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# COVID-19 AND AGEING-RELATED EVENTS

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## ABSTRACT

The first report of patients with the SARS-CoV-2 was in Wuhan on December 2019. In few months the virus was disseminated around the world and has caused millions of deaths. A striking and recurrent finding was the more severe disease and increased numbers of fatal cases in old adults. Vaccines were developed in a record period of time and since then a massive program of vaccination has been installed in several countries. Nevertheless, the decrease in the levels of specific antibody after six months of the first dose in young adults and the reports of fatal cases in vaccinated older patients have suggested that a 3rd dose of vaccine is required. From the first report until now it has been clear that the immune system plays an important role in the disease development and patient outcome. Our group showed recently that healthy old individuals present changes in the immune system that have been reported as immunosenescence and inflammageing. Therefore, our aim was to correlate the findings obtained in healthy old adults with cases of COVID-19 from literature in order to identify possible common factors. The further understanding of how the changes occurring in the immune system during the ageing process can affect the response to SARS-CoV-2 virus could contribute for the development of vaccines or more specific therapies to the aged population.

**Keywords:** SARS-CoV-2, COVID-19, Ageing, Immunosenescence, Inflammageing

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## Introduction

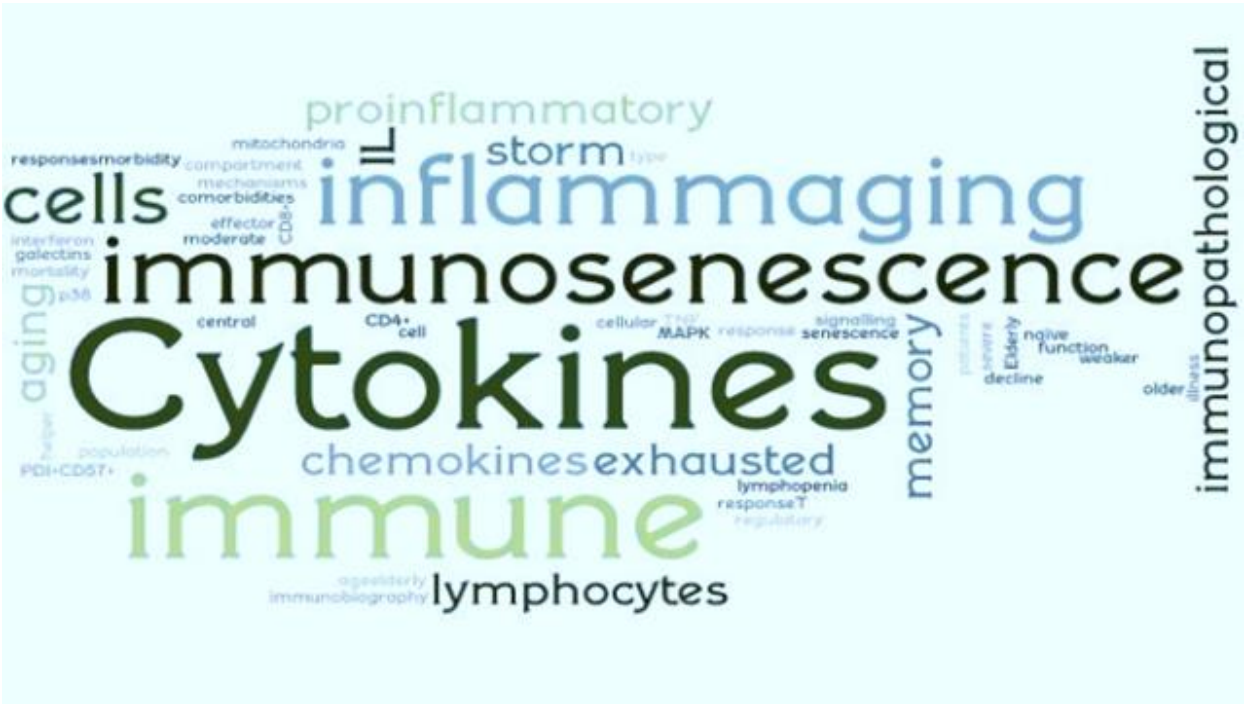
After several cases of pneumonia of unknown etiology in Wuhan (China) and fast spread to other provinces, on January 2020 a novel coronavirus was identified by deep sequencing analysis from patient's swab sample by the Chinese Center for Disease Control and Prevention. [1,2] The initial denomination 2019-nCoV was replaced by severe acute respiratory syndrome-coronavirus-2 or SARS-CoV-2. A public health emergency of international concern was declared by the World Health Organization (WHO). [3] In February 2020 the Chinese Health Authority announced 76,936 confirmed cases of COVID-19 with 2,442 deaths. Deceased patients were mostly old adults and two-thirds males. [4] Data from Wuhan Union Hospital showed that fever and cough were the major symptoms and patients (n=43, 50-73 years) presented comorbidities (hypertension, diabetes, cardiovascular disease, chronic lung disease). In public data (37 deaths and 1,019 survivors, Chinese Public Health Science Data Center) it was observed that survivors were 35 to 57 years and deceased 65 to 81 years. In the group of aged patients, 64.9% presented at least one underlying disease (hypertension, diabetes, cardiovascular disease, chronic lung disease). [5] The transmissibility of the virus was high and by March 3rd, 2020, there was a report of 90,870 confirmed cases and 3,112 deaths around the world. [6] The study of COVID-19 in Washington, in the period that the State was the epicenter of the disease in the US, showed that the median age of the patients was 69 years, with 55% of them presenting comorbidities (hypertension, obesity, cardiovascular disease, diabetes). Severe disease occurred in 49% of cases and overall mortality rate was 33%.[7] A study of the first wave of COVID-19 in Spain showed that from 218,652 cases, the hospitalization occurred in 45.4%, 4.6% needed ICU (Intensive Care Unit), and 11.9% died. Deceased patients had at least one underlying disease (94.8%) and age ≥80 was the stronger predictor of death. [8] In Brazil, from 385,473 deaths (April 2021), 73.1% occurred in individuals older than 60 years. [9] A higher risk of the worst outcome after SARS-CoV-2 was reported for old adults, and mainly for those with comorbidities. [9]

In addition to comorbidities playing an important role in the burden of COVID-19 in old adults, it is reasonable to hypothesize that in this population, a less efficient immune system could contribute to the severity of cases and deaths. During the ageing process the immunity is affected, and thus responses to infections and vaccination are impaired. Changes in the immune system are extensively reviewed elsewhere [10,11] but briefly, bone marrow decreased generation of leukocytes, thymus involution, structural changes in lymph nodes and spleen have a profound impact in the number and functions of cells from the immune system of aged individuals. For T cell subset, it has been reported the decrease of naïve cells, lower T-cell receptor (TCR) diversity, increase of memory cells in terminal differentiation, diminished proliferation, and altered production of cytokines (immunosenescence). In addition, a systemic low-grade of chronic inflammation depicted by an increase in IL-1, TNF-α, C reactive protein (CPR) has also been observed (inflammageing). These changes reported for the immune system have an important impact in the resolution of a viral infection, as it is highly dependent on adaptive immune responses represented by T CD4+, T CD8+, and B cells. In addition, suppressive cells such as myeloid-derived suppressor cells (MDSC) can negatively affect the immune response of T cells. [10,11]

This review was based on extensive database search such as the web of science, world wide

science, google scholar, pubmed, virtual library in healthy, digital library of theses and dissertations. The keywords for this consult were SARS-CoV-2 and Elderly, SARS-CoV-2 and old people, Immune Senescence associated with SARS-CoV-2, Immune Senescence associated with COVID-19. The inclusion criteria consisted of original articles published between January 2020 to July 2021 that matched the objective of the study. It was performed a bias analysis based on the frequency of keywords citations that identified a trend in research during the period from November 2020 to July 2021 as shown in the diagram below:

**Figure 1.** Analysis of research trends by frequency of cited words.




A statistical survey considering the large number of cases in China, Europe e American continent, allowed the collection of published data. Algorithmically, the diagram above complexly and qualitatively presents data that researchers around the world were searching for at the very beginning of the pandemic – minor words - (March to October 2020). Such data are represented by the smaller words and over time, as new discoveries were made, were replaced and evidenced by major words that aligned to specific factors, about chronic inflammation and immunosenescence. (November 2020 to July 2021). These are highlighted by the bigger words.

Recently our group published results from healthy aged adults (80-100 years old) that displayed changes in parameters of the adaptive immune system (T cells) and in MDSC (Table 1). [11] Therefore, the match between our previous article and the reports in literature about COVID-19 was the aim of this review. We found that age-related immune changes were also observed in COVID-19 cases and that the decrease or increase of some parameters were exacerbated during the course of the disease and correlated with the outcome. Therefore, the markers evaluated in this review could be used as a tool for management, prognostic, and therapies in cases of SARS-CoV-2 infection in the aged population.

**Table 1.** Parameters of the immune system in young and old adults

| Immune Parameters | Young adults (n=10) 20-30 years | Old adults (n=12) 80-100 years | Student test p |
|---|---|---|---|
| Leukocytes number ($10^5$) | 83.2±19.4 | 50.7±16.7 | 0.0003 |
| Myeloid-derived suppressor cells (%) | 0.07±0.05 | 0.24±0.19 | 0.006 |
| T CD4+ (%) | 45.9±8.7 | 49.4±11.6 | NS |
| T CD8+ (%) | 25.1±5.6 | 21.3±14.1 | NS |
| CD4+/CD8+ | 1.9±0.5 | 3.3±1.7 | 0.009 |
| Proliferation T CD4+ (%) | 53.4±18.2 | 40.5±19.5 | 0.06 |
| Proliferation T CD8+ (%) | 58.8±21.1 | 42.6±21.7 | 0.05 |
| Naive T CD4+ (%) | 51.5±11.7 | 41.1±25.7 | NS |
| Central Memory T CD4+ (%) | 31.7±10.6 | 21.8±15.4 | 0.045 |
| Effector Memory T CD4+ (%) | 13.6±3.9 | 26.2±24.8 | 0.054 |
| EMRA T CD4+ (%) | 3.1±2.6 | 10.8±12.4 | 0.03 |
| Naive T CD8+ (%) | 54.3±13.7 | 35.7±15.4 | 0.007 |
| Central Memory T CD8+ (%) | 20.4±8.5 | 12.8±7.2 | 0.02 |
| Effector Memory T CD8+ (%) | 10.6±8.9 | 11.4±6.0 | NS |
| EMRA T CD8+ (%) | 13.8±7.6 | 41.0±19.3 | 0.0002 |

EMRA - effector memory re-expressing CD45RA (terminally differentiated). Table adapted from [11]

As shown in Table 1, the statistically significant differences between young and old adults were in leukocytes number, MDSC, and T cells (Central Memory CD4+, EMRA CD4+, Naive CD8+, Central Memory CD8+, EMRA CD8+, Proliferation of CD8+, and ratio CD4+ CD8+).

**Leukocytes**

Leukocytes are generated at bone marrow from Hematopoietic Stem Cells (HSC) and represent less than 1% of total blood cells (adults: 4,0–10,0 × $10^3$ $\mu L^{-1}$) but these numbers can increase ten times due to reservoir pools of these cells in bone marrow, spleen and lymphatic nodules. [12] It has been reported that the number of total leukocytes are reduced during the ageing process. [13] In agreement, our group showed that healthy old adults present a significant decrease in the number of leukocytes in comparison with young individuals. [11]

Ageing has been associated with the loss of ca-

pacity from HSC to self-renewal and hematopoietic regeneration. [14, 15, 16] Intrinsic and extrinsic factors are related to the decrease of leukocytes in periphery which contribute for the reduced immunity with a negative impact in responses to infections and vaccination. [16] In addition to the thymic involution, the diminished generation of HSC progenitors in bone marrow also contributes for the changes observed in blood T cells. [17]

In COVID-19, Huang et al. observed the reduction of leukocytes (less than 4x $10^9$/L in 25% of patients) and lymphopenia (less than 1x$10^9$/L in 63% of patients.[1] Rui et al. (2020) also observed the reduction of leukocytes and lymphocytes in COVID-19 patients older than 90 years. [18] The observed lymphopenia has been associated with the increase of inflammatory markers, severe pneumonia, longer stay at hospital and fatal cases. [19, 20]

**T cells**

In our studied healthy aged population, CD8+ but not CD4+ Naive T cells presented a statistically significant decrease in old individuals compared to the young population (Table 1). It has been shown that thymic involution contributes to the decreased release of naive T cells to the periphery, and homeostatic proliferation is an alternative mechanism to prevent these cells from a higher drop down. [21] Qin et al., [22] observed a positive correlation between age and decrease in the percentage of Naive CD8+ T cells but not for Naive CD4+ T cells. In agreement, Goronzy et al., [23, 24] found that in humans the homeostatic proliferation is a mechanism less effective for T CD8+ cells which in association with a loss in the TCR diversity lead to a reduced potential of these cells in an viral immune response. In COVID-19, Moderbacher et al., [25] found that the percentage of naïve CD4+ and CD8+ T cells were negatively correlated with age and the percentage of naïve CD8+ T cells was reduced both in acute (peak of severe disease) and convalescent patients in comparison with healthy controls. Naïve CD4+ T cells were reduced in the peak of disease severity but the correlation was lost when all COVID-19 cases were evaluated. Considering the importance of naïve T cells activation to mount a virus-specific T cell response, authors suggested that the reduced percentage of these cells could contribute to the worse outcome of patients. Jin et al., [26] observed that during acute infection by COVID-19 there was a significant decrease in naive CD4+ and CD8+ T cells (absolute cell number) whereas activated CD4+ and CD8+ T cells increased in comparison to controls. The complete recovery was not observed at ten-week follow-up post COVID-19. In addition, in convalescent patients, there was an age-associated reduction in absolute number and proportion of naive CD4+ and CD8+ T cells. An age-related increase in activated CD4+ and CD8+ T cells was also found in these patients. [26]

Our healthy aged population (Table 1) presented a significant increase in Central Memory and EMRA CD4+ and CD8+ T cells. Qin et al., [22] found a significant age-related increase in EMRA CD4+ and CD8+ T cells and these results are possibly representative of the effector or exhausted T cells in the aged population. In COVID-19 Bellesi et al., [27] evaluated effector T cells by measuring CD95 and the exhaustion marker PD-1, also present in antigen-mediated T-cell activation. Patients with COVID-19 and older than 65 years (67-93) presented a higher expression of CD8+CD95+ cells in comparison <65 years (29-65). CD8+PD-1+ T cells presented a tendency of higher expression in patients <65 years. Authors suggested that during COVID-19 infection, T cells expressed molecules that could contribute to apoptosis and

exhaustion. Townsend et al., [28] found in patients with COVID-19 a reduction in CD8+ Naive T cells in addition to an increase in CD8+ Effector T cells (CD45RA+CD27-CD197-) and CD8+ Activated T cells (CD38+HLA-DR+). These findings were strongly correlated with age, and in patients older than 60 these changes in CD8+ T cells were displayed for a longer period regardless of disease severity. Westmeier et al., [29] evaluated patients with mild COVID-19 during acute infection. In patients older than 80 effector memory (EM) and terminally differentiated effector (EMRA) CD8+ T cells presented reduction in the cytotoxicity whereas for CD4+ T cell subtypes, no differences were observed when patients and controls were compared. Based on the decreased granzyme A and perforin expression, authors suggested that functional changes in the cytotoxic profile of CD8+ T cells occurred in COVID-19 patients older than 80 in comparison with patients 29-69 years old.

In the healthy population studied, we observed that CD4+ and CD8+ T cells from the old adults presented a reduced rate of proliferation *in vitro* after PHA stimulation, but only CD8+ T cells reached a statistically significant decrease in comparison with the young group (Table 1). In agreement, Murillo-Ortiz et al., [30] showed that old adults (60-65 years old) presented a reduced proliferative capacity of CD4+ and CD8+ T cells after a non-specific stimulus *in vitro* (Con A) in comparison to a young population (20-25 years old). In COVID-19, convalescent patients (28-67 years old) with mild disease presented CD4+ T cells that proliferated homeostatically *in vitro* (with IL-7 and thereafter with overlapping peptides from SARS-CoV-2 spike) and produced IFN-γ. [31] Avendaño-Ortiz et al., [32] found that patients with long hospital stay, regardless of age, presented significant low proliferative rates of CD4+ and CD8+ T cells after in vitro stimulation.

**Myeloid-derived suppressor cells (MDSC)**

Data from our previous study showed that aged individuals presented a significant increment in the percentage of MDSC (Table 1). MDSC can be described as a group of heterogeneous myeloid cells with potent immunosuppressive activity. The increase of MDSC has been reported in cancer, tuberculosis, sepsis and recently in aged individuals. [33] In patients with COVID-19, there was an increase of circulating MDSC both in severe (90% of total mononuclear cells) and mild disease (25% of total circulating mononuclear cells). Recovery was associated with decrease of MDSC frequency and increase of inflammatory cytokines in plasma. [34] In 128 patients (53-75 years old) evaluated, polymorphonuclear (PMN)-MDSC frequency increased, mainly in those requiring ICU, and was correlated with plasma levels of inflammatory markers (IL-1β, IL-6, IL-8, TNF-α). In fatal cases, PMN-MDSC was higher at the hospital admission than in survivors. In addition, there was a strong correlation between PMN-MDSC frequency and fatal outcome (multivariate regression analysis). [35] Falck-Jones et al., [36] found higher frequency of monocyte (M)-MDSC in blood but not in nasopharyngeal or endotracheal aspirates of COVID-19 patients (n=147, 24-78 years). In addition, fewer T cells and increased plasma levels of Arg-1 and IL-6 were also observed. Early M-MDSC percentage was correlated with disease severity (ordinal regression). Tomić et al., [37] observed in patients with mild disease (22-78 years old) a lower frequency and total number of M-MDSC and PMN-MDSC than in patients with severe disease (31-84 years old). COVID-19 patients with severe disease showed increased mRNA expression of ARG-1 in PBMC. In COVID-19 patients (47-67 years old), Reizine et al., [38] found increased MDSC and decreased CD8+ effector memory cells in those with acute

respiratory distress syndrome compared with patients presenting moderate pneumonia.

## Conclusions

In this review we compared the changes occurring in T cells and MDSC between a previously studied healthy aged population (Table 1) and cases of COVID-19 from literature. Common findings observed were reduced leukocytes, decreased Naïve CD8+ T cells, increased Effector Memory CD8+ T cells, and increased Effector Memory Terminally Differentiated CD8+ T cells. In addition, similarities in the diminished capacity of proliferation for both CD4+ and CD8+ T cells and increase of the percentage of MDSC were also similar between the two groups. In COVID-19, changes in T cells proliferation and MDSC were related respectively to long stay at the hospital and severity of the disease/fatal outcome. Considering that the ageing process is not identical for all human beings as it depends on the genetics, habits (diet, exercise, non-smoking) and immunological experiences (lifelong infections, vaccinations), these markers should be confirmed for aged patients in different regions in the world. We conclude that the markers evaluated in this review could be used as a tool for management, prognostic, and therapies in cases of SARS-CoV-2 infection in the aged population.

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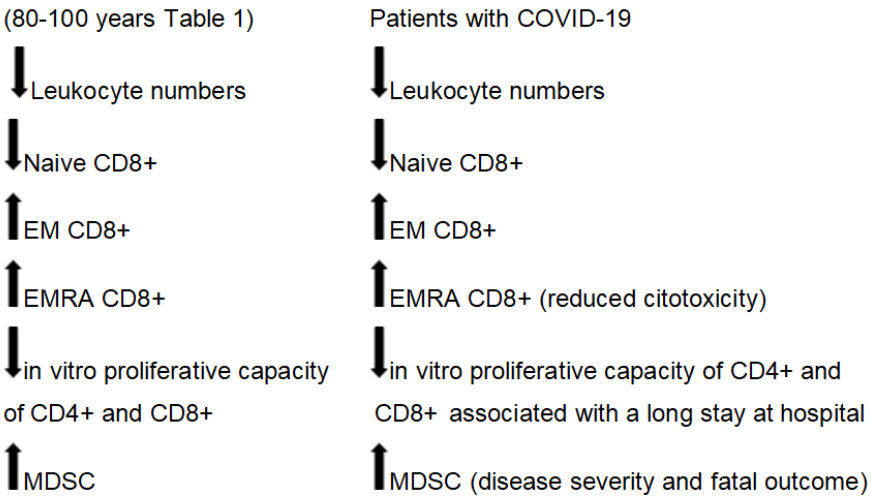
**Figure 2.** Similarities in cells from the immune system observed between healthy aged individuals and cases of COVID-19

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