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*J Immunol* 2020; 205:313-320; Prepublished online 3 June 2020;
doi: 10.4049/jimmunol.2000380
http://www.jimmunol.org/content/205/2/313

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Role of Aging and the Immune Response to Respiratory Viral Infections: Potential Implications for COVID-19

Judy Chen,*†,1 William J. Kelley,*1 and Daniel R. Goldstein*†,‡

Aging impairs immunity to promote diseases, especially respiratory viral infections. The current COVID-19 pandemic, resulting from SARS-CoV-2, induces acute pneumonia, a phenotype that is alarmingly increased with aging. In this article, we review findings of how aging alters immunity to respiratory viral infections to identify age-impacted pathways common to several viral pathogens, permitting us to speculate about potential mechanisms of age-enhanced mortality to COVID-19. Aging generally leads to exaggerated innate immunity, particularly in the form of elevated neutrophil accumulation across murine and large animal studies of influenza infection. COVID-19 patients who succumb exhibit a 2-fold increase in neutrophilia, suggesting that exaggerated innate immunity contributes to age-enhanced mortality to SARS-CoV-2 infection. Further investigation in relevant experimental models will elucidate the mechanisms by which aging impacts respiratory viral infections, including SARS-CoV-2. Such investigation could identify therapies to reduce the suffering of the population at large, but especially among older people, infected with respiratory viruses.

The Journal of Immunology, 2020, 205: 313–320.

In December 2019, a new respiratory illness appeared in Wuhan, Hubei province, China, the symptoms of which included dry cough, fever, difficulty breathing, and pneumonia. Soon after, a novel coronavirus (now known as SARS-CoV-2) was identified as the cause of the disease and has continued to spread and is now recognized as a global pandemic (1). In the intervening months, it has become clear that SARS-CoV-2 is a major threat to global public health; as of May 27, 2020, there have been nearly 5.5 million documented cases of SARS-CoV-2 causing 346,063 deaths globally (2). Importantly, the severity of the disease associated with SARS-CoV-2, COVID-19, depends heavily on host age; in Italy, the disease resulted in a case fatality rate of 0.3% for patients aged 20–40 y (5, 6), possibly because of cross-reactive immunity to different strains (e.g., H3N8) of influenza the adults were infected with during infancy (7). This contrasted to the relative protection of older people during the 1918 pandemic, which may have resulted from prior exposures to similar H1N1 strains of the virus (5–7). Similar phenomena occurred in the 2009 H1N1 pandemic (7). In contrast to prior H1N1 influenza pandemics, humans are naive to SARS-CoV-2, which could partly explain the lack of protection in older people. Thus, to develop effective therapeutics for SARS-CoV-2 (and potentially future viruses), it is crucial to understand the mechanisms of virus-enhanced mortality in older patients.

Although SARS-CoV-2 is still too novel to have undergone extensive scientific investigation, the phenomenon of viral respiratory infections causing severe disease in older patients is well known. Older patients experienced significantly increased mortality in response to both severe acute respiratory syndrome (SARS, also known as SARS-CoV) and Middle Eastern respiratory syndrome and continue to experience enhanced mortality in response to seasonal influenza and other respiratory viruses, such as respiratory syncytial virus (RSV). This effect has been linked to several factors associated with aging, including dysregulated innate immune response resulting in increased neutrophil recruitment and hyperinflammatory signaling, age-associated T cell and B cell defects, and the increased incidence of comorbidities associated with age. These age-associated defects may also be partly responsible for the significantly increased mortality in older patients with SARS-CoV-2.

In this article, we summarize the role of aging in the immune response to respiratory viral infections and speculate as to how
Aging impacts the immune response to SARS-CoV-2. We first provide a general overview on changes in immune function with aging and then discuss specifically how aging impacts immunity to influenza, RSV, and SARS. Additionally, we summarize the clinical observations and limited experimental research on SARS-CoV-2, focusing on potential key cellular players in the enhanced mortality associated with aging and associated comorbidities. Finally, we suggest areas for future investigation to determine the precise mechanisms of enhanced mortality with aging to SARS-CoV-2, which will assist with the development of vaccines and therapeutics for the current pandemic and future similar viral infections.

Aging and immune function

Immune senescence refers to the age-associated deterioration of the immune system. The consequences of aging on the immune system are multifactorial. Older individuals exhibit dysregulated immune responses against pathogens; poor response to vaccination; increased susceptibility to cancers, certain autoimmune disorders, and other chronic inflammatory diseases; and reduced transplant rejection (reviewed in Refs. 8–10). Aging diminishes the proliferative capacity of hematopoietic stem cells and shifts hematopoietic stem cells toward the production of myeloid progenitor cells (11). Aging dysregulates functions of innate immune cells, such as Ag presentation, phagocytosis, and expression of pattern recognition receptors (e.g., TLR) (reviewed in Refs. 12–14). Additionally, aging reduces the production of naïve B cells and T cells as well as their immune function (reviewed in Ref. 9). These factors restrict the naïve T cell and B cell repertoire of the aged host, reducing the ability to fend off new infections and impairing vaccine efficiency with aging. Before infection, aging leads to the accumulation of both Ag-naïve and Ag-experienced CD4+ and CD8+ T cells that have reduced proliferation potential and senescence-like phenotypes, including increased secretion of inflammatory mediators such as TNF-α (15–17). Dysregulated innate immunity also contributes to this chronic low-level increase in circulating inflammatory mediators (18, 19), which could contribute to frailty, defined as increased vulnerability to biological stressors (20). Additionally, aging reduces pulmonary function (21, 22) and impairs lung epithelial barrier integrity (23) to further compromise the ability of aged individuals to fight respiratory infections. Clearly, aging impacts multiple levels of the immune system via complex mechanisms to impair immunity.

Aging and influenza

Seasonal influenza leads to an estimated 300,000 to 650,000 deaths worldwide annually (24). Of these deaths, 70–90% occur in individuals 65 y or older (25, 26). The majority of complications from influenza infections affect the respiratory system, such as secondary bacterial infections, pneumonia, and respiratory failure. However, complications due to influenza are not limited to the respiratory system and can also affect the cardiovascular system (27) and musculoskeletal system (28), which are typically negatively impacted by aging.

Murine models of aging and influenza infection show that aging dysregulates the inflammatory response to influenza infection to increase morbidity and mortality (29, 30). Generally, in murine studies, mice are designated as aged if >18 mo of age. Regarding the innate immune system and influenza, aging has been shown to impact monocytes, alveolar macrophages (AMs), and neutrophils. Although early neutrophil recruitment may protect from influenza infection, excessive neutrophil retention in the lungs during infection is pathological. Neutrophil numbers in the lungs of aged mice are increased as early as day 1 postinfection, and this elevation is maintained throughout the course of infection as compared with young mice (30). The increased number of neutrophils in the lungs can be explained by increased levels of CXCL1 and CXCL2 in the lungs of influenza-infected aged mice (30). Compatible with this finding, aged rhesus macaques (20–24 y of age) exhibit increased levels of IL-8 within the lung during influenza infection compared with younger macaques (10–12 y of age) (31). Similar findings of increased neutrophil numbers and tissue damage in aged lungs have been shown in other models of lung injury, such as LPS inoculation, thermal injury, and exposure to cigarette smoke, indicating that increased numbers of neutrophils are pathological across infectious and noninfectious insults (32–34). Importantly, depletion of neutrophils during later stages (i.e., 1 wk postinfection) of influenza infection improves survival of influenza-infected aged mice and reduces the levels of proinflammatory cytokines (30). However, neutrophil depletion at the time of infection increases mortality (30). This suggests that although neutrophils play a protective role during early influenza infection, increased neutrophil levels in the lungs at later time points postinfection (i.e., day +6) with aging are pathological. This is further evidenced by data indicating that high and prolonged levels of neutrophil-related transcripts in circulating leukocytes (35) and whole blood (36) correlate with severe influenza infection outcomes and morbidity in humans. AMs are professional phagocytes that play a crucial role in viral clearance and in inflammation resolution during the later stages of an influenza infection. Functionally, AMs of aged mice exhibit reduced numbers, inhibited phagocytosis, and an impaired ability to clear apoptotic neutrophils in vivo, implying dysregulated inflammation resolution (37). A murine study in a peritonitis model indicates that aging impairs the production of proresolution mediators, such as resolvins (38), although whether this occurs during and impacts respiratory viral infections is not yet known. Additionally, adoptive transfer of AMs from young mice into the airways of aged mice reduces lung tissue injury due to influenza (37). Inability to clear apoptotic cells from the lung environment can further exacerbate inflammation. Similar results have been shown in human studies (39–41). Overall, these studies suggest that aging impairs the homeostatic functions of AMs and inflammation resolution in response to influenza infection.

Infiltrating monocytes that differentiate into lung macrophages may enhance protection early during influenza viral infection. However, whether aging exerts alterations on recruited macrophages during influenza infection is not clear. Peripheral blood monocytes from older healthy subjects (≥65 y of age) exhibit preserved IL-6 and IL-1β levels but reduced IFN-β, an antiviral cytokine, in response to in vitro infection with influenza (42). Whether this occurs in vivo is not fully elucidated; murine studies have tended to not find major differences in type I IFNs and lung viral load between young and aged mice during the first week of infection (29), although there are increases in viral load during the second week postinfection (43). Increases in viral load have been noted in aged rhesus macaques infected with influenza as compared with young macaques (31). Overall, there is some
evidence of impaired viral control to influenza infection with aging, although this tends to be at later stages of infection, specifically after the first week. This may indicate the inability of the aged adaptive immune response, rather than the innate response, to clear the virus.

Aging impairs the adaptive response to influenza infection in both the T cell and B cell compartments. Aging leads to a reduced frequency of naïve T cells and an increased frequency of memory T cells. Specifically, aged rhesus macaques exhibit reduced numbers of both CD4+ and CD8+ influenza-specific T cells within the lung during the course of influenza infection (31). Additionally, influenza-infected aged mice generate a limited repertoire of influenza-specific CD8+ T cells (44) and reduced number and function of influenza-specific CD8+ memory T cells in the lung and spleen compared with young mice (45, 46). These factors lead to the reduction of the T cell repertoire of the aged host and reduced ability to fend off primary and secondary influenza infections, which has important considerations for vaccine strategies to prevent infection in older people. In addition, the functions of T cells are impaired with aging. Murine studies show that aging impairs the expansion of virus-specific CD8+ T cells following influenza infection (47) and delays the infiltration of CD4+ and CD8+ T cells into the lungs (43, 48). Adoptive transfer experiments of CD8+ T cells and CD4+ T cells indicate that this infiltration defect is partially due to the aged microenvironment (49). CD4+ T cells that have been adoptively transferred into aged mice show impaired recruitment, proliferation, and differentiation after an influenza challenge compared with CD4+ T cells transferred into young mice (50). However, the exact mechanisms by which the aged microenvironment limits T cell functions are not well understood.

One factor that can explain these observations with aging is reduced conventional dendritic cell (cDC) priming of the T cell response. cDCs are APCs that carry influenza Ags to the lung draining lymph nodes (dLNs), where interactions with T cells and B cells shape the adaptive immune response. Following influenza infection, cDCs show delayed infiltration kinetics into the lungs of aged mice (43). Additionally, dendritic cells (DCs) labeled with CFSE exhibit a defect of DC migration to the lung dLN during influenza infection in aged mice (51). This reduction in DC migration is in part due to increased levels of PGD2 in the aged lung environment of both naïve and influenza-infected mice (51). The age-associated defect of DC migration to lymph nodes can also be attributed to cell-intrinsic factors, such as reduced signaling through the PI3K pathway, a positive regulator of DC migration and phagocytosis, as seen with monocyte-derived DCs from older humans (52, 53). Appropriately, there is also a marked increase in phosphatase and tensin homolog (PTEN), a negative regulator of PI3K activity, expression in monocyte-derived DCs from older patients (52). Additionally, in vivo experiments using the OVA transgenic murine system show that cDCs from an aged host have an impaired ability to present Ag on MHC class I and prime CD8+ T cell responses (54), although this has not been directly tested during influenza infection. cDCs also exhibit age-associated impairments in nucleotide-binding domain, leucine-rich-repeat, pyrin domain-containing 3 (NLRP3) inflammasome-activated IL-1β production in vitro and reduced IL-1β secretion during influenza infection in vivo to worsen viral control and mortality (55).

The B cell response to influenza is also impacted by aging. This can be partially attributed to the age-related impairments of CD4+ T cells to fully differentiate into T follicular helper cells following influenza infection (50). Additionally, the T follicular helper cells generated in an influenza-infected aged murine model show reduced expression of CD40L, a critical signal for B cell affinity maturation, class-switching, and differentiation to plasma cells (50). Production of influenza-neutralizing Abs is impaired following an influenza exposure in aged mice, rhesus macaques, and humans (31, 43, 56).

Reductions in Abs may reflect defects in CD4+ T cell help rather than intrinsic B cell defects, although B cell–intrinsic defects have been reported with aging, specifically reduced expression of transcription factors Pax5 and Blimp1 (56, 57). Reductions in Ab titers during influenza infection with aging could also explain reduced efficacy of vaccines with aging both in experimental models (58, 59) and in humans (60). Further studies on how aging impacts T cell memory and humoral immunity will lead to more efficacious vaccines that will protect older people from respiratory viruses such as influenza and SARS-CoV-2.

Overall, aging negatively impacts the immune response to influenza within both the innate and adaptive immune compartments (Fig. 1). However, there are still many areas that are yet to be elucidated; for example, the contributions of the age alterations of the lung and gut microbiome and immunity to influenza remain undetermined.

**Aging and RSV**

Epidemiological data suggest that RSV-associated disease results in rates of infection and disease severity comparable to influenza in older people. Approximately 14,000 RSV-related deaths occur yearly in adults 65 y and older in the United States (61, 62). However, the true number of RSV cases may be underreported; testing for RSV is not performed routinely because the test is not widely available, and there is no clinical application for the results because there are no RSV-targeted treatments (63). Similar to influenza, incidences of RSV infection predominantly occur during the autumn and winter months. Like influenza, chronic conditions such as chronic obstructive pulmonary disease and congestive heart failure contribute to poor outcomes to RSV infection (64).

Regarding experimental studies, a study in mice shows that aging impairs the RSV-specific CD8+ T cell response (65). Similarly, older humans have reduced numbers of RSV-specific CD4+ and CD8+ T cells and reduced IFN-γ secretion by RSV-specific T cells (66). Microarray analysis of lung tissue from young and aged mice infected with RSV show that as early as 2 d postinfection, aged mice exhibit higher levels of cytokine-related transcripts and IFN-related transcripts, such as Ifn7, Oasl7 Ccl8, and Cxc9 compared with young mice (67). This study also showed that before RSV infection, aging leads to upregulation of 113 of the total 373 significantly regulated immune-modulating genes in the lung, suggesting that increased morbidity with aging during RSV may be partially due to an elevated basal inflammatory response, also termed “inflammaging” (19, 67). Even with higher levels of antiviral type I IFN signaling, aged mice still exhibit higher levels of viral load (65, 67). However, there are conflicting reports on the correlation of proinflammatory cytokine levels to RSV disease severity in children and no reports...
CD8+ T cell responses are also dampened with aging. DC due to the reduction in B–T interaction. Both CD4+ and against the virus. The reduced B cell response is in part due to the reduction in B–T interaction. Both CD4+ and CD8+ T cell responses are also dampened with aging. DC migration to the dLN and priming of T cells are impaired. (B) Aging causes dysregulated inflammation in the lungs during respiratory viral infections. Increased levels of chemokines (IL-8) lead to increased recruitment of neutrophils (polymorphonuclear neutrophils [PMN]). Aging causes reduced numbers of AMs and impairs their ability to phagocyte apoptotic neutrophils and debris.

**FIGURE 1.** Aging impacts the immune response to viral respiratory infections. The consequences of aging on the immune response against respiratory viruses can be broadly categorized into (A) impaired adaptive immunity and (B) dysregulated inflammation. (A) Aging reduces the B cell response and the generation of protective Abs against the virus. The reduced B cell response is in part due to the reduction in B–T interaction. Both CD4+ and CD8+ T cell responses are also dampened with aging. DC migration to the dLN and priming of T cells are impaired. (B) Aging causes dysregulated inflammation in the lungs during respiratory viral infections. Increased levels of chemokines (IL-8) lead to increased recruitment of neutrophils (polymorphonuclear neutrophils [PMN]). Aging causes reduced numbers of AMs and impairs their ability to phagocyte apoptotic neutrophils and debris.

that correlate proinflammatory cytokine levels to disease severity in older adults (68–71). These discrepancies may be explained by cohort size, age of the subjects (pediatric), geographic location, type of sample collected (nasal wash versus serum), and cytokines measured (68–71). Overall, these RSV studies show general similarities with the aged immune response to influenza, specifically, heightened inflammatory innate immunity and impaired adaptive immunity.

Although influenza and RSV are the most common respiratory viruses leading to mortality in older people, other respiratory viruses such as rhinovirus, metapneumovirus, and parainfluenza also cause severe burden in older people. One study of 87 nursing home residents with respiratory viral infections showed that 17% of patients were positive for rhinovirus, 9% were positive for metapneumovirus, and 5% were positive for parainfluenza (72). A larger study with 382 participants over a 3-y period in a long-term healthcare facility showed similar results (73). The impact of aging on the immune response to these respiratory viruses is understudied and thus not well understood. However, as these viruses activate many of the same immune pathways, such as type I IFN and Th1 responses, as RSV and influenza, the findings in RSV or influenza models may inform on other respiratory viruses.

**How aging impairs the immune response to SARS-CoV**

Although the exact mechanisms of SARS-CoV-2 mortality in older patients still require extensive research, we may gain some insight through an understanding of SARS-CoV, commonly known as “SARS,” given that the two viruses are ~80% genetically identical (74). Emerging in 2002 in Guangdong Province, China, SARS-CoV eventually spread to 29 countries and resulted in 916 fatalities with a case death rate of 11% before ultimately being controlled (75, 76). Like other coronaviruses, SARS-CoV is an enveloped virus comprising nonsegmented, single-stranded positive-sense RNA (77–79). As is the case with many coronaviruses, SARS-CoV is of animal origin and was transmitted from horseshoe bats to humans via an intermediate host, likely palm civets (78). Soon after SARS-CoV was identified, it was shown that the virus facilitates cellular entry and replication via interactions between the spike (S) protein and angiotensin converting enzyme 2 (ACE2) (80). Similar to SARS-CoV-2 patients (see below), patients infected with SARS-CoV initially present with influenza-like symptoms, including fever, dry cough, chills, diarrhea, body aches, and sore throat, among others (81–83). Some patients progress to acute respiratory distress syndrome, characterized by a severe upregulation of inflammatory cytokines and chemokines, an acute influx of leukocytes into the airspace, and eventually pneumonia and organ failure (84). Importantly, patient age is a major determining factor in disease outcome, with upwards of 50% of patients >50 y eventually dying of the disease (76, 83). Additional risk factors for adverse outcomes include comorbidities such as diabetes, hypertension, and cardiovascular disease (which are more common in older people), high neutrophil count, increased cellular adhesion molecule expression, and high levels of leukocyte-attractive chemokines present in patient serum (82, 83, 85–87). Importantly, many of these clinical features are shared with the current SARS-CoV-2 pandemic (3, 88–92). These additional risk factors point toward dysregulation of the immune system with age, which may also contribute to the increased fatality rate among older people infected with SARS-CoV-2.

Some mechanistic studies indicate that an impaired adaptive immune response contributes to age-associated mortality of SARS (51, 93); however, studies in nonhuman primates largely show that viral replication is similar in aged and young hosts (94, 95), indicating that viral control is not impaired with aging. This suggests that dysregulation of the innate immune system may be a major contributor for the increased mortality for aged hosts. Importantly, there is a significant decrease in ACE2 expression in the lungs of aged rats as compared with young adult rats, suggesting that enhanced cellular entry and replication is likely not responsible for the increased mortality in aged hosts (96). Indeed, there is increased and prolonged expression of inflammatory and innate immune genes in the lungs of aged mice during SARS-CoV infection, with the inflammatory immune response continuing even after the virus is cleared, which likely contributes to immune pathology (97). Importantly, innate immune cell populations, specifically neutrophils, exhibit increased recruitment during the first week postinfection in a mouse model of SARS-CoV infection (98), similar to the neutrophil.
response that occurs in influenza (30). This implies that there is a likely programmed and generalized neutrophil response to a broad range of respiratory viral pathogens.

However, there are conflicting reports as to whether aging upregulates or downregulates the inflammatory innate immune response to SARS-CoV, particularly in nonhuman primate studies. On one hand, one study found that aged macaques (10–18 y of age) infected with SARS-CoV exhibit increased infiltrating immune cells into the airspace and lung damage, increased expression of genes associated with inflammation (particularly the NF-κB gene network), and increased levels of inflammatory cytokines such as IL-8 in the lungs as compared with young adult infected macaques (94). On the other hand, another study found decreased levels of inflammatory cytokines and immune cells in the lungs of similarly aged macaques compared with young macaques (95). This discrepancy may be in part due to the use of two different species of primates; the first study used cynomolgus macaques, whereas the second study used African green monkeys. Despite these differences, both studies found similar viral titers between the young and aged groups, indicating that in this primate model, with high translatibility to humans, aging did not impact viral control. Overall, these two studies, along with similar research on influenza and RSV infections in aging (see above), point to dysregulation of the innate immune system as a contributing factor in the severity of SARS with aging (Fig. 1) and may provide insight into the mechanisms of increased mortality of SARS-CoV-2 in older people.

Speculation as to how aging impacts the immune response to SARS-CoV-2

Although extensive research remains to be done regarding the pathophysiology of SARS-CoV-2 in general and in older patients specifically, we can make some informed speculations using clinical case studies and our knowledge of how other viral respiratory infections impact aged hosts. Like SARS-CoV, SARS-CoV-2 facilitates cellular entry primarily via interaction between the viral S protein and the ACE2 receptor in the lung epithelium (74, 99). Patients infected with SARS-CoV-2 present with influenza-like symptoms, similar to those seen in patients infected with SARS-CoV, as described above (1, 88–90, 100, 101). Whereas some patients recover after periods of mild illness, many patients (estimated between 20 and 50% of patients in varying cohorts) progress to moderate and severe illness, eventually entering acute respiratory distress syndrome (88–90). Emerging evidence suggests that, similar to influenza, ∼50% of patients who die of SARS-CoV-2 have secondary bacterial infections (102).

Although the current SARS-CoV-2 pandemic is an ever-changing situation with outcomes ranging dramatically from country to country, making statistical estimates of the fatality rate difficult to define, the overall case fatality rate may range from 2% (as seen in China) to upwards of 7% (as seen in Italy), with the fatality rate potentially reaching ∼20% or higher among patients >80 y of age (3). In general, poor outcomes (i.e., severe illness, intensive care unit [ICU] care, and death) are heavily associated with advanced age; one patient cohort exhibited a median age of nonsurvivors of 69 y versus 52 y for survivors (90), whereas another patient cohort exhibited a median age of patients requiring ICU care of 66 y versus 51 y for patients not requiring ICU care (88). Furthermore, emerging epidemiological studies reveal some of the immunological features associated with pathophysiology in SARS-CoV-2 patients. Among large patient cohorts (i.e., >100 patients), high neutrophil counts and neutrophil activation, increased serum levels of inflammatory cytokines, and lymphopenia are associated with poor disease outcomes (88–90, 103, 104). Specifically, patients requiring ICU care exhibit a 2-fold elevation in neutrophilia versus non-ICU patients, and nonsurvivors exhibit substantially enhanced neutrophil counts versus survivors after ∼1 wk and continuing through the remainder of the disease (88). Also, nonsurvivors exhibit a 2-fold lower circulating lymphocyte count but a 2-fold increase in IL-6 levels as compared with survivors (90). Furthermore, a case study of a patient who died of SARS-CoV-2 infection demonstrates that the lungs exhibit hyaline membrane formation as well as immune cellular infiltrates, including lymphocytes and granulocytes (101). Conversely, a patient who recovered from SARS-CoV-2 infection exhibited normal neutrophil and lymphocyte counts and low levels of proinflammatory cytokines (100). Thus, a hyperinflammatory innate immune response could contribute to the elevated mortality rate of SARS-CoV-2 in older people, similar to results observed in other respiratory viral infections. Similarly, lymphopenia is associated with higher mortality in influenza infection (105–107), again pointing towards enhanced innate immunity as major contributor to mortality in respiratory viral infections.

As with SARS-CoV and respiratory viral infections, SARS-CoV-2 associates with several comorbidities, which are more prevalent with aging. These comorbidities include hypertension, cardiovascular disease, diabetes, and chronic obstructive pulmonary disease, among others (88–90, 92, 108–112). Importantly, hypertension (23% of surviving group versus 48% of nonsurviving group), diabetes (14% of surviving group versus 31% of nonsurviving group), and chronic obstructive pulmonary disease (1% of surviving group versus 7% of nonsurviving group) are increased among nonsurviving SARS-CoV-2 patients versus survivors (90). Similar findings are observed in patients requiring critical care versus those that do not require critical care: hypertension (58.3% of ICU patients versus 21.6% of non-ICU patients), cardiovascular disease (25% of ICU patients versus 10.8% of non-ICU patients), and diabetes (22.2% of ICU patients versus 5.9% of non-ICU patients) are all increased (88). Notably, critically ill SARS-CoV-2 patients exhibit acute cardiac injury (91, 92, 108, 110, 112). Specifically, nearly 20% of patients with COVID-19 exhibit myocardial injury (108), which leads to a strikingly increased incidence of respiratory distress (58 versus 14% of those without myocardial injury) and <50% survival rate. Importantly, patients with a history of chronic heart failure have a 10-fold increased risk of myocardial injury. Given the expression of ACE2 in cardiac tissue, there is speculation that SARS-CoV-2 may have direct cardiac activity, although that remains to be proven (92, 108). Such a phenomenon was observed in the Middle Eastern respiratory syndrome coronavirus outbreak in 2012 (113); however, Middle Eastern respiratory syndrome coronavirus facilitated cellular entry via the dipeptidyl peptidase-4 pathway, rather than via ACE2 (114). Influenza infection is also associated with cardiovascular disease, particularly congestive heart failure and acute coronary syndromes, and the presence of these diseases enhances the mortality associated with influenza infection (27, 115–117). The recent association of COVID-19 and
Disclosures
The authors have no financial conflicts of interest.

References

Conclusions
Older people exhibit a dampened adaptive immune response with dysregulated innate immunity (particularly, elevated neutrophil counts in the lung) during several respiratory viral infections. As an age-impacted innate immune response is common across a wide range of respiratory viral infections, including in patients with influenza, RSV, and SARS-CoV, dysregulated innate immunity may contribute to increased mortality noted in older people with COVID-19. The development of relevant murine models of SARS infections, such as transgenic murine models expressing human ACE2, which can be infected with either SARS-CoV or SARS-CoV-2 to induce lung damage (119–122), will likely be instrumental to determine the exact mechanisms by which aging impairs host defense and vaccine efficacy to respiratory coronaviruses. These models may reveal that aging both dysregulates innate immunity and impairs adaptive immunity. If so, then targeting innate immunity may represent an effective therapeutic strategy to reduce suffering in the general population and particularly in older people infected with SARS-CoV-2. Importantly, development of effective vaccines in older people will be critical to protect this vulnerable population and the population at large from COVID-19.


