Vulnerability to SARS-CoV-2 infection and disease: ripping the curl after the storm

Microbiology Unit. Laboratory of Public Health. Universidad Rey Juan Carlos, Madrid, Spain

ABSTRACT

SARS-CoV-2 infection now seems to have entered the announced endemic phase. The population’s immunity is increasingly more robust, thanks to successive vaccination and booster campaigns, and the almost inevitable exposure and re-exposure to the virus itself, which has truly served as a natural immunizing mechanism. On the other hand, the genetic drift of the virus is leading it to become another catarrhal agent, as are the other endemic human coronaviruses. However, it should not be lost sight of that there are still segments of the population with susceptibility to severe COVID, who will be candidates to continue receiving vaccine boosters or antiviral drugs in the initial stages of infection.

Keywords: COVID, SARS-CoV-2, vulnerability, comorbidity, frailty

INTRODUCTION

The clinical manifestations of the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection, named as coronavirus infectious disease (COVID), occur in a wide range, that moves from asymptomatic infection to multi-organ failure and death. The probability of having severe disease has been changing throughout the pandemic, mainly for three reasons: the protective effect of vaccination [1], the selection of less lethal SARS-CoV-2 variants – only demonstrated for lineage B.1.1.529 (Omicron, and subsequent subvariants) – [2] and due to the lower severity of reinfections, particularly in vaccinated individuals. According to descriptive epidemiological studies carried out very early in the pandemic [3,4], symptomatic infection was approximately limited to: i) catarrhal symptoms, including mild pulmonary involvement, in 80% of cases; ii) severe pneumonia with hypoxia in 15% of cases; iii) respiratory distress, shock or multiple organ failure in 5% of cases; and iv) death in 2% of cases. At the end of 2021, among the vaccinated population, the probability of serious illness is estimated at 0.015% and death at 0.003% [5].

GENETIC FACTORS

Several genetic variants and epigenetic factors have been associated with severe COVID. SARS-CoV-2 uses several receptors (ACE2, TMPRSS2) for entry to cytoplasm of epithelial cells; certain mutations at ACE2 may increase risk of death, while changes at TMPRSS2 reduce susceptibility to infection. Once pathogen-derived molecules are detected by immune cells, interferons (IFN) and other proinflammatory cytokines are released; mutations at the level of these mediators are related with more intense inflammatory response to infection, and therefore with greater incidence of respiratory distress and thrombotic events.

At the level of HLA receptors, 3p21.31 and 9q34.2 loci are significantly associated with COVID severity. Epigenetic mechanisms including methylation, histon acethylation, and X chromosome inactivation (XCI) also affect COVID outcomes by regulating IFN signaling and ACE2 expression, and immunity-related genes that particularly escape from XCI [6].

DEMOGRAPHY

Age is the main factor that determines the risk of severe COVID. Infection by SARS-CoV-2 is generally mild or asymptomatic in children, adolescents and young people [7,8]. According to various studies in adults, the age segments of under 50 years of age, from 50 to 64 years of age, from 65 to 74 years of age, from 75 to 84 years of age and over 85 years of age can be established to estimate increasing risks of admission for COVID [9]. Mortality is concentrated in patients older than 65 years [10], and increases especially in those older than 80 years [11]. In vaccinated people, a history of SARS-CoV-2 in-
es, a worse prognosis can be expected in the case of chronic obstructive pulmonary disease, severe asthma, cystic fibrosis in adults, interstitial lung disease, history of pulmonary hypertension, pulmonary thromboembolism or tuberculosis. The presence of respiratory failure at the time of diagnosis of COVID is a data of very poor prognosis. In general, the negative effect of these pathologies is more evident if the risk of death is considered [16,17]. Cardiovascular alterations such as arterial hypertension, ischemic heart disease, cardiomyopathies, heart failure or cerebrovascular disease have also been related to severe COVID [18].

Chronic kidney or liver disease, due to the organic dysfunction they entail and regardless of their cause, and certain degenerative neurological diseases (e.g. Down syndrome, dementia) or mental disorders contribute to severe COVID [19].

The degree of frailty and the need for care that it entails, to which age and various chronic debilitating diseases contribute, may be the common reason for this worse prognosis [20].

Immunosuppression is a recognized risk factor for severe COVID-19 or death [21], with many clinical situations contributing to this situation (primary or acquired immunodeficiencies, immunosuppressive treatments for inflammatory diseases or in transplant recipients, cancer treatment, etc.). It is necessary to analyze the specific effect of each disease, of each treatment and the clinical situation of each patient, since, for example, HIV infection under effective antiretroviral treatment does not complicate the evolution of COVID [22]. Oncological disease [23], particularly if it is of hematological origin [24], is one of the most determining factors of severe COVID. Table 1 summarizes the main factors associated with severe COVID.

**LIMITATIONS**

It is not easy to establish the individual weight of many of these factors on the severity of COVID. In the first place, it would be necessary to establish if each factor only affects the severity of the infection, or if it also contributes to a greater risk of death. On many occasions, comorbidities are analyzed generically, using definitions that include diseases with very different prognoses and in different stages of severity. Many conditions identified as risk factors are associated with other comorbidities, which produces statistical associations that do not always indicate causality. In other cases, it is necessary to analyze whether the effect of a certain disease is due to the pathology itself or to the effect of certain drugs commonly used for its treatment. Chronic diseases that cause frailty and dependency lead patients to more frequent exposure to infection, which in itself can increase severity. Additionally, most of the analyzes on prognostic factors come from retrospective studies, with the limitations that this entails when drawing conclusions.

The effect of certain factors on the pathogenesis of COVID itself is unknown; for example, there is still discussion about the risk-benefit of drugs that interfere at the level of the ACE2 receptor or some immunosuppressants. Finally, in most pa-
patients several factors are associated, and it is precisely this sum of risks that probably contributes most to the severity of COVID [5]. Table 2 summarizes the main limitations to detect risk factors related with severe COVID.

Finally, the understanding of the pathways and involved factors that lead to severe COVID is key to identify those populations that are still in need for special attention. It is very likely that universal indication of SARS-CoV-2 vaccination may not be feasible in the future, so that urges to determine most vulnerable populations for whom yearly vaccine may be clear

CONFLICT OF INTEREST

Authors declare no conflict of interest

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