



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



## Review

## COVID-19 mortality as a fingerprint of biological age

M. Cristina Polidori<sup>a,b,\*</sup>, Helmut Sies<sup>c,d</sup>, Luigi Ferrucci<sup>e</sup>, Thomas Benzing<sup>a,b</sup><sup>a</sup> Department II of Internal Medicine and Center for Molecular Medicine Cologne, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany<sup>b</sup> Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany<sup>c</sup> Institute of Biochemistry and Molecular Biology I, Faculty of Medicine, Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany<sup>d</sup> Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany<sup>e</sup> National Institute on Aging, Baltimore, MD, USA

## ARTICLE INFO

## Keywords:

Biological age

Corona virus disease 2019

COVID-19

Frailty

Severe acute respiratory syndrome-corona

virus 2

SARS-CoV-2

## ABSTRACT

Corona virus disease 2019 (COVID-19) is a global emergency able to overwhelm the healthcare capacities worldwide and to affect the older generation especially. When addressing the pathophysiological mechanisms and clinical manifestations of COVID-19, it becomes evident that the disease targets pathways and domains affected by the main aging- and frailty-related pathophysiological changes. A closer analysis of the existing data supports a possible role of biological age rather than chronological age in the prognosis of COVID-19. There is a need for systematic, consequent action of identifying *frail* (not only older, not only multimorbid, not only symptomatic) persons at risk of poor outcomes.

The ongoing severe acute respiratory syndrome-corona virus 2 (SARS-CoV-2) pandemic is a rapidly developing global emergency which already claimed over 100 million cases and 2.2 million lives worldwide as of February 7th, 2021 (WHO Coronavirus Situation Report, 2021). Experience from numerous countries demonstrates that corona virus disease 2019 (COVID-19) is able to overwhelm the healthcare capacities of relatively well-resourced nations and to shut down their economies and societies (Kupferschmidt, 2020).

A major problem in addressing this crisis is the lack of resilience of already overburdened or underdeveloped health care systems that cannot offer sufficient and adequate respiratory support and intensive care. However, an even greater challenge is the growing number of older persons who are both at high risk of developing COVID-19 and to die because of its consequences. In the next sections we describe some observations supporting the viewpoint that beyond age and individual comorbidities the absolute determinants of COVID-19-related poor outcomes might be related to biological age and multidimensional frailty.

### 1. Multimorbidity vs. comorbidities and case-fatality rate (CFR)

Despite the report of case-fatality rate (CFR) of 1.4 % in patients

without comorbidities vs. 13.2 % for patients with cardiovascular disease, 9.2 % for patients with diabetes, 8.4 % for patients with hypertension (WHO, 2021), the interpretation of these data is not unequivocal. For example, there is a lack of clear evidence that COVID-19 CFR is higher in individuals with single comorbidities such as those listed above or cancer, kidney or liver disease, solid organ transplantation requiring immunosuppression. Most of the patients with one of these illnesses are in fact multimorbid (Valderas et al., 2009). In high-income countries, up to 20 % of the population experiences multimorbidity before the age of 40 years (Fortin et al., 2012), with sharply increasing prevalence reaching 75 % at 70 years, after which it remains relatively stable, probably because of selective mortality (Violan et al., 2014). Therefore, the highest mortality rates shown in oldest-old COVID-19 patients are unlikely to be due to cardiovascular comorbidity alone, as the large majority of older persons suffering from it are multimorbid and do not reach an advanced age. Consistent with this hypothesis, available studies with focus on single diseases comorbid to COVID-19 CFR are rare and mostly small-sized (Du et al., 2020a, b; Zhang et al., 2020a, 2020b) and show a relatively young age of the patients - up to 70 years maximum, who in geriatric medicine are considered the *young old*.

Thus far, reports of large COVID-19 patient cohorts may not always

\* Corresponding author at: Ageing Clinical Research, Department II of Internal Medicine and Center of Molecular Medicine Cologne, Faculty of Medicine and University Hospital of Cologne, Cologne, Germany.

E-mail address: [maria.polidori-nelles@uk-koeln.de](mailto:maria.polidori-nelles@uk-koeln.de) (M.C. Polidori).

<https://doi.org/10.1016/j.arr.2021.101308>

Received 7 May 2020; Received in revised form 9 February 2021; Accepted 18 February 2021

Available online 20 February 2021

1568-1637/© 2021 Published by Elsevier B.V.

account for the case fatality caused or conditioned by severe comorbidities. Thus, their use in answering the question of COVID-19-related excess mortality is limited. Indeed, autoptical studies have shown a large proportion of COVID-19-related deaths to occur in patients with pre-existing conditions (Kommoss et al., 2020). Therefore, it becomes pivotal to address the methods of COVID-19 CFR reporting.

## 2. Advanced age

Deaths from COVID-19 occur predominantly among seniors. COVID-19 appears to be particularly dangerous for older men and to essentially spare other vulnerable age groups usually affected by similar viruses.

In China, more than 50 % of COVID-19 deaths occurred in people over 70 years old even though most SARS-CoV-2 infections were being contracted by people who were younger. In adults over age 80, the CFR has reached almost 22 % (WHO-China Joint Mission on Coronavirus Disease, 2020). In the largest samples available, the median age of patients deceased with a COVID-19 infection is 79 years (Onder et al., 2020), while a CFR of up to 27 % in persons older than 85 years was observed in a large sample of cases in the United States (Centers for Disease Control and Prevention, 2020). Similarly high CFR are reported among residents of long term facilities. Also, data from the COVID-19 Lombardy ICU Network in Italy (Grasselli et al., 2020) show that age is the ultimate risk factor for mortality in COVID-19, with rates significantly over 50 % and 40 % at the age 80+ and 70+, respectively, and much less at younger ages.

## 3. Biological age, not chronological age

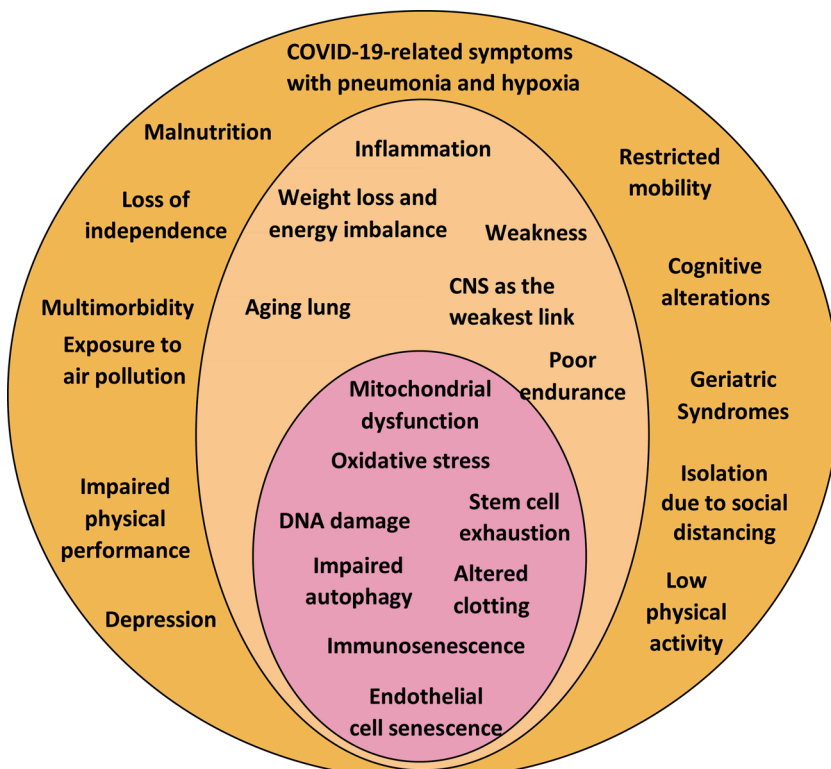
Aging is per definition an inter-individually and intra-individually heterogeneous process, and age-related changes of the lung do not occur at the same rate and to the same extent in all older persons (Polidori, 2020). Accordingly, there are many cases of recovery after COVID-19 severe respiratory distress in the multimorbid oldest old, including one case of a centenarian who had survived the Spanish flu

and the Second World War (Abbatecola and Antonelli-Incalzi, 2020). As a matter of fact, being 80 years old or older cannot be the basis for denying resource allocation in the name of „clinical reasonableness “or „soft utilitarian “approach (Rosenbaum, 2020). There is a huge number of active 80-plus persons worldwide with a remaining, often disability-free, life expectancy of more than 9 years (https://www.ssa.gov/oact/STATS/table4c6.html, latest access on February 7th, 2021).

### 3.1. The frailty model of COVID-19

Are there age-related changes which are particularly relevant to specific pathophysiological mechanisms of COVID-19 disease? In other words: what is the actual phenotype of the patient at highest risk of COVID-19-related mortality?

To answer these questions, it is important to recognize that, similarly to the multifactoriality of age-related diseases, also the pathophysiological mechanisms of COVID-19 challenge the traditional medical paradigm „one cause – one mechanism – one therapy“. From host receptors of SARS-CoV-2 in the cell to the radiologic and histopathologic alterations observed across COVID-19 disease severity stages, all well-established pathways of the physiological ageing process are involved. These include senescence-related receptors CD26 and angiotensin-converting enzyme 2 as well as inflammation-related mechanisms, immunological alterations, hypoxia-related redox signaling changes, and endothelial dysfunction (Polidori, 2020). These alterations paving the way to SARS-CoV-2 pathogenicity including the “cytokine storm” occupy the biomolecular constituents of the aged organism, which can be seen as the inner of three overlapping layers, with the intermediate one being constituted by age-related changes of the lung, and the outer layer representing the clinical presentation of the disease (Fig. 1). We propose that the main reason for high SARS-CoV-2 lethality in advanced age is the impact of COVID-19 on each of the three overlying dimensions of the organism. These dimensions are also commonly used to conceptualize frailty (Ferrucci et al., 2017).



**Fig. 1.** The frailty model of COVID-19. Like in frailty (Ferrucci et al., 2017), the complexity of and pathogenicity of COVID-19 in advanced age goes beyond organ medicine (pneumonia and hypoxemia) and concerns three layers, each strongly affected by SARS-CoV-2. The inner layer includes biological mechanisms hypothesized to be primary causes of frailty, largely predisposing to the SARS-CoV-2-related pathophysiological cascade. The intermediate layer includes biomarkers of frailty and diminished organ reserve, in this case of the lung and of the brain. The outer layer is the clinical presentation of the disease in which pneumonia and hypoxia are only one group of several domains of the ill older patient. Modified from Ferrucci et al., 2017.

### 3.1.1. Layer I, biomolecular changes

Coronavirus is predominantly detected in pneumocytes, less in macrophages and bronchiolar epithelial cells, with hemorrhagic necrosis and lymphocyte depletion in lymph nodes and spleen, indicating a pathological basis of lymphocytopenia (Borges do Nascimento et al., 2020). Regarding the latter, there is a decline in both the production of new naive lymphocytes and the functional competence of memory cell populations with advancing age, which is an established factor in the increasing frequency and severity of breakthrough infections in older persons (Oh et al., 2019). Immunosenescence with low self-renewal capacity of specialized immune cells like lymphocytes might be a facilitating factor of SARS-CoV-2-induced pathogenicity (Franceschi et al., 1998; Akbar and Gilrov, 2020).

Another pivotal factor in the pathophysiology of SARS-CoV-2-induced ARDS is age-related endothelial dysfunction (Donato et al., 2015). During COVID-19, the overproduction of early response proinflammatory cytokines results in the so-called *cytokine storm* and leads to an increased risk of vascular hyperpermeability, multiorgan failure, and eventually death when the high cytokine concentrations are unabated (Jose et al., 2020). Cytokine storm-related vascular hyperpermeability might be particularly dangerous in the aged, already dysfunctional endothelium (Lesniewski et al., 2017).

Thrombosis is commonly observed in small vessels of severely ill COVID-19 patients, also found in extrapulmonary organs free from coronavirus (Campbell and Kahwash, 2020), suggesting alternative mechanisms beyond viral infection, such as hypoxemia and ischemia. Hypoxemia-related cascades are indeed a central node of age-related processes, being oxygen deficiency associated with increased generation of reactive oxygen species (ROS) (Sies and Jones, 2020). Metabolites generated by redox reactions have the capacity to modify macromolecules over time, and cumulative macromolecular damage can contribute to many mechanisms of ageing, including ROS-induced endothelial dysfunction and microthrombotic phenomena (Polidori, 2020). Interestingly, high-dose ascorbic acid (vitamin C), which has shown benefit in sepsis-related acute respiratory distress syndrome (ARDS), may be of use against COVID-19-related symptoms (Carr, 2020).

### 3.1.2. Layer II, multisystem impairment

In the frailty model of Ferrucci et al. (2017), the second layer is defined as the “area of biomarkers” and includes among others neurodegeneration, energy imbalance, and inflammation. In the COVID-19 adaptation of the model, the main actors in this layer are represented by age-related changes in the lung as well as by the so-called *inflammaging* (Franceschi et al., 2000) lowering immune activity but also increasing the autoreactivity of the body. The latter is likely detrimental in older patients affected by the late-stage coronavirus-induced *cytokine storm* (Shenoy, 2020). Under this condition, indeed, the “energy collapse” (Vina et al., 2020) driven by mitochondrial dysfunction and sustained by weight loss, poor endurance and weakness (Fig. 1) is certainly deleterious for the aged organism; a geriatric cascade in these cases is often triggered and leads to failure to thrive (Polidori, 2020).

The most important age-related changes in the lung possibly contributing to COVID-19 pathogenicity are restricted cardiorespiratory function, diminished pulmonary function and strength of respiratory muscles, increased chest wall stiffness as well as diminished forced respiratory volume and oxygen uptake (Valenzuela et al., 2019).

Due to the activation of coagulation pathways during the immune response to infection, thrombin exerts multiple cellular effects which can, in turn, augment inflammation *via* proteinase-activated receptors (PARs) (Jose and Manuel, 2020). While thrombin generation is tightly controlled by negative feedback loops and physiological anticoagulants, such as antithrombin III, tissue factor pathway inhibitor, and the protein C system, during inflammation – as during ageing –, all three of these control mechanisms can be impaired. Altered clotting and crosstalk between coagulation and inflammation as well as of increased D-dimer

levels as possible indicators of co-existence of venous thromboembolism exacerbating in turn ventilation–perfusion mismatch are currently under active investigation (Jose and Manuel, 2020).

### 3.1.3. Layer III, patient-centered, multidimensional factors affecting clinical presentation

COVID-19 older patients’ trajectories and outcomes might be profoundly affected by factors beyond organ medicine which include psychosocial and nutritional status and preexisting dysfunctions (Ferrucci et al., 2017) (Fig. 1). COVID-19 pathogenicity may take strong advantage from malnutrition. While older persons are often malnourished, an optimal nutritional status is fundamental for the adequate functioning of the immune system (Calder et al., 2020). Viral and bacterial infections are often associated with deficiencies in macronutrients and micronutrients, and adequate levels of essential trace elements like selenium are required to counteract viral diseases (Steinbrenner et al., 2015). Interestingly, an association between reported cure rates for COVID-19 and selenium status has been recently observed (Zhang et al., 2020b), and there is some preliminary indication that a healthy diet, along with supplemental antioxidant intake, might be beneficial to COVID-19 patients (Trujillo-Mayol et al., 2021). In addition, restricted mobility, isolation and depressed mood, frequent geriatric syndromes, might be exacerbated by social distancing, a main action taken to limit the spread of the disease. Finally, air pollution, representing the single largest environmental risk to global health, might impact advanced age much more than realized up to date (Mudway et al., 2020), particularly in light of the age-related changes in the lung described above.

Despite attempts to including frailty assessment in COVID-19 protocols (Hewitt et al., 2020; Borenskie et al., 2020; Marengoni et al., 2020; Blomaard et al., 2021), the quality of several identified prognostic COVID-19 models has been judged to be uniformly poor, so that none can be recommended for clinical use to date (Sperrin et al., 2020; Bartoli et al., 2020). For healthcare practitioners working with older persons this is not surprising, as the weight of organ-centred parameters like oxygen saturation and number of existing comorbidities is overcome in advanced age by dynamic, multidimensional aspects usually not identified in clinical routine. Indeed, frailty is not only a dynamic, but most of all a multidimensional condition in which multimorbidity is absent in about one-fourth of patients. On the other hand, only 16 % of multimorbid patients have been classified as frail in a metaanalysis of studies on over 14,000 patients (Marengoni et al., 2011).

## 4. Outlook

Lessons from ageing medicine do suggest that *biological age*, rather than chronological age, of affected patients might be the critical factor to systematically assess COVID-19 infections to avoid excess mortality. Unfortunately, despite active research in the field and promising results (Galkin et al., 2020), there is no currently available specific measure of biological age (Pilotto et al., 2020).

However, there is a well-established surrogate marker of biological age: *frailty*. The frailty phenotype is indeed characterized by a decline in functioning across multiple physiological systems, accompanied by an increased vulnerability to stressors (Fried et al., 2001). It is associated with progressively increasing loss of homeostasis and it prevails in persons with high biological age. Absence of frailty in advanced age is suggestive of young biological age. There are established tools to measure frailty (Dent et al., 2019). It is known that, even in the presence of physiologically diminished organ reserve, older people can compensate for many years. While the frailty phenotype might explain why a proportion of older individuals does not undergo the disastrous consequences of COVID-19, its diagnosis offers physicians a potentially useful way to protect the most vulnerable older adult.

Biological age and frailty, as closely correlated, multifactorial and multidimensional concepts might be best captured by multidimensional tools including biomolecular signatures. Accordingly, specific profiles of



multidimensional frailty as a surrogate marker of biological age can be identified, which strongly increase the risk of poor COVID-related outcomes and, if promptly diagnosed and managed, might restore resilience and ability to thrive.

Taken together, fundamental pathophysiological mechanisms of COVID-19 are also players involved in the main ageing - and frailty-related pathophysiological changes (Ferrucci et al., 2017; Hamczyk et al., 2020; Polidori, 2020; Vina et al., 2018). Interestingly, among the proposed small-molecule therapeutics for the treatment of COVID-19 infection are azithromycin and quercetin - both drugs with significant senolytic activity -, chloroquine-related compounds - which inhibit the induction of the well-known senescence marker beta-galactosidase - and even vitamin C under ICU conditions (Carr, 2020). Of note, there is up to date no single prognostic or therapeutic algorithm able to univocally guide clinical decisions during the pandemic phases preceding and accompanying the vaccination (Sperrin et al., 2020; Bartoli et al., 2020). This is likely due to the multifactoriality, and therefore complexity, characterizing the SARS-Cov-2 infection. To disentangle this complexity, the systematic, consequent action must be implemented of identifying *frail* (not only older, not only multimorbid, not only symptomatic) persons at risk of poor outcomes. Diagnosing frailty will also help understanding and managing critical emerging issues such as therapy response, vaccine effectiveness (Koff et al., 2021) as well as development of the *long COVID syndrome* (Bellan et al., 2021).

## Declaration of Competing Interest

None.

## References

- Abbatecola, A.M., Antonelli-Incalzi, R., 2020. COVID-19 spiraling of frailty in older Italian patients. *J. Nutr. Health Aging*. <https://doi.org/10.1007/s12603-020-1357-1359>.
- Akbar, A.N., Gilrov, D.W., 2020. Aging immunity may exacerbate COVID-19. *Science* 369 (6501), 256–257.
- Bartoli, A., Gabrielli, F., Alicandro, T., Nascimbeni, F., Andreone, P., 2020. COVID 19 treatment options: a difficult journey between failed attempts and experimental drugs. *Int. Em. Med*. <https://doi.org/10.1007/s11739-020-02569-9>.
- Bellan, M., Soddu, D., Balbo, P.E., Baricich, A., Zeppegno, P., Avanzi, G.C., Baldon, G., Bartolomei, G., Battaglia, M., Battistini, S., Binda, V., Borg, M., Cantaluppi, V., Castello, L.M., Clivati, E., Cisar, C., Costanzo, M., Croce, A., Cuneo, D., De Benedittis, C., De Vecchi, S., Feggi, A., Gai, M., Gambaro, E., Gattoni, E., Gramaglia, C., Grisafi, L., Guerriero, C., Hayden, E., Jona, A., Invernizzi, M., Lorenzini, L., Loreti, L., Martelli, M., Marzullo, P., Martino, E., Panero, A., Parachini, E., Patrucco, F., Patti, G., Pirovano, A., Prosperini, P., Quaglino, R., Rigamonti, C., Sainaghi, P.P., Vecchi, C., Zecca, E., Pirisi, M., 2021. Respiratory and psychophysical sequelae among patients with COVID-19 four months after hospital discharge. *JAMA Netw Open*. 4 (1), e2036142 <https://doi.org/10.1001/jamanetworkopen.2020.36142>, 4.
- Bloomaard, L.C., van der Linden, C.M.J., van der Bol, J.M., Jansen, S.W.M., Polinder-Bos, H.A., Willems, H.C., Festen, J., Barten, D.G., Borgers, A.J., Bos, J.C., van den Bos, F., de Brouwer, E.J.M., van Deudekom, F.J.A., van Dijk, S.C., Emmelot-Vonk, M. H., Geels, R.E.S., van de Griend, E.M.M., de Groot, B., Hempenius, L., Kamper, A.M., Kampschreur, L.M., de Koning, M.M.M., Labots, G., Looman, R., Lucke, J.A., Maas, H.A.A.M., Mattace-Raso, F.U.S., El Moussaoui, R., van Munster, B.C., van Nieuwkoop, K., Oosterwijk, L.B., Regtuit, M.E., Robben, S.H.M., Ruiter, R., Salarbaks, A.M., Schouten, H.J., Smit, O.M., Smits, R.A.L., Spies, P.E., Vreeswijk, R., de Vries, O.J., Wijngaarden, M.A., Wyers, C.E., Mooijaart, S.P., 2021. Frailty is associated with in-hospital mortality in older hospitalised COVID-19 patients in the Netherlands: the COVID-OLD study. *Age Ageing*. <https://doi.org/10.1093/ageing/afab018>.
- Boreskie, K.F., Boreskie, P.E., Melady, D., 2020. Age is just a number - and so is frailty: strategies to inform resource allocation during the COVID-19 pandemic. *Afr. J. Emerg. Med*. <https://doi.org/10.1017/cem.2020.358>.
- Borges do Nascimento, I.J., Cacic, N., Abdulazeem, H.M., von Groote, T.C., Jayarajah, U., Weerasekara, I., Esfahani, M.A., Civile, V.T., Marusic, A., Jeroncic, A., Carvas Junior, N., Peric, T.P., Zakarija-Grkovic, I., Meirelles Guimarães, S.M., Bragazzi, L. N., Bjorklund, M., Sofi-Mahmudi, A., Altujjar, M., Tian, M., Arcani, D.M.C., O'Mathúna, D.P., Marcolino, M.S., 2020. Novel coronavirus infection (COVID-19) in humans: a scoping review and meta-analysis. *J. Clin. Med*. pii: E941. <https://doi.org/10.3390/jcm9040941>.
- Calder, P.C., Carr, A.C., Gombart, A.F., Eggersdorfer, M., 2020. Optimal nutritional status for a well-functioning immune system is an important factor to protect against viral infections. *Nutrients* 12 (1181). <https://doi.org/10.3390/nu12041181>.
- Campbell, C.M., Kahwash, R., 2020. Will complement Inhibition be the new target in treating COVID-19 related systemic thrombosis? *Circulation*. <https://doi.org/10.1161/CIRCULATIONAHA.120.047419>.
- Carr, A.C., 2020. A new clinical trial to test high-dose vitamin C in patients with COVID-19. *Crit. Care* 24 (1), 133. <https://doi.org/10.1186/s13054-020-02851-4>.
- Centers for Disease Control and Prevention, 2020. Severe Outcomes Among Patients With Coronavirus Disease 2019 (COVID-19) - United States, February 12 - March 16. <https://www.cdc.gov/mmwr/volumes/69/wr/mm6912e2.htm>.
- Dent, E., Martin, F.C., Bergman, H., Woo, J., Romero-Ortuno, R., Walston, J.D., 2019. Management of frailty: opportunities, challenges, and future directions. *Lancet* 394 (10206), 1376–1386. [https://doi.org/10.1016/S0140-6736\(19\)31785-4](https://doi.org/10.1016/S0140-6736(19)31785-4).
- Donato, A.J., Morgan, R.G., Walker, A.E., Lesniewski, L.A., 2015. Cellular and molecular biology of aging endothelial cells. *J. Mol. Cell. Cardiol.* 89, 122–135. <https://doi.org/10.1016/j.jmcc.2015.01.021>.
- Du, R.H., Liang, L.R., Yang, C.Q., Wang, W., Cao, T.Z., Li, M., Guo, G.Y., Du, J., Zheng, C. L., Zhu, Q., Hu, M., Li, X.Y., Peng, P., Shi, H.Z., 2020a. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. *Eur. Respir. J.* <https://doi.org/10.1183/13993003.00524-2020> pii: 2000524.
- Du, R.H., Liang, L.R., Yang, C.Q., Wang, W., Cao, T.Z., Li, M., Guo, G.Y., Du, J., Zheng, C. L., Zhu, Q., Hu, M., Li, X.Y., Peng, P., Shi, H.Z., 2020b. Prediction for progression risk in patients with COVID-19 pneumonia: the CALL score. *Clin. Inf. Dis.*, [ciaa414](https://doi.org/10.1093/cid/ciaa414) <https://doi.org/10.1093/cid/ciaa414>.
- Ferrucci, L., Fabbri, E., Walston, J.D., 2017. Frailty. In *Hazzard's Geriatrics*. McGraw-Hill, pp. 691–708, 2017.
- Fortin, M., Stewart, M., Poitras, M., Maddocks, H., 2012. A systematic review of prevalence studies on multimorbidity: toward a more uniform methodology. *Ann. Fam. Med.* 142–151. <https://doi.org/10.1370/afm.1337>.
- Franceschi, C., Passeri, M., De Benedictis, G., Motta, L., 1998. Immunosenescence. *Ageing (Milano)* 10 (1998), 153–154.
- Franceschi, C., Bonafè, M., Valensin, S., Olivieri, F., De Luca, F., Ottaviani, E., De Benedictis, G., 2000. Inflamm-aging: an evolutionary perspective on immunosenescence. *Ann. N. Y. Acad. Sci.* 908, 244–254. <https://doi.org/10.1111/j.1749-6632.2000.tb06651.x>.
- Fried, L.P., Tangen, C.M., Walston, J., Newman, A.B., Hirsch, C., Gottdiener, J., Seeman, T., Tracy, R., Kop, W.J., Burke, G., McBurnie, M.A., Cardiovascular Health Study Collaborative Research Group, 2001. Frailty in older adults: evidence for a phenotype. *J. Gerontol. A Biol. Sci. Med. Sci.* 56 (3), M146–56.
- Galkin, F., Mamoshina, P., Aliper, A., de Magalhães, J.P., Gladyshev, V.N., Zhavoronkov, A., 2020. Biohorology and biomarkers of aging: current state-of-the-art, challenges and opportunities. *Ageing Res. Rev.* 101050. <https://doi.org/10.1016/j.arr.2020.101050> [Epub ahead of print].
- Grasselli, G., Zangrillo, A., Zanella, A., Antonelli, M., Cabrini, L., Castelli, A., Cereda, D., Coluccello, A., Foti, G., Fumagalli, R., Iotti, G., Latronico, N., Lorini, L., Merler, S., Natalini, G., Piatti, A., Ranieri, M.V., Scandroglio, A.M., Storti, E., Cecconi, M., Pesenti, A., COVID-19 Lombardy ICU Network, 2020. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *J. Am. Med. Ass.* <https://doi.org/10.1001/jama.2020.5394>, 2020 Apr 6.
- Hamczyk, M.R., Nevado, R.M., Baretino, A., Fuster, V., Andres, V., 2020. Biological versus chronological aging. *J. Am. Coll. Cardiol.* 75, 920–930. <https://doi.org/10.1016/j.jacc.2019.11.062>.
- Hewitt, J., Carter, B., Vilches-Moraga, A., Quinn, T.J., Braude, P., Verduri, A., Pearce, L., Stechman, M., Short, R., Price, A., Collins, J.T., Bruce, E., Einarsson, A., Rickard, F., Mitchell, E., Holloway, M., Hesford, J., Barlow-Pay, F., Cline, E., Myint, P.K., Moug, S.J., McCarthy, K., Study Collaborators, C.O.P.E., 2020. The effect of frailty on survival in patients with COVID-19 (COPE): a multicentre, European, observational cohort study. *Lancet Public Health* 5 (8), e444–e451. [https://doi.org/10.1016/S2468-2667\(20\)30146-8](https://doi.org/10.1016/S2468-2667(20)30146-8).
- Jose, R.J., Manuel, A., 2020. COVID-19 cytokine storm: the interplay between inflammation and coagulation. *Lancet Respir. Med.* [https://doi.org/10.1016/S2213-2600\(20\)30216-2](https://doi.org/10.1016/S2213-2600(20)30216-2) pii: S2213-2600(20)30216-2.
- Koff, W.C., Schenkelberg, T., Williams, T., Baric, R.S., McDermott, A., Cameron, C.M., Cameron, M.J., Friemann, M.B., Neumann, G., Kawakita, Y., Kelvin, A.A., Ross, T.M., Schultz-Cherry, S., Mastro, T.D., Priddy, F.H., Moore, K.A., Ostrowsky, J.T., Osterholm, M.T., Goudsmit, J., 2021. Development and deployment of COVID-19 vaccines for those most vulnerable. *Sci. Transl. Med.* 13 (579), eabd1525 <https://doi.org/10.1126/scitranslmed.abd1525>.
- Kommoss, F.K.F., Schwab, C., Tavernar, L., Schreck, J., Wagner, W.L., Merle, U., Jonigk, D., Schirmacher, P., Longerich, T., 2020. The Pathology of Severe COVID-19-Related Lung Damage. *Arztl. Int.* 117 (29–30), 500–506. <https://doi.org/10.3238/arztebl.2020.0500>.
- Kupferschmidt, K., 2020. The coronavirus czar. *Science* 368, 462–465. <https://doi.org/10.1126/science.368.6490.462>.
- Lesniewski, L.A., Selas, D.R., Walker, A.E., Henson, G.D., Blimline, M.W., Trott, M.W., Bosshardt, G.C., LaRocca, T.J., Lawson, B.R., Zigler, M.C., Donato, A.J., 2017. Dietary rapamycin supplementation reverses age-related vascular dysfunction and oxidative stress, while modulating nutrient-sensing, cell cycle, and senescence pathways. *Ageing Cell* (16), 17–26. <https://doi.org/10.1111/acel.12524>.
- Marengoni, A., Angleman, S., Melis, R., et al., 2011. Aging with multimorbidity: a systematic review of the literature. *Ageing Res. Rev.* 10, 430–439.
- Marengoni, A., Zucchelli, A., Vetrano, D.L., Arrollini, A., Botteri, E., Nicosia, F., Romanelli, G., Beindorf, E.A., Giansiracusa, P., Garrafa, E., Ferrucci, L., Fratiglioni, L., Bernabei, R., Onder, G., 2020. Beyond chronological age: frailty and multimorbidity predict in-hospital mortality in patients with coronavirus disease 2019. *J. Gerontol. A Biol. Sci. Med. Sci.* <https://doi.org/10.1093/gerona/glaa291>.

- Mudway, I.S., Kelly, F.J., Holgate, S.T., 2020. Oxidative stress in air pollution research. *Free Radic. Biol. Med.* <https://doi.org/10.1016/j.freeradbiomed.2020.04.031>.
- Oh, S.J., Lee, J.K., Shin, O.S., 2019. Aging and the immune system: the impact of immunosenescence on viral infection, immunity and vaccine immunogenicity. *Immune Netw.* <https://doi.org/10.4110/in.2019.19.e37>.
- Onder, G., Rezza, G., Brusaferro, S., 2020. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. *J. Am. Med. Ass.* <https://doi.org/10.1001/jama.2020.4683>.
- Pilotto, A., Custodero, C., Maggi, S., Polidori, M.C., Veronese, N., Ferrucci, L., 2020. A multidimensional approach to frailty in older people. *Ageing Res. Rev.* 60, 101047 <https://doi.org/10.1016/j.arr.2020.101047>.
- Polidori, M.C., 2020. Physiology of aging as a basis of complexity in aging medicine and geriatrics. In: Gu, D., Dupre, M.E. (Eds.), *Encyclopedia of Gerontology and Population Aging*. Springer Nature Switzerland AG. [https://doi.org/10.1007/978-3-319-69892-2\\_548-1](https://doi.org/10.1007/978-3-319-69892-2_548-1).
- Rosenbaum, L., 2020. Facing Covid-19 in Italy - ethics, logistics, and therapeutics on the epidemic's front line. *N. Engl. J. Med.* (March), 18. <https://doi.org/10.1056/NEJMp2005492>.
- Shenoy, S., 2020. Coronavirus (Covid-19) sepsis: revisiting mitochondrial dysfunction in pathogenesis, aging, inflammation, and mortality. *Inflamm. Res.* 69 (11), 1077–1085. <https://doi.org/10.1007/s00011-020-01389-z>.
- Sies, H., Jones, D.P., 2020. Reactive oxygen species (ROS) as pleiotropic physiological signalling agents. *Nat. Rev. Mol. Cell Biol.* 21, 363–383. <https://doi.org/10.1038/s41580-020-0230-3>.
- Sperrin, M., Grant, S.W., Peek, N., 2020. Prediction models for diagnosis and prognosis in Covid-19. *Br. Med. J.* 369 <https://doi.org/10.1136/bmj.m1464>.
- Steinbrenner, H., Al-Quraishi, S., Dkhal, M.A., Wunderlich, F., Sies, H., 2015. Dietary selenium in adjuvant therapy of viral and bacterial infections. *Adv. Nutr.* 6, 73–82. <https://doi.org/10.3945/an.114.007575>.
- Trujillo-Mayol, I., Guerra-Valle, M., Casas-Forero, N., Sobral, M.M., Viegas, O., Alarcón-Enos, J., Ferreira, I., Pinho, O., 2021. Western dietary pattern antioxidant intakes and oxidative stress: importance during the SARS-CoV-2/COVID-19 pandemic. *Adv. Nutr.* nmaa171. <https://doi.org/10.1093/advances/nmaa171>.
- Valderas, J.M., Starfield, B., Sibbald, B., Salisbury, C., Roland, M., 2009. Defining comorbidity: implications for understanding health and health services. *Ann. Fam. Med.* 7, 357–363. <https://doi.org/10.1370/afm.983>.
- Valenzuela, P.L., Castillo-García, A., Morales, J.S., Izquierdo, M., Serra-Rexach, J.A., Santos-Lozano, A., Lucia, A., 2019. Physical exercise in the oldest old. *Compr. Physiol.* 9, 1281–1304. <https://doi.org/10.1002/cphy.c190002>.
- Vina, J., Borras, C., Gomez-Cabrera, M.C., 2018. A free radical theory of frailty. *Free Radic. Biol. Med.* 124, 358–363. <https://doi.org/10.1016/j.freeradbiomed.2018.06.028>.
- Vina, J., Ollaso-Gonzalez, G., Arc-Chagnaud, C., De la Rosa, A., Gomez-Cabrera, M.C., 2020. Modulating oxidant levels to promote healthy aging. *Antiox. Redox. Signal.* <https://doi.org/10.1089/ars.2020.8036>.
- Violan, C., Foguet-Boreu, Q., Flores-Mateo, G., 2014. Prevalence, determinants and patterns of multimorbidity in primary care: a systematic review of observational studies. *PLoS One* 9, e102149.
- WHO, 2021. Coronavirus Situation Report (Accessed February 7th, 2021). [https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200430-sitrep-10-1-covid-19.pdf?sfvrsn=2ba4e093\\_2](https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200430-sitrep-10-1-covid-19.pdf?sfvrsn=2ba4e093_2).
- WHO–China Joint Mission, 2020. Report of the WHO–China Joint Mission on Corona Virus Disease 2019 (COVID-19) (PDF). World Health Organization. <https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf>.
- Zhang, L., Zhu, F., Xie, L., Wang, C., Wang, J., Chen, R., Jia, P., Guan, H.Q., Peng, L., Chen, Y., Peng, P., Zhang, P., Chu, Q., Shen, Q., Wang, Y., Xu, S.Y., Zhao, J.P., Zhou, M., 2020a. Clinical characteristics of COVID-19-infected cancer patients: A retrospective case study in three hospitals within Wuhan, China. *Ann. Oncol.* <https://doi.org/10.1016/j.annonc.2020.03.296> pii: S0923-7534(20)36383-3.
- Zhang, J., Taylor, E.W., Bennett, K., Saad, R., Rayman, M.P., 2020b. Association between regional selenium status and reported outcome of COVID-19 cases in China. *Am. J. Clin. Nutr.* 2020 [Lett].