Individualized treatment effect was predicted best by modeling baseline risk in interaction with treatment assignment

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Abstract

Objective: To compare different risk-based methods for optimal prediction of individualized treatment effects from RCTs. **Study Design and Setting**: We simulated RCT data using diverse assumptions for the average treatment effect, a baseline prognostic index of risk (PI), the shape of its interaction with treatment (none, linear, quadratic or non-monotonic) and the magnitude of treatment-related harms (none or constant independent of the PI). In each sample we predicted absolute benefit using: models with a constant relative treatment effect; stratification in quarters of the PI; models including a linear interaction of treatment with the PI; models including an interaction of treatment with a restricted cubic spline (RCS) transformation of the PI; an adaptive approach using Akaike's Information Criterion. We evaluated predictive performance using root mean squared error and measures of discrimination and calibration for benefit. **Results**: The linear-interaction model and the RCS-interaction model outperformed the constant treatment effect model in many simulation scenarios. The RCS-model was optimal when quadratic or non-monotonic deviations from a constant treatment effect were stronger, and when sample size was larger. Larger sample size also supported the adaptive approach. Illustrations in the GUSTO-I trial confirmed these findings. **Conclusion**: An interaction between baseline risk and treatment assignment should be considered to improve treatment effect predictions. Non-linear RCS interactions should be considered only in larger sample sizes.

Keywords: treatment effect heterogeneity absolute benefit prediction models

1. Introduction

Predictive approaches for assessing heterogeneity of treatment effects (HTE) aim at the development of models predicting either individualized effects or which of two (or more) treatments is better for an individual [1]. In prior work, we divided such methods in three broader categories based on the reference class used for defining patient similarity when making individualized predictions or recommendations [2]. First, risk-modeling approaches use prediction of baseline risk as the reference; second, treatment effect modeling approaches also

model treatment-covariate interactions, in addition to risk factors; third, optimal treatment regime approaches focus on developing treatment assignment rules and rely heavily on modeling treatment effect modifiers. A key difference between these approaches is their parsimony in dealing the treatment effect modifiers, with no interaction considered (risk modeling), a limited number of interactions (effect modeling), or a larger set of interactions (optimal treatment regime approaches).

Risk-modeling approaches to predictive HTE analyses provide a viable option in the absence of well-established treatment effect modifiers [3,4]. In simulations, modeling of effect modifiers, i.e. treatment-covariate interactions, often led to miscalibrated predictions of benefit, while risk-based methods proved quite robust [5]. Most often, risk-modeling approaches are carried out in two steps: first a risk prediction model is developed externally or internally on the entire RCT population, "blinded" to treatment; then the RCT population is stratified using this prediction model to evaluate risk-based treatment effect variation [6]. This two-step approach identified substantial absolute treatment effect differences between low-risk and high-risk patients in a re-analysis of 32 large trials [7]. However, even though estimates at the risk subgroup level may be accurate, these estimates may need further refinement for individual patients, especially for patients with predicted risk at the boundaries of the risk intervals. Hence, the risk-stratified approach is useful for exploring and presenting HTE, but is not sufficient for supporting treatment decisions for individual patients.

To individualize treatment effects, the recent PATH statement suggested various risk-based models including a prognostic index of baseline risk (PI) and treatment assignment [3,4]. We aimed to summarize and compare different risk-based models for predicting individualized treatment effects. We simulated RCT settings to compare the performance of these models under different assumptions of the relation between baseline risk and treatment. We illustrated the different models by a case study of predicting individualized effects of treatments for acute myocardial infarction (MI) in a large randomized controlled trial (RCT).

2. Methods

2.1. Simulation scenarios

We simulated a typical RCT that is undertaken to compare a binary outcome (e.g. death) between a group of patients in the treatment arm and a group of untreated patients in the control arm. For each patient we generated 8 baseline covariates $x_1, \ldots, x_4 \sim N(0,1)$ and $x_5, \ldots, x_8 \sim B(1, 0.2)$. Treatment was allocated using a 50:50 split. Outcomes for patients in the control arm were generated from a logistic regression model including all baseline covariates. In the base scenarios coefficient values were such, that the AUC of the logistic regression model was 0.75 and the event rate in the control arm was 20%. Binary outcomes in the control arm were generated from Bernoulli variables with true probabilities $P(y = 1|X, t_x = 0) = \text{expit}(PI) = \frac{e^{PI}}{1+e^{PI}}$.

Outcomes in the treatment arm were generated using 3 base scenarios: absent treatment effect (OR = 1), moderate treatment effect (OR = 0.8) and strong treatment effect (OR = 0.5). We started with simulating outcomes based on true constant relative treatment effects for the 3 base scenarios. We then simulated linear, quadratic and non-monotonic deviations from constant treatment effects using:

$$lp_1 = \gamma_2(PI - c)^2 + \gamma_1(PI - c) + \gamma_0,$$

where lp_1 is the true linear predictor in the treatment arm, so that $P(y = 1|X, t_x = 1) = \text{expit}(lp_1)$. Finally, we simulated scenarios where a constant absolute harm is applied across all treated patients. In this case we have $P(y = 1|X, t_x = 1) = \text{expit}(lp_1) + \text{harm}$.

The sample size for the base scenarios was set to 4,250, since this sample size provides 80% power for the detection of a marginal OR of 0.8 with the standard alpha of 0.5%. We evaluated the effect of smaller or larger sample sizes of 1,063 (4,250 divided by 4) and 17,000 (4250 multiplied by 4), respectively. We also evaluated the effect of worse or better discriminative ability for risk, adjusting the baseline covariate coefficients, such that the AUC of the regression model in the control arm was 0.65 and 0.85 respectively.

Combining all these settings resulted in a simulation study of 648 scenarios (exact settings in the supplementary material). With these scenarios we were able to cover the observed treatment effect heterogeneity in 32 large trials as well as many other potential variations of risk-based treatment effect [7].

2.2. Individualized risk-based benefit predictions

All risk-based methods assume that a risk prediction model is available to assign risk predictions to individual patients. For the simulations we developed a prediction model internally, using logistic regression including main effects for all baseline covariates and treatment assignment. Risk predictions for individual patients were based on treatment assignment to the control arm, that is setting treatment assignment to 0.

A *stratified HTE method* has been suggested as an alternative to traditional subgroup analyses. Patients are stratified into equally-sized risk strata—in this case based on risk quartiles. Absolute treatment effects within risk strata are estimated by the difference in event rate between patients in the control arm and patients in the treated arm. We considered this approach as a reference, expecting it to perform worse than the other candidates, as its objective is to provide an illustration of HTE rather than to optimize individualized benefit predictions.

Second, we considered a model which assumes *constant relative treatment effect* (constant odds ratio). Hence, absolute benefit is predicted from $\hat{\tau}(\boldsymbol{x}) = \text{expit}(PI + \log(\text{OR}))$.

Third, we considered a logistic regression model including treatment, the prognostic index, and their linear interaction. Absolute benefit is then estimated from $\hat{\tau}(\boldsymbol{x}) = \text{expit}(\beta_0 + \beta_{PI}PI) - \text{expit}(\beta_0 + \beta_{t_x} + (\beta_{PI} + \beta_*)PI)$.

We will refer to this method as the *linear interaction* approach.

Fourth, we used *restricted cubic splines* (RCS) to relax the linearity assumption on the effect of the linear predictor [8]. We considered splines with 3 (RCS-3), 4 (RCS-4) and 5 (RCS-5) knots to compare models with different levels of flexibility.

Finally, we considered an adaptive approach using Akaike's Information Criterion (AIC) for model selection. The candidate models were: a constant treatment effect model, a model with a linear interaction with treatment and RCS models with 3, 4 and 5 knots. The extra degrees of freedom were 1 (linear interaction), 2, 3 and 4 (RCS models) for these increasingly complex interactions with the treatment effect.

2.3. Evaluation metrics

We evaluated the predictive accuracy of the considered methods by the root mean squared error (RMSE):

$$\text{RMSE} = \sqrt{\frac{1}{n}\sum_{i=1}^{n}\left(\tau(\boldsymbol{x}_i) - \hat{\tau}(\boldsymbol{x}_i)\right)^2}$$

We compared the discriminative ability of the methods under study using c-for-benefit [9]. The c-for-benefit represents the probability that from two randomly chosen matched patient pairs with unequal observed benefit, the pair with greater observed benefit also has a higher predicted benefit. To be able to calculate observed benefit, patients in each treatment arm are ranked based on their predicted benefit and then matched 1:1 across treatment arms. *Observed* treatment benefit is defined as the difference of observed outcomes between the untreated and the treated patient of each matched patient pair. *Predicted* benefit is defined as the average of predicted benefit within each matched patient pair.

We evaluated calibration in a similar manner, using the integrated calibration index (ICI) for benefit [10]. The observed benefits are regressed on the predicted benefits using a locally weighted scatterplot smoother (loess). The ICI-for-benefit is the average absolute difference between predicted and smooth observed benefit. Values closer to 0 represent better calibration.

3. Results

3.1. Simulations

The linear interaction model outperformed all RCS methods in terms of RMSE in scenarios with true constant relative treatment effect (OR $= 0.8$, N $=$ 4,250 and AUC $= 0.75$), strong linear and even strong quadratic deviations from a constant relative treatment effect (Figure 1; panels A-C). However, with non-monotonic deviations from a constant relative treatment effect, the RMSE of the linear interaction model increased substantially, especially in the presence of treatment-related harms (Figure 1; panel D). In these scenarios, RCS-3 outperformed all other methods

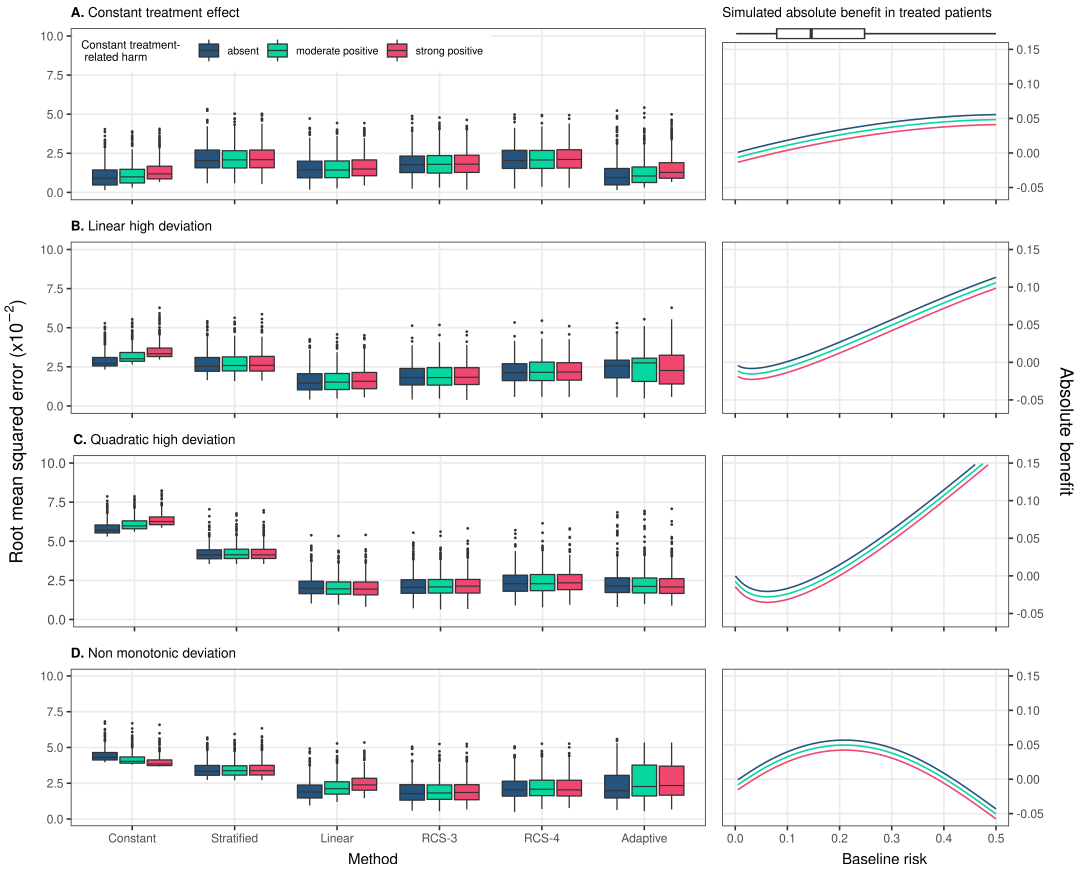

Figure 1: RMSE of the considered methods across 500 replications calculated from a simulated super-population of size 500,000. The scenario with true constant relative treatment effect (panel A) had a true prediction AUC of 0.75 and sample size of 4250. The RMSE is also presented for strong linear (panel B), strong quadratic (panel C), and non-monotonic (panel D) from constant relative treatment effects. Panels on the right side present the true relations between baseline risk (x-axis) and absolute treatment benefit (y-axis). The 2.5, 25, 50, 75, and 97.5 percentiles of the risk distribution are expressed by the boxplot.

in terms of RMSE. As might be expected the constant treatment effect approach had overall best performance under true constant treatment effect settings. It was sensitive to all considered deviations, resulting in increased RMSE. Finally, the adaptive approach had comparable performance to the best-performing method in each scenario. However, in comparison with the best-performing approach, its RMSE was more variable in the scenarios with linear and non-monotonic deviations, especially when also including moderate or strong treatment-related harms. On closer inspection, we found that this behavior was caused by wrongly selecting the constant treatment effect model in a substantial proportion of the replications (Supplement, Figure S1). This problematic behavior was less with larger sample sizes (see below).

Increasing the sample size to 17,000 favored RCS-3 the most, It achieved lowest or close to lowest RMSE across all scenarios (Figure 2). Especially in cases of strong quadratic and non-monotonic deviations RCS-3 had lower RMSE (median 0.011 for strong quadratic deviations and 0.010 for non-monotonic deviations with no treatment-related harms) compared to the linear interaction approach (median 0.013 and 0.014, respectively),

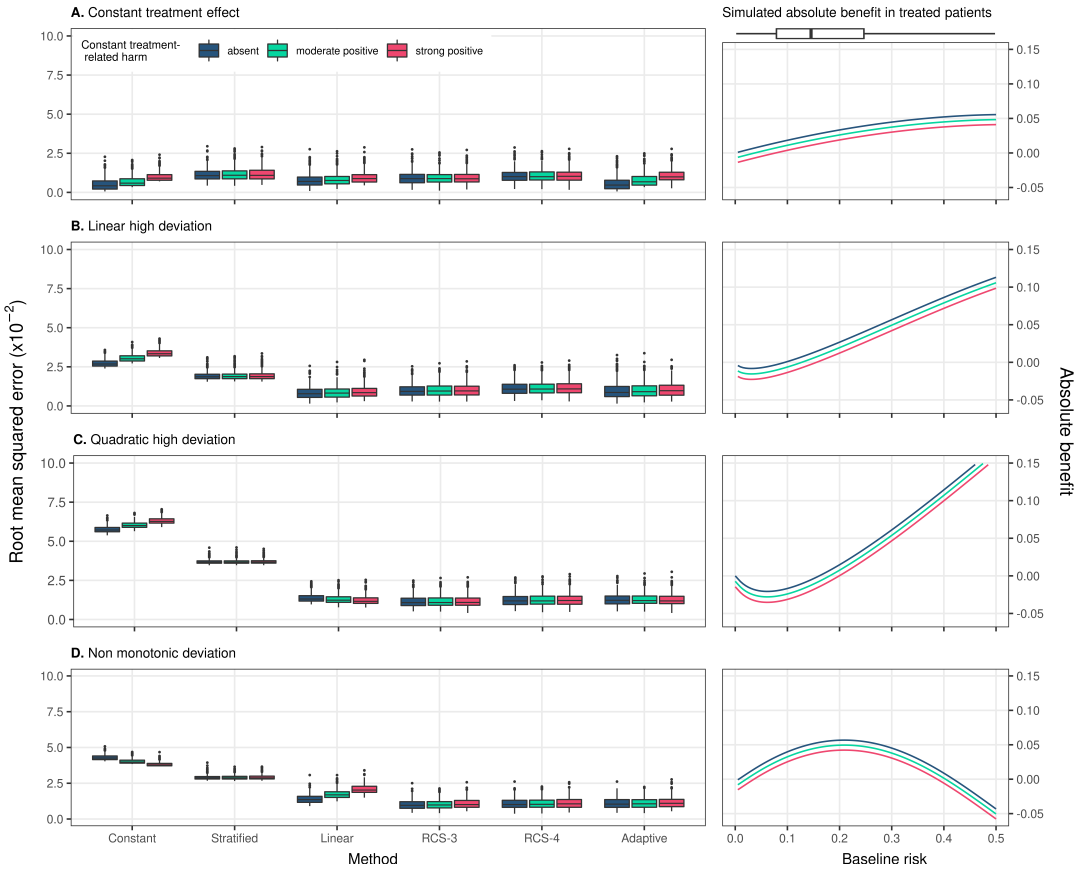

Figure 2: RMSE of the considered methods across 500 replications calculated in simulated samples of size 17,000 rather than 4,250 in Figure 1

regardless of the strength of treatment-related harms. Due to the large sample size, the RMSE of the adaptive approach was even more similar to the best-performing method, and the constant relative treatment effect model was less often wrongly selected (Supplement, Figure S2).

When we increased the AUC of the true prediction model to 0.85 (OR = 0.8 and N = 4,250). RCS-3 had the lowest RMSE in the case of strong quadratic or non-monotonic deviations and very comparable performance to the – optimal – linear interaction model in the case of strong linear deviations (median RMSE 0.016 for RCS-3 compared to 0.014 for the linear interaction model). As observed in the base case scenario the adaptive approach wrongly selected the constant treatment effect model (23% and 25% of the replications in the strong linear and non-monotonic deviation scenarios without treatment-related harms, respectively), leading to more variability of the RMSE (Supplement, Figure S3).

In comparison with the true approach, dsicrimination for benefit in the scenario with a constant relative treatment effect was only slightly lower for the linear interaction model, but substantially lower for the non-linear RCS approaches (Figure 4; panel A). With strong linear or quadratic deviations from a constant relative treatment effect, all methods discriminated quite similarly (Figure 4; panels B-C). In the scenario with non-monotonic

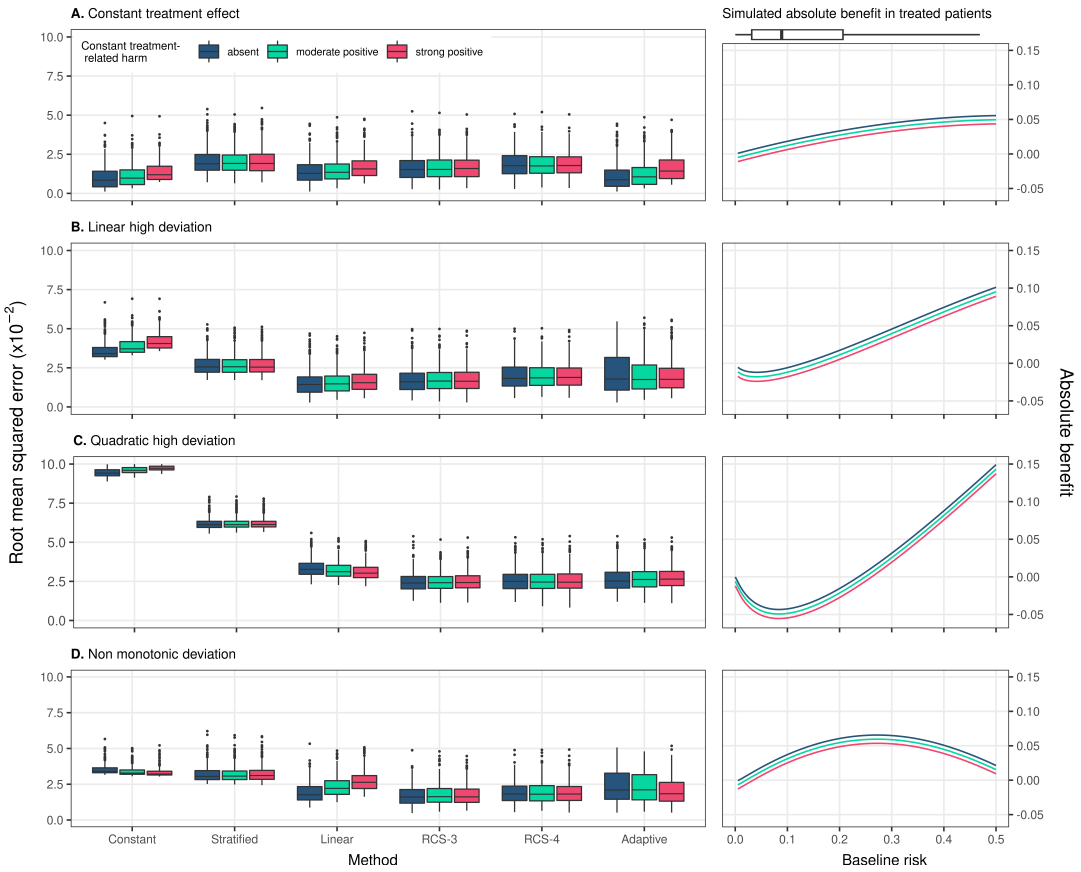

Figure 3: RMSE of the considered methods across 500 replications calculated in a simulated samples 4,250. True prediction AUC of 0.85.

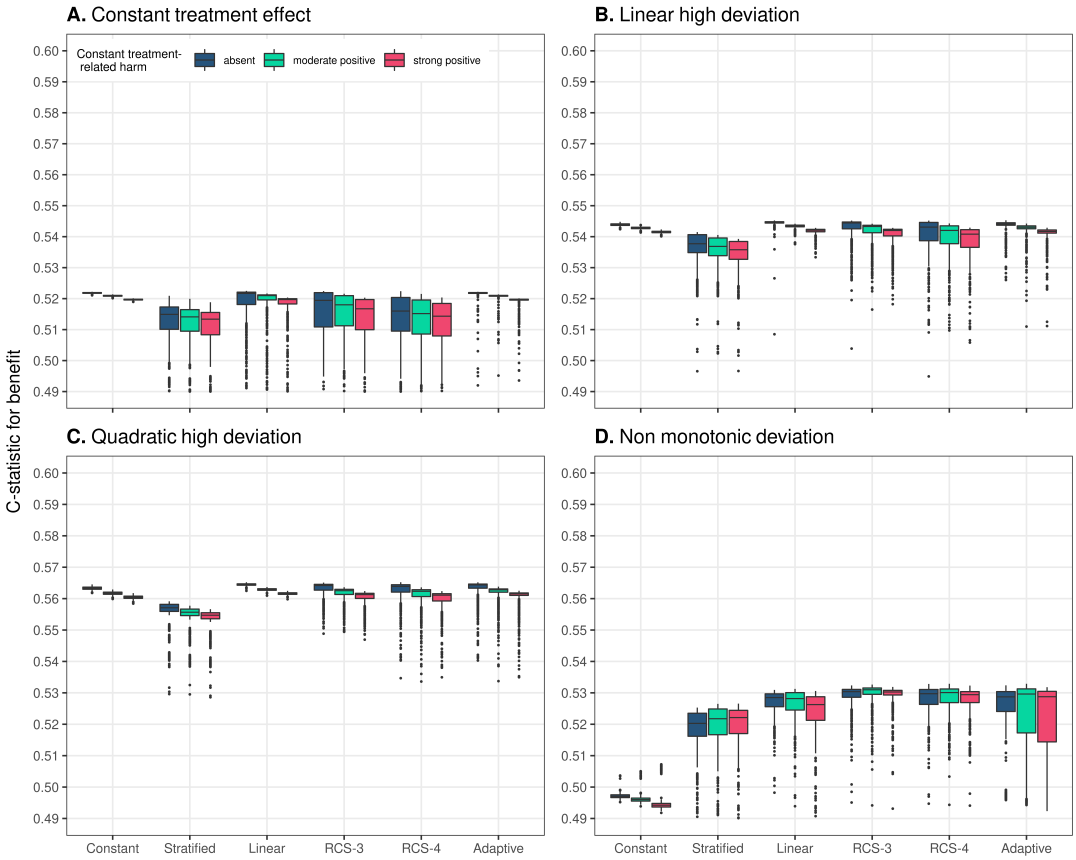

Figure 4: Discrimination for benefit of the considered methods across 500 replications calculated in a simulated samples of size 4,250. True prediction AUC of 0.75.

deviations, the constant effect model had much lower discriminative ability compared to all other methods (median AUC of 0.4971 for the constant effects model, 0.5285 for the linear interaction model and 0.5304 for the best-performing RCS-3; Figure 4; panel D). The adaptive approach was unstable in terms of discrimination for benefit, especially in the presence of treatment-related harms. With increasing number of RCS knots, we observed decreasing median values and increasing variability of the c-for-benefit in all scenarios. When we increased the sample size to 17,000 we observed similar trends, however the performance of all methods was more stable (Supplement, Figure S4). Finally, when we increased the true prediction AUC to 0.85 the adaptive approach in the case of non-monotonic deviations was, again, quite unstable, especially with null or moderate treatment-related harms (Supplement, Figure S5). In these scenarios, the adaptive approach tended to select more often the inferior constant treatment effect method (Supplement, Figure S3)

In terms of calibration for benefit, the constant effects model outperformed all other models in the scenario with true constant treatment effects, but was miscalibrated for all deviation scenarios (Figure 5). The linear interaction model showed best or close to best calibration across all scenarios and only showed worse calibration compared to RCS-3 in case of non-monotonic deviations and treatment-related harms (Figure 5; panel D). The adaptive

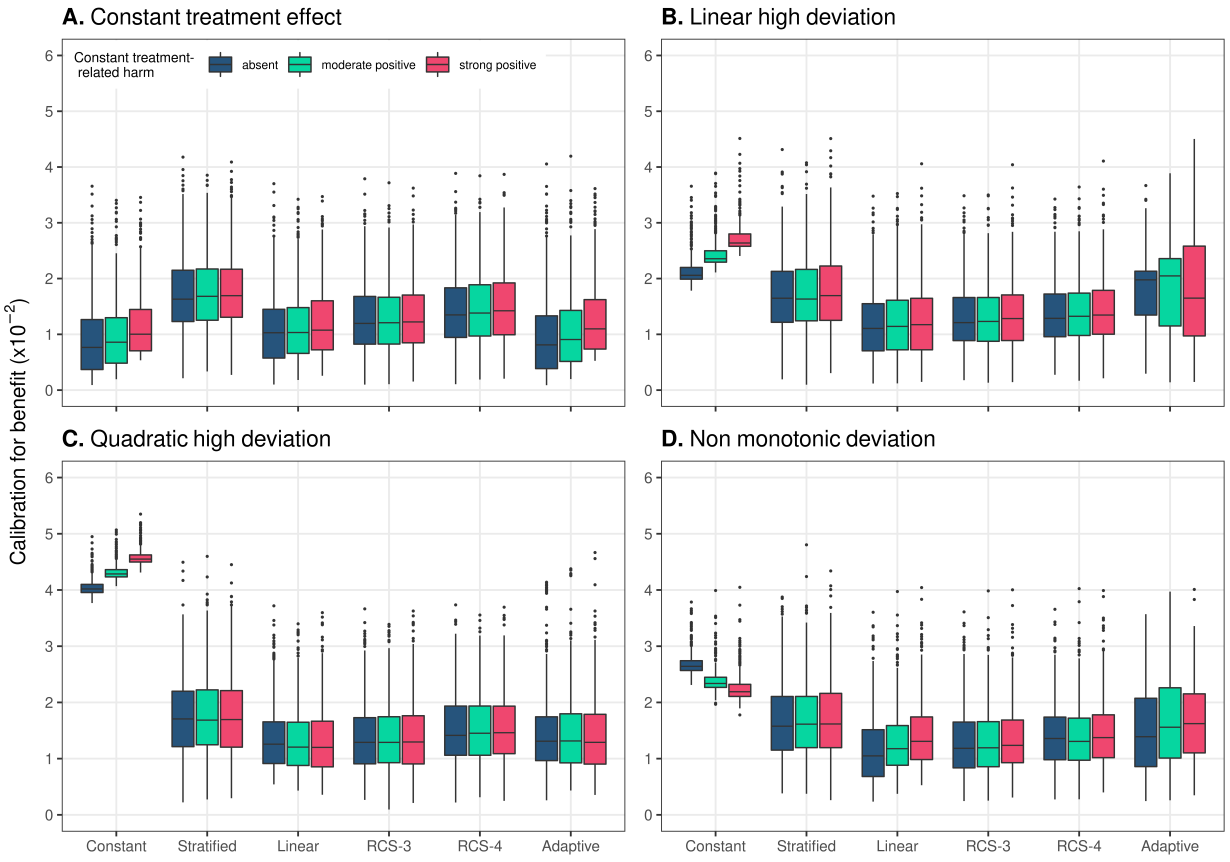

Figure 5: Calibration for benefit of the considered methods across 500 replications calculated in a simulated sample of size 500,000. True prediction AUC of 0.75 and sample size of 4,250.

approach was worse calibrated in scenarios with strong linear and non-monotonic deviations compared to the linear interaction model and RCS-3. When we increased sample size to 17,000 similar conclusions on calibration for benefit could be drawn. As expected, all methods displayed more stable calibration performance due to the larger number of patients (Supplement, Figure S6). When we increased the true prediction AUC to 0.85, the linear interaction model was worse calibrated, on average, than RCS-3 in the case of strong quadratic deviations from constant relative treatment effects (Supplement, Figure S7).

The results from all individual scenarios can be explored online at https://arekkas.shinyapps.io/simulation_viewer/.

3.2. Case study

We demonstrate the different methods for individualizing treatment benefits using data from 30,510 patients with acute myocardial infarction (MI) included in the GUSTO-I trial. 10,348 patients were randomized to tissue plasminogen activator (tPA) treatment and 20,162 were randomized to streptokinase. The outcome of interest was 30-day mortality (total of 2,128 events), recorded for all patients.

In line with previous analyses [11,12], we fitted a logistic regression model with 6 baseline covariates, i.e. age, Killip class, systolic blood pressure, heart rate, an indicator of previous MI, and the location of MI, to predict 30-day mortality risk. A constant effect of treatment was included in the model. When deriving risk predictions for individuals we set the treatment indicator to 0. More information on model development can be found in the supplement.

We used the risk linear predictor to fit the proposed methods under study for individualizing absolute benefit predictions. All methods predicted increasing benefits for patients with higher baseline risk predictions, but the fitted patterns were somewhat different. The adaptive approach selected the model with RCS smoothing with 4 knots. However, for very low baseline risk the decreasing predicted benefit with increasing risk may be somewhat too flexible. The more robust models, such as the linear interaction model and the model with RCS smoothing (3 knots), gave very similar benefit predictions. These models followed the evolution of the stratified estimates very closely and may therefore be preferable for use in clinical practice. The linear interaction model had somewhat lower AIC compared to the model with RCS smoothing (3 knots), slightly better cross-validated discrimination (c-for-benefit 0.526 vs 0.525) and quite similar cross-validated calibration (ICI-for benefit 0.0115 vs 0.0117).

4. Discussion

The linear interaction model and the RCS-3 model both displayed very good performance under many of the considered simulation scenarios, in contrast with the constant relative treatment effect model. The linear interaction model was optimal in cases with smaller sample sizes and moderately performing baseline risk prediction models, that is, it had lower RMSE, was better calibrated for benefit and had better discrimination for benefit, even in scenarios with strong quadratic deviations. In scenarios with true non-monotonic deviations, the linear interaction model was outperformed by RCS-3, especially in the presence of true treatment-related harms. Increasing the sample size or the prediction model's discriminative ability favored RCS-3, especially in scenarios with non-monotonic deviations and in the presence of treatment-related harms.

RCS-4 and RCS-5 proved to be too flexible in all considered scenarios, as indicated by higher RMSE, increased variability of discrimination for benefit and worse calibration of benefit predictions. Even with larger sample sizes and strong quadratic or non-monotonic deviations from the base case scenario of constant relative treatment effects, these more flexible restricted cubic splines did not outperform the simpler RCS-3 These approaches may only be helpful if we expect more extreme patterns of heterogeneous treatment effects compared to the quadratic deviations considered here. Considering interactions in RCS-3 models as the most complex approach often may be reasonable.

The constant treatment effect model, despite having adequate performance in the presence of weak treatment

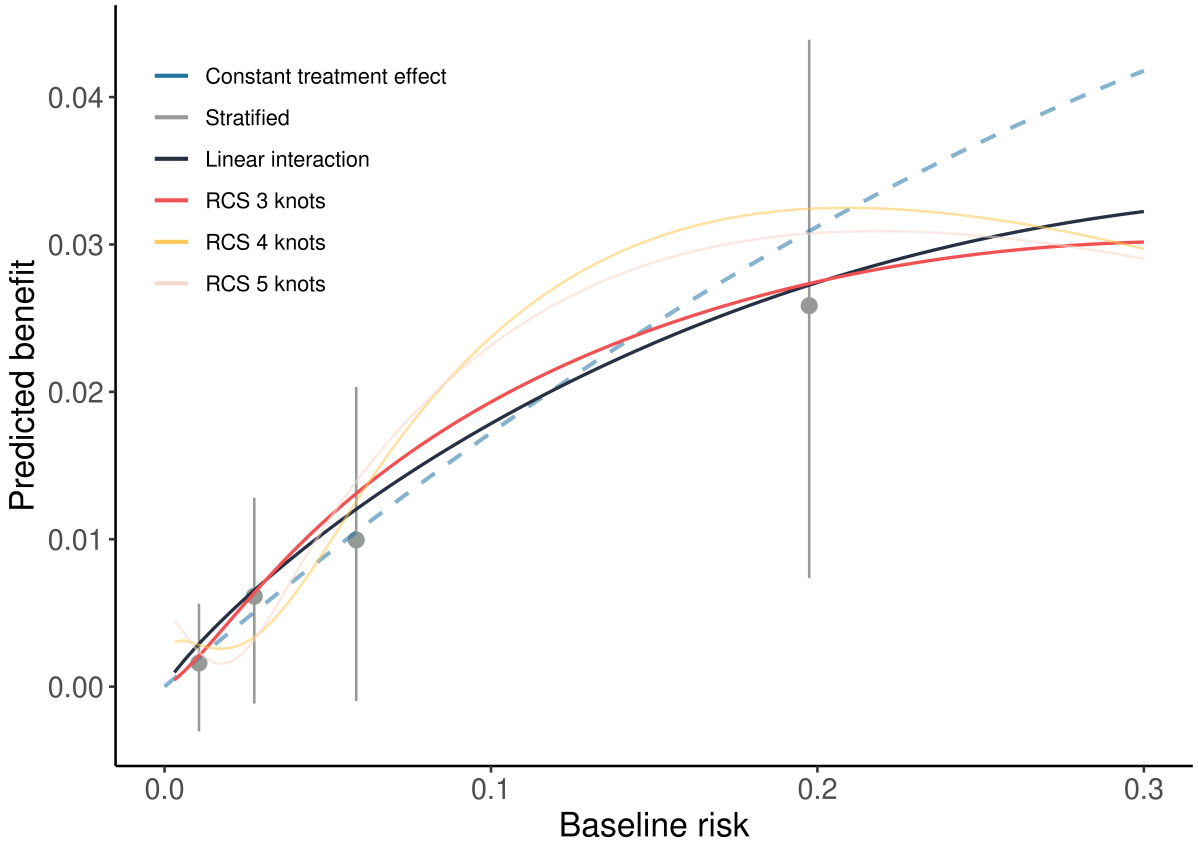

Figure 6: Individualized absolute benefit predictions based on baseline risk when using a constant treatment effect approach, a linear interaction approach and RCS smoothing using 3,4 and 5 knots. Risk stratified estimates of absolute benefit are presented within quartiles of baseline risk as reference.

effect heterogeneity on the relative scale, quickly broke down with stronger deviations from constant relative treatment effects. In these cases, the stratified approach generally had lower error rates compared to the constant treatment effect model. Such stepwise treatment benefit estimates are useful for visually demonstrating treatment effect heterogeneity but may be considered insufficient for making individualized benefit predictions.

Increasing the discriminative ability of the risk model–by increasing the predictor coefficients of the true risk model–reduced RMSE for all methods. This increase in discriminative ability translates in higher variability of predicted risks, which, in turn, allows the considered methods to better capture absolute treatment benefits. As a consequence, the increase in discriminative ability of the risk model also led to higher discrimination between those with low or high benefit (as reflected in values of c-for-benefit). Even though risk model performance is very important for the ability of risk-based methods to predict treatment benefit, prediction model development was outside the scope of this work and has already been studied extensively [5,13,14].

The adaptive approach had adequate performance, following closely on average the performance of the "true" model in most scenarios. With smaller sample sizes it tended to miss the treatment-risk interactions and selected simpler models (Supplementary Table S7). This conservative behavior resulted in increased RMSE variability in these scenarios, especially in the case of true strong linear or non-monotonic deviations from the base case scenario. Therefore, in the case of smaller sample sizes the simpler linear interaction model may be a safer choice for predicting absolute benefits, if a non-constant treatment effect is suspected.

Risk-based approaches to predictive HTE estimate treatment benefit as a function of baseline risk. A limitation of our study is that we assumed treatment benefit to be a function of baseline risk in the majority of the simulation scenarios. We also considered constant moderate and strong treatment-related harms, applied on the absolute scale to expand the range of scenarios in line with previous work (REF!!). Also, we considered a small number of scenarios with true treatment-covariate interactions, in which our main conclusions remained the same (Supplement, XX). Future simulation studies could explore the effect of more extensive deviations from risk-based treatment effects.

Recent years have seen an increased interest in predictive HTE approaches focusing on individualized benefit predictions. In our simulations we only focused on risk-based methods, using baseline risk as a reference in a two-stage approach to individualizing benefit predictions. However, there is a plethora of different methods, ranging from treatment effect modeling to tree-based approaches available in more recent literature [15–17]. Simulations are also needed to assess relative performance and define the settings where these break down or outperform each other.

In conclusion, the linear interaction approach is a viable option with smaller sample sizes and/or moderately performing risk prediction models if we consider a non-constant relative treatment effect plausible. RCS-3 is a better option when non-monotonic deviations from a constant relative treatment effect and/or substantial

treatment-related harms are anticipated. With larger sample size, an adaptive approach – selecting the method with optimal AIC – can also be considered as an automated alternative.

5. References

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