

REVIEWS

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Impact of air pollution and smoking on COVID-19: a review

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Abstract

Background: The 21st century already witnessed many deadly epidemics and pandemics. The major ones were respiratory tract infections like SARS (2003), H1N1 (2009), MERS (2012) and the most recent pandemic COVID-19 (2019). The COVID-19 story begins when pneumonia of unknown cause was reported in the WHO country office of China at the end of 2019. SARS-CoV-2 is the causative agent that enters the host through the receptor ACE2, a component of the renin–angiotensin system.

Main body of the abstract: Symptoms of COVID-19 varies from patient to patient. It is all about the immunity and health status of the individual that decides the severity of the disease. The review focuses on the significant and often prevailing factors, those that influence the lung function. The factors that compromise the lung functions which may prepare the ground for severe COVID-19 infection are interestingly looked into. Focus was more on air pollution and cigarette smoke.

Short conclusion: The fact that the forested areas across the world show very low COVID-19 infection rate suggests that we are in need of the “Clean Air” on the fiftieth anniversary of World Earth Day. As many policies are implemented worldwide to protect from SARS-CoV-2, one simple remedy that we forgot was clean air can save lives. SARS-CoV-2 infects our lungs, and air pollution makes us more susceptible. In this crucial situation, the focus is only on the main threat; all other conditions are only in words to console the situation.

Keywords: COVID-19, SARS-CoV-2, ACE2, Cigarette smoke, Air pollution

Background

The 21st century witnessed already many deadly epidemics and pandemics. Major ones among them are severe acute respiratory syndrome (SARS; 2003), H1N1 (2009), Middle East respiratory syndrome (MERS; 2012), and the most recent and massive outbreak of coronavirus disease 2019 (COVID-19; 2019). Story of COVID-19 begins when pneumonia of unknown cause was reported in China at the end of 2019. On 10th January 2020, the causative agent was found to be a novel coronavirus (2019-nCoV) and on 13th January witnessed its first step out of China in Thailand and later in many other countries. On 30th January, WHO declared the

situation as a Public Health Emergency of International Concern. International Committee on Taxonomy of Viruses named the disease as COVID-19 (coronavirus disease 2019) and the virus as SARS-CoV-2 on 11th February 2020. WHO characterized COVID-19 as a pandemic on 11th March 2020. As of 17th December 2020, the disease spreads worldwide with 1,643,339 deaths and 72,851,747 confirmed cases around the world [1].

The globe was completely thrown upside down by the virus, and researchers are in a continuous effort to search out an effective drug or treatment. The virus is highly infective; it has been an intensive task to prevent its spread from one person to another. Avoiding close contacts, social distancing, isolating infected ones, wearing masks, and hand washing are the major tools to compact COVID-19 worldwide. A major portion of the globe was under lockdown to culminate the sequence.

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From the cases studied worldwide, it is inferred that all those exposed to the virus are not getting infected, and all infected are not showing severe symptoms; the increasingly asymptomatic presence of the virus is detected. It is all about the immunity and health status of the individual. This article reviews how smoking could have adversely affected the consequences of COVID-19.

Main text

The virus

Coronaviruses are enveloped viruses with a crown-like peplomer and helical nucleocapsid. They are pleomorphic, and size ranges between 80 and 160 nm. The viral genome is a single-stranded non-segmented RNA of positive polarity with 27–32-kb size. Coronaviruses are classified into four subclasses on phylogenetic and serological analysis— α , β , γ and δ . SARS-CoV-2, SARS-CoV and MERS belong to β -coronavirus [2]. The genomic structure shows its ability to act as mRNA with 5' cap and 3' poly-(A)-tail. Genomic organization includes 5'cap-leader-UTR-replicase-Spike(S)-Envelope(E)-Membrane(M)-Nucleocapsid(N)-UTR-3'tail. Replicase gene occupies about 20 kb of the genome and the remaining by structural and accessory genes. The leader sequence and untranslated regions (UTRs) contain structural elements for replication and transcription of viral RNA. Each structural and accessory gene begins with transcriptional regulatory sequences needed for their expressions [3].

Host–virus interaction

Angiotensin-converting enzyme 2 (ACE 2) is the receptor that mediates the entry of SARS-CoV-2 to the host cell. The spike (S) protein on the surface of the virus recognizes the specific binding domains on the receptor. The S protein is heavily glycosylated at its N terminus and forms a homotrimer to develop the spike structure. This is cleaved by host cell proteases (furin) to S1 and S2 regions: S1 for receptor binding and S2 for membrane fusion [4]. The S1 region has two domains for receptor recognition, N-terminal domain (NTD), and C-terminal domain (CTD). CTD is the receptor-binding domain in SARS-CoV and MERS [5]. Crystallographic analysis of SARS-CoV and human ACE2 (hACE2) studies proved that SARS-CoV-2 shows strong binding affinities and larger binding interface than SARS-CoV [6]. After binding, the S2 portion undergoes two specific cleavages for separating the S1 portion and exposing fusion peptide. Insertion of this fusion peptide and two heptad repeats of S2 into the host cell membrane form anti-parallel six-helix bundle resulting in the fusion of host cell membrane with the virus membrane and insertion of the viral genome to the host cell [3, 7]. Inside the host cell, the replicase gene gets translated first to

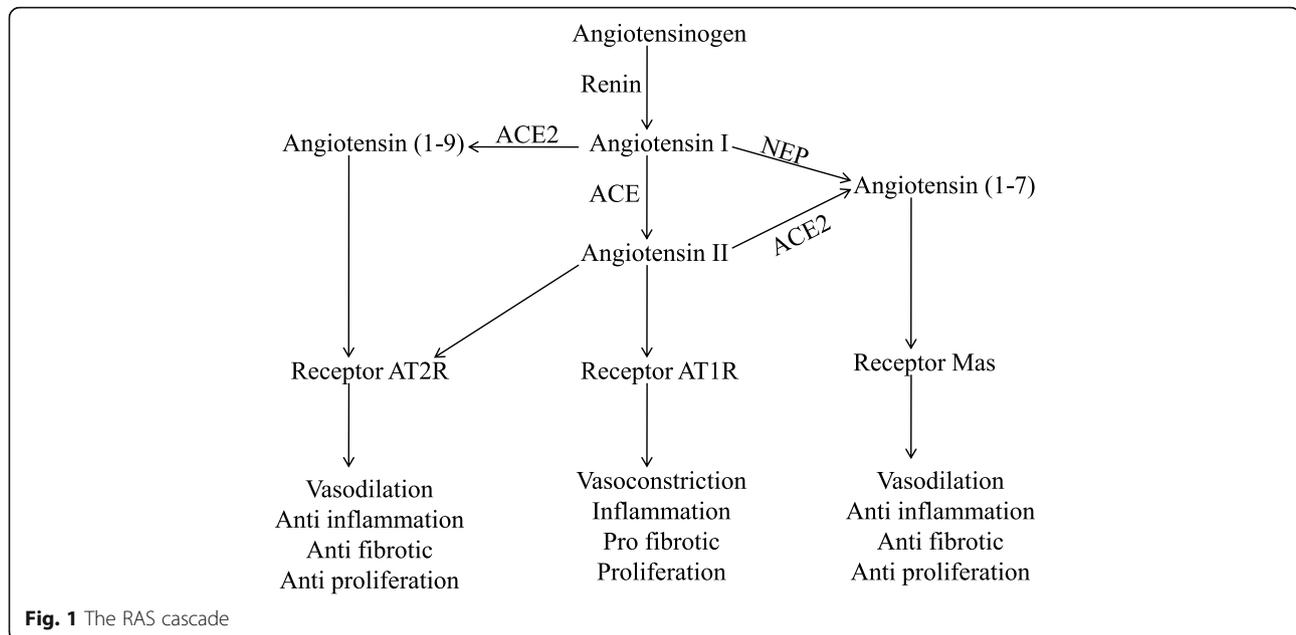
produce polyproteins. Viral proteases cleave them into individual nonstructural proteins and later reassembled to form a replicase-transcriptase complex for viral RNA replication. Viral RNA contains genomic and sub-genomic RNAs. Sub-genomic RNA codes for structural and accessory proteins needed for the viral assembly. After assembly, mature virions get released through the host cell secretory pathway [3].

The receptor

ACE2 is an important enzyme in the renin–angiotensin system (RAS). RAS has been studied for years considering its importance in vascular system homeostasis. The RAS cascade begins with the conversion of angiotensinogen to angiotensin-I (Ang-I) by renin. Ang-I is converted to angiotensin-II (Ang-II) by angiotensin-converting enzyme (ACE). Physiological roles played by Ang-II include vasoconstriction/dilation, vascular permeability, blood pressure & blood volume homeostasis, inflammation, immunity, etc.. ACE has been the target of investigators for years, and many classical antihypertensive drugs are ACE inhibitors [8].

The presence of other angiotensins, their biosynthesis and roles in the RAS cascade has been a question throughout the decades. It was in 2000 that ACE2 was discovered independently by two groups of researchers [9, 10]. ACE2, a carboxy exopeptidase, is related to the synthesis of two classes of angiotensins. It converts Ang-II to Ang(1–7) and Ang-I to Ang(1–9) by removing one amino acid from their carboxy terminals. Ang(1–7) can also be formed by neprilysin (NEP). Considering its role in regulating Ang-II levels, ACE2 is more important in the RAS cascade [11]. Ang-II acts mainly through two receptors; angiotensin type-1 receptor (AT₁R) and type-2 receptor (AT₂R). AT₁R is the primary receptor of Ang-II and its activation leads to vasoconstriction, cell proliferation, inflammatory responses, etc.. AT₂R functions are antagonistic to AT₁R. Ang(1–9) also acts through the receptor AT₂R. Ang(1–7) acts through the receptor Mas and can also oppose the activities induced by AT₁R [12] (Fig. 1).

ACE2, a glycoprotein expressed in the tissues of lungs, kidney, heart and other organs [13]. It is a type-1 integral membrane protein with an extracellular catalytic metallopeptidase domain and a cytoplasmic tail with calmodulin-binding sites. Apart from Ang-II, ACE2 has many other substrates: Ang-I, des-Arg⁹-bradykinin, dynorphin-A, apelin-13, etc. [14]. Implications of ACE2 in diabetes [15], brain injuries [16], cardiac dysfunctions [17] and kidney disorders [18] are also explained well. During acute lung injury, ACE2 protects the organ, while the other components of RAS activate disease pathogenesis. Another interesting fact about ACEs is the shedding of their catalytically active ectodomain [19]. 'A



disintegrin and metalloproteinase' (ADAM) plays a crucial role in this process [20]. The shedding action of ACE2 has significance in SARS-CoV infection also. Viruses, when bound to the receptor, activate ADAM-17, which results in shedding of the receptor as a part of a negative feedback mechanism, thereby preventing disease succession [21].

Immune responses

Clinical features of hospitalized COVID-19 patients in Wuhan city, China reveal that 80% of infected patients are asymptomatic or with mild symptoms [22]. Symptoms of COVID-19 are sore throat, cough, breathing difficulties with fever and fatigue in the initial stages. Severity increases with conditions like lymphopenia, "cytokine storm", pulmonary ground-glass opacity, etc. [23, 24]. Pathogenesis of COVID-19 has been greatly influenced by "cytokine storm" and lymphopenia. "Cytokine storm", a characteristic increase in the level of pro-inflammatory cytokines, induces inflammatory reactions and sepsis; this finally leads to acute respiratory distress syndrome, pneumonia, complete respiratory failure, organ failure and death [25].

Immune responses induced by SARS-CoV-2 have two stages. First is an adaptive immune response, induced during the incubation period or at the less severe state of infection. This is to eliminate viruses and to prevent further progression [26]. Viral antigens are recognized and destroyed, and antibody-secreting cells are activated to secrete specific antibodies. Serological reports of COVID-19 patients reveal that IgM reached its peak value at the 9th day of disease onset and IgG after 2 weeks. Convalescent sera from patients found to neutralize the virus *in vitro*

opened a treatment method [27] and are being used worldwide. When the initial response to eliminate viruses is impaired, they propagate into the host tissues and cause massive destruction. The innate immune system works at this level to prevent tissue damage by inducing inflammatory reactions. Lung inflammation is the main reason behind respiratory disorders during the critical stages of infection [28]. Only least knowledge is now available on innate immune response against SARS-CoV-2. Patient's data on Wuhan city shows an increase in total neutrophils, a decrease in total lymphocytes and an increase in pro-inflammatory cytokines and CRP levels in the blood. Interferon type-I (INF I) and associated pathway showed an effective innate response against the virus [29]. Various reports from China also suggest the importance of many inflammatory markers in the disease including ratio of neutrophil to lymphocyte, hs-CRP, D-dimer and interleukin-6 [30].

The lungs

Being exposed to the external atmosphere, the respiratory tract is always at high risk to get infected. Epithelial cells of the conductive airways offer first-line defence against any foreign agent [31]. The conductive airway epithelium contains luminal cells and basal cells. Ciliated and secretory luminal cells are always in direct contact with foreign agents. The defence mechanism of these cells depends on the extent of microbial attack and condition of the defending cells (damaged or intact). If the epithelial cells are in their baseline conditions without any induction, they offer a constitutive defence, mainly by the luminal cells [32]. This includes a physical barrier, airway surface liquid (ASL) of secretory cells and the

propelling action of the ciliated cells [33]. Antimicrobial peptides, proteins and mucins in the ASL and the keratin sulfate mucin complexes in the cilia contribute much for their functions [34]. Constitutive defence works only on less microbial load; if the microbial load increases, a secondary defence mechanism gets activated. Toll-like receptors and pattern recognition receptors play a major role at this stage. Activated signalling pathways increase the secretion of antimicrobial peptides to ASL and activate the secretion of pro-inflammatory cytokines which will attract the immune cells to the site of infection [35]. Damaged cells can induce the production of damage-associated molecular patterns for activating innate immunity [36]. Dead luminal cells are removed and basal cells take in position; they are the progenitor cells capable of replacing lost cells [37]. Also, epidermal growth factor receptors are activated to repair the damaged cells [38].

Air pollution and respiratory health

WHO estimated death of around seven million people every year due to polluted air. Smokes from our kitchen to the smog that mask our cities are included in this. It causes many severe disease conditions like lung disorders, cancer, cardiac problems, stroke, etc. [39]. The type of pollutants and its sources vary with time, place and season. Major components of outdoor pollutants are particulate matter (PM), CO, SO₂, O₃, NO₂, and lead, among others which are released from industries, vehicles, biomass smoke and forest fires [40]. According to the air quality guidelines of WHO, PM, O₃, NO₂, and SO₂ are the air quality indices [41]. Indoor pollutants are mainly from the combustion of fuels indoors, cigarette smoke and all outdoor sources in mild concentration. Combustion of fuels releases CO, PM, polyaromatic hydrocarbons, NO₂, formaldehyde, SO₂, methane, etc. [42, 43].

Health effects of air pollution are highly detrimental. Lung cancer, chronic obstructive pulmonary diseases (COPD), asthma, respiratory infections, impairment of organ functions and organ failure may result upon exposure to pollutants [44]. The immune system also gets affected by the pollutants which will further complicate the situation [45]. WHO demands that the fatality rate of COVID-19 is connected to the preconditions of patients. Health conditions related to air pollution make the patient more liable to infections. In a study conducted by the School of Public Health, Harvard University, a correlation has been found between air pollution and COVID-19. They reported, “an increase of only 1 µg/m³ in PM 2.5 is associated with a 15% increase in the COVID-19 death rate” [46].

Air pollution and COVID-19

Polluted areas, including air polluted were found infected with more severe cases of COVID-19 [47]. An increase of

air pollutants, to the level of 10 µg/m³ or more, enhanced the daily test positivity rate significantly in many cities of China [48]. The COVID-19-infected areas with high NO₂ pollution were reported having > 78% of mortality at the beginning of the pandemic in Germany, Spain, Italy and France [49]. Similar reports from different parts of the world also correlated between air pollution and COVID-19 severity and mortality. Particulate matter could be one of the highly possible medium for the transport of the SARS-CoV-2 from one source to another. Studies on receptor-mediated drug development for COVID-19 revealed that environmental factors have a strong influence on the expression of the receptor ACE-2, especially in the presence of many pollutants. Higher expressions of ACE-2 were observed in people in polluted areas, and that might be the risk factor for COVID-19 severity and mortality rates [50]. Over expression of ACE-2 by NO₂ interference was reported to be the reason for the severity of COVID-19 cases [51]. WHO also considered that “air pollution has definite effects on the propagation of the virus in human host”.

Cigarette smoke

When compared with other sources of air pollution, cigarette smoke (CS) is in very close proximity with the person's respiratory system, and its effects are common in all the smokers. Cigarette smoke contains harmful and potentially harmful constituents (HPHC) like carcinogens, mutagens, cytotoxic agents, etc. [52]. Inside the respiratory tract, these compounds can affect the integrity of respiratory epithelium. COPD is the main complication. CS can make elevations in ASL components and can activate receptors in the defence mechanism for the release of pro-inflammatory cytokines [53]. In response to cytokines, many immune cells migrate to the site of infection. Alveolar macrophages of a smoker's lung are less mature with condensed cytoplasm and have lost their phagocytic ability [54]. Oxidative stress and apoptotic imbalance in the structural epithelium and immune cells ultimately lead to the destruction of lung tissues [53, 55]. Increased influx of neutrophils at airways is another complication of CS, damaging epithelial cells and the extracellular matrix [56]. Loss of cell integrity, alterations in cytokine profile and inflammation facilitate microbial entry to the respiratory tract. Reports on the effect of smoking on a person's susceptibility to infections conclude that smokers are highly prone to get infected. COPD patients are suggested to take influenza vaccination to prevent the occurrence of exacerbations by viruses. Increase in exacerbation rate increases inflammation and finally leads to the loss of organ function [57].

Cigarette smoke and ACE2

In the lungs, RAS is involved in the pathogenesis of many disease conditions. Lung cells that express RAS elements include alveolar and bronchial epithelium,

pulmonary endothelium, alveolar macrophages, stromal and interstitial fibroblasts, etc. [58]. It is an interesting fact that almost all of these cells express the nicotine receptor also [59]. RAS was upregulated by CS/nicotine under many circumstances [60]. Increase in the conversion rate of Ang-I to Ang-II and ACE activity were observed in rat models [61, 62] and human volunteers [63] immediately after smoking. Animal models of nicotine-induced pulmonary arterial hypertension also showed the pattern of ACE upregulation and ACE2 downregulation [64]. Direct exposure to CS can affect the homeostasis of RAS by upregulating ACE, Ang-II and AT₁R and downregulating ACE2 and AT₂R. High Ang-II level suppresses the ACE2 gene through p38 MAPK signalling pathway mediated by AT₁R and its extracellular signal-regulated kinase [65]. Endothelin-1, a potent inflammatory mediator, can also downregulate ACE2 by acting through receptor ETA on p38 MAPK signalling pathway [66]. Proliferating cells in lung fibrosis showed a decrease in the expression of ACE2 enzyme through cell cycle depended on c-Jun N-terminal kinase pathway [67]. Ang(1–7) also has a feedback inhibition on the expression of ACE2 through its receptor Mas.

Present scenario

In the present scenario of COVID-19, possible reasons behind its contagious nature are being evaluated. Many reports on the potential role of smoking in disease progression have been coming. Compared with non-smokers, smokers may develop severe adverse health effects of COVID-19 [68]. Most of the COVID-19 patients with severe symptoms have one or more coexisting medical conditions like cardiac problems, hypertension, diabetes, brain disorders, etc.. Also, they were older people with a median age of 66 years [69]. Smoking can be a reason for cardiac problems, hypertension and brain disorders, among others, and this can facilitate the progression of infections to severity. Shreds of evidence supporting the negative impact of smoking on lung health and the immune system are available [70].

Smoking status of COVID-19 patients was reported by many (Table 1). In a study on 191 infected persons, 9% of patients who died were current smokers [71]. No death, but severe cases were reported in another study; 3.4% current smokers and 6.9% former smokers were there in the severely affected patients [72]. A study conducted on a larger group of 1099 patients 173 showed severe symptoms. Out of this, 16.9% were current smokers, and 5.2% were former smokers. Besides, 25.5% of current smokers and 7.6% of former smokers were identified among those who were admitted to the ICU or needed mechanical ventilation [73]. In another study on 78 patients, 27.3% had a smoking history which is comparatively larger [74]. In a study on 191 patients admitted to a hospital in Wuhan, only 11 were reported as current smokers, but 5 out of 11 died [71]. Though the reports claim the influence of smoking on the negative progression of COVID-19, statistical significance of the data are lacking. Comparison on the sex of critically ill patients reveals the majority were men [73, 75]. This can be correlated with the high smoking rate among the male population [76]. As of 16th December 2020, countries with the highest number of COVID-19 patients were USA, India, Brazil, Russia and France (Table 2) [77]. The world population review of 2020 [78] records the smoking rate of these countries. Russia is leading with 40.90% followed by France (27.70%), USA (17.25%), Brazil (15.30%) and India (11.15%). Owing to the disastrous outbreak in the USA, the New York City mayor proclaimed “If you are a smoker or a vaper that does make you more vulnerable” [79].

Reports on upregulation of ACE2 by CS are coming in connection with COVID-19 outbreak. An increased expression of ACE2 was observed in the lung tissues from COPD and healthy smokers [80]. An elevated level of ACE2 was observed in the airway epithelium and oral epithelium of smokers when compared with non-smokers. A dose and time-dependent effect of CS on the expression of ACE2 was observed in the lung tissues of mouse models [81] and the small airway epithelium of smokers and COPD patients [82]. Contradictory

Table 1 Smoking status of COVID-19 patients

No. of subjects studied	No. of deaths reported	Others (severe and non-severe)	Current smokers	Former smokers
191 patients [71]	54	137	9% (died) 4% (others)	No information
140 patients [72]	Nil	58 severe 82 non-severe	3.4% (severe) 0% (non-severe)	6.9% (severe) 3.7% (non-severe)
41 patients [22]	6	7 severe 28 non-severe	0% (severe) 11% (non-severe)	No information
1099 patients [73]	Nil	173 severe 926 non-severe	16.9% (severe) 11.8% (non-severe)	5.2% (severe) 1.3% (non-severe)
78 patients [74]	2	9 severe 67 non-severe	27.3% of smokers (death and severe) 3% of smokers (non-severe)	

Table 2 COVID-19 and smoking index

Countries (as of 16th December 2020)	No. of infected [77] ≈M	No. of deaths reported ≈M	Smoking rate [78]	Male smokers	Female smokers	Total population ≈M
USA	17.14	0.31	17.25%	19.50%	15%	331
India	9.93	0.14	11.15%	20.40%	1.90%	1380
Brazil	6.97	0.18	15.30%	19.30%	11.30%	212
Russia	2.71	0.05	40.90%	59%	22.80%	145
France	2.39	0.06	27.70%	29.80%	25.60%	65

statements on ACE2 regulation by smoking have been reported [83, 84]. Smokers may have a higher risk to COVID-19 infection since nicotine can directly impact the putative receptor for the virus, ACE2, and lead to deleterious effects [83], whereas reports also propose nicotine and nicotinic orthosteric and/or allosteric agents as a possible therapy for SARS-CoV-2 infection [84]. Due to the above shown contradictory nature of role of ACE2 in COVID-19 infection and the incompleteness of segregating the subjects of study as smokers, smokers who left smoking and nonsmokers as well as studies showing indifference to the above mentioned smoking groupings in the studies of the impact of air pollution on COVID-19 infection, we have not considered it further in this review.

Conclusions

In the present world of COVID-19, are there any implications related to air pollution? It has to be proved. On the fiftieth anniversary of World Earth Day, we are still demanding the same “Clean Air”. As many policies are implemented worldwide to protect from SARS-CoV-2 one simple remedy that we forgot was clean air can save lives. SARS-CoV-2 infects our lungs and air pollution makes us more susceptible. Smoke, either biomass combustion or from cigarettes, is a proved threat to mankind years back. Either by the upregulation of ACE2, down-regulation of the immune system or by severe respiratory injury smoking contributes directly to the negative progression of this pandemic. WHO Framework Convention on Tobacco Control (FCTC) secretariat was developed against the tobacco pandemic. Many countries failed to implement the aspects of FCTC. Today, several countries are suffering badly, as they failed to approve FCTC [85]. In this crucial situation, the focus is only on the main threat; all other conditions are only in words to console the situation.

Abbreviations

SARS: Severe acute respiratory syndrome; MERS: Middle East respiratory syndrome; COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2; ACE: Angiotensin-converting enzyme; 2019-nCoV: 2019 Novel coronavirus; UTR: Untranslated region; RNA: Ribonucleic acid; NTD: N-terminal domain; CTD: C-terminal domain; hACE2: Human ACE2; RAS: Renin-angiotensin system; Ang: Angiotensin;

AT₁R: Angiotensin type-1 receptor; AT₂R: Angiotensin type-2 receptor; ADAM: A disintegrin and metalloproteinase; NEP: Nephilysin; CRP: C-reactive protein; INF I: Interferon type-I; ASL: Airway surface liquid; WHO: World Health Organization; PM: Particulate matter; CO: Carbon monoxide; SO₂: Sulfur dioxide; O₃: Ozone; NO₂: Nitrogen dioxide; COPD: Chronic obstructive pulmonary diseases; CS: Cigarette smoke; HPHC: Harmful and potentially harmful constituents; MAPK: Mitogen-activated protein kinase; ICU: Intensive care unit; USA: United States of America; FCTC: Framework Convention on Tobacco Control

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The authors declare that all the data collection and preparation of the manuscript were done by themselves. VV collected the data and helped manuscript preparation. AS and MH critically revised and gave final shape to the manuscript. The authors read and approved the final manuscript.

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