Supplementary material to "Investigation of age-treatment interaction in the SPACE trial using different statistical approaches"

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STEPP

Test statistic for the test of the null hypothesis of no covariate-treatment interaction for the STEPP approach:

$$T_{STEPP} = \max_{j=1,\ldots,K} \left(\frac{|\hat{\theta}_j - \hat{\theta}_{ALL}|}{\hat{\sigma}_j} \right), \tag{S1}$$

where $\hat{\theta}_j$ is the estimated treatment effect (as the hazard ratio or the difference in Kaplan-Meier estimates at a given time point between the study groups) in the j^{th} of K subpopulations, $\hat{\theta}_{ALL}$ the according estimate for the whole study population, and $\hat{\sigma}_j$ an estimate for the standard error of the difference between $\hat{\theta}_j$ and $\hat{\theta}_{ALL}$.

Multivariable fractional polynomial interaction

Algorithm for the *FP2-flex1* approach:

1. Select best powers (p_1, p_2) for Z in a model as described in Equation 2 of the manuscript including T as additional covariate by finding the model (out of 36 candidates) with the highest(log-)likelihood.
2. Define the new predictors
   - $Z_{01} = Z^{p_1}$ if $T = 0$ and $Z_{01} = 0$ if $T = 1$
   - $Z_{02} = Z^{p_2}$ if $T = 0$ and $Z_{02} = 0$ if $T = 1$
   - $Z_{11} = 0$ if $T = 0$ and $Z_{11} = Z^{p_1}$ if $T = 1$
   - $Z_{12} = 0$ if $T = 0$ and $Z_{12} = Z^{p_2}$ if $T = 1$
3. Fit the two nested models M_1 with covariates $T, Z_{01}, Z_{02}, Z_{11}, Z_{12}$ and M_2 with covariates T, Z^{p_1}, Z^{p_2} and compare the difference of model deviances with a χ^2 distribution with two degrees of freedom.

Algorithm for the *FP1-flex3* approach:

1. Select the best power transformation (p_1) by finding the model with covariate-treatment interaction (out of 8 candidates) with the highest (log-)likelihood considering the transformed covariates
   - $Z_{01} = Z^{p_1}$ if $T = 0$ and $Z_{01} = 0$ if $T = 1$
   - $Z_{11} = 0$ if $T = 0$ and $Z_{11} = Z^{p_1}$ if $T = 1$

   and treatment group.
2. Find the best power transformation in an according model without a covariate-treatment interaction including the covariates T and Z^{p_1} (the selected transformation can be different to that determined for the model with interaction).
3. Compare the differences of model deviances with a χ^2 distribution with one degree of freedom. As the models might not be nested use of a χ^2 distribution is not well justified from a theoretical point of view and consequently the result should be interpreted as "indicative" rather than as "definitive".

Local partial-likelihood approach

Taylor expansions for $\beta(Z)$ and $f(Z)$ around a marker value of interest z_0:

$$\beta(z) \approx \beta(z_0) + \beta'(z_0)(z - z_0) = \zeta + \eta(z - z_0) \tag{S2}$$

$$f(z) \approx f(z_0) + f'(z_0)(z - z_0) = \alpha + \gamma(z - z_0) \tag{S3}$$

Local partial-likelihood within the neighbourhood of z_0:

$$\begin{aligned} l_{z_0}(\zeta,\eta,\gamma) = \frac{1}{n}\sum_{i=1}^{n} K_h(Z_i - z_0)\,\delta_i\Big\{\zeta\,T_i + \eta\,T_i(Z_i - z_0) + \gamma(Z_i - z_0) - \\ \log\Big(\sum_{j=1}^{n} Y_j(X_i)\,K_h(Z_j - z_0)\,\exp\big(\zeta\,T_j + \eta\,T_j(Z_j - z_0) + \gamma(Z_j - z_0)\big)\Big)\Big\}, \end{aligned} \tag{S4}$$

where ζ, η, and γ are as defined in Equations S2 and S3, $K_h(.)$ is a kernel weight with a given bandwidth of h, δ is the binary status variable, and $Y_j(X_i)$ indicates, whether the observed time of individual j is larger than the observed time of individual i.

Test statistic for the test of the null hypothesis of no covariate-treatment interaction for the local partial likelihood approach:

$$Q_{LPLE} = \max_{1\leq k\leq m}\left(\frac{\{\hat{\beta}(z_k) - \hat{\beta}\}^2}{\widehat{Var}\{\hat{\beta}(z_k) - \hat{\beta}\}}\right), \tag{S5}$$

where $\hat{\beta}$ is the estimated regression coefficient for a model assuming a constant treatment effect over the range of the covariate z, m is the number of covariate values of interest, k indicates the according covariate value and $\hat{\beta}(z_k)$ is the local estimate of the regression coefficient at the covariate value z_k.

Modified covariate approach

The difference between the treatment groups can then be expressed as a hazard ratio and estimated for a given covariate value z as

$$\Delta(z) = \exp\{-\gamma_0' W(z)\}. \tag{S6}$$

To test for a covariate-treatment interaction, the model presented in Equation (4) of the manuscript can be compared with a model including only the transformed treatment variable, but not the covariate of interest, in the matrix W^* using a χ^2 test with an appropriate number of degrees of freedom. The degrees of freedom depend on the transformations used for the covariate of interest in W and consequently in W^* (e.g. spline function, penalized splines, ...).

Point estimates and CIs for given age values

Age		STEPP	Cox	MFPI FP2-flex1	MFPI FP1-flex3	LPLE	Modif. covar.
	Point est.	0.57	0.68	0.70	0.71	0.53	0.70
60	CI (low.)	0.28	0.39	0.40	0.41	0.26	0.42
	CI (upp.)	1.20	1.18	1.23	1.21	1.07	1.16
	Point est.	0.88	0.87	0.99	0.87	0.95	0.94
65	CI (low.)	0.42	0.58	0.61	0.58	0.49	0.62
	CI (upp.)	1.86	1.30	1.60	1.31	1.84	1.43
	Point est.	1.20	1.10	1.26	1.09	1.39	1.31
70	CI (low.)	0.63	0.79	0.82	0.78	0.77	0.87
	CI (upp.)	2.32	1.54	1.93	1.51	2.53	1.98
	Point est.	1.45	1.41	1.48	1.38	1.76	1.61
75	CI (low.)	0.82	0.97	1.01	0.96	1.03	1.02
	CI (upp.)	2.57	2.04	2.16	1.98	2.99	2.56
	Point est.	1.36	1.80	1.64	1.78	1.42	1.83
80	CI (low.)	0.68	1.09	0.98	1.08	0.77	0.97
	CI (upp.)	2.73	2.95	2.74	2.93	2.60	3.44

Table S1: Point estimates for the hazard ratio with according values of the pointwise 95% confidence interval for given age values of 60, 65, 70, 75 and 80 years obtained by the different methods. For STEPP and LPLE a linear interpolation between the two closest estimates was performed to obtain results for the given age values.

STEPP: Subpopulation treatment effects pattern plot
Cox: Cox regression with linear age-treatment interaction
MFPI: Multivariable fractional polynopmial for interaction
LPLE: Local partial likelihood estimation
Modif. covar.: Modified covariate approach