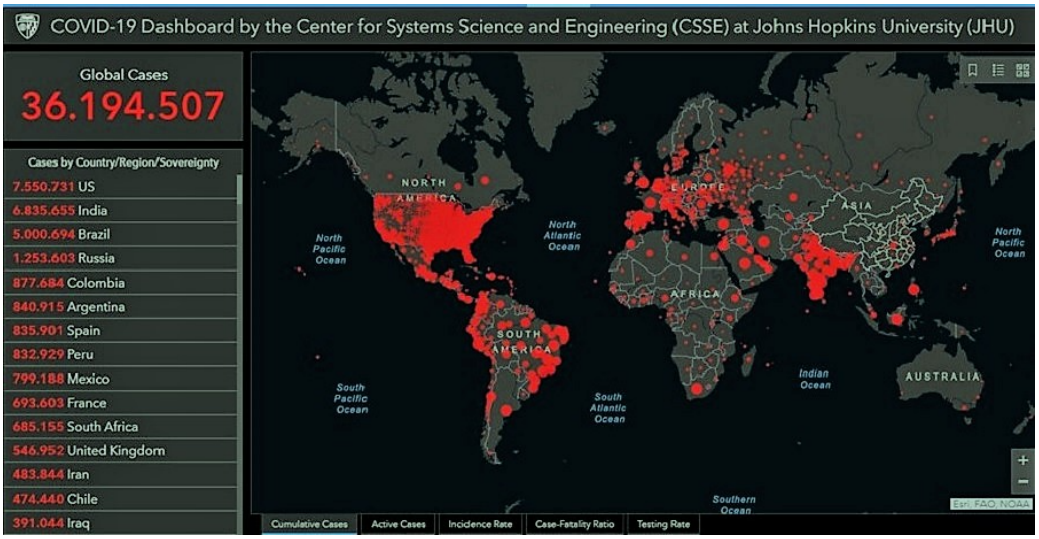

Figure 1. Cumulative confirmed cases last updated 10/8/2020 10:23 a. m. Source: John Hopkins University of Medicine. (https://coronavirus.jhu.edu/map.html). India, Brazil, and Iran are at the top of the ranking.

radon, which is a radioactive gas that comes from the natural decay of uranium in soil, rocks, water and building materials. The amount of background radiation an individual is exposed to depends on many factors, such as home ventilation and altitude. The standard average is estimated at 3 milliSieverts (mSv) per year, a figure that could vary depending on the geographical coordinates.

Healthy population in locations on Earth with higher levels of natural radioactivity show higher amounts of autoimmune biomarkers. China, Iran, Brazil and India are among the countries with the highest natural background radioactivity [29]. It was notable, during the height of the COVID-19 pandemic in 2020, that these places experienced a clear excess in mortality rates (see Figure 1) following inflammatory conditions related to SARS-CoV-2-linked acute respiratory distress syndrome. The radiation-driven biomarkers were common to those exhibited by ARDS and therefore a summative effect could be assumed.

On the other hand, current medicine offers a variety of diagnostic methods and tools that include imaging techniques where patients are exposed to artificial ionizing radiation, such as X-rays, computed tomography (CT), positron emission tomography (PET), gammagraphy, mammography and others. The use of CT has been steadily increasing over the last decades, representing today an indispensable tool in diagnostic X-ray medical imaging [73]. A consequence of this excessive increase, caused by so-called defensive medical decision making, especially in developed countries, is that radiographic studies are largely responsible for exposure to artificial sources of ionising radiation, even if averaged over the entire population of a given country. In particular, pulmonary high-resolution computed tomography (HRCT) is a well-established technique for diagnosing and treating pulmonary complications [71]. Recurrent examinations have highlighted that many patients are falling into a relatively higher absorbed dose group exceeding 100 mSv in the lungs [36]. Investigation of the inflammatory effects of low dose artificial ionizing radiation should lead to the same inflammatory endings as from natural sources or present in the air, but there are not clinical studies to support this assumption

2. Ionising radiation dose response models

The effects of radiation on living matter have diverse consequences on human immunity. Various self-defence pathways are found throughout the dose range, from very low to high levels of absorbed radiation, as stated by the UNSCEAR 2012 Report [74]. According to this publication, dose ranges can be classified into four levels: *very low radiation dose* (VLRD), $\leq$ 10 mSv, as the dose to an individual from multiple conventional radiological

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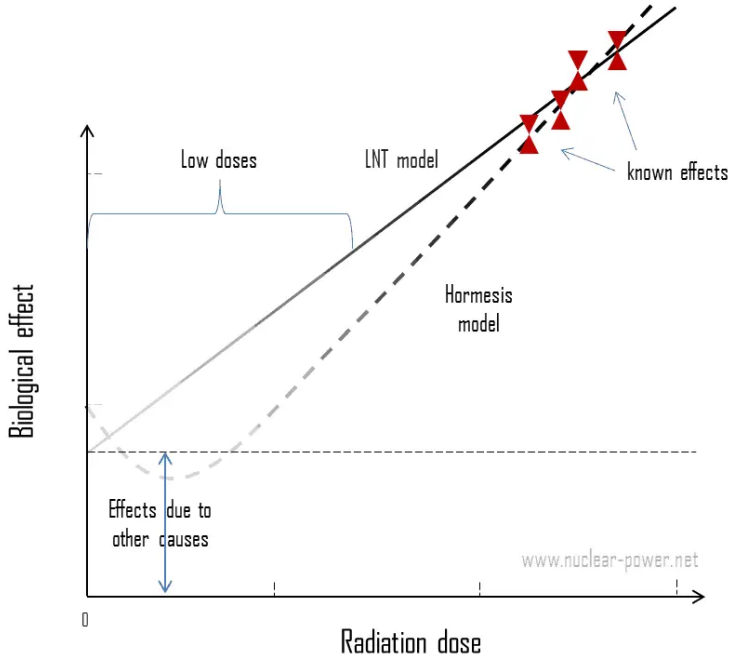

Figure 2. *Linear Non-Threshold model (LNT)*, straight line, versus *Hormesis Linear Non-Threshold (H-LNT)* behavior, *J-shaped* line. Source: https:// aboutradiation.blogspot.com/2019/02/all-about-radiation- hormesis.html.

images without considering either computed tomography (CT) or fluoroscopy; *low radiation dose* (LDR), in the closed interval [10, 100] mSv, as the dose to an individual from multiple whole-body CT scans; *moderate radiation dose* (MRD), in the closed interval [100, 1000] mSv, as the dose to about 100,000 workers in recovery operations after the Chernobyl accident; and *high radiation dose* (HDR), >1000 mSv, as the dose to individuals after severe radiation accidents or from radiotherapy treatments.

Although the classically established hypothesis known as the *Linear Non-Threshold (LNT)* model, scientifically accepted in 1958, according to which the effects of radiation on the survivors of the bombs dropped on Hiroshima-Nagasaki were never sufficiently adjusted, it was assumed that the damage produced on the general population was linear to dose (straight line in Figure 2) [8,37]. Decisions to circumvent peer review of this work in the journal *Science* occurred on at least two occasions. In one of them, it was alleged that the research record had been intentionally falsified [11]. Leading American scientists therefore suppressed evidence of the promotion of an adaptive behaviour. Such hidden protection promoted by the immune system, implied that the body would have learned to protect itself when it is re-irradiated after a first exposure to low doses. This self defense system became known as *hormesis* and was most evident in the range between 10 and 100 mSv (LDR interval) in most mammals [25]. Temporary delayed adaptive protection involves reactive oxygen species (ROS)-induced detoxification, an increased rate of deoxyribonucleic acid (DNA) repair, removal of cells damaged by apoptosis followed by replacement of normal cells and by cell differentiation.

Since low absorbed doses would increase instantly the action of the innate immune system due to hormesis, a *J-shaped* function invalidates the straight growing line of the LNT model (Figure 2). This is possible due to the so-called Bystander effect, that increases the number of death cells in in the neighborhood of the directly beaten ones within the radiation field. This *J-shaped* dose-response curve explains the more pronounced non-linearity radiation risks between low and moderate levels [22]. Hence, it is preferred to talk about a *Hormesis Linear No-Threshold (H-LNT)* model instead of the out of date *LNT* scheme.

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Ionising radiation has an important role on the nuclear factor erythroid 2-related transcription factor (Nrf2) antioxidant response [49], which is the responsible for the adaptive hormetic behaviour. Its activation is highly dependent on the dose interval [9]. Between 500 and 1000 mSv nontoxic radiotherapy treatments are anti-inflammatory at subcellular level [10], forcing polarization shifts from M1 pro-inflammatory predominant population of lung macrophages into M2 anti-inflammatory phenotype [7,10]. The presence of the Nrf2 transcription factor promotes the resolution of the inflammation, recovering cellular redox and protein homeostasis and restoring the tissue. For instance, radiotherapy, as a treatment for pneumonia, has been used since the 30s of the twentieth century with promising results, especially in the case of interstitial viral pneumonia [6]. Openheimer treated 56 patients with life-threatening progressive interstitial pneumonia at a dose of 500 mSv [59]. Patients responded successfully in the first 14 days. However, after 14 days, the responses dropped to 50%. Also, other experimental treatments in animal models with low-dose radiation therapy for influenza virus demonstrated efficacy in nearly half of experimental cases [23]. Below 500 mSv it is induced the expression of Nrf-regulated antioxidant defense genes Nrf1 and Nrf2 simultaneously [42]. The host inflammatory response in this case it is determinant in the severity of the SARS-CoV-2-induced infection [18]. Nrf1 and Nrf2 activation is accompanied by reactive species. At the opposite end, above 1000 mSv, macrophage M2 anti-inflammatory phenotype converts into pro-inflammatory M1 form again [10].

3. Inflammatory biomarkers due to abnormal low dose radiation levels

A well-established limit as a natural background for natural radiation is 20 mSv/year. There are regions where this background radiation is 10 to 15 times higher than what is considered normal. However, there are geographical regions with background radiation 10 to 15 times above the accepted value, so this threshold is not the same everywhere, depending on the composition of the soil of the place. For example, *Taleshmahaleh* and *Chaparsar*, two villages in northern Iran, have values on the order of 260 mSv per year (LDR region and beyond). Analytical studies on their population showed a significantly lower total serum antioxidant level in exposed individuals than in individuals not exposed to high doses of IR [2,28]. These subjects also had higher lymphocyte-induced IL-4 and IL-10 production, and lower IL-2 and IFN-γ production [2,28].

The main radioactive elements that cause natural human exposure to ionising radiation are potassium (K), uranium (U), thorium (Th) and their radioactive decay products, such as radium (Ra) and radon (Rn). When deposited in the lungs, ^{222}Rn, a radioactive noble gaseous element that is part of the ^{238}U [33] decay chain, releases α radiation when inhaled and is associated with biomarkers of inflammation and endothelial dysfunction [57]. Radon gas tends to accumulate indoors, especially in areas with highly permeable soils with a high ^{226}Ra content, resulting in high concentration levels. Chinese workers exposed to natural background radiation from uranium mines, with high indoor concentrations of ^{222}Rn, showed obvious inflammation problems. Two different categories were studied, a control group, underground for < 5 years (cumulative dose < 20 mSv, based on 4 mSv per year) and an experimental group, underground for ≥ 5 years (≥ 20 mSv). Long-term exposed subjects showed up- regulation of pro-inflammatory cytokines, such as IFN-γ, IL-10, IL-6 and TNF-α [43], again within the LDR levels.

Cytokines are the main agents by which immune system cells increase or decrease due to interaction with low doses of radiation. IR induces ROS through the activation of the nucleotide binding domain and repeated inflammation of the inflammasome of the leucine-rich protein 3 (NLRP3) inflammasome, activating the function and number of immune cells by increasing the levels of T lymphocytes and macrophages, which lead to the secretion of various inflammatory mediators, such as NF-κB (Nuclear Factor-κB), IL-1 (Interleukin-1), IL-2 (Interleukin-2), IL-6 (Interleukin-6), IL-8 (Interleukin-8), IL-33 (Interleukin-33), TNF-α (Tumour Necrosis Factor-α), TGF-β (Tumour Growth Factor- β), and IFN-γ (Interferon-γ) [29,38,80]

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Due to its abundance and toxicity, lead (*Pb*) is the second most dangerous element present in the environment, according to the Agency for Toxic Substances and Disease Registry's Priority Substances List. Although lead gasoline has been phased out of many countries, its compounds are still used in aviation fuel. In addition to poisoning by the presence of its stable nuclei, there are also unstable radioactive forms contained in the air, such as Lead-214 (^{214}Pb), which is a β emitter. Lead causes inflammatory responses that produce IL-2, IL-4, IL-8, IL- 1β, IL-6, TNF-α, IFN-γ, and influence immune system cells (T and B lymphocytes, Langerhans cells, and macrophages) and the secretion of Immunoglobulin A (IgA), Immunoglobulin E (IgE), Immunoglobulin G (IgG), endothelin and histamine [55,75].

Tobacco manufacturers were aware of the α radioactivity contained in cigarette smoke since the decade of the 60s of the last century, [81]. Several studies linked vegetable fertilizers containing ^{226}Ra, as well as their radioactive decay products, ^{210}Pb and ^{210}Po [62]. Papastefanou analysed radioactivity in tobacco leaves in fifteen Greek regions, looking for any association between the uptake of radionuclides through soil and the effective dose induced in smokers, mainly of radionuclides product of ^{226}Ra, ^{210}Pb, ^{228}Ra and other artificial isotopes, such as Chernobyl-origin ^{137}Cs [60]. The radiation dose to the bronchopulmonary epithelium by inhalation of ^{210}Po from two packs of cigarettes daily by individual smokers was found to be, at least, seven times higher than that due to natural radioactive sources [62]. Winters et al. estimated that one and a half packs of cigarettes per day produced 80 mSv/year in bifurcation zones of the bronchial epithelium; such a dose is equivalent to 300 chest X-rays per year [78]. The increased of pro-inflammatory cytokines, such as TNF-α and IL-1β, further amplify the inflammation in smoking chronic obstructive pulmonary disease (COPD) patients. IL-1β and TNF-α levels, and the severity of airflow limitations, were deferentially elevated in tobacco smoke associated COPD in comparison to biomass smoke associated COPD [69]. COPD is the leading cause of mortality and morbidity worldwide, and is characterised by abnormal activation of inflammatory cells.

Polluted air can also contain radioactivity. For instance, Lead-210 (^{210}Pb) in aerosols suspended in polluted air in the form of $PM_{2.5}$ (particulate matter with dynamic diameter < 2.5 μm) can be generated as well in the uranium-238 (^{238}U) and radium-226 (^{226}R) disintegration chains, or nitrogen (N) products due to the collision between high energy cosmic rays from the Sun and some specific molecules in the upper atmosphere. Some experimental studies have shown nitrogen dioxide or its chemicals in particulate matter $PM_{2.5}$ remaining deep in the lungs when inhaled for prolonged periods of time; it was also detectable in extrapulmonary regions [77]. Nitric and nitrous acids, or their associated salts, have been observed in the blood and urine after exposure to nitrogen dioxide (NO_2) [77]. The main source of NO_2 is the burning of fossil fuels, which in most large cities comes from motor vehicle and industry exhaust.

Conticini et al. suggested that high levels of air pollution could be considered an additional co-factor of the elevated SARS-CoV-2 mortality recorded in the Northern Italy because of very serious pulmonary inflammation issues in a multitude of elderly subjects in 2020 [16]. Back in 2018, Hodgson showed also that in most of the countries the natural level of radioactive Polonium-210 (^{210}Pb) in urine were below 30 mBq.day^{-1} in 95% of the studied population. However, China and, surprisingly, Italy, with values greater than 20% above that level, were exceptions [30]. Not in vain, Lombardy and Emilia Romagna are between the most NO_2 polluted areas along Europe (see Figure 3). Several studies have shown possible links between air pollution and the severity of lung inflammation due to COVID-19 [16]. Wu et al. estimated a relationship between a 15% increase in the mortality rate by SARS-COV-2 infection and a 1 g.m^{-3} growth in $PM_{2.5}$ concentrations [79]. This relationship represented a 20-fold rise in the risk of death from other causes, such as pulmonary complications or heart disease.

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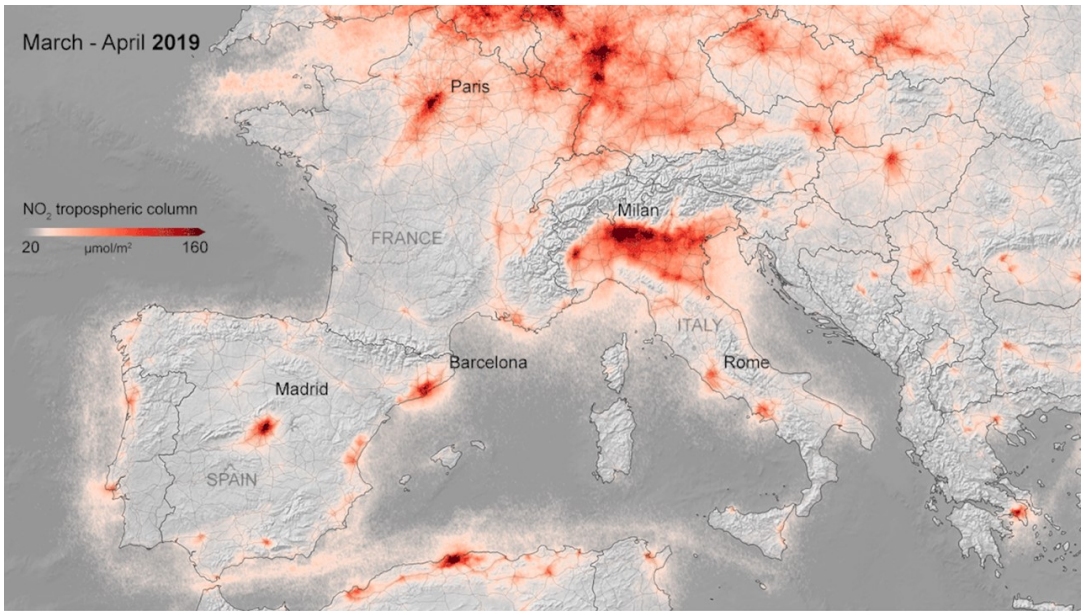

Figure 3. Tropospheric NO_2 concentrations over Europe (March-April, 2019). There are abnormal values over Northern Italy. This is a quite normal situation along the year. Source: Copernicus Sentinel-5P (https://maps.s5p-pal.com/).

4. Inflammatory biomarkers due SARS-CoV-2 infection

COVID-19 can induce severe lung inflammation that results in acute respiratory distress syndrome, respiratory failure, and death, despite artificial ventilation. It is, in such cases, an intense inflammatory reaction, characterised by the infiltration of mono nuclear cells, fibrin exudates, multi nucleate giant cells and thickened alveoli secondary to the proliferation of interstitial fibroblasts. The observed lung hyperinflammation was also found in previous pandemics, such as SARS-CoV (2002) and MERS-CoV (2012) [14].

Most infected people have mild flu-like symptoms, while 5-10% are severe cases with respiratory system involvement and life-threatening pneumonia. Increased levels of pro-inflammatory cytokines have been observed in the bloodstream of the most severe cases. Viral infection causes the activation of the NLRP3 inflammasome in a very important way, leading to the production of cytokines as an inflammatory response; it is what is known as a cytokine storm [32,82]. The macrophage activation syndrome (MAS) is the origin of such a complication, characterised by elevated levels of IL-1, TNF-α and IL-6 produced by M1-type macrophages [50,52,56]. NLRP3 inflammasome promotes damaging responses when it is chronically activated, found in what are called autoinflammatory diseases, like obesity, type2 diabetes, rheumatoid arthritis, systemic lupus erythematosus, osteoarthritis, atherosclerosis, Alzheimer's Disease (AD), Parkinson's Disease (PD), cancer, asthma, and chronic obstructive pulmonary disease (COPD).

When the immune system is confronted with a foreign antigen, for instance, SARS-CoV-2, blood monocytes are recruited into the alveoli, where they differentiate into M1 macrophages that produce cytokines which, in turn, attract neutrophil cells to the alveoli to fight infection, leading to clearance by reactive oxygen species and phagocytosis [47, 52]. The normal response to the eliminated infection is the reversal of polarisation from inflammatory M1 macrophages to anti-inflammatory M2 macrophages, but in ARDS and some other autoimmune disorders the inflammatory state continues, leading not only to lung damage but also to the destruction of multiple normal organs, including kidney failure, heart injury, and ultimately death. The persistence of inflammatory neutrophils in the alveoli and increased concentrations of ROS and TNF are thought to contribute to lung injury.

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Once SARS-CoV-2 infection is initiated, inflammasome activation triggers severe uncontrolled pulmonary fibrosis, with increased NLRP3 caspase-1 activity observed in the lungs, resulting in a simultaneous increase in mature IL-1β and IL-18 levels in the elderly [40]. The production of reactive oxygen species by polluted air induce IL-1β strengthening upon the over expression of the angiotensin-converting enzyme 2 (ACE-2) [4], which is attached to cell membranes in the lungs, heart, kidney, arteries, and intestines [66]. ACE-2 is the gateway for SARS-CoV-2 to get into human cells, infect them and begin their spread throughout the body [66]. Dalan et al. described the same conclusion about SARS-CoV, in its outbreak back in 2003, when the virus infected humans throughout that same ACE-2 receptors [20].

5. Discussion

Hormesis is a dose-response phenomenon whereby low doses of ionising radiation induce beneficial health effects. That is, low doses of low-LET radiation can stimulate the activation of repair mechanisms, which protect against disease, that are not activated in the absence of IR. Proponents of radiation-induced hormesis claim that radioprotective responses in cells and the immune system do not only undermine the harmful effects of radiation, but also act as an inhibitor of spontaneous cancer unrelated to exposure to ionising radiation.

The exposure by natural radiation sources has hardly changed since the 80s of the last century, but the total exposure per capita has almost doubled due to the increase in radiological studies for medical imaging. According to reports from the North American National Council for Radiological Protection and Measurements (https://ncrponline.org), exposure by medical sources has grown from 15% in the early 1980s to 50% today. Computed tomography (CT) alone accounts for 24% of all radiation exposures in the United States, according to a report published in March 2009. In recent years this percentage has been growing exponentially. A number of recent publications have highlighted that recurrent CT has Recurrent CT is found in an effective dose group above 100 mSv [3,63–65]. The authors focused their research on patients whose cumulative effective dose exceeded 100 mSv from 342 hospitals located in the USA. The study included more than 2.5 million patients, with almost 5 million CT scans. Their data suggested values of 174 mSy in the lungs. More than 1% of the CT patients received cumulative doses above this threshold. In some patients, the accumulation period was only one day.

Although actual radiation exposure depends on multiple and varied factors, such as the CT scanner device itself, the length of the scan, the size of the patient, and the sensitivity of the tissue being targeted, the average dose of a chest CT scan would fall within the range of 4 and 18 mSv [53]. According to some epidemiological studies, organ doses corresponding to a common CT study (two or three scans, resulting in a dose in the range of 30 to 90 mSv) show an increased risk of cancer. This evidence is convincingly verified for adult individuals and, very convincingly, for children [5]. This levels are also in the LDR interval.

According to a retrospective report conducted at Tongji Hospital, which was the largest healthcare facility in Wuhan, China, for the treatment of SARS- CoV-2 infected patients, they showed that chest CT was largely used in the follow-up of common COVID-19 cases [15]. Including pediatric cases, 394 patients underwent a total of 1,493 examinations with a mean time interval between disease onset and discharge of 31.68 ± 8.71 days and a median admission time of 19 days [15]. The total number of actually valid CT scans and control CTs, without additional added value, was highly related to the duration of the disease [15].

In another work, on variations in the use of CT protocols and radiation doses in patients with COVID-19 pneumonia in 28 countries according to an IAEA (International Atomic Energy Agency), Homayounieh et al. showed that about 30% of 225 patients underwent 2 to 8 chest CT examinations in less than one month [31]. Although it is estimated that tissue does not express clinically relevant functional impairment at such

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doses, IR has been found to produce pro-inflammatory effects, even when reduced radiation dose exploration protocols are used [35,46,65].

Details are not yet fully understood about the effects of IR on macrophages [61]. While low doses attenuate inflammation by the abscopal effect, at higher levels, such as those applied in radiotherapy, increase systemic anti-tumour immune reactions [27]. The abscopal effect is a phenomenon in which the response to radiation is observed in an organ distant from the irradiated area, that is, the responding cells are not juxtaposed with the irradiated cells.

LDR health effects is controversial. A threshold value of 100 mSv is internationally accepted as a limit beyond an excess of cancer issues is observed in the long term [67]. Although chest CT is a well- established technique for the diagnosis and management of ARDS complications [34], too many patients are reaching a value of 100 mSv or even more at times, due to recurrent X-ray examinations [71] in a very short period of time, which could enhance the inflammatory situation due to the virus itself.

However, it could be possible to overcome the oxidative inflammatory early responses caused by radiation, in this case, using clinical well-proven dietary supplements to satisfy both goals: (a) the use of computed tomography as a valuable diagnostic procedure in the elderly in a more secure manner based on a solid scientific argument that supports and (b) could be a method for instructing physicians on how to better treat their patients via a very simple process of supplementary medication [9]. For instance, N-acetylcysteine (NAC) which was introduced in the 1960s as a mucolytic drug due to its ability to cleave disulphide bridges in mucous protein complexes and, thus, depolymerize mucin molecules [21]. It was later discovered that NAC has an effective antioxidant action, acting as a precursor of reduced glutathione, which provides the organism with crucial defense mechanisms towards toxic agents of various nature [51]. NAC easily penetrates cell membranes and is found as a possible clinical application that cover several pathological conditions involving oxidative stress, including acute and chronic bronchitis, ARDS, and certain cardiovascular diseases [32,80]. Furthermore, NAC can also boost the immune system, suppressing viral replication, and reducing inflammation. Despite these valuable features, NAC has been mostly overlooked during SARS-COV and MERS-COV epidemics, as well as the current COVID-19 pandemic [68].

6. Conclusions

Despite LDR have been largely related with cancer issues based on the studies over the Japanese survivals [44], dose response effects can also be linked to other secondary effects like inflammation and should be taken in consideration in the hormetic zone [39]. As the lower dose interval represents a much more relevant exposure scenario for the general population, as it may have broader public health consequences because of the common and frequent indication of X-ray images in general diagnosis [48], this potential danger should limit drastically the number of those type of IR exams if not antioxidant supplements are prescribed along the process [9].

There are not valid data supporting the use of the accepted *LNT* model in the low-dose range [13,13,22,39], so dose as a surrogate for risk in X-ray imaging is not appropriate, and therefore, the use of the classical ALARA (As Low As Reasonably Achievable) concept might be considered as obsolete [58]. Concerns have been raised over alleged overuse of CT scanning and inappropriate selection of protocol exams. Although computed tomography is crucial in the follow up of ARDS disease, it cannot be forgotten that it is needed an estimation of the equivalent doses in the organs at risk as it is stated, for instance, in the European Union, by the *Council Directive 2013/59/Euratom*, laying down basic safety standards for protection against the dangers arising from exposure to IR [24].

The adaptive response given by hormesis due to an excessive number of CT scans on ICU-admitted patients suffering from COVID-19 dramatically seems to be boosting drastically the viral inflammation. Hormesis protects against cancer but should also be important in auto-inflammatory processes. The interrelationship between the immune

system and IR is complex, multi factorial, and dependent on radiation dose and immune cell type. Higher dose radiation levels usually results in immune suppression, while low values modulates a variety of immune responses that have exhibited the properties of immune hormesis [19]. Inflammatory early effects are difficult to isolate and study independently as they are much more subtle and not so obvious functional alterations, and can be easily confused or be hidden by other comorbidities [48]. secreting cytokines, neutrophils also produce ROS radicals [68]. By taking supplementary diet supplements, like NAC, a powerful scavenger of OH, could effectively prevent cytokine storms and the induction of ROS pulmonary edema and respiratory failure [68].

As conclusion about the excessive use of computed tomography on the elderly population, we hypothesises that the immune effects of artificial IR should be the same as for natural radiation, since the doses to individuals are similar in both scenarios. There is not much information available on artificial radiation, contrary to the effects of natural background.

7. Abbreviations

ACE-2: Angiotensin-converting enzyme-2. AD: Alzheimer's disease. ALARA: As low as reasonably achievable. ALI: Acute Limb Ischemia. ARDS: Acute respiratory distress syndrome. COVID-19: Coronavirus disease-2019. COPD: Chronic obstructive pulmonary disease. CT: Computed tomography. DNA: Deoxyribonucleic acid. HRCT: High resolution computed tomography. H-LNT: Hormesis Linear No-Threshold model. IAEA: International Atomic Energy Agency. ICU: Intensive care unit. ICRP: International Commission on Radiological Protection. IFN-γ: Interferon-gamma. Ig: Immunoglobulin. IR: Ionizing radiation. LDR: Low dose radiation. LNT: Linear no-threshold model. MERS: Middle East Respiratory Syndrome. mSv: Millisievert. NAC: N-acetylcysteine. NF-κB: Nuclear factor-kappa B. NLRP3: Nucleotide binding domain and repeated inflammation of leucine-rich protein 3. NO_2: Nitrogen dioxide. Nrf2: Nuclear factor erythroid 2-related transcription factor. PD: Parkinson's Disease. Pb: Lead. PET: Positron emission tomography. $PM_{2.5}$: Particulate matter with dynamic diameter of 2.5 μm. Po: Polonium. Ra: Radium. ROS: Reactive oxygen species. SARS: Severe acute respiratory syndrome. SARS-COV-2: Severe acute respiratory syndrome coronavirus-2. TGF-β: Transforming growth factor beta. TNF-α: Tumor necrosis factor-alpha. U: Uranium. UNSCEAR: United Nations Scientific Committee on the Effects of Atomic Radiation Sources.

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