Apocalyptic COVID-19 mortality and BMI: a J-shape relationship?

Fulvio Lauretani, Ferdinando Lauretani, Marcello Maggio

Department of Medicine and Surgery, University of Parma, Italy, Geriatric Clinic Unit, University-Hospital of Parma

Abstract. 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. Both of these conditions are really relevant worldwide, 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. (www.actabiomedica.it)

Key words: COVID-19, Coronavirus, BMI, malnutrition, obesity, death

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, may be of apocalyptic dimensions, 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 Word-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 suggests 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).
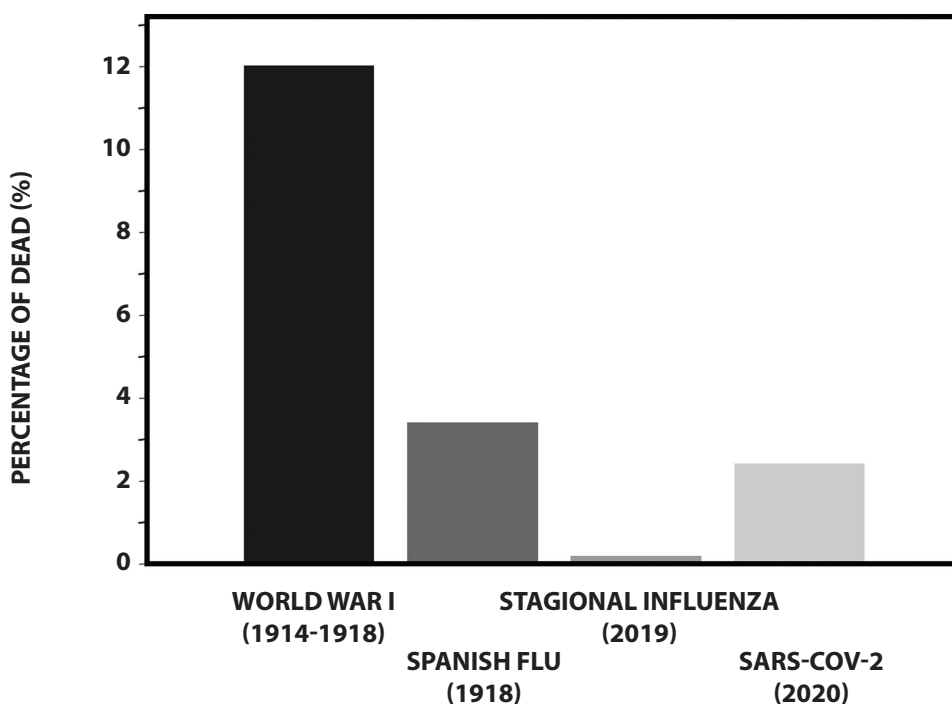
Figure 1. Comparison of the percentage of the mortality between Word War I, Spanish flu, Stagional Influenza and SARS-COV-2 infection.

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[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/m^2 identified as the optimal cut-off value of lower risk of death. A BMI lower than 20 kg/m^2 and greater than 23 kg/m^2 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/m^2 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.

References

1. Report of clustering pneumonia of unknown etiology in Wuhan City. Wuhan Municipal Health Commission, 2019. http://wjw.wuhan.gov.cn/front/web/showDetail/2019123108989.
2. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 2020; 382: 727-33.
3. World Health Organization. Naming the coronavirus disease (COVID-19) and the virus that causes it. Available online: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it
4. Ross JS. Covid-19, open science, and the CVD-COVID-UK initiative. BMJ 2021;373:n898.
5. Patterson GE, McIntyre KM, Clough HE, Rushton J. Societal Impacts of Pandemics: Comparing COVID-19 With History to Focus Our Response. Front Public Health 2021;9:630449. doi: 10.3389/fpubh.2021.630449.
6. Lauretani F, Ravazzoni G, Roberti MF, et al. Assessment and treatment of older individuals with COVID 19 multisystem disease: Clinical and ethical implications. Acta Biomed 2020; 91:150-168.
7. Abu-Raya B, Migliori GB, O'Ryan M, et al. Coronavirus Disease-19: An Interim Evidence Synthesis of the World Association for Infectious Diseases and Immunological Disorders (Waidid). Front Med (Lausanne) 2020;7:572485. doi: 10.3389/fmed.2020.572485.
8. Fajgenbaum DC, June CH. Cytokine Storm. N Engl J Med 2020;383:2255-2273.
9. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. Nature 2020; 579:265-9.
10. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395:497-506.

11. Zhao J, Mangalam AK, Channappanavar R, et al. Airway Memory CD4(+) T Cells Mediate Protective Immunity against Emerging Respiratory Coronaviruses. Immunity 2016;44:1379-91.

12. Coleman CM, Sisk JM, Halasz G, et al. CD8+ T Cells and Macrophages Regulate Pathogenesis in a Mouse Model of Middle East Respiratory Syndrome. J Virol 2016;91: e01825-16.

13. Zhao J, Alshukairi AN, Baharoon SA, et al. Recovery from the Middle East respiratory syndrome is associated with antibody and T-cell responses. Sci Immunol 2017;2:eaan5393.

14. Wang SF, Chen KH, Chen M, et al. Human-leukocyte antigen class I Cw 1502 and class II DR 0301 genotypes are associated with resistance to severe acute respiratory syndrome (SARS) infection. Viral Immunol 2011;24: 421-6.

15. Jordan RE, Adab P, Cheng KK. Covid-19: risk factors for severe disease and death. BMJ 2020;368:m1198.

16. Gao M, Piernas C, Astbury NM, et al. Associations between body-mass index and COVID-19 severity in 6·9 million people in England: a prospective, community-based, cohort study. Lancet Diabetes Endocrinol 2021;9:350-359.

17. Werida RH, El-Gharbawy NM, Mostafa TM. Circulating IL-6, clusterin and irisin in obese subjects with different grades of obesity: association with insulin resistance and sexual dimorphism. Arch Endocrinol Metab 2021; 24:2359-3997000000336.

18. McCarthy K, Hewitt J, Myint PK, Quinn T, Carter B. Frailty and mortality in patients with COVID-19 - Authors' reply. Lancet Public Health 2020;5:e582.

19. Cederholm T, Jensen GL, Correia MITD, et al. GLIM criteria for the diagnosis of malnutrition - A consensus report from the global clinical nutrition community. Clin Nutr 2019;38:1-9.

20. Fedele D, De Francesco A, Riso S, Collo A. Obesity, malnutrition, and trace element deficiency in the coronavirus disease (COVID-19) pandemic: An overview. Nutrition. 2021 Jan;81:111016. doi: 10.1016/j.nut.2020.111016.

———

Correspondence
Received: 23 June 2021
Accepted: 23 June 2021
Prof. Fulvio Lauretani
Associate Professor of Internal Medicine and Geriatrics
Department of Medicine and Surgery, University of Parma
Building 15, Via Gramsci 14, 43126 Parma, Italy
Phone: +39 0521 703325
E-mail: fulvio.lauretani@unipr.it