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Association of telomere length with risk of complications in adult spinal deformity surgery: a pilot study of 43 patients

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OBJECTIVE Risk stratification is a critical element of surgical planning. Early tools were fairly crude, while newer instruments incorporate disease-specific elements and markers of frailty. It is unknown if discrepancies between chronological and cellular age can guide surgical planning or treatment. Telomeres are DNA-protein complexes that serve an important role in protecting genomic DNA. Their shortening is a consequence of aging and environmental exposures, with well-established associations with diseases of aging and mortality. There are compelling data to suggest that telomere length can provide insight toward overall health. The authors sought to determine potential associations between telomere length and postoperative complications.

METHODS Adults undergoing elective surgery for spinal deformity were prospectively enrolled. Telomere length was measured from preoperative whole blood using quantitative polymerase chain reaction and expressed as the ratio of telomere (T) to single-copy gene (S) abundance (T/S ratio), with higher T/S ratios indicating longer telomere length. Demographic and patient data included age, BMI, and results for the following rating scales: the Adult Spinal Deformity Frailty Index (ASD-FI), Oswestry Disability Index (ODI), Scoliosis Research Society-22r (SRS-22r), American Society of Anesthesiology (ASA) classification, and Charlson Comorbidity Index (CCI). Operative and postoperative complication data (medical or surgical within 90 days) were also collected.

RESULTS Forty-three patients were enrolled, including 31 women (53%), with a mean age of 66 years and a mean BMI of 28.5. The mean number of levels fused was 11, with 21 (48.8%) combined anterior-posterior approaches. Twenty-two patients (51.2%) had a medical or surgical complication. Patients with a postoperative complication had a significantly lower T/S ratio (0.712 vs 0.813, p = 0.008), indicating shorter telomere length, despite a mild difference in age compared with patients without a postoperative complication (68 vs 63 years, p = 0.069). Patients with complications also had higher CCI scores than patients without complications (2.3 vs 3.8, p = 0.004). There were no significant differences in sex, BMI, ASD-FI score, ASA class, preoperative ODI and SRS-22r scores, number of levels fused, or use of three-column osteotomies. In a multivariate model including age, frailty, ASA class, use of an anterior-posterior approach, CCI score, and telomere length, the authors found that short telomere length was significantly associated with postoperative complications. Patients whose telomere length fell in the shortest quartile had the highest risk (OR 18.184, p = 0.030).

CONCLUSIONS Short telomere length was associated with an increased risk of postoperative complications despite only a mild difference in chronological age. Increasing comorbidity scores also trended toward significance. Larger prospective studies are needed; however, these data provide a compelling impetus to investigate the role of biological aging as a component of surgical risk stratification.

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KEYWORDS telomere; cellular age; chronological age; complications; deformity surgery

ABBREVIATIONS ASA = American Society of Anesthesiology; ASD-FI = Adult Spinal Deformity Frailty Index; CCI = Charlson Comorbidity Index; CL = cervical 2–7 lordosis; CRP = C-reactive protein; cSVA = cervical SVA; CVA = coronal vertical axis; DEXA = dual-energy x-ray absorptiometry; DVT = deep venous thrombosis; EBL = estimated blood loss; ESR = erythrocyte sedimentation rate; LL = lumbar lordosis; ODI = Oswestry Disability Index; PE = pulmonary embolus; PI = pelvic incidence; PI-LL = PI − LL mismatch; PT = pelvic tilt; RAT = Risk Assessment Tool; SRS-22r = Scoliosis Research Society-22r; SVA = sagittal vertical axis; T1S = T1 slope; T/S ratio = ratio of telomere (T) to single-copy gene (S) abundance; 3CO = three-column osteotomy.

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The number of spine surgeries performed in the United States has increased significantly over the past 20 years, including surgeries for adult spinal deformity.[1–3] These numbers are expected to rise with a growing population of older adults. Postoperative complications have a negative impact on clinical outcomes and significantly increase the cost associated with surgery.[4–7] Risk quantification has an important role in patient selection, preoperative counseling, surgical planning, and even reimbursement. Early risk assessment tools were used to stratify patients according to medical comorbidities and assess "operative risk," such as the American Society of Anesthesiology (ASA) physical status classification.[8] Subsequent efforts, such as the Charlson Comorbidity Index (CCI), were used to quantify risk of 1- and 10-year mortality based on the number and severity of comorbid diseases; however, this tool was not designed specifically for surgical risk assessment.[9]

More recent work has focused on disease-specific or surgery-specific instruments.[9–14] Predictive models are now used to quantify complication risk and spine-specific outcomes such as pseudarthrosis and proximal junctional failure.[15–19]

Recent studies have demonstrated the importance of frailty in preoperative planning and outcomes.[13,20–22] Specific definitions vary, but frailty is typically described as increased vulnerability due to the loss of physiological reserves, including energy, physical ability, cognition, and overall health.[13] Chronological age is often associated with each of these properties and is a major risk factor for functional impairments, chronic disease, and mortality.[23] Given the projected growth of the aging population, there is a pressing need for an improved understanding of the aging process, including biomarkers of biophysiological age and their effects on surgical risk.

Telomeres, the protective end complexes at the terminal ends of chromosomes, comprise tandem short DNA repeats and associated protective proteins.[24] Telomeres protect genomic DNA, and short telomeres are associated with self-reported health status, common diseases of aging, and mortality risk.[25–28] These data, combined with a rapidly growly elderly population, provide an impetus to investigate the role of telomere length as a biomarker of overall health and frailty, particularly in risk stratification for patients undergoing high-risk surgery such as correction of spinal deformity.

Methods

Patient Data

Adult patients (age ≥ 18 years) undergoing surgery were prospectively enrolled. All patients had a diagnosis of spinal deformity with failure of nonoperative therapy. Patients with a diagnosis of tumor or infection were excluded. All study research activities were approved by the Committee on Human Research, our institutional review board. Preoperative demographic data including age, sex, BMI, Oswestry Disability Index (ODI) score, and Scoliosis Research Society-22r (SRS-22r) score were collected. Preoperative dual-energy x-ray absorptiometry (DEXA) T-score and laboratory values were collected, including erythrocyte sedimentation rate (ESR; normal 0–15 mm/hr), C-reactive protein (CRP; normal < 7.5 mg/L), albumin (normal 3.5–4.8 g/dL), and prealbumin (normal 20–37 mg/dL). Surgical variables including the use of a staged (anterior-posterior) approach, number of levels fused, estimated blood loss (EBL), use of three-column osteotomy (3CO), and length of stay were also collected. Preoperative and postoperative radiographic parameters were collected, including sagittal vertical axis (SVA), coronal vertical axis (CVA), pelvic incidence (PI), lumbar lordosis (LL), PI – LL mismatch (PI-LL), and pelvic tilt (PT). For patients with cervical deformities, additional parameters were collected, including cervical SVA (cSVA), cervical 2–7 lordosis (CL), and T1 slope (T1S). The magnitude of correction was calculated as the difference between preoperative and postoperative SVA, LL, and PI-LL. Postoperative complications (either medical or surgical) within 90 days from surgery were included.

Telomere Length Analysis

Preoperative whole blood was acquired and stored at −80°C, and telomere length was assessed using quantitative polymerase chain reaction (qPCR) as previously described.[29,30] Genomic DNA was extracted from whole blood using the QIAamp mini DNA kit (QIAGEN). The telomere qPCR primers were tel1b [5′-CGGTTT(GTTTGG)5GTT-3′], used at a final concentration of 100 nM, and tel2b [5′-GGCTTG(CCTTAC)5CCT-3′], used at a final concentration of 900 nM. The single-copy gene (human beta-globin 1 and 2 [*HBG1* and *HBG2*]) qPCR primers were *HBG1* (5′-GCTTCTGACACAACTGTGTTCACTAGC-3′), used at a final concentration of 300 nM, and *HBG2* (5′-CACCAACTTCATCCACGTTCACC-3′), used at a final concentration of 700 nM. The final reaction mix consisted of the following: 20 mM Tris-hydrochloride, pH 8.4; 50 mM potassium chloride; 200 μM each deoxyribonucleotide triphosphate; 1% dimethyl sulfoxide; 0.4× SYBR green I; 22 ng of *Escherichia coli* DNA; 0.4 U of platinum Taq DNA polymerase (Invitrogen Inc.), and 6 ng of genomic DNA per 11-μl reaction. A 3-fold serial dilution of commercial human genomic DNA containing 26, 8.75, 2.9, 0.97, 0.324, and 0.108 ng of DNA was included in each PCR run as the reference standard. The quantity of targeted templates in each sample was determined relative to the reference DNA sample by use of the maximum second-derivative method in the Roche LC480 program. The reaction was carried out in a Roche LightCycler 480 in 384-well plates, with triplicate wells for each sample. The Dixon Q test was used to exclude outliers from the triplicates. The average of the telomere and single-copy gene triplicate well abundance after outlier removal was used to calculate the ratio of telomere (T) to single-copy gene (S) abundance (T/S ratio) for each sample, which was used to determine the telomere length. The T/S ratio for each sample was measured twice. When the duplicate T/S ratio and initial value varied by more than 7%, the sample was run a third time and the two closest values were reported. Of the 43 samples, 5 were assayed for a third time. The average interassay coefficient of variation of the duplicate value was 2.1% ± 1.5%.

TABLE 1. Patient demographic data

Characteristic	Value
No. of patients	43
Age, yrs	66 ± 10
Female sex	21 (48.8%)
BMI	28.5 ± 5.6
Preop DEXA T-score*	–1.0 ± 1.3
Preop lab values†	
ESR, mm/hr	11.8 ± 12.9
CRP, mg/L	5.4 ± 7.9
Albumin, g/dL	4.3 ± 1.6
Prealbumin, mg/dL	27.2 ± 6.8
ASA class	
1	2 (4.7%)
2	19 (44.2%)
3	22 (51.2%)
CCI score	
Mean	3.1 ± 1.8
0	4 (9.3%)
1	3 (7.0%)
2	9 (20.9%)
3	13 (30.2%)
4	7 (16.3%)
5	2 (4.7%)
6	3 (7.0%)
7	2 (4.7%)
ASD-FI score	
Mean	0.228 ± 0.139
Not frail	29 (67.4%)
Frail	12 (27.9%)
Severely frail	2 (4.7%)
Preop ODI score	46% ± 18%
Preop SRS-22r score	
Total	2.6 ± 0.7
Function	2.6 ± 0.8
Pain	2.2 ± 0.9
Self-image	2.4 ± 0.7
Mental health	3.3 ± 0.8
Satisfaction/dissatisfaction ratio	2.5 ± 1.1
Prior spinal fusion	20 (46.5%)

Values are presented as number (%) of patients or mean ± SD unless otherwise indicated.
* 36 patients.
† 42 patients.

The resulting T/S ratio represents the relative telomere length from total leukocyte in whole blood. T/S ratios were converted to base pairs (bp) by using comparisons determined by Southern blot analysis of DNA samples from human fibroblast IMR90 cultured and harvested at different time points.[31] Differences in cellular age based on telomere length were estimated using an attrition rate of 25 bp/yr.[32]

Risk Assessment

Risk assessment metrics were calculated for each patient. These included the ASA classification,[14] CCI score,[9] Adult Spinal Deformity Frailty Index (ASD-FI) score,[13] SpineSage tool predictive model for medical complications,[10] and spinal Risk Assessment Tool (RAT).[11]

Statistical Analysis

Continuous variables were compared by using the Student t-test or ANOVA, and categorical variables by using the chi-square test. For continuous variables, mean and standard deviation were included. Correlations were assessed using bivariate correlation with the Pearson correlation coefficient. Multivariate analysis was performed using binary logistic regression. Statistical significance was defined as $p < 0.050$. Analysis was performed using SPSS version 27 (IBM Corp.).

Results

Patient Demographics and Surgical Characteristics

A total of 43 patients were enrolled (age 66 ± 10 years, range 39–83 years; 21 women [48.8%]). The mean BMI was 28.5 ± 5.6. The ASA classification distribution was as follows: 2 class 1 (4.7%), 19 class 2 (44.2%), and 22 class 3 (51.2%). The mean DEXA T-score was –1.0 ± 1.3, and the mean laboratory values were as follows: ESR 11.8 ± 12.9 mm/hr, CRP 5.4 ± 7.9 mg/L, albumin 4.3 ± 1.6 g/dL, and prealbumin 27.2 ± 6.8 mg/dL. The mean ASD-FI was 0.228 ± 0.139, with frailty distributions as follows: 29 patients not frail (67.4%), 12 frail (27.9%), and 2 severely frail (4.7%). The mean preoperative ODI score was 46% ± 18%, and the mean total SRS-22r score was 2.6 ± 0.7. Twenty patients had a prior spinal fusion (46.5%). These data are summarized in Table 1.

Among 43 patients, 4 (9.3%) had cervical or cervicothoracic deformities and 39 (90.7%) had thoracolumbar deformities. The mean preoperative radiographic parameters were as follows: SVA 8.6 ± 6.1 cm, CVA –0.8 ± 3.4 cm, PI 55° ± 17°, LL 28° ± 28°, PI-LL 31° ± 21°, and PT 27° ± 11°. Additional values collected among patients with cervical deformities included mean cSVA 3.3 ± 2.3 cm, CL 26° ± 32°, and T1S 36° ± 12°. All patients underwent posterior approach surgery, and 21 patients (48.8%) underwent combined anterior-posterior approach surgery. The mean number of levels were as follows: anteriorly 2 ± 0.7, mean EBL 132 ± 123 ml, and posteriorly 11 ± 4, mean EBL 1559 ± 957 ml. 3CO was used in 18 patients (41.9%). The mean length of stay was 10 ± 7 days. These data are summarized in Table 2.

Postoperative Complications

Twenty-two patients (51.2%) experienced a medical or surgical postoperative complication within 90 days of surgery. Four patients experienced more than one complication. Complications included myocardial infarction (n = 2), respiratory failure (n = 2), cardiac arrest (n = 1), stroke (n = 1), partial bowel obstruction (n = 1), death (n = 1), and reoperation (n = 3). Reasons for operation included realignment failure in 2 patients and deep wound infec-

TABLE 2. Surgical characteristics

Characteristic	Value
No. of patients	43
Deformity location	
Cervical/cervicothoracic	4 (9.3%)
Thoracolumbar	39 (90.7%)
Radiographic parameters	
SVA, cm	8.6 ± 6.1
CVA, cm	−0.8 ± 3.4
PI, °	55 ± 17
LL, °	28 ± 28
PI-LL, °	31 ± 21
PT, °	27 ± 11
cSVA, cm*	3.3 ± 2.3
CL, °*	26 ± 32
T1S,°*	36 ± 12
Anterior stage	21 (48.8%)
Anterior levels fused, no.	2 ± 0.7
Anterior EBL, ml	132 ± 123
Posterior levels fused, no.	11 ± 4
Posterior EBL, ml	1559 ± 957
3CO	18 (41.9%)
Length of stay, days	10 ± 7

Values are presented as number (%) of patients or mean ± SD unless otherwise indicated.
* Among 4 patients with cervical deformity.

TABLE 3. Postoperative complications

Complication Type	Value
No. of patients	22
Myocardial infarction	2
Respiratory failure	2
Cardiac arrest (recovered)	1
Stroke	1
Enterocolitis w/ partial bowel obstruction	1
Death due to interstitial lung disease	1
Reop	
Realignment failure	2
Wound infection	1
Urinary tract infection	4
Cardiac arrythmia	4
Acute kidney injury	3
DVT/PE	2
Ileus	2

Values are presented as total number of patients or number of patients with complications.

tion in 1 patient. Additional complications included urinary tract infection (n = 4), cardiac arrythmia without hemodynamic instability requiring treatment (n = 4), acute kidney injury (n = 3), deep venous thrombosis (DVT) or pulmonary embolus (PE) (n = 2), and ileus (n = 2). These complications are summarized in Table 3.

Comparison of Patients With Postoperative Complications

Patients with and without complications were compared. Patients with a postoperative complication were slightly older (68 vs 63 years, p = 0.069). There was no significant difference in sex, BMI, DEXA T-score, preoperative laboratory values, preoperative ODI, or total SRS-22r scores. Patients with complications did have a slightly higher SRS-22r pain subscore (2.5 vs 1.9, p = 0.033). There were no significant differences in preoperative radiographic parameters; however, patients with complications had slightly lower preoperative PI (50° vs 59°, p = 0.060) and lower preoperative LL (21° vs 37°, p = 0.062). There was no significant difference in magnitude of correction with respect to change in SVA, LL, or PI-LL; prior fusion; use of an anterior-posterior surgical approach; number of levels fused; EBL; or use of 3CO. These data are summarized in Table 4.

Differences in risk stratification metrics were compared between patients with and without complications. There were no significant differences in ASA classification, mean ASD-FI score, or distribution of frail or severely frail patients. The mean CCI score was higher in the complication group (3.8 vs 2.2, p = 0.004). The predicted complication risk calculated by either SpineSage or the RAT was not significantly different between groups. The T/S ratio was significantly lower in the complication group (0.713 vs 0.813, p = 0.008), indicating shorter telomere length among patients who experienced a complication. Approximate telomere length, estimated by converting T/S ratio to base pairs, was also significantly shorter in the complication group (4994 vs 5236 bp, p = 0.008). This represents an estimated difference of 10 years in cellular age between groups, compared with a 5-year difference in chronological age. These data are summarized in Table 5.

Multivariate Analysis

A multivariate analysis was performed using variables that trended toward significance on univariate analysis (p < 0.100). ASD-FI was included based on a compelling rationale and supporting literature. Prior to running the model, we assessed for correlations between telomere length (T/S ratio) and chronological age, frailty, and CCI scores. There were no correlations between telomere length and ASD-FI score (r = 0.063, p = 0.689), CCI score (r = −0.167, p = 0.285), or age (r = −0.249, p = 0.107). Similarly, there was no difference in T/S ratio between nonfrail versus frail/severely frail patients (0.766 vs 0.753, p = 0.757), or patients with ASA class 1–2 compared with ASA class 3 (0.750 and 0.773, p = 0.553). Furthermore, there was no difference in T/S ratio among patients with all posterior or anterior-posterior surgical approaches (0.735 vs 0.790, p = 0.160). When controlling for age, frailty, ASA classification, anterior-posterior approach, CCI, and telomere length, we found that CCI trended toward significance, but only short telomere length (shortest quartile) had a statistically significant association with postoperative complication (OR 18.184, p = 0.030). These data are summarized in Table 6.

TABLE 4. Comparison of patients with and without complications

Characteristic	Complications		p Value
	None (n = 21)	Any (n = 22)	
Age, yrs	63	68	0.069
Female sex	12 (57.1%)	9 (40.9%)	0.287
BMI	28.1	28.9	0.661
Preop DEXA T-score*	–0.9	–1.0	0.985
Preop lab values*			
ESR, mm/hr	11.4	12.3	0.842
CRP, mg/L	5.8	5.0	0.765
Albumin, g/dL	4.6	4.1	0.290
Prealbumin, mg/dL	25.6	28.8	0.130
Preop ODI	50.0%	41.8%	0.138
Preop SRS-22r			
Total	2.5	2.7	0.501
Function	2.5	2.7	0.410
Pain	1.9	2.5	0.033
Self-image	2.3	2.5	0.385
Mental health	3.2	3.3	0.545
Satisfaction/dissatisfaction	2.4	2.6	0.425
Prior spinal fusion	9 (42.9%)	11 (50.0%)	0.639
Radiographic parameters			
Preop SVA, cm	7.7	9.5	0.338
Preop CVA, cm	–0.9	–0.6	0.798
Preop PI, °	59	50	0.060
Preop LL, °	37	21	0.062
Preop PI-LL, °	27	35	0.213
Preop PT, °	27	27	0.980
Magnitude of correction			
ΔSVA, cm	–4.5	–6.2	0.441
ΔLL, °	–21	–23	0.794
ΔPI-LL, °	18	19	0.880
Anterior stage	13 (61.9%)	8 (36.4%)	0.094
Anterior levels fused, no.	2.3	1.8	0.075
Anterior EBL, ml	148	106	0.464
Posterior levels fused, no.	10.8	11.7	0.418
Posterior EBL, ml	1383	1727	0.244
3CO	9 (42.9%)	9 (40.9%)	0.897

Δ = change in preoperative versus postoperative value.
* Among patients with available data.

TABLE 5. Comparison of risk stratification tools in patients with and without complications

Characteristic	Complications		p Value
	No (n = 21)	Yes (n = 22)	
ASA class			
1	1 (4.8%)	1 (4.5%)	0.973
2	12 (57.1%)	7 (31.8%)	0.095
3	8 (38.1%)	14 (63.6%)	0.094
CCI score			
Mean	2.3	3.8	0.004
0	3 (14.3%)	1 (4.5%)	0.272
1	3 (14.3%)	0 (0%)	0.066
2	7 (33.3%)	2 (9.1%)	0.051
3	4 (19.0%)	9 (40.9%)	0.119
4	3 (14.3%)	4 (18.2%)	0.729
5	0 (0%)	2 (9.1%)	0.157
6	1 (4.8%)	2 (9.1%)	0.578
7	0 (0%)	2 (9.1%)	0.157
ASD-FI score			
Mean	0.229	0.228	0.997
Not frail	16 (76.2%)	13 (59.1%)	0.232
Frail	4 (19.0%)	8 (36.4%)	0.206
Severely frail	1 (4.8%)	1 (4.5%)	0.973
SpineSage tool			
Major complication	16.7%	20.1%	0.353
All complications	45.6%	49.3%	0.419
Spinal RAT			
Any complication	30.2%	31.6%	0.778
Cellular data			
T/S ratio	0.813	0.713	0.008
Telomere length, bp	5236	4994	0.008

Discussion

Risk stratification will play a critical role in the future of spine surgery, particularly for the treatment of adult deformity. Tools that integrate patient physiology, disease burden, and surgical invasiveness to quantify the risk of treatment will allow surgeons to accurately communicate with patients. This will allow for more accurate informed consent and shared decision-making. In certain cases, these tools will allow surgeons to tailor their treatment plan to accommodate an appropriate risk profile. An accurate assessment of complication risk will also provide important information to payers in a climate of increased scrutiny over costs and transition toward bundled payments. Advances in technology will allow surgeons to leverage big data to develop more nuanced, disease-specific point-of-care risk stratification tools that can guide decision-making in real time.

Early risk stratification tools, such as ASA classification, are blunt instruments designed to streamline communication and provide a general summary of comorbidities and overall health without specific quantification of perioperative risk. Subsequent iterations, such as the CCI, attempted to quantify broad risks, such as all-cause mortality, based on a select group of comorbidities. Although not specifically designed for surgical patients, the CCI has been found to predict survival and outcomes for surgical treatments such as radical prostatectomy.[33] The American College of Surgeons National Surgery Quality Improvement Program (ACS NSQIP) surgical risk calculator was developed using a multicenter cohort of over 1.4 million patients across multiple specialties to provide quantitative assessments of outcomes, including death, pneumonia, surgical site infection, DVT, and others.[12] Although pub-

TABLE 6. Multivariate analysis

Variable	OR (95% CI)	p Value
Age	0.982 (0.852–1.131)	0.796
Frail or severely frail	0.713 (0.099–5.113)	0.736
ASA class 3	2.266 (0.327–15.701)	0.408
Anterior-posterior approach	0.240 (0.037–1.569)	0.136
CCI score	2.222 (0.842–5.868)	0.107
Telomere length (T/S ratio), quartile		
4th (longest)	Ref	0.190
3rd	4.667 (0.482–45.244)	0.184
2nd	4.207 (0.396–44.720)	0.234
1st (shortest)	18.184 (1.334–247.858)	0.030

licly available, the ACS NSQIP does not include elements specific to spine surgery and has been outperformed by spine-specific risk calculators.[11]

More recently, risk stratification tools have been deployed specifically for spine surgery. Lee et al. used a single-center, prospective registry of nearly 1500 patients to predict complications.[10] This publicly available tool (SpineSage) uses a combination of patient comorbidities and surgical invasiveness to predict the risk of major medical complications with a receiver operator curve characteristic of 0.81. Veeravagu et al. developed the Risk Assessment Tool (RAT), which incorporates medical comorbidity data with preoperative diagnosis (degenerative disease, tumor, trauma, or infection), surgical approach (anterior or posterior), location (cervical or thoracolumbar), number of levels, and use of bone morphogenetic protein, among other variables.[11] The RAT generates predictions for the risk of medical and surgical complications and is publicly available. Additionally, efforts by the International Spine Study Group and European Spine Study Group have led to the development of predictive models for the occurrence of major complications, hospital readmissions, and unplanned reoperations in adult spinal deformity.[34] Subsequent models have been used to predict reaching the minimal clinically important difference and spine-specific complications such as pseudarthrosis and proximal junctional failure.[15–17] Frailty, a relatively new diagnosis that is characterized by reduced physiological reserve and increased vulnerability to injury, has also been used as a risk stratification tool for spine-specific complications such as pseudarthrosis and proximal junctional failure, as well as wound complications and reoperation.[13,35,36]

As medicine enters the age of big data, our risk stratification tools will evolve accordingly. Future iterations of these tools will incorporate increasingly large and complex variables. For example, instead of classifying patients as diabetic or nondiabetic, future algorithms will likely utilize quantitative measures of the disease, such as hemoglobin A1c, to build a more accurate patient profile. Given the abundance of literature confirming age as an important component of risk stratification, we will likely move beyond simple chronological age when quantifying perioperative risk.[25,26] If proven to be useful, biomarkers of cellular aging and physiological reserve will be incorporated into risk calculators to further improve their accuracy.

Functional and physiological decline are inevitable consequences of aging; however, the process is highly variable, and chronological age alone does not accurately reflect physiological reserve.[37–39] Telomeres are highly regulated regions at the ends of chromosomes that comprise tandem short DNA repeats and associated protective proteins.[24] The degree of telomere shortening is roughly proportional to the risk of common disease of aging and mortality.[25,26] Telomere length typically shortens with age; however, it is important to recognize that regulation of telomere length is a complex, dynamic process. Interestingly, there are some data to suggest that lifestyle changes can affect telomere length.[40] There are few studies investigating associations between telomere length and surgery or postoperative complications. Jongbloed et al. showed that bariatric surgery led to a temporary increase in telomere length, likely due to reversal of metabolic syndrome.[41] Morton et al. studied a similar population of patients undergoing gastric bypass; their findings were notable given that patients with high levels of low-density lipoprotein (LDL) and CRP had an increase in telomere length at 1 year, whereas those with low LDL and CRP levels had a decrease in telomere length.[42] This observation suggests that high-risk patients may benefit most from surgical intervention, a finding that has been seen in patients with cervical deformity.[21] To our knowledge, no previously reported studies have investigated telomere length as a component of surgical risk stratification. Future treatment paradigms may incorporate telomere length (or other measures of biological age), along with frailty and comorbidity indices, into preoperative risk assessment tools in order to better predict complications and outcomes (Fig. 1).

Alternative estimates for cellular age utilize DNA methylation, which is used to calculate epigenetic age.[43–46] These methylation patterns correlate with chronological age and are associated with age-related health outcomes and may capture some aspects of susceptibility to disease and health-related outcomes.[47–49] Recent efforts have attempted to measure cellular age through metabolomics, which involve characterizing metabolites using mass spectroscopy.[50] Given the growing population of older adults, significant emphasis has been placed on the science of aging, and advances in this field will allow better characterization of the cellular age of patients, which may play an important role in understanding physiological reserve. In turn, these data will likely play an increasing role in surgical risk stratification, and thus neurosurgeons seeking to treat adult spinal deformity are well poised to utilize these tools since surgical plans can be tailored based on risk.

There are several limitations to this study, primarily related to small sample size. However, this is a pilot study involving a novel paradigm that utilizes biological or cellular age in a cohort of patients undergoing complex spine surgery. We observed a trend between high comorbidity scores and complications. However, other high-risk surgical characteristics such as severe frailty and use of 3CO were not associated with higher rates of postoperative complications, likely due to the small sample size.

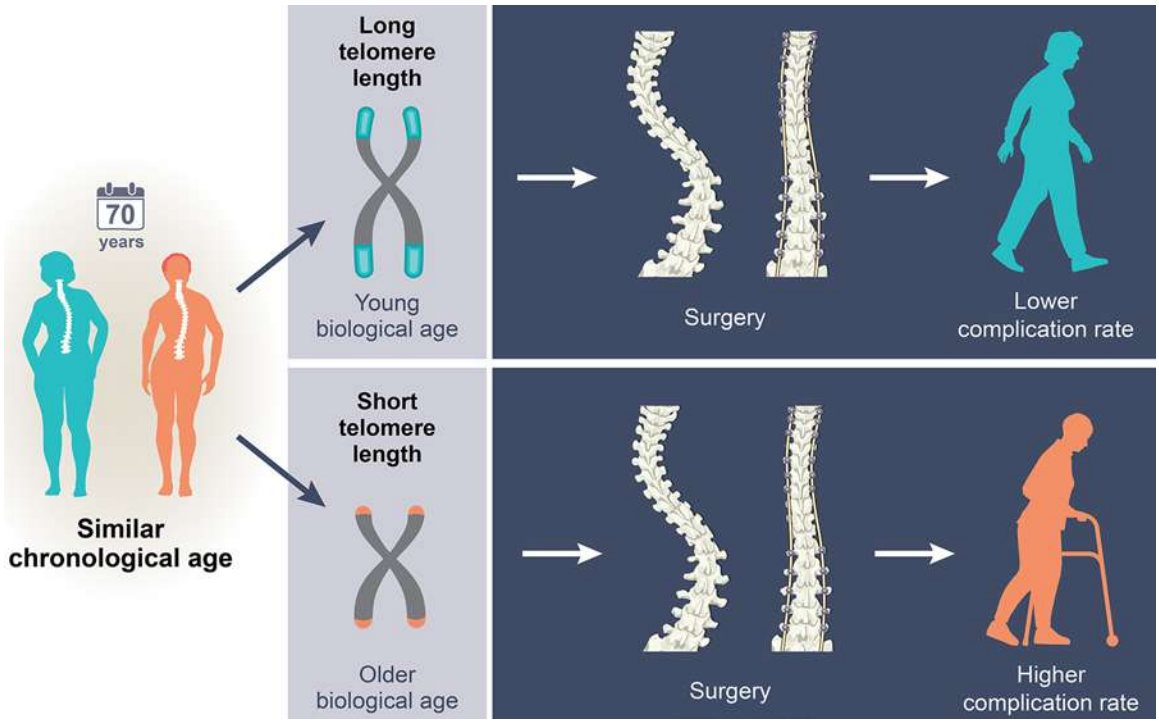

FIG. 1. Potential effect of biological age on patient complications after spinal deformity surgery. Despite similar baseline demographic and surgical variables, patients with shorter telomere length, or older biological/cellular age, may be at increased risk of postoperative complications. © Kenneth X. Probst, published with permission. Figure is available in color online only.

Furthermore, given the small cohort, we included any complication (medical or surgical) with varying degrees of severity, so the results must be interpreted accordingly.

In summary, we present what is to our knowledge the first study of telomere length in adult spinal deformity surgery. We found that telomere length was significantly shorter among patients who developed a postoperative complication despite no difference in chronological age. We were limited by a small cohort size and cannot yet use telomere length alone to predict perioperative risk; however, this pilot study provides compelling data to support further investigation of the role of biomarkers of aging in surgical risk stratification.

Conclusions

Risk stratification will play an increasingly important role in the future of spine surgery. In this pilot study of 43 adult spinal deformity patients, we identified significantly shorter telomere length among patients with postoperative complications, despite no significant difference in chronological age. Comorbidity burden also trended toward a significant effect on postoperative complications. Larger prospective studies are needed; however, these data provide impetus to investigate the integration of biomarkers of aging into contemporary risk stratification tools.

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Supplemental Information

Previous Presentations

This work was presented as a podium presentation at the annual meeting of the Scoliosis Research Society on September 24, 2021, in St. Louis, Missouri.

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