New Model Shows Link Between Telomere Length and Risk of COVID-19 Mortality

By:
Joseph M. Raffaele
MD

The COVID-19 pandemic is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a zoonotic, single-stranded positive RNA virus that first emerged in Wuhan, China in late 2019[1] As of August 2022, the World Health Organization (WHO) has confirmed over 577 million cases and 6.4 million deaths from COVID-19 worldwide.[2]

The fatality ratios for SARS-CoV-2 infections are highest among the elderly (≥80 years) and range from 8% to 36%.[3,] The findings suggest that age-related mechanisms, such as the progressive shortening of telomere length with age, may play an integral role in the severity and mortality of COVID-19.

According to a recent study from University of Washington, short hematopoietic cell telomere length (HCTL) may be why vulnerability to COVID-19 increases dramatically among the elderly.[5] Without adequate clonal expansion capacity, a process dependent on telomere length, these populations may be at risk of developing a shortfall in T-cells, leading to lymphopenia and severe disease.[6,7,8]

Telomere Length and Its Importance in the Fight Against COVID-19

Telomeres are specialized structures that cap the end of chromosomes, protecting them from damage and providing genomic integrity.[9] In addition to their protective role, telomeres can be considered **aging clocks** in cells. Every time cells undergo mitosis (cell division), telomeres also follow suit – to an extent. Telomeres get shorter with each division until they reach a point at which they are unable to bind telomere-capping proteins. Because they are then sensed as exposed DNA ends, a DNA damage response is triggered, ultimately resulting in cellular senescence and cessation of replication.[10]

In recent years, telomere length has been recognized as one of the best biomarkers of an organism's biological age as well as aging-related pathological conditions.[11] Its attractiveness as a biomarker of aging includes:[12]

- Its correlation with chronological age across an organism's lifespan
- Its predictive power of one's susceptibility to a disease and mortality
- Its responsiveness to various exposures (adverse and beneficial)
- Its ability to be used to track changes in human aging rate

Telomere length is a heritable trait that displays relatively robust synchrony among all human leukocytes and hematopoietic cells.[13] For example, people with long telomeres in one leukocyte subset have relatively long telomeres in other leukocyte subsets.

Apart from genetics, no other factor has a bigger impact on telomere length than aging. Older people tend to have a higher inflammatory response to antigens, a phenomenon coined 'inflammaging.' Aging of the immune system also drains the proliferative capacity of telomere length-dependent T-cells, which then affects the ability to suppress infections.[14]

These effects are particularly evident in a SARS-CoV-2 infection, in which the body is confronted with the demand for massive clonal expansion of T-cells to offset the lymphopenia that arises from falling T-cell counts.[15,16]

One study from Belgium compared the telomere lengths of 70 hospitalized patients with COVID-19 to those of 491 healthy volunteers. Froidure and colleagues found that a significant proportion of patients had short telomeres (<10th percentile) compared to the reference cohort. Short telomeres were linked to greater disease severity, defined as ICU admission or death without ICU.[17]

Moreover, developing immunity to SARS-CoV-2 requires naive T-cells to proliferate and differentiate into SARS-CoV-2-antigen-specific effector/memory T-cells.[16,18] Based on this evidence, the authors of the current study speculate that short telomeres in naive T-cells may also impede adaptive immunity to the infection even without lymphopenia.

Developing the Model

Anderson and colleagues developed a model examining the relationship between age-related decline in telomere length-dependent T-cell clonal expansion capacity with COVID-19 mortality.

To build the model, they used records from the Centers for Disease Control and Prevention (CDC) and the 2019 U.S. Census for COVID-19 and non-COVID-19 mortalities as well as data from studies whose HCTL had been measured prior to the pandemic.[4]

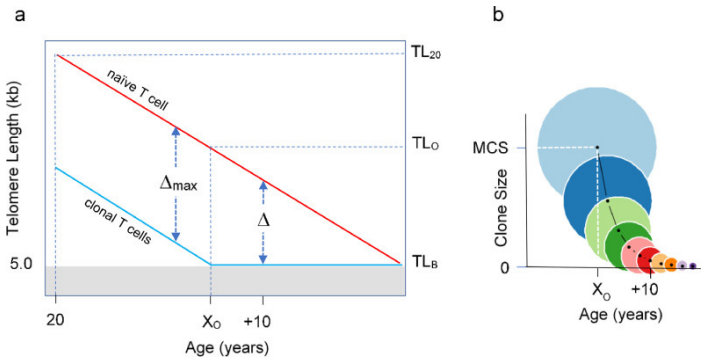
The team made the following assumptions about T-cell replication, telomere length, and T-cell clone size for their model:

- The "**telomeric brink**" (TL_B) or the point of telomere length-dependent termination of T-cell replication, is 5 kb.
- The length of a telomere in a naive T-cell at age 20 (TL_{20}) shortens at a rate of 0.03 kb/year until it reaches the telomeric brink.
- A naive T-cell can generate a **maximal clonal size** of 2^{20} (approximately 1 million) T-cells through 20 replications.
- Most memory T-cells are formed during childhood and early adulthood, periods during which maximal clonal size can be achieved due to long HCTL.
- "**Telomeric onset**" (TL_O) or the shortest T-cell telomere length that can achieve maximal clonal size, is 6.4 kb. A naive T-cell reaches telomeric onset at the "**age of onset**," after which it can only generate a limited clonal size because a full expansion drops the telomere length below the telomeric brink. Telomere length contributes to the telomeric onset, i.e., long T-cell telomeres reach it at a later age of onset compared to shorter T-cell telomeres.

Results

According to the model, naive T-cells are capable of generating the maximal clonal size (MCS) of 2^{20} memory T-cells in response to an antigen before the age of onset (X_0). But their ability to do so declines in an exponential manner once this age is reached. In one decade after the age of onset, the naive T-cells' clonal expansion capacity was shown to be only **5% of the maximal clonal size**.

Figure 1

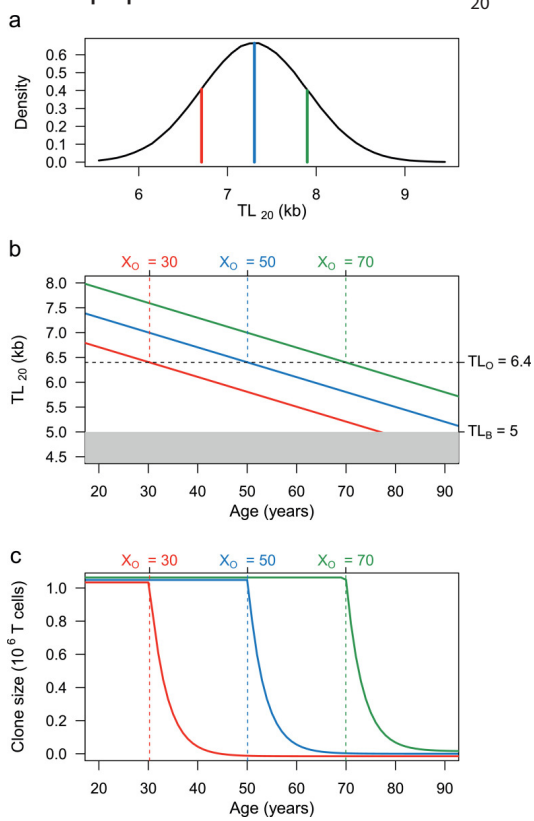


Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8970968/

Specifically, a person with an average HCTL can attain maximal clone size up to the age of 50. Plots generated using the model suggest that limited clonal size is roughly equivalent to maximal clonal size. After that, however, naive T-cells rapidly decline in their clonal expansion capacity, coinciding with the dramatic increase in COVID-19 mortality among the elderly.

Figure 2 shows the population distribution of TL_{20} and age-dependent changes in T-cell telomere length and in T-cell clone size.

Figure 2



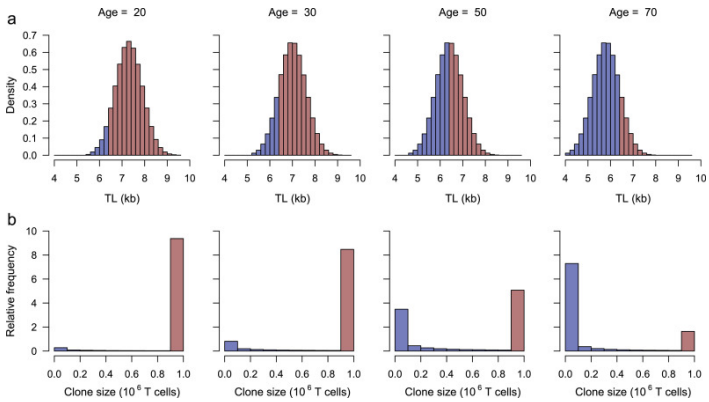
Population distribution of T-cell TL at age 20 (TL20), T-cell TL shortening with age, and age-dependent change in T-cell clone size (CS). (**a**) displays the TL20 distribution, showing mean TL = 7.3 kb (), long TL (mean + SD) = 7.9 kb (), and short TL (mean – SD) = 6.7 kb ( ). (**b**) displays age-dependent change in T-cell for mean, long and short TL20. Past the telomeric onset (TLO = 6.4 kb), TL is insufficient to produce MCS because a full clonal expansion drops TL below the telomeric brink (TLB = 5 kb). The TLO is reached at different ages of onset (XO), i.e., an older age for T-cells with long T-cell telomeres and younger with T-cells with short telomeres. The age-dependent T-cell TL shortening (0.03 kb/year) for T cells with mean, long, and short telomeres at TL20 is shown by the lines. (**c**) shows that the T-cell CS is partitioned by the XO into plateau and slope regions. T cells with mean, long, or short TL20 achieve MCS on the CS plateau, but their CS exponentially collapses (slope) once their TLs shorten below TLO and exceed XO (at different ages).

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8970968/

The plots in Figure 2 were used to describe Figure 3, which displays the shifts in naive T-cell telomere length distribution and relative frequency of T-cell clone size in the population. In the distribution graphs, the blue and red bars indicate telomere lengths that fall below and above the telomeric onset, respectively. As shown, the proportion of the population with telomere lengths above the telomeric onset declines with age, falling to just 10% at age 70.

The bar graphs in Figure 3 show the relative frequency of the clonal size formed by naive T-cell clonal expansion. The maximal clonal size occurs in 9 out of 10 individuals at the age of 20, in whom naive T-cell telomere length is greater than the telomeric onset. In contrast, at age 70, less than 2 out of 10 people can generate the maximal clonal size.

Figure 3



Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8970968/

Perhaps the most exciting finding from this study was that the model was also able to explain the high variability in age of onset across a population. Because telomere length is heritable, there are differences in their lengths between people at every age, and the age of onset can also vary between individuals.

For example, an individual with long T-cell telomeres may be able to achieve maximal clonal size up to 70 years of age, while someone with short telomere lengths is able to do so up until they're 30 years old. This finding suggests that younger adults who develop severe COVID-19 may have done so due to their short T-cell telomere length, which limited their ability to achieve maximal clonal size in the face of the infection.

What Does the Model Tell Us About Telomere Length and COVID-19 Mortality?

The COVID-19 pandemic has highlighted the role of telomere length on mortality from aging-related disease. A SARS-CoV-2 infection presents two levels of challenges: creating SARS-CoV-2-specific memory T-cells *and* replenishing lost naive

T-cells. Both of these processes depend on HCTL, which shorten naturally with age and thereby limit the clonal expansion capacity of T-cells.

The insights gained from this model may help healthcare practitioners use telomere length parameters to identify individuals who may be most susceptible to severe COVID-19. These individuals may also show early waning of immunity after a SARS-CoV-2 vaccination, leaving them vulnerable to a novel variant of the virus.

By identifying patients with short telomeres, healthcare professionals may be able to better stratify risk of severe COVID-19 and allocate resources such as booster vaccines, antivirals, and monoclonal antibodies more effectively than by relying on chronological age alone.

Author Bio:

Joseph M. Raffaele, MD

Joseph Raffaele received his BA in philosophy from Princeton University and his MD from Hahnemann University Medical School in 1989. Dr. Raffaele did his internal medicine residency at The New York Hospital/Cornell University Medical Center and was formerly a clinical assistant professor of medicine at Dartmouth Medical School while in practice at the Hitchcock Clinic. Dr. Raffaele is a member of the American College of Physicians, is board certified in internal medicine, and is a diplomate of the American Academy of Anti-aging Medicine.

In 1995 Dr. Raffaele began researching and developing a scientifically-based treatment program and co-founded PhysioAge Medical Group. Since 1997 Dr. Raffaele has been focused on age longevity medicine and biomarkers of aging.

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