

COVID in Older People: Some Answers, New Questions

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According to the World Health Organization (WHO), SARS-Cov-2 pandemic is close to an end. Thus, some reflections about the magnitude of this disease in older people are necessary. First of all, people over 65 years-old have been the most affected population due to coronavirus disease. Despite not being the age range with the highest number of people infected (12.17% of the total cases), it has been the age group with the highest mortality rate (74.22%) (1). A series of risk factors have been identified that could explain this excess of mortality compared to younger people, such as proinflammatory biomarkers, polypharmacy, gender, or comorbidities. However, there was a common denominator between COVID-19 and its mortality in all the studies carried out in this population: the baseline functional status (even more than comorbidity or the severity of the disease) (2-5). Once more, the functionality (along with age and gender, non-modifiable factors) is a strong prognostic tool in old people. Unfortunately, it is still one of the most ignored variable, not only as a prognostic factor. The work by Melo et al published in this issue of the JNHA (6) comes to add new pieces of knowledge in the interaction between frailty and acute diseases, in this case, COVID-19 disease. In this retrospective cohort study carried out in 7 Veterans Health Administration medical centers the authors show a dose-response relationship between frailty, assessed by FI-LAB, and in-hospital mortality, prolonged length of stay, higher rates of intensive care unit admission, and transfer. However, these interesting results, that reinforce the evidence linking functional status with the in-hospital outcomes in patients with COVID, have to be taken with caution for several reasons. The first one is related to the population included in the study, a young sample with a mean age of 66 years-old, including people younger than 60 and in which we do not know how many people are over 60-65. Taking into account that the highest rates of mortality have been seen in the population older than 75 years-old, the under-representation of the people in this age-range can bias (likely decreasing the true effect of frailty) the results. In this regard is worthy to mention that people with the lowest grade according to the FILAB are the youngest one, supporting the previous reasoning. Not to mention that almost the whole participants of the study were male (94% overall sample size), so maybe an adjustment by gender would not be necessary. On the other hand, the FI-LAB uses some laboratory and clinical parameters (such as lymphocytes, neutrophils, renal and liver function,

pulse, blood pressure, temperature, oxygen saturation) to assess frailty in individuals without acute infection. But most of these variables are affected by SARS-Cov-2 infection, which could lead to a high risk of bias: in these patients, are we measuring frailty or disorders due to coronavirus disease? At the end of the day, we are assessing a cluster of lab biomarkers plus some very simple clinical issues (i.e. blood pressure), which could produce some doubts about the accuracy of the test used. Lastly but not least, an adjustment by baseline functional status should have done to avoid a possible bias, being one of the most important predictor factors of fatality outcomes due to COVID-19 in old people.

But function is not only a risk factor for adverse outcomes in people with COVID-19, including those admitted to the hospital, but also in those who did not need hospitalization. Functional impairment is also a consequence of COVID and COVID-hospitalization at short-, mid-, and long-term in older people with coronavirus disease in whom important functional and cognitive decline (quality of sleep, anxiety, and depression) have been reported (7, 8).

The different explanations of the functional impairment in older people with SARS-Cov-2 could classify in three groups: biological changes due to the infection, the hospitalization process and pharmacological treatment itself, and a lower physical activity of moderate-high intensity during quarantine. Among the first ones, it is important to mention the inflammatory response related to the infection that produces a muscle hypoxia, mitochondrial dysfunction, and higher metabolic disorders. This inflammation, when associated with nutritional deficits plus low physical activity, encourages the loss of muscle mass and sarcopenia (8). Additionally, hospitalization process and some pharmacological treatments (corticosteroids) increase the risk of some functional items (frailty, loss of functional capacity, disability) (9), especially in those with higher dependency (Barthel Index <40/100) (10). According to different studies, functional decline could be observed between 30-47% of older people after 6 months of discharged for COVID-19 (11, 12). According to a Spanish study, this functional impairment remains even until 18 months post-COVID infection (Barthel index decline in 47.6% and FRAIL scale worsening in 52.1% of the participants)(13), emphasizing that functional status does not recover spontaneously. Lastly, the lower physical activity due to confinement, could have accelerated the development of sarcopenia, associated with an increase of fat mass. Even more,

a loss of muscle function is calculated in 10% of old population during the pandemic, increasing, once more, the risk of frailty and sarcopenia (7).

According to these findings, there is a need not only to put a special emphasis on caring for patients hospitalized due to COVID showing a poor functional status, but also to avoid the infection of this older people. And the best way of achieving that objective is vaccination. And frailty seems to play a role in the effectiveness of such approach. As it is reported in another elegant study from the same group of the Veteran administration led by Dr. Jorge Ruiz published in this issue of JNHA, showing that the effectiveness of the mRNA based vaccines against SARS-Cov-2 is diminished in frail people (14)

In this second study, an inverse relationship between frailty and the effectiveness of SARS-Cov-2 vaccine is shown. The methodological approach to answer the research question is based on the test negative case control study, a method which is growing in the last years to evaluate the effectiveness of vaccines. Although it offers some advantages to assess this effectiveness, it also raises the risk of some biases. In a recent published systematic review, authors claim for caution when interpreting the results of these studies, especially if vaccination has demonstrated to reduce disease severity in breakthrough infections (15), as it is the case with this vaccine. Nevertheless, this study adds new evidence previously obtained by the same group about the effectiveness of the vaccine (16). Vaccination is one of the most cost-effectiveness and important interventions in primary prevention of infection disease. Notwithstanding, to prevent infection diseases in older population is an important challenge, taking into account the immunosenescence process (leading to a lower response to vaccination and a higher decrease of generated antibodies) as well as the functional impairment and risk of frailty associated to infection disease (especially in those who require hospital admission). The conclusion of this study corroborates the known data of relationship between immunity and inflammatory response plus frailty.

Taking them as a whole, these two studies highlight the peculiarity of frail patients also in the case of infection by SARS-Cov-2. It should have clinical implications regarding both the prevention through vaccination and the functional characterization when admitted to a hospital in order to identify people at the higher risk and promoting interventions.

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