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). 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) 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. 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.

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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), “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 and expedited building of hospitals. Low- and middle-income countries (85% of the world) 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.

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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.

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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.

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

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