Introduction

In December 2019, a cluster of pneumonia cases of unknown cause was reported in Wuhan city, the capital of Hubei province in China (1). The novel coronavirus, subsequently named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified via deep sequencing of patients’ respiratory tract samples (2); the disease was designated in February 2020 by the World Health Organization (WHO) as coronavirus disease 2019 (COVID-19) (3). The WHO declared COVID-19 as a pandemic on 11 March 2020.

At the end of April 2021, almost 130 million people have been infected with SARS-CoV-2 worldwide and nearly three million (2.3%) have died (4). Therefore, this disease has induced again catastrophic events, comparable with the Spanish fever related to the flu H1N1 virus, occurred from 1918 to 1920 (5).

Infact, the pandemic influenza mortality ranged from 0.03 percent of the world’s population during the 1968 H3N2 pandemic to 1-3 percent of the world’s population during the 1918 H1N1 pandemic. Hence the SARS-CoV-2 mortality was really high, in terms of percentage, similarly to the Spanish fever.

However, the absolute number of deaths during the World-War I and also during the Spanish fever was really higher than during SARS-CoV-2 (about ten of million versus millions of persons worldwide) (Figure 1).

The main cause of mortality during SARS-CoV-2 is the presence of severe pulmonary insufficiency due to interstitial pneumonias (6).

Pulmonary CT in more than 90% of SARS-CoV-2 patients shows an initial interstitial pneumonia whose characteristics are similar to pneumonias caused by other agents such as H1N1 and chlamydia.

In most patients with SARS-CoV-2 pneumonias, the radiological picture evolves rapidly within the first 72 hours after admission together with the emergence of other signs, indicative of additional diseases and a parallel worsening of the clinical conditions (7).

As during the Spanish fever, pulmonary thrombosis was a common finding at the autoptic table. The common finding of sudden increase in D-dimer levels in SARS-CoV-2 patients with pneumonias suggest the presence of a similar mechanism in these patients. Use of contrast CT and close monitoring of D-dimer levels would be highly indicated and lead to using adequate doses of anticoagulant (6).
Immune response to SARS-CoV-2

From the pathophysiology point of view, interstitial pneumonia is related to the cytokine storm produced by the organism as reply to this infection (8). Even this event, defined as the production of excessive amounts of cytokines, has been observed in H1N1 virus isolated from the 1918 pandemic, as compared with common reference strains of the virus that causes influenza A, triggered marked pulmonary inflammation in mice. In details, IL-6 has the key role on inducing pneumonia and higher is the serum levels of the IL-6 greater is the risk of developing interstitial pneumonia. However, other pro-inflammatory cytokines are involved in the diseases. Globally, SARS-CoV stimulate the innate immune system leading to the release of antiviral cytokines, in particular type-1 interferons (IFNs), which suppress viral replication, although many viruses could have developed mechanisms to evade this response (9).

Thus, an increase in neutrophils and a decrease in lymphocytes characterizes COVID-19 patients, and appears to be correlated with severity of disease (10). High levels of pro-inflammatory cytokines and chemokines occur in more severe diseases, including elevated IL-2, IL-6, IL-7, TNF-α, G-CSF, MCP-1, MIP-1α and IP-10. Plasma pro-inflammatory cytokine levels were relatively unaffected in COVID-19 patients with mild-moderate disease, and but these patients had a decrease in circulating monocyte populations, possibly due to efflux to the site of infection (10).

A rise in antibody-secreting cells, follicular helper T cells and anti-SARS-CoV-2 IgG and IgM antibodies was reported in a patient prior to recovery (10). Finally, even CD4+ and CD8+ T-cells are important in controlling viral infections, including SARS-CoV (11-12), and might protect from SARS-CoV-2 infection. However, the relative lymphopenia which accompanies SARS-CoV-2 infection (13) might suggest viral-induced suppression of immunity or lymphocyte trafficking to infection site. A Th1 response is thought to be required for SARS-CoV-2, but over exuberant CD8+ T-cell response may contribute to immunopathology (14).
Risk factors for hospitalization and death

Many studies have examined the risk factors potentially involved in the severity of SARS-CoV-2 disease (15). While 80% of patients had mild disease, 15.7% developed severe disease, most of which were older than 65 years and with coexisting morbidities including COPD, diabetes mellitus and/or hypertension, and only 5% were critical, requiring ventilatory or extracorporeal membrane oxygenation (ECMO) support (7).

However, it was recently shown a stronger role as risk factor for hospitalization and death in persons affected by COVID-19 was shown for the body mass index (BMI).

In details, a recent study has found a not linear (J-shaped) relationship between BMI and death (16), with 23 kg/m² identified as the optimal cut-off value of lower risk of death. A BMI lower than 20 kg/m² and greater than 23 kg/m² were associated with an increased risk of death. In particular, for all the BMI values above 23 there was a linear increased death for each one point of increase.

The relationship between BMI and severity of disease during SARS-CoV-2 infection is somewhat unsurprisingly. Since it is very well-known that adipose tissue produces for itself IL-6 (17), it becomes more probable that having larger amount of adipose cells, during the SARS-CoV-2 infection, might be associated with an exaggerated cytokine storm. The sequelae of inflammatory responses include damage in many tissues especially lung, with a total invasion of the lung parenchymal with diffuse alveolar damage and/or organizing pneumonia.

On the other hand, having BMI lower than 20 kg/m² could reflect persons with malnutrition (undernutrition type), and probably with secondary sarcopenia or different severity of frailty, particularly frequent in older persons (18).

Hence, based on existing data, BMI could be considered the strongest key element for defining “FRAIL/VULNERABLE” persons during SARS-CoV-2 infection. National authorities should be taking into account these data for planning future preventive measured and vaccination and avoiding an increase of mortality due to COVID-19 infection.

BMI is an expression of obesity and one of phenotypic criteria of undernutrition (19-). Both of these conditions are really relevant worldwide (20), suggesting the need of implementing the knowledge on the importance of nutrition for general health and also for preventing severe forms of COVID-19 infection.

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