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.

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 the number of people aged 65 and over globally will exceed the number of people aged 15 and over to 24 years of age.

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 IstitutoSuperiore 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.

It is therefore essential to identify these patients to guarantee their protection through effective preventive intervention, 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: 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.

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

Studies have demonstrated that 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.

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CoV-2 as well as other coronaviruses can use the angiotensin-converting enzyme 2 (ACE2) protein for cell entry.3-12

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 host8-10 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 ACE2, in context of the pandemic,2 as drugs capable of influencing the expression of ACE2, in

**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.25

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.28-31

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.32,33

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.34 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.31

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.35-31

Thus, prevalent CVD may be a marker of accelerated immunologic aging/ dysregu-
lution 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;15 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.

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.

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 autopic 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 ‹ 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 recommendations54 based only on some evidence indicating that a markedly increased D-dimer value, in particular in patients who develop CIDs 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 contraindica-

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.

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