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Telomere Maintenance-Associated Transcriptional States Mark a Proliferative and Genomically Unstable Axis in Myelodysplastic Syndromes

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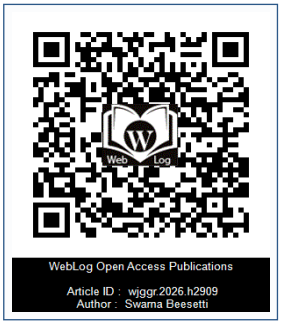

Abstract

Background: Myelodysplastic Syndromes (MDS) exhibit substantial biological heterogeneity driven by diverse molecular mechanisms. While telomere dysfunction has been implicated in MDS pathogenesis, its relationship to cellular programs, clonal architecture, and clinical outcomes remains incompletely defined.

Methods: We scored a curated telomere maintenance gene set by single sample Gene Set Enrichment (ssGSEA) score of 39 curated telomere maintenance genes in a public MDS transcriptomic cohort (n=183) and related it to pathway activity; we then examined mutation patterns, burden, and survival in an independent genomic cohort (n=3,323), using IPSS M risk to contextualize findings.

Results: Telomere maintenance activity was strongly positively associated with proliferative and cell cycle programs, including E2F targets ($\rho \approx 0.84$), G2M checkpoint ($\rho \approx 0.83$), and chromosomal instability (CIN70; $\rho \approx 0.85$), and negatively associated with p53 signaling and apoptosis (all FDR<0.05). Continuous analysis confirmed these relationships independent of categorical grouping. In the independent cohort, high-risk disease was characterized by increased mutation burden and enrichment of mutations in ASXL1 and spliceosome genes, while TP53 mutation remained the strongest predictor of inferior survival in multivariable analysis (HR=2.59). Survival analysis demonstrated significantly worse outcomes in high-risk patients (log-rank $p<0.0001$).

Interpretation: These findings identify a transcriptional state correlated with telomere maintenance gene expression that is associated with proliferative and genomically unstable features and adverse outcomes; causal effects on clonal progression cannot be inferred. Integration across cohorts supports an association between higher telomere maintenance gene expression, proliferative/genomically unstable transcriptional programs, and adverse clinical context, but causal inferences cannot be made.

Conclusion: Telomere-associated transcriptional programs define a biologically and clinically relevant axis of disease in MDS, linking cellular state, genomic features, and patient outcomes.

Keywords: Myelodysplastic Syndromes; Telomere Maintenance; Chromosomal Instability; Clonal Hematopoiesis; ssGSEA; IPSS-M; TP53; ASXL1

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Introduction

Myelodysplastic Syndromes (MDS) represent a heterogeneous group of clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis, peripheral blood cytopenias, and variable risk of transformation to Acute Myeloid Leukemia (AML) [1, 2]. The genomic landscape of MDS is dominated by somatic mutations in epigenetic regulators (DNMT3A, TET2, ASXL1, EZH2), spliceosome components (SF3B1, SRSF2, U2AF1, ZRSR2), cohesion complex genes (STAG2, RAD21), and tumor suppressors (TP53), many of which arise in the context of Clonal Hematopoiesis Of Indeterminate Potential (CHIP) and expand under selective pressure over time [3-5].

Telomere biology has emerged as a key determinant of hematopoietic ageing and clonal evolution [6, 7]. Telomeres, the repetitive nucleoprotein structures that cap chromosome ends, shorten with each cell division and provide a molecular clock for replicative senescence [8]. In hematopoietic stem cells, telomere erosion has been associated with genomic instability, aberrant DNA damage signaling, and impaired self-renewal [9]. Germline mutations in telomerase components (TERT,

TERC, DKC1) cause telomere biology disorders associated with bone marrow failure, and shorter leukocyte telomere length that has been associated with MDS risk [10, 11]. However, direct measurement of telomere length in bulk patient samples is technically challenging, and the transcriptional correlates of telomere maintenance activity in MDS have not been systematically characterized [12].

Single-sample Gene Set Enrichment Analysis (ssGSEA) offers a powerful approach to quantify pathway activity from bulk transcriptomic data without requiring matched telomere length measurements [13]. By scoring the expression of curated telomere maintenance genes across patient samples, a telomere maintenance activity score can be generated that reflects activation of telomere maintenance programs in proliferating cells under replicative stress rather than telomere shortening itself [14].

In this study, we applied a two-cohort integrative design using publicly available MDS transcriptomic and genomic data. We hypothesized that higher telomere maintenance activity scores would associate with proliferative and chromosomally unstable programs and reduced p53 mediated surveillance. We further hypothesized that clinical contexts enriched for high risk mutational and survival features would overlap with this transcriptional axis.

These findings reveal that the telomere maintenance activity score marks a distinct transcriptional axis characterized by high chromosomal instability, E2F and G2M checkpoint activation, and suppression of p53-mediated surveillance patterns consistent with clonal stress adaptation and providing a publicly reproducible framework for integrating transcriptional telomere states with genomic and clinical MDS data. Throughout, we use 'telomere maintenance activity score' to denote a transcriptomic surrogate of maintenance pathway engagement, not a direct measure of telomere dysfunction or length.

Methods

Study design and data sources

Dataset A: GSE19429 [15, 16] was retrieved from the NCBI Gene Expression Omnibus (GEO) using the GEOquery R package. This dataset comprises gene expression profiles from 183 MDS patient bone marrow samples profiled on the Affymetrix HG-U133Plus2 platform.

Dataset B: The IWG-PM MDS cohort (mds_iwg_2022) was downloaded from the cBioPortal for Cancer Genomics (www.cbioportal.org) [17]. This cohort comprises 3,323 MDS patients with somatic mutation data, IPSS-R and IPSS-M risk scores, and overall survival data. No patient-level data were shared between cohorts.

Telomere maintenance gene set

A curated gene set of 39 telomere maintenance genes was assembled from published reviews [18] and cross-referenced with REACTOME_TELOMERE_MAINTENANCE. The gene set comprised key components of telomere biology, including the shelterin complex (TERF1, TERF2, TERF2IP, ACD, TINF2, POT1, TPP1), the telomerase holoenzyme (TERT, TERC, DKC1, NOP10, NHP2, GAR1, TCAB1, RTEL1), and the CST complex (CTC1, STN1, TEN1). It further included ALT-associated recombination factors (ATRX, DAXX, RAD51, BLM, TOP3A, RMI1, RMI2), additional telomere maintenance regulators (HNRNPA1, HNRNPA2B1, PIF1, DNA2, RECQL, RECQL4, RECQL5, WRN, BRIP1), and telomere chromatin modifiers (H3F3A, H3F3B, SETDB1, SUV39H1, SUV39H2) [19, 20]. Of the 39 genes in this curated set, 33 were detectable in the GSE19429 dataset.

Transcriptomic processing and activity scoring

Raw expression data from GSE19429 were extracted, and probe-level measurements were collapsed to gene-level expression by averaging probes mapping to the same gene [21]. The resulting expression matrix was quantile-normalized using limma (normalizeBetweenArrays). Telomere maintenance activity scores were computed for each sample using single-sample Gene Set Enrichment Analysis (ssGSEA), as implemented in the GSVA Bioconductor package. This score reflects the relative transcriptional activity of telomere maintenance pathways and does not represent a direct measure of telomere length. Samples were stratified into tertiles (Low, Mid, High) based on the distribution of telomere maintenance activity scores across the cohort.

Pathway scoring

Ten MSigDB Hallmark gene sets (v2023.2) and the CIN70 chromosomal instability signature were scored using ssGSEA [22, 23]. Spearman's rank correlation assessed associations between the telomere maintenance activity score and each pathway. P-values were Benjamini-Hochberg adjusted [24].

Clinical risk stratification-Dataset B

Patients were classified as high-risk (IPSS-M: High, Moderate-High, Very-High) or low-risk (all remaining categories) [25]. Where IPSS-M was unavailable, IPSS-R (High, Very-High) was used as a fallback for risk stratification. Clinical risk group was used to contextualize genomic and outcome features that may overlap with the proliferative, genomically unstable state identified in Dataset A; no direct telomere activity scores were available in this cohort.

Somatic mutation analysis

Somatic mutations were restricted to a predefined set of 22 MDS/CHIP driver genes. For each patient, binary mutation indicators were generated to denote the presence or absence of mutations in each gene. Enrichment of individual mutations in high-risk versus low-risk groups was assessed using Fisher's exact test, with resulting *P*-values adjusted for multiple testing using the Benjamini-Hochberg method. Mutation co-occurrence patterns were evaluated using Pearson's phi coefficient, and genes were ordered by hierarchical clustering to facilitate visualization of correlation structure.

Survival analysis

Overall survival was estimated using Kaplan-Meier methods implemented in the survival R package, with group comparisons performed using the log-rank test. Multivariable Cox proportional hazards regression models included TP53 mutation, ASXL1 mutation, spliceosome mutation status, total mutation burden, and clinical risk group as covariates. Model discrimination was assessed using the concordance index (C-index). All reported associations are observational, and causal inference is not implied.

Software and reproducibility

All analyses were conducted in R (version 4.4) [26]. Key packages included GEOquery, limma, GSVA, GSEABase, msigdbr, survival, survminer, ggplot2, patchwork, pheatmap, corrplot, dplyr, and broom [27]. Complete R code is provided as Supplementary Data. All primary datasets are publicly available from the Gene Expression Omnibus (GSE19429) and cBioPortal (mds_iwg_2022).

Results

Telomere maintenance activity marks a distinct transcriptional state in MDS

Using gene set enrichment analysis of curated telomere maintenance genes, a telomere maintenance activity score for each sample in the GSE19429 MDS cohort (n=183) was derived. This score reflects transcriptional activation of telomere maintenance pathways, rather than direct telomere length measurement.

The telomere maintenance activity score exhibited a continuous distribution across samples (Supplementary Figure S1), enabling stratification into low, intermediate, and high activity groups (n=67, 66, and 67, respectively).

To define the biological context of this transcriptional state, we evaluated associations between telomere maintenance activity and canonical cellular pathways. The telomere maintenance activity score was positively associated with proliferative and cell cycle-related programs, including E2F targets, G2M checkpoint, MYC signaling, and chromosomal instability (CIN70), and negatively associated with p53 signaling, apoptosis, and inflammatory pathways (Figure 1; all FDR-adjusted $p<0.05$).

Continuous analysis confirms association with proliferation and genomic instability

To validate these findings without reliance on categorical grouping, continuous correlation analysis was performed. Telomere maintenance activity showed a strong positive association with chromosomal instability (CIN70; $\rho=0.85$) and G2M checkpoint activity ($\rho=0.83$), and an inverse association with p53 pathway activity ($\rho=-0.45$) (Figure 2).

These relationships indicate that higher telomere maintenance activity is associated with a proliferative, genomically unstable cellular state with reduced damage surveillance. The continuous nature of these associations argues against group-driven artefacts and supports a genuine linear relationship across the full score range. Although points are colored by tertile for visualization, correlation analyses used the continuous telomere maintenance activity score.

Pathway-Level changes define a coordinated biological program

Unsupervised visualization of pathway activity across samples confirmed a coordinated shift in biological programs across telomere activity groups (Supplementary Figure S2). High telomere maintenance activity was characterized by enrichment of cell cycle and DNA replication programs, while low activity samples demonstrated relatively higher expression of stress-response and apoptotic pathways.

Together, these findings support the existence of a telomere-associated transcriptional axis in MDS that reflects underlying cellular state rather than a single molecular event. The coordinated suppression of p53 and apoptosis programs in cells with high maintenance activity is consistent with a clonally selected state in which damage surveillance has been circumvented, permitting continued proliferation under genomic stress.

High-Risk disease exhibits distinct mutation patterns consistent with this biological state

To evaluate genomic correlates, an independent cohort of patients with MDS from the IWG 2022 dataset was analyzed (n=3,323). Because gene expression data were not available in this cohort, the clinical risk group (IPSS-M) was used as a contextual proxy to interpret genomic associations.

High-risk disease was significantly enriched for mutations in ASXL1 (OR≈2.94, FDR<0.001; n=944 mutated) and spliceosome genes (SF3B1, SRSF2, U2AF1, ZRSR2) (OR≈1.34, FDR<0.05; n=1,724 mutated). TP53 mutations appeared depleted in high-risk groups (Figure 3), a finding likely influenced by the design of IPSS M scoring and cohort composition rather than indicating a protective effect of TP53 mutation; this is addressed further in the survival analysis below. High-risk patients also exhibited a significantly greater overall mutation burden (Wilcoxon $p\approx5\times10^{-56}$; Supplementary Figure S3), consistent with increased genomic complexity.

Collectively, these findings indicate that high-risk disease is characterized by elevated mutation burden, ASXL1 dysregulation,

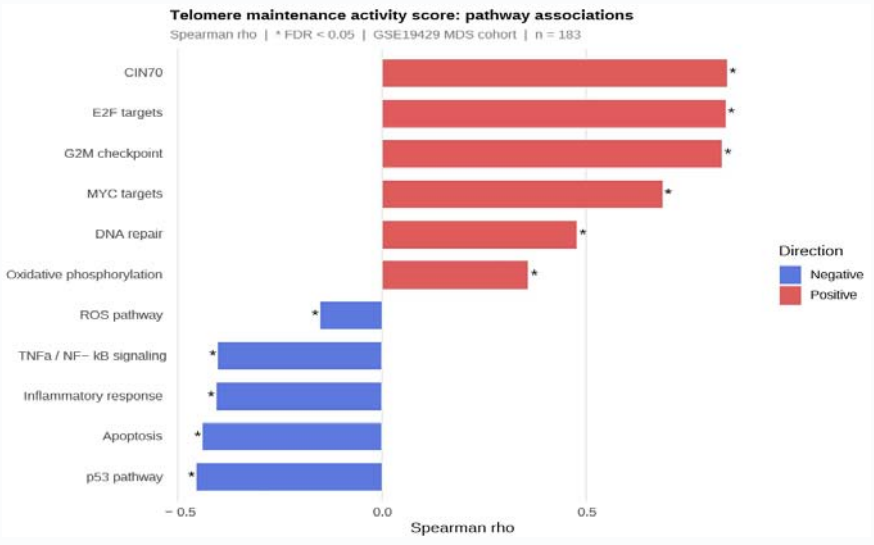

Figure 1: Telomere maintenance activity score associations with pathway programs. Bar chart showing Spearman rank correlation coefficients (ρ) between the telomere maintenance activity score and 11 Hallmark pathway programs plus CIN70 in GSE19429 (n=183). Red bars: positive associations; blue bars: negative associations. Asterisks denote FDR<0.05. Score reflects telomere maintenance gene transcriptional activity, not telomere length.

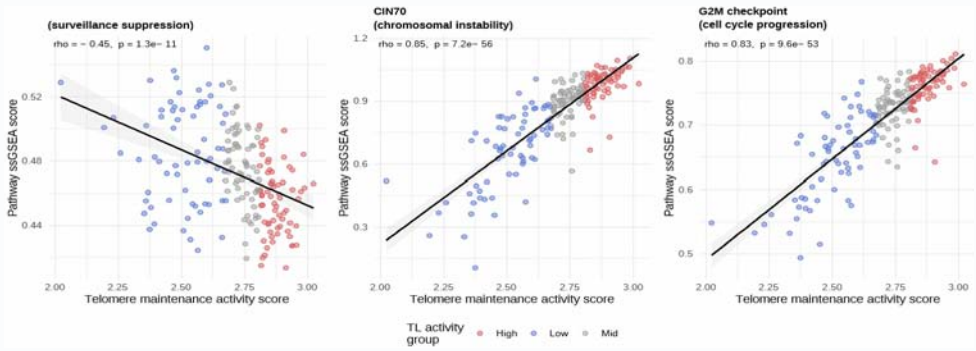

Figure 2: Continuous associations between telomere maintenance activity score and key pathway programs. Scatter plots (n=183) showing p53 pathway suppression, CIN70 chromosomal instability, and G2M checkpoint activation across the telomere maintenance activity score range. Points colored by tertile (Low = blue, Mid = grey, High = red). Spearman *ρ* and *p* annotated.

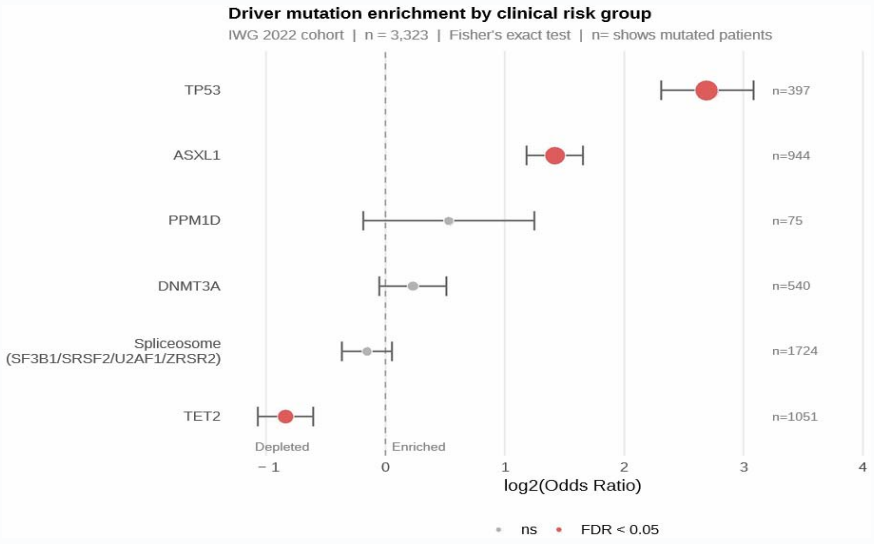

Figure 3: Driver mutation enrichment in high-risk versus low-risk MDS. Forest plot of Fisher's exact test results in the IWG 2022 cohort (n=3,323). High-risk defined by IPSS-M (High, Moderate-High, Very-High; n=1,328) *vs*. low-risk (n=1,797). Points sized by −log10(*p*-value); red=FDR<0.05. n=annotations show mutated patient counts. TP53 depletion reflects IPSS-M scoring dynamics; TP53 mutation remains the strongest survival predictor in multivariable analysis.

and disruption of spliceosome genes, consistent with a proliferative, genomically unstable cellular state that shares features with the proliferative, genomically unstable state identified in Dataset A, although direct telomere activity could not be assessed.

Clinical outcomes reflect the same disease axis

Survival analysis in the IWG 2022 cohort demonstrated significantly worse overall survival in high-risk patients compared with low-risk patients (log-rank $p<0.0001$; Figure 4). Median overall survival was approximately 18 months in high-risk patients versus 50 months in low-risk patients.

In multivariable Cox proportional hazards regression (n=3,015; events=1,507), TP53 mutation emerged as the strongest predictor of adverse outcome (HR=2.59, 95% CI 2.26-2.97, $p<2\times10^{-16}$), followed by high-risk group (HR=1.64), mutation burden (HR=1.07 per mutation), and ASXL1 mutation (HR=1.38) (Figure 5). The model demonstrated moderate discrimination (C-index=0.667). Proportional hazards assumptions were evaluated using Schoenfeld residuals and were not significantly violated for included covariates.

Importantly, the strong survival impact of TP53 mutation reconciles its apparent depletion in high-risk groups observed in enrichment analyses. This reflects differences between transcriptional pathway activity and mutational status, as well as the structure of IPSS-M risk assignment, which does not uniformly classify all TP53-mutant cases into the highest-risk categories.

Collectively, these results demonstrate that the genomic and biological features identified across datasets are clinically meaningful and independently associated with adverse outcomes, supporting the relevance of the telomere-associated transcriptional state in MDS.

Discussion

In this study, we identify a telomere-associated transcriptional state in Myelodysplastic Syndromes (MDS) that marks a proliferative and genomically unstable disease axis. This state is characterized by coordinated activation of cell cycle progression, proliferation, and chromosomal instability pathways, coupled with suppression of p53-mediated damage response programs. Importantly, the derived score does not measure telomere length directly but instead captures transcriptional activation of telomere maintenance machinery. This pattern likely reflects a stress-adapted cellular state in which telomere function is actively maintained to sustain proliferation despite genomic instability.

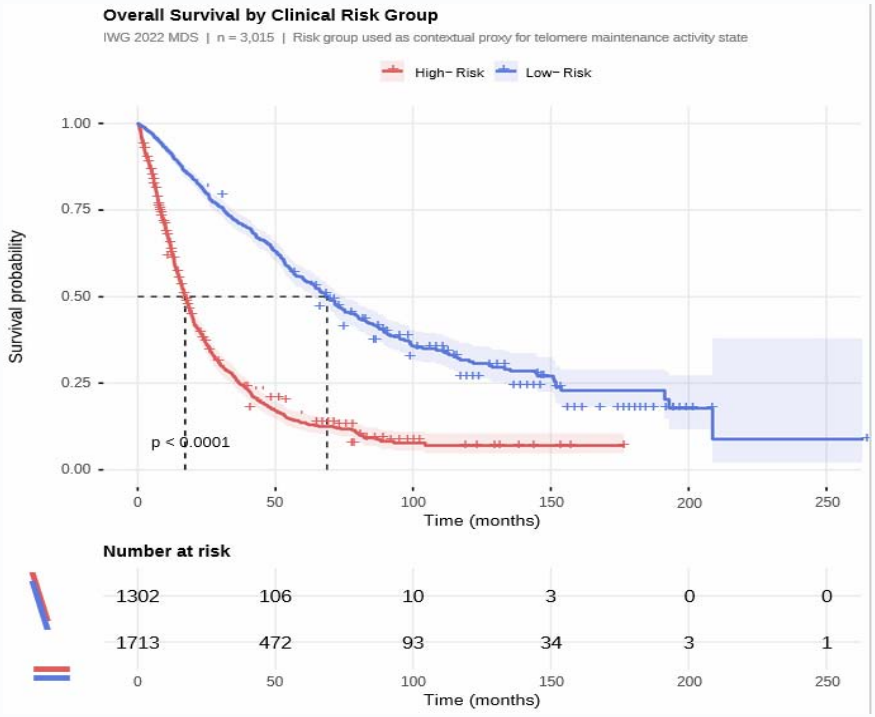

Figure 4: Overall survival by clinical risk group. Kaplan-Meier curves for high-risk (red; n=1,302) and low-risk (blue; n=1,713) patients (n=3,015 total). Log-rank $p<0.0001$. Dashed lines indicate median survival. Number-at-risk table below.

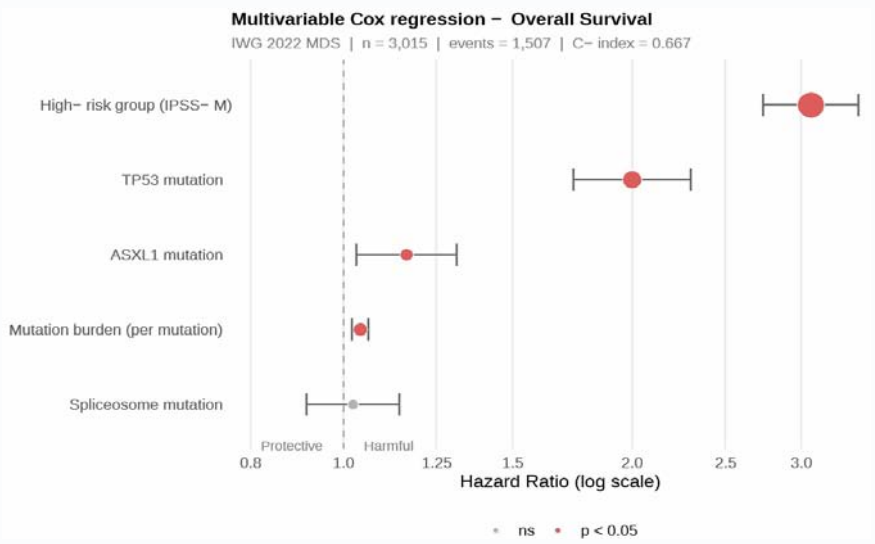

Figure 5: Multivariable Cox proportional hazards regression. Forest plot (n=3,015, events=1,507). Points sized by −log10(*p*-value); red=$p<0.05$. C-index=0.667. Results represent associations; causal inference is not implied.

Using a two-cohort analytical design, we demonstrate that this transcriptional state aligns with genomic and clinical hallmarks of high-risk disease. Although gene expression and mutational data were not available within the same cohort, three independent lines of evidence converge to support a coherent biological axis: (i) activation of proliferative and chromosomal instability programs in Dataset A, (ii) enrichment of adverse mutations and increased mutational burden in Dataset B, and (iii) poor survival outcomes observed in the same independent genomic cohort. This triangulated approach strengthens biological interpretation while deliberately avoiding overextension of causal claims and provides a reproducible framework applicable to other hematological malignancies. While the individual components of this axis, chromosomal instability signatures, ASXL1 and spliceosome mutations, and TP53 associated risk are well documented, this study demonstrates that a telomere maintenance-associated transcriptomic score aligns with this composite high-risk program.

Biologically, these findings support a model in which cells exhibiting high telomere maintenance activity represent stress-adapted, clonally selected populations. Enhanced proliferation in the setting of impaired damage surveillance creates a permissive

environment for chromosomal instability and clonal evolution [28]. This milieu is consistent with the emergence of mutations in genes such as ASXL1 and spliceosome components, which were enriched in higher-risk disease and are known to confer adverse prognosis in MDS [29, 30]. The inverse relationship between telomere maintenance activity and p53 pathway expression further supports a shift away from canonical checkpoint control mechanisms.

At first glance, this transcriptional pattern appears to contrast with classic telomere biology, in which telomere attrition triggers DNA damage responses, p53 activation, and apoptotic or senescent outcomes. However, this apparent paradox is resolved by recognizing that our score captures transcriptional upregulation of telomere maintenance programs rather than telomere dysfunction [31]. We propose that high scores reflect actively cycling cells that have maintained telomere function and evaded checkpoint enforcement, allowing persistence of genomically unstable clones. This interpretation is further supported by the strong correlation between telomere maintenance activity and the CIN70 chromosomal instability signature (ρ=0.85), a validated predictor of adverse outcomes across multiple tumor types. Co-activation of these programs in MDS is consistent with established links between dysfunctional telomere regulation and chromosomal instability in hematological malignancies [9]. An important alternative interpretation is that the telomere maintenance activity score primarily reflects a generic proliferative state, given its strong correlations with E2F and G2M programs and CIN70. While many telomere maintenance genes are functionally linked to replication stress responses, we cannot fully disentangle telomere specific biology from generic cell cycle activation in bulk data. Future work incorporating direct telomere length measurements and cell type resolved transcriptional data will be required to clarify this distinction.

Current findings also clarify the relationship between transcriptional suppression of p53 signaling and genomic disruption of TP53. While telomere maintenance activity was inversely correlated with p53 pathway expression in Dataset A, TP53 mutation remained the strongest predictor of poor survival in Dataset B. These observations reflect distinct molecular layers of checkpoint impairment rather than conflicting biology. Transcriptional suppression of p53 signaling and structural genomic loss of TP53 represent complementary mechanisms that converge on reduced damage surveillance [32]. The apparent depletion of TP53 mutations within the IPSS-M high-risk group likely reflects known calibration features of the IPSS-M model and does not diminish the dominant adverse prognostic impact of TP53 mutation status itself.

Several limitations warrant consideration. First, the telomere maintenance activity score is derived from gene expression and does not provide a direct measurement of telomere length or structure. Second, the absence of matched expression and mutation data necessitated indirect cross-cohort interpretation. Third, causal relationships between telomere-associated transcriptional states and clonal evolution cannot be established from observational data alone. Finally, while the primary expression cohort (GSE19429, n=183) is modest in size, the strength of observed associations (ρ>0.80) suggests robust underlying biological signals. Moreover, both datasets are predominantly cross sectional and cannot determine whether high telomere maintenance activity is a driver, a consequence, or simply a correlate of clonal evolution.

Future studies should compute telomere maintenance activity scores within large genomic cohorts that include matched transcriptomic data, such as Beat AML or TCGA AML. Integration with direct measurements of telomere length would enable dissection of the relationships among telomere structure, maintenance gene expression, and clinical outcome. Single-cell RNA sequencing approaches may further resolve the cellular compartments exhibiting telomere maintenance activity and clarify their contribution to disease progression [33].

In summary, we define a telomere-associated transcriptional state in MDS that is tightly linked to proliferation, chromosomal instability, and suppression of damage response pathways. This state aligns with adverse mutation patterns and poor clinical outcomes observed in independent cohorts, supporting a model in which telomere maintenance activity reflects a biologically and clinically meaningful axis of disease progression. These findings extend the understanding of how telomere biology intersects with clonal evolution in myeloid malignancies and provide a conceptual and analytical template for future studies across related disorders.

Declaration of AI and AI-assisted Technologies in the Writing Process

During the preparation of this work, the author used AI and AI-assisted Technologies to check spelling and grammar. After using this tool, the author reviewed and edited the content as needed and takes full responsibility for the content of the publication.

Author Contributions

SB was responsible for the conception of ideas presented, writing, and the entire preparation of this manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The author declares no conflict of interest.

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