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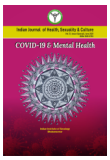

Review Article

Potential determinants of age-related severity in COVID-19

Enara Arevalillo-Gozalo
Pediatric Nurse, Department of Pediatric Oncology, Donostia-San Sebastian Hospital, Paseo Dr. Begiristain, Donostia-San Sebastián, Guipúzcoa, Spain

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Abstract

Global pandemics have emerged from time-to-time during the history of the human species. In this regard, the recent outbreak of the corona virus disease 19 (COVID-19) probably represents the most significant public health emergency ever faced since the beginning of the modern era due to its dramatic impact on the health, the economy, and the quality of life of the societies worldwide. In this context, the understanding of the main possible factors behind the age-related increased morbidity in COVID-19 seems crucial to yield insights into pathogenesis and the informed management and to design new therapeutic approaches personalized to different patient profiles. Among these factors, the possible changes in angiotensin-converting enzyme 2 expression and local angiotensin metabolism in the lung, the chronic low-grade inflammation and changes in the innate and adaptive immune system, and physiological and anatomical changes of the respiratory system that are developed with age have probably a crucial role. Besides, other changes inherent to age, such as muscular sarcopenia or diminished gas exchange in the alveoli, may play a role in facilitating the bad prognosis of the disease. Thus, here I summarize the most important changes that may drive the increased risk of suffering life-threatening complications with age in COVID-19.

Keywords:
COVID-19, Aging, Prognosis, SARS-CoV-2, Severity

Corresponding author: Enara Arevalillo-Gozalo
Email: enara.arevalillogozalo@osakidetza.eus
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Introduction

Coronavirus (CoVs) family encompasses 4 different genera of RNA viruses (alpha-CoV, beta-CoV, gamma-CoV, and delta-CoV) with a capacity of infecting human and animal cells and to cause diverse diseases affecting respiratory, enteric, renal, and neurological tissues (Fehr and Perlman, 2015).

Remarkably, coronaviruses have a relatively high potential to find new host species due to changes in their spike protein of the membrane. Together with the existence of permanent reservoirs of viruses in some exotic animals (Graham and Baric, 2010) and the degradation of ecosystems worldwide, this feature facilitates the contact between these and humans. Thus, corona viruses and future viral diseases are set to be some of the most important challenges to be faced by human societies in the following generations. In this context, a new global pandemic has recently emerged due to a new coronavirus first found in patients with severe bilateral pneumonia in Wuhan, China, named SARS-CoV-2 (Huang et al., 2020; Ren et al., 2020; Zhu et al., 2020).

SARS-CoV-2 is part of the lineage B of the beta-coronavirus genus (Corona viridae Study Group of the International Committee on Taxonomy of Viruses, 2020). It causes the corona virus disease-19 (COVID-19) that may manifest with a plethora of symptoms, including fever, malaise, cough, dysgeusia, dyspnoea, and diarrhea, among others. In some patients, progressive lung injury is developed with bilateral pneumonia and acute respiratory distress syndrome (ARDS), leading to multi-organ failure and death in a subset of patients (Rothan and Byrareddy, 2020). Notably and, in contrast with other viral infections, such as influenza, the susceptibility to have the asymptomatic infection and its severity vary dramatically with age. Thus, people younger than 30 (particularly children) seem much less likely to display any symptoms at all compared to those from 30 to 59 years (0.16 as likely). In contrast, people older than 59 have a two-fold increase in the risk of developing symptoms after infection (Dong et al., 2020; Wu et al., 2020). In the same line, an update recently published about the mortality of the disease has shown that, compared with seasonal influenza, there is a dramatic increase of deaths associated with age in subjects suffering COVID-19, with a mortality ranging from 0.0026 in children to more than 8% in people above the age of 70 (Ruan, 2020).

Thus, age itself constitutes the most critical risk factor for the development of complications in COVID-19. Besides, the mortality seems to be related, with the presence of co-morbidities, which are obviously more frequent in older individuals (Yang et al., 2020; Zhou et al., 2020). However, the increased prevalence of other pathologies with increasing age may not be enough to explain the roughly 4% per year increase in the risk of developing COVID-19 symptoms, as observed in adults above 30 (Wu et al., 2020). Moreover, severe disease complications have also been reported in relatively young adults with no other known previous conditions. Hence, there might be other factors directly influencing the age-dependent severity of symptomatology.

It is widely known that the respiratory and the immune systems are in close connection. The respiratory tract is in permanent contact with environmental molecules and microorganisms that can directly trigger an immune response. In this conundrum, there are several anatomical and physiological features in both the respiratory and the immune systems that are directly influenced by age and may play a vital role in the disease's prognosis. Unravelling these factors is critical to approaching the disease from a global perspective that allows clinicians and scientists to understand the pathogenic disease mechanisms and, thus, develop new treatments and therapeutic approaches. In this review, I will assess such features, and in the light of recent findings, new insights into the novel paths of research will be suggested.

Infection mechanism of SARS-CoV-2: The importance of membrane ace 2 expression and its protective role against acute lung injury

Current SARS-CoV-2 has several similarities with the SARS-CoV coronavirus, which caused a severe acute respiratory syndrome outbreak in East Asia in 2003 (Zhou et al., 2020). Notably, the angiotensin-converting enzyme 2 (ACE2), present predominantly in type-2 alveolar epithelial cells (Zhao et al., 2020), acts as the cellular receptor for the spike protein (S protein) of the SARS-CoV (Li et al., 2003) and the same has been also recently observed for the novel SARS-CoV-2 (Ou et al., 2020; Letko et al., 2020). In SARS-CoV-2 infection, there is a clathrin-mediated endocytosis of both ACE2 and the virus to the host cell after the attachment of the S protein of the virus to ACE2. Remarkably, this process induces the activity of the ADAM 17 protein in the host cell, which in turn promotes the shedding of the remaining ACE2 receptors in the membrane (Clarke and Turner, 2012). Therefore, the viral infection reduces the overall expression of ACE2 in the lung, and, presumably, this process occurs similarly in SARS-CoV-2 infection.

Importantly, ACE2 acts as a counter regulatory enzyme of ACE enzyme, degrading the Angiotensin II (the key effector peptide of the Renin-Angiotensin System, RAS) into Angiotensin-(1-7) (Boehm and Nabel, 2002; Corvol et al., 1995; Skeggs et al., 1980). The ACE is widely expressed in the endothelial of the lung's capillary blood vessels (Studdy et al., 1983), which makes the lung act as a circulation-borne endocrine system that releases Angiotensin II in the bloodstream (Kuba et al., 2006).

On the other hand, the local effects of the lung's RAS system have some pathological implications. In pulmonary hypertension and fibrosis, there is an upregulation of the expression of the profibrotic cytokine transforming growth factor-β1, inducing a transformation of fibroblasts into myofibroblasts and prompting an accumulation of collagen in the tissue (Kuba et al., 2006; Lavoie and Sigmund, 2003; Weber, 1997). Moreover, Angiotensin II also induces a pro-inflammatory signaling cascade in cells mediated by its angiotensin receptor 1 (AT1). This signaling cascade results in an increased expression of specific cytokines, chemokines, and adhesion molecules, which promote the immune system's activation, increase platelet aggregation, and interrupt the anti-inflammatory effects of insulin, and enhance vascular permeability (Dandona et al., 2007; Kuba et al., 2006).

Regarding the ACE2, it influences the metabolism of other proteins not RAS-related, such as the kinin-kallikrein system (KKS), Apelin-13, and dynorphin A peptide (Wohlfart and Wiemer, 2004). In addition, it is also implied in the bradykinin signaling pathway, where it hydrolyses and inactivates the active bradykinin metabolite [des-Arg973]-BK (DABK). In this network, the diminished activity of ACE2 increases the amount of active DABK, which enhances its signaling through the specific bradykinin receptor 1 (BKB1R), triggering fluid extravasation neutrophil recruitment in the lungs (Sodhi et al., 2018). Thus, the maintenance of a correct physiological expression of ACE2 in the lung is crucial for the lung homeostasis (Imai et al., 2005). In this context, the pathogenic mechanism of SARS-CoV-2 infection clears the presence of ACE2 in cell membranes altering the lung ACE-ACE2 balance (Yan et al., 2020). An imbalance of the lung's RAS system has been observed in other conditions, such as nephropathy, diabetes, and hypertension

(Heras et al., 2012; Muñoz-Durango et al., 2016; Ribeiro-Oliveira et al., 2008). Similarly, local lung injury may be facilitated by excessive accumulation of Angiotensin II, inducing an increase in pro-inflammatory cytokines, fluid extravasation, and neutrophil recruitment and facilitating ARDS in COVID-19 (Kuba et al., 2005), which would worsen the prognosis of the disease.

Concerning aging, no differences have been found in RAS between neonates, children, adults, and older persons with ARDS (Schouten et al., 2019). However, it is not known if the same may apply to healthy subjects. On this regard, preclinical models have shown that there is an age-dependent decrease of ACE2 expression in the lung that is directly related to induced acute lung injury severity (Schouten et al., 2015; Schouten et al., 2016), and it has been recently observed that the overall body-expression of ACE2 is decreased with age in humans (Chen et al., 2020). Therefore, although there is still a controversy in this aspect and more research is needed, aging might have a role in promoting a progressive imbalance in lung's ACE-ACE2 homeostasis. If that is the case, lower levels of ACE2 receptors in their respiratory tract might protect older subjects from being infected with SARS-CoV-2 compared to younger subjects. However, once acquired, decreased ACE2 levels would predispose to develop lung injury due to increased inflammation and fluid leakage from blood vessels to alveoli. This hypothesis could partly explain both the increasing severity and mortality with age and the high prevalence of asymptomatic cases estimated in young subjects (Wang et al., 2020).

Immune response to COVID-19 and the deleterious effect of age

Clinical findings

After the infection of the host cells, the immune system is activated to neutralize the pathogen. In this sense, increased total neutrophils (38%), reduced total lymphocytes (35%), increased serum interleukin (IL)-6 (52%), and increased c-reactive protein (84%) are common findings in hospitalized COVID-19 patients (Zhou et al., 2020). In addition, increased levels of other pro-inflammatory cytokines (IL-2, IL-7, IL-10, granulocyte-colony stimulation factor (G-CSF), interferon-gamma induced protein-10 (IP-10), monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1 alpha (MIP-1A), and tumor necrosis factor alfa (TNFα) have also been observed in severe cases (Huang et al., 2020). Notably, these features are shared with SARS and Middle-East Respiratory Syndrome (MERS), another respiratory disease outbreak that occurred in 2012 in Saudi Arabia caused by another coronavirus (Zumla et al., 2015). Thus, lymphopenia and an abnormal increase of pro-inflammatory cytokine profile (i.e., 'cytokine storm') happened in SARS and MERS outbreaks (Nicholls et al., 2003; Wong et al., 2004) could play a vital role in the prognosis of COVID-19. Particularly, the so-called 'cytokine storm' can prompt a viral sepsis and could dramatically increase lung injury, predisposing subjects to other complications such as pneumonitis, ARDS, shock, multi-organ failure, and death (Prompetchara et al., 2020).

The innate immune system

It is not fully understood how the cytokine storm occurs in patients. In this regard, current knowledge shows that corona viruses seem to be specially prepared to evade both the viral particles' immune detection and mitigate the human immune response. These features allow the viruses to escape the host immune response at least in the first stages of the disease, which would explain their relatively longer incubation periods compared to other agents that cause

respiratory infections, such as influenza (Prompetchara et al., 2020).

When the virus gets into the host cell, a genomic viral RNA or double-strand RNA (dsRNA) can appear in the cytoplasm. This RNA is usually recognized by proteins such as toll-like receptors (TLR) 3 and 7 & the cytosolic RNA sensor RIG-I/MDA5 (Prompetchara et al., 2020). These proteins will then generate an internal signaling cascade mediated by interferons (IFN) and NF-κB resulting in IFN-I expression and other pro-inflammatory cytokines. IFN-I is, thereafter, released to the extracellular space, where IFNAR receptor will activate the JAK-STAT pathway to induce the expression of IFN-stimulated genes (ISGs) in the nucleus under the control of IFN-stimulated response element (ISRE) containing promoters (de Wit et al., 2016). Overall, IFN-1 is the crucial factor for the early limitation of the virus spreading throughout the tissue, due to its immunomodulatory role that promotes macrophage-mediated phagocytosis of antigens and restriction of natural killer (NK) cells to infected target cells and T/B cells (Li et al., 2020). Both SARS-CoV and MERS-CoV are known to interfere within the production and the signaling effects of IFN-I (Kindler et al., 2016), resulting in an impaired early suppression of viral replication and dissemination throughout the tissue. In relation to SARS-CoV-2, its long incubation period (Xia et al., 2020), along with its genomic similarities with both SARS-CoV and MERS-CoV (Lu et al., 2020), allows arguing that SARS-CoV-2 probably uses similar strategies to modulate the IFN-I mediated innate immune response in COVID-19. However, other mechanisms could also play a role.

The lack of proper early IFN-I activation would cause a dramatic 'unnoticed' increase of the infected subjects' viral load. Then, as viral replication increases, a sudden hyper production of IFN-I may occur, with a substantial increase of influx of hyper inflammatory neutrophils and monocytes-macrophages in the tissue. These cells would further enhance the overall inflammatory response, damaging the alveoli and causing pneumonia and/or ARDS (Prompetchara et al., 2020). This might explain, in part, the extremely low incidence of COVID-19 in children since they would be protected by their robust innate immune system (Simon et al., 2015). Hence, although this represents the usual scenario according to the current knowledge in SARS and MERS, it is still not known which cell type acts as the main effector of the cytokine storm in COVID-19. In this regard, although alveolar epithelial cells containing ACE2 receptors are the primary target cells for SARS-CoV-2, it is well known that the SARS virus has shown the ability to infect monocytes and dendritic cells, whereas MERS-CoV infects monocytes and T cells (Chu et al., 2016; Law et al., 2005). Besides, lung epithelial cells, macrophages, and dendritic cells all express cytokines to some extent during influenza infection (Iwasaki and Pillai, 2014). Therefore, along with the previously mentioned potential increase of local Angiotensin favoring inflammatory processes, other infection mechanisms and other target cells cannot be discarded for SARS-CoV-2. Thus, it is crucial to find the main effector/s of the cytokine storm in COVID-19 to implement strategies to boost or modulate the innate immune system.

The adaptive immune system

Although the innate immune system plays a predominant role in controlling viral infections, particularly in the early stages, the adaptive immune system might be essential to control the disease when the innate immune system does not achieve the

pathogen's proper clearance. As stated before, COVID-19 patients display a partial immune suppression stage following the pro-inflammatory phase that is characterized by lymphopenia, with a remarkable reduction in the amount of peripheral CD4+ and CD8+ lymphocytes. Besides, this immune profile correlates with the risk of developing community-acquired pneumonia due to secondary bacterial infections (Zhou et al., 2020) and the severity of COVID-19 (Liu et al., 2020). Unfortunately, the pathophysiological mechanisms leading to lymphopenia in COVID-19 are still unknown.

In this regard, SARS-CoV-2 RNA is present in blood samples of COVID-19 patients (Huang et al., 2020), and pseudo-typed viral particles have shown remarkable T-cell infective properties in culture. Interestingly, the infective ability of these SARS-CoV-2 particles was much higher than that of SARS-CoV viral particles, which may indicate that other receptors could mediate the entry of SARS-CoV-2 into T cells (Wang et al., 2020). Thus, although it remains speculative, it is quite possible that in COVID-19 patients, particularly those with a higher number of viral particles throughout the circulatory system, SARS-CoV-2 could directly infect T cells in vivo, eventually leading to lymphopenia and causing and impaired antiviral response of the adaptive immune system.

On the other hand, the lack of evidence regarding the adaptive immune system activation profile in COVID-19 patients hampers extracting firm conclusions. Regarding SARS-CoV-2 patients, it has been reported that disease severity correlated with the level of CD4+ T cell response, particularly with those cell populations able to produce several cytokines (IFN-I, IL-2, and TNF-α), but not with the memory CD8+ cell response. Besides, strong T cell response significantly correlated with higher neutralizing antibody levels in the blood while subjects that died had more serum type 1 T helper 2 (Th2) cytokines (IL-4, IL-5, IL-10) as compared to the non-fatal group (Li et al., 2008). About MERS-CoV, the early rise of CD8+ T cells correlated with disease severity. In contrast, Th1 cell presence was more frequent at the convalescent phase (Shin et al., 2019). Thus, and as other authors have pointed out, Th1 type response probably has a crucial role for successful control of SARS-CoV-2 once the innate immune system is overcome (Prompetchara et al., 2020).

The effect of aging in the immune system and the risk for severe COVID-19

Symptomatology

Aging induces profound changes in both the innate and the adaptive immune systems. Basically, there is a decline in response to exogenous antigens, in a process that is known as immune-senescence. One of this process's main features is the presence of a chronic inflammatory state characterized by increased levels of circulating cytokines and chemokines such as IL-6, IL-1β, IL-8, and TNFα (Fulop et al., 2011). Although several factors might influence the development of this chronic inflammatory state, one of the most important features is the chronic antigenic stimulation of the immune system cells by damaged molecules, leading to the chronic activation of macrophages (Franceschi et al., 2006) that prompt the liberation of inflammatory signals above normal physiological levels. Moreover, neutrophils and antigen-presenting cells, such as macrophages or dendritic cells, show a decrease in their phagocytosis capacity with age. This hinders the adequate presentation of antigens to lymphocytes through major histocompatibility complex (MHC) molecules (Fulop et al., 2011). Besides, current evidence

suggests a decrease in the activity of NK cells associated with an increase in the risk of suffering viral infections (Hazeldine and Lord, 2013).

On the other hand, the thymus, which is the site of T lymphocyte production, suffers progressive atrophy known as thymic involution (Anderson et al., 2013). Notably, this process is characterized by a progressive accumulation of adipose tissue that substitutes the original cells of the organ, causing a decline in naive T cells' production capacity (Boren and Gershwin, 2004; Sansoni et al., 2008). Moreover, along with the decrease in the number of naive T lymphocytes, the lymphocytic activation profile is also affected with age, favoring the Th-2 like immune response profile (Delves and Roitt, 2000) that is associated with an increased production of IL-5 and IL-10 (Boren and Gershwin, 2004), and decreased Th-1 like cytotoxic response. Therefore, the basal increased inflammatory state, the changes observed in antigen presentation and recognition, the decreased amount of naive T lymphocytes, and the change in the activation profile of lymphocytes lead to compromise of the innate and the adaptive immune in older subjects. This may hinder a proper response against SARS-CoV-2 (Appay et al., 2010), generating a delay in the development of a correct response and facilitating the spreading of the virus.

Respiratory system changes related to aging

Aging also has a significant impact on the respiratory system. Besides the integrity of the lung parenchyma, other respiratory mechanics structures are of crucial importance, such as the diaphragm and other accessory muscles, the spine, and the ribs (Kovacs et al., 2013; Laghi and Tobin, 2003; Sharma and Goodwin, 2006). Changes in the structure of the thoracic cavity and an increase in lung collagen tissue with age lead to a decrease in lung's elasticity (Janssens, 2005). Additionally, muscles in elderly individuals have less mitochondrial adenosine triphosphate reserves, making it difficult to sustain a sudden increase in metabolic demand when its required (Kovacs et al., 2013). Moreover, the decrease in the total amount of muscular tissue with aging, known as sarcopenia, also affects the respiratory system's muscles (Bordoni et al., 2020). All these changes in respiratory muscles cause a reduction of the force-generating capacity, decreasing the ability of the muscles to expel harmful particles through movements such as cough (Elliott et al., 2016). On the other hand, secretions are continuously produced by mucociliary cells covering the walls of the airways and cleared by the centripetal movement of these cells' cilia (Haas et al., 2007). In aging, a discoordination on the beat of these cilia occurs, which facilitates the accumulation of exogenous particles and mucus at the base of the lungs, increasing the risk for respiratory infections (Ho et al., 2001). Besides, gas exchange through the alveolar-capillary membrane is produced by a physical-chemical mechanism that includes ventilation, diffusion of CO2 and O2 mediated mainly by hemoglobin (Hb) and bicarbonate, and perfusion (Taylor and Johnson, 2010; Wagner, 2015). After the age of 50 years, there is a homogeneous degeneration of the elastic fibbers around the alveolar duct, resulting in enlargement of distal airspaces. Furthermore, there is a decrease in the bronchiolar diameter, a rib-cage kyphoscoliosis (an abnormal curvature of the spine in both a coronal and sagittal plane), and calcification of the intercostal cartilage, all of these resulting in an increased respiratory resistance with the diminished expiratory flow and augmented lung residual volume. Conversely to these changes with age, the reduction of the supporting tissue results in premature closure of small airways

during normal breathing, leading to the alveoli's impaired capacity to empty during the expiratory phase (Janssens, 2005; Mahler and O'Donnell, 2014). This leads to an air trapping and hyperinflation known as 'senile emphysema'. Over time, this process may promote a progressive disintegration of alveolar walls, resulting in the alveoli's flattening and hindering the gas exchange (Sharma and Goodwin, 2006).

Moreover, the pulmonary surfactant produced by the same type II pulmonary epithelial cells that are infected by SARS-CoV-2, significantly reduces the surface tension in the alveoli preventing their collapse during expiration (Daniels and Orgeig, 2003; Haagsman and Van Golde, 1991). Two large hydrophilic proteins, SP-A and SP-B, constitute a small portion of surfactant and play an important role in antimicrobial activity. Increased levels of these proteins have been related with increased susceptibility to fungal or bacterial infections (Han and Mallampalli, 2015). On a note, in mice, both SP-A and SP-B increase with age (Moliva et al., 2014), but this has not been observed in humans (Betsuyaku, 2004). Thus, further research is needed in this area.

When SARS-CoV-2 infection occurs, pneumocytes containing ACE2 receptors are damaged. As explained, this causes an increase in liquid extravasation from the alveolar capillaries. Therefore, regardless of the effect of age in surfactant components, the lung's surfactant balance is probably affected during the viral infection.

To summarize, all of those above age-mediated structural changes cause the respiratory system to undergo progressive deterioration, paving the way for opportunistic infections and hypoxemia, and increasing the requirements for supplemental oxygen or in tubation in COVID-19 patients.

Other factors

Although the factors mentioned above are the main determinants of the increased risk of SARS-CoV-2 infection with age, other factors may also influence the progression of the disease in this population, such as air pollution caused mainly through fossil fuel consumption (Ogen, 2020). One of the most crucial pollutants is nitrogen dioxide (NO2), which is known to cause an inflammatory response in the airways and the induction of the synthesis of pro-inflammatory cytokines from airway epithelial cells. Moreover, these cells are particularly susceptible to death when exposed to NO2. Besides, elevated NO2 atmospheric concentration is markedly associated with increased likeliness to suffer respiratory infections and related mortality, and it is also responsible for generating some harmful secondary pollutants such as nitric acid (HNO3) and ozone (O3) (Ogen, 2020). Thus, older subjects living in areas with elevated atmospheric concentrations of NO2 would have a higher risk of suffering from complications in the course of the COVID-19 when compared to individuals living in areas with low contamination.

Importantly, platelets are the critical mediators of inflammation and act as sensors of infectious agents through the interaction of cell surface receptors and pathogens (pathogen pattern recognition receptors) or immune system derivatives (immunoglobulin Fc receptors and complement receptors). Thus, the activation of and the interactions between macrophages, monocytes, endothelial cells, platelets, and lymphocytes may play a critical role in the procoagulant effect of certain viral infections (Giannis et al., 2020).

In this regard, changes have also been observed recently related to blood coagulation in patients with COVID-19. These patients

develop thrombocytopenia (36.2%) and elevated D-dimer (46.4%) (Guan et al., 2020), which is the main product of the degradation of fibrin by plasmin, and it is generated in the final step of thrombus formation. Moreover, the rates of these factors are further elevated in severe cases (57.7% and 59.6%, respectively) (Guan et al., 2020). Both thrombocytopenia and elevated D-dimer can be caused by multiple pathogenic mechanisms, including endothelial dysfunction (Varga et al., 2020), von Willebrand factor elevation, Toll-like receptor activation, and tissue-factor pathway activation. These elevated rates reflect an excessive triggering of the coagulation cascade and platelets that lead to disseminated intravascular coagulation (DIC) (Giannis et al., 2020).

As age increases, there are changes in blood viscosity determinants, with increased fibrinogen concentration and decreased hemoglobin, red blood cell count, and platelet count (Coppola et al., 2000). Although it is merely speculative, the increase of fibrinogen concentration in the blood of elderly subjects may favor the development of DIC, worsening the outcome of the disease in advanced stages.

Conclusions and future perspectives

As noted above, several small changes may occur progressively with age, both in the respiratory and immune systems that all together could remarkably favor the development of severe complications in COVID-19 (Figure. 1).

First, ACE-ACE2 balance might be altered in the lung of older subjects, which would be further modified after SARS-CoV-2 infection. This alteration of the lung's RAS system would facilitate vascular permeability, increase local inflammation, and induce specific innate immune cells such as macrophages and neutrophils. Besides, the immune system avoiding mechanism of SARS-CoV-2 could cause a delay in the trigger of an early innate immune response in patients. In the context of aging, the pathogen recognition ability of macrophages could be partly hampered due

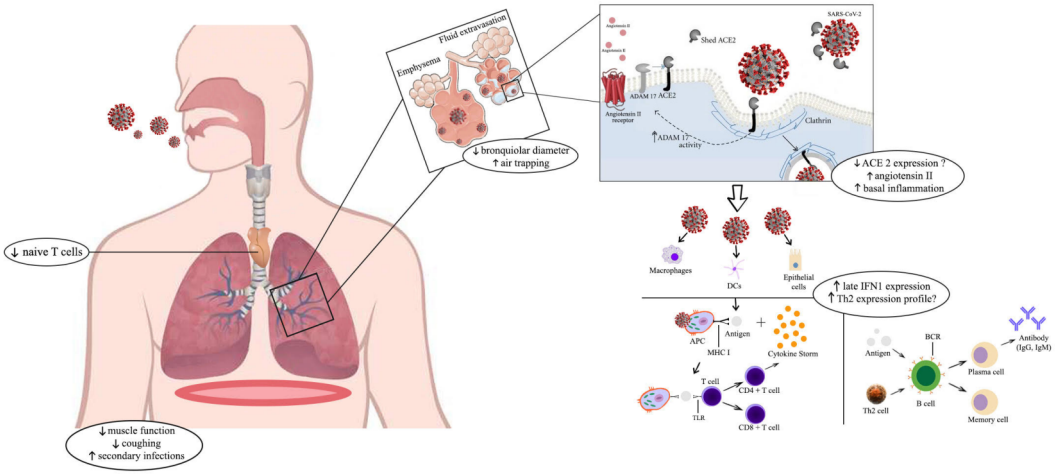

Figure 1: Graphical summary of the most important age-related changes that could influence the prognosis in COVID-19. ACE2: Angiotensin-converting enzyme II; APC: antigen-presenting cells; BCR: B-cell receptors; DC: Dendritic cells; IFN1: Interferon 1; IgG & IgM: Immunoglobulins G and M; MHC1: Major histocompatibility complex 1; Th2: T cell helper type 2; TLR: Toll-like receptor; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

to chronic inflammation. Therefore, these changes would markedly delay the early immune response against the virus. In later stages and after substantial viral replication, the lungs' immune cells would produce a dramatic and exacerbated sudden increase of pro-inflammatory cytokines, favoring ARDS development and severe lung damage. Moreover, the adaptive immune system (i.e., T cells) suffers progressive changes with age, with less naïve T cells and increased Th2 profile of the remaining cells. In the context of SARS-CoV-2 infection, these changes would slow down an adaptive cytotoxic response and would hamper fast recovery from the infection.

Other changes naturally occurring with age in the respiratory system, such as decreased air exchange efficiency, increased air trapping, decreased muscular tone of the rib-cage, and alterations in mucociliary cells, would difficult the expulsion of pathogenic particles from the lungs and facilitate secondary infections by opportunistic microbes. Finally, other factors such as prolonged exposure to environmental toxins or increased blood viscosity may also impair the disease's outcome in older adults.Thus, the identification of different COVID-19 profiles could serve to develop personalized treatments directed to each case. Some of these treatments focused on the alterations analysed in the present review have already shown promising results in basic or clinical reports, such as the administration of the soluble form of ACE2 receptor (Monteil et al., 2020), immune-modulatory drugs like Tocilizumab or corticosteroids (Luo et al., 2020; Wang et al., 2020), or anticoagulants (Kollias et al., 2020).

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