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BACKGROUND

- Telomeres are repetitive nucleotide structures at the end of eukaryotic chromosomes. (**Figure 1**)
- Telomere length variation can cause chromosomal instability, thus influencing the risk and prognosis of several cancers.
- Several studies have demonstrated an association between telomere length and colorectal cancer (CRC) risk, though the relationship with colorectal cancer survival is less clear.
- Both longer and shorter telomeres have been previously reported to be associated with poorer survival in CRC patients.

Figure 1. Telomere structure.



OBJECTIVE

To investigate the association between circulating leukocyte telomere length and survival among newly diagnosed stage I-IV colorectal cancer patients in the ColoCare Study.

METHODS

- Study population:** The ColoCare Study (ClinicalTrials.gov Identifier: NCT02328677) is a multi-center cohort of newly-diagnosed stage I-IV CRC patients recruited prior to surgery. As part of the study, clinicodemographic data, biospecimens and information on lifestyle factors, symptoms and health outcomes are collected at baseline and up to 5 years after diagnosis. N=92 colorectal cancer patients enrolled at the ColoCare Study site in Heidelberg, Germany, were included in the current analysis (**Table 1**).
- Exposure assessment:** Baseline genomic DNA from blood leukocytes was extracted from eligible study participants. Telomere length (T) relative to a single copy gene (S) was measured in extracted DNA using the multiplex quantitative polymerase chain reaction.
- Outcome assessment:** Time to event was computed as time from CRC surgery to either death or recurrence. Progression free survival (PFS) for each patient was defined as time to disease recurrence or death from any cause, while overall survival (OS) was defined as time to death from any cause.
- Statistical analysis:** Hazard ratios (HR) and 95% confidence intervals (CIs) were computed for OS and PFS using Cox proportional hazards regression models, adjusting for confounders. Telomere length (T/S ratio) was log transformed to make the distribution approximately normal.

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RESULTS

- Median T/S ratio for telomere length was 0.48 (0.31-0.94).
- Median follow up time for PFS was 65.2 months and for OS was 66.2 months.
- Progression-Free Survival (PFS)**
 - When evaluated on a continuous scale, each unit decrease in the T/S ratio was associated with a 14% poorer survival in age-and sex-adjusted models (HR[95% CI] =1.14[0.22-5.88]), however the results did not reach statistical significance.
 - K-M curves for PFS are shown in **Figure 2**.
 - When categorized as quartiles of telomere length, we observed poorer survival for the shortest quartile compared to the longest in fully adjusted models, p-trend_{PFS}=0.88. (**Table 2**).
 - Fully adjusted HRs for T/S ratio both as a continuous variable (after smoothing cubic splines) as well as by quartiles of telomere length are plotted in **Figure 3**.
- Overall Survival (OS)**
 - HRs for telomere length quartiles presented a non-linear association with overall survival. In a fully adjusted model, we observed poorer OS in the shortest quartile of telomere length (HR[95% CI] =2.25[0.47-10.79]) (**Table 2**).

Table 1. Clinicodemographic characteristics of study participants.

Participants (N=92)	Variable (mean ± SD) / N (%)			
Age (years)	62.8 (±11.9)			
Sex (Male)	67.4			
BMI (kg/m ²)	26.2 (±3.6)			
Smoking status (Ever)	65.2			
Tumor site	Colon 51.1	Rectum 48.8		
Tumor stage	I 19.6	II 28.3	III 28.3	IV 18.5

Figure 2. Kaplan Meier survival curves for PFS comparing longer vs. shorter telomere length.

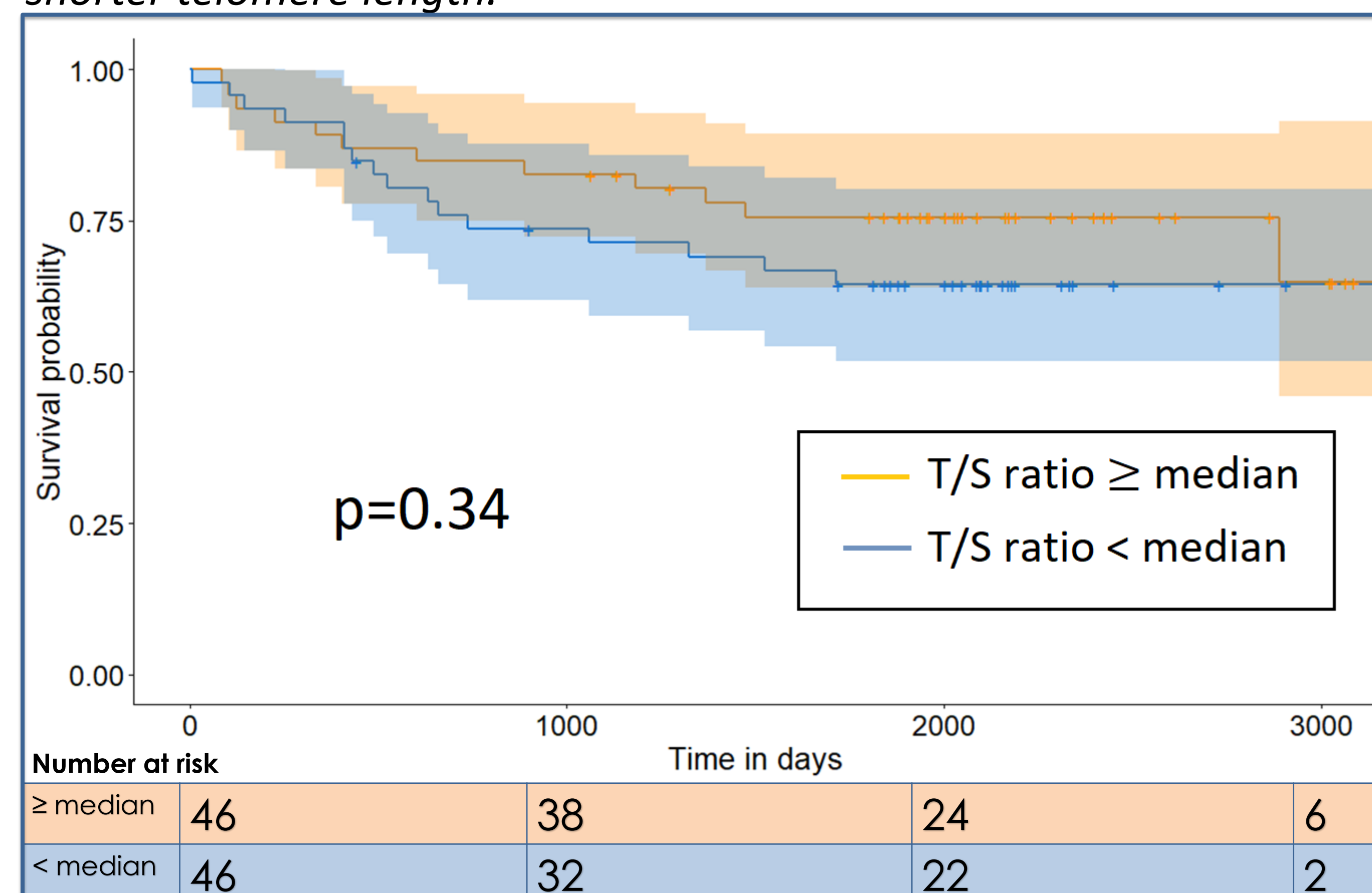
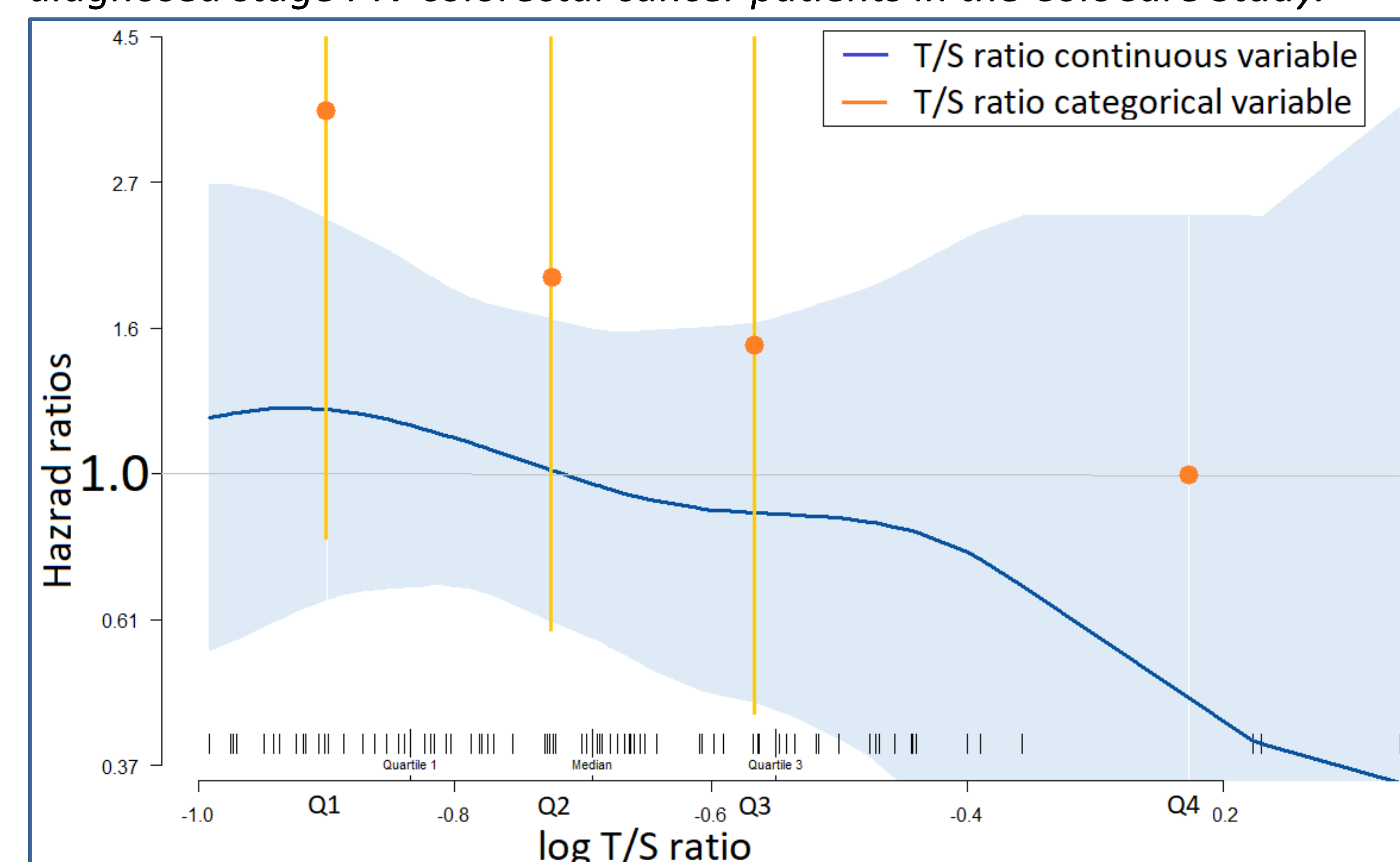


Table2. HR (95% CI) for PFS and OS by quartiles of telomere length.

T/S ratio quartile	PFS		OS	
	Age/ sex adjusted	Fully adjusted ¹	Age/ sex adjusted	Fully adjusted ¹
Q1 shortest	1.37 (0.45-4.17)	3.58 (0.85-15.08)	0.86 (0.26-2.83)	2.25 (0.47-10.79)
Q2	1.12 (0.38-2.69)	1.86 (0.50-6.95)	1.01 (0.33-3.09)	2.02 (0.47-8.65)
Q3	0.83 (0.26-2.69)	1.64 (0.44-6.58)	0.90 (0.28-2.91)	2.46 (0.58-10.37)
Q4 reference	1.00	1.00	1.00	1.00

¹age, sex, BMI, smoking status, alcohol intake, supplement intake, NSAID use, physical activity, treatment, and tumor stage

Figure 3. Fully adjusted HRs (95% CI) for PFS including telomere length as a continuous variable and categorized by quartiles among newly diagnosed stage I-IV colorectal cancer patients in the ColoCare Study.



CONCLUSIONS

- Our results suggest that individuals with shorter telomeres may have poorer progression-free and overall survival after colorectal cancer diagnosis.
- Larger populations are needed to further evaluate telomere length as a prognostic biomarker in colorectal cancer progression.