Journal of Human Environment and Health Promotion
Print ISSN: 2476-5481 Online ISSN: 2476-549X

Real-Life Toxicants as an Emerging Challenge in the Rehabilitation of COVID-19 Survivors

Rana Dizaji *

Department of Food Safety and Hygiene, School of Public Health, Zanjan University of Medical Sciences, Zanjan, Iran .

***Corresponding author:** Department of Food Safety and Hygiene, School of Public Health, Zanjan University of Medical Sciences, Zanjan, Iran . Tel: +98 912 6417281
E-mail address: rana.dizaji@ yahoo.com

ARTICLE INFO

Article type:
Review article

Article history:
Received: 29 MARCH 2022
Revised: 30 APRIL 2022
Accepted: 28 MAY 2022

DOI: 10.52547/jhehp.8.2.69

Keywords:

Toxicant
COVID-19 survivors
Oxidative stress
Risk management

ABSTRACT

Awareness of COVID-19 infection, as a public crisis, makes an emergency condition for survivors. Regarding the importance of early rehabilitation, we should pay particular attention to the potential risk of real-life toxicants in COVID-19 survivors. The adverse effects underlying COVID-19 infection lead to persistent sequelae in survivors. In addition, complete rehabilitation is challenging in seriously-ill patients due to cytokine storm severity, inflammation, oxidative stress, and cell death contributing to multi-organ damage. Different foods, environmental/occupational pollutants, and unhealthy lifestyles are real-life examples of toxicants that can pose redox imbalance and oxidative damage to the biological system. The key concept is that survived patients with persistent tissue damage, low-grade inflammation, oxidative stress, and fibrosis are susceptible to real-life toxic stressors, which have the potential for oxidative stress. Moreover, fibrosis are susceptible to toxic stressors, which can induce harmful effects by promoting oxidative stress and pro-inflammatory components. This paper attempted to elucidate a vital toxicological concept in which the existing sequelae of COVID-19 survivors increase the potential risk of real-life toxicants and to propose a practical strategic approach to reduce toxicant exposure.

Abbreviation: Lipid radical (L•), Lipid peroxyl radical (LOO•), Lipid alkoxyl radical (LO•), particulate matter (PM), reactive oxygen species (ROS), ultra-fine particle (UFP).

1. Introduction

1.1 COVID-19 as a complicated condition

According to World Health Organization (WHO), COVID-19 is a global public health emergency that threatens millions of individuals [1]. In other words, an increasing number of survivors with a long-lasting sequela is a serious concern regarding survivors' health outcomes. COVID-19 triggers several harmful effects, resulting in direct viral effects and excessive reactive oxygen species (ROS) levels. In addition, pro-inflammatory cytokine storms associated with antioxidant source depletion enhance a cascade of biological events in severe COVID-19 patients [2-7]. New evidence has indicated that this syndrome has long-term consequences on cardiovascular, respiratory, and immunological systems. Furthermore, it might be persistent in rehabilitation in severely-ill COVID-19 patients [8, 9]. There are several pollutants with pro-oxidant properties that mediate oxidative damage of vital biomolecules: lipid, protein, and nucleic acid. Therefore, enhanced lipid peroxidation (LOO·, L·, and LO·) mediates cell membrane disruption and cell death.

How to cite: Dizaji R. Real-Life Toxicants as an Emerging Challenge in the Rehabilitation of COVID-19 Survivors . *J Hum Environ Health Promot.* 2022; 8(2): 69-76.

It initiates the immune response in the cell microenvironment, threatening the surrounding cells [10]. It could also impair cellular function; in fact, it contributes to organ dysfunction. Several contaminates as an exogenous source of reactive oxygen/nitrogen species are related to internal sources (injury and disease) by playing a collaborating role in the pathophysiology of multi-organ dysfunction. It should be noted that survivors of COVID-19 infection at the rehabilitation stage are susceptible to toxic stressors even more than healthy individuals; hence, taking care of the survivors would be a huge burden. This paper aimed to clarify a vital toxicological concept in which the existing sequela of COVID-19 survivors increases the potential risk of real-life toxicants exposure (environmental/occupational and food) and lifestyle-related stressors. Further, we proposed a practical strategic approach to reduce toxicant exposure.

1.2 The immunological outcome in COVID- 19 survivor

The immune system mediates a complex process involved in COVID-19 elimination and recovery from viral infection. However, immune system disability in virus elimination is associated with disease progression and severe lethal stage. Therefore, variable immune system responses are related to various clinical features and lead to persistent sequelae [11, 12]. Immunologically, inflammation and tissue damage are tightly linked processes. Consequently, an unregulated host immune system response leads to the excessive release of the inflammatory components, contributing to multi-organ damage. Accordingly, pro-inflammatory cytokines and oxidative stress cause cell death. Furthermore, in the positive loop, it leads to the exaggerated outcome contributing to the pathophysiological role of COVID-19 in organ damage and could also be implicated in persistent sequelae in survivors [10]. From the toxicological aspect, which is ignored in the COVID-19 outbreak, immune system dysfunction was significantly correlated with toxic stressors that cannot eliminate the virus. Also, real-life toxicants perturb immune system function [13, 14], thus contributing to tissue damage, disease progression, and defect rehabilitation in COVID-19 infection.

1.3 Immunological events depend on the stage of COVID-19 infection

Immunological studies have demonstrated that intensive inflammation response occurs in virus- the independent stage of infection [11]. Based on this evidence, following the virus replication stage(ten days post – infections and virus clearance) inflammation in the lung was more intensive until day 28[15]. Notably, in tissue inflammation, many of the inflammatory receptors (TNF-α) on the cell surface, related to inflammatory cytokine expression, are involved in the cell death process and, in positive feedback, damage-associated molecular patterns(DAMP) and reactive oxygen species induce inflammation [16-18]. Inflammation was shown to be associated with cell stress-related components and increased the risk of fibrosis [19]. Based on the evidence, heart failure is attributed to infection, toxin, and injury, which could be mediated by cell death, inflammation, and fibrosis, leading to persistent low-grade systemic inflammation and organ failure [20]. In addition, a lung fibrosis model study indicated that excessive reactive oxygen species promote cell death by triggering pulmonary injury, inflammation, and fibrosis [21-23]. Lung and heart fibrosis and inflammation attributed to COVID-19 infection increase the risk of real-life toxicants, lead to exaggerated harmful effects in survivors that may contribute to tissue dysfunction.

1.4 Real-life toxicants as a collaborating factor in COVID-19 survivors

Public exposure to real-life toxicants mainly by environmental/ occupational and food contaminants such as air pollution, metal, particulate matter (PM), poly aromatic hydrocarbon (PAH), polychlorinated biphenyls (PCB), acrylamide, ultraviolet radiation (UV), and Wi-Fi in combination with an unhealthy lifestyle, triggers a great deal of adverse effect. Chemicals combine exposure causes cumulative risk exposure leading to multiple risk factors in our daily life. Environmental factors critically impact the severity and progression steps of several diseases [24]. Awareness of COVID-19 as a public emergency makes emergency conditions for survivors. Notably, survivors with the persistent sequela (related to the severity of disease) [8] as a susceptible subgroup are definitely at risk of toxicant exposure in general and in combination with an unhealthy lifestyle, which increases the potential risk of toxicant exposure, leads to various adverse effects in the survivors.

1.5 Air Pollutant, risk of complex noxious substance exposure

Air pollution has been a global concern, and currently, with the worldwide outbreak of COVID-19, it has become a priority for COVID-19 survivors′ health. Remarkably, the severe harmful effects of air pollution occur at the permitted level by national standards [25, 26]. Air pollution in highly populated urban areas increases urbanization, and traffic-related pollution is the primary concern in societies[25]. In complex exposure, air pollution is composed of a mixture of substances. It mainly includes gaseous pollutants, volatile and semi-volatile organic compounds[27] such as benzene, naphthalene, aldehydes species, and polycyclic aromatic hydrocarbons, which cause several harmful effects in collaborating with particulate matter[25].

1.6 Respiratory system effects of air pollution

Air pollution may enhance several adverse effects, such as upper respiratory irritation, chronic respiratory disease, lung cancer, and acute respiratory infections [28, 29]. It is reported that nitrogen oxides, inhaled fine, and ultra-fine particulate matter (UFP) emitted in road traffic generate ROS through the Fenton reaction and increase the susceptibility to respiratory infections[16]. Excess ROS overwhelms the

antioxidant system, triggers inflammation response in the alveolar epithelium, promotes pro-inflammatory transcription factors expression, and releases inflammatory mediators [23, 30], which could worsen lung condition status with persistent lesion and disease, especially in the COVID-19 outbreak.

1.7 Cardiovascular effects of air pollution

The high incidence of heart injury among COVID-19 survivors and the effect of air pollution on the cardiovascular system could be a challenge to disease prevention. Several studies have confirmed that increased cardiovascular risk of mortality and morbidity[31] attribute to short and long-term exposure to air pollution. [32, 33]. Mechanistically, oxidative stress induction has been confirmed to be a key way in different processes underlying air pollution-induced cardiovascular mortality, mainly due to UFP composition especially transition metal composition, which catalyzes irritant production and induces reactive oxygen species formation[25]. Additionally, clinical studies have identified that traffic-related air pollution plays a crucial role in promoting systemic vascular oxidative damage, enhanced endothelial dysfunction, plaque formation, and up-regulation of oxidative stress biomarkers in exposed individuals [34-37]. Numerous studies have indicated a positive correlation between road traffic emission exposure and DNA methylation resulting in DNA oxidation in the blood[38, 39]. The gene expression profiling revealed that traffic-related pollutants in drivers, garage workers, and street police officers increase inflammatory gene expression (TLR_2,4, NF-K_β) [39, 40].

1.8 Air pollution effect in the susceptible subgroup

Air pollution plays a key role in cardiovascular mortality among the exposed population, namely patients and elderly people. Individuals with low inflammation status, such as diabetes, hypertension, congestive heart failure, and respiratory conditions, are at significant risk of cardiovascular complications. In older adults exposed to airborne particulate matter, the promoted inflammatory indicator (WBC_s, CRP, and IL-6) leads to heart complications. Given the importance of health in society, the risk of death from air pollution is high in susceptible people, particularly those with cardiovascular complications [41].

1.9 Pesticides

Pesticide exposure occurs in the occupational environment, food and water residue, and inhalation, increasing the risk of several adverse effects[42]. Chemicals, in particular pesticides, in the work environment creates a toxic condition, and those who directly use chemicals are at higher risk of adverse effects. Pesticide exposure could be due to occupational activity, in which pesticide adverse effects are related to oxidative stress promotion and alter the antioxidant defense system[43] (Fig1). Regarding workers exposed to contaminants, controlling the risk of work environmental risks and reducing adverse effects on them need biological monitoring, as well as removal or replacement of risk factors with safe substances to maintain workers′ general health and COVID-19 survivors.

1.10 Metal

Metal naturally exists in the human environment, which could contaminate soil/water and agricultural crop; however, some levels of human exposure to potential toxic metal is inevitable. Following absorption in the human body, most heavy metals are dangerous, even in small amount, since after a while tends to accumulate in the human body[44]. Metal-catalyzed redox reactions mediate oxidative damage, which is a key chemical reaction in metal toxicology. The heavy metal enhances the variety of reactive oxygen species promotion and glutathione depletion, which leads to DNA damage, protein denaturation, and lipid peroxidation. Further, it affects changes in gene expression contributing to cell function disturbance. There is considerable evidence revealing the cardiovascular effect of heavy metals related to high blood pressure[45] and could be contributed to atherosclerotic heart disease [14]. Metal exposure could be one of the cumulated risk factors in COVID-19 survivors.

1.11 Control risk of air pollution

Considering the high prevalence of respiratory complications and heart injury in COVID-19 survivors and their susceptibilities, we should consider air pollution risk control an avoidable approach for preventing morbidity and mortality risk of respiratory and cardiovascular complications.

1.12 An unhealthy lifestyle collaborates adverse toxicant effects

Lifestyle factors, particularly smoking, may directly or indirectly impact the toxicity of toxicants, mainly by mediating reactive oxygen species. Lifestyle could exacerbate the adverse effects of real-life toxicants exposure. However, emerging evidence has indicated that a positive lifestyle change (regular exercise, food consumption, quitting smoking, and alcohol consumption) can reduce the risk of toxicants [46].

1.13 Cigarette smoking, survival- related risk factor

Smoking is a major public health issue that is an avoidable cause of several diseases like lung cancer, heart disease, and vascular dysfunction [47, 48]. Concerning the COVID-19 infection in smokers, other researchers reported that smokers have higher ACE_2 expression. Therefore, smokers have more virus receptors in airway epithelial than non-smokers [49]. Cigarette smoke constitutes a highly complex mixture of noxious gases, aerosol liquids, and small particles, which cause harmful and carcinogenic effects [50]. Certain smoke constituents could be metabolized, and their metabolites could increase reactive oxygen/nitrogen species.

Activated oxygen species cause acute effects of cigarette smoke by increasing the oxidative stress process because of reduced antioxidant sources and inflammation [48, 51, 52]. The lung is a prominent direct target for various oxidant compositions in cigarette smoke, and the oxidative reaction hurts lung cells[53]. Moreover, other factors that could negatively affect smokers include unhealthy nutritional habits leading to insufficient intake of antioxidants and drinking a large amount of alcohol during smoking. They all result in vital biomolecule oxidative damage, inflammatory response, and vascular dysfunction in cigarette smokers. Pro-inflammatory cytokines (IL-6, TNF-α, and IL-1β) and systemic inflammation mediate lifestyle-related disease in chronic smokers [54]. Findings have demonstrated that smoker patients are at risk of a lower level of antioxidants; thus, oxidative damage is more dangerous in them than in non-smokers [48].

2. Discussion

2.1 A new challenge in the health of COVID-19 survivors

There is a global concern about overexposure to the mixture of real-life toxicants among the public. In our daily life, the broad spectrum of undesired toxicants has the potential to evoke adverse health effects. Therefore, the variety of adverse effects and the diversity of toxicants have caused additional concerns in the rehabilitation phase of COVID-19 survivors as a susceptible subgroup with a persistent sequela. As noted in this review, in the recovery phase, survivors of COVID-19 infection are at risk of antioxidant source depletion during the viral infectious stage and the low-grade inflammation status related to the sequela [20], which raises the potential risk of oxidative damage. Furthermore, several toxicants enhance oxidative disturbance. The close interplay between host inflammation and oxidative stress attributed to disease (virus, microbe), leading to cell dysfunction and microenvironment perturbation, contributes to disease progression and longer infection rehabilitation (Fig 1). Underlying the public health issue, we should assess the risk of oxidative imbalance related to real-life toxicants in survivors′ health. The harmful effects of toxicants considerably depend on the dose-response assessment in survivors of COVID-19 infections. Since internal factors of the individual can affect the toxic response, it is important to recognize factors such as age, sex, and underlying disease of survivors (blood pressure, asthma, cardiovascular disease, diabetes, obesity) who are exposed to real-life contaminants, the above-mentioned factors directly affect the disease progression. Moreover, magnified hazards in cumulative pollutants in daily life would be a great hazard in the exposure of susceptible individuals and make a complex situation.

2.2 Protection of survivors requires comprehensive strategies for the risk management

Supporting the growing population of survivors and their rapid rehabilitation requires hazard identification, such as various adverse effects of toxicants in the risk assessment process. These are the cornerstone to reducing the risk of disease progression. In order to reduce toxicants, we should pay particular attention to develop coordinated strategies for COVID-19 risk management. (Fig 3). Individuals should be responsible for reducing the virus spread and be less exposed to pollutants to maintain their health by changing their unhealthy lifestyles, such as quitting smoking and alcoholism, exercising regularly, and reducing the pollutant released into the environment and workplace. Social responsibility could provide environmental safety and promote healthy lifestyle programs. Governments could offer health resources to policymakers to guarantee air quality, work environmental safety, monitor contaminants and pesticide/chemical regulation, and minimize pollution to prevent serious public health problems. Responsibility for rehabilitation, particularly for COVID-19 survivors, should be a concerted effort to reduce the spread of the disease and prompt rehabilitation among survivors. Although rehabilitation in COVID-19 survivors is most important to avoid illness progression in society, these strategies help everyone benefit from the risk management of toxicant exposure, not just those who survive.

3. Conclusion

Awareness of COVD-19 survivors′ health follows toxicant exposures. This paper indicated the adverse effects of COVID-19 infection on survivors and the potential risk of exposure to real-life toxicants regarding the susceptibility in the recovery phase. Over million recovered individuals are the susceptible subgroup regarding the persistent sequela. New clinical evidence has indicated long-term adverse effects of COVID-19 on cardiovascular, respiratory, and immunological systems. Most survivors are at risk of oxidative stress due to exposure to toxicants, which could contribute to disease progression. This approach has the potential to reduce the negative effects, control, and manage the risk by placing the responsibility on individuals, society, and decision-makers to increase the health quality in society.

Authors' Contributions

Rana Dizaji: Conceptualization; writing; Editing .

Conflicts of Interest

The author declares that there is no conflict of interest.

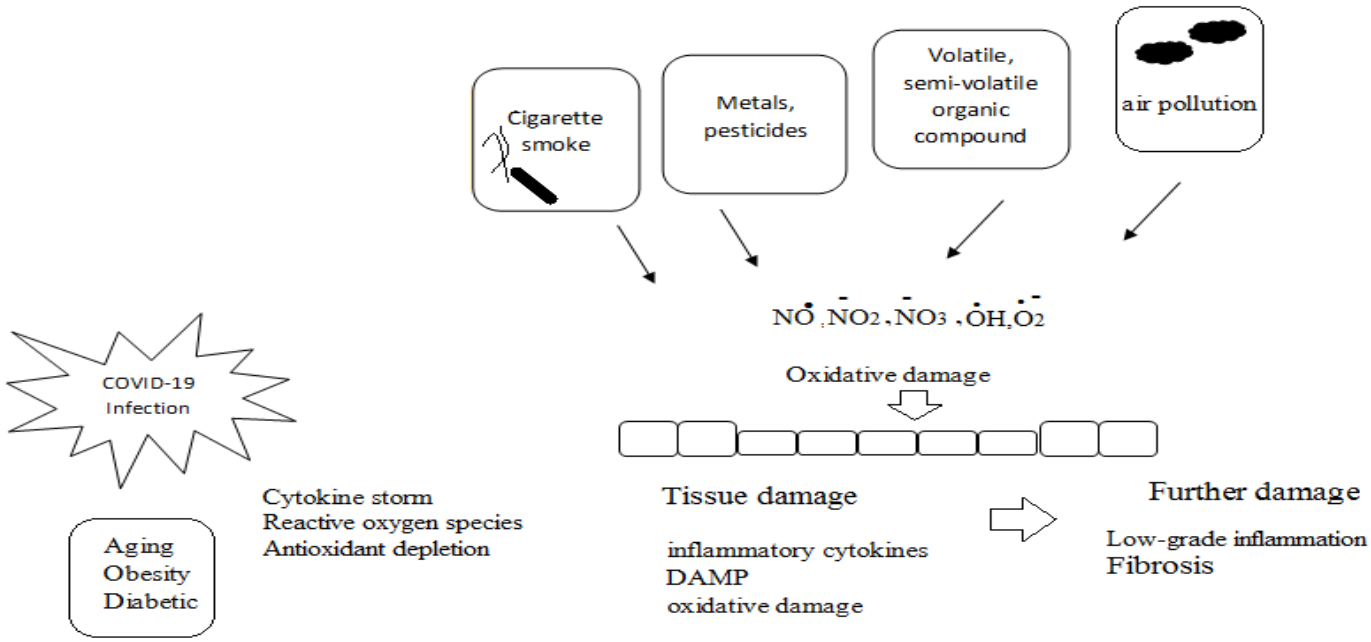

Figure 1: Collaborating role of real-life toxicants in the survivor disease progression. Considering tissue damage and antioxidant depletion in survivors after the acute stage of the disease and virus elimination, in which cells are located in a pooled environment with inflammatory cytokine(viral in depending stage), excessive reactive oxygen species, and damage- associated molecular pattern (DAMP),enhance several kinds of regulated cell death, along with effects of oxidative stress- related to exogenous toxicant such as smoking cigarette, inhaled particulate and gaseous matter related to air pollution or occupational exposure and endogenous source of oxidative damage, which are attributed to antioxidant depletion or overwhelming of the antioxidant system, leading to the disease progression and fibrosis. In particular, the cumulative hazard with the increased risk of oxidative damage may complicate the health condition.

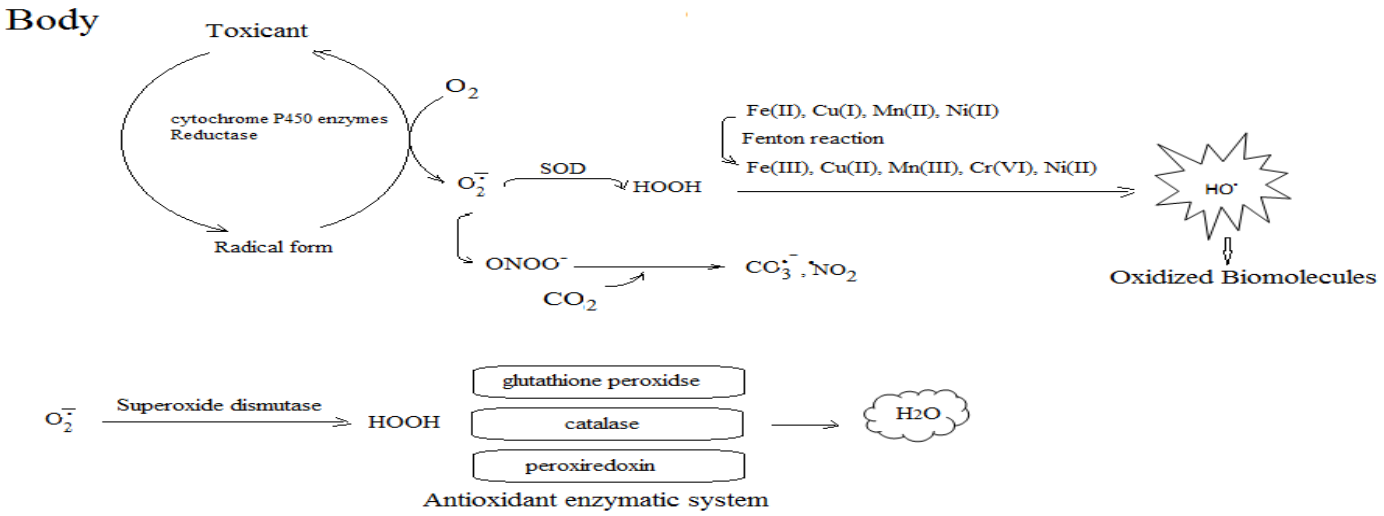

Figure 2: Toxication of the xenobiotic and free radical formation and detoxication system. Xenobiotics form free radicals by accepting or losing an electron, and thus by transferring the extra electron to molecular oxygen, they form a superoxide anion radical ($O_2^{\bullet -}$). Several pathways in the body convert ($O_2^{\bullet -}$) to much more reactive compounds. Elimination of ($O_2^{\bullet -}$) in the body is an important mechanism carried out by superoxide dismutase (SOD), which is converted to superoxide (HOOH). Subsequently, detoxication of HOOH occur by no enzymatic (glutathione) and enzymatic system (glutathione peroxidase, peroxiredoxin, and catalase) produce H2O.

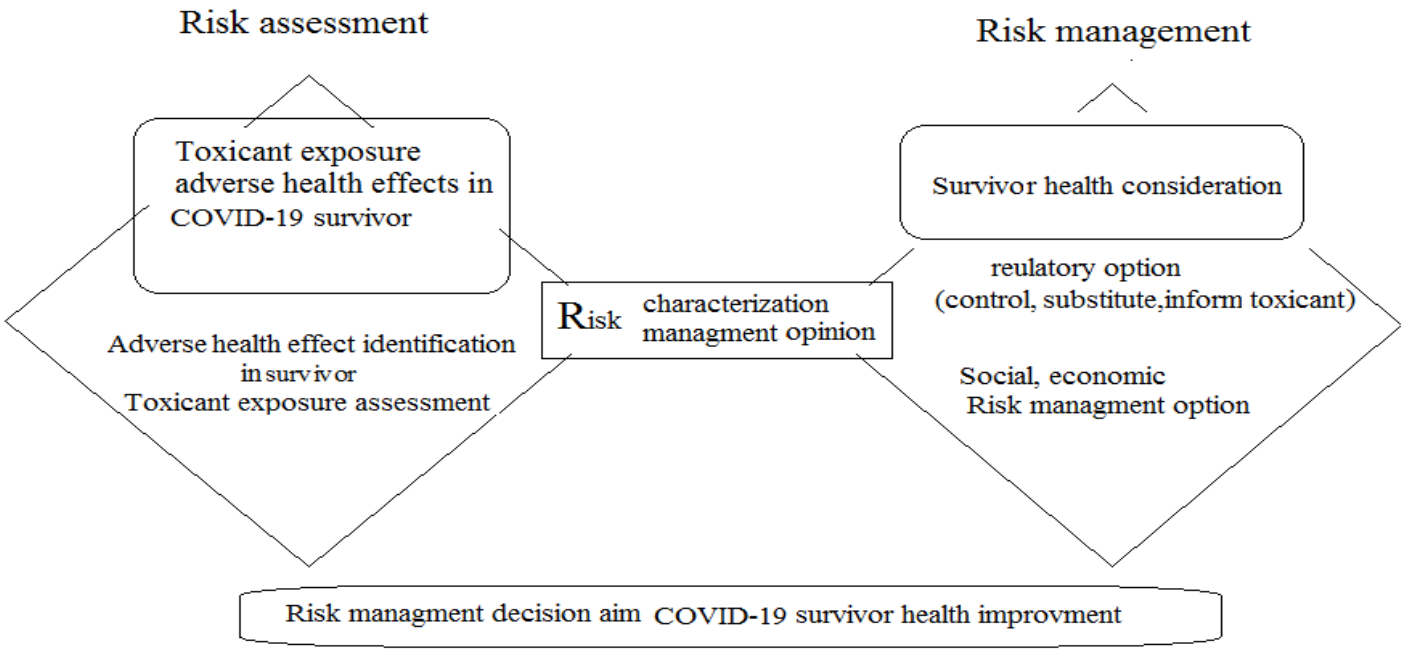

Figure 3: Control risk of toxicant adverse health effects on the COVID-19 survivor framework. Risk assessment of adverse health effects of real-life toxicants on COVID-19 survivors requires identifying adverse health effects as well as type, level, and duration of exposure, which provide the incidence of risk, and also robust of evidence and proper action for COVID-19 risk management. Improvement of COVID-19 survivors' health is possible by effective management regarding social and economic, mainly by banning, substituting, or informing about toxicants.

Acknowledgments

The author thanks Zanjan University of Medical Science for supporting the current study.

References

1. Leung T. Short-and Potential Long-Term Adverse Health Outcomes of COVID-19: a Rapid Review. *Emerging Microbes & Infections*. 2020; 9(1): 2190-9.

2. Meftahi GH, Jangravi Z, Sahraei H, Bahari Z. The Possible Pathophysiology Mechanism of Cytokine Storm in Elderly Adults with COVID-19 Infection: the Contribution of "Inflame-Aging". *Inflammation Research*. 2020; 69(9): 825-39.

3. Vaninov N. In the Eye of the COVID-19 Cytokine Storm. *Nature Reviews Immunology*. 2020; 20(5): 277.

4. Laforge M, Elbim C, Frère C, Hémadi M, Massaad C, Nuss P, Becker C. Tissue Damage from Neutrophil-Induced Oxidative Stress in COVID-19. *Nature Reviews Immunology*. 2020; 20(9): 515-6.

5. Delgado-Roche L, Mesta F. Oxidative Stress as Key Player in Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) Infection. *Archives of Medical Research*. 2020.

6. Pincemail J, Cavalier E, Charlier C, Cheramy-Bien JP, Brevers E, Courtois A, Rousseau AF. Oxidative Stress Status in COVID-19 Patients Hospitalized in Intensive Care Unit for Severe Pneumonia. A Pilot Study. *Antioxidants*. 2021; 10(2): 257.

7. Mohiuddin M, Kasahara K. The Emerging Role of Oxidative Stress in Complications of COVID-19 and Potential Therapeutic Approach to Diminish Oxidative Stress. *Respiratory Medicine*. 2021; 187:106605.

8. Korupolu R, Francisco GE, Levin H, Needham DM. Rehabilitation of Critically ill COVID-19 Survivors. *The Journal of the International Society of Physical and Rehabilitation Medicine*. 2020; 3(2): 45.

9. Cueto-Robledo G, Porres-Aguilar M, Puebla-Aldama D, del Pilar Barragán-Martínez M, Jurado-Hernández MY, García-César M, Roldan-Valadez E. Severe Pulmonary Hypertension: an Important Sequel after Severe Post-Acute COVID-19 Pneumonia. *Current Problems in Cardiology*. 2022; 47(3): 101004.

10. Sarhan M, von Mässenhausen A, Hugo C, Oberbauer R, Linkermann A. Immunological Consequences of Kidney Cell Death. *Cell Death & Disease*. 2018; 9(2): 1-15.

11. García LF. Immune Response, Inflammation, and the Clinical Spectrum of COVID-19. *Frontiers in Immunology*. 2020; 11: 1441.

12. Merad M, Blish CA, Sallusto F, Iwasaki A. The Immunology and Immunopathology of COVID-19. *Science*. 2022; 375(6585):1122-7.

13. Kostoff RN, Briggs MB, Porter AL, Hernández AF, Abdollahi M, Aschner M, Tsatsakis A. The Under-Reported Role of Toxic Substance Exposures in the COVID-19 Pandemic. *Food and Chemical Toxicology*. 2020:111687.

14. Klaassen CD. Casarett and Doull′ s Toxicology: the Basic Science of Poisons. McGraw-Hill New York. 2013;1236.

15. Clay CC, Donart N, Fomukong N, Knight JB, Overheim K, Tipper J, Harrod KS. Severe Acute Respiratory Syndrome-Coronavirus Infection in Aged Nonhuman Primates is Associated with Modulated Pulmonary and Systemic Immune Responses. *Immunity & Ageing*. 2014; 11(1): 1-16.

16. Agmon E, Solon J, Bassereau P, Stockwell BR. Modeling the Effects of Lipid Peroxidation During Ferroptosis on Membrane Properties. *Scientific Reports*. 2018; 8(1): 1-11.

17. Tang D. Ferroptosis: Molecular Mechanisms and Health Implications. *Cell Research*. 2020:1-19.

18. Dizaji R, Sharafi A, Pourahmad J, Abdollahifar MA, Vatanpour H, Hosseini MJ. Induction of two Independent Immunological Cell Death Signaling Following Hemoglobinuria-Induced Acute Kidney Injury: In Vivo Study. *Toxicon*. 2019; 163: 23-31.

19. Leopold JA. Cellular Mechanisms of Aortic Valve Calcification. *Circulation: Cardiovascular Interventions*. 2012; 5(4): 605-14.

20. Briasoulis A, Androulakis E, Christophides T, Tousoulis D. The Role of Inflammation and Cell Death in the Pathogenesis, Progression and Treatment of Heart Failure. *Heart Failure Reviews*. 2016; 21(2): 169-76.

21. Vénéreau E, Ceriotti C, Bianchi ME. DAMPs from Cell Death to New Life. *Frontiers in Immunology*. 2015; 6: 422.

22. Mack M. Inflammation and fibrosis. *Matrix Biology*. 2018; 68: 106-21.

23. Li R, Wang Y, Qiu X, Xu F, Chen R, Gu W, Liu C. Difference on Oxidative Stress in Lung Epithelial Cells and Macrophages Induced by Ambient Fine Particulate Matter (PM 2.5). *Air Quality, Atmosphere & Health*. 2020; 13: 789-96.

24. Cosselman KE, Navas-Acien A, Kaufman JD. Environmental Factors in Cardiovascular Disease. *Nature Reviews Cardiology*. 2015; 12(11): 627.

25. Miller MR. Oxidative Stress and the Cardiovascular Effects of Air Pollution. *Free Radical Biology and Medicine*. 2020.

26. Beelen R, Raaschou-Nielsen O, Stafoggia M, Andersen ZJ, Weinmayr G, Hoffmann B, Hoek G. Effects of Long-Term Exposure to Air Pollution on Natural-Cause Mortality: an Analysis of 22 European Cohorts Within the Multicentre ESCAPE Project. *The Lancet*. 2014; 383(9919): 785-95.

27. Liu C, Zhang Y, Weschler CJ. The Impact of Mass Transfer Limitations on Size Distributions of Particle Associated SVOCs in Outdoor and Indoor Environments. *Science of the Total Environment*. 2014; 497: 401-11.

28. Nazar W, Niedoszytko M. Air Pollution in Poland: A 2022 Narrative Review with Focus on Respiratory Diseases. *International Journal of Environmental Research and Public Health*. 2022; 19(2): 895.

29. Kampa M, Castanas E. Human Health Effects of Air Pollution. *Environmental Pollution*. 2008; 151(2): 362-7.

30. Ghio AJ, Carraway MS, Madden MC. Composition of Air Pollution Particles and Oxidative Stress in Cells, Tissues, and Living Systems. *Journal of Toxicology and Environmental Health, Part B*. 2012; 15(1): 1-21.

31. Pope III CA, Turner MC, Burnett RT, Jerrett M, Gapstur SM, Diver WR, Brookn RD. Relationships Between Fine Particulate Air Pollution, Cardiometabolic Disorders, and Cardiovascular Mortality. *Circulation Research*. 2015; 116(1): 108-15.

32. Bhatnagar A. Cardiovascular Effects of Particulate Air Pollution. *Annual Review of Medicine*. 2022; 73: 393-406.

33. Faustini A, Rapp R, Forastiere F. Nitrogen Dioxide and Mortality: Review and Meta-Analysis of Long-Term Studies. *European Respiratory Journal*. 2014; 44(3): 744-53.

34. Rossner JrP, Rossnerova A, Sram RJ. Oxidative Stress and Chromosomal Aberrations in an Environmentally Exposed Population. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*. 2011; 707(1-2): 34-41.

35. Ren C, Fang S, Wright RO, Suh H, Schwartz J. Urinary 8-hydroxy-2′-Deoxyguanosine as a Biomarker of Oxidative DNA Damage Induced by Ambient Pollution in the Normative Aging Study. *Occupational and Environmental Medicine*. 2011; 68(8): 562-9.

36. Hoffmann B, Moebus S, Mohlenkamp S, Stang A, Lehmann N, Dragano N, Jockel KH. Residential Exposure to Traffic is Associated with Coronary Atherosclerosis. *Circulation*. 2007; 116(5): 489-96.

37. Hoffmann B, Moebus S, Kröger K, Stang A, Möhlenkamp S, Dragano N, Jöckel KH. Residential Exposure to Urban Air Pollution, Ankle-Brachial Index, and Peripheral Arterial Disease. *Epidemiology*. 2009: 280-8.

38. Vinzents PS, Møller P, Sørensen M, Knudsen LE, Hertel O, Jensen FP, Loft S. Personal Exposure to Ultrafine Particles and Oxidative DNA Damage. *Environmental Health Perspectives*. 2005; 113(11): 1485-90.

39. Bind MA, Baccarelli A, Zanobetti A, Tarantini L, Suh H, Vokonas P, Schwartz J. Air Pollution and Markers of Coagulation, Inflammation and Endothelial Function: Associations and Epigene-Environment Interactions in an Elderly Cohort. *Epidemiology (Cambridge, Mass)*. 2012; 23(2): 332.

40. Romieu I, Moreno-Macias H, London SJ. Gene by Environment Interaction and Ambient Air Pollution. *Proceedings of the American Thoracic Society*. 2010; 7(2):116-22.

41. Cohen G, Steinberg DM, Keinan-Boker L, Levy I, Chen S, Shafran-Nathan R, Gerber Y. Preexisting Coronary Heart Disease and Susceptibility to Long-Term Effects of Traffic-Related Air Pollution: A Matched Cohort Analysis. *European Journal Of Preventive Cardiology*. 2020: 2047487320921987.

42. Gupta S, Gupta K. Bioaccumulation of Pesticides and Its Impact on Biological Systems. *Pesticides in Crop Production: Physiological and Biochemical Action*. 2020: 55-67.

43. Lee KM, Park SY, Lee K, Oh SS, Ko SB. Pesticide Metabolite and Oxidative Stress in Male Farmers Exposed to Pesticide. *Annals of Occupational and Environmental Medicine*. 2017; 29(1): 5.

44. Madkour LH. Toxic Effects of Environmental Heavy Metals on Cardiovascular Pathophysiology and Heart Health Function: Chelation Therapeutics. *UPI J. Pharm. Med. Health Sci.(UPI-JPMHS)*. 2018; 1(1):19-62.

45. Dizaji R, Bakhtiarian A, Ghazi KM, Mohaghegh A, Emami KF. The Relationship Between the Blood Lead Level and Blood Pressure. 2004.

46. Hoffman JB, Hennig B. Protective Influence of Healthful Nutrition on Mechanisms of Environmental Pollutant Toxicity and Disease Risks. *Annals of the New York Academy of Sciences*. 2017; 1398(1): 99.

47. Chao MR, Cooke MS, Kuo CY, Pan CH, Liu HH, Yang HJ, Hu CW. Children are Particularly Vulnerable to Environmental Tobacco Smoke Exposure: Evidence from Biomarkers of Tobacco-Specific Nitrosamines, and Oxidative Stress. *Environment International*. 2018; 120: 238-45.

48. Kamceva G, Arsova-Sarafinovska Z, Ruskovska T, Zdravkovska M, Kamceva-Panova L, Stikova E. Cigarette Smoking and Oxidative Stress in Patients with Coronary Artery Disease. *Open Access Macedonian Journal of Medical Sciences*. 2016; 4(4): 636.

49. Berlin I, Thomas D, Le Faou AL, Cornuz J. COVID-19 and Smoking. *Nicotine and Tobacco Research*. 2020; 22(9): 1650-2.

50. Niemann B, Rohrbach S, Miller MR, Newby DE, Fuster V, Kovacic JC. Oxidative Stress and Cardiovascular Risk: Obesity, Diabetes, Smoking, and Pollution: Part 3 of a 3-Part Series. *Journal of the American College of Cardiology*. 2017; 70(2): 230-51.

51. De Flora S, Balansky R, La Maestra S. Rationale for the Use of N-Acetylcysteine in Both Prevention and Adjuvant Therapy of COVID-19. *The FASEB Journal*. 2020; 34(10): 13185-93.

52. Bruno RS, Traber MG. Vitamin E Biokinetics, Oxidative Stress and Cigarette Smoking. *Pathophysiology*. 2006; 13(3): 143-9.

53. Sundar IK, Yao H, Rahman I. Oxidative Stress and Chromatin Remodeling in Chronic Obstructive Pulmonary Disease and Smoking-Related Diseases. *Antioxidants & Redox Signaling*. 2013; 18(15): 1956-71.

54. Sanada F, Taniyama Y, Muratsu J, Otsu R, Shimizu H, Rakugi H, Morishita R. Source of Chronic Inflammation in Aging. *Frontiers in Cardiovascular Medicine*. 2018; 5:12.