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Severe COVID-19 and Telomere Shortening: Overview of Roles and Effects

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Abstract

The importance of telomeres as special structures at the ends of chromosomes is gradually gaining prominence. They are composed of short, multi-repeated non-transcribed sequences (TTAGGG) and binding proteins, and their main role is to protect chromosome ends from degradation. Recent studies have shown that the length of telomeres may affect the outcome of COVID-19 infection, and the severity of COVID-19 is associated with shortened or dysfunctional telomeres, which may be an important factor contributing to the deterioration of the patient's condition. In conjunction with this, COVID-19 patients with longer telomeres tended to have better outcomes compared to those with shorter telomeres. This suggests that telomere length can be used as a potential marker to predict the progress of COVID-19 patients' recovery, highlighting the potential role of telomeres in the immune system. The involvement of telomeres in the recovery and virological processes of COVID-19 patients demonstrates that telomeres contribute to the maintenance of chromosome stability and promote the normal restoration of cellular functions during the recovery process, thereby improving patient outcomes. This review examines the complex relationship between telomere length and COVID-19 disease. Telomere abnormalities may exacerbate lung injury and fibrosis in COVID-19 patients, while COVID-19 infection accelerates telomere shortening, leading to premature cellular senescence. The aim of this review is to gain a deeper understanding of how telomere length affects disease severity and how COVID-19 in turn affects telomere structure and function. In addition, the impact of COVID-19 on the aging process is explored to provide scientific rationale and insights for the development of targeted therapeutic interventions in the future.

Keywords

Telomere, COVID-19, SARS-CoV-2, T Cell, Aging

1. Introduction

The World Health Organization (WHO) declared the coronavirus disease 2019 (COVID-19) as a pandemic on March 11, 2020, after it was initially discovered in China in December of 2019 [1]. The widespread spread of COVID-19, which was triggered by the SARS-CoV-2 virus, has had a dramatic impact on the global health system and profoundly altered the perception of viral diseases [2]. Among these impacts, the role of biomarkers in assessing disease progression, predicting recovery and long-term health consequences is particularly critical [3]. The clinical presentation of COVID-19 is highly heterogeneous, ranging from asymptomatic and mild to severe and even fatal, with host factors such as age, gender and co-morbidities being key determinants of disease severity and progression, and ageing itself significantly increasing the risk of severe COVID-19 illness and death [4]. Telomeres, as protective structures at the ends of chromosomes, are considered important markers of cellular senescence and disease, and are associated with the severity of COVID-19 [5]. Researchers are exploring the potential role of telomeres in regulating disease severity and patient recovery and have found that shorter telomeres may be associated with severe clinical manifestations and poor prognosis in COVID-19, including an increased risk of ICU admission and mortality [6]. Therefore, by exploring in depth how telomere length affects COVID-19 severity and long-term health outcomes, we are better able to provide a scientific basis for developing more effective rehabilitation strategies [7]. With further research, the role of telomeres as biomarkers in the rehabilitation of COVID-19 patients will receive increasing attention, and we will delve into the relationship between COVID-19 and telomeres in this review [8].

2. Telomere and Aging

Telomeres are conserved DNA sequences located at the ends of eukaryotic chromosomes, protecting the integrity of the chromosomal genome from damage [9]. However, due to the "end-replication problem", which refers to the inability of DNA polymerase to fully replicate the ends of the chromosomes, this leads to shortening of the telomeres with each cell division, and ultimately the telomeres are too short for the cell to continue dividing, which triggers cellular senescence [10] [11]. It acts as a protective cap at the end of eukaryotic chromosomes, invading the double-stranded telomere region through its single-stranded overhanging portion to form a t-loop, thereby building and maintaining a structure at the end of the chromosome that prevents double-stranded DNA breaks from occurring at the end of the chromosome and triggering a DNA damage response [12], whereas the loss of telomere function can lead to genetic instability and a decrease in cell viability [13]. Therefore, understanding how telomeric macromolecular structures contribute to ATM regulation and its potential dissociation from non-homologous end-joining (NHEJ)-dependent telomere fusion control is critical for cellular senescence and tumor suppression [14]. However, mitosis leads to telomere depletion during senescence to a critical length where cells stop dividing, triggering senescence or dysfunction [10].

Cells lose viability when telomeres become extremely short, so telomeres are considered a molecular clock and are used as biomarkers for a variety of diseases [15]. There are several potential factors affecting telomere structure and function, for example, telomeres have the potential to act as mediators of chronic psychosocial stress leading to disease [16]; lifestyle can lead to telomere shortening, such as obesity [17]; and telomere length in the foetus or newborn is also affected by external factors, such as stress and nutrition [18].

Telomerase, a specialized reverse transcriptase, utilizes its inherent RNA template to extend the G-rich strand of telomeres in human cells [19]. The mammalian telomere system uses repeats synthesized by telomerase as shelterbelt binding sites to block the DNA damage response, while a six-subunit protein complex called shelterin addresses chromosome end protection by specifically binding to TTAGGG sequences, in both double-stranded and single-stranded forms [20]. A telomere with a long enough tract length and intact shelterin components are necessary to shield a chromosomal end from harmful degradation, triggering DNA damage responses, and involvement in recombination or fusion processes that destabilize the genome [21]. Six proteins make up the human shelterin complex: protection of telomeres 1 (POT1), repressor/activator protein 1 (RAP1), telomere repeat binding factor 1 (TRF1), TRF2-interacting nuclear protein 2 (TIN2), and TPP1-interacting protein 1 [22].

In recent years, telomeres have been proposed as one of the biomarkers of organismal aging [23]. Although telomere length, and its attrition over time, is extremely variable among individuals, it is thought to be stable from childhood through young adulthood but begins to decrease in older adulthood [24]. When telomere length is reduced below a certain threshold, tissue regeneration is disrupted, cellular replicative senescence occurs, and dysfunction occurs [25]. For example, the shortening of white blood cell telomeres as individuals age is considered a potential indicator of biological aging and is commonly associated with age-related illnesses [25]. Loss of telomerase activity shortens telomeres, destabilizes chromosome ends, triggers genomic instability and cell growth arrest or apoptosis, and then reaches the "Hayflick limit", leading to cellular senescence [26]. Genetics has linked the most pronounced manifestations of telomere system and telomerase dysfunction in humans to the etiology of lung disease [27], the length of which is negatively impacted by environmental factors such as pollutants, smoking, and oxidative stress, potentially accelerating shortening and elevating the risk of aging-related diseases [28]. New research indicates that certain cancer treatments such as chemotherapy and radiotherapy can trigger the development of senescent cells [29]. Activation of oncogenes is usually achieved through aberrant expression of their active variants, which play a role in the formation of distinctive cellular features associated with replicating senescent and stress-induced premature senescence (SIPS) cells [30]. In this context, senescence therapy is an effective therapeutic intervention that can be used to remove ageing cells from the patient's body, thereby eliminating the risk of pathological processes [31]. In addition to this, cellular senescence is now considered to be an

important factor in COVID-19 diseases, as senescence is also present in these diseases [32]. Telomere protection 1 (POT1) is a key element of the shelterin complex, which is responsible for safeguarding telomeric single-stranded DNA (ssDNA), which has been connected to various processes such as DNA damage response, tumor formation, and aging, with its levels being correlated to the aging process [33]. It is evident that there is a significant link between senescence, age and telomeres, yet further research is needed to gain a deeper understanding of these complex interactions in human cells and tissues [31].

Figure 1 exhaustively reveals a unique structure at the end of a chromosome, the telomere. The DNA sequence of a telomere exhibits a specific repeating pattern, as shown in the figure, and usually consists of recurring sequence units like TTAGGG/AATCCC. At telomeres, there exists a critical protein complex, Shelterin, which consists of six proteins that work in concert to maintain the structure and function of telomeres and ensure chromosome stability and integrity, including RAP1, TRF2, TRF1, TIN2, TPP1, and POT1. When Shelterin function is abnormal, telomeres may not be effectively protected, which may lead to the gradual reduction of telomere length.

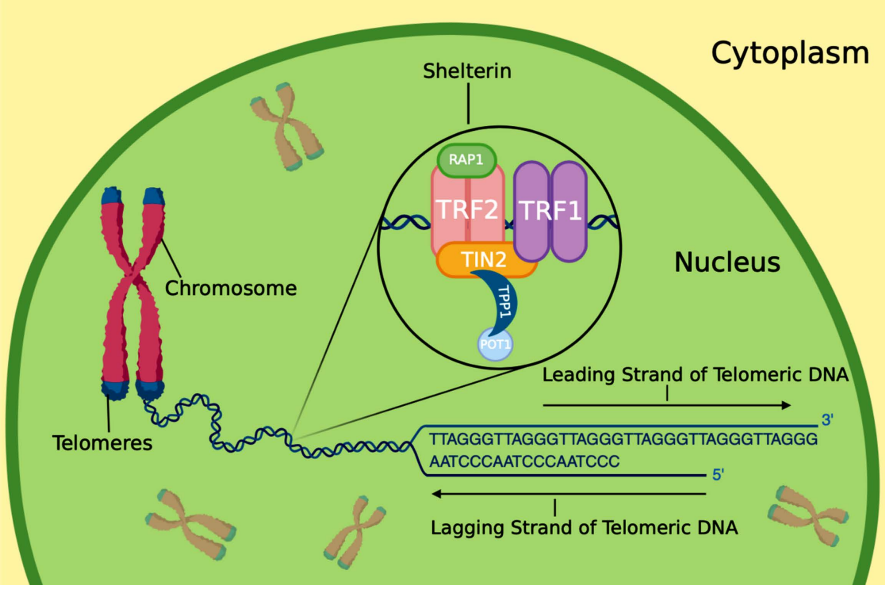

Figure 1. Telomeric DNA sequences and Shelterin proteins.

3. COVID-19

Coronaviruses (CoVs) are a highly diverse family of enveloped positive-sense single-stranded RNA viruses [34], which is caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2) [35]. The SARS-CoV-2 genome is a single-stranded positive-sense RNA encapsulated within a 75 - 150 nm membrane envelope covered with glycoprotein spikes, giving it a crown-like appearance, and has a length of about 30 K nucleotides [36]. The 5' region, which accounts for more than two-thirds of the genome, encodes the orf1ab polyprotein, whereas the

remaining third of the 3′ end contains genes encoding structural proteins, including the spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins [37]. SARS-CoV-2 uses angiotensin receptor (ACE)-2 to enter cells, and an increase in ACE-2 promotes greater susceptibility of the virus to infect cells [38]. DNA damage, particularly due to telomere attrition or shedding, enhances ACE2 expression, thereby facilitating SARS-CoV-2 infection and entry [39]. SARS-CoV-2 infects vascular endothelial cells via the ACE-2 receptor, leading directly to injury [40].

A potential pathway for the phenomenon of telomere shortening in COVID-19 patients can be an inflammatory response within the body. Prolonged exposure to hyperoxia can lead to oxygen toxicity, overwhelming cellular antioxidant capacity and leading to oxidative damage, which increases aging biomarkers such as telomere shortening and inflammation [41]. The organs in the body that are most susceptible to severe damage from COVID-19 are the lungs [42]. The diversity of clinical presentations of SARS-CoV-2 infection is one of the greatest challenges of COVID-19. SARS-CoV-2 infection often triggers a long-lasting severe lymphopenia, characterized by a significant decline in T-cell counts, which is strongly correlated with the severity of COVID-19 disease, which in turn affects immune system function and may exacerbate disease progression [43]. The SARS-CoV-2 virus also affects the heart, respiratory system, liver, kidneys and the central nervous system of the brain [44]. Typical laboratory findings of COVID-19 are lymphopenia, elevated C-reactive protein and erythrocyte sedimentation rate, with lymphopenia resulting from lymphocyte necrosis or apoptosis [45]. The severity of COVID-19 infections is influenced by the virulence of the SARS-CoV-2 variants and the host immune response, with clinical manifestations ranging from asymptomatic infections to severe inflammatory syndromes and multiple organ dysfunction [46]. Common clinical symptoms including fever, malaise, cough, shortness of breath, pulmonary oedema, ARDS or multi-organ failure [47]. Critical cases of COVID-19 are marked by significant lung injury, a reduction in lymphocyte levels, an increase in neutrophil counts, and the presence of macrophage and neutrophil infiltrates in both blood and lung tissues [48].

This review mentions six of the following conditions that may occur because of COVID-19 infection: Respiratory failure, Inflammaging, Senescent T cells, Immunosenescence, Advanced Biological Age and Epigenetic Changes, and we will further discuss Senescent T cells next. COVID-19 patients exhibit shorter telomere length, a phenomenon strongly associated with T-cell immunodeficiency and active DNA damage, which may accelerate T-cell apoptosis [49]. A notable decrease in T-cell count serves as an indicator of severe COVID-19 [50]. The two functionally distinct subsets of T lymphocytes (T-cell) are CD4+ T helper cells (Th) and CD8+ cytotoxic T lymphocytes (CTL) [51]. As a key part of the body's immune system, T cells, both CD4+ and CD8+, perform complementary and indispensable immune functions during viral infections, both enhancing innate immunity to inhibit viral replication and synergizing with antibodies to prevent infection [52]. In turn,

excessive telomere depletion may lead to aging of immune cells, increased genomic instability of CD8+ T cells, and even dysregulation of the immune response, which may exacerbate the severity of neoclonal pneumonia in the elderly [53]. Immunosenescence is a process associated with accelerated aging and telomere shortening, in which patients with shorter telomeres exhibit reduced T-cell proliferative capacity and a higher proportion of senescent T cells [54]. To compensate for COVID-19 induced T-cell lymphopenia and the dramatic reduction in T-cell numbers, rapid and large-scale T-cell clonal expansion has become an urgent need, an expansion process that is closely linked to the maintenance and change in telomere length [7]. The shortening of telomeres and the subsequent accumulation of DNA damage resulting from these shortened telomeres have been identified as significant indicators of the aging process [23]. Damage to the protective structure of this chromosome end affects tissue regeneration, leading to an imbalance with or even exacerbating COVID-19 [55].

Severe COVID-19 may accelerate telomere wear and shorten telomere length, and the accumulation of DNA damage with age affects genomic and chromosomal regions, with telomeres particularly susceptible to age-related factors [56]. As short telomeres limit T cell proliferation, this may impair T cell recovery in the fight against COVID-19, leading to T cell imbalance, lymphopenia, and decreased ability to clear SARS-CoV-2, thereby increasing the risk of severe COVID-19 [57]. Therefore, the risk of T-cell shortage is higher in older people infected with SARS-CoV-2 because telomeres shorten with age and telomerase activation in T-cells is not sufficient to prevent their shortening, affecting T-cell clonal expansion [58]. Individuals who fall within the lower percentiles of telomere length and the higher percentiles of short telomeres are at an increased risk of experiencing severe pathologies associated with COVID-19 [55]. According to a study by Davis *et al.*, the susceptibility to SARS-CoV-2 infection in children (under 20 years of age) is about half that of adults (over 20 years of age), and the prevalence of symptomatic COVID-19 infection is 21%, with older people being at significantly greater risk of serious illness [41]. Thus, older adults with limited T-cell clonal expansion capacity due to telomere shortening are at increased risk of T-cell lymphopenia following their infection with COVID-19, which in turn may increase COVID-19 mortality rates [59]. Understanding the role of telomeres and T-cell function in the pathogenesis of COVID-19 is critical to the development of effective therapeutic strategies to mitigate the severe impact of the virus in the elderly population.

Figure 2 depicts the structural features of a coronavirus, with a viral core consisting of a nucleocapsid protein (N), a spiny glycoprotein (S), a membrane protein (M), a lipid bilayer, an RNA viral genome and an envelope protein (E). In addition, this diagram shows six serious consequences that can result from COVID-19 infection of the human body. The virus can damage the lungs, leading to respiratory failure, which can be severe and life-threatening. At the same time, it affects the immune system, leading to a change in T-cell diversity and affecting the body's

immune response to the virus. Viral infections may also trigger inflammatory phenomena that accelerate the aging process of the body. In addition to this, the function of the immune system decreases and Immunosenescence occurs, which means that the body's immune system is less able to defend itself against pathogens. Viral infections may also trigger Epigenetic Changes, which may lead to an accelerated aging process by advancing the biological age of the body. Taken together, COVID viral infections not only pose a direct threat to human health but may also accelerate the aging process by affecting the immune system and causing inflammation.

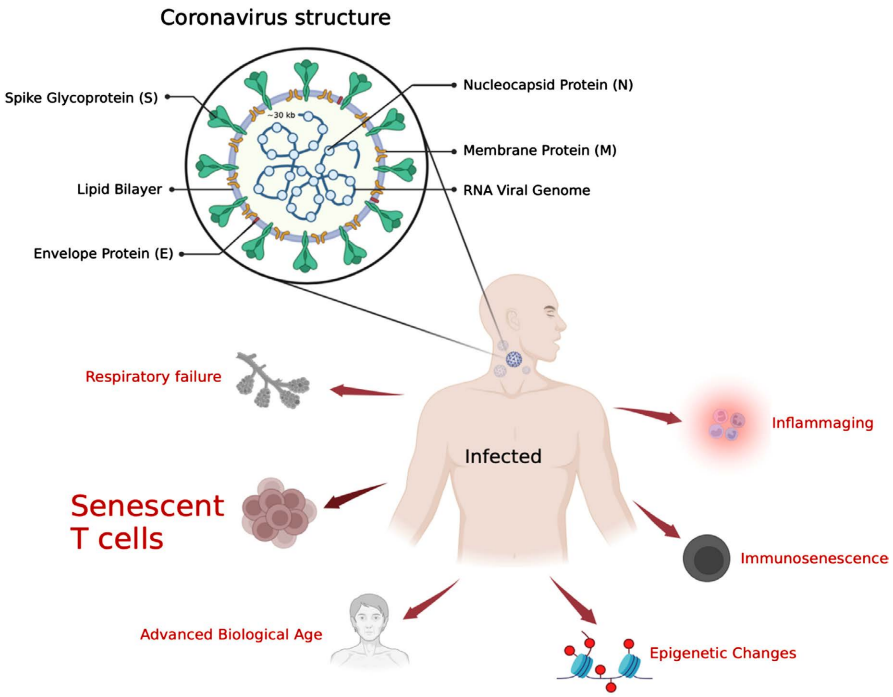

Figure 2. Structural features of coronaviruses and subsequent symptoms.

4. Association between Severe COVID-19 and Telomere Shortening

There is an association between COVID-19 and leukocyte telomere length (LTL): patients with severe COVID-19 had shorter telomeres compared to patients with milder post-COVID-19, suggesting a significant correlation between LTL and COVID-19 severity was significantly correlated [60]. There was a correlation between the severity of COVID-19 and the degree of lymphopenia, and the proportion of lymphocytes in the blood was negatively correlated with the severity and prognosis of the disease [61]. Telomere length can be directly or indirectly controlled and its shortening inhibited by regulating various enzymes including telomerase, ACE2, Furin, TMPRSS2, DPP4, LDHA, LDHB, ATM, ATR, ALT, AST, and FASN, which is expected to control the severity of COVID-19 [62]. Another way to predict disease in COVID-19 is that ACE2-expressing ciliated epithelial cells in the mucosa of the upper respiratory tract of patients with COVID-19 should show signs of cellular senescence, which is the primary site of viral-host

encounters and viral replication [63]. In pre-pandemic biopsy samples of nasopharyngeal mucosal samples from patients with COVID-19, senescence markers showed higher reactivity in patients with COVID-19 compared to those without overt respiratory infection [63] [64]. Studies have shown that critically ill patients have lower granulocyte counts in the white blood cell (WBC) component than mildly ill COVID-19 patients, which may help predict disease severity [65] [66]. Another key feature of severe COVID-19 is the macrophage activation syndrome (MAS), in which macrophage chemokine CCL2 and other chemokines that attract macrophages, as an important component of the vascular endothelial senescence-associated secretory phenotype (SASP), are involved in the process of macrophage recruitment to the vascular endothelium in the upper respiratory mucosa [63] [67] [68]. Upon encountering VIS cells, the senescent secretory profile was further enhanced by a state transition reprogramming macrophages into CD86+CD14+CD163+ pro-inflammatory, M1-like cells characterized by positive SA-β-gal staining, elevated $p16^{INK4a}$ expression, and presentation of SASP [63] [67] [69]. Given the mobility of these macrophages, they may respond to chemokines secreted by cells in the lower respiratory tract injured by SARS-CoV-2 infection [70], and thus the lungs of patients with severe COVID-19 showed higher levels of CD86+ macrophage infiltration and stronger SASP-like cytokine expression [63] [71]. The fact that patients may face prolonged symptomatic or systemic non-recovery after recovering from SARS-CoV-2 infection reveals that the virus exerts a far-reaching and potentially pathologically consequential effect on host cells that is not limited to the elicitation of an immunopathogenic response [72]. Overall, SARS-CoV-2 infection not only triggers an immune response, but may also have far-reaching effects on host cells, leading to prolonged symptoms or systemic non-recovery after recovery, demonstrating the complexity of viral action.

5. Telomere Length and T Cell Activity in COVID-19 Patients

Recent studies have shown that the length of telomeres, a potential biomarker, is an important factor influencing COVID-19 mortality [8]. Telomere shortening is considered a marker of COVID-19 severity and may identify patients at higher risk of morbidity and mortality due to SARS-CoV-2 infection, and the study also noted that T-cell lymphopoiesis may be disrupted in those infected with short telomeres [73]. There is a suggestion that shorter telomere lengths may be related to patients' chronic illnesses and underlying health problems that reflect a weakened immune system and reduced function, which makes it more difficult for them to fight off attacks by the COVID-19 virus [5]. Studies have shown that extensive proliferation of T cells following viral infection is associated with shortened telomeres, impaired replication and reduced immunocompetence, and that those with shorter leukocyte telomeres have a higher risk of hospitalization for any infection and pneumonia [74]. The distinguishing feature of severe COVID-19 is profound T-cell lymphopenia, whereas T-cell proliferation is dependent on telomere length, which shortens with age [57]. At the same time, lymphocyte

telomere length shortens with age, and short telomeres may hinder telomere-dependent T cell clonal expansion during COVID-19 infection [59]. Shorter telomere lengths prior to infection may have reduced the proliferative capacity of the T-cell population, compromising the effective response to SARS-CoV-2 and reducing lymphopoiesis post-infection, and may have contained a higher proportion of senescent T-cells and reduced the number of functional cells [75]. This demonstrates that the shortening of telomeres to a critical and threshold length significantly restricts the ability of immune cells to proliferate [76]. This is the reason why shorter telomere lengths are associated with poorer immune responses to infections and the occurrence of serious diseases [77]. Short telomeres may exacerbate T-cell loss in COVID-19 patients by affecting the proliferative capacity of T-cells, leading to lymphopenia, reduced clearance of SARS-CoV-2, and increased risk of severe disease [57]. Reduced telomere length in hematopoietic cells was similarly correlated with pulmonary fibrosis in cases of post-COVID-19, indicating a potential relationship between shortened telomere length in T cells and heightened lung damage during the infection [78]. Therefore, an increased length of telomeres may offer protection against lung fibrosis following COVID-19, while a reduced telomere length could result in more severe conditions due to the diminished regenerative capacity of cells after SARS-CoV-2 infection [79]. It is also important to note the decrease in telomere-dependent lymphocytes in elderly patients, which increases the probability of complications when infected with SARS-CoV-2 [57]. For example, the shorter telomeres of hematopoietic cells in the elderly and in patients with cardiovascular disease may impede CD4/CD8 lymphopoiesis under COVID-19, increasing the risk of severe illness and death, whereas theoretically all adults with low TL distribution may be susceptible to COVID-19-associate CD4/CD8 declines due to telomeres that are too short to sustain a rapid replicative response to an acute massive loss of lymphocytes, and are thus susceptible to a COVID-19-associated CD4/ CD8 decline is severely affected [8]. This can be explained by two major changes in the immune system with age-functional decline (immune senescence) affecting the ability to recognize and respond to pathogens, and an increase in systemic inflammation (inflammatory ageing) stemming from an overactive alarm system but with diminished defense effectiveness [80]. The severity of neocoronary pneumonia was affected by immune dysregulation as evidenced by the excessive inflammatory response triggered by SARS-CoV-2 and delayed adaptive immune response, etc., and a significant reduction in the number of CD4+ versus CD8+ T-cells was observed, especially in critically ill patients [81]. It follows that the severity of COVID-19 is higher in patients in the lower percentile of telomere length [55].

6. Does COVID-19 Affect Aging

COVID-19 disease caused by the SARS-CoV-2 virus primarily affects the lungs and other organs and accelerates cellular ageing, including through shortening of telomeres (leading to defective tissue regeneration and organ dysfunction), a key

ageing pathway, and COVID-19 symptoms are exacerbated by the phenomenon of short telomeres in elderly patients and shorter telomeres in the blood of recovered patients [82]. The severity of the COVID-19 diagnosis increased with the age of the patient, with lower lymphocyte counts and with increased turbidity of the lungs on CT at admission, showing a clear age predisposition [83]. Although COVID-19 can affect people of all ages, middle-aged and older people are at higher risk of hospitalization and death compared to children [84]. COVID-19 affects older people disproportionately, with more severe symptoms and a higher risk of hospitalization and death [85]. Older adults (WHO: ≥60 years of age; CDC: ≥65 years of age) infected with COVID-19 are at higher risk of serious illness and death and have the highest morbidity and mortality rates [86]. Populations susceptible to severe COVID-19 include those with underlying medical conditions, the immunocompromised, and the elderly, whose declining immune systems make them more susceptible and exacerbate the response to infection [87]. It was found that SARS-CoV-2-infected patients exhibited accelerated epigenetic ageing, and their DNA methylation (DNAm) age was significantly higher than that of the healthy population in a variety of clock models (e.g. Horvath, Hannum, skin-Horvath and GrimAge) [88]. It was also recently established that older persons infected with SARS-CoV-2 have impaired telomere length-dependent T-cell proliferative response, which is linked to the severe T-cell lymphopenia in older adults [31]. In conclusion, accelerated epigenetic ageing is associated with the risk of SARS-CoV-2 infection and the development of severe COVID-19, which in turn affects the epigenetic clock and telomere depletion, accelerating epigenetic ageing and potentially contributing to postneocoronary syndrome, although this effect is reversible in some patients [88].

7. Dose COVID-19 Affect Telomere Length

COVID-19 may disrupt the epigenetic clock and telomere length, and although the two are often considered independent factors, DNA methylation aging occurred in parallel with telomere shortening in all observations [88]. The correlation between the DNA methylation-based telomere length estimation method and the PCR-based telomere length estimation method, which is recognized as an accurate quantification method, is relatively weak [89]. Mongelli *et al.* utilized a PCR assay to measure telomere length, discovering a reduction in telomere length among survivors of COVID-19 [90]. Meanwhile, TL was significantly shorter in the long-term COVID-19 group compared with the no COVID-19 group [91]. Most COVID-19 hospitalized patients have an increased frequency of short telomeric individuals with severe lymphopenia and T-lymphocyte telomeres that may be shortened by acute infection [6]. SARS-CoV-2 infection may lead to a shortening of the relative mean length of telomeres in blood cells, especially leukocytes, in COVID-19 recovered patients, suggesting direct erosion of telomeres [92].

In addition, SARS-CoV-2 infection appears to trigger a fibrosis-like phenotype in the lungs and kidneys, suggesting that viral infection may deplete tissue regenerative potential, and that short telomeres significantly increase with age in

COVID-19 patients, with telomere length negatively correlating with disease severity [55]. For example, SARS-CoV-2 infects a wide range of cells in the body, including ATII cells in the lungs, potentially damaging them and accelerating regenerative cell renewal, whereas younger individuals with long telomeres can support additional divisions to promote repair, whereas older individuals with short telomeres may not be able to proliferate and regenerate, leading to tissue failure [55]. The shortened relative mean length of telomeres observed in the group of COVID-19 recovered patients may indicate that SARS-CoV-2 infection can directly lead to telomere erosion in blood cells (especially leukocytes), which in turn affects chromatin remodeling protein activity in chromosomal telomere regions, leading to altered epigenetic regulation of multigene expression [92] [93]. Of the data provided in the table below, three papers mentioned that infection with COVID-19 results in shortening of telomeres; two papers did not give a clear conclusion on the relationship with the two. For example, Study 1 demonstrated a significant negative correlation between telomere length distribution and age [94]. Study 2 showed that telomere shortening was significantly faster in patients diagnosed as "severe-acute" than in patients diagnosed as "mild-moderate", and that telomeres were shorter in all patient age groups had shorter telomeres [55]. Study 4 did not reach a definitive conclusion on the relationship, but still elucidated that there was an increase in DNAmAge of approximately 9 years in the COVID-19 patient group, with no significant difference in the control group [90]. Study 5 summarizes the mean LTL of COVID-19 patients from multiple studies and concludes that there is no significant difference in telomere length between non-severe and severe COVID-19 patients [5]. Although the mechanisms by which existing studies show that COVID-19 may affect telomere length and the epigenetic clock are not yet fully understood, there is still a potential association between infection with COVID-19 and telomere shortening, suggesting that viral infections may have a profound effect on the aging process and tissue regenerative capacity of host cells. Notably, women with lower relative telomere length were three to four times more likely to die from COVID-19, while there was no correlation in men [95]. Therefore, more objective and accurate research data should fully consider the relationship between COVID-19 and telomere length due to gender differences between men and women.

Table 1 presents a summary of five studies investigating the impact of COVID-19 on telomere length, with sample sizes varying from 83 to 7653 participants. The first three studies indicated a significant negative relationship between COVID-19 and telomere length, suggesting a potential link to telomere shortening and cellular senescence. In contrast, the last two studies yielded Indeterminate results and showed an unspecified effect. Variations in research methodologies, participant selection, and statistical analysis techniques may influence the precision and dependability of the findings. This table summarises basic information from five studies; different studies have come to different conclusions about the relationship between COVID-19 infection and telomere length, and further research is needed to elucidate the underlying mechanisms and influencing factors.

Table 1. Effect of infection with COVID-19 on telomere length.

	Covid Patients Number	Conclusion
Study 1 [94]	251	Negative Relationship
Study 2 [55]	83	Negative Relationship
Study 3 [76]	100	Negative Relationship
Study 4 [90]	261	Indeterminate
Study 5 [5]	7653	Indeterminate

8. Conclusions

This review explores the differences in telomere length between patients with non-critical and critical neocoronary pneumonia, further supporting the idea of telomere shortening as a marker of cellular senescence and revealing the potential relationship between this physiologic phenomenon and the severity of COVID-19. Multiple studies have shown that telomere length shortening not only promotes the process of cellular senescence as COVID-19 disease progresses, but also tends to show a negative correlation trend with the degree of COVID-19 deterioration. At the same time, telomere length shortening may negatively affect the proliferative capacity of T-cells, which may lead to lymphocytopenia and exacerbate the disease in COVID-19 patients. In addition, COVID-19 infection will also activate many immune cells, especially T cells, and the process of frequent division will accelerate the shortening of T cell telomeres, leading to premature senescence of T cells and loss of their original activity and function, which to a certain extent affects the course of COVID-19 treatment.

DNA methylation age (DNAm) is significantly accelerated in COVID-19 patients compared to healthy individuals, as reflected by multiple biological clock assessments (e.g., Horvath, Hannum, skin Horvath, and GrimAge, among others), and these epigenetic aging is prevalent in COVID-19 patients and is not age-stratified (young vs. old) limitations. It has been hypothesized that the accumulation of epigenetic senescence and telomere depletion after SARS-CoV-2 infection may also be one of the important causative factors of postneocoronary syndrome, and that this irreversible epigenetic senescence may serve as a biomarker for assessing the risk of postneocoronary syndrome. Although the above tabulated data and various studies have explored the relationship between telomere length and COVID-19 to varying degrees, there is still no definitive conclusion directly regarding telomere length and COVID-19 infection, which still needs to be supported by many future scientific studies and extensive data. The emergence of SARS-CoV-2 virus variants, on the other hand, requires timely updating of diagnostic methods and scientific research and development of therapeutic drugs aimed at effectively preventing and protecting the population from the virus and precisely addressing the immune response to the virus and its variant forms. At the same time, in-depth exploration of the specific mechanisms between telomere

length and COVID-19 infection will provide a more scientific theoretical basis for the development of new therapeutic strategies.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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