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Letter to the Editor

Association with the actual blood group is the ONLY culprit in ABO and COVID-19 disease severity

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Dear Editor,

The Severe respiratory system coronavirus-2 (SARS-CoV-2) is the virus responsible for the 2019 coronavirus disease (COVID-19) emerged in late 2019 in China leading to a global pandemic. Susceptibility and disease severity in individuals infected with SARS-CoV-2 virus, varies with a range of presentations from completely asymptomatic disease to acute respiratory distress syndrome. Studies have been conducted to look at risk factors for disease acquisition and severity. Risk factors identified for disease severity include age, presence of diabetes, cardiac disease & pulmonary disease. Other risk factors for disease severity were less understood and have been debated, including blood type. Historically, host susceptibility to different infectious diseases has been shown to be related to blood group system. Blood groups are receptors for toxins and microorganisms, where they can facilitate colonization, adherence, transduction, and cellular uptake of microorganisms.

ABO blood grouping is the most used blood grouping system in medical practice. The gene encoding for the ABO blood group is located on human chromosome 9. There are four main blood groups based on the ABO system - A, B, AB, and O. A and B blood group antigens are formed through the action of specific glycosyl transferase enzymes that add distinct glycan (monosaccharide polymers) to the H precursor antigen. The O blood group antigen results from a base deletion in the O allele, inducing a frameshift mutation that eliminates glycosyl transferase activity. This leads to expression of only the H antigen, the base for the ABO blood groups. ABO antigens are widely expressed on the surface of red blood cells, epithelial and endothelial cells.. Naturally occurring plasma antibodies react against non-self ABO antigens, providing the immunological basis for blood type compatibility testing prior to transfusions.

Studies have shown that there is a significant association between ABO blood groups and COVID-19 severity. The main association with O blood group being protective from COVID-19 infection while blood group A being associated with severe disease and blood group B associated with increased risk in mild-moderate disease. Wu et al., 2020 analyzed 6 studies in a meta-analysis (31,100 patients were included in the analysis) and found that blood group A patients were at risk of COVID infection, while AB blood group patients were at risk of severe disease. In addition, patients with blood group O were at lower risk of disease and disease severity [1]. Ellinghaus et al., 2020, conducted genome wide association study including 1980 patients with COVID-19 and severe disease. They found a clear association with locus 3p21.31 and with locus 9q34.2. The locus 9q34.2 contains the ABO blood group. Further analysis of the specific blood showed a higher risk of severe COVID-19 with group A individuals and a protective effect for group O [2].

Most studies conducted to analyze the association between ABO blood groups and COVID-19 disease susceptibility and severity had a major methodology issue. They analyzed data by using a comparison between the blood group positive cases and all those negative for it. In other words, A blood group against non-A blood group. Almost all studies found that O blood group is protective, thus having the O group in the comparison group (non-A) will influence the results.

Zhang et al., 2021, used the blood group O as the comparison group, thus found that all blood groups were risk for the severe disease [3]. They found that, all non-O blood groups (n = 275,953) compared to O blood group (n = 211,412) carried a 23% increase in COVID-19 hospitalization (OR 1.23 95% CI 1.00–1.51). Showing that blood group O is protective from severe disease while all other blood groups carry risk for the disease.

Is it the ABO blood group antigens or the natural antibodies to A and B that is responsible for the association with disease outcome?

Mortensen et al., 2023, found that anti-A (IgG) blood group to be associated with enhanced protection from COVID in a dose-response, the higher the titer of anti-A the higher the protection [4]. They also found that anti-B antibodies (IgM) were associated with lower susceptibility to COVID-19. They suggested that the pre-existing anti-A and anti-B have anti-viral effect through activating T cell responses. This is highlighted by the study of Guillonet al in 2008, that showed using *in vitro* studies that the association with blood group O is through the naturally occurring IgG antibodies which appears to be related to their titers; the higher the titers the more effective the blocking of the virus [5].

The association between blood group O and protection from COVID-19 and severe disease is mainly due to the higher titers of the naturally

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occurring IgG anti-A and anti-B antibodies. Association with the actual blood groups is the only culprit.

Declaration of competing interest

All authors declare no conflict of interest.

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