sciendo

Acta Pharm. **73** (2023) 29–42
https://doi.org/10.2478/acph-2023-0002

Mini-review

Intensive critical care and management of asthmatic and smoker patients in COVID-19 infection

DONGMING LU[1]
OBAID YAQOOB[2]
MANISH KUMAR[3,4]
AJAY SINGH KUSHWAH[2,*]
RAHUL KUMAR SHARMA[2]
DEVINDER KUMAR[2]
YOGENDRA MAVAI[5]
RUKAIYA KHAN[6]

[1] *Department of Pulmonary and Critical Care Medicine, Jinling Hospital Nanjing University School of Medicine Nanjing, Jiangsu, 210000, China*

[2] *Department of Pharmacology, Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela (An Autonomous College), Ropar, Punjab 140111, India*

[3] *Chitkara College of Pharmacy, Chitkara University,Punjab, 140401, India*

[4] *Department of Neurosurgery College of Medicine, Penn State Health Milton S. Hershey Medical Center The Pennsylvania State University Pennsylvania 17033-0850, USA*

[5] *IPS College of Pharmacy, Shivpuri Link Road Gwalior, M.P., 474001, India*

[6] *Abhilashi College of Pharmacy, Nerchowk Mandi, H.P., 175008, India*

Accepted August 1, 2022
Published online August 1, 2022

ABSTRACT

This century's most serious catastrophe, COVID-19, has been dubbed "the most life-threatening disaster ever". Asthmatic persons are even more prone to COVID-19's complex interplay with the underlying inflammatory condition. In order to protect themselves against COVID-19, asthmatic patients must be very vigilant in their usage of therapeutic techniques and drugs (*e.g.*, bronchodilators, 5-lipoxygenase inhibitors), which may be accessed to deal with mild, moderate, and severe COVID-19 indications. People with asthma may have more severe COVID-19 symptoms, which may lead to a worsening of their condition. Several cytokines were found to be elevated in the bronchial tracts of patients with acute instances of COVID-19, suggesting that this ailment may aggravate asthma episodes by increasing inflammation. The intensity of COVID-19 symptoms is lessened in patients with asthma who have superior levels of T-cells. Several antibiotics, antivirals, antipyretics, and anti-inflammatory drugs have been suggested to suppress COVID-19 symptoms in asthmatic persons. Furthermore, smokers are more likely to have aggravated repercussions in COVID-19 infection. Being hospitalized to critical care due to COVID-19, needing mechanical breathing, and suffering from serious health repercussions, are all possible outcomes for someone who has previously smoked. Smoking damages airways and alveoli, which significantly raises the risk of COVID-19-related health complications. Patients with a previous record of smoking are predisposed to severe COVID-19 disease symptoms that essentially require a combination of bronchodilators, mucolytics, antivirals, and antimuscarinic drugs, to cope with the situation. The present review discusses the care and management of asthmatic and smoker patients in COVID-19 infection.

Keywords: COVID-19, asthma, smoking, critical care, SARS-CoV-2

*Correspondence, e-mail: kushwah_ph05@yahoo.co.in; ajay@copbela.org

AN OVERVIEW OF COVID-19

Coronavirus is a genus of viruses that may infect people, birds, and animals, producing colds, coughs, fevers, and alveolar pneumonia-like symptoms, such as shortness of breath. COVID-19 is hailed as the utmost severe epidemic of the 21stcentury. It was widely assumed at the onset that it began at a seafood market in Wuhan, China (1). The World Health Organization (WHO) designated this virus the 2019-nCov, which is a scientific word meaning "new" (n for a novel). Bats are thought to be the virus's natural reservoir since traces of the virus were detected in bats for the first time. SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2), COVID-19, the 2019 Novel Coronavirus (2019-nCov), the 2019 Coronavirus, and the Wuhan Coronavirus are all names for this neoteric virus. Because of the high rate of transmission, people are more susceptible to this viral illness. Fever, tiredness, dry cough, sore throat, and breathing problems are common symptoms in COVID-19 patients (2). On January 30, 2020, COVID-19 has asserted a public health crisis, and on March 11, 2020, it was pronounced a worldwide pandemic (3). The most impacted countries were the United States, India, France, Germany, United Kingdom, Italy, China and Brazil. In July 2022, approx. 580 million total cases of Covid-19 worldwide were recorded, and still, there are about 23.5 million total active cases as of July 31, 2022. Approximately 550 million people have recovered, yet about 6.4 million people have died. COVID-19 positive cases were confirmed in about 44 million persons in India, with a recovery rate of around 98 %. This virus has a 5.1-day incubation period on average (2–14 days). COVID-19 symptoms include fever, lethargy, dry cough, muscular discomfort, dyspnea, pneumonia, and, in many instances, a reduction in leukocyte counts. In addition to the aching (tender) pharynx, diarrhoea, pink eye (inflammation of the conjunctiva), headache, skin rashes, and discolouration of the fingers, digits, or toes, COVID-19 symptoms include high temperature, chills and tiredness (4). COVID-19 was first thought to be a widespread respiratory illness in 2020, however, it was subsequently discovered that persons with asthma and smokers would be at an elevated risk of severe disease and death (5). Smoking and using E-cigarettes both increase the likelihood and severity of lung infections, owing to the damage done to the upper airways and the resulting loss in pulmonary immune function. Smokers, in particular, are at an elevated hazard of illness and death owing to coronavirus infection (6). In this review, we focus on the link between COVID-19 and asthma/smoking, as well as their treatment.

ASTHMA AND COVID-19

Hazards of COVID-19 to asthmatic patients

People of all ages may suffer from asthma, including children, adults and the elderly. Asthma is defined by a rise in hyper-responsiveness to the tracheobronchial structures caused by a variety of peripheral provocations, which finally narrow the airway tract. Asthma is described as "a long-term inflammatory condition that aggravates the airway pathogenesis in the lungs and necessitates numerous cells and organelle components" (7), according to National Institutes of Health (NIH) recommendations from 1991, 1997 and 2007. Around 339 million people worldwide suffer from asthma and associated symptoms in some form. Even industrialized nations are not immune to its effects; thousands of

individuals in the United States suffer asthma-like symptoms. In India, it is estimated that one in every three adults suffers from asthma. Coughing fits, wheezing fits, shortness of breath (dyspnea), and chest tightness, are the most likely/common asthma symptoms (8, 9). Many allergens may induce bronchospasm, constriction, respiratory tract infection, hypersensitivity reactions, and contraction of the airway zone, which can make inhalation (or exhalation) difficult. Allergens may also play a role in these responses; however, exercise may also trigger them. Some medications, such as morphine, non-steroidal anti--inflammatory medicines (NSAIDs, such as indomethacin, ibuprofen, fenoprofen, ketorolac, and naproxen), β-antagonists, and angiotensin-converting enzyme (ACE) blockers, for example, perindopril, lisinopril, ramipril, and enalapril (by causing coughing), might exacerbate asthma symptoms (10).

Asthma is a systemic condition that starts with the activation of a large number of inflammatory cells, causing lasting alterations in the lower and upper respiratory organs. These modifications in the shape of the bronchial tract are referred to as airway remodelling. Repeated inflammation stimulus *via* matrix peptides and growth factors generated by inflammatory biomolecules and immune cells causes these alterations (11).

COVID-19 aetiology is more likely to deteriorate in the elderly and those with a medical history of diabetes, severe asthma or heart disease. Although it is thought that people with chronic asthma who are infected with the virus may have poorer results, COVID-19 may increase asthma symptoms in severe asthmatics, much like other viral diseases. Many cytokines, including interleukins (*e.g.*, IL-1, IL-6, IL-12), tumour necrosis factor-α (TNF-α), interferon-γ (IFN-γ) and others, have been shown to be higher in the blood of COVID-19 positive individuals, which may have implications for lung inflammation and injury.

SARS (severe acute respiratory syndrome) is a kind of acute respiratory syndrome. The heart, blood arteries, lungs, and gut of the host cell are where Coronavirus 2 (SARS--CoV-2) connects to ACE-2 receptors. As a result, COVID-19 is provided to asthmatic patients with significant respiratory symptoms. A sizable fraction of patients have ARDS (acute respiratory distress syndrome), and as a result, the painful symptoms are linked to real hyper cytokinesis specific for IL-6, which may lead to mortality (12).

Asthma is most usually caused by respiratory viruses. Among the causes of asthma aggravations, the human rhinovirus is recognized as the most potent and frequent. SARS--CoV-2 is also linked to the progress of asthma, which is a hazard marker for the COVID--19-linked injury. COVID-19 causes shortness of breath and a dry cough, and it's also linked to moderate asthma worsening. High temperature is more than often associated with COVID-19, although it may also be detected in some infection-related aggravation of asthma. As a result, COVID-19 screening techniques are required for everyone with respiratory issues or asthma (13).

As a first-line treatment, severe asthma is managed using inhalers and biological agents/drugs, such as omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab. Other therapy alternatives, such as bronchial thermoplasty (B.T.), are the two mainstay therapies for severe asthmatics that have not been able to manage their symptoms after receiving their first treatment. If any patient has an acute attack, they should contact their physicians if their symptoms worsen. Assume that your severe asthma is under control: there is no need to go to the hospital on a frequent basis in such instances. Patients who meet the emergency requirements must be sent to the hospital right away (14).

Researchers from Rutgers University in New Jersey discovered that individuals with no indicators of asthma had nil greater hazard of contracting COVID-19 compared to asthmatic individuals. Researchers identified a drop in T-cell levels in COVID-19, while asthmatic individuals with COVID-19 had higher circulating T-lymphocyte expression, which seems to safeguard them from the severity of SARS-CoV-2 (15).

Critical care and management of COVID-19 with asthma

A number of monoclonal antibodies that target type-2 inflammatory pathways and hence, prevent asthma attacks are the most often recommended medications in the treatment of asthma. Omalizumab, anti-IL-4 and anti-IL13 antibodies are found to decrease the worsening of asthmatic symptoms as another kind of therapy. Asthma and COVID-19 have an inflammatory burst trait, making it possible to treat them both with the same treatment. Because of this, anti-inflammatory medicines and biologicals (*e.g.*, monoclonal antibodies) may be used to treat both of these respiratory conditions by targeting a distinct yet common route. Clazakizumab (NCT04343989), tocilizumab (NCT04306705, NCT04346355), and siltuximab (NCT04330638) have all been tested in clinical studies to see how they affect IL-6 in patients (16, 17).

Critical care and management of mild cases of COVID-19 with asthma

Patients with asthma who are tested positive for the virus must be quarantined promptly so as to halt the spread of the infection. The affected subject must be isolated in a confined area that has adequate oxygenation. To keep track of the patient's status, a medical checkup must be performed on a regular basis. Local First Referral Units (FRUs), COVID Care Centers, or district/regional community health care centres may treat mild symptoms. The patient's medical history must be documented. Every day, the temperature and oxygen saturation levels must be monitored. A patient's additional risk factors must be taken into consideration. In the event of an emergency, transport the patient to a local COVID hospital. Maintaining an oxygen saturation level (SpO_2) higher than 94 % is required. Antipyretics such as paracetamol should be used in the event of a fever. In order to avoid a dry cough, antitussives may be prescribed. Food and water must be provided to the sufferer (patient) in order for them to recover. If the patient has shortness of breath, he or she should use an emergency inhaler provided by their doctor. Inhaling salbutamol, an alpha-2 agonist, is usually all that is needed to avoid an attack. Prophylactic usage of antimalarial medicine hydroxychloroquine may be administered to those individuals with hazard issues of more serious illnesses or patients over the age of sixty (averted in case QTc is > 480 ms). Supplemental vitamin C and zinc pills may be used. Hydroxychloroquine may be supplied as a preventative precaution to healthcare workers, such as police and paramilitary, who have direct touch with patients. On day 1, they may take 400 mg b.d., trailed by 400 mg one time in 7 days for the next 49 days as the official regimen. Even though children under the age of 15 are not allowed to use it, nursing mothers, and individuals with cardiovascular issues are. Paracetamol is used to treat fever. Favipiravir (favilavir), an anti-influenza medication, was recently licensed for use in India for mild to moderate cases. An RNA polymerase inhibitor having an affinity for RNA viruses is the powerful RNA-dependent RNA polymerase (RNA replication) blocker. In clinical settings, a loading dose of 1.8 g two times on 1st day, which is trailed by a maintenance dose of 0.8 g b.d., and is continued for 7 days, is commonly followed (18–20).

Critical care and management of moderate cases of COVID-19 with asthma

Patients with mild COVID-19 indicators, such as pneumonia, copious bronchial secretions, and chest blockage, must be kept in isolation at the outset, and if their condition worsens, they should be transported to a neighbouring emergency centre. The most important clinical parameters, such as respiratory rate and SpO_2, should be checked on a regular basis. A pulse oximeter should always be used to assess oxygen levels. A comprehensive blood count (CBC) accompanied by entire lymphocyte enumeration, renal tests, hepatic markers estimation, 12-lead ECG, X-ray of the thoracic cavity, assessing vital indicators (*e.g.*, breathing, HR), *etc*., should be performed in order to properly examine the patient. In case SpO_2 goes less than the usual limits, oxygen is administered. PCM 500 mg is a common antipyretic that is used three times daily. If necessary, an antitussive is administered. On the first day, 400 mg of hydroxychloroquine is taken twice a day, trailed by 200 mg two times a day for the next 4 days following the correct ECG check (hydroxychloroquine shall be averted if QTc is > 480 ms). When it comes to treating moderate asthma, beta-2 agonists and steroids such as the combination of salmeterol + fluticasone propionate, formoterol + budesonide, *etc*., have been excellent options. Reduced incidence of asthmatic exacerbation has also been shown with the usage of leukotriene receptor antagonists, for instance, montelukast and zafirlukast, as well as 5-lipoxygenase (5-LOX) inhibitors, for instance, zileuton. Methylprednisolone (0.5–1 mg kg^{-1}, *i.v.*) is given for 3 days in the presence of elevated inflammatory markers. Antibiotics such as azithromycin (500 mg, *p.o.*) once a day and ceftriaxone (1 g, *i.v.*) two times a day, are administered in the co-presence of secondary bacterial infections. Patients exhibiting minor indicators may be offered experimental medications like remdesivir or tocilizumab. Steroids (0.1–0.2 mg kg^{-1}) or methylprednisolone (0.5–1 mg kg^{-1}) are given intravenously for five days (18–20).

Critical care and management of severe cases of COVID-19 with asthma

It is necessary to provide intensive treatment to patients with severe COVID-19 symptoms and asthma. To treat shock or hypoxemia, such individuals must be supplied oxygen quickly. Oxygen is administered at 5 L min^{-1} up to SpO_2 is 93–97 %. Children under the age of 15 are vented to keep their SpO_2 levels above 94 %. Various kinds of oxygen masks, such as a basic face mask, a nasal cannula, and a mask with a storage-buffer bag, shall every time be available on hand for patients' use. The use of a high-flow nasal cannula (HFNC) for oxygen administration is used if normal oxygen therapy is not being tolerated by patients. HFNC produces 100 % humidified and heated (37 °C) oxygen at a flow rate of 60 L min^{-1}. Observation of fluids must be carried out on a frequent basis. Chronic medical monitoring is necessary for patients with ARDS who need daily ventilation for 16–18 hours. In the event of a subsequent bacterial infection, azithromycin 500 mg tablet once a day and piperacillin/tazobactam (4.5 mg *i.v.*) are administered t.d. for five days. For the first hour, high dosages of inhaled beta-2 agonists are administered, which may be taken for up to four hours. In certain cases, anticoagulants like enoxaparin injection may be necessary. A dosage of 400 mg b.d. for one day trailed by 200 mg b.d. for 14 consecutive days is also an option for medications like hydroxychloroquine. Lopinavir 400 mg or ritonavir 100 mg b.d. will be given for the following 14 days. Tocilizumab immunomodulatory treatment may be completed as well if desired. Steroids with a dose range of 0.2–0.4 mg kg^{-1} or methylprednisolone in doses of 1–2 mg kg^{-1} are administered intravenously

over the course of a 10-day period. First-day administration of 200 mg *i.v.* of remdesivir may be trailed by five days of 100 mg *i.v.* for moderate to severe patients. Sputum, CBC, culturing the pleural fluid, and SpO_2 must all be monitored on a regular basis in the event that a patient has pneumonia. Severe acquired pneumonia may be controlled for the

Table I. Basic care and treatment options for COVID-19 positive asthmatic patients

Mild cases	Ref.
Attack aversion by β_2 agonists (*e.g.*, salbutamol *via* nasal route)	1
Multivitamin supplements, for example, vitamin C, D, E and zinc	1, 12
Anti-tussive, *e.g.*, dextromethorphan, benzonatate	1, 14
Persons working in healthcare: As prophylactic hydroxychloroquine (400 mg two times on 1st day up to 49 days with 400 mg once every 7 days (contraindicated < 15 years age, breastfeeding mothers, and cardiovascular patients)	1
Antipyretics (*e.g.*, paracetamol) in high body temperatures	13
Anti-influenza therapy (*e.g.*, favipiravir 1.8 g b.d. on 1st day, 0.8 g b.d. for 14 days)	1
Moderate cases	
If SpO_2 < 92 % then O_2 provided	13
Hydroxychloroquine (400 mg b.d. on 1st day, 200 mg b.d. 2nd day onwards up to 6th day)	14
Multivitamins and supplements, *e.g.*, vitamin C and zinc tablets	18
Anti-tussive, *e.g.*, dextromethorphan, benzonatate	1
Avert asthma (β_2 agonists +corticosteroids,*e.g.*, salmeterol + fluticasone propionate, or formoterol + budesonide, *etc.*)	14
Antipyretics (paracetamol) for high body temperature	1
Abrogate asthmatic aggravation (leukotriene receptor antagonist,*e.g.*, montelukast, zafirlukast and 5-lipoxygenase inhibitor, *e.g.*, zileuton)	16
Methylprednisolone (0.5–1 mg kg^{-1} day 1–3, *i.v.*) to abolish inflammatory cascade	14
Azithromycin (500 mg o.d. for 5 days), ceftriaxone (1000 mg, *i.v.* b.d. for 5 days for bacterial infection	18
Remdesivir or tocilizumab in moderate symptoms as investigational drugs	19
Severe cases	
O_2 5 L min^{-1} till SpO_2 is > 92–96 %	1, 20
Children < 15 years of age are aerated to retain SpO_2 > 94 %	1
Vitamin C and zinc tablets	1
Anti-tussive, *e.g.*, dextromethorphan, benzonatate	1, 12
High β_2 agonists doses after 15–20 min to 240 min	1, 13
Hydroxychloroquine (400 mg b.d. on 1st day, 400 mg b.d. 2nd day onwards up to 14th day)	19
Lopinavir or ritonavir (100 mg b.d.) against viral infection	18
Antipyretics (paracetamol) in high body temperature	13
Remdesivir (200 mg *i.v.* 1st day and 100 mg 2nd – 5th day)	19
Doxycycline oral 200 mg tablet on 1st day and 100 mg from 2nd – 6th day (for severe acquired pneumonia)	1, 13 20
Azithromycin (500 mg o.d. for 5 days), piperacillin/tazobactam (4.5 mg *i.v.* t.d. for 5 days)	19
Dexamethasone (0.2–0.4 mg kg^{-1}) or methylprednisolone (1–2 mg kg^{-1}) for 10 days	18

following 5 days with doxycycline 200 mg tablet (oral route) on 1stday, trailed by 100 mg (18–20). Table I shows the specific therapy recommendations centred on the seriousness of the COVID-19 indicators.

SMOKING AND COVID-19

A risk of COVID-19 to smokers

More than 1.1 billion people throughout the world smoke every day, and the contemporary figure is expected to soar to 1.3 billion by 2025 as reported by the WHO (21). It is believed that tobacco smoke contains more than 5,000 different compounds, many of which are known carcinogens or poisons (22), and that this combination is the primary source of exposure for both humans and other living species (23). When it comes to the progress and aggravation of several breathing disorders involving microbial invasion as well (24, 25), smoking is a key hazard component. Chronic obstructive pulmonary disease (COPD) and lung melanoma are both clearly linked to tobacco smoking in general (26, 27). It has also been shown that COVID-19 advances more rapidly in COPD patients. Because smoking is a significant element in the progress of COPD, it may have a comparable influence on symptoms (23, 26). Smoking was shown to have no effect on the severity of COVID-19 in a recent meta-analysis (6). The heterogeneity among the studies was modest in this meta-analysis, which comprised just five investigations in total (1).

Suffice it to say that smoking has been linked to an expanded hazard of community--acquired pneumonia (CAP) (28, 29) owing to the disruption of respiratory epithelial repair and healing caused by tobacco smoke. One of the most significant risk factors for a respiratory tract infection is smoking, for instance, active, passive and third-hand smoke exposure, all of which include the act of smoking cigarettes (30, 31). Smoking has long been recognized to have a detrimental effect on lung health. Smoking damages the immune strength in the respiratory tract, which renders smokers highly predisposed to undeterred microbial invasions, as previously stated (32). Tobacco smoking has been linked to Middle East Respiratory Syndrome (MERS) infection and death in previous studies (33, 34). There was a greater risk of MERS-related death among smokers compared to non/never-smokers (35). The fact that both MERS-CoV and SARS-CoV-2 are representatives of the Coronaviridae family isn't enough to render people additionally vulnerable to SARS infection with CoV-2 or a worsening of the prognosis of COVID-19.

Critical care and management of COVID-19 patients with a smoking history

COVID-19 development is hampered by smoking. In comparison to non-smokers, smokers display a far greater chance of contracting COVID-19 contamination. All communities across the globe have a high prevalence of tobacco smoking (36). An estimated 8–8.5 million people die each year as a result of their dependence on cigarettes. Tobacco smoking exacerbates the issue because COVID-19 spreads by salivary droplets and triggers acute lung pneumonia in humans. Smokers present a bigger probability of COVID-19 illness because of their reduced lung performance and prone to cleanliness behaviours (37). Exhaled smoke, coughing, and salivary droplets contaminated with SARS-COV-2 from infected individuals pollute surfaces, posing health risks to those who breathe in this

contaminated air (38). The WHO has issued a number of recommendations for preventing the spread of viral illnesses, including washing hands for 15–20 seconds with soap and water and using an alcohol-based sanitiser after every encounter. Keep a 1-meter space between you and the next person. Despite this, keep your hands away from your eyes, nose and mouth (39). Tobacco smoking cessation and a reduction might be an effective way to slow the transmission of the virus. Because of this, governments and the general public alike should enact and enforce stringent measures to reduce smoking (40). Smokers should be segregated and only allowed to smoke in designated places that meet strict cleanliness requirements (such as cigarette holders or filters) and have enough ventilation. Conventional cigarettes, electronic cigarettes, and water pipes should not be used for re-use or sharing. After a single usage, cigarette stubs, gadgets, and their attachments should be thrown away to avoid spreading the disease. For those who want to quit smoking, therapeutic nicotine formulations may also be utilized in the process. Nicotine (41) reactivates the nicotine cholinergic system, which had been rendered dysfunctional. Nicotine is widely accepted and has been used for decades due to its low cost and attractive safety compliance (42). On the other hand, since it may be purchased over the counter, there is a risk of abuse

Table II. Therapeutic options for COVID-19 positive smoker patients

Therapy	Ref.
Salbutamol (β_2 agonists): 1–2 puffs if breathlessness occurs up to a maximum of 4–5 times a day[a]	14, 19, 25
Formoterol (β_2 agonists): 12 μg (inhalation) every 12-hour maximum dose 24 μg	19, 26
Indacaterol (β_2 agonists): 75 μg orally once a day	26
Terbutaline (β_2 agonists): 250 μg, 3 to 4 times per day by nebulizer	13
Ipratropium (antimuscarinic): 500 mg *via* nebulizer 3 or 4 times per day	13, 14, 26
Tiotropium(antimuscarinic): 2.5 μg, maximum dose 2 puffs per day	14, 25
Gylcopyronium (antimuscarinic): 25 μg, *i.e.*, one inhalation b.d.	14, 26
Aclidinium (antimuscarinic): 400 μg, *i.e.*, one inhalation b.d.	1
Beclomethasone dipropionate: 800 μg daily	14, 25
Budesonide: 200 μg, 2 inhalations orally twice a day, max dose is 4 inhalations	1
Theophylline: Not more than 400 mg per day	1
Carbocisteine syrup (mucolytic): 15 mL t.d.	14
Carbocisteine capsule (mucolytic): 375 mg t.d.	13, 14
Doxycycline: 100 mg daily	19, 20
Azithromycin: 250–500 mg daily for 1 week	18, 20
Roflumilast: 250 μg per day for 28 days, max dose is 500 μg per day for 28 days	19, 20
O_2 therapy: 16 hours a day or as required	1, 19
Nicotine replacement therapy	41
Varenicline (reduce crabbing for nicotine)	41
Antipyretics (*e.g.*, paracetamol) in high body temperatures	18, 19
Anti-influenza therapy (*e.g.*, favipiravir 1.8 g b.d. on 1st day, 0.8 g b.d. for 14 days)	1, 18-20
Remdesivir or tocilizumab	19, 20

[a] 1 puff = 100 μg

(41). As smoking happens to be the single chief reason for severe respiratory disorders such as COPD and emphysema, hence, treatment of these in the ailing patient becomes mandatory even in the presence of COVID-19 symptoms (Table II).

Correlation between angiotensin-converting enzyme (ACE), smoking and COVID-19

In regard to COVID-19, ACE-2 has garnered all the limelight on the planet (43). These include the respiratory system, the heart, and the digestive system (44). ACE-2 is a type II trans-membrane metallocarboxypeptidase subtype that converts angiotensin II into a variety of metabolites, including angiotensin 1–9 and 1–7 (45, 46). Type-II pneumocytes exhibit the presence of ACE-2 (47). It has a critical role in the control of blood pressure and heart activity, however, its involvement in the thoracic cavity is less clear (48, 49). In spite of the fact that certain research has shown no correlation between the ACE-2 genetic polymorphism and COVID-19 invasion, numerous other investigations have found that the receptor plays a major effect (50–53). The structural similarity between the ACE-2 receptor and the coronavirus promotes their interaction (54). Studies demonstrate that smokers reveal an enhanced appearance of the ACE-2 receptor relative to non-smokers (55, 56). SARS-CoV-2 infection may be more likely to occur in smokers because of this (57). New approaches to treating COVID-19, in particular in smokers, may benefit from therapeutic targeting of ACE-2 (Fig. 1).

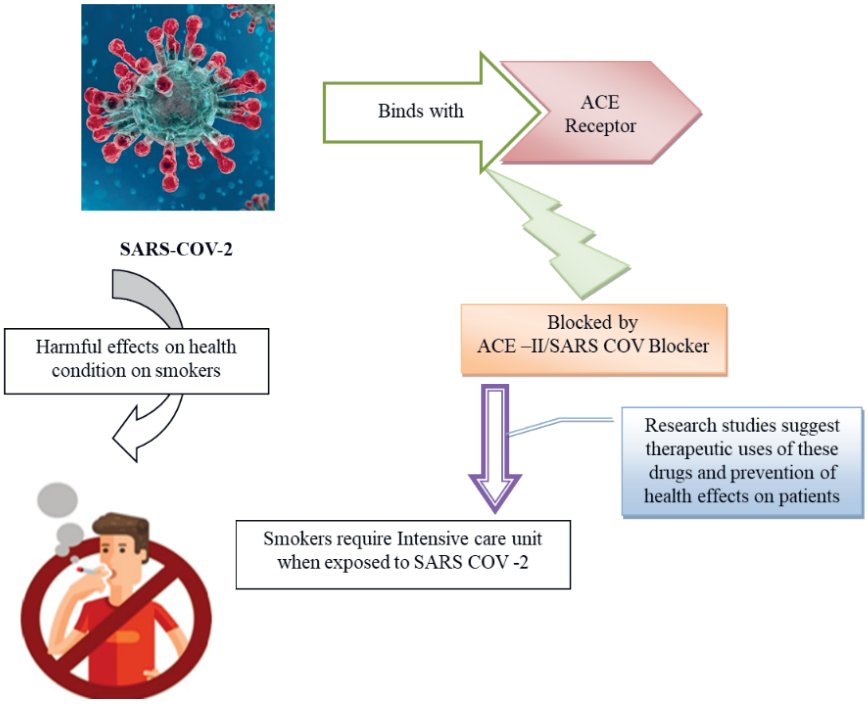


Fig. 1. Relation between SARS-CoV 2 and ACE-2 receptor in smoking patients.

Critical care and management of COVID-19 with an asthmatic patient with a smoking history

Tobacco abuses and asthma in COVID-19 patients both have significant negative implications on the patient's overall health, prognosis and treatment options. Compared to non-smokers with asthma, smokers with asthma had a greater risk of developing COVID-19 illness. Smoking in asthma patients with the COVID-19 virus alters airway inflammation, ACE-2, and corticosteroid insensitivity, all of which contribute to the negative consequences of smoking. While quitting smoking in a COVID setting may help alleviate symptoms and improve lung function, the poor success rate of this strategy underscores the need for new approaches to the care of these individuals.

Many transcriptome data sets of lung samples from healthy never- and ever-smokers and asthmatic patients show that ACE-2 gene expression is up-regulated in smokers relative to non-smokers. ACE-2-producing goblet cells are also found in the lungs of those who have ever smoked compared to those who have never smoked. Many components of the RAS (renin-angiotensin system) are affected by nicotine's action in the body's many organ systems; nicotine up-regulates renin, ACE, and AT1R expression and activity in the ACE/AT-II (angiotensin II)/AT1R 1-7 arm, while downregulating ACE2 and AT2R expression and activity in the compensatory ACE-2/angiotensin 1–7 arm. SARS-CoV-2 may get passage into the lungs more easily *via* the bronchial epithelium of asthmatics who smoke cigarettes, but this does not always mean that they are at greater risk of getting COVID-19 pneumonia.

CONCLUSIONS

The COVID-19 outbreak rocked the globe since it poses a serious danger to human health. Considering the COVID-19 epidemic, severe asthma treatment is now a major issue that will continue until herd immunity is developed soon. Some cytokines have increased in severe instances of COVID-19, and this might aggravate asthma attacks by causing more inflammation in the bronchial tracts. More research is required, but it seems that biologicals for acute/critical asthma might not raise the possibility of infection or serious COVID-19 and may even be beneficial. Smoking and COVID-19 have been shown to have a direct relationship, with smokers being more susceptible to the infection than non-smokers. Increased ACE-2 levels are linked to an enhanced danger of SARS-COV-2 illness in those who smoke. Individuals' susceptibility to the COVID-19 infection may be reduced by treating ACE-2 and quitting smoking. SARS-COV-2 transmission may be slowed down by reducing or quitting smoking. Smoking is a major issue in the current pandemic and cessation of smoking poses a huge challenge to the healthcare system across the globe. Smoking cessation must be amongst the primary goals in anti-COVID-19 strategies and also a general health improvement and well-being of people.

Abbreviations, acronyms, symbols. – 2019-nCov – 2019-novel coronavirus, 5-LOX – 5-lipoxygenase, ACE – angiotensin-converting enzyme, ARDS – acute respiratory distress syndrome, AT1R – angiotensin II type 1 receptor, AT-II – angiotensin II, b.d. – *bis in die*, B.T. – bronchial thermoplasty, CAP – community-acquired pneumonia, CBC – comprehensive blood count, COPD – chronic obstructive pulmonary disease, COVID-19 – Coronavirus disease 2019, ECG – electrocardiograph, HFNC – high-flow nasal cannula, HR – heart rate, IFN-γ – interferon-γ, IL – interleukin, MERS – Middle East Re-

spiratory Syndrome, NSAIDs – non-steroidal anti-inflammatory drugs, o.d. – *omni die* (every day, once daily), QTc – QT corrected for heart rate, RNA – ribonucleic acid, SARS – Severe Acute Respiratory Syndrome, SARS-CoV-2 – Severe Acute Respiratory Syndrome Coronavirus 2, SpO_2 – oxygen saturation, t.d. – ter in die (three times a day), TNF-α – tumor necrosis factor-α.

Acknowledgments. – We are thankful to Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela (an autonomous college) Ropar (Punjab) to provide the necessary facilities for the completion of this study.

Author's contribution. – Dongming Lu(conception and design of content and critical revision of the article); Obaid Yaqoob (literature survey and drafting of the article); Manish Kumar (English language editing and critical revision of the article); Ajay Singh Kushwah (conception and design of content, write the article; corresponding author); Rahul Kumar Sharma(conceived and designed the content); Devinder Kumar (English language editing and proofreading); Yogendra Mavai (literature survey and critical revision of the article) and Rukaiya Khan (proofreading and language editing).

Conflicts of interest. – The authors declare no conflicts of interest.

Funding. – This research has not received any specific grant

REFERENCES

1. S. Ghosh, S. Das, R. Mondal, S. Abdullah, S. Sultana, S. Singh, A. Sehgal and T. Behl, A review on the effect of COVID-19 in type 2 asthma and its management, *Int. Immunopharmacol.* **91** (2021) Article ID 107309 (13 pages); https://doi.org/10.1016/j.intimp.2020.107309
2. D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang, B. Wang, H. Xiang, Z. Cheng, Y. Xiong, Y. Zhao, Y. Li, X. Wang and Z. Peng, Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China, *JAMA* **323**(11) (2020) 1061–1069; https://doi.org/10.1001/jama.2020.1585
3. O. I. Oyeniran and T. Chia, Novel coronavirus disease 2019 (COVID-19) outbreak in Nigeria: how effective are government interventions?, *Ethics Med. Public Health* **14** (2020) Article ID 100515 (2 pages); https://doi.org/10.1016/j.jemep.2020.100515
4. Q. Li, X. Guan, P. Wu, X. Wang, L. Zhou, Y. Tong, R. Ren, K. S. M. Leung, E. H. Y. Lau, J. Y. Wong, X. Xing, N. Xiang, Y. Wu, C. Li, Q. Chen, D. Li, T. Liu, J. Zhao, M. Liu, W. Tu, C. Chen, L. Jin, R. Yang, Q. Wang, S. Zhou, R. Wang, H. Liu, Y. Luo, Y. Liu, G. Shao, H. Li, Z. Tao, Y. Yang, Z. Deng, B. Liu, Z. Ma, Y. Zhang, G. Shi, T. T. Y. Lam, J. T. Wu, G. F. Gao, B. J. Cowling, B. Yang, G. M. Leung and Z. Feng, Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia, *N. Engl. J. Med.* **382** (2020) 1199–1207; https://doi.org/10.1056/NEJMoa2001316
5. J. Hartmann-Boyce, J. Gunnell, J. Drake, A. Otunla, J. Suklan, E. Schofield, J. Kinton, M. Inada-Kim, F. D. R. Hobbs and P. Dennison, Asthma and COVID-19: review of evidence on risks and management considerations, *BMJ Evid-Based Med.* **26**(4) (2021) Article ID 195 (8 pages); https://doi.org/10.1136/bmjebm-2020-111506
6. I. B. Ahluwalia, M. Myers and J. E. Cohen, COVID-19 pandemic: an opportunity for tobacco use cessation, *Lancet Pub. Health* **5** (2020) e577 (1 page); https://doi.org/10.1016/S2468-2667(20)30236-X
7. J. W. Mims, Asthma: definitions and pathophysiology, *Int. Forum Allergy Rhinol.* **5** (2015) S2–S6; https://doi.org/10.1002/alr.21609
8. J. A. Krishnan, R. F. Lemanske, G. J. Canino, K. S. Elward, M. Kattan, E. C. Matsui, H. Mitchell, E. R. Sutherland and M. Minnicozzi, Asthma outcomes: Symptoms, *J. Allergy Clin. Immunol.* **129**(3) (2012) S124–S135; https://doi.org/10.1016/j.jaci.2011.12.981
9. J. Bousquet, E. Mantzouranis, A. A. Cruz, N. Aït-Khaled, C. E. Baena-Cagnani, E. R. Bleecker, C. E. Brightling, P. Burney, A. Bush, W. W. Busse, T. B. Casale, M. Chan-Yeung, R. Chen, B. Chowdhury, K. F. Chung, R. Dahl, J. M. Drazen, L. M. Fabbri, S. T. Holgate, F. Kauffmann, T. Haahtela, N. Khal-

taev, J. P. Kiley, M. R. Masjedi, Y. Mohammad, P. O'Byrne, M. R. Partridge, K. F. Rabe, A. Togias, C. van Weel, S. Wenzel, N. Zhong and T. Zuberbier, Uniform definition of asthma severity, control, and exacerbations: Document presented for the World Health Organization consultation on severe asthma, *J. Allergy Clin. Immunol.* **126**(5) (2010) 926–938; https://doi.org/10.1016/j.jaci.2010.07.019

10. F. T. Ishmael, The inflammatory response in the pathogenesis of asthma, *J. Am. Osteopath. Assoc.* **111**(11, Suppl. 7) (2011) S11-S17; https://doi.org/10.7556/jaoa.2011.20014
11. C. J. Oliphant, J. L. Barlow and A. N. J. McKenzie, Insights into the initiation of type 2 immune responses, *Immunology* **134**(4) (2011) 378–385; https://doi.org/10.1111/j.1365-2567.2011.03499.x
12. M. Morais-Almeida and J. Bousquet, COVID-19 and asthma: To have or not to have T2 inflammation makes a difference?, *Pulmonology* **26**(5) (2020) 261–263; https://doi.org/10.1016/j.pulmoe.2020.05.003
13. E. M. Abrams, G. W. 't Jong and C. L. Yang, Asthma and COVID-19, *CMAJ* **192**(20) (2020) E551; https://doi.org/10.1503/cmaj.200617
14. T. Tabassum, A. Rahman, Y. Araf, Md. A. Ullah and M. J. Hosen, Management of asthma patients during the COVID-19 pandemic: pathophysiological considerations to address the challenges, *Beni-Suef Univ. J. Basic Appl. Sci.* **11**(20) (2022) Article ID 20 (14 pages); https://doi.org/10.1186/s43088-022-00204-4
15. K. E. J. Philip, S. Buttery, P. Williams, B. Vijayakumar, J. Tonkin, A. Cumella, L. Renwick, L. Ogden, J. K. Quint, S. L. Johnston, M. I. Polkey and N. S. Hopkinson, Impact of COVID-19 on people with asthma: a mixed methods analysis from a UK wide survey, *BMJ Open Resp. Res.* **9** (2022) e001056 (9 pages); https://doi.org/10.1136/bmjresp-2021-001056
16. J. Darveaux and W. W. Busse, Biologics in asthma – The next step toward personalized treatment, *J. Allergy Clin. Immunol.: In Practice* **3**(2) (2015) 152–160; https://doi.org/10.1016/j.jaip.2014.09.014
17. S. Atal and Z. Fatima, IL-6 Inhibitors in the treatment of serious COVID-19: A promising therapy?, *Pharm. Med.* **34** (2020) 223–231; https://doi.org/10.1007/s40290-020-00342-z
18. U. Agrawal, R. Raju and Z. F. Udwadia, Favipiravir: A new and emerging antiviral option in COVID-19, *Med. J. Armed Forces India* **76**(4) (2020) 370–376; https://doi.org/10.1016/j.mjafi.2020.08.004
19. S. Sharma, S. Basu, N. P. Shetti and T. M. Aminabhavi, Current treatment protocol for COVID-19 in India, *Sensors Int.* **1** (2020) Article ID 100013 (3 pages); https://doi.org/10.1016/j.sintl.2020.100013
20. A. Parasher, COVID-19: Current understanding of its pathophysiology, clinical presentation and treatment, *Postgrad. Med. J.* **97** (1147) (2021) 312–320; https://doi.org/10.1136/postgradmedj-2020-138577
21. V. Bilano, S. Gilmour, T. Moffiet, E. T. d'Espaignet, G. A. Stevens, A. Commar, F. Tuyl, I. Hudson and K. Shibuya, Global trends and projections for tobacco use, 1990–2025: an analysis of smoking indicators from the WHO comprehensive information systems for tobacco control, *Lancet* **385**(9972) (2015) 966–976; https://doi.org/10.1016/s0140-6736(15)60264-1
22. R. Talhout, T. Schulz, E. Florek, J. Van Benthem, P. Wester and A. Opperhuizen, Hazardous compounds in tobacco smoke, *Int. J. Environ. Res. Public Health* **8** (2011) 613–628; https://doi.org/10.3390/ijerph8020613
23. M. Ezzati and A. D. Lopez, Estimates of global mortality attributable to smoking in 2000, *Lancet* **362**(9387) (2003) 847–852; https://doi.org/10.1016/s0140-6736(03)14338-3
24. S. J. Brake, K. Barnsley, W. Lu, K. D. McAlinden, M. S. Eapen and S. S. Sohal, Smoking upregulates angiotensin-converting enzyme-2 receptor: A potential adhesion site for novel coronavirus SARS-CoV-2 (Covid-19), *J. Clin. Med.* **9**(3) (2020) Article ID 841 (7 pages); https://doi.org/10.3390/jcm9030841
25. M. D. Shastri, S. D. Shukla, W. C. Chong, Rajendra KC, K. Dua, R. P. Patel, G. M. Peterson and R. F. O'Toole, Smoking and COVID-19: What we know so far, *Resp. Med.* **176** (2021) Article ID 106237 (7 pages); https://doi.org/10.1016/j.rmed.2020.106237
26. N. M. Siafakas, P. Vermeire, N. B. Pride, P. Paoletti, J. Gibson, P. Howard, J. C. Yernault, M. Decramer, T. Higenbottam, D. S. Postma and J. Rees, Optimal assessment and management of chronic

obstructive pulmonary disease (COPD), *Eur. Resp. J.* **8**(8) (1995) 1398–1420; https://doi.org/10.1183/09031936.95.08081398

27. D. Milner, The physiological effects of smoking on the respiratory system, *Nurs. Times* **100** (2004) 56–59.
28. J. Almirall, I. Bolibar, M. Serra-Prat, J. Roig, I. Hospital, E. Carandell, M. Agusti, P. Ayuso, A. Estela and A. Torres, New evidence of risk factors for community-acquired pneumonia: a population-based study, *Eur. Resp. J.* **31**(6) (2008) 1274–1284; https://doi.org/10.1183/09031936.00095807
29. H. Müllerova, C. Chigbo, G. W. Hagan, M. A. Woodhead, M. Miravitlles, K. J. Davis and J. A. Wedzicha, The natural history of community-acquired pneumonia in COPD patients: A population database analysis, *Resp. Med.* **106**(8) (2012) 1124–1133; https://doi.org/10.1016/j.rmed.2012.04.008
30. S. Cohen, D. A. Tyrrell, M. A. Russell, M. J. Jarvis and A. P. Smith, Smoking, alcohol consumption, and susceptibility to the common cold, *Am. J. Public Health* **83**(9) (1993) 1277–1283; https://doi.org/10.2105/ajph.83.9.1277
31. J. D. Kark, M. Lebiush and L. Rannon, Cigarette smoking as a risk factor for epidemic A(H1N1) influenza in young men, *N. Engl. J. Med.* **307** (1982) 1042–1046; https://doi.org/10.1056/nejm198210213071702
32. Z. Zhou, P. Chen and H. Peng, Are healthy smokers really healthy?, *Tob. Ind. Dis.* **14** (2016) Article ID 35 (12 pages); https://doi.org/10.1186/s12971-016-0101-z
33. L. Arcavi and N. L. Benowitz, Cigarette smoking and infection, *Arch. Intern. Med.* **164**(20) (2004) 2206–2216; https://doi.org/10.1001/archinte.164.20.2206
34. J.-E. Park, S. Jung, A. Kim and J.-E. Park, MERS transmission and risk factors: a systematic review, *BMC Public Health* **18** (2018) Article ID 574 (15 pages); https://doi.org/10.1186/s12889-018-5484-8
35. H.-S. Nam, J. W. Park, M. Ki, M.-Y. Yeon, J. Kim and S. W. Kim, High fatality rates and associated factors in two hospital outbreaks of MERS in Daejeon, the Republic of Korea, *Int. J. Infect. Dis.* **58** (2017) 37–42; https://doi.org/10.1016/j.ijid.2017.02.008
36. C. Sherman, Health effects of cigarette smoking, *Clin. Chest Med.* **12**(4) (1991) 643–658; https://doi.org/10.1016/S0272-5231(21)00814-5
37. K. Palipudi, S. A. Rizwan, D. N. Sinha, L. J. Andes, R. Amarchand, A. Krishnan and S. Asma Prevalence and sociodemographic determinants of tobacco use in four countries of the World Health Organization: South-East Asia region: findings from the global adult tobacco survey, *Indian J. Cancer* **51** (Suppl. 1) (2014) S24–S32; https://doi.org/ 10.4103/0019-509X.147446
38. R. M. Benjamin, Exposure to tobacco smoke causes immediate damage: A report of the surgeon general, *Public Health Rep.* **126**(2) (2011) 158–159; https://doi.org/10.1177/003335491112600202
39. W.-J. Guan, Z.-Y. Ni, Y. Hu, W.-H. Liang, C.-Q. Ou, J.-X. He, L. Liu, H. Shan, C.-L. Lei, D. S. C. Hui, B. Du, L.-J. Li, G. Zeng, K.-Y. Yuen, R.-C. Chen, C.-L. Tang, T. Wang, P.-Y. Chen, J. Xiang, S.-Y. Li, J.-L. Wang, Z.-J. Liang, Y.-X. Peng, L. Wei, Y. Liu, Y.-H. Hu, P. Peng, J.-M. Wang, J.-Y. Liu, Z. Chen, G. Li, Z.-J. Zheng, S.-Q. Qiu, J. Luo, C.-J. Ye, S.-Y. Zhu and N.-S. Zhong (for the China Medical Treatment Expert Group for Covid-19), Clinical characteristics of coronavirus disease 2019 in China, *N. Engl. J. Med.* **382** (2020) 1708–1720; https://doi.org/10.1056/nejmoa2002032
40. K. Vapalahti, A.-M. Virtala, A. Vaheri and O. Vapalahti, Case-control study on Puumala virus infection: smoking is a risk factor, *Epidemiol. Infect.* **138**(4) (2009) 576–584; https://doi.org/10.1017/s095026880999077x
41. A. K. Boutou, G. Pitsiou, T. Kontakiotis and I. Kioumis, Nicotine treatment and smoking cessation in the era of COVID-19 pandemic: an interesting alliance, *ERJ Open Res.* **6**(3) (2020) Article ID 00306-2020 (3 pages); https://doi.org/10.1183/23120541.00306-2020
42. H. A. Tindle, P. A. Newhouse and M. S. Freiberg, Beyond smoking cessation: Investigating medicinal nicotine to prevent and treat COVID-19, *Nicotine Tob. Res.* **22**(9) (2020) 1669–1670; https://doi.org/10.1093/ntr/ntaa077

43. S. J. Brake, K. Barnsley, W. Lu, K. D. McAlinden, M. S. Eapen and S. S. Sohal, Smoking upregulates angiotensin-converting enzyme-2 receptor: A potential adhesion site for novel coronavirus SARS-CoV-2 (Covid-19), *J. Clin. Med.* **9**(3) (2020) Article ID 841 (7 pages); https://doi.org/10.3390/jcm9030841

44. K. P. F. Chan, T. F. Ma, W. C. Kwok, J. K. C. Leung, K. Y. Chiang, J. C. M. Ho, D. C. L. Lam, T. C. C. Tam, M. S. M. Ip and P. L. Ho, Significant reduction in hospital admissions for acute exacerbation of chronic obstructive pulmonary disease in Hong Kong during coronavirus disease 2019 pandemic, *Resp. Med.* **171** (2020) Article ID 106085 (6 pages); https://doi.org/10.1016/j.rmed.2020.106085

45. M. A. Crackower, R. Sarao, G. Y. Oudit, C. Yagil, I. Kozieradzki, S. E. Scanga, A. J. Oliveira-dos-Santos, J. da Costa, L. Zhang, Y. Pei, J. Scholey, C. M. Ferrario, A. S. Manoukian, M. C. Chappell, P. H. Backx, Y. Yagil and J. M. Penninger, Angiotensin-converting enzyme 2 is an essential regulator of heart function, *Nature* **417** (2002) 822–828; https://doi.org/10.1038/nature00786

46. D. Harmer, M. Gilbert, R. Borman and K. L. Clark, Quantitative mRNA expression profiling of ACE 2, a novel homologue of angiotensin converting enzyme, *FEBS Lett.* **532**(1–2) (2002) 107–110; https://doi.org/10.1016/s0014-5793(02)03640-2

47. I. Hamming, W. Timens, M. Bulthuis, A. Lely, G. Navis and H. van Goor, Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis, *J. Pathol.* **203**(2) (2004) 631–637; https://doi.org/10.1002/path.1570

48. S. D. Crowley, S. B. Gurley, M. I. Oliverio, A. K. Pazmino, R. Griffiths, P. J. Flannery, R. F. Spurney, H.-S. Kim, O. Smithies, T. H. Le and T. M. Coffman, Distinct roles for the kidney and systemic tissues in blood pressure regulation by the renin-angiotensin system, *J. Clin. Invest.* **115**(4) (2005) 1092–1099; https://doi.org/10.1172/JCI23378

49. C. Tikellis and M. C. Thomas, Angiotensin-converting enzyme 2 (ACE2) is a key modulator of the renin angiotensin system in health and disease, *Int. J. Pept.* **2012** (2012) Article ID 256294 (8 pages); https://doi.org/10.1155/2012/256294

50. B. Coutard, C. Valle, X. de Lamballerie, B. Canard, N. G. Seidah and E. Decroly, The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade, *Antiviral Res.* **176** (2020) Article ID 104742 (5 pages); https://doi.org/10.1016/j.antiviral.2020.104742

51. K. E. Follis, J. York and J. H. Nunberg, Furin cleavage of the SARS coronavirus spike glycoprotein enhances cell–cell fusion but does not affect virion entry, *Virology* **350**(2) (2006) 358–369; https://doi.org/10.1016/j.virol.2006.02.003

52. F. Li, Structure of SARS coronavirus spike receptor-binding domain complexed with receptor, *Science* **309**(5742) (2005) 1864–1868; https://doi.org/10.1126/science.1116480

53. M. Saadat, No significant correlation between ACE Ins/Del genetic polymorphism and COVID-19 infection, *Clin. Chem. Lab. Med.* **58**(7) (2020) 1127–1128; https://doi.org/10.1515/cclm-2020-0577

54. D. Wrapp, N. Wang, K. S. Corbett, J. A. Goldsmith, C.-L. Hsieh, O. Abiona, B. S. Graham and J. S. McLellan, Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation, *Science* **367**(6483) (2020) 1260–1263; https://doi.org/10.1126/science.abb2507

55. J. M. Leung, C. X. Yang, A. Tam, T. Shaipanich, T.-L. Hackett, G. K. Singhera, D. R. Dorscheid and D. D. Sin, ACE-2 expression in the small airway epithelia of smokers and COPD patients: Implications for COVID-19, *Eur. Respir. J.* **55**(5) (2020) Article ID 2000688 (5 pages); https://doi.org/10.1183/13993003.00688-2020

56. J. C. Smith, E. L. Sausville, V. Girish, M. L. Yuan, K. M. John and J. M. Sheltzer, Cigarette smoke exposure and inflammatory signaling increase the expression of the SARS-CoV-2 receptor ACE2 in the respiratory tract, *Devel. Cell* **53** (2020) 514–529; bioRxiv preprint posted April 26, 2020; https://doi.org/10.1101/2020.03.28.013672

57. J. Qi, Y. Zhou, J. Hua, L. Zhang, J. Bian, B. Liu, Z. Zhao and S. Jin, The scRNA-seq expression profiling of the receptor ACE2 and the cellular protease TMPRSS2 reveals human organs susceptible to SARS-CoV-2 infection, *Int. J. Environ. Res. Public Health* **18**(1) (2021) Article ID 284 (17 pages); https://doi.org/10.3390/ijerph18010284