

Acceleration of COVID-19 Severity in Arsenic Accumulated Patient: Review

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Abstract: *With unexpected explosion of pandemic COVID-19, we all are living with a great deal of insecurity. COVID-19 overview and severity are associated with heavy metals exposure. Arsenic ranked first in list of 20 hazardous substances by renowned agencies associated with variety of life threatening health effects. The objective of this review is to discuss on the role of arsenic exposure and its toxicity related to COVID-19 severity. The existing data demonstrated that arsenic toxicity with the lung function concerned with respiratory dysfunction, respiratory diseases along with respiratory arsenic toxic mechanism. Therefore, reduction of toxic metal exposure may be considered as a potential tool for reducing susceptibility and severity of virus affecting respiratory system, including COVID-19. In this fact, we concluded that particular attention must be paid to the load/levels of arsenic elements in COVID-19 as well as post COVID patients. We proposed that toxic metal exposure like arsenic may be also considered as a potential risk factor for post COVID-19 severity in present review. The exposure to air pollutants as well as to toxic arsenic accumulated in different organs in the severe patients should be escaped as much as possible to reduce the possibilities of viral infections, like COVID-19 to save the precious life of human being.*

Keywords: Arsenic, Arsenic toxicity, respiratory infection, COVID-19.

I. INTRODUCTION

Coronavirus SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) is responsible for Corona Virus Disease 2019 (COVID-19) that first occurred in October and is caused immense outburst in December 2019 [1]. During this period, more than 30 million people were affected, and measured more than 950,000 deaths Worldwide and it have been categorized by World Health Organization (WHO) as a global pandemic [2]. Primarily the virus affects the respiratory system, affecting COVID-19 pneumonia, ultimately in severe cases due to cytokine and vascular dysfunction resulting in systemic inflammation [3-8]. Though, the infection is in elevation level, and it is mandatory requirement for recognizing the factors to reduce the risk of COVID-19. Social distancing, hand washing, and vaccinations are some important Public health practices which being help to reduce the spread and impact of infections. It could be accepted by a large population with a medical priority at this pandemic situation[9].

Somewhere else the environmental pollutants like heavy metals are believed to contribute in the occurrence of chronic diseases observed in the current pandemic [10-13]. It has been testified that most of the people and HIV-infected patients at high risk of HIV have considerably higher accumulation of heavy metals in body[14,15]. Though, it is necessary to examine accumulations of heavy metals among COVID-19 patients as heavy metals are one of the environmental pollutants. Theoretically, the heavy metals accumulation assured marks to those individuals who are susceptible to coronavirus disease 2019. Most COVID-19 infected people competes it efficiently bad with few or no symptoms. This is illustrating feature of it[16-19]. These conditions are associated with the bioaccumulation of heavy metals such as Copper (Cu), Nickel (Ni), Chromium (Cr), Cadmium (Cd), Lead (Pb), Arsenic (As) etc. Each year we



normally recollect such heavy metals in the different organs of the body more than we excrete from it. Considerably senior citizens have higher heavy metal concentration in their blood than young people [20].

The typical immune response is more than enough to overcome the virus. However there is a small population section that is not able to do this. These conditions like age, hypertension, obesity, and diabetes that increase your risk for yielding to the virus [21]. Nevertheless, amongst them, only about 1/3 articles are shown with the search term “metals and COVID-19”. Therefore, given to the importance of metal toxicity concerning with the human health, the objective of the study was to discuss the role of toxic arsenic exposure in development of arsenic toxicity effects to human being with respiratory dysfunction and its immune-toxicity in COVID-19 patients. Such interference of arsenic toxicity with another severe viral load in COVID-19 infected patient, does any treatment affect patient’s capability to fight off COVID-19? PubMed and Scopus databases were used for the bibliographic search [22,102].

II. FAMILY- CORONAVIRIDAE

Coronaviruses are belonging to *Coronaviridae* family in which, positive-stranded enveloped RNA viruses are included which infect amphibians, birds, and mammals. The viral genome is having length of 26–32 kilobases as well as typically decorated with large (~20 nm), club- or petal-shaped surface projections called as peplomers or spikes [23,24]. The family *Coronaviridae* is allocated into two subfamilies, *Coronavirinae* and *Torovirinae*. On the base of their nucleocapsids, it can be distinguished as the toroviruses have unique helical doughnut-shaped nucleocapsids and virions are roughly spherical in symmetry including large spike (S) glycoprotein that outspreads from the virus envelope. In the interior of the subfamily *Coronavirinae*, there are four genera, alpha, beta, gamma, and delta coronaviruses shown in Figure 1.

All family members share the same unique strategy for mRNA synthesis whereby the polymerase complex jumps or moves from one region of the template to a more distant region. Synthesis of the polymerase complex may explain RNA recombination high rate that take place during genome replication. Together the coronaviruses and toroviruses are enteric and respiratory tract pathogens, ordinarily linked with only mild disease or in apparent infection. However, human Severe Acute Respiratory Syndrome (SARS) coronavirus and the Middle East Respiratory Syndrome (MERS) coronavirus cause severe respiratory diseases [25,101]

III. HEAVY METAL: ARSENIC IN NATURE

Arsenic is highly ubiquitous in nature and it can be found naturally in water, soil and rocks and at times the certain quantity of arsenic is also found in living organism like plants, animals and microbes. Although in small amount it is occasionally present in air too. The environment gets enriched by arsenic due to various natural activities that include erosion of rocks, fires in the dense forest areas and even through volcanic eruption. The industrialization has resulted in wide spread distribution of arsenic as many industrial products contain arsenic. Certain common industrial products that acts as a source of arsenic, includes paints and dyes, herbicides, wood preservatives, pharmaceutical products and various types of semi-conductor materials. Many manmade activities also results in enriching the environment with arsenic that includes the processes like mining, smelting, burning of fossils fuels, pulp and paper production and manufacturing of cement [27].

IV. ARSENIC TOXICITY

Arsenic is a metalloid and occurs naturally forming more than 200 odd minerals. Most of the minerals contain arsenic in different oxidation states and are able to enter into the groundwater resources resulting in severe arsenic pollution. Water contaminated with arsenic is not a localized problem but it is widespread and has been reported in more than 30 countries in the world [28]. The Chronic Arsenic Toxicity (CAT) is generally referred to as ‘arsenicosis’. CAT has now become a standard term used by WHO [29]. There are various levels of toxicity due to the arsenic exposure in the environment.



V. ARSENIC TOXICITY EFFECT IN HUMAN

The portal of entry of arsenic is generally ingestion and inhalation and among this drinking water acts as the major source of intake of arsenic for animals and humans [30]. Apart from this in certain cases food may also acts as a secondary source of arsenic exposure [31]. More than 90% of the ingested organic arsenic by humans is generally found in sea food and such organic arsenates are also absorbed by the gastro intestinal tract. In some animals like rabbits oral entry of arsenic from contaminated soil has been reported [32].

The arsenic in fecal matters to the extent of 95% of oral intake of Arsenite (AsIII) supports the absorption of arsenic [33]. The renal tract is also used for arsenic management because urinary tract can remove 55-80% of Arsenite (AsIII) and Arsenate (AsV) intake [34-37]. Both MMA and DMA are observed to about 75-80% by the gastrointestinal tract. And interesting phenomenon of absorption of AsIII and AsV is their inter-convertibility due to oxidation and reduction. When As III is absorbed a part of its oxidized to AsV resulting in a mixture of As III and AsV in the blood. Similarly when AsV is absorbed a part of its reduced to AsIII resulting in a mixture of AsIII and AsV in the blood. Once the blood carries AsIII it reaches the liver where enzymatic methylation of AsIII results in the formation of Mono-Methyl Arsenic (MMA) and Di-Methyl Arsenic (DMA). AsIII, AsV, MMA and DMA possess the capacity to remain bound to the tissues depending upon the rate of methylation. MMA derivative converted into DMA derivative but neither of them gets de-methylated to As III or AsV. These methylated forms of arsenic is somewhat less toxic than AsIII and AsV, as all such moieties travel through the blood they tend to accumulate in the skin, bone and muscles. And the half-life of such deposited arsenic varies from 2-40 days has been reported in Figure 2 [38].

Once absorbed blood becomes the main carrier of arsenic to different organs. Arsenic is well distributed and can be seen in bones, kidney, lungs, muscles, excretory or storage organs such as nails and hairs. Interestingly nails and hairs show the highest concentration of arsenic. There are many reports to suggest trans-placental transfer of arsenic. Trivalent arsenic is found to be predominant species [39]. Trivalent arsenic are generally deposited in kidneys liver, bile, brain, skeleton and skin much higher than pentavalent arsenic (*Health assessment document for inorganic arsenic*) [40].

As a source a wide range of health related arsenic toxicity in humans can be mild, acute or even chronic. Some of the common health effects of arsenic include neoplasia, melanosis, melanokeratosis, hyper pigmentation, chromosomal aberrations, skin, bladder and lung cancer, peripheral vascular, cardio-vascular and cerebro-vascular diabetes, ARO (Adverse Reproductive Outcomes), neuropathy, paraesthesias, dysfunction of sensory nerves, apoptosis and necrosis developing brain cells, oxidative stress related gene expression, altered DNA methylation and cell proliferation, bone marrow depression, hypertension, hepatocellular carcinoma, hepatic fibrosis, black foot illness and teratogenesis. A detailed effect of arsenic in humans, their geographical distribution and reporting authors were analyzed in Table 1 [41].

VI. IMMUNOTOXICITY IN HUMANS DUE TO ARSENIC EXPOSURE

Chronic arsenic exposure is well-known to be strongly associated with the incidence of viral infections due to its immuno-toxic effect on the one side whereas arsenic compounds are used as the potential antiviral agent also inhibiting SARS-CoV-2 viral proteins as assessed by *in silico* docking analysis on the other side. This is the dual nature of arsenic in viral diseases such as COVID-19 in contrast with other heavy metals [35].

Nevertheless due to various types of toxicological effects are affected and the patient shows abnormalities like increased salivation, irregular dyspepsia, abdominal cramps and acute loss of weight, in the chronic cases diminished sexual activity is also reported [32,58]. In case of acute oral arsenic poisoning with the dose more than 8 gm arsenic /kg shows respiratory disorders. Hyper ingestion of arsenic may cause serious effects on cardiovascular systems [56,59]. Inorganic arsenic compounds are usually neurotoxic and peripheral neuropathy has been reported [60].

Arsenic also has carcinogenic effects inorganic arsenic has been shown to be skin and lung carcinogens [61,62]. Continuous and cumulative arsenic exposure has been shown to cause lung cancer in smelter workers [63]. Similarly, cumulative exposure of arsenic has been correlated with respiratory cancers in proper smelting employees [64]. A



chromosomal aberration has been shown to occur in peripheral blood lymphocytes in the person exposed with arsenic. Sodium arsenate has been found to inhibit DNA repair inheritance particularly in skin biopsy cells and in lymphocytes [58].

VII. TOXIC METALS/METALLOIDS: ARSENIC AND COVID-19

In recent decades, excessive contamination and the environmental pollution is a prime importance at the present generation. Although arsenic being a toxic metal which pollutes soil, water, including plants resulting in severe threats for the animal kingdom including human. On the other hand, the outburst and occurrence of the SARS with MERS have taken an unusual attention to these severe pathogens, predominantly in respiratory tract infections. Environmental pollutants have a significant influence on the severity of the respiratory problems in COVID-19 patients, which can adversely affect the respiratory system. Particulate matter (PM), Nitrogen oxides, Sulfur dioxide, Ozone, Carbon monoxide, Volatile Organic Compounds (VOCs) as well as Polycyclic Aromatic Hydrocarbons (PAHs) is among the outdoor air pollutants that adversely affect the respiratory system in humans [65]. With the above specified pollutants, exposure to certain toxic metals/metalloids such as arsenic, cadmium, chromium, lead or vanadium can also cause negative effects on the human respiratory system [66-68].

Zeng *et al.*, (2021a) revealed that various metals/metalloids like arsenic, chromium, copper, cadmium, mercury manganese, and thallium in the urinary concentrations were allied with the prospects of severity of the COVID-19. Authors have mentioned that trace elements should be persistently monitored, not only just for the identification of COVID-19, but also to evaluate the vibrant changes that appear in COVID-19 patients [69].

VIII. MECHANISMS OF RESPIRATORY ARSENIC TOXICITY

Air route reactivity, redness, and alteration increased by arsenic exposure with peribronchial thickening [70]. Arsenic induced lung damage with apoptotic cell death is due to mitochondrial dysfunction along with oxidative and endoplasmic reticulum stress [71,72]. Inflammatory and pro-oxidant effects in lungs and Reactive Oxygen Species (ROS) by arsenic exposure may be associated to arsenic-induced up-regulation of NF- κ B (Nuclear Factor kappa-B) and MAPK (Mitogen Activated Protein Kinase) activity, along with variation in Nrf2 (Nuclear factor erythroid 2-related factor) signaling shown in Figure 3 [73,74]. Arsenic has a capability of up-regulation of phosphorylates IKK α and IKK β and NF- κ B heterodimer p65/50 to activate or repress target gene expression m/RNA and protein expression in corresponding with a reduction in I κ B α levels in lungs [75]. It is significant that high-dose of arsenic intensified inflammatory responses with weak autophagy activation while low-dose of arsenic exposure was revealed [76]. Weaken expression of genes being complicated in mucus production (Clca3, Muc5b), lung morphogenesis (Sox 2), and ciliary function (Ttc21a) [77]. Due to arsenic exposure, it was also revealed to impair the whole immune system of body.

IX. DISCUSSION

Environmental pollutants, including the heavy metals or metalloids, are believed to be associated with the viral epidemic/pandemic incidence [13]. Not only arsenic but other heavy metals including Cadmium (Cd), Lead (Pb) and Zinc (Zn) are becoming significant environmental pollutants and their toxicity is causing world-wide problem. Some of the toxicity of these elements is becoming increasingly common in India with different geological regions. Subsequently arsenic having large diversity and capability to increase health issues as, we all are surviving in nature with arsenic exposure. CAT is generally referred to as 'arsenicosis'. It has now become a standard term used by WHO²⁹. The metalloid arsenic is also trans-mobilized into the farming systems through many natural geochemical processes, use of arsenic based pesticide, mining operations, irrigation of various lands with arsenic contaminated groundwater etc. [78,79]. The common problems associated with exposure of arsenic along with the viral diseases and its immunotoxicity might be severe in immune system that's why it should be focus in acute as well as chronic diseases.



There are many factors that affects the absorption by the gastrointestinal tract and inhalation that results in the toxic effects in the lungs and other parts in the body. At the extents of damage, when the particles are larger than $10\mu\text{m}$ they get deposited in the nasopharynx and rarely enter into the deeper lung tissues. However, when the particles are between $5-10\mu\text{m}$, they are generally cleansed by the mucociliary action of the ciliated epithelium of the air passage ways and when the particles are less than $2\mu\text{m}$ in size they can penetrate deep into the lungs straight into the alveoli [80,81]. Likewise, arsenic toxicity stuck into respiratory system as well as entire organs of human body with low immune power. Arsenic exposure is the risk factors in COVID-19 patients as well as in healthy human at all.

Arsenic is well distributed and can be seen in bones, kidney, lungs, muscles, excretory or storage organs such as nails and hairs. Interestingly nails and hairs show the highest concentration of arsenic [58]. Again more arsenic recollect in the human body than it excrete from the body. Considerably higher heavy metal concentration found in the blood of senior citizens than young people [20]. Means concentration of heavy metals like arsenic increased day by day throughout the life.

At times combination of techniques has also been used such as ultra-filtration and reverse osmosis but these technologies are highly cost intensive. Biological remediation technologies are more advantageous as either living cells or dead cells or even biosynthesized molecules can be used for arsenic remediation [82]. So, this is much needed part regarding to emphasis on proper arsenic detection as well as diagnosis in patients as it deposited in different organs of the body and arsenic remediation in environment.

Respiration is important mechanism for all living being. Respiratory diseases having a key role of the respiratory system which are targeted in COVID-19 associated with higher disease severity [83]. Intherapeutic methods for management of the disease and reducing its menace for the disease assessment, estimation of other exposing toxicity is also essential [84-86]. National Cancer Institute is conducting a large study of people with cancer who have COVID-19 to learn about risk factors for COVID-19 and help to doctors to manage treatment for patients with cancer and COVID-19 in the future [87]. In view of the role of arsenic toxicity as effector in particulate pollution, toxicity as well as their respiratory, immunotoxicity, and proinflammatory effects, we proposed that toxic arsenic metal exposure in the patient's body may be also considered as non-ignorable risk factor for COVID-19 as well as post COVID severity at times.

Zeng *et al.* (2021a)[69] determined in COVID-19 patient's urine sample, levels of various essential and toxic metals/metalloids, including arsenic, cadmium, chromium, copper, lead, manganese, mercury, selenium and thallium, in order to establish the potential relationship with the severity of the disease and the outcomes. Thus among the severe cases, it is concluded that urinary concentrations of these trace elements were associated factors for the prognosis of severe COVID-19.

X. CONCLUSION

In the outlook of arsenic diversity around and it's concomitant toxicity to the wide range of living organisms, it is highly commanding to treat the arsenic rich environment so as to reduce the probable health effects and related toxicity. The present review was marked at assessing the relationship between arsenic toxicity is a silent risk factor and the health outcomes related with the COVID-19 as well as post-COVID era. We are in the position to conclude that acceleration of the viral severity in arsenic accumulated patients is not just a COVID-19 issue, but a warning for future pandemics. Particular attention must be paid to the load/levels of essential trace elements such as arsenic.

Based on the results of most studies, chronic exposure to certain air pollutants like arsenic is leading to more severe and lethal forms of COVID-19 and delays/complicates the recovery of patients suffering this disease. In general the exposure to air pollutants, and toxic metal/metalloids in particular, should be avoided as much as possible to reduce the possibilities of all viral infections, including SARS-CoV-2 by the new invented technologies. Over time, viruses such as the one that causes COVID-19 can change (mutate), which can result in new variants of the virus. These variants might have slightly different traits than the original and appear around the World as worldwide pandemic.



COVID-19 pandemic continues to have a serious impact on many people with co-morbidities. Long-term pollutant exposure like arsenic affects natural immunity and increases susceptibility to viral agents and virus-infected cell. Such other viral infections may indirectly reveal negative impact of arsenic on antiviral immunity. Arsenic toxicity with another severe viral load along with COVID-19, severity tolerance might be possible by human which could be persistently monitored and would be helpful in the evaluation of the dynamic changes in patients with COVID-19 by regular laboratory specimen tests by practitioners. In the future, identification of microchip based tests would be allowed for more progressive treatment or inhibition measures towards arsenic toxicity.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

TABLES AND FIGURES

Table1| Effect of arsenic in humans, their geographical distribution, and reporting authors.

Effect and/or symptoms	Countries	References
Neoplasia and induced DNA damage	France	[42,43]
And inhibit DNA hypermethylation	USA	
Malanosis,melanokeratosis (malignancy) in adults	Bangladesh & India	[44]
Hyperpigmentation, keratosis,weakness,anaemia, burning sensation of eyes, solid swelling of legs,liver fibrosis,chronic lung disease, gangrene of toes,neuropathy	Bangladesh Bangladesh Bangladesh & India Bangladesh Bangladesh	[45-48]
Chromosomal abressions and chromatic exchanges	India	[49]
Skin cancer	Bangladesh India USA USA USA Bangladesh India	[46, 48, 50-54]
Diabetes,Bladder cancer	USA	[51]
Lung cancer Peripheral vascular, Cardiovascular, cerebrovascular disease	USA	[51, 53]
Adverse reproductive outcomes neuropathy	USA Bangladesh- India India	[46, 50, 51]
Apoptosis and nechrosis developed in the brain cells	India	[55]
Bone marrow Dipression, Gastrointestinal disturbances	USA	[53, 56]
Hepatocellular carcinima	China	[57]
Acute intake results:vometting,diarrohea,low blood pressure and high heart beat	USA	[56]
Teratogenesis in unborn children	Bangladesh	[45]



This table is based on the former information in paper [41].

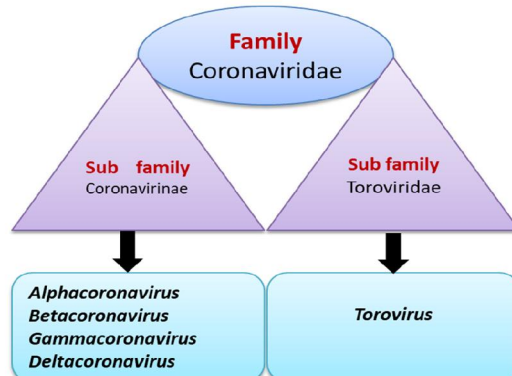


Figure. 1| Taxonomy of family *Coronaviridae* (Modified Figure is Adapted from REF. [26])

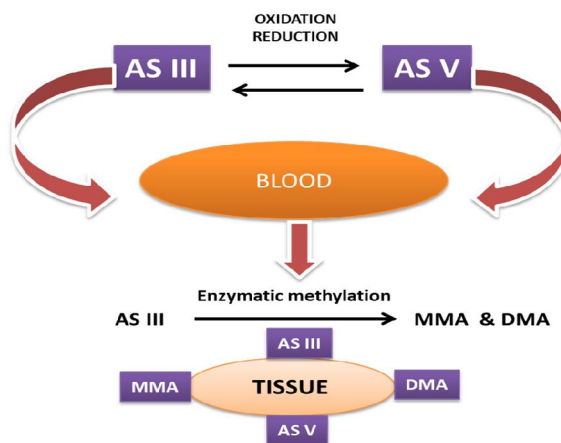


Figure. 2 Phenomenon of tissue bounded forms of arsenic in human. Arsenite (AsIII), Arsenate (AsV), Mono-Methyl Arsenic (MMA) and Di-Methyl Arsenic(DMA) possess the capacity to remain bound to the tissues depending upon the rate of methylation).

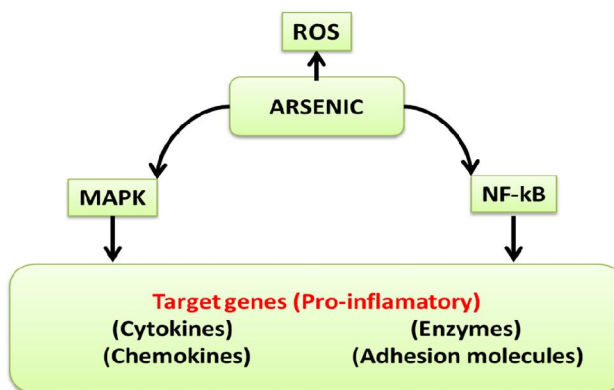


Figure. 3| Pro-inflammatory mechanism of arsenic exposure [88-91]. Inflammatory and pro-oxidant effects in lungs and Reactive Oxygen Species (ROS) by arsenic exposure may be associated to arsenic-induced up-regulation of NF- κ B (Nuclear Factor kappa-B) and MAPK (Mitogen Activated Protein Kinase) activity, along with variation in Nrf2 (Nuclear factor erythroid 2-related factor) signaling.

