





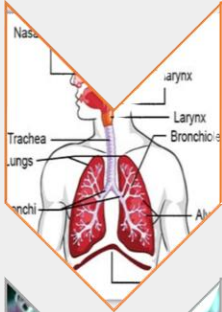
# **THE SCIENCE ON SMOKING AND COVID-19**

**Catherine O. Egbe, PhD**

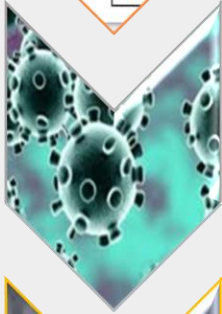
*(Specialist Scientist, Alcohol Tobacco and Other Drug Research Unit, SAMRC)*

NCAS webinar presentation: 22 April 2020

# OUTLINE



- The human respiratory system
- Diseases of the respiratory system
- Smoking, secondhand smoke exposure & diseases of the respiratory system



- The infection pathway of COVID-19
- Who is at risk of contracting COVID-19
- Clinical presentation of COVID-19



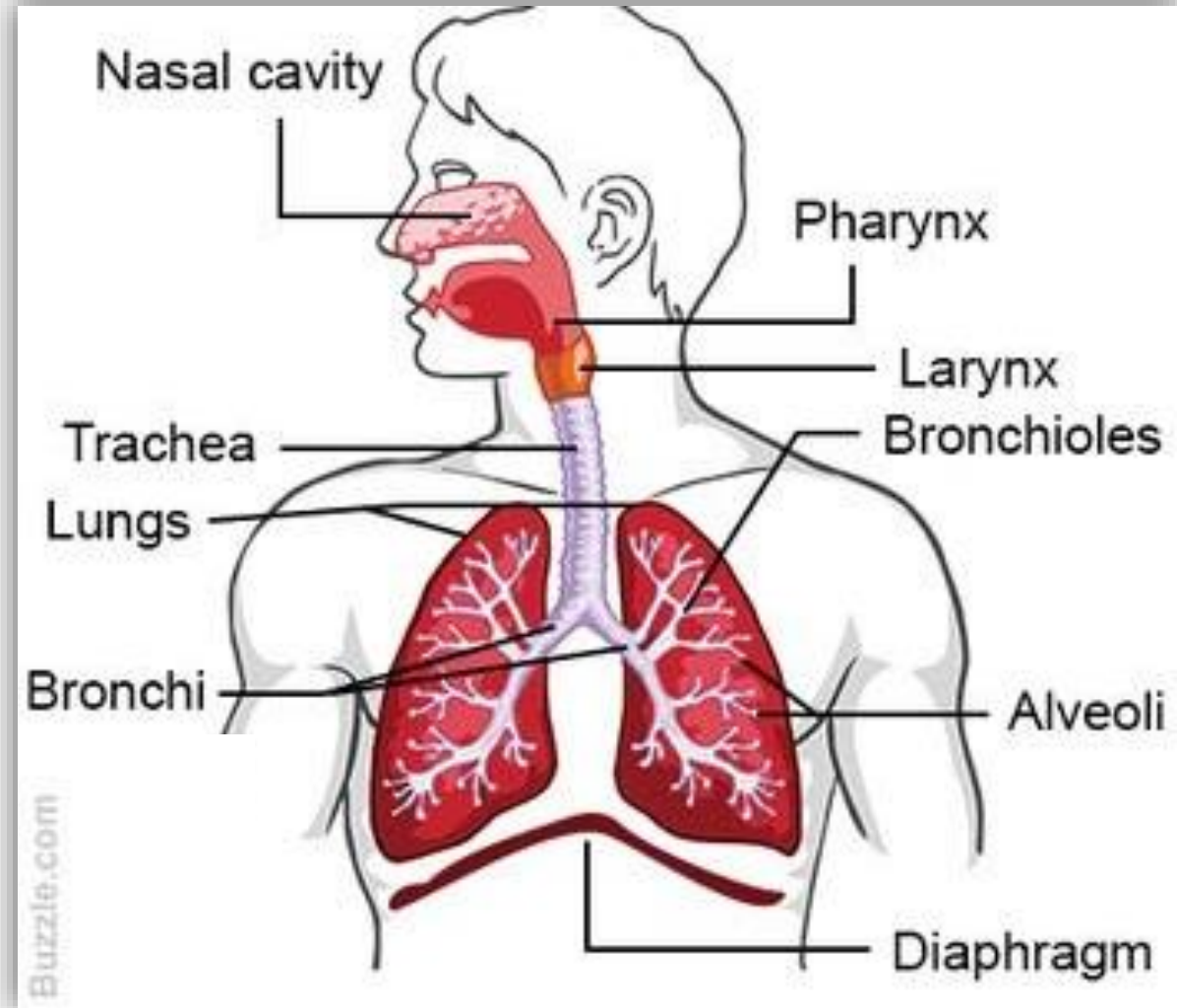
- Risks of contracting Coronavirus and of developing severe illness from COVID-19
- How are smokers at risk of Covid-19?



- Smoking & COVID-19: the scientific evidence so far

# THE HUMAN RESPIRATORY SYSTEM

- Nose and nasal cavity
- Sinuses
- Mouth
- Throat (pharynx)
- Voice box (larynx)
- Windpipe (trachea)
- Diaphragm
- Lungs
- Bronchial tubes/bronchi
- Bronchioles
- Air sacs (alveoli)
- Capillaries



# DISEASES OF THE RESPIRATORY SYSTEM

Common diseases of the respiratory system include:

- **Asthma.** Your airways narrow and make too much mucus
- **Bronchiectasis.** Inflammation and infection make your bronchial walls thicker
- **Chronic obstructive pulmonary disease (COPD).** This long-term condition gets worse over time. It includes bronchitis and emphysema
- **Pneumonia.** An infection causes inflammation in your alveoli. They might fill up with fluid or pus
- **Tuberculosis.** A bacterium causes this dangerous infection. It usually affects your lungs but might also involve your kidney, spine, or brain
- **Lung cancer.** Cells in your lung change and grow into a tumor. This often happens because of smoking or other chemicals you've breathed in
- **Cystic fibrosis.** This disease is caused by a problem in your genes and gets worse over time. It causes lung infections that don't go away
- **Pleural effusion.** Too much fluid builds up between the tissues that line your lungs and chest
- **Idiopathic pulmonary fibrosis.** Your lung tissue becomes scarred and can't work the way it should
- **Sarcoidosis.** Tiny clumps of inflammatory cells called granulomas form, often in your lungs and lymph nodes

*Source: WebMD Medical Reference Reviewed by Melinda Ratini, DO, MS on November 15, 2019*

# How Tobacco Smoke Causes Disease

The Biology and Behavioral Basis  
for Smoking-Attributable Disease

A Report of the Surgeon General



U.S. Department of Health and Human Services

# SMOKING AND DISEASES OF THE RESPIRATORY SYSTEM

These diseases have been linked to smoking long before  
COVID-19:

- Chronic Obstructive Pulmonary Disease (COPD)
  - Emphysema
  - Chronic bronchitis
  - Asthma
- 
- Tuberculosis\* (exacerbated by smoking)

*How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General. Atlanta (GA): Centers for Disease Control and Prevention (US); 2010. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK53017/>*

# PRINCIPAL NONMALIGNANT RESPIRATORY DISEASES CAUSED BY CIGARETTE SMOKING

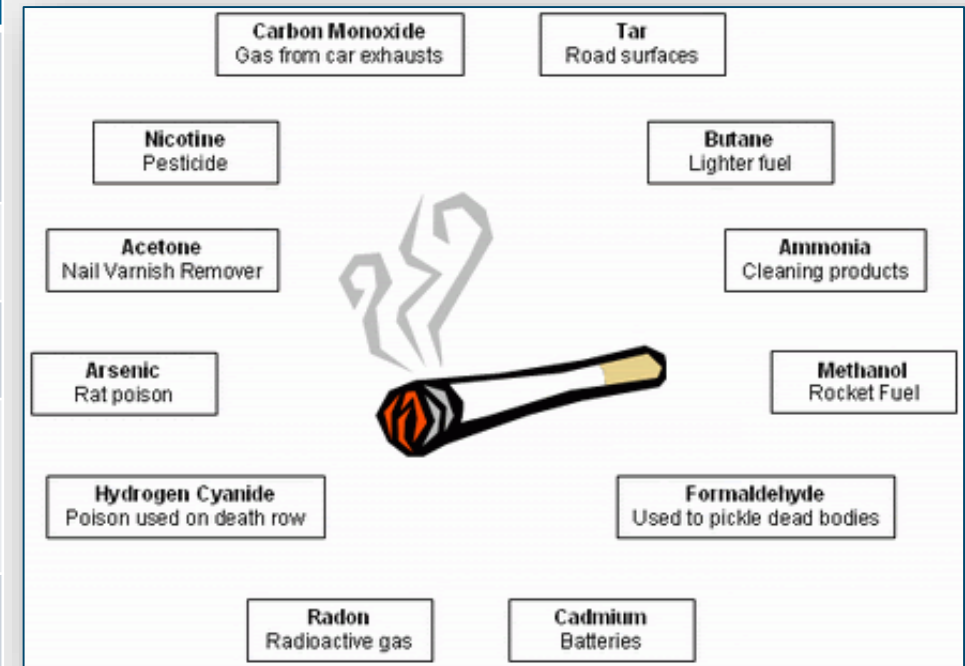
<b>Chronic obstructive pulmonary disease (COPD)</b>	A preventable and treatable disease characterized by airflow limitation that is not fully reversible. The limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences.
<b>Emphysema</b>	Permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis. In patients with COPD, either condition may be present. However, the relative contribution of each to the disease process is often difficult to discern.
<b>Chronic bronchitis</b>	Chronic productive cough for 3 months in each of 2 successive years in a patient in whom other causes of productive chronic cough have been excluded.
<b>Asthma</b>	A chronic inflammatory disease of the airways in which many cell types play a role—in particular, mast cells, eosinophils, and T lymphocytes. In susceptible persons, the inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and/or in the early morning. These symptoms are usually associated with widespread and variable airflow obstruction that is at least partly reversible either spontaneously or with treatment. The inflammation also causes an associated increase in airway responsiveness to a variety of stimuli.

Source: American Thoracic Society 2000 and American Thoracic Society/European Respiratory Society Task Force 2005.

Source: *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General*. Atlanta (GA): Centers for Disease Control and Prevention (US); 2010. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK53017/>

# SELECTED COMPONENTS OF CIGARETTE SMOKE AND POTENTIAL MECHANISMS OF INJURY

Component	Mechanism
Acrolein	Cilia toxic, impairs lung defenses
Formaldehyde	Cilia toxic, irritant
Nitrogen oxides	Oxidant activity
Cadmium	Oxidant injury, promotion of emphysema
Hydrogen cyanide	Oxidative metabolism of cells affected



Source: *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General*. Atlanta (GA): Centers for Disease Control and Prevention (US); 2010. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK53017/>



# CAUSAL CONCLUSIONS ON SMOKING AND DISEASES OF THE RESPIRATORY TRACT OTHER THAN CANCER: US SURGEON GENERAL REPORT (2004 & 2006)

## Active Smoking

The evidence is sufficient to infer a **causal conclusion** between smoking and

- Acute respiratory illnesses, including pneumonia, in persons without underlying smoking-related chronic obstructive lung disease
- Impaired lung growth during childhood and adolescence
- Early onset of decline in lung function (during late adolescence and early adulthood)
- A premature onset of and an accelerated age-related decline in respiratory symptoms related to lung function in children and adolescents, including coughing, phlegm, wheezing, and dyspnea
- Asthma-related symptoms (i.e., wheezing) in childhood and adolescence
- All major respiratory symptoms among adults, including coughing, phlegm, wheezing, and dyspnea
- Poor asthma control
- Chronic obstructive pulmonary disease morbidity and mortality
- A reduction of lung function in infants of mothers who smoked during pregnancy

Source: *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General*. Atlanta (GA): Centers for Disease Control and Prevention (US); 2010. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK53017/>

# Secondhand Smoke

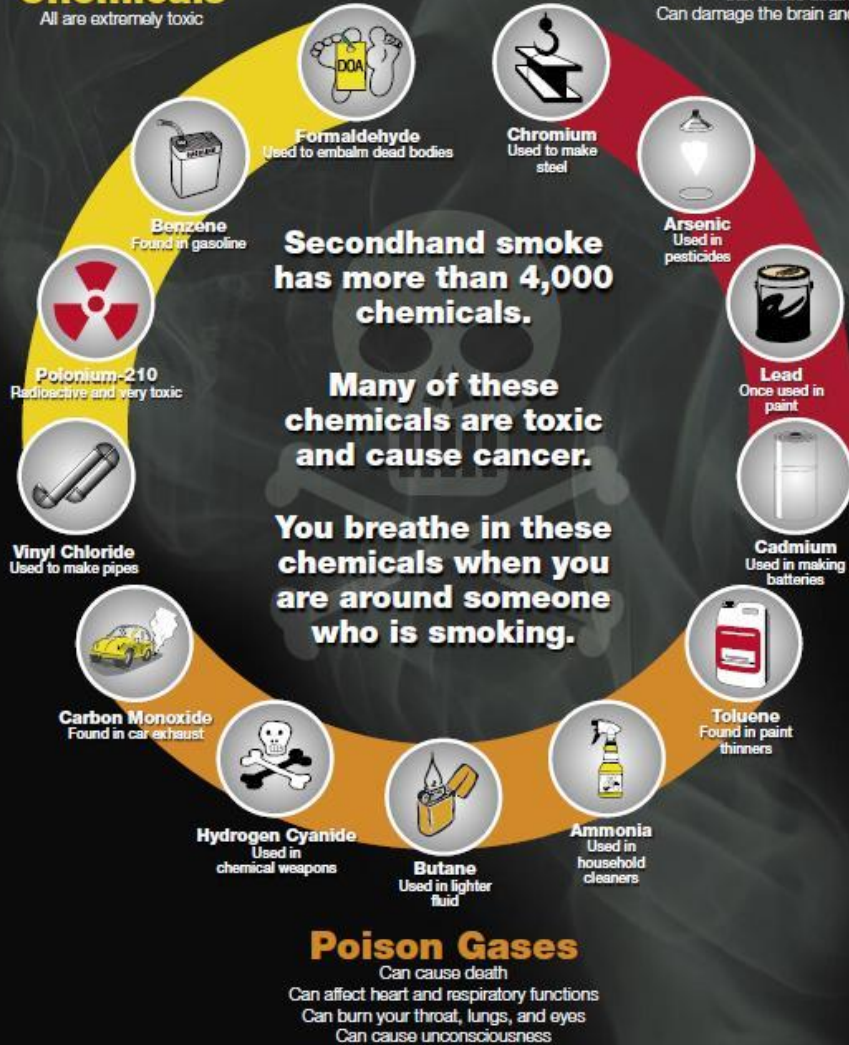
is toxic

## Cancer Causing Chemicals

All are extremely toxic

## Toxic Metals

Can cause cancer  
Can cause death  
Can damage the brain and kidneys



## Poison Gases

Can cause death  
Can affect heart and respiratory functions  
Can burn your throat, lungs, and eyes  
Can cause unconsciousness

## Secondhand smoke

It hurts you. It doesn't take much. It doesn't take long.

# DISEASES CAUSED BY EXPOSURE TO SECONDHAND SMOKE

## Involuntary Exposure to Tobacco Smoke

The evidence is sufficient to infer a **causal conclusion** between secondhand smoke exposure  
From parental smoking and

- Lower respiratory illnesses in infants and children
- Middle ear disease in children, including acute and recurrent otitis media and chronic middle ear effusion
- Cough, phlegm, wheeze, and breathlessness among children of school age
- Ever having asthma among children of school age
- Onset of wheeze illnesses in early childhood

From maternal smoking during pregnancy and

- Persistent adverse effects on lung function across childhood

After birth and

- Lower level of lung function during childhood

And

- Odor annoyance
- Nasal irritation

Source: U.S. Department of Health and Human Services 2004, 2006.

Source: *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General*. Atlanta (GA): Centers for Disease Control and Prevention (US); 2010. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK53017/>

# INFECTION PATHWAY OF COVID-19

**SARS-CoV 2 UPDATE**

**CLARIFICATION**

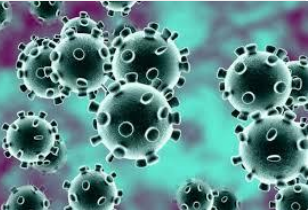
NAME OF THE VIRUS (formerly novel coronavirus):  
**SARS-CoV 2**  
Severe Acute Respiratory Syndrome Coronavirus 2

NAME OF THE DISEASE:  
**COVID-19**  
Coronavirus Disease

REFERENCE: Science Policy Centre (2020). "Report number on naming of the coronavirus disease 2019 (COVID-19) and SARS-CoV-2." Available from <https://www.spc.ac.uk/news/2020/03/24/coronavirus-naming>.

**Earth Shaker** @earthshakerph

# INFECTION PATHWAY OF COVID-19



Public health intervention  
(hygiene practices)



Coronavirus gets into the body

Mucous membrane of Mouth, eyes and nose

Virus infects the upper and lower resp. tracts

Virus travels down the airways, irritating the resp. tract and causing inflammation

Immune system fights back, lungs and airways become inflamed

Source: <https://www.webmd.com/lung/what-does-covid-do-to-your-lungs#2>

# WHO IS AT RISK OF CONTRACTING COVID-19?

- Anyone! As long as you stand the chance of being in contact with someone who is carrying the virus, or touching a contaminated surface, you stand the risk of catching it
- Disclaimers!
  - Catching the virus  $\neq$  developing serious illness from it
  - Catching the virus  $\neq$  dying from it

## ACTIVE CASES

**1,668,583**

Currently Infected Patients

**1,611,245** (97%)

in Mild Condition

**57,338** (3%)

Serious or Critical

## CLOSED CASES

**826,713**

Cases which had an outcome:

**655,649** (79%)

Recovered / Discharged

**171,064** (21%)

Deaths

# CLINICAL PRESENTATION OF COVID-19

Public health intervention?

?

?

**Asymptomatic carriers**

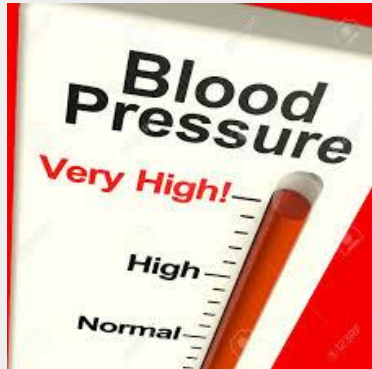
**Immune system fights back, lungs and airways become inflamed**

**MILD TO MODERATE CASES: ~80%**  
(Dry cough, sore throat, pneumonia, lung infection with inflamed alveoli)

**SEVERE CASES: ~14%**  
Both lungs infected, lungs fill with fluids and debris, serious pneumonia, alveoli filled with mucus and fluid, shortness of breath, difficulty breathing

**CRITICAL CASES: ~5%**  
Damage to the wall and inner linings of the alveoli and lungs; lungs become more inflamed and filled with fluid, severe pneumonia (Acute Respiratory Distress Syndrome – ARDS; lungs need a ventilator)

# WHO IS AT RISK OF DEVELOPING SEVERE ILLNESS FROM COVID-19?



## Who is at risk of developing severe illness?

While we are still learning about how COVID-2019 affects people, older persons and persons with pre-existing medical conditions (such as high blood pressure, heart disease, lung disease, cancer or diabetes) appear to develop serious illness more often than others.

Source: WHO, 2020 (<https://www.who.int/news-room/q-a-detail/q-a-coronaviruses#:~:text=symptoms>)

# HOW ARE SMOKERS AT RISK OF COVID-19?

- Mostly due to the smoker's exposure to toxins from tobacco and the way these toxins affect the respiratory system
- These toxins in tobacco compromise the immune system and weaken the body's ability to fight diseases
- Those exposed to secondhand smoke also face the same risks as above
- The act of sharing the waterpipe/hubbly can lead to the spread of coronavirus
- The act of smoking (touching the mouth with the hand) goes against practice of good hygiene aimed at stopping the spread of the virus



**“Any kind of tobacco smoking is harmful to bodily systems, including the cardiovascular and respiratory systems. COVID-19 can also harm these systems.”**

**- WHO, 2020**



# SMOKING & COVID-19: THE SCIENTIFIC EVIDENCE SO FAR

Original Article

Chinese Medical Journal\*

## Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease

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<sup>3</sup>Department of Respiratory and Critical Care Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, China;

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### Abstract

**Background:** Since early December 2019, the 2019 novel coronavirus disease (COVID-19) has caused pneumonia epidemic in Wuhan, Hubei province of China. This study aims to investigate the factors affecting the progression of pneumonia in COVID-19 patients. Associated results will be used to evaluate the prognosis and to find the optimal treatment regimens for COVID-19 pneumonia.

**Methods:** Patients tested positive for the COVID-19 based on nucleic acid detection were included in this study. Patients were admitted to 3 tertiary hospitals in Wuhan between December 30, 2019, and January 15, 2020. Individual data, laboratory indices, imaging characteristics, and clinical data were collected, and statistical analysis was performed. Based on clinical typing results, the patients were divided into a progression group or an improvement/stabilization group. Continuous variables were analyzed using independent samples *t*-test or Mann-Whitney *U* test. Categorical variables were analyzed using Chi-squared test or Fisher's exact test. Logistic regression analysis was performed to explore the risk factors for disease progression.

**Results:** Seventy-eight patients with COVID-19-induced pneumonia met the inclusion criteria and were included in this study. Efficacy evaluation at 2 weeks after hospitalization indicated that 11 patients (14.1%) had deteriorated, and 67 patients (85.9%) had improved/stabilized. The patients in the progression group were significantly older than those in the disease improvement/stabilization group (66 [51, 70] vs. 37 [32, 41] years,  $U = 4.932$ ,  $P = 0.001$ ). The progression group had a significantly higher proportion of patients with a history of smoking than the improvement/stabilization group (27.3% vs. 3.0%,  $\chi^2 = 9.291$ ,  $P = 0.018$ ). For all the 78 patients, fever was the most common initial symptom, and the maximum body temperature at admission was significantly higher in the progression group than in the improvement/stabilization group (38.2 [37.8, 38.6] vs. 37.5 [37.0, 38.4]°C,  $U = 2.057$ ,  $P = 0.027$ ). Moreover, the proportion of patients with respiratory failure (54.5% vs. 20.9%,  $\chi^2 = 5.611$ ,  $P = 0.028$ ) and respiratory rate (34 [18, 48] vs. 24 [16, 60] breaths/min,  $U = 4.030$ ,  $P = 0.004$ ) were significantly higher in the progression group than in the improvement/stabilization group. C-reactive protein was significantly elevated in the progression

- Efficacy evaluation at 2 weeks after hospitalization indicated that 11 patients (14.1%) had deteriorated, and 67 patients (85.9%) had improved/stabilized
- 
- The progression group had a significantly higher proportion of patients with a history of smoking than the improvement/stabilization group

# SMOKING & COVID-19: THE SCIENTIFIC EVIDENCE SO FAR

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 5 March 2020 | doi:10.20944/preprints202003.0078.v1

Article

## Susceptibility Analysis of COVID-19 in Smokers Based on ACE2

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<sup>2</sup> Department of Respiratory Medicine, The Second Affiliated Hospital of Soochow University, Suzhou, 215004, China;

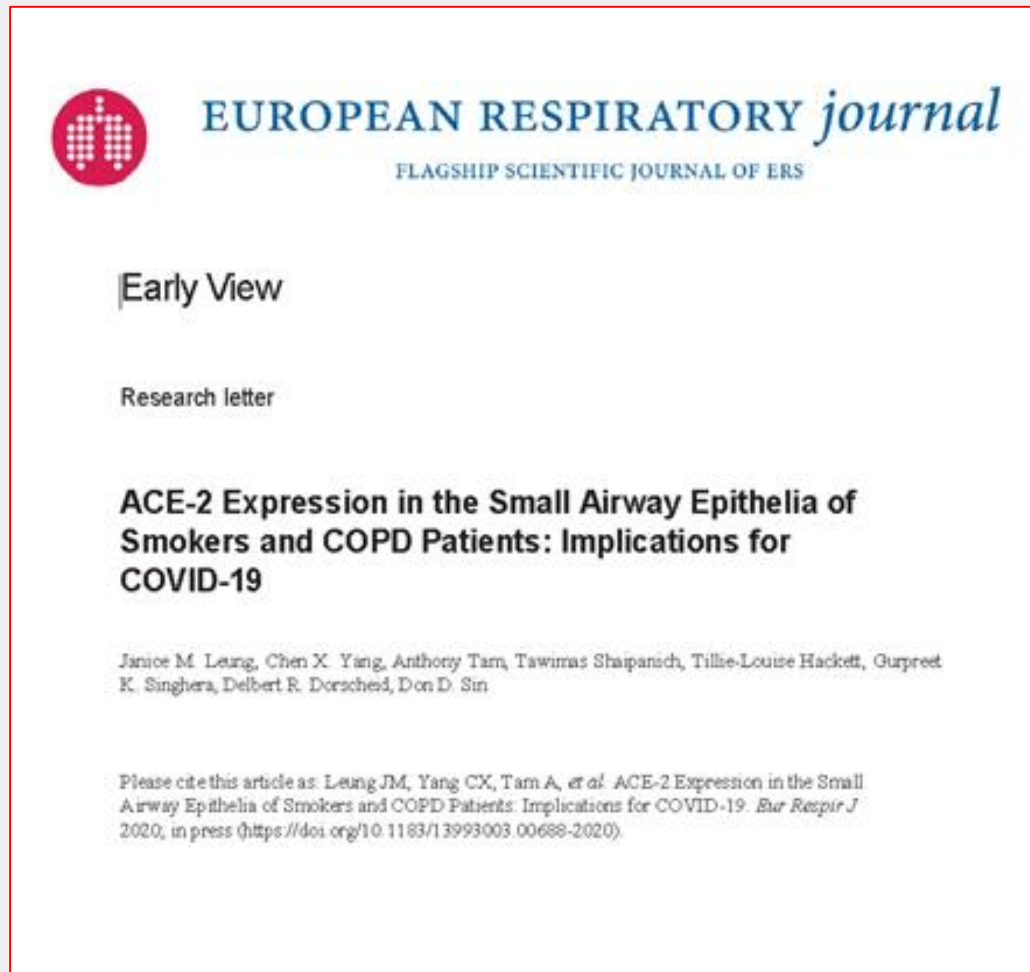
\* Correspondence: aljxcr@suda.edu.cn; Tel.: +86-0512-65881038

**Abstract: Background:** Cigarette smoking (CS) is a global public health problem and a high-risk factor for various diseases. In December 2019, a novel coronavirus (COVID-19) was identified in Wuhan, China. Because ACE2 has been identified as a receptor for COVID-19, we hypothesize that CS affects the expression pattern of ACE2 in respiratory tract, causing differences in susceptibility to the virus. **Methods:** Three datasets (GSE994, GSE17913, and GSE18344), were downloaded from the Gene Expression Omnibus (GEO) database. Correlation and enrichment analysis were used to evaluate the function of ACE2. Also, the different expression of ACE2 in different groups of three datasets were analyzed. **Results:** Genes associated with ACE2 were enriched in important biological processes such as viral processes and immune response. Elevated ACE2 were found in intrapulmonary airways (GSE994) and oral epithelial cells (GSE17913) of smokers but not those of non-smokers or former smokers. Significant dose- and time-dependent relationships between CS and ACE2 expression were observed in mouse lung tissues, and long periods without smoking were found to significantly reduce ACE2 expression. **Conclusions:** Both human and rat data confirmed that CS could induce increased ACE2 in the respiratory tract, indicating that smokers have a higher susceptibility to COVID-19.

**Keywords:** Cigarette smoke; ACE2; COVID-19; susceptibility

- Angiotensin-converting enzyme-2 (ACE2) is an enzyme attached to the outer surface (cell membranes) of cells in the lungs, arteries, heart, kidney, intestine
- ACE2 also serves as the entry point into cells for some coronaviruses including SARS-Cov-2
- Long periods without smoking were found to significantly reduce ACE2 expression
- Both human and rat data confirmed that cigarette smoking could induce increased ACE2 in the respiratory tract, indicating that smokers have a higher susceptibility to novel coronavirus (HCoV-19)

# SMOKING & COVID-19: THE SCIENTIFIC EVIDENCE SO FAR



- Active cigarette smoking and COPD up-regulate ACE-2 expression in lower airways, which in part may explain the increased risk of severe COVID-19 in these populations
- History of smoking was identified as a factor that led to the progression of COVID-19 pneumonia
- These findings highlight the importance of smoking cessation for these individuals

# SMOKING & COVID-19: THE SCIENTIFIC EVIDENCE SO FAR

Articles

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 **Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study**

Fei Zhou\*, Ting Yu\*, Ronghui Du\*, Guohui Fan\*, Ying Liu\*, Zhibo Liu\*, Jie Xiang\*, Yeming Wang, Bin Song, Xiaoying Gu, Lulu Guan, Yuan Wei, Hui Li, Xudong Wu, Juyang Xia, Shengjin Tu, Yi Zhang, Hua Chen, Bin Cao

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See Comment page 1014

This online publication has been corrected. The corrected version first appeared at [thelancet.com](https://www.thelancet.com) on March 12, 2020.  
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(F Zhou MD, G Fan MS, Z Gu MD, Y Wang MD, J Gu PhD, H Li MD, Y Zhang MD, Prof R Cao MD)  
Department of Tuberculosis and Respiratory Disease (T Yu MD, Y Liu MD, B Song MS, Y Wu MS, S Tu MD, Prof H Chen MD) and Department of Clinical Laboratory (Xiang MS), and GCP Center (X Wu MS), Beiqian

**Summary**  
**Background** Since December, 2019, Wuhan, China, has experienced an outbreak of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Epidemiological and clinical characteristics of patients with COVID-19 have been reported but risk factors for mortality and a detailed clinical course of illness, including viral shedding, have not been well described.  
**Methods** In this retrospective, multicentre cohort study, we included all adult inpatients (≥18 years old) with laboratory-confirmed COVID-19 from Jinyintan Hospital and Wuhan Pulmonary Hospital (Wuhan, China) who had been discharged or had died by Jan 31, 2020. Demographic, clinical, treatment, and laboratory data, including serial samples for viral RNA detection, were extracted from electronic medical records and compared between survivors and non-survivors. We used univariable and multivariable logistic regression methods to explore the risk factors associated with in-hospital death.  
**Findings** 191 patients (135 from Jinyintan Hospital and 56 from Wuhan Pulmonary Hospital) were included in this study, of whom 137 were discharged and 54 died in hospital. 91 (48%) patients had a comorbidity, with hypertension being the most common (58 [30%] patients), followed by diabetes (36 [19%] patients) and coronary heart disease (15 [8%] patients). Multivariable regression showed increasing odds of in-hospital death associated with older age (odds ratio 1·10, 95% CI 1·03–1·17, per year increase;  $p=0\cdot0043$ ), higher Sequential Organ Failure Assessment (SOFA) score (5–65, 2·61–12·23;  $p<0\cdot0001$ ), and d-dimer greater than 1 µg/mL (18–42, 2·64–128·55;  $p=0\cdot0033$ ) on admission. Median duration of viral shedding was 20·0 days (IQR 17·0–24·0) in survivors, but SARS-CoV-2 was detectable until death in non-survivors. The longest observed duration of viral shedding in survivors was 37 days.  
**Interpretation** The potential risk factors of older age, high SOFA score, and d-dimer greater than 1 µg/mL could help clinicians to identify patients with poor prognosis at an early stage. Prolonged viral shedding provides the rationale for a strategy of isolation of infected patients and optimal antiviral interventions in the future.

- Among those that died of Covid-19, 9% were current smokers compared to 4% among those that survived, with no statistically significant difference between the smoking rates of survivors and non-survivors ( $p=0.21$ )

# SMOKING & COVID-19: THE SCIENTIFIC EVIDENCE SO FAR

Received: 17 February 2020 | Revised: 18 February 2020 | Accepted: 18 February 2020  
DOI: 10.1111/all.14238

Check for updates

ORIGINAL ARTICLE  
Epidemiology and Genetics

Allergy WILEY

## Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China

Jin-jin Zhang<sup>1</sup> | Xiang Dong<sup>1</sup> | Yi-yuan Cao<sup>2</sup> | Ya-dong Yuan<sup>3</sup> | Yi-bin Yang<sup>4</sup> | You-qin Yan<sup>5</sup> | Cezmi A. Akdis<sup>6</sup> | Ya-dong Gao<sup>1</sup>

<sup>1</sup>Department of Allergy, Zhongnan Hospital of Wuhan University, Wuhan, China  
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<sup>3</sup>Department of Respiratory and Critical Care Medicine, Second Hospital of Hebei Medical University, Shijiazhuang, China  
<sup>4</sup>Department of Respiratory and Critical Care Medicine, Zhongnan Hospital of Wuhan University, Wuhan, China  
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<sup>6</sup>Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland

Correspondence  
Ya-dong Gao, Department of Allergy.

**Abstract**  
**Background:** Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been widely spread. We aim to investigate the clinical characteristic and allergy status of patients infected with SARS-CoV-2.  
**Methods:** Electronic medical records including demographics, clinical manifestation, comorbidities, laboratory data, and radiological materials of 140 hospitalized COVID-19 patients, with confirmed result of SARS-CoV-2 viral infection, were extracted and analyzed.  
**Results:** An approximately 1:1 ratio of male (50.7%) and female COVID-19 patients was found, with an overall median age of 57.0 years. All patients were community-acquired cases. Fever (91.7%), cough (75.0%), fatigue (75.0%), and gastrointestinal symptoms (39.6%) were the most common clinical manifestations, whereas hyper-

- Among severe patients (n=58), 3.4% were current smokers and 6.9% were former smokers, in contrast to non-severe patients (n=82) among which 0% were current smokers and 3.7% were former smokers
- Although the study showed that COPD and smoking populations were less likely to be infected with SARS-CoV-2, but the outcome of SARS-CoV-2 infection in smokers may be more severe

# SMOKING & COVID-19: THE SCIENTIFIC EVIDENCE SO FAR

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

## Clinical Characteristics of Coronavirus Disease 2019 in China

W. Guan, Z. Ni, Yu Hu, W. Liang, C. Ou, J. He, L. Liu, H. Shan, C. Lei, D.S.C. Hui, B. Du, L. Li, G. Zeng, K.-Y. Yuen, R. Chen, C. Tang, T. Wang, P. Chen, J. Xiang, S. Li, Jin-lin Wang, Z. Liang, Y. Peng, L. Wei, Y. Liu, Ya-hua Hu, P. Peng, Jian-ming Wang, J. Liu, Z. Chen, G. Li, Z. Zheng, S. Qiu, J. Luo, C. Ye, S. Zhu, and N. Zhong, for the China Medical Treatment Expert Group for Covid-19\*

ABSTRACT

**BACKGROUND**  
Since December 2019, when coronavirus disease 2019 (Covid-19) emerged in Wuhan city and rapidly spread throughout China, data have been needed on the clinical characteristics of the affected patients.

**METHODS**  
We extracted data regarding 1099 patients with laboratory-confirmed Covid-19 from 552 hospitals in 30 provinces, autonomous regions, and municipalities in mainland China through January 29, 2020. The primary composite end point was admission to an intensive care unit (ICU), the use of mechanical ventilation, or death.

**RESULTS**  
The median age of the patients was 47 years; 41.9% of the patients were female. The primary composite end point occurred in 67 patients (6.1%), including 5.0% who were admitted to the ICU, 2.3% who underwent invasive mechanical ventilation, and 1.4% who died. Only 1.9% of the patients had a history of direct contact with wildlife. Among nonresidents of Wuhan, 72.3% had contact with residents of Wuhan, including 31.3% who had visited the city. The most common symptoms were fever (43.8% on admission and 88.7% during hospitalization) and cough

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Zhong at the State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Disease, Guangzhou Institute of Respiratory Health, First Affiliated Hospital of Guangzhou Medical University, 151 Yanjiang Rd., Guangzhou, Guangdong, China, or at nanshan@vip.163.com.

\*A list of investigators in the China Medical Treatment Expert Group for Covid-19 study is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Guan, Ni, Yu Hu, W. Liang, Ou, He, L. Liu, Shan, Lei, Hui, Du, L. Li, Zeng, and Yuen contributed equally to this article.

This article was published on February 28, 2020, and last updated on March 6, 2020, at NEJM.org.

- 173 had severe symptoms, and 926 had non-severe symptoms. Among the patients with severe symptoms, 16.9% were current smokers and 5.2% were former smokers
- In contrast to patients with non-severe symptoms where 11.8% were current smokers and 1.3% were former smokers

# SMOKING & COVID-19: THE SCIENTIFIC EVIDENCE SO FAR

Editorial Tobacco Induced Diseases

## COVID-19 and smoking: A systematic review of the evidence

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COVID-19 is a coronavirus outbreak that initially appeared in Wuhan, Hubei Province, China, in December 2019, but it has already evolved into a pandemic spreading rapidly worldwide<sup>1,2</sup>. As of 18 March 2020, a total number of 194909 cases of COVID-19 have been reported, including 7876 deaths, the majority of which have been reported in China (3242) and Italy (2505)<sup>3</sup>. However, as the pandemic is still unfortunately under progression, there are limited data with regard to the clinical characteristics of the patients as well as to their prognostic factors<sup>4</sup>. Smoking, to date, has been assumed to be possibly associated with adverse disease prognosis, as extensive evidence has highlighted the negative impact of tobacco use on lung health and its causal association with a plethora of respiratory diseases<sup>5</sup>. Smoking is also detrimental to the immune system and its responsiveness to infections, making smokers more vulnerable to infectious diseases<sup>6</sup>. Previous studies have shown that smokers are twice more likely than non-smokers to contract influenza and have more severe symptoms, while smokers were also noted to have higher mortality in the previous MERS-CoV outbreak<sup>7,8</sup>.

Given the gap in the evidence, we conducted a systematic review of studies on COVID-19 that included information on patients' smoking status to evaluate the association between smoking and COVID-19 outcomes including the severity of the disease, the need for mechanical ventilation, the need for intensive care unit (ICU) hospitalization and death.

The literature search was conducted on 17 March 2020, using two databases (PubMed, ScienceDirect), with the search terms: ['smoking' OR 'tobacco' OR 'risk factors' OR 'smoker\*'] AND ['COVID-19' OR 'COVID 19' OR 'novel coronavirus' OR 'sars cov-2' OR 'sars cov 2'] and included studies published in 2019 and 2020. Further inclusion criteria were that the studies were in English and referred to humans. We also searched the reference lists of the studies included.

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- Smoking is most likely associated with the negative progression and adverse outcomes of COVID-19

# SMOKING & COVID-19: THE SCIENTIFIC EVIDENCE SO FAR

## Articles

### Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China



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#### Summary

**Background** A recent cluster of pneumonia cases in Wuhan, China, was caused by a novel betacoronavirus, the 2019 novel coronavirus (2019-nCoV). We report the epidemiological, clinical, laboratory, and radiological characteristics and treatment and clinical outcomes of these patients.

**Methods** All patients with suspected 2019-nCoV were admitted to a designated hospital in Wuhan. We prospectively collected and analysed data on patients with laboratory-confirmed 2019-nCoV infection by real-time RT-PCR and next-generation sequencing. Data were obtained with standardised data collection forms shared by WHO and the International Severe Acute Respiratory and Emerging Infection Consortium from electronic medical records. Researchers also directly communicated with patients or their families to ascertain epidemiological and symptom data. Outcomes were also compared between patients who had been admitted to the intensive care unit (ICU) and those who had not.

**Findings** By Jan 2, 2020, 41 admitted hospital patients had been identified as having laboratory-confirmed 2019-nCoV infection. Most of the infected patients were men (30 [73%] of 41); less than half had underlying diseases (13 [32%]), including diabetes (eight [20%]), hypertension (six [15%]), and cardiovascular disease (six [15%]). Median age was 49.0 years (IQR 41.0–58.0). 27 (66%) of 41 patients had been exposed to Huanan seafood market. One family cluster was found. Common symptoms at onset of illness were fever (40 [98%] of 41 patients), cough (31 [76%]), and myalgia or fatigue (18 [44%]); less common symptoms were sputum production (11 [28%] of 39), headache (three [8%] of 38), haemoptysis (two [5%] of 38), and diarrhoea (one [3%] of 38). Dyspnoea developed in 23 (55%) of 40 patients (median

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- In this study, none of those who needed to be admitted to an ICU (n=13) was a current smoker. In contrast, three (3) patients from the non-ICU group were current smokers



# SMOKING & COVID-19: THE SCIENTIFIC EVIDENCE SO FAR

- Only in one study was active smoking found to be a significant predictor of COVID-19 severity
- In four studies the association was not statistically significant
- Despite a trend towards higher risk after pooling individual data, no significant association could be found between active smoking and severity of COVID-19
- Active smoking does not apparently seem to be significantly associated with enhanced risk of progressing towards severe disease in COVID-19

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Letter to the Editor

**Active smoking is not associated with severity of coronavirus disease 2019 (COVID-19)**

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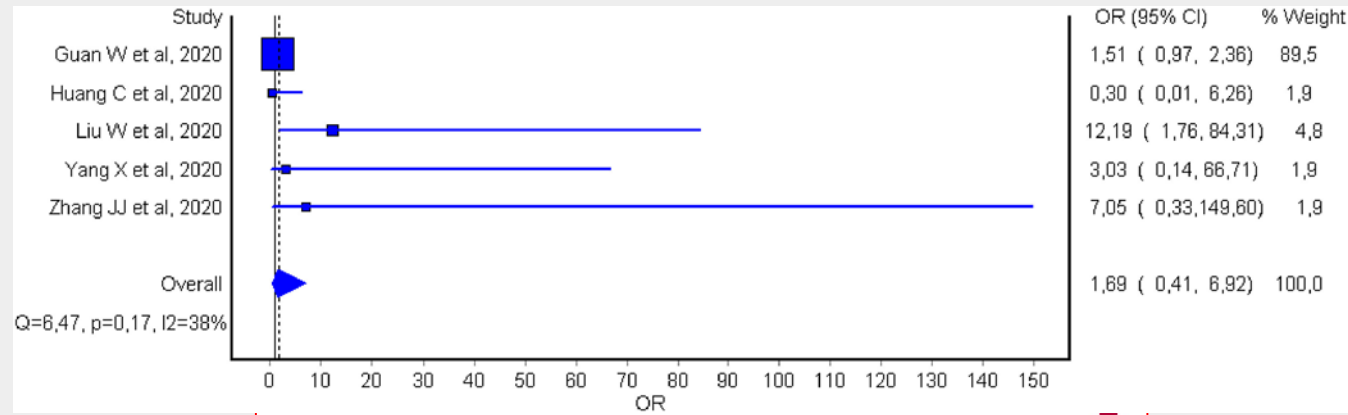
In the ongoing coronavirus disease 2019 (COVID-19) pandemic, some unique clinical features have been described [1]. In a report of 44,672 cases from China, a case fatality rate of 2.8% for males versus only 1.7% for females was observed [2]. It has been hypothesized that this may be due a higher prevalence of comorbidities among males, in particular the rate of smoking, which is reported to be 52.1% in men and 2.7% among women in China [3]. However, decreased levels of angiotensin converting enzyme 2 (ACE2), the reported host receptor of the virus responsible of COVID-19 (severe acute respiratory syndrome coronavirus 2; SARS-CoV-2), are observed in smokers [4,5]. In this article, we aimed to investigate the association between active smoking and severity of COVID-19 illness.

A electronic search was conducted in Medline (PubMed interface), Scopus and Web of Science, using the keywords "smoking" OR "cigarette" AND "coronavirus 2019" OR "COVID-19" OR "2019-nCoV" OR "SARS-CoV-2", between 2019 and present time (i.e., March 9, 2020), without language restriction. The title, abstract and full text of all documents captured with these search criteria were scrutinized, and those reporting the rate of active smokers in COVID-19 patients with clinically validated definition of severe disease were included in this meta-analysis. The reference list of the identified studies was also analyzed (forward and backward citation tracking) for detecting other potentially eligible articles.

A meta-analysis was then performed, with estimation of the odd ratio (OR) and its 95% confidence interval (95% CI) in patients with or without severe forms of COVID-19. The statistical analysis was carried out using MetaXL, software Version 5.3 (EpiGear International Pty Ltd., Sunrise Beach, Australia). The study was carried out in accordance with the declaration of Helsinki and with the term of local legislation.

Overall, 27 documents could be initially identified based on our search criteria and from the reference lists, 22 of which were excluded after title, abstract or full text reading, since they were review articles (n=4), commentaries or other editorial materials (n=2), they did not deal with COVID-19 disease (n=11), or did not provided the rate of active smokers in patients with or without severe disease (n=5). Therefore, 5 studies could finally be included in our meta-analysis.

# SMOKING & COVID-19: THE SCIENTIFIC EVIDENCE SO FAR



## Articles

### Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study



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#### Summary

**Background** An ongoing outbreak of pneumonia associated with the severe acute respiratory coronavirus 2 (SARS-CoV-2) started in December, 2019, in Wuhan, China. Information about critically ill patients with SARS-CoV-2 infection is scarce. We aimed to describe the clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia.

**Methods** In this single-centered, retrospective, observational study, we enrolled 52 critically ill adult patients with SARS-CoV-2 pneumonia who were admitted to the intensive care unit (ICU) of Wuhan Jin Yin-tan hospital (Wuhan, China) between late December, 2019, and Jan 26, 2020. Demographic data, symptoms, laboratory values, comorbidities, treatments, and clinical outcomes were all collected. Data were compared between survivors and non-survivors. The primary outcome was 28-day mortality, as of Feb 9, 2020. Secondary outcomes included incidence of SARS-CoV-2-related acute respiratory distress syndrome (ARDS) and the proportion of patients requiring mechanical ventilation.

**Findings** Of 710 patients with SARS-CoV-2 pneumonia, 52 critically ill adult patients were included. The mean age of the 52 patients was 59.7 (SD 13.3) years, 35 (67%) were men, 21 (40%) had chronic illness, 51 (98%) had fever. 32 (61.5%) patients had died at 28 days, and the median duration from admission to the intensive care unit (ICU) to death was 7 (IQR 3–11) days for non-survivors. Compared with survivors, non-survivors were older (64.6 years [11–2] vs 51.9 years [12–9]), more likely to develop ARDS (26 [81%] patients vs 9 [45%] patients), and more likely to receive

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	Survivors (n=20)	Non-survivors (n=32)	All patients (n=52)
Age, years	51.9 (12.9)	64.6 (11.2)	59.7 (13.3)
Age range, years			
30–39	6 (30%)	0	6 (11.5%)
40–49	3 (15%)	3 (9%)	6 (11.5%)
50–59	4 (20%)	9 (28%)	13 (25%)
60–69	6 (30%)	11 (34%)	17 (33%)
70–79	1 (5%)	7 (22%)	8 (15%)
≥80	0	2 (6%)	2 (4%)
Sex			
Female	6 (30%)	11 (34%)	17 (33%)
Male	14 (70%)	21 (66%)	35 (67%)
Exposure			
Exposure to Huanan seafood market	9 (45%)	8 (25%)	17 (33%)
Exposure to patients*	2 (10%)	8 (25%)	10 (19%)
Chronic medical illness	5 (25%)	16 (50%)	21 (40%)
Chronic cardiac disease	2 (10%)	3 (9%)	5 (10%)
Chronic pulmonary disease	2 (10%)	2 (6%)	4 (8%)
Cerebrovascular disease	0	7 (22%)	7 (13.5%)
Diabetes	2 (10%)	7 (22%)	9 (17%)
Malignancy	1 (5%)	1 (3%)	2 (4%)
Dementia	0	1 (3%)	1 (2%)
Malnutrition	0	1 (3%)	1 (2%)
<b>Smoking</b>	2 (10%)	0	2 (4%)

Data are n (%) or mean (SD), unless otherwise specified. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. \*Patients who have confirmed SARS-CoV-2 infection or are highly suspected of being infected.

**Table 1: Demographics and baseline characteristics of patients with severe SARS-CoV-2 pneumonia**

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