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Published in:
Heart

DOI:
10.1136/heartjnl-2020-318654

Publication date:
2021

Document Version
Peer reviewed version

Link to publication in Discovery Research Portal

Citation for published version (APA):
Romaine, S. P. R., Denniff, M., Codd, V., Nath, M., Koekemoer, A., Anker, S. D., Cleland, J. G., Filippatos, G., Levin, D., Metra, M., Mordi, I. R., Ouwerkerk, W., Ter Maaten, J. M., van Veldhuisen, D. J., Zannad, F., Ng, L. L., van der Harst, P., Lang, C. C., Voors, A. A., ... Samani, N. J. (2021). Telomere length is independently associated with all-cause mortality in chronic heart failure. *Heart*, [318654]. https://doi.org/10.1136/heartjnl-2020-318654

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Romaine *et al*. (2021) – Telomere length is independently associated with all-cause mortality in chronic heart failure

Author Accepted Manuscript

This article has been accepted for publication in *Heart* (2021) following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/heartjnl-2020-318654.

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Telomere length is independently associated with all-cause mortality in chronic heart failure

Short Title: Telomere length and heart failure outcomes

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Word Count: 3,000

Funding: BIOSTAT-CHF was funded by a grant from the European Commission (FP7-242209-BIOSTAT-CHF).

Disclosures: All authors declare no conflicts of interest relevant to the work in this manuscript.

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Abstract

Objective: Patients with heart failure have shorter mean leucocyte telomere length (LTL), a marker of biological age, compared with healthy subjects, but it is unclear whether this is of prognostic significance. We therefore sought to determine whether LTL is associated with outcomes in patients with heart failure.

Methods: We measured LTL in patients with heart failure from the BIOSTAT-CHF Index (N = 2,260) and BIOSTAT-CHF Tayside (N = 1,413) cohorts. Cox proportional hazards analyses were performed individually in each cohort and the estimates combined using meta-analysis. Our co-primary endpoints were all-cause mortality and heart failure hospitalisation.

Results: In age- and sex-adjusted analyses, shorter LTL was associated with higher all-cause mortality in both cohorts individually and when combined (meta-analysis HR [per SD decrease in LTL] = 1.16 [95% CI = 1.08 – 1.24]; $P = 2.66 \times 10^{-5}$), an effect equivalent to that of being four years older. The association remained significant after adjustment for the BIOSTAT-CHF clinical risk score to account for known prognostic factors (HR = 1.12 [1.05 – 1.20]; $P = 1.04 \times 10^{-3}$). Shorter LTL was associated with both cardiovascular (HR = 1.09 [95% CI = 1.00 – 1.19]; $P = 0.047$) and non-cardiovascular deaths (HR = 1.18 [1.05 – 1.32]; $P = 4.80 \times 10^{-3}$). There was no association between LTL and heart failure hospitalisation (HR = 0.99 [0.92 – 1.07]; $P = 0.855$).

Conclusion: In patients with heart failure, shorter mean leucocyte telomere length is independently associated with all-cause mortality.

Keywords: Telomere, heart failure; biological age

Key Questions

What is already known about this subject?

Telomere length is a marker of biological age, as distinct from chronological age. Patients with heart failure have been shown to have shorter mean leucocyte telomere length (LTL) compared with healthy controls. However, whether there is a relationship between LTL and prognosis in heart failure is unclear, with existing studies providing conflicting evidence, limited by either a small number of events or the inclusion of only individuals with a specific type of heart failure.

What does this study add?

In the largest analysis of telomere length and heart failure outcomes to date, this study provides strong evidence of a significant association between shorter LTL and increased all-cause mortality, but not heart failure hospitalisation, in patients with heart failure. Importantly, this association remained present after adjusting for chronological age and established prognostic risk factors.

How might this impact on clinical practice?

Although the study does not have an immediate impact on clinical practice, it provides a strong evidence base for further studies to investigate the potentially causal relationship between shorter telomere length and heart failure prognosis, as well as exploring the role of telomeres in heart failure pathogenesis.

Introduction

Telomeres are dynamic complexes of repeat DNA sequences and associated proteins at the end of chromosomes that act to protect them during replication. There is marked inter-individual variation in lengths of telomeres from birth and there is strong genetic determination of telomere length.[1] Furthermore, telomeres shorten with each cell division and in response to environmental stresses.[2] When shortening reaches a critical point, telomere damage signalling induces cellular senescence and altered transcriptional profiles, including the production of inflammatory mediators.[2,3] As such, shorter telomere length is considered a marker of biological age and has been increasingly linked to a wide variety of common age-associated diseases.[2,4,5]

Patients with heart failure have been reported to have shorter mean leucocyte telomere length (LTL) than healthy controls.[6] However, very few studies have investigated whether there is a relationship between telomere length and prognosis in heart failure and these have provided conflicting evidence, limited either by a small number of events or the inclusion of only individuals with a specific type of heart failure.[7,8] Therefore, we sought to determine the association between LTL and prognosis in heart failure patients (defined as all-cause mortality and unscheduled heart failure hospitalisation) in a large, observational study of patients with both reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF) and a range of aetiologies (including both ischaemic and non-ischaemic).

Methods

Study population

These analyses used data from BIOSTAT-CHF, a European-wide multicentre observational study of patients with worsening symptoms of heart failure.[9,10] The study consists of an Index cohort (N=2,516) recruited from 69 centres across 11 European countries and a second (Tayside) cohort (N=1,738) recruited from six centres across Scotland, both between 2010 and 2014.

Key inclusion criteria for the Index cohort were symptoms of new-onset or worsening heart failure, along with objective evidence of cardiac dysfunction, defined as left ventricular ejection fraction ≤ 40% and/or plasma B-type natriuretic peptide (BNP) >400 pg/mL and/or plasma N-terminal prohormone of BNP (NT-proBNP) >2,000 pg/mL. Key inclusion criteria for the Tayside cohort were a confirmed diagnosis of heart failure and a previously documented admission with heart failure that required treatment with diuretics. Patients in both cohorts were ≥18 years of age, receiving oral or intravenous diuretics but suboptimal medical therapy, defined as <50% target doses of angiotensin converting enzyme inhibitors/angiotensin II receptor blockers and/or beta-blockers, according to 2008 European Society of Cardiology guidelines.[11] Patients were recruited either as in-patients or out-patients and underwent optimisation of heart failure therapy during the first three months of the study.

All patients provided written informed consent to participate in BIOSTAT-CHF and its sub-studies, which were conducted in concordance with the declaration of Helsinki and approved by national and local ethics committees.

Outcome measurements

We employed two co-primary endpoints: all-cause mortality and unscheduled heart failure hospitalisation. We chose to analyse these endpoints separately as different factors may contribute to these outcomes and our primary goal was to address a biological question rather than an overall clinical outcome/benefit question. Secondary endpoints were cardiovascular mortality and non-cardiovascular mortality, as determined by the BIOSTAT-CHF principal investigators.[9]

Clinical risk score

To adjust our survival analyses for clinical and laboratory variables already known to affect prognosis, we employed BIOSTAT-CHF clinical risk scores for all-cause mortality and heart failure hospitalisation.[10] We selected these scores as they were derived specifically from within BIOSTAT-CHF and have been shown to outperform previously published risk prediction models in our cohorts.[10] The components of each score and their cut-offs are as follows: for mortality = age (>70 years), blood urea nitrogen (>11 mmol/L), NT-proBNP (>4,000 pg/mL), haemoglobin (<12 g/dL) and beta-blocker use at baseline; for heart failure hospitalisation = age, heart failure hospitalisation in the previous year, peripheral oedema, systolic blood pressure (<140 mmHg) and estimated glomerular filtration rate (eGFR; <40 mL/min).[10] Adjustment for the BIOSTAT-CHF clinical risk scores was achieved by stratifying analyses by the appropriate point score model.

Telomere length measurement

Mean LTL was measured using a well-established quantitative polymerase chain reaction (qPCR) based technique and expressed as a ratio (T/S) of telomere repeat length (T) to copy number of a single copy gene, 36B4 (S) for each sample. Full details of this method have been published previously,[12] and additional details are provided in the **Supplementary Methods** and **Supplementary Table 1**. To facilitate comparisons across the two cohorts, telomere lengths were Z-standardised.

Statistical analyses

All statistical analyses were performed using R Version 3.4.4 in RStudio Version 1.1.453.[w1,w2] We confirmed normal distribution of LTLs prior to analyses and therefore transformation was not performed. The associations of LTL with baseline demographic and clinical characteristics (including age, sex, ischaemic aetiology, and heart failure classification) were assessed using both univariate and multivariate (age- and sex-adjusted) linear regression, with LTL as the response variable.

The associations of LTL with all-cause mortality and heart failure hospitalisation were assessed using Cox proportional hazards regression using the 'survival' package in R.[w3] We confirmed that assumptions for each test were met, including proportionality of hazards, which was assessed using individual and global Schoenfeld tests. Telomere length was analysed as both a continuous trait (with hazard ratios presented per SD decrease in LTL) and split into quartiles (with hazard ratios presented relative to those with the longest LTL). We employed two models for each endpoint: Model 1 = LTL adjusted for age and sex; Model 2 = LTL adjusted for age, sex, and BIOSTAT-CHF risk

score. Sensitivity analyses replacing the risk scores with their individual components were also performed. Cause-specific survival analyses were performed by censoring patients who died of an alternative cause at the time of death. Interactions were tested by adding multiplicative terms, in addition to the main effects, to the respective Cox models. We performed a sensitivity analysis for the hospitalisation outcome to allow for the competing risk of death.[13] Competing risk models were adjusted for age, sex and BIOSTAT-CHF risk score, allowing the risk score to vary over time and satisfy the proportional hazards assumption. All analyses were performed separately in each cohort. Combined estimates were generated using fixed-effects inverse-weighted meta-analyses with the R package 'meta'.[w4] Details of data visualisation and the generation of age- and sex-adjusted LTL quartiles are provided in the **Supplementary Methods**.

To aid interpretation of the impact of LTL on all-cause mortality, we convert the estimate for LTL into an equivalent in terms of increasing chronological age. To achieve this, we calculate the ratio of the LTL and age log-hazard ratios from the survival model for all-cause mortality (Model 1).

Statistical significance was defined as $P<0.05$; formal adjustments for multiple testing were not applied.

Patient and public involvement

Patients or the public were not directly involved in the design, conduct, reporting, or dissemination of this research.

Results

Patient characteristics and outcomes

After exclusion of patients with no outcome data (N=145), no or insufficient quality DNA (N=431), and LTL outliers (N=5), a total of 3,673 patients were included in the current analyses (Index = 2,260; Tayside = 1,413). Key baseline characteristics of both cohorts are shown in **Table 1**, with extended characteristics shown, per TL quartile, in Supplementary Tables 2A and 2B. Differences in the proportion of patients with HFpEF between cohorts are reflective of differences in inclusion criteria.

In the Index cohort, after a median follow-up of 21.3 months (IQR = 15.4 – 27.1), there were 596 (26.4%) deaths and 571 (25.3%) patients hospitalised for heart failure. Follow-up in the Tayside cohort was longer (median [IQR] = 23.6 [14.2 – 34.3] months) and a higher proportion of patients died (32.6%) or were hospitalised for heart failure (26.4%). When follow-up was limited to one or two years, event numbers were similar (**Supplementary Table 3**).

Confirmation of known telomere length associations

Using multivariate linear regression with age and sex as independent variables, we confirmed the known association of LTL with age in both cohorts, with older patients having shorter telomeres (Index: B=-0.033, P=2.05x10^{-92}; Tayside: B=-0.023, P=1.92x10^{-19}; **Supplementary Figure 1**). Similarly, we observed the established finding that men have shorter telomeres than women (Index: B=-0.271, P=1.08x10^{-10}; Tayside: B=-0.191, P=4.10x10^{-4}; **Supplementary Figure 1**).

Telomere length and heart failure subgroups

After adjusting for age and sex using multivariate linear regression, we found that patients with ischaemic aetiology heart failure had shorter LTL than those with non-ischaemic heart failure (Combined: N=3,426, B=-0.088; CI=-0.151 to -0.024; P=0.007*)*. No difference in LTL was observed between patients with HFpEF compared with HFrEF (Combined: N=2,759, B=-0.074 [95% CI = -0.174 to 0.025]; P=0.144).

Telomere length and mortality

As a continuous trait, after adjusting for age and sex, shorter LTL was associated with an increase in all-cause mortality (**Table 2**; Combined HR [per SD decrease in LTL] = 1.16 [1.08 – 1.24]; P=2.66x10^{-5}). The associations remained significant after adjustment for the BIOSTAT-CHF mortality risk score (**Table 2**; Combined HR = 1.12 [1.05 – 1.20]; P=1.04x10^{-3}). **Figure 1** shows the age-, sex- and risk

score-adjusted hazard ratio for all-cause mortality across the range of telomere lengths in both cohorts, relative to the mean telomere length. Sensitivity analysis using individual components of the BIOSTAT-CHF mortality risk score as independent variables gave a similar association (Combined: N = 3,075; HR = 1.11 [1.03 – 1.20]; P=5.70x10^{-3}).

In cause-specific analyses, the association between shorter LTL and mortality was observed amongst patients who died from cardiovascular (CV) causes (CV deaths = 677; HR = 1.09 [95% CI = 1.00 – 1.19]; P=0.047) and non-CV causes (Non-CV deaths = 380; HR = 1.18 [1.05 – 1.32]; P=4.80x10^{-3}; **Supplementary Table 4**).

Interestingly, the association between shorter LTL and mortality appeared stronger amongst patients with non-ischaemic heart failure aetiology than those with ischaemic aetiology (**Supplementary Table 5**). In age- and sex-adjusted analyses, shorter LTL was associated with mortality in both groups. However, after adjustment for the BIOSTAT-CHF risk score, shorter LTL was associated with increased mortality only amongst non-ischaemic aetiology patients (HR = 1.16 [95% CI = 1.01 – 1.32]; P=0.030), with only a non-significant trend observed for ischaemic aetiology patients (HR = 1.07 [95% CI = 0.98 – 1.16]; P=0.120). However, when included in the survival analyses of all patients, there was no evidence of an interaction between aetiology and LTL in either the Index (P=0.701) or Tayside (P=0.108) cohorts.

When LTL was analysed as quartiles, similar results were obtained (**Supplementary Table 6**). After adjusting for age and sex, those with the shortest LTL were more likely to reach the mortality endpoint than those with the longest LTL (Q4 vs. Q1; Combined HR = 1.38; 95% CI = 1.15 – 1.66; P=0.001; **Figure 2**). After adjusting for the BIOSTAT-CHF mortality risk score, those with the shortest LTL were 27% more likely to die during follow-up than those with the longest LTL (Q4 vs. Q1: Combined HR = 1.27 [1.06 – 1.53]; P=0.011).

To provide a clinical context for the impact of shorter LTL on mortality in heart failure, we compared its effect with that of chronological age. A one-year increase in age was associated with an all-cause mortality HR of 1.037 (95% CI = 1.030 – 1.044). Therefore, a one SD shorter LTL had an effect equivalent to that of being 4.04 years older.

Association of telomere length with heart failure hospitalisation

In contrast to mortality, we found no association between LTL and heart failure hospitalisation after adjustment for age and sex (Combined HR = 1.01 [0.94 – 1.09]; P=0.706) and adjustment for age, sex and the BIOSTAT-CHF hospitalisation risk score (Combined HR = 0.99 [0.92 – 1.07]; P=0.855; **Table 2**). When analysed as quartiles, comparable results were obtained (**Supplementary Table 7**). Sensitivity

analysis using individual components of the BIOSTAT-CHF hospitalisation risk score gave a similar finding (Combined HR = 1.03 [0.95 – 1.11]; *P*=.507), as did a competing risks analysis, performed to ensure the competing risk of death did not influence hospitalisation (**Supplementary Table 8**).

Discussion

In the largest study of telomere length and outcome amongst heart failure patients to date, we show that mean circulating leucocyte telomere length is independently associated with all-cause mortality in this population. Using two large, observational studies totalling more than 3,600 patients with a broad spectrum of heart failure aetiologies and phenotypes and over 1,000 deaths, we found that after adjustment for age and sex, a one standard deviation decrease in LTL was associated with a 16% increase in all-cause mortality, equivalent to an effect of being four years older. This association remained significant, with a 12% increase in mortality, even after accounting for known prognostic factors. In contrast, we found no association between LTL and heart failure hospitalisation.

Two previous studies have examined the association between LTL and outcomes in heart failure. In a sub-study of the CORONA trial, Haver *et al.* found that LTL was univariately associated with their primary endpoint (a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke) with weak trends of association demonstrated for all-cause and cardiovascular mortality. However, these associations were not statistically significant after correction for age and gender.[7] In keeping with our results, Haver *et al.* also found no association between LTL and hospitalisation for worsening heart failure.[7] In an analysis of 890 chronic heart failure patients in a sub-study of COACH, van der Harst *et al*.[8] found that shorter LTL was associated with a combined end-point of all-cause mortality or heart failure hospitalisation, even after adjustment for age, sex and additional univariate predictors of outcome. However, secondary analyses demonstrated that this association was driven primarily by heart failure hospitalisation and not mortality.[8]

There are several possible explanations for the differences observed between these studies and our findings. For example, CORONA only included patients with heart failure and coronary artery disease (CAD). However, the most important factor is likely to be the increased power afforded to our study by its size and high event-rate – we included over 1,000 deaths and almost 950 heart failure hospitalisations. This compares to just 93 deaths and 214 hospitalisations in COACH. In CORONA, the primary endpoint was reached in 575 patients and 758 patients were hospitalised due to heart failure.

Several observations have linked telomere dynamics to cardiomyocyte biology and cardiac function. Sharifi-Sanjani *et al.* demonstrated that cardiomyocyte telomeres from patients with heart failure were shorter than from healthy donor hearts, independent of age.[14] This appeared to be a distinct signature in cardiomyocytes, as telomere length in smooth muscle cells was not different between failing and non-failing hearts.[14] With aging, telomerase knockout mice hearts showed shortening

of telomeres, attenuated proliferation and increased apoptosis of cardiomyocytes, and greater cardiac remodelling and left ventricular failure.[15] On the other hand, enhanced expression of telomerase reverse transcriptase in rat cardiomyocytes preserved telomere length, and induced cardiomyocyte proliferation, hypertrophy and survival.[16] We have previously shown an association between longer LTL and greater left ventricular mass, suggesting that longer telomeres may protect against myocardial loss with age.[17]

Despite these observations, interestingly, we found that shorter LTL was associated with both cardiovascular and non-cardiovascular mortality, with the association with the latter, if anything, being somewhat stronger (**Supplementary Table 4**). This finding, along with the lack of any association of shorter LTL with heart failure hospitalisation, suggests that the association with mortality that we have seen may not be directly due to an impact of shorter telomeres on cardiac function. However, it is worth noting that the hospitalisation endpoint may be prone to bias due to factors that could prevent hospitalisation, including access to services, patient preference and death.

Nevertheless, in this context, it is important to note that a wide range of other age-related diseases, including some cancers[18] and Alzheimer's disease[19] with potential impact on mortality have also been associated with shorter telomeres. Indeed, perhaps the strongest evidence exists for an association between shorter LTL and CAD.[20-25] Furthermore, studies have also shown evidence of an association with all-cause mortality in patients with CAD.[26] However, we found no evidence that the association between shorter LTL and all-cause mortality in heart failure was being driven by the association with CAD. In fact, the association of shorter LTL with increased mortality in heart failure was nominally stronger in patients without CAD (**Supplementary Table 5**).

Supporting our findings, in an analysis of 3,259 participants and 1,525 deaths from the Cardiovascular Health Study, Framingham Heart Study, and Women's Health Initiative, shorter LTL was associated with increased all-cause mortality, with the strongest association seen for deaths not attributed to cancer or cardiovascular causes.[27] Furthermore, a recent meta-analysis of 25 studies including 121,749 participants from the general population found that a one standard deviation shorter telomere length was associated with a 9% increase in all-cause mortality risk.[28] Taken altogether it would seem that at least a substantial proportion of the observed association of shorter telomeres with increased mortality in patients with heart failure is not due to the presence of heart failure *per se*.

Our study does have some limitations. Firstly, we measured telomere length in circulating leukocytes. Whilst this is an established measurement that is frequently employed in epidemiological studies, it may not reflect telomere length in cardiac-specific cells. Additionally,

whilst we have demonstrated a robust and replicated independent association between shorter LTL and all-cause mortality in patients with heart failure, we are unable to provide evidence of a mechanism or causal relationship. Similarly, as our analyses were cross-sectional in nature, we are unable to quantify the rate of telomere attrition in each patient, which has been suggested to be increased in heart failure,[29] and predictive of all-cause mortality in CAD patients.[30] Consequently, future work should seek to determine whether telomere length has a causal role in both the development and prognosis of heart failure. Such approaches should not only include mechanistic *in-vitro* and *in-vivo* animal studies, but also genetic techniques such as Mendelian randomisation, when populations with sufficient patients and event numbers are available.

Conclusion

In a large cohort of patients with heart failure, we have demonstrated a significant independent association between shorter LTL and increased all-cause mortality, but not heart failure hospitalisation. However, determining whether there is a causal relationship between telomere length and prognosis in patients with heart failure, whether telomere shortening represents a disease-specific biomarker, or whether our observation simply reflects biological ageing as a marker of reduced physiological reserve and increased susceptibility to clinical deterioration, requires further investigation.

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Figure Legends

Figure 1: Age-, sex- and risk score-adjusted hazard ratio for all-cause mortality across the range of LTLs in the Index and Tayside cohorts, relative to the mean LTL. Lines represents median of all simulations; dark shading represents central 50% and light shading represents minimum and maximum simulated values.

Figure 2: Kaplan-Meier curves for all-cause mortality, split by age- and sex-adjusted quartiles for LTL in both the Index and Tayside cohorts. Tables represent the number of patients at risk at each time point in each quartile.

Contributorship Statement

SPRR, VC, MN, CPN, and NJS were responsible for project conceptualisation, methodology, formal data analyses and drafting the manuscript. MD, VC, ALK, SDA, JGC, GF, DL, MM, IRM, WO, JMtM, DJvV, FZ, LLN, PvdH, CCL, AAV, and NJS were responsible for data acquisition. All authors contributed to critical revision of the manuscript, approved the final version for publication and are accountable for all aspects of the work. SPRR and NJS are responsible for the overall content as guarantors.

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Tables

Table 1: Key baseline characteristics of Index and Tayside cohorts in BIOSTAT-CHF telomere analyses

Variable	Index Cohort (N = 2,260)	Tayside Cohort (N = 1,413)
Demographics		
Sex (male)	73.1 (1653)	66.0 (933)
Age (years)	69.00 (12.07)	74.26 (10.37)
BMI (kg/m^2)	27.94 (5.58)	29.10 (6.36)
Current smoker	13.7 (309)	12.4 (174)
Clinical profile		
NYHA Class		
I	2.5 (55)	0.9 (13)
II	35.5 (779)	39.3 (555)
III	49.3 (1082)	44.9 (634)
IV	12.7 (278)	14.9 (210)
Heart failure classification		
HFrEF (LVEF < 40%)	80.5 (1612)	45.7 (621)
HFmrEF (LVEF 40 to 49%)	12.8 (256)	25.5 (346)
HFpEF (LVEF ≥ 50%)	6.7 (135)	28.8 (391)
Heart failure history		
Ischaemic aetiology	61.2 (1232)	66.7 (943)
HF hospitalisation in previous year	31.0 (700)	27.0 (375)
Medical history		
Hypertension	62.9 (1422)	59.4 (837)
Diabetes mellitus	33.1 (748)	33.5 (472)
Medication at baseline		
ACEi or ARB	71.2 (1609)	69.5 (977)
Beta-blocker	82.7 (1868)	72.5 (1019)
MRA	52.6 (1188)	30.7 (431)
Laboratory measurements		
eGFR (mL/min/1.73m^2; CKD-EPI)	60.27 (22.84)	60.42 (22.58)
NT-proBNP (ng/L)	2724 [1215, 5760]	1341 [511, 3488]

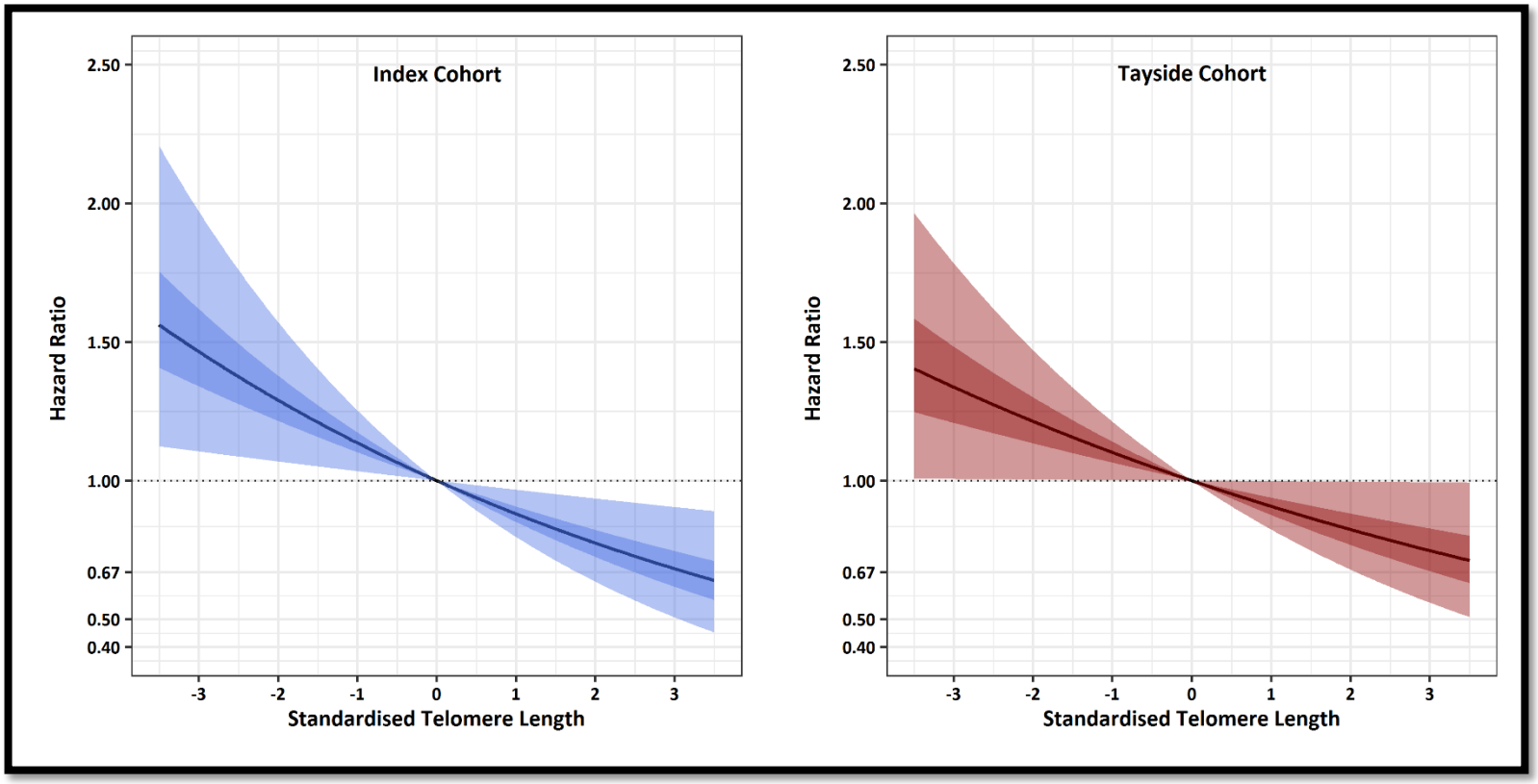
Continuous variables are expressed as mean (SD) or median [interquartile range]. Categorical variables are expressed as % (N). ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration equation; eGFR = estimated glomerular filtration rate; HF = heart failure; HFmrEF = HF with moderately reduced ejection fraction; HFpEF = HF with preserved ejection fraction; HFrEF = HF with reduced ejection fraction; MRA = Mineralocorticoid Receptor Antagonist; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide; NYHA = New York Heart Association.

Table 2: Association of LTL with all-cause mortality and heart failure hospitalisation, assessed by Cox proportional hazard regression

		Index Cohort (N = 2,260)			Tayside Cohort (N = 1,413)			Combined (N = 3,673)		
Endpoint	**Model**	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
All-cause mortality	**1**	1.17	1.07 – 1.29	1.03×10^{-3}	1.14	1.04 – 1.26	8.08×10^{-3}	1.16	1.08 – 1.24	2.66×10^{-5}
	2	1.14	1.04 – 1.25	7.55×10^{-3}	1.10	1.00 – 1.22	.050	1.12	1.05 – 1.20	1.04×10^{-3}
Heart failure hospitalisation	**1**	0.98	0.89 – 1.08	.682	1.06	0.95 – 1.18	.308	1.01	0.94 – 1.09	.706
	2	0.95	0.87 – 1.05	.331	1.05	0.94 – 1.16	.418	0.99	0.92 – 1.07	.855

Model 1 = age- and sex-adjusted analyses; Model 2 = age- and sex-adjusted analyses, stratified by the appropriate BIOSTAT-CHF risk score. Hazard ratios represent change in risk per one standard deviation decrease in telomere length. Hazard ratios for other variables included in the models are not shown.
Deaths – Index = 596; Tayside = 461; Combined = 1,057
Heart failure hospitalisation – Index = 571; Tayside = 373; Combined = 944

Figures



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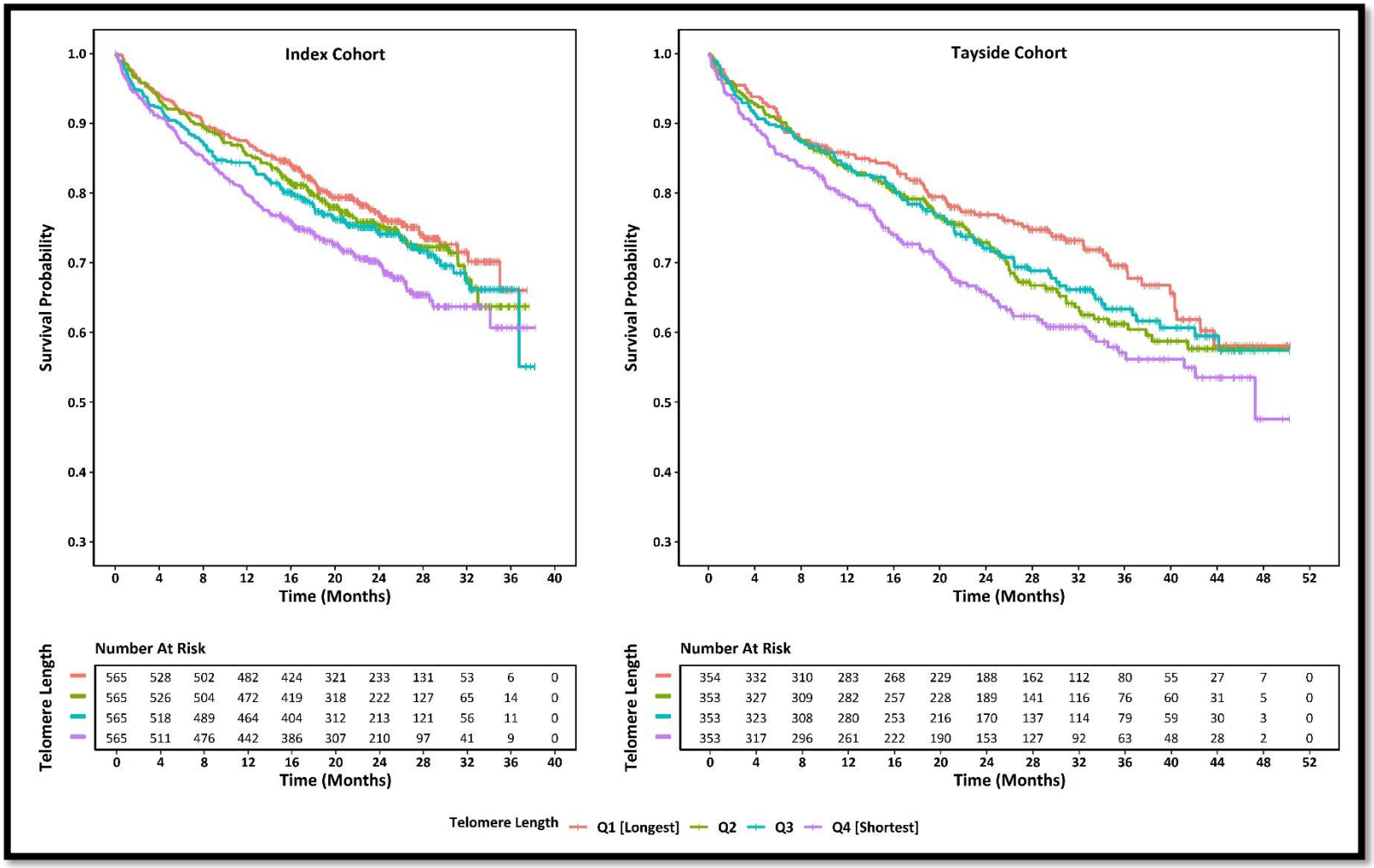

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