

THE NEW CHALLENGE OF GERIATRICS: SAVING FRAIL OLDER PEOPLE FROM THE SARS-COV-2 PANDEMIC INFECTION

GEMELLI AGAINST COVID-19 GERIATRIC TEAM*

* Gemelli Against COVID-19 Geriatric Team: F. Landi, C. Barillaro, A. Bellieni, V. Brandi, A. Carfi, M. D'Angelo, D. Fusco, G. Landi, R. Lo Monaco, A.M. Martone, E. Marzetti, F. Pagano, C. Pais, A. Russo, S. Salini, M. Tosato, A. Tummolo, F. Benvenuto, G. Bramato, L. Catalano, F. Ciciarello, I. Martis, S. Rocchi, E. Rota, A. Salerno, M. Tritto, A. Sgadari, G. Zuccalà, R. Bernabei. Corresponding author: Francesco Landi, MD, PhD, Fondazione Policlinico Universitario "Agostino Gemelli" IRCCS, Catholic University of the Sacred Heart, L.go F. Vito 8, Rome 00168, Italy, Phone: +39 (06) 5190028, e-mail: francesco.landi@unicatt.it

In December 2019, a relevant number of patients affected by a mysterious pneumonia has been documented in Wuhan, China (1). Around the end of last year, the causative agent of this unexplained pneumonia has been identified as a new coronavirus. This virus has been "baptized" as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the relative disease has been called as coronavirus disease 2019 (COVID-19) by the World Health Organization. The COVID-19 epidemic is spreading in China and all over the world now as pandemic infection (1).

The aim of this review is primarily to analyze the epidemiology of COVID-19 in the older population, the clinical manifestation and diagnosis, the potential therapeutic strategies, and the role of the geriatrician in managing this infection emergency.

SARS-CoV-2 infection

The pathogen that causes COVID-19 disease is a new coronavirus that has been isolated in the late January 2020, called SARS-CoV-2 (2). Coronaviruses are a big group of extremely diverse single-stranded RNA viruses. Considering the relationship of its genetic sequence to that of other known coronaviruses, SARS-CoV-2 probably originated in bats. The animal that host SARS-CoV-2 between a bat reservoir and humans is unknown (2). Even though this new coronavirus has some genetic structures that matching with the other coronavirus, it has specific gene sequences that are substantially different from the gene sequences of other known coronaviruses (3).

Apart of the genetic characteristics, the envelope spike (S) protein is really important for infectious mechanism of coronavirus. This S protein facilitates receptor binding and membrane fusion and it is important for inducing the host tropism and at the same time the transmission power (3). Angiotensin converting enzyme II (ACE2) is actually known as cell receptor for SARS-CoV2 (4). Analogous to the known SARS-CoV, SARS-CoV-2 utilize ACE2 as the entry point in the ACE2-expressing cells, suggesting SARS-CoV-2 share the similar life cycle with other SARS-CoV (4). It is important to highlight that S protein of SARS-CoV-2 binds ACE2 with around from 10- to 20-fold greater attraction than S protein of SARS-CoV (5). This high affinity of S protein for human ACE2 probably has facilitate the rapid spread of SARS-CoV-2

in human populations. Increasingly, evidence shows continued human-to-human transmission, along with many disseminated cases across the entire globe (6).

Epidemiology

The World Health Organization (WHO) has declared COVID-19 disease a public health emergency of international concern. Even though no age-group is protected from the SARS-CoV-2 infection, the burden is absolutely higher and most severe among persons aged 70 years and over, with a well-known mortality rates of more than 20% among octogenarians (7). The presence of multiple pre-existing comorbidities is related with more severe COVID-19 infection manifestation, reflecting the presence of pre-existent physical and/or cognitive frailty. It is now evident that the COVID-19 disease vulnerable and dying population encompasses the older persons and people with underlying medical conditions (such as cardiovascular diseases, diabetes mellitus, renal failure, respiratory diseases), which needs more attention and care (8,9). Recent evidences demonstrate that in Italy there is the highest proportion of older patients with COVID-19 disease and that the rate of older people may partially clarify the differences in the number of cases and in the case-fatality rates observed among countries. Overall, deaths for COVID-19 infection are largely detected among older, male patients who at the same time have multiple comorbidities.

Mitigation strategy for SARS-CoV-2 infection is indispensable to allow optimal care for all patients (especially for older people), preservation of all other important hospital services (i.e., surgery, oncology, hematology), and delivery of specific support for affected people directly in the community and public services in this pandemic era. In this respect, it is important to highlight that the significant higher rates of fatal cases in Italy, compared with other countries, might reflect the older population of Italy and underline the need to adapt the mitigation plan to local demographics.

Clinical features

The range of clinical presentations of COVID-19 disease have been described varying from asymptomatic infection to severe respiratory failure (10). The common clinical manifestations include fever, cough, fatigue, myalgia, shortness

SAVING FRAIL OLDER PEOPLE FROM THE SARS-COV-2 PANDEMIC INFECTION

of breath, sore throat, and headache. In addition, patients may have also gastrointestinal symptoms, with diarrhea and vomiting. Some patients may have taste and smell disturbances, too. While interstitial pneumonia is present in most COVID-19 disease patients, pleuritic chest pain is present in only few cases.

Based on the severity of symptoms, laboratory parameters and radiologic characteristics, patients are classified as mild, severe, and critical types (11). Mild patients had non pneumonia or mild pneumonia with moderate signs and symptoms. Severe patients had numerous clinical symptoms, including fever and cough, blood oxygen saturation less than 94%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio less than 300, respiratory frequency of 30 or more acts per minute, and/or lung infiltrates more than 50%. Finally, critical patients had severe conditions, such respiratory failure, septic shock, and/or multiple organ dysfunction or failure.

Common clinical laboratory findings comprise leucopenia and lymphopenia. In particular lymphopenia is one of the key feature of COVID-19 disease (12). Lactate dehydrogenase and creatinine kinase are elevated, too. Patients frequently have normal serum levels of pro-calcitonin, while the C-reactive protein is almost always above the normal range. Most patients had the elevation of D-dimer that should be considered as a marker of worsen disease (12).

Based on the current evidence, most of the patients have a good prognosis, while a few patients develop critical condition, particularly the older subjects and those patients with chronic underlying multimorbidity. The negative progression of disease tends to be faster in older people that are at higher risk to suddenly develop an acute respiratory distress syndrome (ARDS). Other less common complications are arrhythmia, septic shock, acute kidney injury, acute cardiac injury, liver dysfunction and secondary infection.

Diagnosis

Real Time PCR (RT-PCR) method is usually utilized to find causative viruses from respiratory secretions (13). During the SARS-CoV-2 transmission, RT-PCR has been considered as the primary clinical laboratory diagnostic test.

Different specific and sensitive assays of the SARS-CoV-2 genome were proposed to detect viral RNA in clinical specimens. The sampling source and/or the method to perform the throat/nasal swab may affect RT-PCR testing results. Some studies report that the positive rate of RT-PCR for pharyngeal swab samples is about 60% in early stage of SARS-CoV-2 infection. These results suggest that RT-PCR test should be interpret with caution (13).

Blood oxygen saturation and blood gas analysis are both essential to identify patients at higher risk of developing respiratory distress. Oxygen saturation (SaO₂) of 94% or less while patients are breathing ambient air or a ratio of the partial pressure of oxygen (PaO₂) to the fraction of inspired oxygen

(FiO₂) of less than 300 mmHg are suggestive of respiratory illness.

Figure 1

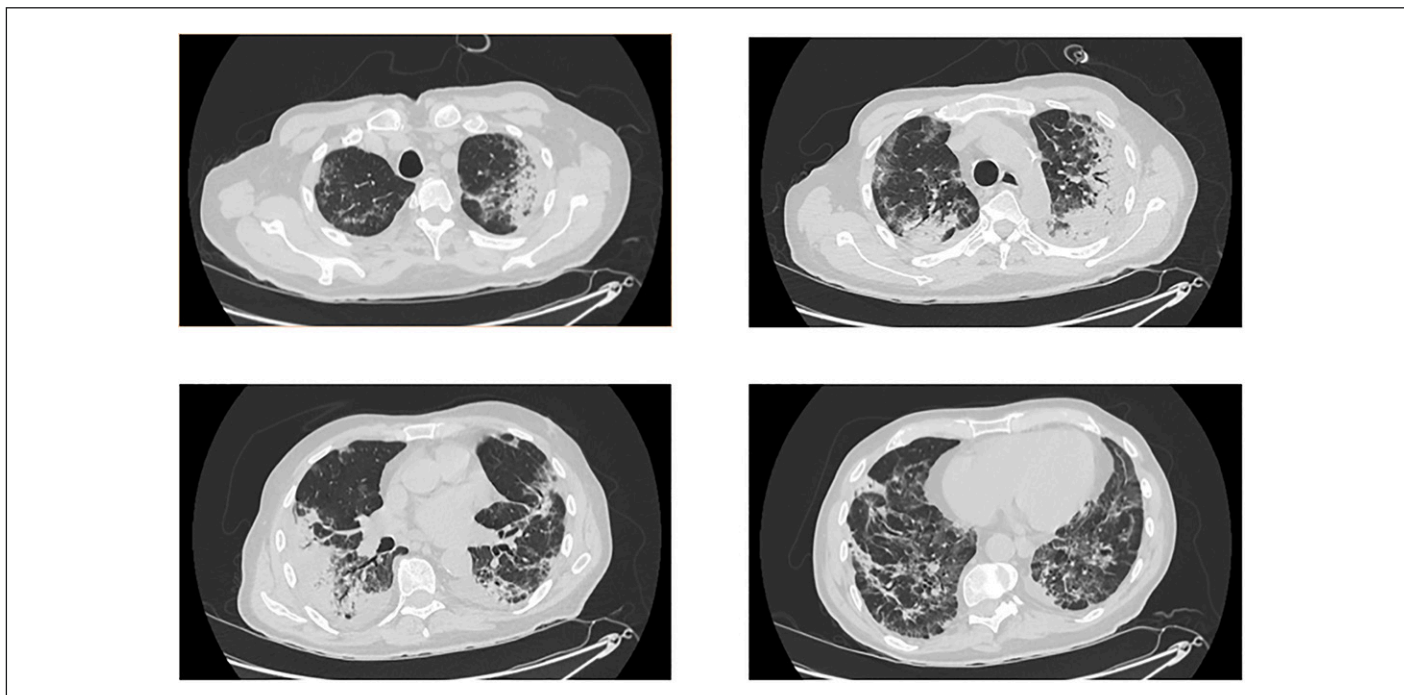
Antero-posterior chest radiograph shows patchy ground-glass opacities (78-year-old man)



The radiologic presentation of COVID-19 disease is different and sometime suddenly progressing (14). Chest X-ray may be useful as an initial screening, but to assess the severity of the disease and better orientate the therapeutic choices and the use of the intensive care unit, the chest CT scan is mandatory. Most of patients suffer from at least two affected lobes and some patients have five affected lobes. The common manifestations observed in these patients are patchy ground glass opacities and eventually patchy consolidation which are mostly spread in the middle, peripheral and posterior area of the lung (15). Fibrous stripes may emerge when the SARS-CoV-2 infection is worsened. Radiologists suggest that it is possible classify four different stages based on CT scan (16). In early stage, ground glass opacities is the main radiological evidence disseminated in the lower lobes unilaterally or bilaterally. In second stage, diffuse and bilateral ground glass opacities and consolidation are evident in more than two lobes. In third stage, diffuse ground glass opacities and more dense consolidation are more numerous and evident. After these active stages, it is possible to observe an extensive ground glass opacities with consolidation progressively absorbed (16).

Figure 2

Chest CT shows diffuse ground-glass opacities, consolidation area, and both ground-glass opacities with consolidation (78-year-old man)



Potential therapeutic interventions

Isolation is the first and the most effective measure of containing SARS-CoV-2 infection (17). Efficient surveillance is the prerequisite for impeding the source and spread of infections. It is important to highlight that older people living in long-term care facilities (such as nursing homes and rehabilitative centers), are particularly vulnerable populations who are at a higher risk for infection due to living in close proximity to others. Thus, long-term care facilities need to have special precautions and protocols to defend residents, employees, and visitors. In this respect the role of geriatricians is crucial for the prompt identification, isolation and care of suspected and confirmed patients affected by COVID-19 disease. This early identification is essential to limit as much as possible the spread of infection among residents in the long-term care facilities. The geriatricians have the responsibility to evaluate the health status of new residents before the admission to immediately identify if the subject suffers of any signs of respiratory disease, comprising fever, cough or dyspnea, too. For all the other residents it is mandatory to assess at least twice a day for the onset of a fever ($\geq 37.0^{\circ}\text{C}$), cough, dyspnea, and any other symptoms potentially correlated to the SARS-CoV-2 infection.

Empirical therapy for COVID-19 disease mainly comprise symptomatic and antiviral drugs. The first helpful interventions are important for treating patients immediately at the onset of symptoms, including oxygen therapy, antibacterial therapy,

and nutrient supplements. In particular, for critically ill patients, high-flow oxygen therapy and the possible use of more aggressive therapies, such as non-invasive and invasive respiratory support are applied (18).

Many studies document the potential effects of the antiviral drugs (darunavir, lopinavir, and ritonavir) to reduce viral load and eventually to prevent the respiratory complications (12, 19, 20). Unfortunately, no conclusive results are available demonstrating positive effects of these drugs. Recently, Cao and colleagues (21) have documented no benefit with lopinavir-ritonavir treatment beyond standard care in hospitalized adult patients with severe SARS-CoV-2 infection. Remdesivir has potential a broad-spectrum activity against viruses such as MERS and SARS in vitro and experimental animal models (14). This antiviral drug is reported to have a positive result in the treatment of a patient with COVID-19 disease in the United States (22). However, the efficacy of all these antiviral drugs for SARS-CoV-2 infection need to be confirmed by randomized, controlled clinical trials.

Recent studies have focused on the potential benefit of chloroquine, a largely used antimalarial drug, in the treatment of patients infected by SARS-CoV-2. It has been previously reported that chloroquine could inhibit SARS-CoV and is studied for treating COVID-19 in some clinical studies in China. In a recent study, Gao and colleagues report that, in more than 100 patients, the chloroquine phosphate is better compared to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a

SAVING FRAIL OLDER PEOPLE FROM THE SARS-COV-2 PANDEMIC INFECTION

virus negative conversion, and shortening the disease course (23). Chloroquine is utilized to prevent and to treat malaria and, at the same time, it is used as an anti-inflammatory drug for the treatment of rheumatoid arthritis and lupus erythematosus. Some evidences documented that it has potential antiviral properties enhancing endosomal pH needed for virus/cell fusion, as well as interfering with the glycosylation process of SARS-CoV cellular receptors (24).

Tocilizumab is a humanized antiinterleukin-6-receptor monoclonal antibody that inhibits interleukin-6 signaling used as treatment in rheumatoid arthritis. Tocilizumab is administered intravenous experimentally in the treatment of COVID-19 disease in China and now in Italy with some encouraging results (25). However, the hypothesis that tocilizumab can restore T cell counts in COVID-19 disease patients, by suppressing IL-6 signal, is actually not fully explored (26). Sarilumab is the other antiinterleukin-6-receptor monoclonal antibody drug that could be used to treat Covid-19 patients in order to reduce the pulmonary inflammation and to prevent the onset of respiratory distress. At present there is no scientific evidence even if in Italy Sarilumab is used experimentally in some patients. Future clinical investigations will help to better define the use of these agents.

The role of geriatrician

The COVID-19 disease is certainly an infectious disease with the manifestation of interstitial pneumonia and severe acute respiratory syndrome (27). The team of medical doctors that is mainly involved has preferably been composed by infectious disease specialists, pneumologists and anesthesiologists. However, given the epidemiology of COVID-19 disease and the higher risk population for negative outcome, the involvement of geriatricians for the correct evaluation and management of these patients is important not only in the community but also in the hospital.

These patients die because of age and comorbidity and are in need of doctors able to deal with such conditions. The geriatrician is the specialist who best can manage the multidimensional health problems of the older subjects, with a great aptitude and skill to cope multimorbid and complex patients (28). Second, geriatricians are the doctors who best know the principles of teamwork and are able to adapt the protective measures (i.e., in long-term care and rehabilitation) according to the needs of the patients in close collaboration with the other health care professionals (i.e., head nurse, nurse, aid nurse, physiotherapist, occupation therapist) and family. The geriatrician is the doctor who can manage the environmental and social isolation imposed by the SARS-CoV-2 infection. In particular, the geriatrician will be able to manage the onset of the most important geriatric syndromes, such as bed rest, sarcopenia, malnutrition, urinary incontinence and delirium (29,30). Finally, geriatricians can act as the “sentinel” for the best possible treatment based on the clinical

and functional conditions and not only on the basis of age.

For the healthcare system in all the countries, it will be essential as quickly as possible to plan for the increase in demand and to recognize how reconfigure services to cope. The COVID-19 pandemic disease has shown the problem of all health care service (31). The high prevalence of older subjects in Western countries puts the health and social systems in a catastrophic crisis because it decompensates for problems otherwise better overcome in younger people. The early assessment of these problems in the community and in long-term care settings can prevent these systemic crises and, as a consequence, a new and modern health care system based on integrated approach is mandatory. Moreover, it is important to plan the new hospital organization shifting healthcare resources and expertise, such as geriatricians, to treat and manage the old subjects who become seriously ill. Based on the Italian experience, the Gemelli against COVID-19 Geriatrics team strongly suggests to all the Countries that in the near future will face the same Italian situation, that the geriatric care teams must be integrated into the management of this SARS-CoV-2 infection crisis (32).

Conclusion

Despite all the aggressive restraint and inhibition efforts, the COVID-19 disease continues to increase, and the total number of infected patients in the World is growing day by day. Many health care systems will be stressed beyond the ability by the demands of enhancing the number of patients affected by COVID-19 disease. Help for all the health-care professionals working on the frontline should be absolutely prioritised. All governments must now take important action to better aggressively combat the outbreak and dissemination of SARS-CoV-2 infection. COVID-19 disease is a huge risk to large segments of the population, mainly for older people and for those patients with pre-existing health comorbidities.

Conflicts of Interest: None.

Ethical Standards: The article is in accordance to ethical standards.

References

1. Phelan AL, Katz R, Gostin LO. The Novel Coronavirus Originating in Wuhan, China: Challenges for Global Health Governance. *JAMA* 2020 Jan 30. doi: 10.1001/jama.2020.1097.
2. Xu J, Zhao S, Teng T, Abdalla AE, Zhu W, Xie L, Wang Y, Guo X. Systematic Comparison of Two Animal-to-Human Transmitted Human Coronaviruses: SARS-CoV-2 and SARS-CoV. *Viruses*. 2020 Feb 22;12(2). pii: E244. doi: 10.3390/v12020244.
3. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. *Lancet* 2020 Feb 15;395(10223):470-473.
4. Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, Li T, Chen Q. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int J Oral Sci*. 2020 Feb 24;12(1):8.
5. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, Tan KS, Wang DY, Yan Y. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. *Mil Med Res* 2020 Mar 13;7(1):11.
6. Ou X, Liu Y, Lei X, Li P, Mi D, Ren L, Guo L, Guo R, Chen T, Hu J, Xiang Z, Mu Z, Chen X, Chen J, Hu K, Jin Q, Wang J, Qian Z. Characterization of spike glycoprotein

THE JOURNAL OF NUTRITION, HEALTH & AGING

- of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. *Nat Commun* 2020 Mar 27;11(1):1620.
7. Prem K, Liu Y, Russell TW, Kucharski AJ, Eggo RM, Davies N. The effect of control strategies to reduce social mixing on outcomes of the COVID-19 epidemic in Wuhan, China: a modelling study. *Lancet Public Health* 2020 Mar 25. pii: S2468-2667(20)30073-6.
8. D'Adamo H, Yoshikawa T, Ouslander JG. Coronavirus Disease 2019 in Geriatrics and Long-term Care: The ABCDs of COVID-19. *J Am Geriatr Soc* 2020 Mar 25. doi: 10.1111/jgs.16445.
9. Zhang L, Ma L, Sun F, Tang Z, Chan P. A Multicenter Study of Multimorbidity in Older Adult Inpatients in China. *J Nutr Health Aging* 2020;24(3):269-276.
10. He F, Deng Y, Li W. Coronavirus disease 2019: What we know? *J Med Virol* 2020 Mar 14. doi: 10.1002/jmv.25766.
11. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* 2020 Feb 24. doi: 10.1001/jama.2020.2648.
12. Li Q, Guan X, Wu P, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J Med* 2020;382(13):1199-1207.
13. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. *N Engl J Med* 2020;382(12):1177-1179.
14. Zhang C, Huang S, Zheng F, Dai Y. Controversial treatments: an updated understanding of the Coronavirus Disease 2019. *J Med Virol* 2020 Mar 26. doi: 10.1002/jmv.25788.
15. Yang W, Cao Q, Qin L et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): A multi-center study in Wenzhou city, Zhejiang, China. *J Infect* 2020;80(4):388-393.
16. Pan F, Ye T, Sun P et al. Time Course of Lung Changes On Chest CT During Recovery From 2019 Novel Coronavirus (COVID-19) Pneumonia. *Radiology* 2020 Feb 13;200370. doi: 10.1148/radiol.2020200370.
17. Wilder-Smith A, Freedman DO. Isolation, quarantine, social distancing and community containment: pivotal role for old-style public health measures in the novel coronavirus (2019-nCoV) outbreak. *J Travel Med* 2020;27(2). pii: taaa020. doi: 10.1093/jtm/taaa020.
18. Liu K, Chen Y, Lin R, Han K. Clinical feature of COVID-19 in elderly patients: a comparison with young and middle-aged patients. *J Infect* 2020 Mar 11. pii: S0163-4453(20)30116-X. doi: 10.1016/j.jinf.2020.03.005.
19. Chan JF, Yuan Z, Kok KH et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet* 2020;395(10223):514-523.
20. Wang D, Hu B, Hu C et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020 Feb 7. doi: 10.1001/jama.2020.1585.
21. Cao B, Wang Y, Wen D et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med* 2020 Mar 18. doi: 10.1056/NEJMoa2001282.
22. Holshue ML, DeBolt C, Lindquist S et al. First Case of 2019 Novel Coronavirus in the United States. *N Engl J Med* 2020;382(10):929-936.
23. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends* 2020 Mar 16;14(1):72-73.
24. Yan Y, Zou Z, Sun Y et al. Anti-malaria drug chloroquine is highly effective in treating avian influenza A H5N1 virus infection in an animal model. *Cell Res* 2013;23(2):300-2.
25. Harrison C. Coronavirus puts drug repurposing on the fast track. *Nat Biotechnol* 2020 Feb 27. doi: 10.1038/d41587-020-00003-1.
26. Chen G, Wu D, Guo W et al. Clinical and immunologic features in severe and moderate Coronavirus Disease 2019. *J Clin Invest* 2020 Mar 27. pii: 137244. doi: 10.1172/JCI137244.
27. Livingston E, Bucher K. Coronavirus Disease 2019 (COVID-19) in Italy. *JAMA*. 2020 Mar 17. doi: 10.1001/jama.2020.4344.
28. Morales-Martínez F. Editorial: A Teaching Geriatric Hospital. *J Nutr Health Aging* 2019;23(1):4-8.
29. Pitkälä KH, Martin FC, Maggi S, Jyväkorpi SK, Strandberg TE. Status of Geriatrics in 22 Countries. *J Nutr Health Aging* 2018;22(5):627-631.
30. Sánchez A, Villalba-Mora E, Peinado IS, Rodríguez-Maña L. Integrated Care Program for Older Adults: Analysis and Improvement. *J Nutr Health Aging* 2017;21(8):867-873.
31. Heymann DL, Shindo N. COVID-19: what is next for public health? *Lancet*. 2020 Feb 22;395(10224):542-545.
32. Thompson R. Pandemic potential of 2019-nCoV. *Lancet Infect Dis*. 2020 Mar;20(3):280.