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SHORT REPORT
Valvular heart disease

Longer leukocyte telomere length is associated with myeloid inflammation and increased mortality after transcatheter aortic valve replacement

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Aims Inflammatory activation of leukocytes may limit prognosis of patients (pts) with severe aortic valve stenosis (AS) undergoing transcatheter aortic valve replacement (TAVR). Leukocyte telomere length (LTL) is a marker of proliferative capacity and inflammatory responsiveness but the impact of LTL on the prognosis in AS remains elusive. The aim of this study was to analyse the association of LTL with inflammatory markers and prognosis of pts undergoing TAVR.

Methods and results LTL was analysed using quantitative real-time PCR in 285 consecutive pts (median age 82 years) undergoing TAVR and correlated with 18-month all-cause mortality. C-reactive protein was significantly elevated in pts with the longest LTL ($P = 0.017$), paralleled by increased procalcitonin (PCT) serum levels ($P = 0.0006$). This inflammatory reaction was accompanied by increased myeloid cells in the highest LTL tertile, mainly a rise in circulating neutrophils ($P = 0.0025$) and monocytes ($P = 0.01$). Multivariate analysis revealed LTL (HR 2.6, 95%CI 1.4–5.1, $P = 0.004$) and PCT levels (HR 4.3, 95%CI 1.7–11.0, $P = 0.003$) as independent predictors of mortality.

Conclusions Longer LTL is associated with increased mortality after TAVR. This might be explained by enhanced proliferative capacity of cells resulting in myeloid and systemic inflammation. Our findings suggest that targeting the specific inflammation pathways could present a novel strategy to augment survival in selected patients with degenerative aortic stenosis.

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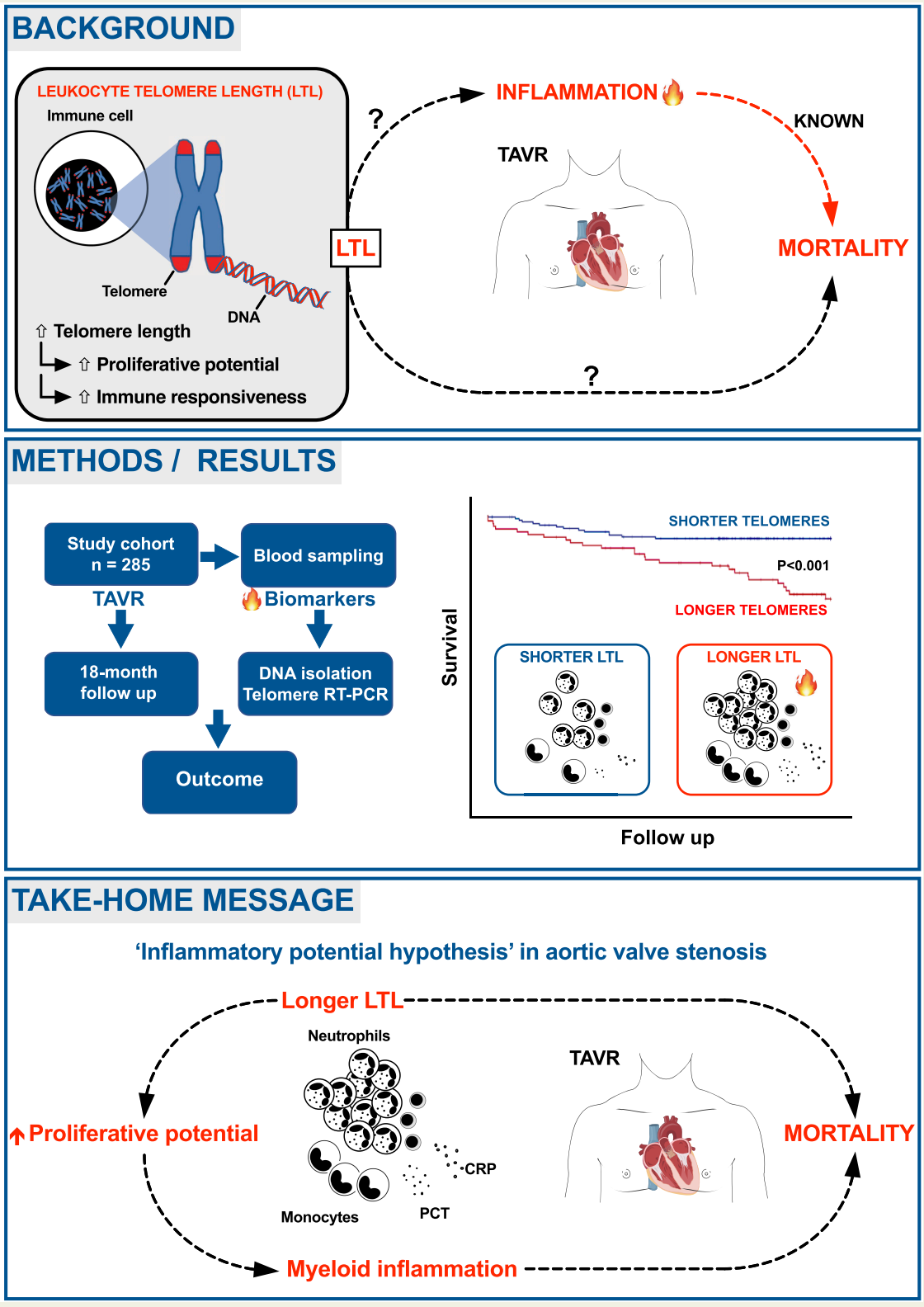
Graphical Abstract



Keywords TAVR • Telomeres • Leukocytes • Inflammation

Introduction

Transcatheter aortic valve replacement (TAVR) has become a standard treatment option in the management of elderly patients with severe aortic valve stenosis (AS).[1] However, we could previously show that excessive bloodborne inflammation, characterized by activation of circulating leukocytes, may limit patients' prognosis.[2,3] Understanding mechanisms of inflammatory aggravation in the aged population with AS may facilitate development of therapeutic interventions to confer prognostic benefit in patients undergoing TAVR. One of the hallmarks of aging are changes in the protecting DNA ends of chromosomes, so called telomeres. Telomeres shorten during every cell division and have been therefore regarded as a cellular clock. Within the hematopoietic system, telomere shortening may lead to proliferative impairment and cellular senescence, whereas longer telomeres maintain cell division activity and inflammatory responsiveness of immune cells.[4] The association of telomere length with systemic inflammation and prognosis in elderly patients with degenerative aortic stenosis undergoing TAVR remains elusive.[5] In the present study, we assessed telomere length in circulating leukocytes and its impact on 18-month survival in patients following TAVR.

Methods

Patient cohort and blood sampling

285 consecutive patients with severe aortic valve stenosis undergoing TAVR were enrolled at the Heart Center Bonn between June 2016 and August 2017. The median follow-up time of the study patients was 430 (IQR: 364–570) days. The study flow diagram is shown in *Figure 1A*.

All patients gave written consent and the study was approved by the local ethics committee (Ethikkommission der Medizinischen Fakultät der Rheinischen Friedrich-Wilhelms-Universität Bonn, REC ref. 187/19 and 077/14). Whole blood samples were drawn directly prior to TAVR procedure, along with serological diagnostics. EDTA blood aliquots were frozen at −80°C, and stored until use.

DNA isolation and telomere length analysis

DNA was isolated from blood samples using QIAgen QIAamp® 96 DNA Blood Kit (Qiagen; Cat. No: 51161). Peripheral blood mean leukocyte telomere length (LTL) was assessed as abundance of telomeric template vs. a single copy gene (36B4); following a previously published quantitative real-time PCR method[6] with some modifications at the Newcastle University BioScreening Core Facility. Samples were analysed in triplicate. The intra-assay coefficient of variation was 4.19% while the inter-assay coefficient of variation was 3.97%. Samples in the top 5% or the bottom 5% of the distribution, as well as those samples with no valid data on first run, were reassessed.

Statistical analysis

All data are presented in *n* (%) or median and interquartile range (IQR), where appropriate. The baseline characteristics of the participants are presented in tertiles, and statistical comparison conducted by the Kruskal-Wallis test or chi-square test for continuous or categorical variables, respectively. For identification of independent predictors all variables were subjected to a decision tree algorithm (DTA) implemented in SPSS V. 26. For estimation of hazard ratios, DTA-identified independent predictors were further included in a multivariate Cox regression model. Log-rank test was used to calculate significance between Kaplan-Maier curves. A *P*-value of less than 0.05 was considered significant. All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences, version 26.0, IBM, USA).

Results

Patient population

We included 285 consecutive TAVI patients with a median age of 82 [IQR 78–85] years in our prospective study, well balanced between genders (49% male; *Table 1*). As to be expected, this population had a high proportion of cardiovascular risk factors, including diabetes (26%) and dyslipidemia (71%). Patients clearly showed a phenotype of vascular ageing by displaying a frequent history of coronary artery disease (60%), previous stroke (10%), peripheral artery disease (32%) and carotid arterial disease (31%). Cardiac function was impaired as reflected by slightly reduced left ventricular ejection fraction (58 [48–65]%) but most noticeable high NT-proBNP serum levels of 2387 [1030–5588] pg/mL, suggesting also heart failure with preserved ejection fraction in many patients. Distribution of baseline parameters was evenly spread among all three LTL tertiles, with the exception of gender. Here, surprisingly, male gender was represented stronger in the highest compared to lowest LTL tertile (60% vs. 41%, $P = 0.044$).

Peri-procedural parameters

Aortic valve area prior to TAVI was as expected around 0.7 cm^2 across all TL tertiles. While implanted valve types differed significantly between the groups, complications at 30 days were all similar, as was antiplatelet and anticoagulation therapy at discharge (data not shown).

Pre-procedural inflammatory markers and leukocyte populations

Platelets did not differ between tertiles, nor did basophils or eosinophils. Interestingly, C-reactive protein was significantly elevated in the patient group with the longest leukocyte telomeres (6.0 [2.2–12.5] vs. 3.8 [1.7–10.6] mg/L), paralleled by increased procalcitonin serum levels (0.08 [0.06–0.11] vs. 0.06 [0.04–0.09] ng/L). This inflammatory reaction was accompanied by increased myeloid cells in the highest TL tertile, mainly a 20% rise in circulating neutrophils (5.2 [4.2–6.1] vs. 4.3 [3.5–5.5] cells/nl) and in monocytes (0.73 [0.58–0.87] vs. 0.65 [0.53–0.79] cells/nl, *Table 2*).

Telomere length and mortality

Decision tree algorithm (DTA) model revealed only leukocyte telomere length (above the identified cut-off value of 2764 base pairs) and procalcitonin (above the calculated cut-off value of 0.6 ng/ml) as independent predictors of mortality (*Figure 1B*). While there was also a univariate association between gender and mortality ($P = 0.042$), the subsequently performed multivariate Cox regression confirmed the dichotomized LTL (HR 2.6, 95% CI 1.4–5.1, $P = 0.004$) and PCT (HR 4.3, 95% CI 1.7–11.0, $P = 0.003$) values to be independent predictors. When dividing the population in low and high LTL, those patients with LTL above 2764 base pairs clearly demonstrated increased mortality. At 540 days follow-up survival in the high LTL group was only 76% compared to 92% for those with LTL ≤ 2764 base pairs (Log-rank $P < 0.001$, *Figure 1C*). Patients at risk (high

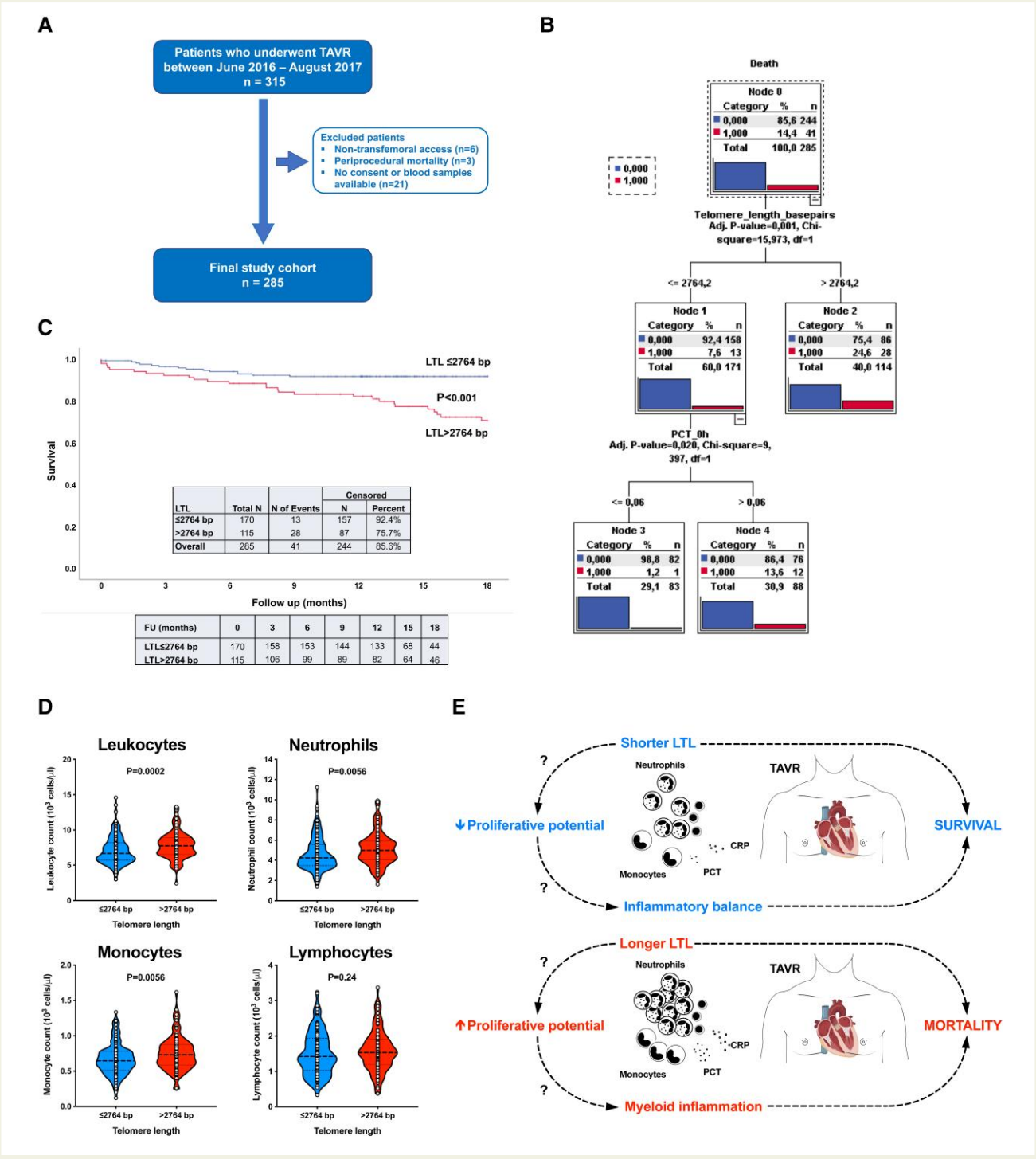


Figure 1 (*A*) Study flow chart. (*B*) Decision tree algorithm (DTA) applied for the identification of predictors of death after TAVR. Decision node category counts are visualized as bar charts. The algorithm allows identifying the strongest predictors for event of interests and defining cut-offs in continuous cofounder and then estimation of event probability depending on value of the variable in regard to defined cut-off. On the block chart, LTL of 2764 bp (as identified by the algorithm) is shown as a first node. The patients with LTL >2764 had poor prognosis and the patients with LTL ≤2764 were further distinguished in two arms, depending on serum procalcitonin (PCT) levels. These two variables were revealed to be predictive and were further included in Cox Regression for estimation of Hazard Ratio. (*C*) Kaplan-Maier curves (crude analysis) by telomere length cutoff showing significantly increased all-cause mortality in patients with longer telomeres (>2764 base pairs, bp). (*D*) Violin plots showing increased counts of myeloid cells (neutrophils and monocytes) with patients at higher risk (LTL above cutoff). (*E*) 'Inflammatory potential hypothesis' postulating an increased myeloproliferative potential and enhanced myeloid inflammation, which might contribute to increased mortality post TAVR in patients with longer LTL.

Table 1 Patient baseline (pre-TAVR) characteristics according to telomere length tertiles

		Leukocyte telomere length			
	Total ($n = 285$)	**1st tertile 2257 bp [2187–2337] ($n = 95$)**	**2nd tertile 2661 bp [2567–2757] ($n = 95$)**	**3rd tertile 3150 bp [2990–3396] ($n = 95$)**	***P* value**
Age (years)	82 [78–85]	81 [78–85]	82 [79–85]	82 [76–85]	0.69
Male gender, *n* (%)	140 (49.1)	39 (41.1)	45 (47.4)	56 (60.0)	0.044
Body mass index (kg/m^2)	26.4 [23.8–29.4]	26.0 [23.2–28.9]	26.5 [24.0–29.6]	26.8 [24.0–29.9]	0.34
Diabetes, *n* (%)	75 (26.3)	28 (29.5)	25 (26.3)	22 (23.2)	0.61
Dyslipidemia, *n* (%)	203 (71.2)	65 (68.4)	67 (70.5)	71 (74.7)	0.68
Hypertension, *n* (%)	240 (84.2)	74 (77.9)	85 (89.5)	81 (85.3)	0.09
Hemodialysis, *n* (%)	8 (2.8)	2 (2.1)	3 (3.2)	3 (3.2)	0.88
Carotid disease, *n* (%)	89 (31.2)	23 (24.2)	36 (37.9)	30 (31.6)	0.14
Peripheral arterial disease, *n* (%)	92 (32.3)	24 (25.3)	38 (40.0)	30 (31.6)	0.09
Coronary artery disease, *n* (%)	172 (60.4)	57 (60.0)	55 (57.9)	60 (63.2)	0.76
Prior PCI, *n* (%)	87 (30.5)	27 (28.4)	32 (33.7)	28 (29.5)	0.71
Previous myocardial infarction, *n* (%)	25 (8.8)	4 (4.2)	12 (12.6)	9 (9.5)	0.12
Prior cardiac surgery, *n* (%)	37 (13.0)	12 (12.6)	15 (15.8)	10 (10.5)	0.55
Atrial fibrillation, *n* (%)	140 (49.1)	47 (49.5)	49 (51.6)	44 (46.3)	0.77
Prior pacemaker, *n* (%)	45 (15.8)	11 (11.6)	17 (17.9)	17 (17.9)	0.39
Previous stroke, *n* (%)	28 (9.8)	7 (7.4)	10 (10.5)	11 (11.6)	0.60
COPD, *n* (%)	40 (14.0)	12 (12.6)	14 (14.7)	14 (14.7)	0.89
Pulmonary artery pressure (mmHg)	32 [20–42]	30 [19–42]	31 [20–40]	33 [20–42]	0.53
Left ventricular ejection fraction (%)	58 [48–65]	59 [47–64]	58 [50–65]	58 [47–65]	0.99
Logistic EuroSCORE (%)	14.2 [8.8–23.2]	11.5 [8.4–22.3]	15.1 [10.1–27.3]	14.9 [8.9–22.9]	0.28
EuroSCORE II (%)	4.4 [2.8–7.2]	4.1 [2.4–7.2]	4.8 [3.6–7.3]	4.1 [2.8–7.1]	0.1
STS score (%)	3.4 [2.3–5.1]	3.0 [2.3–5.0]	3.9 [2.4–5.3]	3.2 [2.0–5.1]	0.09
Laboratory findings					
eGFR (mL/min/1.73m^2)	57.0 [42–70.0]	57.0 [41–70]	52.0 [41–69]	60.5 [45–70]	0.39
NT–proBNP (pg/mL)	2387 [1030–5588]	2387 [1094–6131]	2384 [1049–5160]	2392 [878–5680]	0.99
Albumin (g/L)	39.6 [36.1–42.8]	39.2 [34.6–43.2]	40.8 [37.1–42.9]	38.9 [35.4–41.9]	0.22

LTL) showed significantly increased counts of circulating myeloid cells, both neutrophils (5.0 [4.0–5.9] vs. 4.2 [3.5–5.6] cells/nl, $P = 0.0056$) and monocytes (0.73 [0.58–0.88] vs. 0.65 [0.51–0.78], cells/nl, $P = 0.0056$, high vs. low LTL, respectively, *Figure 1D*).

Discussion

This is the largest study to date using advanced telomere length measurement methodology, intented to shed more light on the unclear relationship between LTL and mortality after TAVR.[5] Our results find LTL measured directly prior to TAVR to be an independent predictor of survival at 18 months post intervention. Although at first glance this may seem a surprising result, given that individuals with shorter leukocyte telomere length have a higher risk for coronary events as well as death from infections,[4] patients undergoing TAVR represent a very different patient population. They are typically septua- or octogenarians, where telomere length shortening over time has been shown to be associated with a lower risk of cardiovascular mortality.[7] In fact, studies in murine models showed that very short telomeres can be protective from atherosclerosis,[8] presumably secondary to the lack of myeloid cell proliferation which is a hallmark of this pro-inflammatory disease. However, the translation of these results into human cardiovascular disease remains unclear, given profound differences in telomere biology between humans and mice.

Shortened peripheral blood telomere length is a surrogate of mainly two processes in the leukocyte compartment: First, an age-dependent decline of TL in all leukocyte populations, triggered by a loss of TL in their stem- and progenitor cells. Secondly, short LTL can represent a shift in leukocytes from subpopulations with long telomeres (myeloid cells) to those with shorter telomeres (in particular memory lymphocytes).[9]

In our case, patients in the highest TL tertile had in fact a much higher proportion of neutrophils and monocytes, accompanied by raised C-reactive protein and procalcitonin. Hence, the most likely explanation for our findings is that patients with subtle but specific pre-operative activation of a pro-inflammatory cascade, potentially the inflammasome, display adverse outcome following TAVR. Therefore TL seems to function as a surrogate parameter in these patients for enhanced myeloid inflammation ('Inflammatory potential hypothesis', *Figure 1E*). Recently, an activation of monocytes has been postulated as a novel, shear-stress related mechanism of pathology in

Table 2 Baseline (pre–TAVR) inflammatory markers according to telomere length tertiles

	Total (n = 285)	Leukocyte telomere length			*P* value
		1st tertile 2257 bp [2187–2337] (*n* = 95)	2nd tertile 2661 bp [2567–2757] (*n* = 95)	3rd tertile 3150 bp [2990–3396] (*n* = 95)	
Leukocytes (10^3 cells/µl)	7.10 [5.98–8.54]	6.52 [5.56–7.79]	7.20 [5.87–8.79]	7.82 [6.56–9.05]	0.0005
Neutrophils	4.49 [3.65–5.80][a]	4.09 [3.37–5.26][b]	4.41 [3.55–5.81][c]	5.19 [4.19–6.12][d]	0.0025
Lymphocytes	1.48 [1.11–1.91][a]	1.40 [0.93–1.90][b]	1.72 [1.18–2.06][c]	1.47 [1.12–1.76][d]	0.037
Monocytes	0.67 [0.56–0.82][a]	0.64 [0.49–0.76][b]	0.68 [0.56–0.82][c]	0.73 [0.58–0.87][d]	0.01
Eosinophils	0.18 [0.09–0.27][a]	0.19 [0.68–0.27][b]	0.17 [0.09–0.27][c]	0.18 [0.12–0.27][d]	0.72
Basophils	0.04 [0.03–0.06][a]	0.04 [0.02–0.05]	0.04 [0.03–0.06]	0.04 [0.03–0.06]	0.3
Platelets (10^3 cells/µl)	210 [176–256]	199 [163–246]	212 [181–259]	216 [179–259]	0.24
C–reactive protein (mg/L)	4.0 [1.7–10.2]	3.8 [1.7–10.6]	3.2 [1.4–8.2]	6.0 [2.2–12.5]	0.017
Procalcitonin (ng/mL)	0.08 [0.05–0.1]	0.06 [0.04–0.09]	0.08 [0.05–0.10]	0.08 [0.06–0.11]	0.0006

[a]data available from 229 pts.
[b]1st tertile *n* = 74 pts.
[c]2nd tertile *n* = 76 pts.
[d]3rd tertile *n* = 79 pts.

patients with severe aortic valve stenosis, also pointing out the beneficial anti-inflammatory effects achieved by the TAVR procedure.[10] Nevertheless, we and others have shown recently that despite successful valve replacement, a considerable number of patients might still remain at risk of adverse outcomes when harbouring an inflammatory background, potentially co-driven by specific CHIP (clonal haematopoiesis of indeterminate potential) mutations[3,11] the occurrence of which might also be triggered by long LTL.[12]

Our current findings add more evidence to the association between excess inflammation and prognosis after TAVR, but also suggest that a clinical trial targeting a specific myeloid inflammation pathway, possibly by interleukin-1-beta antagonists, could present a novel strategy to augment survival in those patients with persistent inflammation.

Lead author biography

Jedrzej Hoffmann, M.D., Following Medical School, I completed my doctoral degree at Frankfurt University, investigating telomere length in different leukocyte subpopulations in patients with heart failure. I further pursued my speciality training as Cardiology Registrar in Bad Nauheim and Frankfurt to receive board certification in 2018. In addition to the clinical training, I was involved in several postdoctoral research projects with focus on immunosenescence and leukocyte activation in cardiovascular disease. As a CMR Fellow, I continue my commitment to cardioimmunology by investigating inflammatory markers and cardiac imaging biosignatures to improve personalized prognostics and therapeutic targeting in myocardial remodelling and inflammation.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Conflict of interest: M.V.-N. and J.-M.S. report consultancy activities for Abbott, Boston Scientific, Edwards, and Medtronic. All other authors have no conflicts of interest related to the subject of the article.

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