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Editorial

It's Past Time to Figure Out How Comorbidities Contribute to The Severity of Covid-19

George Brown*

University of Aberdeen, Slovenia

Corresponding Author*

George Brown
University of Aberdeen, Slovenia.
E-mail: brown.george9671@gmail.com

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Introduction

The introduction of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) from China has put human lives in jeopardy. Asymptomatic, mild, or severe pneumonia-like symptoms characterise Coronavirus Disease 2019 (COVID-19). COVID-19 people with diabetes, COPD, CVD, hypertension, cancer, HIV, and other comorbidities may face a life-threatening scenario. To enter the cell, SARS-CoV-2 uses ACE-2 receptors present on the surface of the host cell. Certain comorbidities are linked to increased ACE-2 receptor expression and proprotein convertase release, which aids viral entrance into host cells. The COVID-19 patient enters a vicious infectious loop of life as a result of the comorbidities, which are strongly linked to severe morbidity and mortality. Individuals with comorbid conditions must take extra precautions and be managed carefully. In this study, we concentrated on the impact of common morbidities in COVID-19 patients and reviewed therapy methods in light of recent developments. We discovered few materials describing the relationship between COVID-19 and comorbidities; nonetheless, this review defines the broader spectrum of comorbidities that COVID-19 patients face.

At the end of December 2019, the Chinese city of Wuhan reported pneumonia cases of unclear origin. The causal agent was discovered as a novel coronavirus (2019-nCoV), now known as SARS-CoV-2, and coronavirus illness as COVID-19 on January 7, 2020 [1]. The disease quickly spread across China and crossed international borders, resulting in approximately 7 million confirmed cases and >0.4 million deaths worldwide [2]. The four genera of Coronaviruses (CoVs) are αCoV, βCoV, γCoV, and δCoV. Only αCoV and βCoV are known to cause illness in mammals among these taxa. Severe acute respiratory syndrome (SARS) in 2003 and Middle East respiratory syndrome (MERS) in 2012 were recognised to be caused by βCoVs, which were known to induce serious life-threatening respiratory illnesses. SARS-CoV-2 is also a member of the βCoV family, which is an enveloped virus with a positive sense-RNA genome that is responsible for COVID-19 [3]. SARS-genome CoV-2's has 96 percent resemblance to bat CoV RaTG13, according to genomic study. SARS-CoV shares evolutionary similarities with Rhinolophus affinis, Bat-SL-CoVZC21, and then Bat-SL-CoVZC45, indicating that it originated in the Chinese chrysanthemum bat. The genomic sequencing and evolutionary investigation of SARS-CoV-2 revealed that 79.5 percent of the genome matched that of SARS-CoV, and bats have been suggested as probable reservoirs for the virus that transmitted it to humans via an unnamed intermediary host. Pangolin has recently been discovered to have 99 percent genomic similarity with SARS-CoV-2, implying that it plays an important role in viral transmission and infection [4]. SARS-CoV-2 is spread *via* zoonotic animals or human-to-human contact via respiratory droplets.

For the past two years, a novel coronavirus known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been responsible for a global pandemic, with nearly 280 million infections and 5.4 million fatalities by the end of 2021. Bedside observations indicated individuals at higher risk of severe coronavirus disease-2019 (COVID-19)-related pneumonia and death as soon as the pandemic broke out. The most significant factor related to death was age. Diabetes, obesity, previous hypertension, cancer, and chronic renal, cardiovascular, and respiratory disorders were all linked to a higher risk of severe respiratory symptoms, which could lead to hospitalisation or possibly ICU admission. The most severe individuals died from refractory acute respiratory injury despite the use of high-flux oxygen, mechanical ventilation, and even extracorporeal membrane oxygenation, as well as bacterial and mycological super infections, thromboembolic sequelae, and multi organ failure. Anti-COVID-19 treatments such as repurposed antiviral, immunomodulatory, and anticoagulant medicines were widely employed in addition to supportive care, however they were ineffective [5].

The question of how comorbidities may add to the severity of COVID-19 remains unsolved. It's worth looking into whether underlying comorbidities increase the risk of contamination by facilitating SARS-CoV-2 entry or replication in the targeted cells, thereby increasing the viral load; whether they alter the host's immune response to the viral infection by precipitating the cytokine storm; or whether they simply increase the disease burden in frailer patients. Understanding the molecular pathways that may be involved can aid in the development of extremely effective targeted anti-COVID-19 treatments in the future. A propensity to severe COVID-19 manifestations was first suggested to be due to a gene polymorphism. The discovery of heightened vulnerability in specific patient subgroups prompted a search for gene signals engaged in important host antiviral defence mechanisms and/or mediators of inflammatory organ damage using genome-wide association (GWAS) [6]. In four critically ill SARS-CoV-2 infected young males, putative loss-of-function variants of X-chromosomal Toll-like receptor (TLR)7 associated with impaired type-I and II interferon responses were identified, providing insight into COVID-19 pathogenesis and underlying the essential protective role of type-I interferon immunity against SARS-CoV-2 [7]. Later, it was discovered that X-linked recessive TLR7 deficiency is a highly penetrant genetic aetiology of serious COVID-19 pneumonia, with a prevalence of 1.8 percent in male patients under 60 years old. Other gene possibilities were explored for their potential to aid viral replication, change the immune response, and/or explain interindividual variability in innate and adaptive immune responses. COVID-19 pneumonia is caused by inborn defects of type-I interferon immunity that are dependent on TLR3 and IRF7. B cell autoimmune phenocopy of inborn defects of type-I interferon immunity was found to be responsible for life-threatening COVID-19 pneumonia in at least 2.6 percent of women and 12.5 percent of men in international cohorts. Type-I autoantibodies neutralise it. 2 of 4 interferons were shown to account for 20% of severely ill COVID-19 patients over 80 and overall mortality, predating SARS-CoV-2 infection and significantly rising in prevalence after the age of 70 years. A global network of researchers also established a mechanism for discovering, recruiting, and genetically profiling individuals who are naturally resistant to SARS-CoV-2 infection. The protective effect of the O allele among the ABO blood classes, which may function as co-receptors for SARS-CoV-2, was validated in a meta-analysis involving 50,000 patients from 46 studies. GWAS has discovered a variation near the angiotensin-converting enzyme-2 (ACE2), the major cell receptor of SARS-CoV2, as able to give protection, potentially through lowering ACE2 expression on SARS-CoV-2-targeted cells. An endoplasmic reticulum transmembrane protein called Transmembrane Protein 41B (TMEM41B) was identified as essential for permissive infection using a genome-wide CRISPR knockout screen for SARS-CoV-2 infection, with a potential relationship between its level of expression and COVID-19 severity. Gene polymorphism, on the other hand, could not account for all individual vulnerabilities. Changes in the expression of genes involved in type-I interferon signalling and viral replication pathways have been linked to comorbiditiesHeparan sulphate proteoglycans, in addition to ACE2, have been discovered to interact with the viral spike protein, explaining why changes in their expression could lead to higher sensitivity to COVID-19. Because SARS-CoV-2 entry necessitates sequential cleavage of the spike protein, which is synthesised as an inactive precursor, at the S1/S2 and S20 cleavage sites to mediate membrane fusion, proteases involved in these processes may influence individual susceptibility to COVID-19 if their baseline activity varies according to comorbidities. During attachment to the cell surface, cell surface proteolytic enzymes such as the transmembrane serine protease isoform 2 (TMPRSS2) and the human airway trypsin-like protease (HAT or TMPRSS11D) break the SARS-CoV-2 spike protein. Other endolysosomal transmembrane serine proteases (TTSPs) and cathepsins (mainly cathepsin L) help prime the spike protein and degrade the extracellular matrix, allowing SARS-CoV-2 to infect the host cells. Furthermore, the discovery of a four-amino-acid insertion (PRRA) at the S1/S2 boundary in the SARS-CoV-2 spike protein sequence suggested that furin or furin-like proteases may be involved in the production of virions in host cells, influencing the level of viral replication and thus the severity of the

disease. The renin-angiotensin-aldosterone and kinin–kallikrein systems have both been linked to the cytokine storm seen in COVID-19 patients. Because ACE2 inactivates des-Arg9-bradykinin, SARS-CoV-2-induced ACE2 inhibition enhances bradykinin 1-receptor effects. a metabolite of bradykinin SARS-CoV-2 reduces the effects of the bradykinin 2-receptor by blocking cathepsin L, which is present at the infection site and implicated in bradykinin production. Vasoconstriction and promotion of pro-fibrotic, apoptotic, and inflammatory signalling in SARS-CoV-2-targeted tissues could be caused by dysregulation of the renin-angiotensin-aldosterone balance and overactivation of the angiotensin II type-I receptor axis. Breidenbach and colleagues investigated the expression of various genes that might facilitate SARS-CoV-2 entry using various SARS-CoV-2-targeted organ tissues obtained from 1968 patients with common comorbidities known to increase the risk of COVID-19 severity in a study published in the journal. Gene expression in whole-tissue homogenate was mapped using single-cell RNA sequencing and compared to international databases. Surprisingly, the tissue region with the highest gene expression differed depending on the comorbidity, implying complicated and non-uniform underlying mechanisms that support patient susceptibility. Accordingly, the highest levels of ACE2 expression were found in cancer patients' pulmonary tissues, obese patients' renal tissues, diabetic heart failure patients' cardiac tissues, and coronary disease patients' peripheral blood mononuclear cells. In patients with hypertension, cancer, and a history of smoking, there was a significant increase in the expression of TTSPs, including TMPRSS2 and HAT, across the SARS-CoV-2-targeted organ systems as compared to healthy persons. Breidenbach's findings, when combined with molecular biology research looking at gene activation, inhibition, or deletion, corroborated the role of SARS-CoV-2 entry-related gene expression patterns in the outcome of COVID-19 patients. However, since SARS-CoV-2-mediated endothelial alterations are a well-established non-organ-specific injury-related at least in part to modifications in bradykinin receptor expression and activity, these researchers' findings were limited by their whole-tissue-homogenate-based approach, which included the vascular component of each tissue type, their findings were limited by their whole-tissue-homogenate-based approach, which included the vascular component of each tissue type. As a result, before linking the identified tissue-specific gene expression patterns with the relevant comorbidities, these preliminary data must be evaluated with caution. To summarise, we still have a long way to go in terms of better understanding the sensitivity of patients with comorbidities to severe COVID-19 patterns. All of the work done so far will be extremely important in understanding the pathophysiology of SARS-CoV-2 infection and developing particular curative and preventive medicines in the coming years to protect at-risk groups and reduce morbidity and mortality.

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