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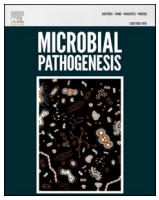

Malaria infection and telomere length: A review

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ABSTRACT

Telomere shortening is a key hallmark of cellular aging, and its association with various infectious diseases is well-documented. However, the role of telomere dynamics in malaria pathogenesis remains underexplored. In addition to its influence, malaria infection not only modulates signals within immune cells but also drives telomere shortening in these cells via diverse mechanisms, potentially leaving long-term imprints on human health. Acute malaria infections initiate rapid telomere degradation, promote accelerated cellular senescence, and suppress telomerase expression with possible partial recovery as the parasite clears during treatment. Conversely, prolonged exposure to Plasmodium infection, prevalent among individuals residing in highly endemic regions like Africa, is often aggravated by coexisting infections, potentially exacerbating malaria pathogenesis, accelerating telomere length shortening, and increasing susceptibility to age-related ailments. Herein, we review recent findings into the effects of malaria on telomere attrition, shedding light on possible mechanisms and key factors contributing to this process. Additionally, we present an overview of how oxidative stress and inflammatory mediators contribute to telomere length shortening in malaria. Furthermore, we discuss the potential of telomere length as a biomarker for malaria severity and treatment outcomes.

1. Introduction

Since the dawn of the 21st century, the global life expectancy has improved; however, significant disparities persist, particularly in sub-Saharan Africa, where infectious diseases like malaria continue to pose severe health challenges [1,2]. Malaria remains a primary global health concern. It is mainly caused by the parasite P. falciparum and spreads through bites from infected female Anopheles mosquitoes. It remains endemic in many low-resource settings [3,4]. In 2023, the World Health Organization (WHO) estimated 263 million cases worldwide. Africa remains disproportionately the hardest hit with 246 million cases and accounting for over 95 % of global deaths [5], with Nigeria topping the list [6,7]. Malaria is a persistent killer in Nigeria, claiming 95,000 young lives annually [6,8]. Beyond the staggering death toll, malaria disrupts the body's balance, triggering immune responses that accelerate aging at the cellular level, leaving lasting damage long after the infection is gone [9].

The interplay between malaria infection and host immunity, especially an increased activation and proliferation of white blood cells, creates a stressful environment that may profoundly alter the host's redox balance, inducing secretion of free radicals (ROS) and inflammatory cytokines [10–12]. The burden of ROS and inflammation not only worsens malaria pathology but also leads to accelerated cellular aging [13]. Growing evidence suggests a strong connection between malaria infection and premature cellular senescence and aging in white blood cells [14,15]. Cellular aging, also known as cellular senescence, is the gradual decline in a cell's ability to function and divide over time [16]. As cells age, they enter a state of irreversible growth arrest, often accompanied by improved gene expression, release of proinflammatory molecules such as senescence-associated secretory phenotype (SASP), including reduced regenerative capacity [17]. Cellular aging plays a very important role in age-related ailments [18]. These diseases can be influenced by environmental stressors, including infections like Plasmodium [14,19]. Among other indicators, the two most important biomarkers of cellular aging are telomere length (TL) shortening and the cell senescence marker, Cyclin-Dependent Kinase Inhibitor 2A (CDKN2A) [20].

Biological age, which reflects lifestyle, underlying health conditions,

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telomere shortening, and epigenetic changes, provides a more accurate measure of physiological aging and functional capacity of an organism than chronological age, which refers to the actual number of years a person has lived, measured from birth to the present [21]. TLs act as a key predictor of the biological aging process [22,23]. Telomeres, which are like the plastic tips on shoelaces, are specialized DNA-protein structures located at the ends of linear chromosomes, consisting of repetitive nucleotide sequences (TTAGGG in humans) and associated shelterin proteins. They serve as protective caps that prevent chromosomal degradation, end-to-end fusions, and unwanted DNA repair activities [24,25]. However, with each cell division, telomeres progressively shorten, eventually triggering cellular senescence or apoptosis when they become critically short, thereby playing a crucial role in aging and disease processes [22,26]. The increasing recognition of the critical role of telomere biology in human diseases has profound implications for both clinical applications and research endeavors [27,28]. In fact, scientists now recognize TL as a valuable molecular marker for cellular aging [23]. Several studies have investigated the dynamics of telomeres in relation to infectious diseases [29,30]. For instance, Viral infections, such as COVID-19, HIV, and hepatitis B and C, have been associated with accelerated telomere shortening [31–34]. Parasitic infections, including Trypanosoma and Leishmania species, also induce telomere attrition in host immune cells [35].

The relationship between TL and infectious diseases, particularly malaria, has garnered increasing attention in recent years. While telomere biology has been extensively studied in the context of cancer, aging, and chronic diseases [20,36], its role in infectious diseases, especially malaria, is an emerging field. In the past decade, researchers focused on studies connecting TL to infectious diseases such as HIV, hepatitis [37,38]. These investigations suggested that chronic infections accelerate telomere attrition due to increased immune cell turnover and persistent inflammation. Leukocyte TL was identified as a predictor of immune resilience, with shorter telomeres correlating with higher susceptibility to infections and disease severity [29,39,40]. Evidence from recent works has identified a link between TL and malaria infection [41,42]. However, the mechanisms underlying these associations remain unexplored. This review investigates the link between malaria infection and telomere length, addressing its role in cellular aging, potential mechanisms, biomarkers for early detection, and future research directions.

2. Telomere length and infectious diseases

Telomere shortening is a key factor influencing host susceptibility to infectious diseases, as it limits cellular lifespan and functionality [30,43]. This process is accelerated by infections due to heightened cellular turnover and inflammation [44], resulting in premature cellular aging, especially in immune cells such as B and T lymphocytes [45,46]. Chronic inflammation and immune activation during infections lead to telomere attrition, which impacts immune cell functionality and host resistance [47,48]. Leukocyte telomere shortening is associated with reduced proliferative capacity and an increased risk of pathogenic infections [43,49,50].

Viral infections, in particular, exacerbate telomere erosion and contribute to immune exhaustion. For instance, shorter telomeres have been linked to increased severity and susceptibility in diseases like COVID-19 [51–53]. Research by Cohen et al. demonstrated that patients with shorter leukocyte TL were more at risk for general respiratory infections [54]. Moreover, people with reduced TLs may be more vulnerable to diseases such as pneumonia [55]. Chronic infections with viruses such as human papillomavirus (HPV) and hepatitis also significantly impact telomere dynamics [56]. The Epstein–Barr virus (EBV) caused extensive telomere shortening in antigen-specific $CD8^+$ T cells, leading to impaired immune function and T-cell senescence [43,57]. Similarly, patients tested for HIV infection showed reduced leukocyte TL, regardless of other factors [58,59].

Bacterial infections can also contribute to telomere shortening. For instance, exposure to Salmonella enterica in wild-derived mice has been shown to lead to telomere erosion, correlating with increased mortality [30]. Longer telomeres in younger individuals have been associated with greater resistance to diseases [49,60]. Studies, such as those by Eisenberg and colleagues, highlight that early-life infections, including diarrheal diseases, can predict telomere length in adulthood, indicating a long-term impact on cellular aging [61]. Another study pointed out that patients with a higher risk of hospitalization had shorter TLs due to infectious diseases [50].

In low-income countries, where coinfections are widespread, the burden on the immune system is even greater. Repeated infections not only weaken immune defenses but may also accelerate telomere shortening, further compromising the body's ability to fight disease. A study examining the impact of single and co-infections on telomere length found that both HIV and parasitic infections independently drive telomere attrition and accelerate biological aging [58]. However, the potential compounding effect of malaria-parasite coinfections on telomere dynamics remains an underexplored area, with no studies reported to date. These studies put together suggest TL as a biomarker for predicting immune resilience against infections, with shorter telomeres predicting an increased susceptibility to infections and disease severity.

3. Malaria and telomere length

A few studies have provided evidence of a link between malaria and alterations in aging markers such as telomere length. The first study linking malaria to telomere shortening, published in 2015, showed that malaria accelerates telomere attrition in bird blood cells and reduces lifespan. The research confirmed that loss of telomere length was significantly associated with intensity of parasite during the acute phase of infection, leading to decreased fitness and reduced lifespan [62]. Asghar and colleagues went on to investigate whether malarial infection causes parallel telomere shortening across different organs. Their results showed that malaria leads to synchronized telomere attrition in both blood and tissue cells, reinforcing the systemic impact of Plasmodium infection on cellular aging [63]. A follow-up study in travelers with imported malaria showed that an acute P. falciparum infection also affects cellular aging markers, including TL in humans [14].

Due to the complexity of studying cellular aging in natural infections, researchers used the controlled human malaria infection (CHMI) model and found that malaria infection led to accelerated telomere shortening, increased cellular senescence markers, and transient suppression of telomerase activity, with partial recovery post-treatment [64]. Leveraging on the promising results from the CHMI model, Miglar et al. reported that even a single low-density P. falciparum infection accelerated cellular aging by increasing inflammatory cytokines and reducing antioxidant gene expression—effects that reversed after successful parasite clearance. They also recorded an increased parasite density that correlated positively with inflammatory cytokines and CDKN2A levels [13]. In 2023, Miglar in his research convincingly established that malaria infection accelerates cellular aging in humans [65]. Recently, a study expanded on malaria-telomere research by analyzing the impact of malaria on populations in different ethnic groups across four malaria-endemic nations in sub-Saharan Africa. Their findings confirm a strong association between shorter telomeres and malaria endemicity [41]. Additional research confirmed that malaria endemicity is linked to shorter leukocyte telomere length (LTL) [42]. This means that chronic malaria imposes an immune cell-specific effect on populations living in regions with high malaria prevalence.

Similar to studies on human subjects, evidence from animal models suggests that parasitic infections may lead to telomere shortening. For example, one study found that blue tits (Cyanistes caeruleus) infected with avian malaria had shorter telomeres, although the effect was sex-specific, with females having longer TLs than their male counterparts [66]. Other researchers established that telomere shortening occurs as a

long-term consequence of infectious diseases in natural animal populations [67]. However, unlike the impact on the human immune system, which weakens as telomeres diminish, the consequences of TL shortening in wild animals have conflicting conclusions [68]. Analysis of blood and tissues from birds revealed that malaria infection caused concurrent telomere shortening in multiple organs [63]. Another study showed that experimentally infected birds had more rapid telomere attrition and attained faster senescence compared to controls [69].

Put together, these studies provide valuable evidence that TL could be used as a tool for infectious disease diagnosis both in animal and human models [60,70–72]. However, in the case of humans, it has yet to be established as a widely used method in clinical settings, making this an area for further research. Table 1 summarizes key studies focused on the assessment of telomere shortening in malaria patients.

4. Malaria coinfections, biological aging, and telomere length

In low- and middle-income countries, particularly in sub-Saharan Africa and Southeast Asia, malaria often coexists with other infectious diseases due to shared socioeconomic, environmental, and climatic risk factors, such as poverty, poor sanitation, and vector proliferation [7,73,74]. These co-infections can complicate malaria pathogenesis, leading to more severe clinical outcomes and potentially amplifying the effects on cellular aging processes like telomere shortening. This section explores common malaria co-infections, their impact on immune function and inflammation, and the subsequent implications for biological aging, telomere dynamics, and disease etiology.

4.1. i. Common malaria coinfections with bacterial, viral, or parasitic infections

Malaria frequently co-occurs with bacterial infections, such as invasive Salmonella typhimurium or non-typhoidal Salmonella (NTS) in children, which can lead to bacteremia and increased mortality [75]. Other bacterial co-pathogens include Streptococcus pneumoniae, causing pneumonia, and Gram-negative bacteria associated with sepsis [76]. Viral co-infections are also prevalent; for instance, HIV-malaria co-infection is widespread in endemic regions, with HIV impairing anti-malarial immunity and malaria exacerbating HIV viral load [77–79]. Hepatitis B virus (HBV) and hepatitis C virus (HCV) co-infections with malaria have been documented in Nigeria and other African countries, altering hematological and liver function indices [80–82]. Dengue virus co-infection with Plasmodium is emerging in tropical areas, leading to overlapping symptoms and diagnostic challenges [83]. Covid-19 Parasitic co-infections include helminths like Schistosoma mansoni or soil-transmitted helminths (e.g., Ascaris lumbricoides, hookworms), which modulate host immunity and may either protect against or exacerbate malaria severity depending on the context [53,84–86].

4.2. Role of Co-infections in immune suppression and inflammation

Co-infections synergistically impair the host immune response, leading to profound immunosuppression and heightened inflammation. For example, in HIV-malaria co-infection, HIV depletes $CD4^+$ T cells, weakening adaptive immunity, while malaria induces regulatory T-cell expansion and cytokine dysregulation, further suppressing effective parasite clearance [77,78,87]. Bacterial co-infections like NTS exploit malaria-induced anemia and macrophage dysfunction, promoting systemic invasion and chronic inflammation via elevated pro-inflammatory cytokines (e.g., TNF-α, IL-6) [74]. Viral co-infections such as HBV/HCV with malaria intensify hepatic inflammation, as seen in altered liver enzymes and reduced immune surveillance [82]. Parasitic helminth co-infections often shift immunity toward a Th2 response, dampening Th1-mediated anti-malarial defenses and prolonging inflammatory states [84,88]. Overall, these interactions create a vicious cycle of

Table 1
Summary of studies on telomere dynamics, malaria, and aging.

	Category	Key Findings	Study Population	Study Method	References
1	Telomere Dynamics and Malaria	Malaria endemicity is linked to telomere shortening.	Sub-Saharan Africans	Cross-sectional genetic association study	[32]
		Shorter TL in leukocytes of people living in areas of high malaria endemicity.	Global human studies	Cross-sectional study	[35]
		Telomere attrition observed during controlled malaria infection.	Humans	Experimental infection study	[52]
		Plasmodium infection accelerates TL shortening	Humans	Retrospective cohort study	[53]
		Chronic infection due to malaria causes rapid telomere degradation	Birds	Observational study	[58]
		Malaria infection induces TL attrition in various body tissues.	Birds	Longitudinal observational study	[36]
2	Malaria and Cellular Aging	Malaria triggers long-term cellular aging	Humans	12-month longitudinal study	[62]
		P. falciparum infection accelerates cellular aging	Humans	Retrospective cohort study	[52]
3	General Infectious Diseases and Telomere Length	Pathogen burden correlates with shorter leukocyte telomeres	USA Human population	Observational study	[43]
		The severity of COVID-19 infection is associated with TL shortening	Humans	Systematic Review & Meta-analysis	[60]
		Infectious diseases impose long-term costs on telomere lengths	Birds	Observational field study	[56]
		Association of HIV infection with TL shortening	HIV-infected individuals	Cross-sectional study	[49]
		Infection drives telomere attrition	Birds	Controlled experimental study	[38]
4	Inflammation, Stress, and Aging	Telomere shortening is linked to inflammation	Humans	Observational study	[63]

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Table 1 (*continued*)

Category	Key Findings	Study Population	Study Method	References
	and immune responses.			
	Chronic stress accelerates aging and telomere shortening.	Humans	Observational study	[64,65]

immune exhaustion, increased pathogen persistence, and sustained release of inflammatory mediators.

iii. Role of immune suppression and inflammation in biological aging and telomere shortening

The immunosuppression and chronic inflammation from co-infections accelerate biological aging by driving excessive immune cell turnover and oxidative stress, key contributors to telomere attrition [89,90]. Persistent inflammation increases ROS production, directly damaging telomeric DNA and inhibiting telomerase activity [91,92]. For instance, in HIV-malaria co-infection, the compounded immune activation leads to rapid T-cell proliferation and senescence, resulting in shorter leukocyte telomeres compared to mono-infections [37,93]. Similarly, helminth-malaria co-infections prolong inflammatory exposure, exacerbating telomere shortening in immune cells through upregulated SASP factors [37,94]. Studies on viral-bacterial co-infections (e.g., malaria with pneumococcal disease) show that inflammation-mediated oxidative stress correlates with accelerated cellular senescence markers like CDKN2A and reduced telomere length [76,95,96]. This process mirrors findings in other chronic co-infections, where inflammation shortens telomeres by 100–200 base pairs per year, far exceeding normal aging rates [37,97].

4.4. Role in Co-infection-associated disease etiology

The interplay of immune suppression, inflammation, biological aging, and telomere shortening contributes to severe disease etiology in co-infected individuals. For example, studies in Nigeria demonstrated that malaria and hepatitis B co-infections significantly alter hematological and liver function indices, weakening immune responses and intensifying hepatic inflammation, hepatocyte damage, fibrosis, and increased risk of hepatocellular carcinoma. These processes are linked to telomere dysfunction and premature aging [33,82]. In HIV-malaria cases, accelerated telomere attrition heightens susceptibility to opportunistic infections, immune senescence, and age-related comorbidities like cardiovascular disease [93,98]. Helminth-malaria co-infections may lead to chronic anemia and organ damage (e.g., renal or hepatic), where shortened telomeres impair tissue repair and exacerbate pathology [37,98]. Bacterial co-infections like malaria-NTS increase sepsis risk, with inflammation-driven aging contributing to multi-organ failure [75]. These outcomes prompt the need for integrated management strategies in endemic areas to mitigate long-term aging effects.

5. Mechanisms of malaria-induced telomere shortening

Although increasing evidence suggests that malaria infection triggers a cascade of molecular and cellular events that contribute to accelerated telomere shortening in white blood cells, the specific mechanisms remain unclear [60,99].

5.1. Oxidative stress and inflammation

Oxidative stress, just like inflammation, has been described as a “double-edged sword”. Both play very important roles in normal physiological processes like immune response and cell signaling, and can also be implicated in tissue damage and onset of long-term disorders when excessive [100]. Malaria infection profoundly alters the host’s redox balance, inducing significant oxidative stress and inflammation [11,99]. The interplay between malaria-induced oxidative stress, inflammation, and TL has been established [101]. The parasite’s life cycle, particularly its intraerythrocytic phase, generates substantial quantities of ROS [91]. These highly reactive molecules may damage vital cellular components, like lipids, amino acids, and nucleic acids, escalating the oxidative environment [102]. The repetitive guanine-rich sequences are known to be vulnerable to ROS-mediated damage [102]. The host’s immune response to the infection further exacerbates oxidative stress, as activated immune cells, including white blood cells, release additional ROS during their efforts to eliminate the parasites [91].

Simultaneously, the infection triggers a robust inflammatory response, mounted by the released pro-inflammatory cytokines and the recruitment of immune defense cells to the infection site [44,101,103]. Because of their cytotoxic nature, ROS can directly aid in pathogen destruction. However, excessive ROS production may come at a cost, harming immune cells by inducing DNA damage and accelerating telomere shortening [104]. Mitochondria play a key role in ferroptosis, an iron-dependent form of regulated cell death driven by lipid peroxidation and oxidative damage. Malaria parasites depend on redox homeostasis for survival, and inducing ferroptosis disrupts this balance, creating an antiparasitic effect [105]. Since oxidative stress is a key factor in telomere shortening and immune cell aging during malaria infection, ferroptosis-driven redox disruption could further accelerate telomere attrition and immune senescence, potentially influencing disease severity and immune recovery.

Chronic inflammation, a hallmark of malaria, contributes significantly to telomere attrition [47,101,106]. The sustained inflammatory environment may further promote ROS production and cellular damage, ultimately accelerating telomere shortening in white blood cells [92]. It is evident the interplay between oxidative stress and inflammation creates a vicious cycle, where each process amplifies the other, leading to increased telomere damage and shortening.

5.2. Immune cell activation and proliferation

The host’s immune system mounts a complex and multifaceted response to malaria infection. This response involves the activation and proliferation of various white blood cell populations, including B- and T-lymphocytes, and antigen-presenting cells (APCs) [18,43]. The rapid expansion of these immune cells is essential for controlling parasite replication and preventing severe disease [18]. However, this increased cellular turnover comes at a cost: each cell division leads to further telomere shortening [69,107]. The rate at which telomeres shorten varies among different white blood cell subsets [49,108]. For instance, lymphocytes, particularly those involved in the adaptive immune response, might undergo more rapid telomere shortening due to their extensive proliferation and differentiation [42,109].

Monocytes, involved in both innate and adaptive immunity, may also experience significant telomere shortening due to their active participation in the inflammatory response [110]. The degree of telomere attrition in each subset likely depends on the specific roles of these cells in mounting an immune response against the *Plasmodium* parasite, the duration, and intensity of the infection. Future studies should track telomere dynamics over time, considering infection severity, co-infections, and genetic factors to clarify their role in malaria immunity.

iii. Direct parasite effects

The indirect effects of Plasmodium infection on TL in leukocytes through oxidative stress and immune activation are well-documented.

However, the possibility of direct parasite effects remains largely unexplored [111]. It is conceivable that Plasmodium parasites, or their secreted products, might directly interact with white blood cells, interfering with telomere maintenance mechanisms [32,21]. Asghar Muhammad found that when birds are experimentally infected with avian malaria, they show faster telomere attrition in blood and tissues of major organs compared to controls [63]. This suggests that malaria infection can induce systemic stress, leading to telomere shortening in various tissues, including leukocytes in hematopoietic tissue. However, this area requires further investigation.

Moreover, Plasmodium can directly cause DNA damage in host cells [103,112,113]. Studies have shown that exposure to DNA damage leads to telomere length dynamics, including elongation as a response to damage [114]. However, the overall effect in the context of malaria appears to be telomere shortening, possibly due to the overwhelming DNA damage induced by the parasite [63]. The identification of specific parasite molecules that might target telomeres or telomere-associated proteins would be crucial for elucidating such mechanisms. Furthermore, studying the impact of different Plasmodium species and strains on white blood cell telomere length could shed light on the potential for direct parasite effects.

5.4. *Environment and genetic influence*

Populations of African ancestry tend to have longer telomeres than non-Africans, a pattern seen across generations. However, scientists are still trying to understand the genetic and environmental factors that influence this difference [41,115]. Recent results, however, show that genetics only partly affect telomere shortening [41] and that populations in regions with high malaria prevalence may experience rapid telomere shortening due to a combination of genetic predispositions and environmental exposures, including infectious diseases. Leukocyte telomere length (LTL) in this group of persons tends to be negatively associated with malaria endemicity, suggesting that factors prevalent in these regions contribute to telomere attrition [41]. Telomere dynamics are highly influenced by environmental and genetic factors, with stressors like radiation, pollution, and psychological pressure accelerating their shortening. For example, radiation exposure in Chernobyl's bank voles revealed tissue-specific telomere responses, including telomerase upregulation in some tissues [116]. Pollution similarly shortens telomeres via oxidative stress and inflammation [117], while studies in yeast cells demonstrate that stressors like alcohol or high temperatures alter TL through distinct pathways [118]. Several other factors, such as altitude, climate, dietary behavior, and lifestyle, also influence telomere dynamics [19,119–121]. Given that these sub-Saharan African regions face a high burden of infections, with malaria being a major threat, it is likely that infectious diseases play a significant role in telomere shortening, further compounding the effects of genetic and environmental factors.

6. Methodological considerations and research gaps

Several methodological factors are important to consider when evaluating studies on malaria's impact on telomere length. First, the methods used to measure telomere length vary across studies (e.g., real-time quantitative PCR, flow cytometry), and these methods can have different sensitivities and limitations [14,40,63]. Second, the choice of study design (cross-sectional vs. longitudinal) influences the ability to assess the temporal dynamics of telomere length changes in response to infection [14,64]. Although acute infections can lead to temporary telomere shortening, the long-term effects of chronic or recurrent infections are less well-defined. Longitudinal studies, like that by Asghar and Co., offer a more comprehensive understanding of telomere response to malaria infection [14], but they are more resource-intensive and prone to participant dropout. Third, the definition of "malaria infection" itself varies across studies, ranging from acute infections to chronic, low-level parasitemia [14,40,65]. This heterogeneity can make it challenging to compare findings across different studies.

There are several significant research gaps that need to be addressed. Firstly, longitudinal studies are to be adopted as there is a need to fully understand the long-term impact of malaria infection on TL in populations living across endemic areas [41,65]. These studies should consider factors such as the frequency and intensity of malaria exposure, age at first infection, and genetic predisposition to telomere shortening. Secondly, focused research is needed to elucidate the underlying mechanisms of TL attrition during malaria [14]. This includes exploring the roles of oxidative stress, inflammation, and telomerase activity. Thirdly, more research is needed to explore sex-specific differences in telomere responses to malaria infection [66]. Finally, comparative studies across different Plasmodium species and host species are necessary to better understand the generalizability of findings and identify conserved mechanisms of telomere response to malaria [14,64].

7. Clinical relevance of telomere length in malaria diagnosis and prognosis

Given the substantial evidence linking malaria infection to telomere shortening, TL has emerged to be considered a potential molecular marker for assessing the impact of malaria on the human host [23,53]. Shortened telomeres are linked to weakened immune function, greater susceptibility to infections, and an increased risk of illness and death [29]. Monitoring telomere length could provide valuable insights into disease severity, treatment response, and long-term health risks [28,122]. For example, individuals with shorter telomeres prior to infection might experience more severe malaria or slower recovery [41,101,123]. Similarly, persistent telomere shortening after infection could indicate a greater vulnerability to future infections or the development of chronic diseases [43,58].

Telomere length is gaining attention as a potential predictor of malaria outcomes [60,124,125]. Studies have explored whether pre-infection TL can predict the likelihood of developing severe malaria or the risk of mortality [14,64]. While some studies have shown promising results, further research is required to validate telomere length as a reliable prognostic tool in diverse populations and under various clinical settings [60,125]. The development of standardized methods for the accurate measurement of TL and establishing a robust reference range are crucial for the clinical application of this biomarker [64,126]. Moreover, further investigation is needed to determine whether interventions aimed at protecting telomeres or promoting telomere repair could improve outcomes in malaria patients [127–129].

The establishment of a strong relationship between TL and the effectiveness of antimalarial treatment is another important area of investigation. It is possible that individuals with shorter telomeres might exhibit a less robust response to treatment or a higher risk of relapse [123,130]. Research on this link may offer insights for developing personalized treatments based on an individual's telomere profile. The correct interpretation of TL values as a marker could also aid in identifying individuals at high risk of developing long-term complications associated with malaria, allowing for proactive interventions to mitigate these risks [29,40].

8. Prospective insights and research directions

Infections such as HIV, COVID-19, hepatitis, helminths, and malaria have all been shown to negatively impact TL, with each contributing to telomere attrition through different mechanisms [58]. HIV, for instance, is associated with chronic immune activation, leading to accelerated telomere shortening over time [59]. Similarly, COVID-19 can provoke prolonged inflammatory responses that may further erode telomeres [51,131], p. 19]. Helminth infections can induce immune modulation, resulting in a dysregulated immune response that can also contribute to telomere attrition [35]. Malaria, known for causing acute immune

responses, has been linked to significant telomere shortening during infection [69,89]. When these infections occur simultaneously as coinfections, the compounded effects can exacerbate the rapid erosion of telomeres, resulting in accelerated cellular aging and increased vulnerability to other diseases [37].

Future research should investigate the specific mechanisms by which these infections interact to influence telomere dynamics, as well as analyze these dynamics in populations with malaria and other chronic infections like HIV to understand compounded effects on cellular aging, immune function, and overall health [37]. Longitudinal studies examining the effect of different coinfection combinations on TL and cellular aging will provide valuable insights into effective interventions and public health strategies. Addressing this gap could provide essential insights for managing chronic diseases in malaria-endemic areas. The study of telomeres and telomerase in malaria has garnered scientific interest, with some shedding light on their complex roles in host-parasite interactions. Yet, there are still important questions waiting to be answered. For instance:

- More long-term studies are required to track how telomere length changes in people living in malaria-endemic areas.
- The exact mechanisms connecting Plasmodium infections to telomere regulation remain unclear and underexplored.
- A holistic approach that combines genetics, immunology, and epigenetics is still lacking, leaving gaps in our understanding of telomere-related processes in malaria.
- Data collected from malaria-endemic regions was limited to four sub-Saharan countries: Tanzania, Ethiopia, Botswana, and the Republic of Cameroon, leaving a significant gap in research [41]. Many other endemic African nations, including Nigeria, the most populous and hardest hit, remain unexplored in these studies.

9. Conclusion

Experimental results from both human and animal studies consistently support the hypothesis that Plasmodium infections trigger accelerated telomere shortening. Shorter leukocyte telomere lengths (LTL) have been linked to the prevalence of Plasmodium infection. While acute infections often lead to telomere loss, the extent and potential reversibility of this effect depend on factors such as parasite load, duration of exposure, host genetic makeup, and history of prior infections.

The mechanisms driving telomere depletion likely stem from the effect of ROS generated by the parasite itself or its released products, inflammatory cytokines released by activated white blood cells, continued activation, and rapid immune cell turnover. Critically short telomeres are associated with increased susceptibility to infectious diseases and a diminished response to treatment. However, the long-term implications of this telomere erosion remain unclear. Longitudinal studies targeting high-burden and densely populated regions such as Nigeria are essential for generating comprehensive data to inform public health decision-making.

Furthermore, the role of Plasmodium co-infections in telomere dynamics remains largely unexplored. Comparative studies across different Plasmodium species and host populations could reveal conserved mechanistic patterns of how the host system responds to Plasmodium infection and ensuing telomere dynamics in response to malaria triggers. TL measurement could serve as a rapid diagnostic tool for early detection of severe malaria, which could influence treatment strategies and help identify patients at greater risk of rapid telomere shortening, particularly in cases of co-infection.

CRediT authorship contribution statement

Theophilus N. Wakai: Writing – review & editing, Writing – original draft, Visualization, Methodology, Conceptualization. **Carrin Fiamitia:** Writing – review & editing, Data curation, Conceptualization. **Emmanuel B. Oba:** Writing – review & editing, Writing – original draft, Data curation. **Shalom N. Chinedu:** Writing – review & editing, Validation, Supervision, Conceptualization. **Israel S. Afolabi:** Writing – review & editing, Validation, Supervision, Conceptualization.

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Abbreviations

The following abbreviations are used in this manuscript:

CDKN2A – Cyclin-Dependent Kinase Inhibitor 2A
CHMI – Controlled Human Malaria Infection
DNA – Deoxyribonucleic Acid
LTL – Leukocyte Telomere Length
ROS – Reactive Oxygen Species
SASP – Senescence-Associated Secretory Phenotype
TL – Telomere Length

Data availability

No data was used for the research described in the article.

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