Commentary

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ABO blood group predisposes to COVID-19 severity and cardiovascular diseases

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Ever since the first outbreak in Wuhan China December 2019, novel coronavirus disease (COVID-19) has rapidly spread to many other regions and become a global health threat. So far, COVID-19 has affected over 200 countries and the mortality rate reached as high as 8% in Italy.[1] The novel pathological agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), uses angiotensin-converting enzyme 2 (ACE2) during transmission.[2] One important epidemiological clinical characteristic of COVID-19 is the enrichment of severe patients with cardiovascular disease carriers especially hypertension.[3]

Hypertension is the global leading cause of mortality and represents the most important factor predisposing the risk of developing cardiovascular diseases. Hypertensive patients typically have over-elevated ACE/ANGII axis, in which ACE positively regulates the level of angiotensin II (ANGII) in the renin–angiotensin–aldosterone system (RAS). Drugs that inhibit the RAS, namely ACE inhibitors and angiotensin receptor antagonists (ARAs), are common medications for hypertension management.[4] While ACE is hypertension promoting, ACE2 counterbalances the effects of ACE and delivers many beneficial effects to human health including attenuating inflammatory response and redox stress.[5]

It was reported that the ABO blood group is associated with ACE activity and ACE inhibitor-induced cough among Chinese patients with essential hypertension.[6,7] That is, the GATC haplotype of the four polymorphisms of the *ABO* gene (rs8176746, rs8176740, rs495828, rs12683493), which is prevalent among non-O blood type patients, is positively associated with ACE activity.[6] Thereby, O blood type carriers should have lower ACE levels and a higher probability of enjoying protection from ACE2-conveyed benefits. Consistent with this, blood type O carriers have a higher interleukin 6 (IL-6) level than non-type O carriers.[8] IL-6 is a proinflammatory cytokine triggering the production of acute-phase proteins such as C-reactive protein. As higher levels of C-reactive protein were detected among ACE-inhibitor-induced coughers than controls,[9] we would expect a positive relationship between IL-6 secretion and ACE inhibitor and/or ACE2. A genome-wide association study (GWAS) found that blood type O carriers have increased IL-6 levels than individuals carrying the other blood group types,[8] suggesting the advantages of blood type O over the other types in maintaining the dominant role of ACE2 in the RAS and thus a reduced risk of developing hypertension.

On the contrary, the A allele of the ABO blood group has been associated with an increased risk of developing cardiovascular diseases as reported by several studies.[10] The A antigen might protect P-selectin and intercellular cell adhesion molecule 1 (ICAM1) from enzymatic cleavage by promoting stronger and longer binding of leukocytes to them on the vascular wall; more adhesion molecules attached to the endothelial cells would on one hand increase adhesion and inflammation but on the other hand decrease circulation.[11] These collectively predispose type A carriers to a higher likelihood of developing cardiovascular diseases and aggregate disease situations once these individuals were exposed to redox stresses such as in the case of virus infection.

Therefore, individuals having an O blood group type are less likely to develop cardiovascular diseases and severe COVID-19 and, on the contrary, patients carrying an A blood group type, especially those already having been diagnosed with cardiovascular diseases in particular hypertension, are more likely to develop severe COVID-19 once infected (Figure 1). These individuals need to be quarantined and protected from SARS-CoV-2 infection or under special medical care to be prevented from deterioration and severe progression.

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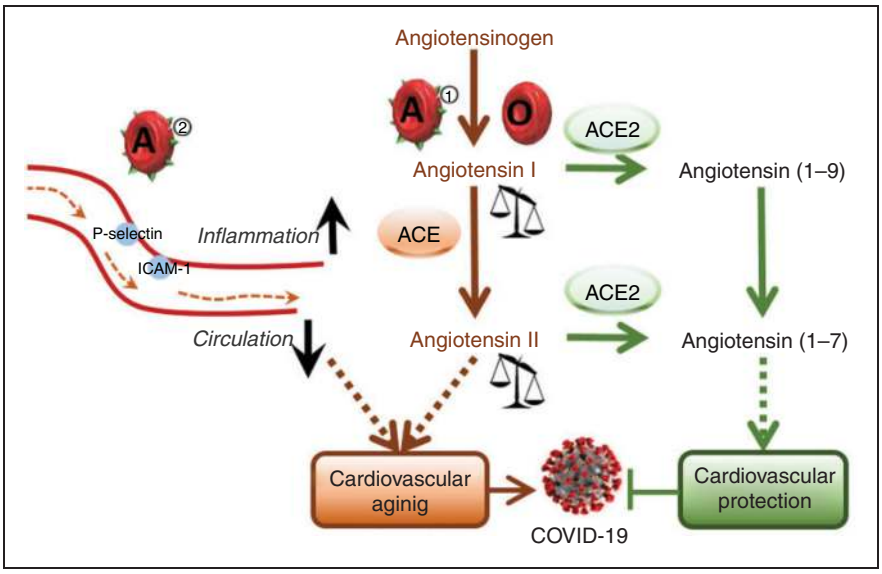

Figure 1. Conceptual Illustration on the predisposing role of ABO blood type to cardiovascular diseases and COVID-19 severity. Blood O type is protective against the development of cardiovascular diseases and severe COVID-19 as it is associated with lower angiotensin-converting enzyme (ACE) level and higher ACE2 activity. Blood A type is risky for the development of cardiovascular diseases and severe COVID-19 due to: (a) its positive association with ACE activity, and (b) the attachment of adhesion molecules on the vascular wall that increases inflammation and decreases blood circulation.

Although ABO blood type and/or cardiovascular diseases are prognostic of COVID-19 patient severity, they are not risk factors predisposing to the risk of getting SARS-CoV-2 infection. This is attributable to the dual roles played by ACE2 (the primary receptor mediating SARS-CoV-2 cell entry), that is, mediating SARS-CoV-2 entry and being protective against cardiovascular diseases, which makes COVID-19 risk and severity a pair of paradoxes.

Declaration of conflicting interests

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