CORRESPONDENCE

Clinical Characteristics of Covid-19 in China

TO THE EDITOR: According to the World Health Organization (WHO), the case definition for surveillance of returning travelers requires that they need to present with fever and at least one respiratory symptom to be considered as having suspected cases of coronavirus disease 2019 (Covid-19).[1] In their article regarding 1099 patients with laboratory-confirmed Covid-19 at hospitals across China during the first 2 months of the pandemic, Guan et al. (Feb. 28 online publication, available at NEJM.org)[2] present compelling data supporting the need for a reassessment of these criteria. The authors found that only 43.8% of the patients presented with fever on admission, although fever developed in 88.7% during hospitalization. That means that if those travelers were returning from affected areas, more than half would not be suspected of having Covid-19, which would result in undetected patients who can spread the virus. This issue may be particularly relevant in low-income countries with less structured health care systems, which could not provide adequate follow-up of these travelers.

The study by Guan et al. suggests that fever is not the hallmark of the onset of Covid-19. Other studies have shown rates of fever from 83 to 98% on admission.[3,4] We believe that a case definition requiring fever and at least one respiratory symptom may lead to an underdiagnosis of a substantial proportion of patients with early Covid-19 and lead to increased transmission of the virus.

Alexandre P. Zavascki, M.D., Ph.D.
Universidade Federal do Rio Grande do Sul
Porto Alegre, Brazil
azavascki@hcpa.edu.br

Diego R. Falci, M.D., Ph.D.
Hospital Moinhos de Vento
Porto Alegre, Brazil

No potential conflict of interest relevant to this letter was reported.

This letter was published on March 27, 2020, at NEJM.org.

1. World Health Organization. Global surveillance for human infection with coronavirus disease (COVID-19): interim guidance. February 27, 2020 (https://www.who.int/publications-detail/global-surveillance-for-human-infection-with-novel-coronavirus-(2019-ncov)).
2. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. DOI: 10.1056/NEJMoa2002032.
3. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
4. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507-13.

DOI: 10.1056/NEJMc2005203

TO THE EDITOR: In their article on the first cases of Covid-19 across China, Guan et al. use descriptive statistics to account for the events: 15.7% of patients with severe cases of the infection, 5% who were treated in the intensive care unit (ICU), and 1.4% who died. The mortality reported here is not to be confused with the true case fatality ratio, since 93.6% of the patients had not yet reached an outcome at the time of data censoring (January 31). As stated in the WHO consensus with respect to the 2002–2003 epidemic of severe acute respiratory syndrome (SARS),[1] "simple methods for calculating case fatality ratios from aggregate data will not give reliable estimates during the course of an epidemic."

It is also important to qualify current mortality estimates, which are based on a health system with incredible response capabilities, including entire regions in quarantine[2] and expedited building of hospitals. Low- and middle-income countries (85% of the world)[3] with already strained health systems should interpret developing data cautiously. The case fatality ratio in each system will depend on the active efforts made to prevent and slow the spread of the virus.

Andre T.C. Chen, M.D., Ph.D.
George B. Coura-Filho, M.D., Ph.D.
Marília H.H. Rehder, M.D., Ph.D.
Instituto do Cancer do Estado de São Paulo
São Paulo, Brazil
andre.chen@hc.fm.usp.br

Dr. Rehder reports being employed as a global patient safety physician at Eli Lilly do Brasil. No other potential conflict of interest relevant to this letter was reported.

This letter was published on March 27, 2020, at NEJM.org.

1. World Health Organization. Consensus document on the epidemiology of severe acute respiratory syndrome (SARS). 2003 (https://www.who.int/csr/sars/en/).
2. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382:727-33.
3. The World Bank Group. Low & middle income. 2019 (https://data.worldbank.org/income-level/low-and-middle-income).

DOI: 10.1056/NEJMc2005203

TO THE EDITOR: Guan et al. cite hypertension and diabetes as the coexisting conditions that pose the highest risk of complications in patients with Covid-19. Do the authors have any data regarding the percentage of patients in their study who were receiving angiotensin-receptor blockers (ARBs) or angiotensin-converting–enzyme (ACE) inhibitors and whether such treatment had any effect on the incidence of infection, severity of disease, or their defined primary composite end point of admission to an ICU, the use of mechanical ventilation, or death?

Since SARS-CoV-2 (the virus causing Covid-19) infects cells through the ACE2 receptor,[1-3] the addition of an ARB may decrease the infectivity and potential injury caused by the virus. In addition, the use of an ACE inhibitor may worsen the situation. ARBs do not block the ACE2 receptor well, but there is some crossover, with each individual ARB having a different degree of affinity to the angiotensin II type 1 (AT1) receptor and to the angiotensin II type 2 receptor (AT2)[4]; ARBs also have an effect on the production of chymase and angiotensin II.[5] At this point, do the authors have information on these questions?

J. Douglass Rolf, M.D.
Kelowna Respiratory Clinic
Kelowna, BC, Canada
roldresp@kelresp.com

No potential conflict of interest relevant to this letter was reported.

This letter was published on March 27, 2020, at NEJM.org.

1. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020;395:565-74.
2. Hofmann H, Pyrc K, van der Hoek L, Geier M, Berkhout B, Pöhlmann S. Human coronavirus NL63 employs the severe acute respiratory syndrome coronavirus receptor for cellular entry. Proc Natl Acad Sci USA 2005;102:7988-93.
3. Imai Y, Kuba K, Rao S, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature 2005;436:112-6.
4. Siragy HM. Angiotensin receptor blockers: how important is selectivity? Am J Hypertens 2002;15:1006-14.
5. Huang XR, Chen WY, Truong LD, Lan HY. Chymase is upregulated in diabetic nephropathy: implications for an alternative pathway of angiotensin II-mediated diabetic renal and vascular disease. J Am Soc Nephrol 2003;14:1738-47.

DOI: 10.1056/NEJMc2005203

TO THE EDITOR: Guan et al. observed severe cases of Covid-19 at higher frequency in patients with diabetes, hypertension, cardiovascular disease, or a history of smoking. SARS-CoV-2 uses as its host receptor ACE2,[1] which is highly expressed in the lungs and converts angiotensin II (Ang II) to angiotensin 1–7 (Ang 1–7).[2] The axis consisting of ACE2, Ang 1–7, and Mas receptor opposes the vasoconstrictive, proinflammatory, and pro-oxidative properties of the ACE–Ang II–AT1 axis.[2] Decreased ACE2 levels are reported in patients who have a history of diabetes, hypertension, cardiovascular disease, or smoking.[2,3] We suspect that virus binding attenuates residual ACE2 activity, which leads to further imbalance between Ang II and Ang 1–7. High circulating levels of Ang II induce pulmonary vasoconstriction, which promotes ventilation–perfusion mismatch and increases vascular permeability, inflammation, and oxidative stress and can lead to acute lung injury or acute respiratory distress syndrome (ARDS).[4] Thus, we encourage investigation of AT1 blockers, Ang 1–7, and recombinant ACE2 as potential therapeutic agents to mitigate acute lung injury or ARDS in patients with severe Covid-19.

Brandon M. Henry, M.D.
Cincinnati Children's Hospital Medical Center
Cincinnati, OH
brandon.henry@cchmc.org

Jens Vikse, M.D.
Stavanger University Hospital
Stavanger, Norway

No potential conflict of interest relevant to this letter was reported.

This letter was published on March 27, 2020, at NEJM.org.

1. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS. J Virol 2020;94(7):e00127-20.
2. Tikellis C, Thomas MC. Angiotensin-converting enzyme 2 (ACE2) is a key modulator of the renin angiotensin system in health and disease. Int J Pept 2012;2012:256294.
3. Oakes JM, Fuchs RM, Gardner JD, Lazartigues E, Yue X. Nicotine and the renin-angiotensin system. Am J Physiol Regul Integr Comp Physiol 2018;315:R895-R906.

4. Zhang H, Baker A. Recombinant human ACE2: acing out angiotensin II in ARDS therapy. Crit Care 2017;21:305.

DOI: 10.1056/NEJMc2005203

THE AUTHORS REPLY: We concur with Zavascki and Falci that approximately half the patients with Covid-19 would have been underdiagnosed if the diagnostic criteria had been solely based on the presence of fever. This finding was similar to the result of a study involving 81 patients with varying disease severity showing that approximately 30% of the patients in whom Covid-19 was diagnosed were afebrile on admission.[1] Our findings might have been attributable to the variation in the predominant symptoms or signs among the study population and the different timing of examination. As the correspondents point out, fever developed in nearly 90% of the patients in our study during their hospital stay. Therefore, afebrile patients with a recent contact history and radiologic manifestations consistent with atypical pneumonia on admission should be screened for Covid-19 by viral nucleic acid assay of respiratory samples.

Chen and colleagues express concern regarding the validity of the estimated case fatality rate during the epidemic. A more precise estimate could have been derived from a study that included a longer follow-up duration among all study patients. Given the urgency to inform clinicians worldwide, we defined the censoring time as the data cutoff (January 31), when a considerable proportion of the patients remained in the hospital. In spite of this shortcoming, our mortality estimate (1.4%) was close to the national official estimates (2.0 to 3.5%) between February and March.[2]

Rolf comments on a valuable approach to determine the effect of ARBs on the clinical outcomes of patients with Covid-19. However, given the urgency and the incompleteness of records in some participating sites, plus the variable length of follow-up, our database cannot convincingly address further the potential benefits of this class of medication.

We appreciate the suggestions of Henry and Vikse, who propose the use of angiotensin 1 blockers, Ang 1–7, and recombinant human ACE2 in patients with Covid-19. We are planning to initiate a clinical trial that compares the effects of an intravenous infusion of recombinant ACE2 (at a dose of 0.4 mg per kilogram of body weight twice daily for 7 days) plus the standard of care, as compared with the standard of care alone, on the time course of body temperature and the dynamics of viral loads (ClinicalTrials.gov number, NCT04287686). The hope is that such treatment with a novel class of medications may show a benefit in patients with Covid-19.

Wei-jie Guan, Ph.D.
Nan-shan Zhong, M.D.
First Affiliated Hospital of Guangzhou Medical University
Guangzhou, China
nanshan@vip.163.com

Since publication of their article, the authors report no further potential conflict of interest.

This letter was published on March 27, 2020, at NEJM.org.

1. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis 2020 February 24 (Epub ahead of print).
2. World Health Organization. Coronavirus disease (COVID-2019) situation reports. 2020 (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/).

DOI: 10.1056/NEJMc2005203