Quantifying the association between progression-free survival and overall survival in cancer trials

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Overview

Motivation

- In oncology trials, different clinical endpoints can be considered to analyse the survival times of patients:

  Overall survival (OS): time from randomization until death

  Progression-free survival (PFS): time from study entry until progression or death depending on what occurs first

- Progression-free survival can be used as a surrogate endpoint for cancer survival (e.g., efficient in terms of costs and time)

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Main interest: Approaches to quantifying the association between PFS and OS to provide an indication of the extent to which PFS may be an effective surrogate for OS.

Background

- Some existing approaches to estimating the correlation between PFS and OS:
  - parametric and semi parametric copula models
  - non-parametric method based on inverse probability of censoring weights
  - model-based methods

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  - parametric and semi parametric copula models
  - non-parametric method based on inverse probability of censoring weights
  - model-based methods
- Assumption: the preferable measurement of the association between PFS and OS is the Kendalls's tau rank correlation

Existing approaches

Copula models

- Estimation of the marginal joint distribution and the dependency structure between *PFS* and *OS* by using Copula functions.

Disadvantage: Copula models don't take into account the fact that $PFS \leqslant OS$

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Non-parametric methods based on inverse probability of censoring weights (IPCW)

- In the presence of censoring, the concordance status cannot always be derived for (PFS,OS) of two patients
- The IPCW scheme weights the evaluable pair (PFS, OS) of two patients by the inverse estimated probability of being evaluable.

Advantage: No assumptions required about either the dependence structure or the marginal distributions of the times to PFS and OS
Disadvantage: Requires strong assumptions about censoring.

Model-based method

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Li and Zhang (2015) presented a parametric multi-state model describing the Pearson correlation between survival outcomes PFS and OS
Assumptions:

- Semi-Markov model (imminient future only dependent on the time spent in the present state)
- Weibull hazard functions to describe the transition intensities
  - Shape parameters are constant between the states in the msm $\Rightarrow$ 4 parameters $\lambda_1, \lambda_2, \lambda_3, \alpha$

Model-based method

This multi-state model is parametrized

- hazard of progression: $\pi_{01}(t) = \lambda_1 \alpha t^{\alpha-1}$
- hazard of death before progression: $\pi_{02}(t) = \lambda_2 \alpha t^{\alpha-1}$
- hazard of death given progression: $\pi_{12}(s) = \lambda_3 \alpha s^{\alpha-1}$

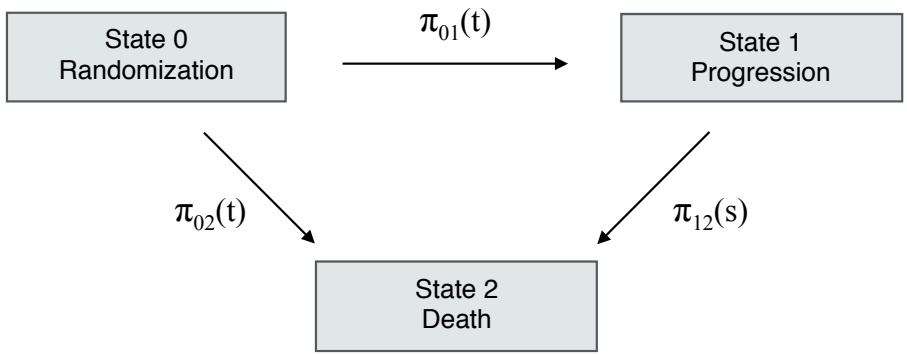

Figure: The three-state illness death model for cancer survival

After estimating the parameters via maximum likelihood, they can be used for a closed-form expression for the Pearson correlation between PFS and OS

Model-based method

Restrictions of the model-based approach of Li and Zhang (2015)

- Paper uses a simplification by assuming the same shape parameter α for the three Weibull functions
- A non-linear dependence between PFS and OS is expected, as time-to-event outcomes would be highly positively skewed
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$\Longrightarrow$ **Generalized model-based method**: Extension of proposed model to allow Kendall rank correlation coefficient for illness-death models and to enable different shape parameters for each transition function.

Monte-Carlo methods for evaluating the model-based Kendall's tau

- Calculation of Kendall's τ: Integrals are analytically intractable.
- Lack of a closed form expression
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- For a model where S and T are continuous, Kendall's tau can be written as

$$\tau = 4P(S_1 > S_2, T_1 > T_2) - 1$$

- Simulating $2M$ pairs of (S_i, T_i), $P(S_1 > S_2, T_1 > T_2)$ can be estimated as

$$\hat{P}(S_1 > S_2, T_1 > T_2) = M^{-1} \sum_{i=1}^{M} I(S_i > S_{i+M}, T_i > T_{i+M})$$

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- By using *the simulation delta method*, the confidence interval for τ_{mod} can be obtained

Simulations: General Setting

- Assumption: true underlying model is an illness-death model
- Sample size of each data set: 1000, number of simulations: 1000
- Uniform distributed censoring for each scenario:
  20%/ 45% of patients whose OS time is censored

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- Scenario C
  - Investigation of the sensitivity of the illness-death model-based method to misspecification $\rightarrow$ Non-markov assumption

Boxplots for the scenario A

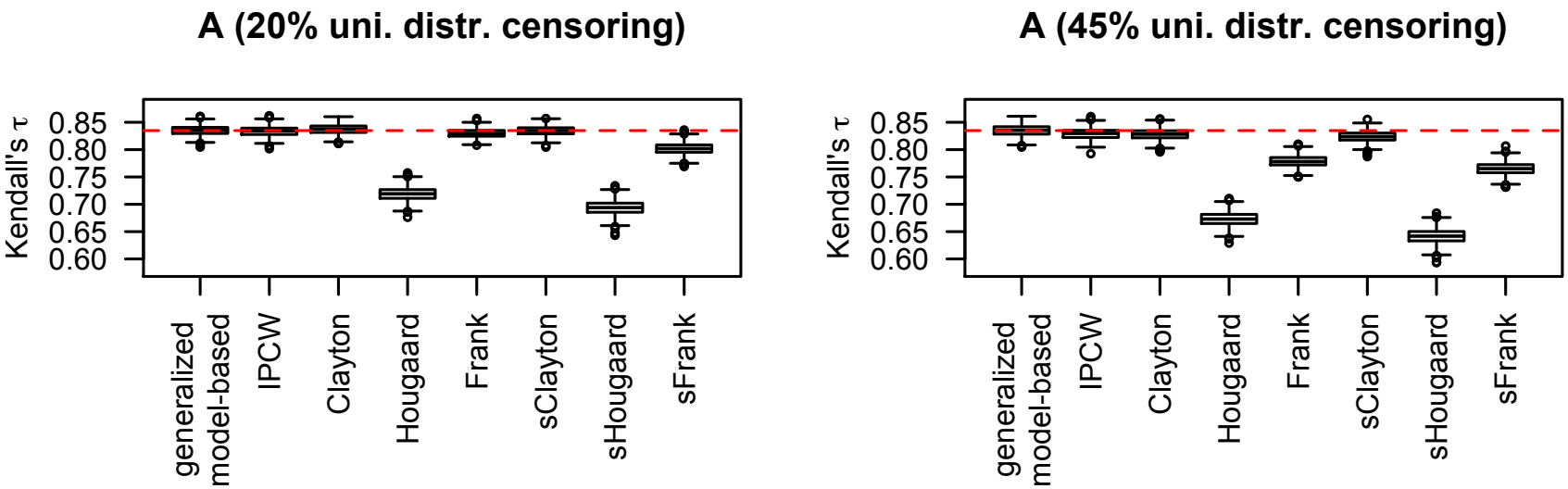


Figure: Box-plots of estimates of Kendall's tau from 8 methods. Dashed red line indicates the true value.

Contour plot for the scenario A

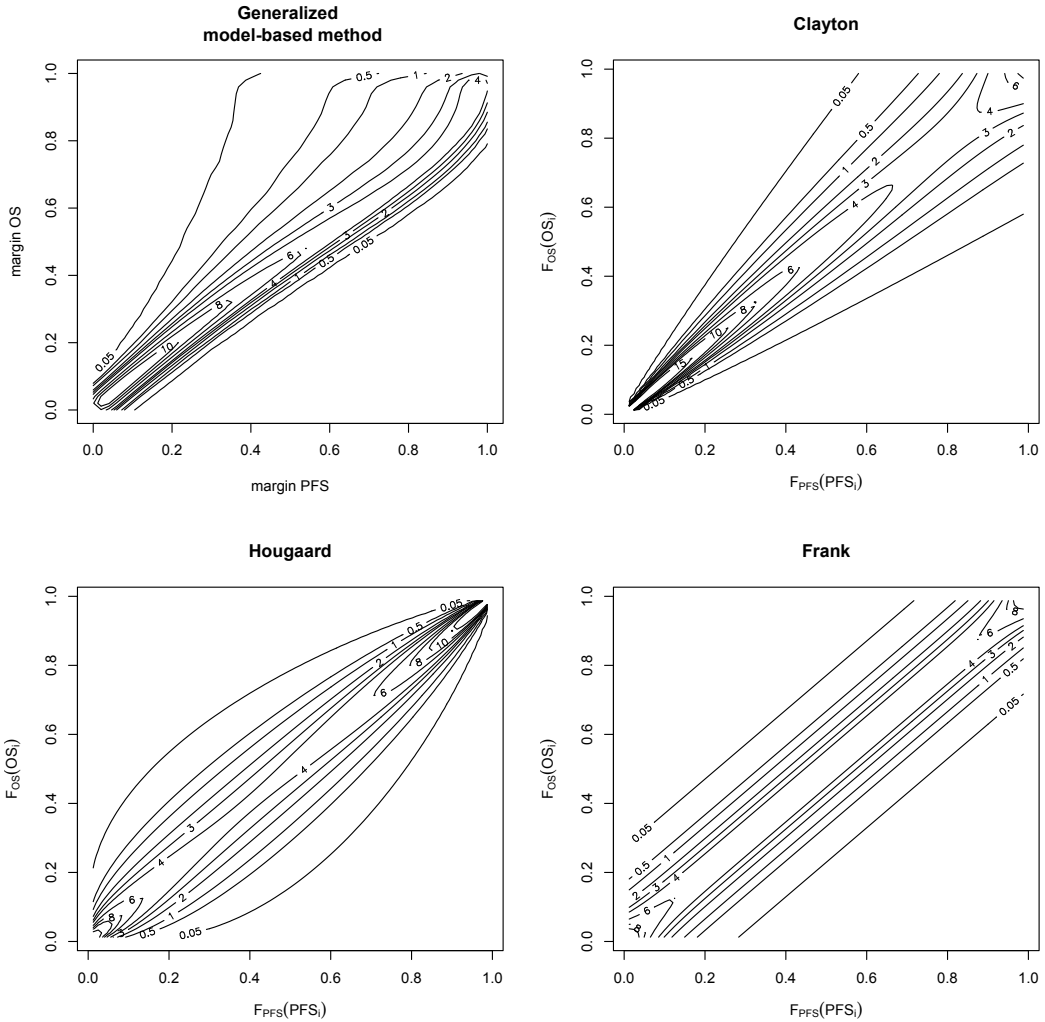
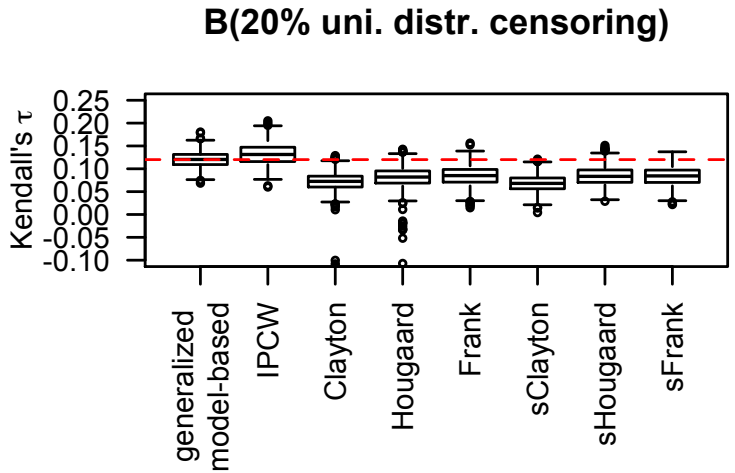


Figure: Realistic simulation case: Contour plots for the bivariate density function. Model based Kendall's tau τ is 0.836.

Boxplots for the unrealistic scenario (B) and non-markov scenario (C)

Figure: Box-plots of estimates of Kendall's tau from all methods. Dashed red line indicates the true value.



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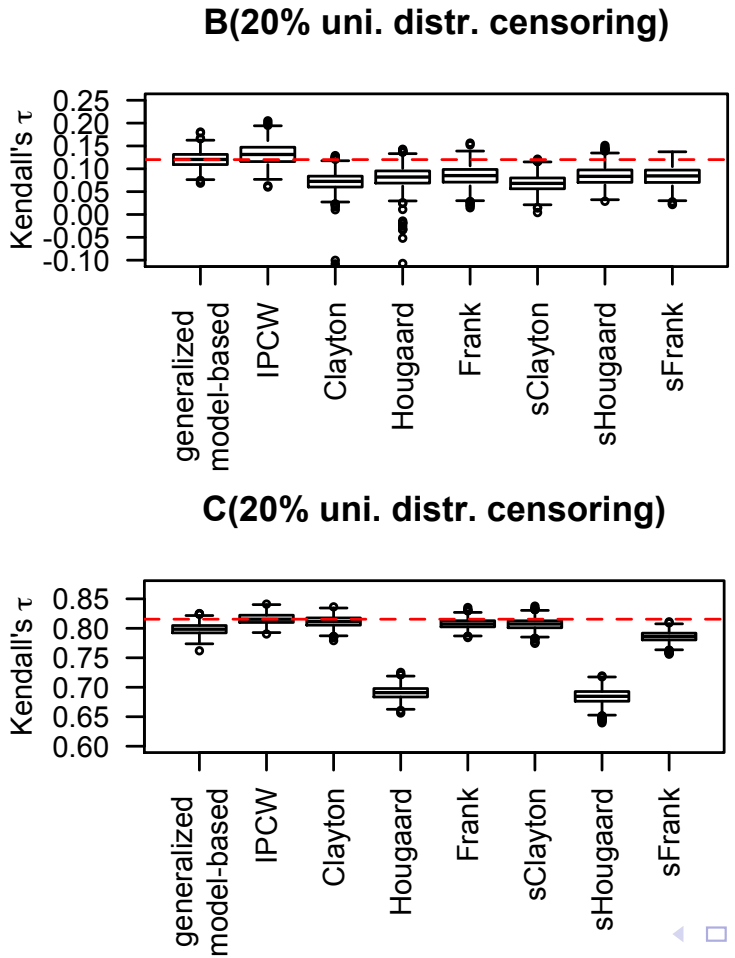

Application

Description of the clinical trial of treatments for colon cancer

- Investigation of the effectiveness of two adjuvant therapies in improving surgical cure rates in stage III colon cancer.
- Randomization of 929 Patients to observation, treatment levamisole alone or to a combination of levamisole plus fluorouracil.
- Measurements: time to progression and time to death
- Median follow-up time: 6.5 years
- Maximum follow-up time: 9.1 years,
  $\rightarrow$ 43%/46% would be yet to experience the PFS time/OS time.
  $\rightarrow$ considerable extrapolation beyond the follow-up period is required to fully characterize the distributions.

Application

Application of the methods to the data from the clinical trial

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$$\Downarrow$$

- None of the Weibull-based models represented an adequate fit to the data.
- To improve the model fit we considered Royston-Parmar (RP) flexible parametric models:
- We consider models for which the cumulative log-hazard function $\log H(t)$ is modelled as a natural cubic spline $s(x, \gamma)$ with respect to log time $x := \log t$.

Application

Flexible splines

- Boundary knots k_{min}, k_{max} at the lowest and highest uncensored event times
- Internal knots $k_1, \ldots, k_m$ with $k_1 > k_{min}$ and $k_m < k_{max}$ at quantiles of the distribution of uncensored event times.

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$\Rightarrow$ Natural cubic spline:

$$s(x, \gamma) = \gamma_0 + \gamma_1 x + \gamma_2 \nu_1(x) + \ldots + \gamma_{m+1} \nu_m(x),$$

where $\nu_j(x)$ is jth spline basis function for $j = 1, \ldots, m$:

$$\nu_j(x) = (x - k_j)_+^3 - \lambda_j (x - k_{\min})_+^3 - (1 - \lambda_j)(x - k_{\max})_+^3,$$

where $\lambda_j = (k_{\max} - k_j)/(k_{\max} - k_{\min})$ and
$(x - a)_+ = \max(0, x - a)$.

Application

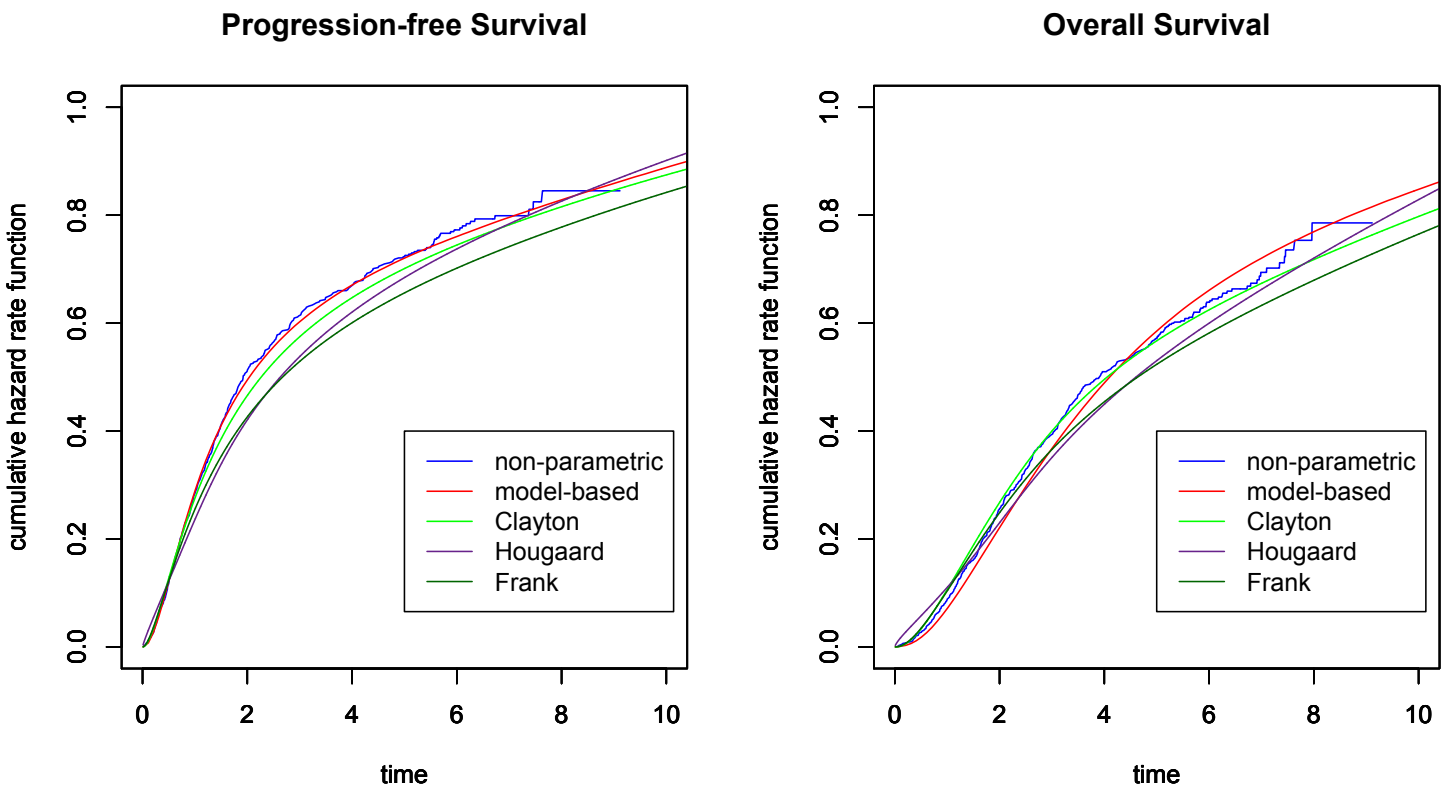

Figure: Nelson-Aalen and model-based estimates of the marginal cumulative hazard functions for PFS and OS where the parametric models are fitted using Royston-Parmar distributions

Application

Table: Comparison of estimates of Kendall's τ derived from each of methods and associated standard errors for the colon cancer dataset.

model	Kendall's τ	standard error
generalized model-based method	0.836	0.01152
IPCW estimator	0.834	0.01084
one-stage fully parametric model(Clayton)	0.845	0.00921
one-stage fully parametric model (Hougaard)	0.736	0.01311
one-stage fully parametric model (Frank)	0.806	0.01003
two-stage semi-parametric model (Clayton)	0.830	0.00957
two-stage semi-parametric model (Hougaard)	0.668	0.12606
two-stage semi-parametric model (Frank)	0.767	0.03121

- One similarity to the simulation results:
  High sensitivity to choice of copula, as the values of the Kendall's τ differ in the different copula models as well.

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Accommodation of treatment into the models for Kendall's τ

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Completely separate models fit to each treatment arm:

Table: Kendall's τ and standard error for each treatment arm

	RP model-based method		RP Clayton model		IPCW method	
Treatment arm	Kendall's τ	se	Kendall's τ	se	Kendall's τ	se
Control group	0.786	0.023	0.810	0.017	0.802	0.020
Treatment "Lev" group	0.804	0.023	0.816	0.018	0.805	0.021
Treatment "Lev+5FU" group	0.903	0.015	0.912	0.011	0.901	0.014

It is of interest whether Kendall's τ between PFS and OS is different for each treatment arm
$\Rightarrow$ Treatment affects the degree of dependence between PFS and OS,
as Lev and Lev+5FU decreases the hazard of progression and hence increases the proportion of patients for whom PFS equals OS.

Discussion

- The estimate of Kendall's tau is sensitive to the choice of copula.
  - Clayton Copula may be appropriate in cancer survival, as it focuses on the dependence in the lower tail of the bivariate density function

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- Generalized model-based method
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  - Parametric assumptions about the transition intensities have to be taken into account.
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- The estimate of Kendall's tau is sensitive to the choice of copula.
  - Clayton Copula may be appropriate in cancer survival, as it focuses on the dependence in the lower tail of the bivariate density function
- Generalized model-based method
  - Relies on the underlying model being close to correctly specified
  - Parametric assumptions about the transition intensities have to be taken into account.
  - Use of hazard functions based upon flexible natural cubic splines
- Censoring: It is assumed the time of progressioen/death can be observed up to right-censoring
  - In practice: assessments of progression are intermittent resulting in different right-censoring times for progression and death and interval-censored progression times

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Thank you very much for your attention!

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