Leukocyte telomere length associated with glioma risk and survival

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Abstract

Background: Relative telomere length (RTL) in leukocytes has been linked to risks of many cancers, although how leukocyte RTL contributes to adult glioma has rarely been studied.

Aim: We performed a case-control study to evaluate the association between RTL in leukocytes and glioma risk in 565 glioma patients and 1130 healthy controls.

Methods and results: Overall, mean leukocyte RTL was significantly higher in cases than controls (P < .001). Longer RTL was associated with a 1.32-fold increased risk of glioma (odds ratio [OR] = 1.32, 95% confidence interval [CI] = 1.13-1.64). In quartile analysis, a significant dose-response relationship was noted (P < .001). Compared to the first quartile with shortest RTL, the fourth quartile with longest RTL was associated with 1.51-fold elevated risk of glioma (OR = 1.51, 95% CI = 1.10-2.18). In further stratified analysis by clinical characteristics at baseline, the significant relationship was observed among cases with aggressive tumor characteristics, including glioblastoma multiforme (GBM), high tumor grade, and absence of IDH mutation and 1p/19q co-deletion. Finally, we evaluated leukocyte RTL in GBM prognosis. We found that longer RTL was associated with increased probability of overall survival (hazard ratio [HR] = 0.88, 95% CI = 0.70-0.98), and progression/recurrence-free survival (HR = 0.81, 95% CI = 0.60-0.93) in patients with primary GBM.

Conclusion: Our findings indicate that longer RTL is significantly associated with glioma risk, and the association differs by tumor aggressiveness. Also, RTL in leukocyte could be a prognostic predictor of survival and progression in patients with GBM.

KEYWORDS
glioma, risk, survival, telomere length

1 | INTRODUCTION

Telomeres are critical in the maintenance of chromosome stability and integrity.¹ The shortening of telomeres acts as an indicator for cellular senescence as telomere length decreases with age, shortening by ~30-200 bp after each mitotic division.² The speed of telomere shortening varies significantly among individuals and is influenced by...
genetic and nongenetic factors. Due to its relatively low variability across different tissues, telomere length has been suggested as a promising biomarker for age-related diseases, including cancer, Alzheimer’s disease, type-2 diabetes, and cardiovascular disease.

Both shorter and longer telomeres can lead to tumorigenesis in the cell microenvironment by impacting cell apoptosis or senescence. Critical telomere shortening can induce abnormal recombination, chromosomal degradation, and end-to-end telomeric fusions, leading to chromosomal instability and potential tumorigenesis. On the other hand, maintaining long telomeres for longer periods can predispose cells to escaping growth arrest and delay cellular senescence, increasing the chance for genetic aberrations, chromosomal instability, and possible malignant transformation. Additionally, alterations in genes affecting telomere length, and the absence of shelterin complex that guards telomeres, are also associated with various cancer types.

Glioma is the most common and highly malignant brain tumor, and is associated with very poor prognosis. The most aggressive type of glioma is glioblastoma (GBM), associated with a dismal median survival of only 12-15 months. To date, only a few established risk factors in glioma have been identified, including high-dose ionizing radiation exposure, inherited tumor syndromes (e.g., neurofibromatosis type I and II), absence of asthma and respiratory allergies, male gender, European ethnicity, older age, and a few genetic variants. In the last decade, mounting evidence has shown that telomere maintenance plays a key role in glioma development, as telomere dysregulation may contribute to glioma susceptibility, initiation, and prognosis. Genetic variants in telomere maintenance genes such as TERC, TERT, RTEL, OBFC1, and POT1 are associated with glioma risk.

Few studies have evaluated the relationship of leukocyte telomere length with glioma risk and clinical outcomes. In a recent Swedish glioma case-control study, longer leukocyte relative telomere length (RTL) was associated with modest increased risk of glioma. In a Chinese population, Wang et al reported that both longer and shorter leukocyte RTL were associated with an increased risk of glioma, finding a U-shaped association between RTL and glioma risk. Only one study was conducted in the US population and no significant association was identified, although the study used small sample size. However, the investigators found that short leukocyte RTL was linked with an elevated risk of glioma specifically among men. In terms of clinical outcomes, the prognostic value of leukocyte RTL in glioma has only been assessed in one study. Short leukocyte telomere length was reported to be significantly associated with poor survival outcomes.

In the current case control study using 565 glioma patients and 1130 healthy controls, we examined the relationship between leukocyte RTL and glioma risk. Among 276 patients with primary GBM, we then investigated the prognostic impact of leukocyte RTL in survival and disease progression.

## METHODS

### 2.1 Study population

Detailed recruitment method for glioma patients and healthy controls was reported in our previous publication. In brief, a total of 565 glioma patients and 1130 healthy controls were included in the study. The cases were newly diagnosed histologically confirmed glioma patients seen at The University of Texas M. D. Anderson Cancer Center (MDACC) between April 2014 and July 2018. Healthy controls were unrelated clinic visitors and spouses. Cases and controls were frequency-matched on age (±5 years), gender, and ethnicity. Written informed consent was acquired from each study participant. The demographic, clinical, and follow-up data for the cases were extracted from medical record review. For each case, overall survival was estimated from glioma diagnosis to the date of death from glioma or to the date of last patient follow-up visit. Progression/recurrence-free survival was estimated from the date of glioma diagnosis to the date of glioma progression/recurrence, the date of death from disease, or the last follow-up date. The epidemiologic data from the controls were acquired from a questionnaire. The Institutional Review Board of MDACC approved the study.

### 2.2 Relative telomere length assessment

Genomic DNA, which was isolated from whole blood samples using the QIAamp Maxi DNA kit (Qiagen, Valencia, CA), was used to evaluate the RTL using the real-time quantitative polymerase chain reaction (PCR) method, which was detailed in our previous publications. In general, we used the ratio of the telomere repeat copy number (T) to the single gene (human globulin [HGB]) copy number (S) as a measure to quantify the overall RTL. The telomere and HGB PCRs were assessed on separate plates with the same samples in the same well positions. We included controls (negative and positive), a calibrator DNA, and a standard curve in each run. The standard curve ranging from 0.625 to 20 ng DNA was generated by a serial of twofold dilution of a DNA sample (the same DNA sample for all runs). To maintain the high quality,
the coefficient for each standard curve needs to be $\geq 0.99$ ($R^2$). We also set 0.25 (for the $Ct$ values) as the satisfactory standard deviations. In this study, low intra- and interassay variation coefficients were observed (<3% and <5%, respectively).

### 2.3 Data analysis

Data analyses were performed using SPSS statistical package (Version 21, SPSS Inc., Chicago, IL). First, we log transformed the RTL data. General linear regression was used to inspect differences between cases and controls for the mean RTL correlated with categorical clinical features. Similarly, general regression analysis was applied to assess the differences between selected categorical demographic and clinical characteristics for the mean RTL within case and control groups. Age and gender were adjusted upon necessary. Unconditional multivariate logistic regression was applied to estimate the relationship between RTL and glioma risk. Odds ratios (ORs) and 95% CIs were estimated. The RTL variable was studied as a continuous variable, a categorical variable divided by the median value in controls, and a categorical variable based on quartile distributions in controls. The dose response was assessed in the quartile analysis. In further stratified analysis, the relationship between RTL and glioma risk by tumor characteristics was assessed. The relationships between survival and RTL among GBM patients were assessed as hazard ratios (HRs) and 95% CIs using the Cox proportional hazards model, adjusted for covariates, including age, gender, ethnicity, smoking status, Karnofsky Performance Scale (KPS) score, timing of blood drawn, IDH1 mutation status, body mass index (BMI), seizure and diabetes medication. We used the Schoenfeld residuals to assess the fitness of proportional hazards assumption. In the categorical analysis, all patients were dichotomized by the median RTL in event-free group. All statistical tests were two-sided, and the level of statistical significance was set at 0.05.

### 3 RESULTS

The leukocyte RTL by demographic and clinical variables in cases and controls was summarized in Table 1. Overall, mean RTL was significantly higher in glioma cases than controls after adjusting age and gender (0.79 vs 0.75, $P < .001$). When demographic characteristics classified the subjects, the significant differences between cases and controls were only observed in certain categories, including men, women, never smokers, normal BMI, and overweight. When stratified by demographic variables within case and control groups, as expected, RTL was inversely correlated with age in both cases and controls ($P = .007$, $P < .001$, respectively). On the other hand, RTL was positively correlated with BMI in the control group ($P = .042$). With the increase of BMI category from normal weight to overweight and obesity, mean RTL increased steadily. When the cases were stratified by clinical variables, including histopathology, tumor grade, IDH mutation status, and 1p/19q co-deletion status, mean RTL was not differed significantly by clinical characteristics. In terms of the timing of obtaining blood samples for the cases, nearly 20% study subjects (19.3%) had their blood drawn before surgery, 49.7% of them had blood drawn after surgery, 11.5% of them had blood drawn during or after chemoradiation, and 19.5% of them had their blood drawn during or after adjuvant chemotherapy. Mean RTL was not differed significantly by the timing of obtaining blood samples. When we examined the GBM patients only, we found that mean RTL was significantly higher in GBM cases who were still alive or were without recurrence or progression after 2-year follow-up, compared to their counterparts ($P = .036$ and $P = .034$, respectively).

Next, we examined the association between leukocyte RTL and risk of glioma (Table 2). First, we treated RTL as a continuous variable. After controlling for age, gender, smoking status, and BMI, those with longer RTL had a 1.32-fold increased risk of glioma (OR = 1.32, 95% CI = 1.13-1.64). When RTL was dichotomized into two groups (high or low) using the median RTL in the control group as cutoff point, we found that those with longer RTL had a 1.54-fold greater risk of glioma (OR = 1.54, 95% CI = 1.20-1.96) compared to those with shorter RTL. In the quartile analysis, we used quartile values of RTL in the control group as cutoff points. Compared to those with shortest RTL (first quartile), those in the third and fourth had a 40 and 51% increased risk of glioma (OR = 1.40, 95% CI = 1.03-2.02; OR = 1.51, 95% CI = 1.10-2.18, respectively). In further analysis, we observed a statistically significant dose-response relationship ($P < .001$).

We examined whether the relationship between leukocyte RTL and risk of glioma differed by clinical features (Table 3). We found that the significant relationship was merely observed among those with aggressive tumor characteristics including GBM subtype (OR = 1.50, 95% CI = 1.18-2.29), high tumor grade (grade III or IV) (OR = 1.45, 95% CI = 1.09-2.38), absence of IDH1 mutation (OR = 1.42, 95% CI = 1.05-2.93), and absence of 1p/19q co-deletion (OR = 1.43, 95% CI = 1.04-3.47).

Finally, we evaluated the association of leukocyte RTL with overall survival and progression/recurrence-free survival in patients with primary GBM using Cox proportional hazard regression analysis (Table 4). As a continuous
| Variable                      | Total cases (n = 565) | Mean (SD) | Controls (n = 1,130) | Mean (SD) | P value* |
|-------------------------------|-----------------------|-----------|----------------------|-----------|----------|
| Total                         |                       | 0.79 (0.23) |                      | 0.75 (0.21) | <.001    |
| Age                           |                       |           |                      |           |          |
| <52                           | 282 (49.9%)           | 0.83 (0.29) | 565 (50.0%)          | 0.80 (0.26) | .128     |
| =52                           | 283 (50.1%)           | 0.75 (0.32) | 565 (50.0%)          | 0.72 (0.24) | .127     |
| P value**                     | .007                  |           |                      | <.001     |          |
| Gender                        |                       |           |                      |           |          |
| Female                        | 209 (37.0%)           | 0.79 (0.30) | 463 (41.0%)          | 0.75 (0.27) | .031     |
| Male                          | 356 (63.0%)           | 0.80 (0.24) | 667 (59.0%)          | 0.76 (0.23) | .040     |
| P value**                     | .681                  |           |                      | .281      |          |
| Smoking history               |                       |           |                      |           |          |
| Ever smoker                   | 240 (42.5%)           | 0.77 (0.30) | 432 (38.2%)          | 0.74 (0.31) | .225     |
| Never smoker                  | 296 (52.4%)           | 0.82 (0.29) | 644 (57.0%)          | 0.76 (0.29) | .003     |
| P value**                     | .051                  |           |                      | .335      |          |
| BMI                           |                       |           |                      |           |          |
| Normal                        | 274 (48.5%)           | 0.76 (0.34) | 538 (47.6%)          | 0.71 (0.26) | .021     |
| Overweight                    | 201 (35.6%)           | 0.79 (0.30) | 457 (40.4%)          | 0.74 (0.29) | .044     |
| Obese                         | 90 (15.9%)            | 0.82 (0.31) | 135 (11.9%)          | 0.78 (0.30) | .335     |
| P value**                     | .052                  |           |                      | .042      |          |
| Timing of blood draw          |                       |           |                      |           |          |
| Newly diagnosed, presurgery   | 109 (19.3%)           | 0.78 (0.33) |                      |           |          |
| Newly diagnosed, postsurgery  | 281 (49.7%)           | 0.79 (0.31) |                      |           |          |
| Newly diagnosed, during or immediately post chemoradiation | 65 (11.5%) | 0.79 (0.35) | | |
| Newly diagnosed, during or immediately post adjuvant chemotherapy | 110 (19.5%) | 0.79 (0.34) | | |
| P value**                     | .528                  |           |                      |           |          |
| Histopathology                |                       |           |                      |           |          |
| GBM                           | 276 (48.8%)           | 0.80 (0.31) |                      |           |          |
| Non-GBM                       | 289 (51.2%)           | 0.78 (0.32) |                      |           | .451     |
| P value**                     | .052                  |           |                      | .042      |          |
| Tumor grade                   |                       |           |                      |           |          |
| I and II                      | 184 (32.6%)           | 0.76 (0.28) |                      |           | .071     |
| III/IV                        | 381 (67.4%)           | 0.81 (0.32) |                      |           |          |
| P value**                     | .071                  |           |                      |           |          |
| IDH mutation status           |                       |           |                      |           |          |
| Negative                      | 198 (35.0%)           | 0.82 (0.33) |                      |           | .092     |
| Positive                      | 111 (19.6%)           | 0.75 (0.38) |                      |           |          |
| Unknown                       | 256 (45.3%)           |           |                      |           |          |
| P value**                     | .685                  |           |                      |           |          |

(Continues)
**TABLE 1** (Continued)

| Variable          | Total cases (n = 565) | Mean (SD) | Controls (n = 1,130) | Mean (SD) | P value* |
|-------------------|-----------------------|-----------|----------------------|-----------|----------|
| GBM only          |                       |           |                      |           |          |
| Vital status      |                       |           |                      |           |          |
| Alive             | 143 (51.8%)           | 0.83 (0.32)|                      |           |          |
| Dead              | 133 (48.2%)           | 0.75 (0.31)|                      |           |          |
| P value**         | .036                  |           |                      |           |          |
| Recurrence/progression |              |           |                      |           |          |
| Yes               | 205 (74.3%)           | 0.74 (0.33)|                      |           |          |
| No                | 71 (25.7%)            | 0.84 (0.37)|                      |           |          |
| P value**         | .034                  |           |                      |           |          |

*P-value comparing mean relative telomere length between cases and controls. Age and gender were adjusted as appropriate.

**P-value comparing mean relative telomere length between groups defined by selected characteristics. Age and gender were adjusted as appropriate.

**TABLE 2** Risk of gliomas as estimated by relative telomere length

| Continuous variable | Cases          | Controls        | Odds ratio (95% CI)* |
|---------------------|----------------|-----------------|----------------------|
| Total               | 565 (100%)     | 1,130 (100%)    | 1.32 (1.13-1.64)     |
| By median in controls |                |                 |                      |
| Low                 | 228 (40.4%)    | 570 (50.4%)     | 1.00                 |
| High                | 337 (59.6%)    | 560 (49.6%)     | 1.54 (1.20-1.96)     |
| By quartile in controls |            |                 |                      |
| First               | 107 (18.9%)    | 270 (23.9%)     | 1.00                 |
| Second              | 129 (22.8%)    | 287 (25.4%)     | 1.14 (0.81-1.58)     |
| Third               | 155 (27.4%)    | 276 (24.4%)     | 1.40 (1.03-2.02)     |
| Fourth              | 174 (30.8%)    | 297 (26.3%)     | 1.51 (1.10-2.18)     |

P for trend trend < .001

ORS were adjusted by age, gender, smoking status, and BMI category.

**TABLE 3** Risk estimation by glioma tumor characteristics

|                      | Odds ratio (95% CI) |
|----------------------|---------------------|
| GBM vs non-GBM       |                     |
| GBM                  | 1.50 (1.18-2.29)    |
| Non-GBM              | 1.16 (0.74-2.58)    |
| Low grade vs high grade |               |                     |
| Low grade            | 1.23 (0.69-2.46)    |
| High grade           | 1.45 (1.09-2.38)    |
| IDH status           |                     |
| Negative             | 1.42 (1.05-2.93)    |
| Positive             | 1.06 (0.56-3.59)    |
| 1p/19q status        |                     |
| Negative             | 1.43 (1.04-3.47)    |
| Positive             | 1.26 (0.49-3.16)    |

ORS were adjusted by age, gender, ethnicity, smoking status, and BMI category.
**TABLE 4** Relative telomere length associated with 2-year survival in patients with primary glioblastoma

|                        | RTL               | Event, n (%) | Event-free, n (%) | Adj. HRs (95%CI)* |
|------------------------|-------------------|--------------|-------------------|-------------------|
| Overall                | Continuous        | 146 (100%)  | 130 (100%)        | 0.88 (0.70, 0.98) |
|                        | By median in event-free |            |                   |                   |
| Low                    |                   | 85 (58.2%) | 66 (50.8%)        | Reference         |
| High                   |                   | 61 (41.8%) | 64 (49.2%)        | 0.68 (0.43, 0.90) |
| Progression/recurrence-free | Continuous     | 205 (100%)  | 71 (100%)         | 0.81 (0.60, 0.93) |
|                        | By median in event-free |            |                   |                   |
| Low                    |                   | 129 (62.9%)| 36 (50.7%)        | Reference         |
| High                   |                   | 76 (37.1%) | 35 (49.3%)        | 0.59 (0.32, 0.90) |

*Adjusted by age, sex, smoking status, KPS score, time of blood drawn, seizure, and diabetes medication/metformin, dyslipidemia diagnosis, IDH1 mutation status, and BMI.

4 | DISCUSSION

In the current study, we utilized a case-control method to evaluate the relationship between leukocyte RTL and glioma risk. We found that mean RTL in blood leukocytes was significantly higher in glioma cases than controls, and longer RTL was significantly associated with glioma risk. In further stratified analysis by clinical characteristics at baseline, we found that the relationship between RTL and glioma risk was only apparent among cases with aggressive tumor characteristics. Furthermore, among GBM patients, we found that longer RTL was associated with better overall survival and progression/recurrence-free survival.

To date, only 3 studies evaluated the association of leukocyte telomere length with glioma risk and the results were inconsistent. Our results confirmed that longer leukocyte RTL was associated with increased glioma risk shown in the Swedish and Chinese studies. However, Wang et al reported a U-shaped association between RTL and glioma risk, where shorter RTLS in leukocytes were also associated with higher glioma risk. On the other hand, the study conducted in US population reported that short RTL was associated with increased risk of glioma among men, but not among women. The conflicting results may be due to differences in study populations. Telomere length has been reported to vary dramatically in different populations, even within same regions such as Europe. The inconsistency may be also related to the percentage of immune cells in leukocytes, since telomere length may vary across different types of immune cells. The biological mechanism behind the association between leukocyte telomere length and cancer risk is still unclear. One proposal is that longer telomeres may allow cells to escape growth arrest and delay cell senescence, thereby leading to subsequent genomic instability and carcinogenic transformation. To further support the role of longer telomere length in glioma risk, studies have identified several telomere-related genetic variants as glioma risk factors, including variants near TERC genes, TERT genes, and the rare variant in the POT1 gene, which are shown to be associated with longer telomere length. A recent publication studying 95,568 individuals found that genetic variants related to long telomeres are associated with an increased overall cancer risk among the general population.

Another interesting finding in our study is that the significant association between longer RTL and glioma risk was only observed among those with aggressive tumor characteristics, including GBM subtype, high tumor grade (grade III or IV), absence of IDH mutation, and absence of 1p/19q co-deletion. Our results are consistent with Swedish study reports that showed that longer RTL was not associated with risk of glioma in patients with IDH mutation or with 1p/19q co-deletion. Therefore, are alterations in leukocyte telomere length part of the cancer etiology or are they just the consequences of the cancer disease? Due to the limitation in our study design, we are unable to answer this question. However, based on the fact that the positive association was only evident among those with aggressive tumor characteristics, leukocyte RTL is more likely a tumor biomarker for glioma.

We noticed that longer RTL was correlated with better overall survival and progression/recurrence-free survival in GBM patients in further analysis. To date, only one study assessed the prognostic value of leukocyte RTL among glioma patients. In the study, patients with short RTL showed poor overall survival and progression/recurrence-free survival, consistent with our results in GBM patients. A few tumor tissue-based studies have been completed within the past several years. Lotsch et al examined telomerase-associated parameters in GBM tissue, and found that GBM patients lacking hTERT expression and telomerase activity had markedly longer telomeres and significantly longer survival. On the other hand, longer RTL or TERT promoter mutations in glioma tissue specimens were significantly associated with glioma patients’
poor survival in another study. The underlying mechanism for the association between leukocyte RTL and GBM prognosis remains elusive. A few studies in other cancer types indicate that RTL is correlated with the host immune function. However, Chen et al reported that no significant difference of systemic immunological parameters between glioma patients with different telomere length was observed. Additional research is desired to elucidate the essential mechanisms between the observed associations of leukocyte RTL.

One limitation of our study is the lack of matched glioma tumor tissues. Even though telomere length within an organism is relatively stable and its variability across different tissues is low, telomere length still varies among specific tissues and even among different cell populations in the given sample from the same individual. Future investigations of RTL association with glioma risk using glioma tissue and correlation with findings from leukocytes are warranted. Another limitation of our study is that leukocyte RTL was only measured once, and qPCR ratio does not assess all telomeres of various lengths at every chromosome end in each cell. Validation of our results using more advanced or high-throughput methods in the future is necessary. Lastly, previous studies have linked asthma and allergy to shorter RTL and decreased risk of glioma, and the association between leukocyte RTL and glioma risk may be influenced by allergies, BMI, and smoking. Our results of the association of RTL and glioma risk were only adjusted by BMI and smoking, but not by asthma and allergy as the allergy data were not available.

Nevertheless, this study exhibited a relationship between long leukocyte RTL and risk of glioma. We also noticed that longer RTL was correlated with better survival outcomes among GBM patients. Future validation studies, particularly in larger prospective cohorts, and mechanistic studies to reveal the underlying molecular mechanism are needed.

**CONFLICT OF INTEREST**
The authors declare that they have no conflict of interest.

**ETHICS APPROVAL**
All procedures performed in this study were approved by the Institutional Review Board at M D Anderson Cancer Center and in accordance with the ethical standards of 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**INFORMED CONSENT**
Written informed consent was obtained from all participants.

**DATA AVAILABILITY STATEMENT**
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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