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Telomere Length Is Associated with Increased Risk of Cardiovascular Events in Patients with End-Stage Kidney Disease on Hemodialysis

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Keywords
Aging · Chronic kidney disease · End-stage kidney disease · Hemodialysis · Cardiovascular disease · Telomere length

Abstract

Introduction: Patients with chronic kidney disease, especially those with end-stage kidney disease (ESKD) on hemodialysis (HD), are at increased risk for cardiovascular disease (CVD), including myocardial infarction and ischemic stroke. A shortening in telomere length, as a parameter for accelerated vascular aging, is an established biomarker for CVD in the general population. We aimed to elucidate the role of telomere length in ESKD patient on HD and its association with cardiovascular outcomes. ***Methods:*** Telomere length was measured in a prospective population-based cohort study of prevalent HD patients. DNA was isolated from whole blood, sampled at baseline, and analyzed for telomere length via a qPCR-based approach. The risk for the occurrence of the independently adjudicated three-point major adverse cardiovascular event outcome (myocardial infarction, ischemic stroke, and cardiovascular death) was statistically analyzed considering the competing risk of non-cardiovascular death. ***Results:*** In the cohort of 308 patients with ESKD (115 [37.3%] women, median [25th–75th percentile] age: 67.0 [56.8–76.0]), the median telomere length was 1.51 kb (25th–75th percentile 0.6–3.2 kb). The 3P-MACE outcome occurred with an incidence rate of 9.4 per 100 patient-years. Patients with longer telomere length more frequently had vascular nephropathy compared to patients with shorter telomere length. Interestingly, patients in the highest quartile of telomere length had a 1.8-fold increased risk for 3P-MACE (95% CI: 1.051–3.201, p = 0.033), after multivariable adjustment for age, history of stroke, myocardial infarction, venous thromboembolism, presence of heart valve replacement, atrial fibrillation, smoking, anticoagulation, or immunosuppressive use. ***Conclusion:*** Surprisingly, in this high-risk cohort of patients with ESKD on HD, longer telomere lengths were associated with increased risk of cardiovascular events.

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Introduction

In patients with chronic kidney disease (CKD), especially in those with end-stage kidney disease (ESKD) on hemodialysis, cardiovascular disease (CVD) is the major cause of morbidity and mortality. The prevalence of CVD in patients on chronic HD is greater than 50%, and the risk of cardiovascular death is 20-fold higher than in the general population [1, 2]. Chronic oxidative stress, chronic volume overload, inflammation, and other aspects of uremic milieu, alongside a high prevalence of comorbidities, including diabetes, hypertension, congestive heart failure, atrial fibrillation, and atherosclerosis, are likely reasons for the high prevalence of CVD and its associated mortality in this patient population [2].

The impaired kidney function, in patients with ESKD on HD, has a central role in an accelerated aging process. The combination of stressors, compounded by oxidative stress, hyperphosphatemia, inflammation, and defective antiaging mechanisms, together with the uremic milieu forms an allostatic overload, leading to a mismatch of biological and chronological aging and further to a gradual vascular integrity loss resulting in early vascular aging [3]. This results in a vascular smooth muscle cell phenotype underlying an increases cardiovascular risk and atherosclerosis [4].

Biological aging may be determined by analyzing the DNA methylation, mitochondrial DNA copy number, histone modification, and telomere length [5–7]. Telomere length is a well-known biomarker and represents the capacity of replication and the cumulative damage to the genome of somatic cells [8–10]. Telomeres are conserved tandem repeats at chromosomal ends and are influenced by several factors, like inflammation, lifestyle factors, and oxidative stress [11]. Furthermore, telomere length shortens with age, more precisely, in each somatic cell division cycle by 50–200 bp through the incomplete synthesis of the lagging strand. When telomeres reach a critically short length, cellular senescence and cell cycle arrest are initiated affecting the lifespan of an individual, which contributes to certain age-related and degenerative diseases, like CKD [5, 9–13]. The aim of our study was to elucidate the role of telomere length, as a biomarker for biological aging, and its association with cardiovascular outcomes in patients with ESKD on HD.

Materials and Methods

Study Cohort

The current analysis was performed within the framework of the Vienna Investigation of Atrial Fibrillation and Thromboembolism in Hemodialysis patients (VIVALDI) study, a prospective population-based cohort study, which has been described in detail previously [14]. Briefly, patients with ESKD on maintenance HD and aged 18 years or older were eligible for inclusion and were recruited between April 2014 and July 2015. Exclusion criteria were pregnancy, suspected pregnancy, breastfeeding, hospitalization at the time of enrollment, or incapacity of consenting. In total, the VIVALDI study includes a cohort of 625 patients with ESKD on HD, and participants were prospectively followed for a maximum of 1,350 days. Whole blood samples for DNA isolation were available from 308 patients. We only included samples where whole blood samples were available, DNA isolation succeeded, and were without impurities, and qPCR approach obtained more than single read for telomere length. All study participants provided written informed consent, and the study protocol was approved by the Local Ethics Committees in Vienna (EC vote 1146/2014 and EK-14-099-0614), and the study was conducted in accordance with the Declaration of Helsinki and its later amendments.

Outcomes

A classical three-point major adverse cardiovascular event (3P-MACE) outcome of myocardial infarction, ischemic stroke, and cardiovascular death was prospectively recorded through patient interviews, chart reviews, and consultation with treating nephrologists. Outcomes were independently adjudicated by specialists in cardiology, vascular medicine, and neurology. The mortality outcome was cross-referenced with the Austrian death registry.

Blood Sampling

Blood samples were drawn from patients by atraumatic and sterile antecubital venipuncture in plasma vacuum tubes containing 0.129 mmol/L sodium citrate before commencing a HD session. Samples were processed within 1 h of blood draw and stored accordingly at −20°C until measurement.

DNA Isolation

The DNA was isolated from whole blood samples with the Maxwell automated system and its respective Blood DNA Kit (Promega Maxwell RSC Blood DNA Kit AS1400).

Measurement of Average Human Telomere Length

The average telomere length was measured with a quantitative polymerase chain reaction (qPCR) based method from ScienCell (AHTLQ #8918). In brief, two primer sets were used, a telomere primer to determine the telomere sequence and the single copy reference (SCR) primer set to determine a 100 bp-long region on human chromosome 17 serving as normalization reference. qPCR

Table 1. Distribution and frequency of patient characteristics among patients with long or short telomere lengths (cutoff median 1.51 kb)

	Total cohort (N = 308)	Telomere length below the 75th percentile at 3.227 kb (N = 231)	Telomere length above the 75th percentile at 3.227 kb (N = 77)	p value*
Age, median (IQR)	67 (56.4–76)	68 (57–76)	65 (53–74)	0.241
Male sex, %	193 (62.7)	141 (61.0)	52 (67.5)	0.308
BMI, median	24.7 (22.2–28.8)	24.6 (22.4–28.6)	26.0 (21.8–30.0)	0.614
Cumulative time on hemodialysis, median, years	3 (1–6)	2.7 (1.0–6.0)	3 (1.0–5.3)	0.567
History of kidney transplant	52 (16.9%)	37 (16.0)	15 (19.5)	0.482
Immunosuppressive use	22 (7.1%)	16 (6.9)	6 (7.8)	0.798
Etiology of ESKD, *n* (%)				
Diabetic NP	72 (23.4)	55 (23.8)	17 (22.1)	0.756
Vascular NP	63 (20.5)	37 (16.0)	26 (33.8)	0.001
Glomerulonephritis	37 (12.0)	28 (12.1)	9 (11.7)	0.919
Atrophic NP	36 (11.7)	32 (13.9)	4 (5.2)	0.041
Cystic nonhereditary NP	22 (7.1)	17 (7.4)	5 (6.5)	0.798
Hereditary NP	18 (5.8)	16 (6.9)	2 (2.6)	0.161
Nephrectomy	11 (3.6)	6 (2.6)	5 (6.5)	0.111
Toxic NP	8 (2.6)	8 (3.5)	0 (0)	0.098
Other or unknown causes	41 (13.3)	32 (13.9)	9 (11.7)	0.628
Comorbidities, *n* (%)				
History of stroke or TIA	61 (19.8)	48 (20.8)	13 (16.9)	0.458
History of myocardial infarction	44 (14.3)	29 (12.6)	15 (19.5)	0.133
Coronary artery disease	118 (38.3)	86 (37.2)	32 (41.6)	0.499
Artificial heart valve	22 (7.1)	17 (7.4)	5 (6.5)	0.798
History of VTE	33 (10.7)	20 (8.7)	13 (16.9)	0.043
Peripheral artery disease	94 (30.5)	76 (32.9)	18 (23.4)	0.116
Diabetes	114 (90.3)	85 (36.8)	29 (37.7)	0.892
Hypertension	278 (90.3)	208 (90.0)	70 (90.9)	0.824
Congestive heart failure	90 (29.2)	71 (30.7)	19 (24.7)	0.311
Cancer history or active	78 (25.3)	57 (24.7)	21 (27.3)	0.650
Current and past smokers	137 (44.5)	102 (44.2)	35 (45.5)	0.843
History of major bleeding	25 (8.1)	18 (7.8)	7 (9.1)	0.718
Anticoagulation use	72 (23.4)	54 (23.4)	18 (23.4)	0.999

Immunosuppressive agents including tacrolimus, sirolimus, mycophenolate mofetil, ciclosporin, azathioprine, and prednisolone. *p value calculated for comparison of subgroups short compared long telomere distribution among patient characteristics using Mann-Whitney U test.

was conducted on the Bio-Rad CFX384 Real-Time System using equivalent software. For referencing, a genomic DNA samples with known telomere length was used to calculate the absolute telomere length of the samples. The following cycling conditions were used: denaturation at 95°C for 10 min; 36 cycles of 95°C for 20 s and 52°C for 20 s and 65°C for 5 s and 95°C for 5 s. Samples were run in duplicates, and the delta C_T method was used to calculate results. The relation to reference genomic DNA results in the calculated average telomere length. Results are given in kilobase (kb) per chromosome end.

Statistical Analysis

Statistical analyses were calculated with the statistical package SPSS 27 for Windows® (IBM, NY, USA) and STATA (Version 15.1; STATA Corp., College Station, TX, USA). Summary of the baseline characteristics are listed using descriptive statistics (percentages, frequencies, median, interquartile range). Normality was calculated with the Shapiro-Wilk test. Between-group comparisons of continuous variables were analyzed using the Mann-Whitney U test or Student's t test, and between-group comparisons of categorical variables were tested

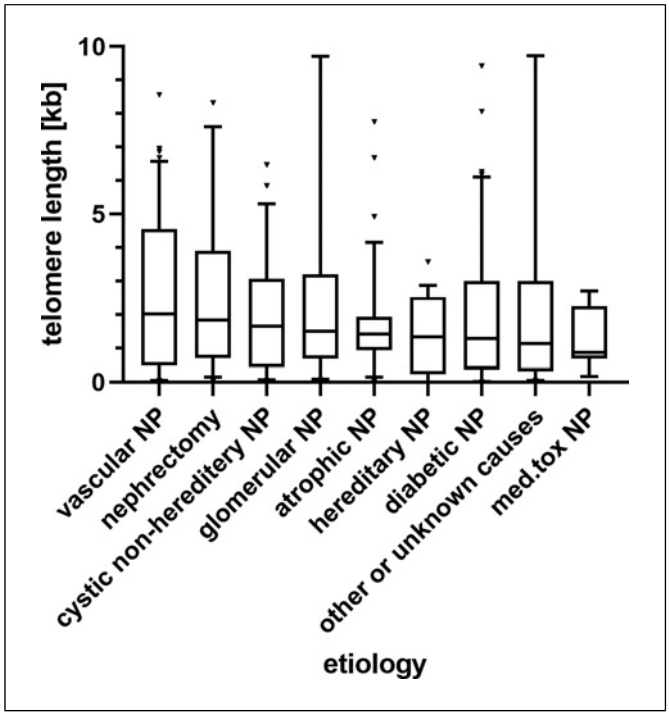

Fig. 1. Distribution of telomere length in patients according to nephropathy etiologies. NP, nephropathy; med.tox. NP, toxic nephropathy.

using χ^2 test. For analysis of the association of telomere length with outcome, we categorized telomere length into long telomeres above the 75th percentile, as well as a continuous variable, and dichotomized at the median, to reflect the distribution in this cohort. Significance level was set to a p value (p) ≤ 0.05. For the risk of outcome occurrence, we computed the univariable subdistribution hazard ratio (SHR) and 95% confidence interval (95% CI), using competing risk regression according to Fine and Gray and considering non-cardiovascular death as the competing event. Covariables for multivariable adjustment were selected in a stepwise backward regression model among known canonical risk factors for cardiovascular events and immunosuppressive treatment for its known effect on telomere length.

Results

The patient cohort consists of 308 patients with a median age of 67 (25th–75th percentile 56.4–76) years (193 males [62.7%] and 115 females [37.3%]). The distribution and frequency of patient characteristics are described in Table 1. The median telomere length was 1.5 kb (25th–75th percentile 0.6–3.2 kb). Patients with shorter telomeres (cutoff at 75th percentile 3.2 kb) were older (68 years vs. 65 years), albeit not statistically significant (p = 0.241) (Table 1). Chronological age and telomere length were inversely correlated with a correlation coefficient (r) of −0.117 (p = 0.040). Patients with longer telomere length more frequently had vascular nephropathy compared to patients with short telomere length (N = 26 [33.8%] vs. N = 37 [16.0%], p = 0.001; Table 1). The distribution of telomere length according to etiology of nephropathy is shown in Figure 1. Patients with vascular nephropathy had the longest telomere lengths.

Patients with a short telomere length less frequently had a history of VTE compared to patients with a long telomere length (13 [16.9%] vs. 20 [8.7%], p = 0.043). Other comorbidities such as history of stroke or myocardial infarction, coronary artery disease, or diabetes were equally distributed with regard to on the telomere length.

Outcomes

During a median observation time of 1,238 (25th–75th percentile: 1,167–1,299) days, 3P-MACE occurred in 65 (21.1%) patients, with 18 (5.8%) patients having myocardial infarction, 23 (7.5%) ischemic stroke, and 36 (11.7%) patients died of cardiovascular death. The incidence rate of 3P-MACE was 9.4 per 100 patient-years. All-cause death was recorded in 124 patients (40.3%). Frequency, incidence rates, and case-fatality rates of outcomes during the prospective observation period are shown in Table 2.

Association of Telomere Length and Prospective Outcomes

A long telomere length, defined as a telomere length above the 75th percentile (at 3.2 kb) of the study cohort, was borderline significantly associated with an increased risk of occurrence of the 3P-MACE outcome (SHR 1.654, 95% CI: 0.991–2.762), p = 0.054; Table 3) in univariable competing risk regression analysis. Adjusted for age, history of stroke, myocardial infarction, or venous thromboembolism, presence of heart valve replacement, atrial fibrillation, smoking, anticoagulation, or immunosuppressive use, patients with long telomere length had 1.8-fold increased risk of 3P-MACE (95% CI: 1.05–3.21, p = 0.033; Table 3; Fig. 2a). This association was strongly influenced by the increased risk of myocardial infarction in patients with long telomere lengths. Patients with long telomere length (above the 75th percentile) had a 3.3-fold increased risk of myocardial infarction (95% CI: 1.35–8.24, p = 0.009; Fig. 2b). The risk for occurrence of ischemic stroke, CV death, and all-cause death was not significantly increased with longer telomere length

Table 2. Frequency and incidence rates of prospective outcomes

	Frequency	Incidence rate per 100 patient years
3P-MACE	65 (21.1%)	9.4
Myocardial infarction	18 (5.8%)	2.5
Ischemic stroke	23 (7.5%)	3.2
CV death	36 (11.7%)	4.9
All-cause death	124 (40.3%)	17.0

(Table 3; Fig. 2c-e). Shorter telomere lengths were not associated with occurrence of cardiovascular events (Table 3).

Discussion

In this prospective, population-based cohort study, we observed that a longer telomere length (defined as telomere length above the 75th percentile of the distribution in the total study population) was associated with an increased risk of occurrence of the 3P-MACE outcome. The strongest association was observed with myocardial infarction with a 3.3-fold increased risk in patients with a longer telomere length. The association between telomere length and 3P-MACE was robust after multivariable adjustment to rule out confounders. Overall, our results were unexpected, as ESKD patients are generally perceived as a population with ageing-related, acquired cardiovascular risk.

In most previous studies investigating telomere length and cardiovascular risk, an attrition of telomeres was associated with increased risk of CVD [15–17]. For instance, in the study by Scheller Madrid et al. [15] including 66,618 individuals, shorter telomeres were associated with a higher risk for ischemic heart disease. In contrast to our study cohort, these patients have been recruited from the general population. Other studies, however, did not show a linear association between leukocyte telomere length and the risk of coronary heart disease (CHD) in the general population [18, 19]. Further, Ye et al. [19] demonstrated that there is no linear association between leukocyte telomere length and the occurrence of CHD in the general population. The risk for CHD was elevated for those in the shortest and middle tertile, compared to those in the longest tertile. Interestingly, after adjustment for traditional risk factors, inflammatory markers and demographics, participants with a telomere in the middle tertile of the telomere distribution turned out to have an elevated risk for CHD and those with the shortest tertile had a nonsignificantly elevated risk [19]. In our study, we measured the telomere length in whole blood samples instead of in leukocytes subtypes. In line with our findings, the effect of adjusting for confounders in this general population study reveals that patients with the shortest telomere lengths may not have the highest cardiovascular risk.

A reason for unexpected results of the association of a long telomere length with an increased risk of 3P-MACE in our cohort of patients with ESKD on HD could be that this patient population is not homogenous in their medical history, leading up to ESKD. Particularly, patients with vascular nephropathy in our cohort had the longest median telomere length (2.02 kb, 25th–75th percentile 0.61–4.98 kb) (Fig. 1). In comparison, the group of patients with diabetic nephropathy, the underlying etiology of ESKD in most patients, had the shortest median telomere lengths (1.39 kb, 25th–75th percentile 0.37–3.05 kb). Further, patients with a history of long-term uncontrolled diabetes or hypertension, ending in advanced kidney failure, likely have a different cardiovascular risk profile compared to patients with glomerulonephritis or congenital kidney diseases, who generally have fewer comorbidities and accumulated CHD disease burden.

While we found an expected relationship between increasing age and decreasing telomere length, although with weak correlation (correlation coefficient (r) −0.117, p = 0.040), there are some possible explanations, why short telomeres were not associated with increased cardiovascular risk. In general, CKD patients suffer from chronic inflammation and oxidative stress, leading to an overall shortening of telomeres [20, 21]. Patients with shorter telomeres may have developed an inherent resilience or better adaption to CKD-related stressors, leading to increased survival on HD and lowering the cardiovascular risk. Furthermore, there might be differences in telomere shortening and regenerative capacity of telomerase as well as potential compensatory mechanism between CKD patients and the general population. Moreover, the presence of uremic toxins can induce cellular senescence without shortening of telomeres but with increased cardiovascular risk [21–24]. This summarizes the need for further research

Table 3. Association of telomere length with occurrence of outcomes

	3P-MACE		Myocardial infarction		Ischemic stroke		CV death		All-cause death	
	univariable SHR (95% CI)	multivariable SHR (95% CI)[a]	univariable SHR (95% CI)	multivariable SHR (95% CI)[a]	univariable SHR (95% CI)	multivariable SHR (95% CI)[a]	univariable SHR (95% CI)	multivariable SHR (95% CI)[a]	univariable SHR (95% CI)	multivariable SHR (95% CI)[a]
Telomere length above 75th percentile	1.654 (0.991–2.762), $p = 0.054$	**1.834 (1.051-3.201), $p = 0.033$***	**3.150 (1.258-7.889), $p = 0.014$***	**3.336 (1.349-8.244), $p = 0.009$***	1.640 (0.697–3.859), $p = 0.257$	1.933 (0.739–5.057), $p = 0.179$	1.002 (0.474–2.119), $p = 0.995$	1.104 (0.503–2.427), $p = 0.805$	0.901 (0.596–1.361), $p = 0.620$	1.024 (0.676–1.551), $p = 0.911$
Telomere length below 25th percentile	0.770 (0.428–1.387), $p = 0.384$	0.700 (0.389–1.258), $p = 0.233$	0.354 (0.082–1.531), $p = 0.165$	0.350 (0.076–1.603), $p = 0.176$	0.800 (0.297–2.152), $p = 0.658$	0.703 (0.269–1.837), $p = 0.472$	0.972 (0.455–2.075), $p = 0.941$	0.996 (0.461–2.149), $p = 0.991$	0.993 (0.664–1.486), $p = 0.974$	0.932 (0.619–1.403), $p = 0.734$
Telomere length median cutoff	1.237 (0.760–2.013), $p = 0.392$	1.316 (0.782–2.215), $p = 0.301$	2.766 (0.982–7.790), $p = 0.054$	2.709 (0.855–8.584), $p = 0.090$	1.140 (0.503–2.582), $p = 0.754$	1.310 (0.561–3.056), $p = 0.533$	0.828 (0.430–1.595), $p = 0.573$	0.847 (0.434–1.654), $p = 0.627$	0.901 (0.633–1.282), $p = 0.561$	0.991 (0.962–1.419), $p = 0.961$
Telomere length continuous	1.031 (0.972–1.092), $p = 0.309$	1.057 (0.991–1.127), $p = 0.094$	1.073 (0.996–1.156), $p = 0.064$	1.077 (0.991–1.169), $p = 0.081$	1.032 (0.942–1.131), $p = 0.496$	1.071 (0.954–1.203), $p = 0.247$	1.018 (0.932–1.111), $p = 0.696$	1.044 (0.948–1.149), $p = 0.380$	0.987 (0.936–1.040), $p = 0.617$	1.013 (0.960–1.070), $p = 0.632$

[a]Multivariable adjustment for age, history of stroke, myocardial infarction, or venous thromboembolism, presence of heart valve replacement, atrial fibrillation, smoking status, anticoagulation, or immunosuppressive use. *Bold format was used to highlight significant associations ($p < 0.05$).

to focus on the potential for distinct telomere dynamics and compensatory mechanisms in CKD.

As previously reported, shortening of the telomere length and progression of CKD have been suggested to stand in a bidirectional relationship, forming a vicious cycle of accelerated biological aging [25]. A study from Kidir et al. [26] showed an increased telomerase activity in patients with CKD stage 5D. In the study, 120 patients with CKD stage 2–5 were included, and telomerase activity in peripheral mononuclear cells was measured using the telomerase repeated amplification protocol assay. They found that the telomerase activity in peripheral mononuclear cells was positively correlated with the CKD stage. In contrast, a previous study from Zhang et al. [27] revealed that there is no association of telomere length with kidney function. In detail, the authors evaluated the relationship between telomere length and baseline kidney function in a Chinese population. Out of 471 participants with the same age range, the telomere restriction fragment of leukocytes in peripheral blood was analyzed. While telomere length rate was affected by age, there was no association between reduced kidney function and telomere shortening [27]. To enhance the understanding of CKD progression and its association with cardiovascular risk and telomere length, unraveling telomerase function and telomere dysfunctionality mechanisms may be of importance [22, 28].

In search for potential explanations of our observation, we found no significant difference between dialysis vintage and telomere length, which could have been an expected relationship as long-term ESKD and HD dependence would be expected to lead to shortened telomeres. However, we observed that patients with short telomere lengths less frequently had a history of VTE compared to patients with long telomere length. The impact of these findings in perspective to cardiovascular events is difficult to gauge given the small group of patients with this comorbidity. There are currently no data on the association of telomere length and venous thromboembolism in ESKD patients, but the finding that a history of VTE is more common among patients with longer telomeres may go along with our finding of higher risk of 3P-MACE among patients with longer telomeres.

There are some limitations and strengths of our study that we would like to address. The role of telomere length in biological aging may be limited to a surrogate biomarker, influenced by yet unknown confounders, instead of a causal relationship. Further, we did not investigate the telomere length in specific blood components, like leukocytes and platelets, as only whole blood samples stored at −80°C were available. Measuring the telomere length in the subset of leukocytes would allow an analysis in a more

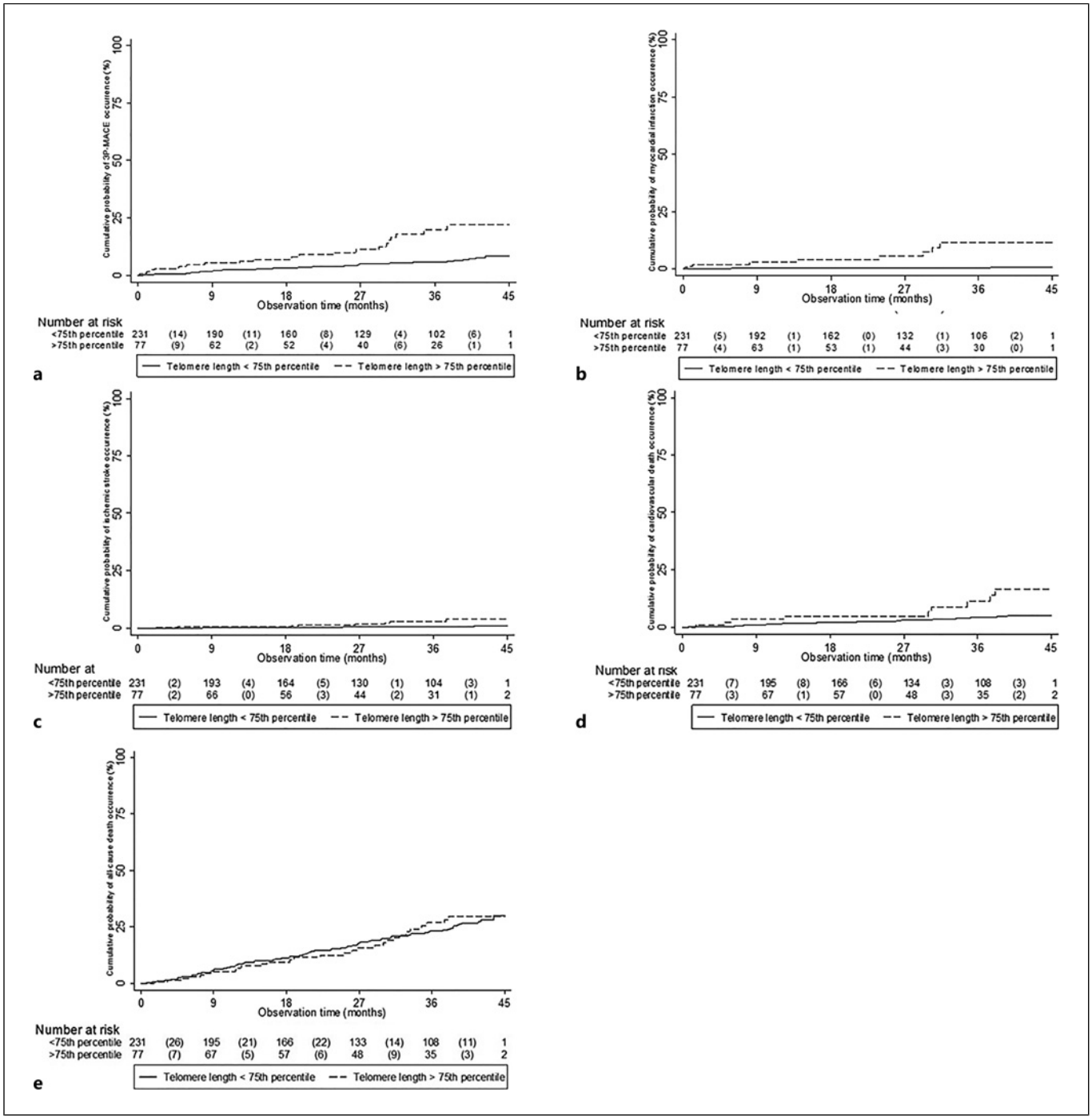

Fig. 2. Cumulative probability of outcome occurrence adjusted for covariable age, history of stroke, myocardial infarction, or venous thromboembolism, presence of heart valve replacement, atrial fibrillation, smoking, anticoagulation, or immunosuppressive use. The solid line denotes the cumulative probability over time in patients with telomere lengths below the 75th percentile, the dashed line patients above the 75th percentile. **a** Cumulative probability of 3P-MACE event occurrence. **b** Cumulative probability of myocardial infarction occurrence. **c** Cumulative probability of ischemic stroke occurrence. **d** Cumulative probability of CV death occurrence. **e** Cumulative probability of all-cause death occurrence.

homogeneous population of cells since the distribution of leukocyte cells can influence the average telomere length as well as provide insights into specific biological processes and conditions [29]. In contrast, whole blood contains a mixture of various cell types, including erythrocytes, leukocytes, and platelets, and provides an average telomere length across all cells present in the sample [30]. Additionally, the VIVALDI cohort is heterogeneous in the entities of underlying nephropathies and patient histories, leading to ESKD. The group of patients with diabetic nephropathy is also relatively small compared to other HD cohorts. Cohorts with large numbers of diabetic nephropathy may have a more uniform cardiovascular risk. A strength of our study is the detailed patient history of this cohort along with the detailed prospective capture of outcomes and independent event adjudication. This investigation is, to our knowledge, the first to investigate telomere length as a risk factor for cardiovascular outcomes in a prospective cohort of ESKD patients.

Conclusion

In our study, patients with telomere length in the highest quartile (defined a long telomere length) had an increased risk of occurrence of the 3P-MACE outcome. Importantly, we could show that patients with a long telomere length had a 3.3-fold increased risk of myocardial infarction. Our counterintuitive findings characterized a group of ESKD patients with high cardiovascular risk.

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Statement of Ethics

The VIVALDI study was approved by the Local Ethics Committee of the Medical University of Vienna (EC vote 1146/2014 and EK-14-099-0614). All patients included in the analysis provided written informed consent to participate in the study. VIVALDI is conducted in accordance with the Declaration of Helsinki and its later amendments.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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Author Contributions

Cihan Ay, Marcus Säemann, and Oliver Königsbrügge designed the study; Rafaela Vostatek and Oliver Königsbrügge contributed to data acquisition, data analysis, data interpretation, and manuscript writing; Oliver Königsbrügge, Matthias Lorenz, Philipp Hohensinner, Renate Klauser-Braun, Sabine Schmaldienst, Ingrid Pabinger, Marcus Säemann, and Cihan Ay revised the work critically for important intellectual content. All authors agreed to be accountable for all aspects of the work and approved publication.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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