COVID-19 and cardiovascular disease in elderly patients: a challenge in the challenge

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Abstract

On 11 March 2020, the World Health Organization declared a pandemic state, in relation to the spread of the severe acute respiratory syndrome-coronavirus disease-2, responsible for the coronavirus disease-2019 (COVID-19).

The pandemical blast of COVID-19 uncovered well known weakness of financial chain and put our economic organizations facing off dramatic consequences if new strategies will not be developed to adapt health-care on detailed sub-groups of patients.

Frail individual aged >65 years affected by cardiovascular disease are an aged population that showed a particular attitude to contract infection and a higher mortality rate compared to general population.

In this brief article, we will focus on the management of issues related to cardiovascular patients facing coronavirus infection, in particular in the most fragile groups of the population such as the elderly, increasingly numerous and affected by multimorbidity.

Protecting aged populations will be a central question, probably primary in everyone's interest.

Introduction

In late 2019, infection with a novel beta-coronavirus, subsequently named severe acute respiratory syndrome-coronavirus disease-2 (SARS-CoV-2), was reported in people who had been exposed to a seafood market in Wuhan, China, where live animals were sold. Since then, there has been rapid spread of the virus, leading to a global pandemic of coronavirus disease-2019 (COVID-19).

Increased human mobility and ready access to international travel have accelerated the rate of microbial transmission worldwide and global pandemics are a persistent threat.

On 11 March 2020, the World Health Organization declared a pandemic state, in relation to the spread of the SARS-CoV-2 virus, responsible for the COVID-19 disease.[1]

As of April 5, 2020, over 1,200,000 people have been identified worldwide and over 65,000 dead.

The level of contagiousness of SARS-CoV-2 appears higher compared to other coronavirus epidemics known as SARS and Middle East respiratory syndrome (MERS), element that can explain both the rapid spread of the virus that its danger, especially in the weaker sections of the population such as the elderly.

The COVID-19 experience offers a window on the profound long-term global demographic challenges that the world is facing.

According to the United Nations, the projections indicate that by 2050 there will be more than twice as many people over the age of 65 than children under the age of 5 and that the number of people aged 65 and over globally will exceed the number of people aged 15 and over to 24 years of age.[2]

COVID-19 is a rapidly evolving epidemic with uncertain clinical characteristics that could face further recovery and acceleration of the infection.

This new global health emergency highlighted the vulnerability of the elderly population to emerging diseases.

In fact, in Italy, according to data from the *Istituto Superiore di Sanità* (referring to 4 May 2020) the lethality of the disease progressively increases with age, passing from 10% relative to the age group of 60-69 years, to 24.3% in the 70-79 age group, 29.2% between 80-89 years, 24.8% for the over 90 years, respectively.

As we age, the health conditions associated with aged, in particular non-communicable diseases such as cardiovascular diseases, neoplasms, metabolic and autoimmune diseases, combined with treatments for these pathologies and with immune senescence, can substantially influence the responses to vaccines and infectious diseases.[3]

It is therefore essential to identify these patients to guarantee their protection through effective prevention, treatment and monitoring procedures.

Previous experiences with SARS and MERS had made us reflect on how viral respiratory disease outbreaks can threaten public health, but associated extrapulmonary manifestations and their prolonged consequences are often overlooked.

At the beginning, the COVID-19 disease had been identified as a pathology with involvement of the respiratory tract, with the possibility of evolving towards severe interstitial pneumonia and acute respiratory distress syndrome (ARDS); however progressively increasing data highlight the possibility that in addition to the lungs, the heart is also being revealed, day after day, a possible target of the coronavirus and cardiovascular diseases seem to represent a multiplier of the risk of death in the event of an infection with COVID-19:[4-6] hypertensives, coronary artery patients, and diabetics would be more at risk of complications and of poor outcome.

COVID-19, arterial hypertension and aged

Some Chinese studies have pointed out that the presence of high blood pressure (odds ratio [OR] 2.36, 95% confidence interval [CI] 1.46- 3.83) and cardiovascular disease (OR 3.42, 95% CI 1.88-6.22) have consistently been reported to be more common among patients with Covid-19 who have had severe illness, been admitted to the intensive care unit, received mechanical ventilation, or died than among patients who have had mild illness.[7]

These conditions appear to track closely with advancing age,[8] which is emerging as the strongest predictor of COVID-19-related death.[6]

Studies have demonstrated that SARS-

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CoV-2 as well as other coronaviruses can use the angiotensin-converting enzyme 2 (ACE2) protein for cell entry.[9-12]

ACE2 is a type I integral membrane protein that serves many important physiologic functions: ACE2 is counterregulatory to the activity of angiotensin II generated through ACE1 and is protective against detrimental activation of the renin–angiotensin–aldosterone system: ACE2 degrades Angiotensin II to angiotensin-[1-7], which exerts vasodilatory, anti-inflammatory, antifibrotic, and antigrowth effects.[13]

In studies about humans, tissue samples from 15 organs have shown that ACE2 is expressed broadly, including in the heart and kidneys, as well as lung where plays a protective role, but which it represents the main entry site for SARS-CoV-2 into human host[8,9] the lung alveolar epithelial cells.[14,15]

From a pathogenic point of view, evidence has been provided that binding of viral spikes glycoprotein to ACE2 receptor leads to its down-regulation with impairment of a lung protective pathway and subsequent lung damage in the course of SARS-CoV infection, contributing to viral pathogenicity.[15] Down-regulation of ACE2 causes excessive production of angiotensin (ANG) II by the related enzyme ACE with stimulation of ANG type 1a receptor (AT1R) and enhanced lung vascular permeability, facilitates the initial neutrophil infiltration in response to bacterial endotoxin.[16,17] and may result in unopposed angiotensin II accumulation and local RAAS activation.

Some experimental observations on rats had shown that the expression of ACE2 decreases drastically with aging;[18] this could provide an explanation on how differential levels of ACE2 in the heart and lung tissues of older adults compared to young people, together with comorbidities and an altered immune system, may favor the different virulence spectrum of the disease observed among patients with COVID-19. Restoration of ACE2 through the administration of recombinant ACE2 appeared to reverse this devastating lung-injury process in preclinical models of other viral infections.[19,20]

The interaction between the SARS viruses and ACE2 have led to debate regarding the potential use of RAAS blockers in the context of the pandemic, 2, as drugs capable of influencing the expression of ACE 2, in part responsible for disease virulence.[21-23] In contrast to available animal models, there are few studies in humans regarding the effects of RAAS inhibition on ACE2 expression, data are lacking regarding the effects of RAAS inhibitors on lung-specific expression of ACE2, and further mechanistic studies in humans are needed to better define the unique interplay between SARS-CoV-2 and the RAAS network.[24]

In a recent study, Mancia *et al*.[25] found that patients with COVID-19 had an higher baseline prevalence of cardiovascular conditions and diseases (hypertension, coronary heart disease, heart failure, and chronic kidney disease); in this patients the treatment with RAAS blockers do not modify susceptibility to COVID-19 applies to both sexes as well as to younger and older persons: in the study, neither ACE inhibitors nor ARBs showed an independent association with COVID-19 in patients with mild-to-moderate disease or in those with severe disease. Moreover, patients with COVID-19 had much more frequent use of loop diuretics and mineralocorticoid-receptor antagonists than controls, and treatment with loop diuretics was associated with an increased risk of COVID-19 in the multivariable analysis (appropriate experimental designs would be required to clarify this issue).

On the basis of the available evidence, several influential authors claim that, despite the theoretical concerns and uncertainty regarding the effect of RAAS inhibitors on ACE2 and the way in which these drugs might affect the propensity for or severity of COVID-19, the abrupt withdrawal of RAAS inhibitors in hypertensive and especially in high-risk patients, including those who have heart failure or have had myocardial infarction, may result in clinical instability and adverse health outcomes.[22]

COVID-19, comorbidities, cardiovascular disease in elderly

Whereas reports outside of China are limited, data from Italy suggest similar mortality rates and an elevated risk for death in patients with comorbidities.[26]

The death rate associated with COVID-19 is also considerably higher compared with the most recent World Health Organization estimate of seasonal influenza mortality rate of <0.1%, and may reach much higher rates in elderly patients, those with comorbidities and in those for whom efficient intensive care support is absent.[27]

First, COVID-19 was identified primarily as a respiratory disease with pictures of severe interstitial pneumonia and the risk of acute respiratory distress syndrome.

However, the clinical observation of patients affected by the new pandemic has focused attention on the possible development of associated myocardial damage which constitutes a critical component in the progression towards serious complications and unfavorable outcome.

The pathogenesis of cardiac involvement associated with SARS-CoV-2 may reflect a process of replication and dissemination of the virus through the blood or the lymphatic system from the respiratory tract.

Alternatively, SARS-CoV-2 could trigger an exaggerated inflammatory response that can cause myocardial injury.[28-47]

Mechanisms that lead to CVD are increasingly recognized to overlap with pathways that regulate immune function.

For instance, age is the strongest risk factor for CVD and the effect of aging on immune function may be equally important for COVID-19 susceptibility and severity.

In fact, age-related changes begin early in life with the drop-in production of both T and B lymphocytes. It therefore happens that, once activated, both T and B cells exhibit reduced proliferation and differentiation in lymph nodes. As a consequence, with aging, the immune responses to a new emerging infection are reduced, often ineffective, with many fewer effector cells, that are also less well armed by antimicrobial molecules, making them less effective in defending against infection.[48,49]

The age-dependent defects in T-cell and B-cell function and the excess production of type 2 cytokines could lead to a deficiency in control of viral replication and more prolonged proinflammatory. In addition, some studies have shown, among the pathological characteristics of patients with COVID-19 that the peripheral CD4 and CD8 T cell counts were substantially reduced, while their state was hyperactivated, a condition that explains, in part, the serious immune system injury in this patient.[50] Since depressed immunity is manifested by decreased immune cell populations including T cells, patients can easily cause the onset of cytokine storm when encountering massive virus invasion Moreover, previous studies in macaques inoculated with SARS-CoV found that older macaques had stronger host innate responses to virus infection than younger adults, with an increase in differential expression of genes associated with inflammation, whereas expression of type I interferon beta was reduced.[51]

Other traditional cardiovascular disease risk factors such as diabetes and hyperlipidemia

Affect immune function, and conversely, dysregulated immunologic status corresponds with elevated risk of incident CVD.[28-31]

Thus, prevalent CVD may be a marker of accelerated immunologic aging/ dysregu-

lation and relate indirectly to COVID-19 prognosis.

Cardiac involvement can take various aspects: from acute coronary syndromes and myocardial infarction, to the exacerbation of heart failure, to myocarditis, to arrhythmias. Heart problems are not always secondary to respiratory problems; sometimes, in fact, they start first and independently of the extent of respiratory impairment (pneumonia, respiratory failure).

The patients most at risk of heart complications from COVID-19, in addition to those with known heart disease, are the elderly and those with cardiovascular risk factors, In severe cases, COVID-19 may present as pneumonia, the ARDS, with or without both distributive and cardiogenic shock, to which elderly populations with pre-existing medical comorbidities are the most vulnerable.[31-37]

As pointed out in the work of Tian-Yuan Xiong *et al.*[38] in previous coronavirus infections, the severity of primary respiratory syndrome and the risk of adverse outcomes were greater in patients with pre-existing cardiovascular disease;[35] electrocardiographic changes and elevation of troponin suggested the development of an underlying myocarditis, while echocardiography demonstrated frequent sub-clinical left ventricular diastolic impairment, with a greater likelihood of the need for mechanical ventilation in those with systolic impairment and reduced fraction of ejection.[36,37]

Several studies have documented the importance of Troponin I levels (cTnI) as a predictive value of severity in COVID-19 patients hospitalized with more severe forms than those with milder forms: approximately 19-28% of patients hospitalized with moderate forms and severe COVID-19 developed acute myocardial damage, evidenced by an increase in troponin, 50-60% of whom experienced death, with higher mortality among patients with progressively increased troponin levels and history of disease cardiovascular,[39-41] however mortality was increased, compared to patients without acute myocardial damage, even in those who did not have a known prior cardiovascular disease.

In COVID-19 individuals without cardiovascular disease and without an increase in troponin values, the risk of death is less than 5-10%. Based on these data, some authors suggest that cardiac damage biomarkers should be monitored in all COVID-19 patients, or at least those with the highest cardiovascular risk.

Several pathophysiological mechanisms have been hypothesized to explain the frequent rise in troponin levels in patients hospitalized with COVID-19.[39-42]

Among these, the first is secondary to the stabilization of pre-existing atherosclerotic plaques, a phenomenon already described in the course of other viral and inflammatory syndromes,[43-45] related to the so-called *cytokine storm*; another mechanism would be based on the marked increase in the demand for oxygen by the myocytes, secondary to infection and inflammation, with consequent ischemia; another hypothesis would be the possibility of direct myocardial damage with a picture of fulminant myocarditis, as already documented in some cases of MERS.

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A further mechanism would concern a worsening of hemodynamic stability triggered by hypoxia with the development of acute stress heart disease.

Finally, data, still anecdotal, is emerging that report autoptic observations of extensive thrombosis of the microcirculation.[46]

So, according to some Chinese studies, SARS-CoV-2 pneumonia seems to be complicated by coagulopathy, with a significant prognostic impact that is under study.

In a multicenter retrospective cohort study from China, elevated D-dimer levels (>1 g/L) were strongly associated with in hospital death, even after multivariable adjustment (odds ratio: 18.4; 95% CI: 2.6 to 128.6; p ¼ 0.003).[52] The development of vascular inflammation may also contribute to the hypercoagulable state and endothelial dysfunction in such patients. In the setting of critically ill COVID-19 patients who demonstrate clinical deterioration as evidenced by hypoxia or hemodynamic instability, thromboembolic disease should be considered.[53] There is evidence that stresses that multi-organ damage is more likely in patients with sepsis if they develop coagulopathy and that inhibiting thrombin synthesis can have a positive impact in reducing mortality. In fact, ISTH has provided recommendations[54] based only on some evidence indicating that a markedly increased D-dimer value, in particular in patients who develop CID with a thrombotic phenotype, is associated, in patients infected with SARS-CoV-2, high mortality. Therefore a widely available treatment is represented by a prophylactic dose of LMWH which must be considered in all patients, even non-critical ones, who require hospitalization for the COVID-19 infection, in the absence of contraindications (bleeding active and platelet count below 25x109/L), and taking due account of glomerular filtrate levels. It is known that LMWH, in addition to protecting critically ill patients from venous thromboembolism, has been shown to have anti-inflammatory properties: based on the immuno-thrombosis model, which highlights a bidirectional relationship between the immune system and thrombin generation, blocking thrombin by heparin may dampen the inflammatory response.[55] However, one of the better known non-anticoagulant properties of heparin, its anti-inflammatory function, may also be relevant in setting of COVID-19 infection in which high levels of proinflammatory cytokines have been reported. However, urged the need for more data from larger studies.

Conclusions

This unprecedented crisis provides an essential reason on how we must think now of the best way to manage the care of sick elderly people, for their own good, also in consideration of the costs and stresses in the short and long term for the health system.

Outlining the principles of effective immunity in the elderly will allow us to develop new strategies for wider disease prevention and control in older populations.

Diseases with pandemic potential, transmitted by vectors and favored by climate change, can put global health at risk and in particular in the most fragile groups of the population such as the elderly, increasingly numerous and affected by multimorbidity.

Protecting aged populations will be a key question, probably primary in everyone's interest.

References

1. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19-11 March 2020. Available from: https://www.who.int/dg/speeches/detail/whodirector-general-s-opening-remarks-at-the-mediabriefing-on-covid-19-11-march-2020 Accessed: March 12, 2020.
2. United Nations. World population prospects 2019. New York: United Nations. Available from: https://population.un.org/wpp/
3. Alpert A, Pickman Y, Leipold M, et al. A clinically meaningful metric of

immune age derived from high-dimensional longitudinal monitoring. Nat Med 2019;25:487-95.
4. Li B, Yang J, Zhao F, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol 2020;109:531-8.
5. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol 2020;17:259-60.
6. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult in patients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020 [E-pub ahead of print].
7. Guan WJ, Ni ZY, Zhong et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382: 1708-20.
8. Wu JT, Leung K, Bushman M, et al. Estimating clinical severity of COVID-19 from the transmission dynamics in Wuhan, China. Nat Med 2020;26:506-10.
9. Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003;426:450-4.
10. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARSCoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181:271-80.e8.
11. Li W, Zhang C, Sui J, et al. Receptor and viral determinants of SARS-coronavirus adaptation to human ACE2. EMBO J 2005;24:1634-43.
12. Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 2020;367:1260-3.
13. Li XC, Zhang J, Zhuo JL. The vasoprotective axes of the renin-angiotensin system: physiological relevance and therapeutic implications in cardiovascular, hypertensive and kidney diseases. Pharmacol Res 2017;125:21-38.
14. Hamming I, Timens W, Bulthuis MLC, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus: a first step in understanding SARS pathogenesis. J Pathol 2004;203:631-7.
15. Coppolino G, Presta P, Nicotera R, et al. COVID-19 and renal disease in elderly patients. Geriatric Care 2020;6:9029.
16. Zhang H, Penninger JM, Li Y, et al. Angiotensin-converting enzyme 2 (ACE2) as a SARSCoV- 2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med 2020;46:586-90.
17. Sodhi CP, Wohlford-Lenane C, Yamaguchi Y, et al. Attenuation of pulmonary ACE2 activity impairs inactivation of des-Arg9 bradykinin/BKB1R axis and facilitates LPS-induced neutrophil infiltration. Am J Physiol Lung Cell Mol Physiol 2018;314:L17-31.
18. Xie X, Chen J, Wang X, et al. Age-and gender-related difference of ACE2 expression in rat lung. Life Sci 2006;78:2166-71.
19. Zou Z, Yan Y, Shu Y, et al. Angiotensin-converting enzyme 2 protects from lethal avian influenza A H5N1 infections. Nat Commun 2014;5:3594.
20. Gu H, Xie Z, Li T, et al. Angiotensin-converting enzyme 2 inhibits lung injury induced by respiratory syncytial virus. Sci Rep 2016;6:19840.
21. Esler M, Esler D. Can angiotensin receptor- blocking drugs perhaps be harmful in the COVID-19 pandemic? J Hypertens 2020;38:781-2.
22. Vaduganathan M, Vardeny O, Michel T, et al. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. N Engl J Med 2020;382: 1653-9.
23. Danser AHJ, Epstein M, Batlle D. Renin-angiotensin system blockers and the COVID-19 pandemic. Hypertension 2020;75:1382-5.
24. Vaduganathan M, Vardeny O, Michel T, et al. Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19. NEJM 2020;382:1653-9.
25. Mancia G, Rea F, Ludergnani M, et al. Renin-Angiotensin-Aldosterone System Blockers and the Risk of Covid-19. NEJM 2020 [Epub ahead of print].
26. Porcheddu R, Serra C, Kelvin D, et al. Similarity in case fatality rates (CFR) of COVID-19/SARS-COV-2 in Italy and China. J Infect Dev Ctries 2020; 14:125-8.
27. World Health Organization. Coronavirus Disease 2019 (COVID-19) Situation report-46. Accessed: 6 March, 2020.
28. Zidar DA, Al-Kindi SG, Liu Y, et al. Association of lymphopenia with risk of mortality among adults in the US general population. JAMA Network Open 2019;2:e1916526.
29. Libby P, Ridker PM, Hansson GK; Leducq Transatlantic Network on Atherothrombosis. Inflammation in atherosclerosis: from pathophysiology to practice. J Am Coll Cardiol 2009;54: 2129-38.
30. Tall AR, Yvan-Charvet L. Cholesterol, inflammation and innate immunity. Nat Rev Immunol 2015;15:104-16.
31. Saltiel AR, Olefsky JM. Inflammatory mechanisms linking obesity and metabolic disease. J Clin Invest 2017;127:1-4.
32. 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.
33. 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;323:1061-9.
34. Murthy S, Gomersall CD, Fowler RA. Care for critically ill patients with COVID-19. JAMA 2020;323:1499-500.
35. Badawi A, Ryoo SG. Prevalence of comorbidities in the Middle East respiratory syndrome coronavirus (MERS-CoV): a systematic review and meta-analysis. Int J Infect Dis 2016;49: 129-33.
36. Li SS, Cheng C, Fu C, et al. Left ventricular performance in patients with severe acute respiratory syndrome: a 30-day echocardiographic follow-up study. Circulation 2003;108:1798-803.
37. Harris JE, Shah PJ, Korimilli V, Win H. Frequency of troponin elevations in patients with influenza infection during the 2017-2018 influenza season. Int J Cardiol Heart Vasc 2019;22:145-7.
38. Xiong TV, Redwood S, Prendergast B, Chen M. Coronaviruses and the cardiovascular system: acute and long-term implications. Eur Heart J 2020;41: 1798-800.
39. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020;368:m1091.
40. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 2020 [Epub ahead of print].
41. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020 [Epub ahead of print].
42. Bonow RO, Fonarow GC, O'Gara PT, Yancy CW. Association of coronavirus disease 2019 (COVID-19) with myocardial injury and mortality. JAMA Cardiol 2020 [Epub ahead of print].
43. Madjid M, Miller CC, Zarubaev VV, et al. Influenza epidemics and acute respiratory disease activity are associated with a surge in autopsy-confirmed coronary heart disease death: results from 8 years of autopsies in 34,892 subjects. Eur Heart J 2007;28:1205-10.
44. Nguyen JL, Yang W, Ito K, et al. Seasonal influenza infections and cardiovascular disease mortality. JAMA Cardiol 2016;1:274-81.
45. Kwong JC, Schwartz KL, Campitelli

MA, et al. Acute myocardial infarction after laboratory-confirmed influenza infection. N Engl J Med 2018;378:345-53.
46. Phend C. COVID-19: abnormal clotting common in more severe disease – Chinese clinicians on the early front lines argue for anticoagulation. MedpageToday 2020; March 24. Available from: https://www.medpagetoday.com/infectiousdisease/covid19/85577
47. Inciardi RM, Lupi L, Zaccone G, et al. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020 [Epub ahead of print].
48. Brien JD, Uhrlaub JL, Hirsch A, et al. Key role of T cell defects in age-related vulnerability to West Nile virus. J Exp Med 2009;206:2735-45.
49. Smithey MJ, Renkema KR, Rudd BD, Nikolich-Zugich J. Increased apoptosis, curtailed expansion and incomplete differentiation of CD8(+) T-cells combine to decrease clearance of L. monocytogenes in old mice. Eur J Immunol 2011;41:1352-64.
50. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acuterespiratory distress syndrome. Lancet Respir Med 2020 [Epub ahead of print].
51. Smits SL, de Lang A, van den Brand JMA, et al. Exacerbated Innate Host Response to SARS-CoV in Aged Non-Human Primates. PLoS Pathog 2010;6: e1000756.
52. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020 [Epub ahead of print].
53. Driggin E, Madhavan MV. Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the COVID-19 Pandemic. JACC 2020;75:2352-71.
54. Thachil J. The versatile heparin in COVID-19. J Thromb Haemost 2020; 18:1020-2.
55. Gaertner F, Massberg S. Blood coagulation in immunothrombo- sis-At the frontline of intravascular immunity. Semin Immunol 2016;28:561-9.