Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Towards precision management of cardiovascular patients with COVID-19 to reduce mortality

To the Editor:

It is suggested that COVID-19 patients with pre-existing cardiovascular diseases (CVDs) should be prioritized for interdisciplinary management, because of their higher risk for complications or mortality in COVID-19.[1] Suppression of the classical angiotensin converting enzyme (ACE)–angiotensin II (angII)–angiotensin receptor (AT) 1 axis may be part of the treatment of COVID-19 while decreasing CVD complications and mortalities. ACE increases angiotensin production, causing vasoconstriction, inflammatory responses, and oxidative distress via the classical ACE–angII–AT 1 axis.[2] The pathophysiology of severe COVID-19 involves overwhelming inflammatory responses and cytokine storm, which is also likely caused by the excessive activation of the classical ACE–angII–AT 1 axis.[2] Consequently, inhibition of this axis could likely reduce the inflammatory response and mortality rates among patients with COVID-19. This was consistent with the finding that continued use of ACE inhibitors (ACEI) or angiotensin receptor blockers (ARB) throughout the hospital stay was associated with lower rates of death, intubation and possibly the length of stay in patients with pneumonia.[3,4] Treatments of COVID-19 and CVD may thus both target this same ACE pathway.

However, CVDs include a broad range of conditions affecting the heart or blood vessels with different severity, which may lead to heterogeneities in the linkage between CVDs and COVID-19 mortality. To better understand that linkage and make it more useful for the treatment and prevention of COVID-19 among CVD patients in clinical settings, e.g., precision management, we need to further explore possible mechanisms underlying that linkage. The pathophysiology of COVID-19 involves the unmet oxygen demand from its supply, also known as hypoxia. As most CVD patients may experience hypoxia to different degrees, the existence of hypoxia may increase their mortality risk of COVID-19 relative to those without pre-existing CVDs. COVID-19 infects host cells through ACE2 molecules, causing acute myocardial injury and potentiating chronic damage to the cardiovascular system. Lower levels of ACE2 mediates the occurrence of cytokine production that can cause or is the result of the imbalance between oxygen supply and demand,[2,5] similar to the pathophysiology of type 2 myocardial infarction in COVID-19, especially in those with underlying CVDs. Going one step further, we postulate that CVD patients with a poorer tolerance to hypoxia may have higher morality risks of COVID-19, which may also apply to healthy people. A poor hypoxia tolerance indicates that the body has to activate the ACE–angII–AT 1 axis, at occasions, to a pathological degree which also causes systematic inflammation, incurring vulnerability to infection even death.

People with a better tolerance to hypoxia usually reside in high altitudes. A rough estimate of the association between altitude and COVID-19 mortality at provincial level in China was conducted on the basis of the COVID-19 epidemiological data from outbreak to 15 March 2020 (the last day before issuing the regulation of the 14-day isolation for arrivals at Beijing), during which most COVID-19 patients had stayed home for the Chinese Spring Festival holiday and hence were diagnosed or died from the disease in their hometown provinces. Our postulation was supported by a general negative association between the median altitude and COVID-19 mortality rates (Fig 1). People from high altitude areas usually have chronic respiratory alkalosis with higher minute ventilation and lower $PaCO_2$, both of which facilitate oxygen delivery to tissue under hypoxic environments. In contrast to people from high-altitude areas, when a non-acclimated healthy individual is rapidly exposed to a high-altitude environment, the circulating ACE levels increase because insufficient tissue oxygen supply, and an augmented ACE response from hypoxia causes inflammatory responses in the body or even lead to high altitude pulmonary edema.[5] Similar inflammatory conditions occur in COVID-19 patients with dyspnea, and without appropriate management, a small portion of them develop pulmonary edema and even acute respiratory distress syndrome.

Understanding the adaptability of high-altitude residents to hypoxia may shed light on the likely lower COVID-19 mortality within this population. In a meta-analysis on high-altitude adaptation, researchers found that populations residing at high altitudes were more likely to have ACE gene I/I or I/D rather than D/D as compared to people residing at low altitudes.[6] Meanwhile, the prevalence of the I allele was commonly associated with low ACE activities, irrespective of ethnicity or altitude of residence.[7] These findings indicate that the ACE gene (I/I) polymorphism, from generations of adaptation to high altitude, is likely the protective factor against lung injuries, including in COVID-19.

In conclusion, the alignment between our postulated clinical mechanisms and epidemiological estimates, despite some confounding factors, enables us to propose a novel hypothesis between patients of high-altitude origin and their lower mortality risk of COVID-19. This is to be further tested by medical research teams with access to larger numbers of COVID-19 cases who might originate from a broad geographical distribution with different altitudes. We suggest, therefore, considering patients' epidemiological information (e.g., birthplace and residential history) when implementing precision management of CVD patients with COVID-19, to enhance mortality risk reduction.

Statement of Conflict of Interest

None of the authors have any conflicts of interests with regard to this publication.

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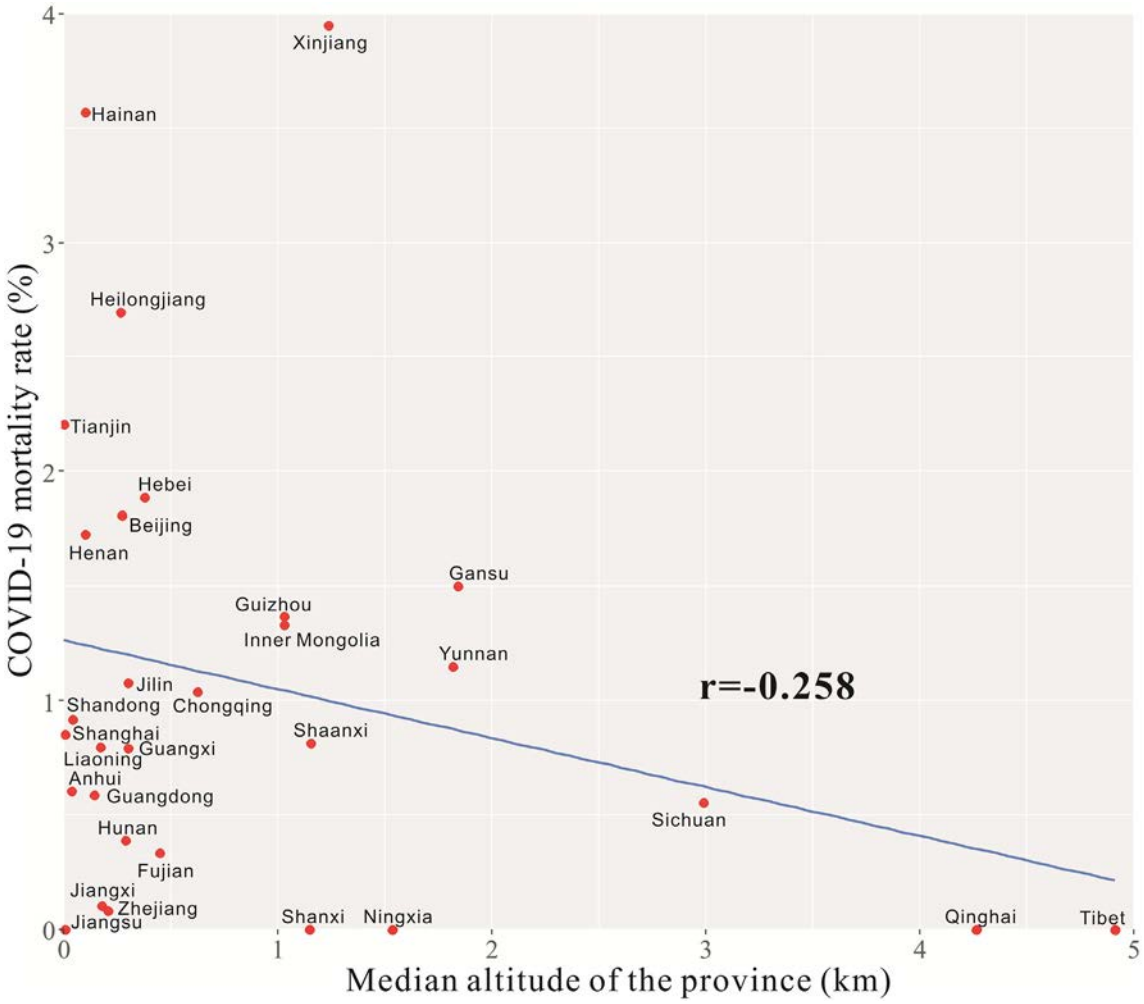

Fig 1. Associations between the median altitude and COVID-19 mortality rates at provincial level in China, on the basis of COVID-19 epidemiological data from outbreak to 15 March 2020 (Hubei Province was excluded as the lockdown of Wuhan, the capital city of Hubei Province, has kept patients from going back to hometown provinces).

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