

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 interactions should be considered only in larger sample sizes.

Keywords: treatment effect heterogeneity absolute benefit prediction models

¹ 1. Introduction

² Predictive approaches for assessing heterogeneity of treatment effects (HTE) aim at the development of
³ models predicting either individualized effects or which of two (or more) treatments is better for an individual
⁴ [1]. In prior work, we divided such methods in three broader categories based on the reference class used for
⁵ defining patient similarity when making individualized predictions or recommendations [2]. First, risk-modeling
⁶ approaches use prediction of baseline risk as the reference; second, treatment effect modeling approaches also
⁷ model treatment-covariate interactions, in addition to risk factors; third, optimal treatment regime approaches

8 focus on developing treatment assignment rules and rely heavily on modeling treatment effect modifiers. A key
9 difference between these approaches is their parsimony in dealing the treatment effect modifiers, with no interaction
10 considered (risk modeling), a limited number of interactions (effect modeling), or a larger set of interactions
11 (optimal treatment regime approaches).

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

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

29 **2. Methods**

30 *2.1. Simulation scenarios*

31 We simulated a typical RCT that is undertaken to compare a binary outcome (e.g. death) between a group of
32 patients in the treatment arm and a group of untreated patients in the control arm. For each patient we generated
33 8 baseline covariates $x_1, \dots, x_4 \sim N(0, 1)$ and $x_5, \dots, x_8 \sim B(1, 0.2)$. Treatment was allocated using a 50:50
34 split. Outcomes for patients in the control arm were generated from a logistic regression model including all
35 baseline covariates. In the base scenarios coefficient values were such, that the AUC of the logistic regression
36 model was 0.75 and the event rate in the control arm was 20%. Binary outcomes in the control arm were generated
37 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:

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

38 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
39 simulated scenarios where a constant absolute harm is applied across all treated patients. In this case we have
40 $P(y = 1|X, t_x = 1) = \text{expit}(lp_1) + \text{harm}$.

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

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

49 2.2. Individualized risk-based benefit predictions

50 All risk-based methods assume that a risk prediction model is available to assign risk predictions to individual
51 patients. For the simulations we developed a prediction model internally on the entire population, using a logistic
52 regression model with main effects for all baseline covariates and treatment assignment. Risk predictions for
53 individual patients were derived by setting treatment assignment to 0. Another common approach is to derive the
54 prediction model solely on the control patients, however this approach has been shown to lead to biased benefit
55 predictions [5,8,9].

56 A *stratified HTE method* has been suggested as an alternative to traditional subgroup analyses [3,4]. Patients
57 are stratified into equally-sized risk strata—in this case based on risk quartiles. Absolute treatment effects within
58 risk strata are estimated by the difference in event rate between patients in the control arm and patients in the
59 treated arm. We considered this approach as a reference, expecting it to perform worse than the other candidates,
60 as its objective is to provide an illustration of HTE rather than to optimize individualized benefit predictions.

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

63 Third, we considered a logistic regression model including treatment, the prognostic index, and their linear

64 interaction. Absolute benefit is then estimated from $\hat{\tau}(\mathbf{x}) = \text{expit}(\beta_0 + \beta_{PI}PI) - \text{expit}(\beta_0 + \beta_{tx} + (\beta_{PI} + \beta_*)PI)$.

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

66 Fourth, we used *restricted cubic splines* (RCS) to relax the linearity assumption on the effect of the linear
67 predictor [10]. We considered splines with 3 (RCS-3), 4 (RCS-4) and 5 (RCS-5) knots to compare models with
68 different levels of flexibility.

69 Finally, we considered an *adaptive approach* using Akaike's Information Criterion (AIC) for model selection.

70 More specifically, for the adaptive approach we ranked the constant relative treatment effect model, the linear
71 interaction model, and the RCS models with 3, 4, and 5 knots based on their AIC and selected the one with
72 the lowest value. The extra degrees of freedom were 1 (linear interaction), 2, 3 and 4 (RCS models) for these
73 increasingly complex interactions with the treatment effect.

74 *2.3. Evaluation metrics*

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

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

76 We compared the discriminative ability of the methods under study using c-for-benefit [11]. The c-for-benefit
77 represents the probability that from two randomly chosen matched patient pairs with unequal observed benefit,
78 the pair with greater observed benefit also has a higher predicted benefit. To be able to calculate observed benefit,
79 patients in each treatment arm are ranked based on their predicted benefit and then matched 1:1 across treatment
80 arms. *Observed* treatment benefit is defined as the difference of observed outcomes between the untreated and
81 the treated patient of each matched patient pair. *Predicted* benefit is defined as the average of predicted benefit
82 within each matched patient pair.

83 We evaluated calibration in a similar manner, using the integrated calibration index (ICI) for benefit [12]. The
84 observed benefits are regressed on the predicted benefits using a locally weighted scatterplot smoother (loess).
85 The ICI-for-benefit is the average absolute difference between predicted and smooth observed benefit. Values
86 closer to 0 represent better calibration.

87 For each scenario setting we performed 500 replications, within which all the considered models were fitted.

88 For comparing between models we simulated a super-population of size 500,000 for each scenario. We calculated
89 RMSE and discrimination and calibration for benefit of the models derived in each replication of our simulation
90 settings within this super-population. ## Empirical illustration

91 We demonstrated the different methods for individualizing treatment benefits using data from 30,510 patients
92 with acute myocardial infarction (MI) included in the GUSTO-I trial. 10,348 patients were randomized to tissue

93 plasminogen activator (tPA) treatment and 20,162 were randomized to streptokinase. The outcome of interest
94 was 30-day mortality (total of 2,128 events), recorded for all patients.

95 In line with previous analyses [13,14], we fitted a logistic regression model with 6 baseline covariates, i.e. age,
96 Killip class, systolic blood pressure, heart rate, an indicator of previous MI, and the location of MI, to predict
97 30-day mortality risk. A constant effect of treatment was included in the model. When deriving risk predictions
98 for individuals we set the treatment indicator to 0. More information on model development can be found in the
99 supplement (Supplement, Section 8).

100 **3. Results**

101 **3.1. Simulations**

102 The linear interaction model outperformed all RCS methods in terms of RMSE in scenarios with true constant
103 relative treatment effect ($OR = 0.8$, $N = 4,250$ and $AUC = 0.75$), strong linear and even strong quadratic deviations
104 from a constant relative treatment effect (Figure 1; panels A-C). However, with non-monotonic deviations from a
105 constant relative treatment effect, the RMSE of the linear interaction model increased substantially, especially in the
106 presence of treatment-related harms (Figure 1; panel D). In these scenarios, RCS-3 outperformed all other methods
107 in terms of RMSE. As might be expected the constant treatment effect approach had overall best performance
108 under true constant treatment effect settings. It was sensitive to all considered deviations, resulting in increased
109 RMSE. Finally, the adaptive approach had comparable performance to the best-performing method in each scenario.
110 However, in comparison with the best-performing approach, its RMSE was more variable in the scenarios with
111 linear and non-monotonic deviations, especially when also including moderate or strong treatment-related harms.
112 On closer inspection, we found that this behavior was caused by wrongly selecting the constant treatment effect
113 model in a substantial proportion of the replications (Supplement, Figure S3). This problematic behavior was less
114 with larger sample sizes (see below).

115 Increasing the sample size to 17,000 favored RCS-3 the most, It achieved lowest or close to lowest RMSE
116 across all scenarios (Figure 2). Especially in cases of strong quadratic and non-monotonic deviations RCS-3
117 had lower RMSE (median 0.011 for strong quadratic deviations and 0.010 for non-monotonic deviations with no
118 treatment-related harms) compared to the linear interaction approach (median 0.013 and 0.014, respectively),
119 regardless of the strength of treatment-related harms. Due to the large sample size, the RMSE of the adaptive
120 approach was even more similar to the best-performing method, and the constant relative treatment effect model
121 was less often wrongly selected (Supplement, Figure S4).

122 When we increased the AUC of the true prediction model to 0.85 ($OR = 0.8$ and $N = 4,250$). RCS-3 had the
123 lowest RMSE in the case of strong quadratic or non-monotonic deviations and very comparable performance to

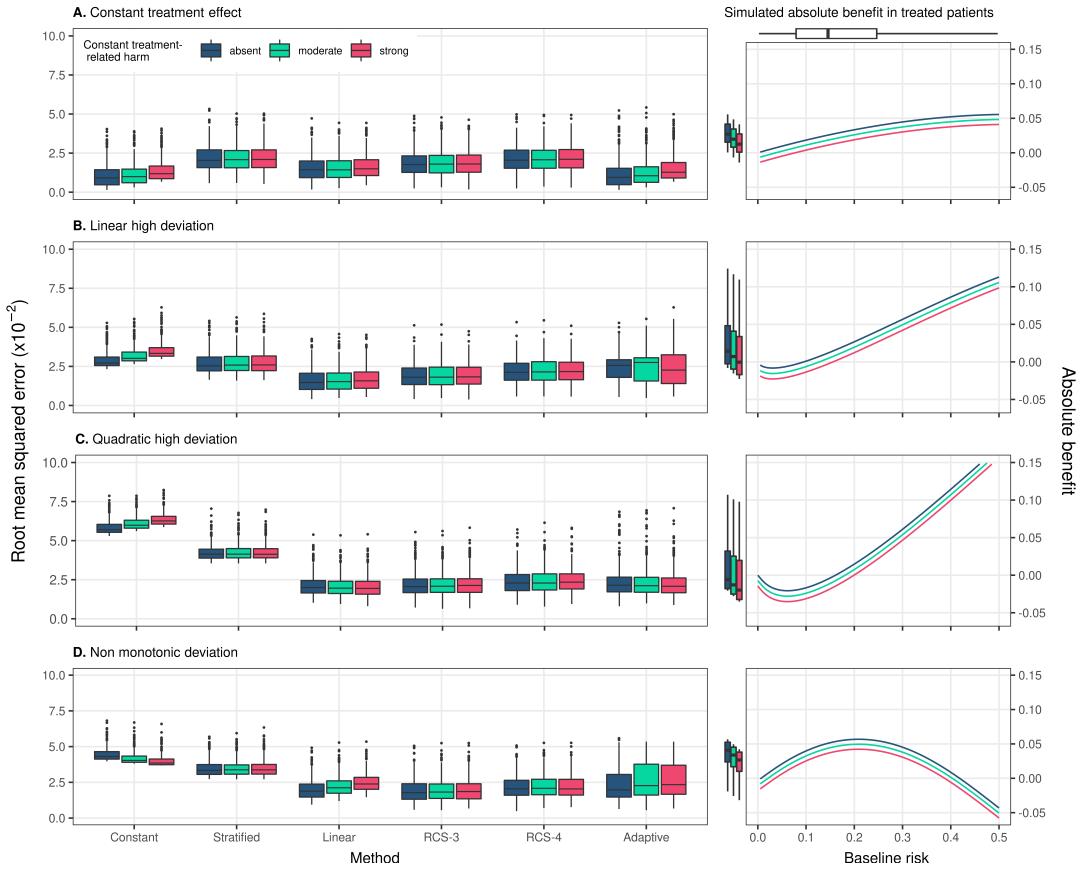


Figure 1: RMSE of the considered methods across 500 replications calculated from a simulated super-population of size 500,000. The scenario with true constant relative treatment effect (panel A) had a true prediction AUC of 0.75 and sample size of 4250. The RMSE is also presented for strong linear (panel 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 on the top. The 2.5, 25, 50, 75, and 97.5 percentiles of the true benefit distributions are expressed by the boxplots on the side of the right-handside panel.

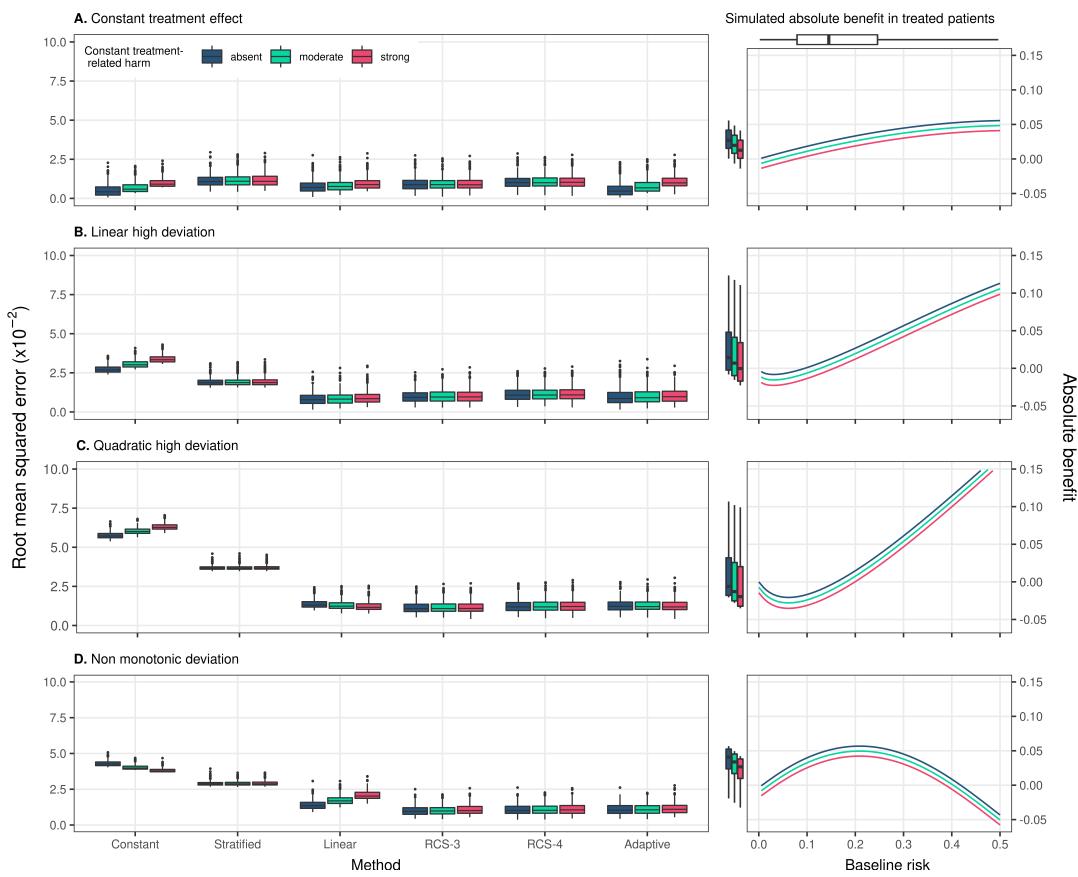


Figure 2: RMSE of the considered methods across 500 replications calculated in simulated samples of size 17,000 rather than 4,250 in Figure 1. RMSE was calculated on a super-population of size 500,000

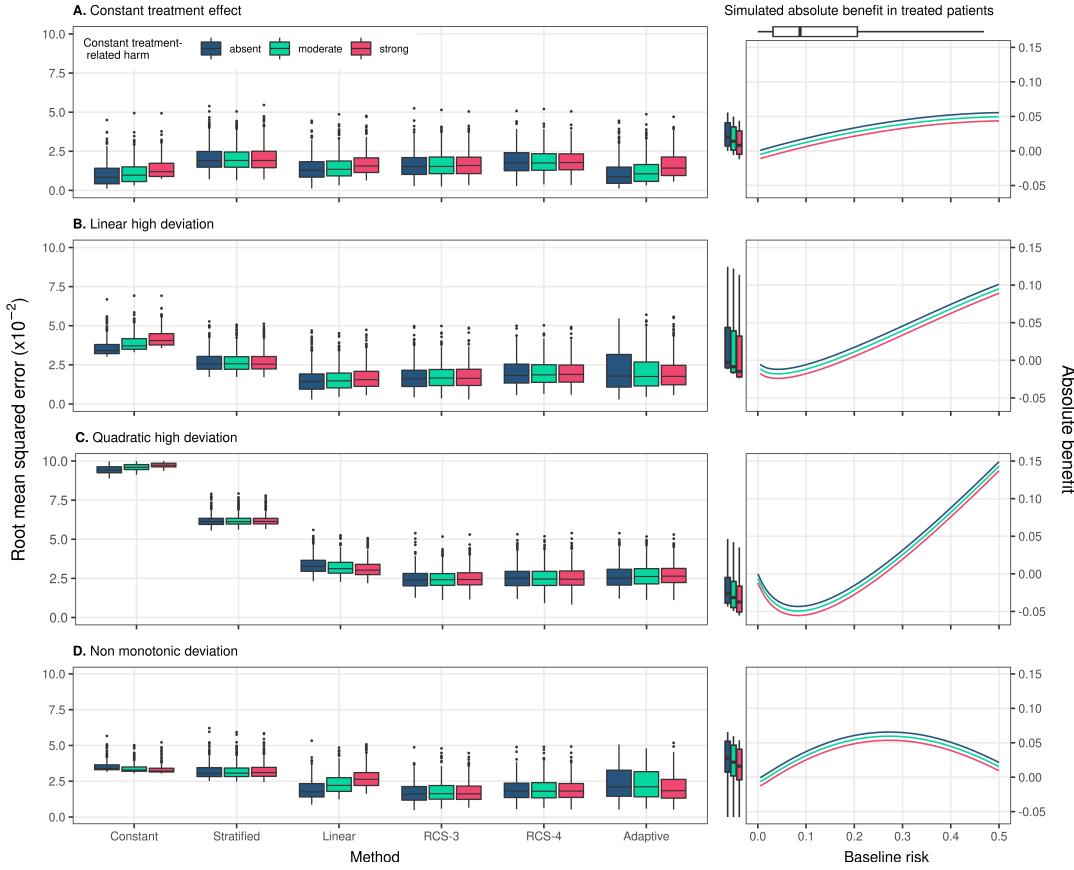


Figure 3: RMSE of the considered methods across 500 replications calculated in simulated samples 4,250. True prediction AUC of 0.85. RMSE was calculated on a super-population of size 500,000

124 the – optimal – linear interaction model in the case of strong linear deviations (median RMSE 0.016 for RCS-3
 125 compared to 0.014 for the linear interaction model). As observed in the base case scenario the adaptive approach
 126 wrongly selected the constant treatment effect model (23% and 25% of the replications in the strong linear and
 127 non-monotonic deviation scenarios without treatment-related harms, respectively), leading to more variability of
 128 the RMSE (Supplement, Figure S5).

129 When assuming a true constant relative treatment effect, discrimination for benefit was only slightly lower
 130 for the linear interaction model, but substantially lower for the non-linear RCS approaches (Figure 4; panel A).
 131 With strong linear or quadratic deviations from a constant relative treatment effect, all methods discriminated
 132 quite similarly (Figure 4; panels B-C). In the scenario with non-monotonic deviations, the constant effect model
 133 had much lower discriminative ability compared to all other methods (median AUC of 0.4971 for the constant
 134 effects model, 0.5285 for the linear interaction model and 0.5304 for the best-performing RCS-3; Figure 4; panel
 135 D). The adaptive approach was unstable in terms of discrimination for benefit, especially in the presence of
 136 treatment-related harms. With increasing number of RCS knots, we observed decreasing median values and
 137 increasing variability of the c-for-benefit in all scenarios. When we increased the sample size to 17,000 we observed

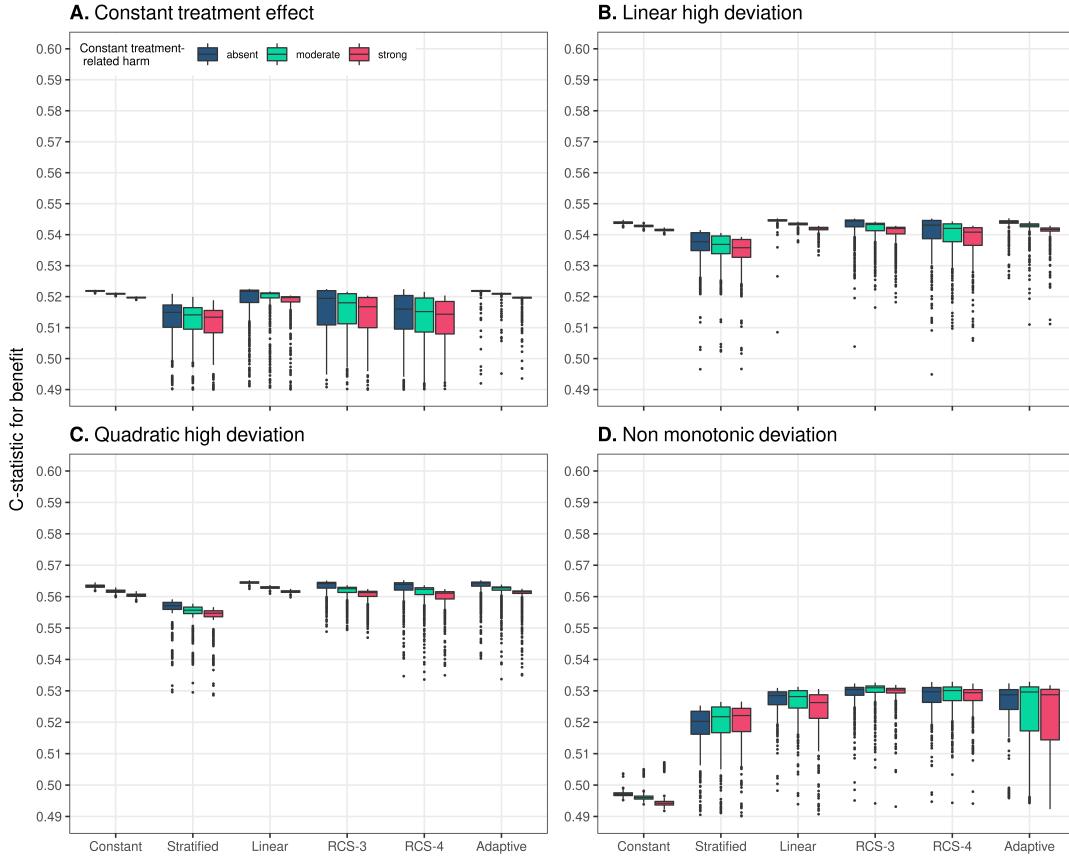


Figure 4: Discrimination for benefit of the considered methods across 500 replications calculated in a simulated samples of size 4,250. True prediction AUC of 0.75.

138 similar trends, however the performance of all methods was more stable (Supplement, Figure S6). Finally, when
 139 we increased the true prediction AUC to 0.85 the adaptive approach in the case of non-monotonic deviations was,
 140 again, more conservative, especially with null or moderate treatment-related harms (Supplement, Figure S5).

141 In terms of calibration for benefit, the constant effects model outperformed all other models in the scenario with
 142 true constant treatment effects, but was miscalibrated for all deviation scenarios (Figure 5). The linear interaction
 143 model showed best or close to best calibration across all scenarios and only showed worse calibration compared
 144 to RCS-3 in case of non-monotonic deviations and treatment-related harms (Figure 5; panel D). The adaptive
 145 approach was worse calibrated in scenarios with strong linear and non-monotonic deviations compared to the linear
 146 interaction model and RCS-3. When we increased sample size to 17,000 similar conclusions on calibration for
 147 benefit could be drawn. As expected, all methods displayed more stable calibration performance due to the larger
 148 number of patients (Supplement, Figure S6). When we increased the true prediction AUC to 0.85, the linear
 149 interaction model was worse calibrated, on average, than RCS-3 in the case of strong quadratic deviations from
 150 constant relative treatment effects (Supplement, Figure S7).

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

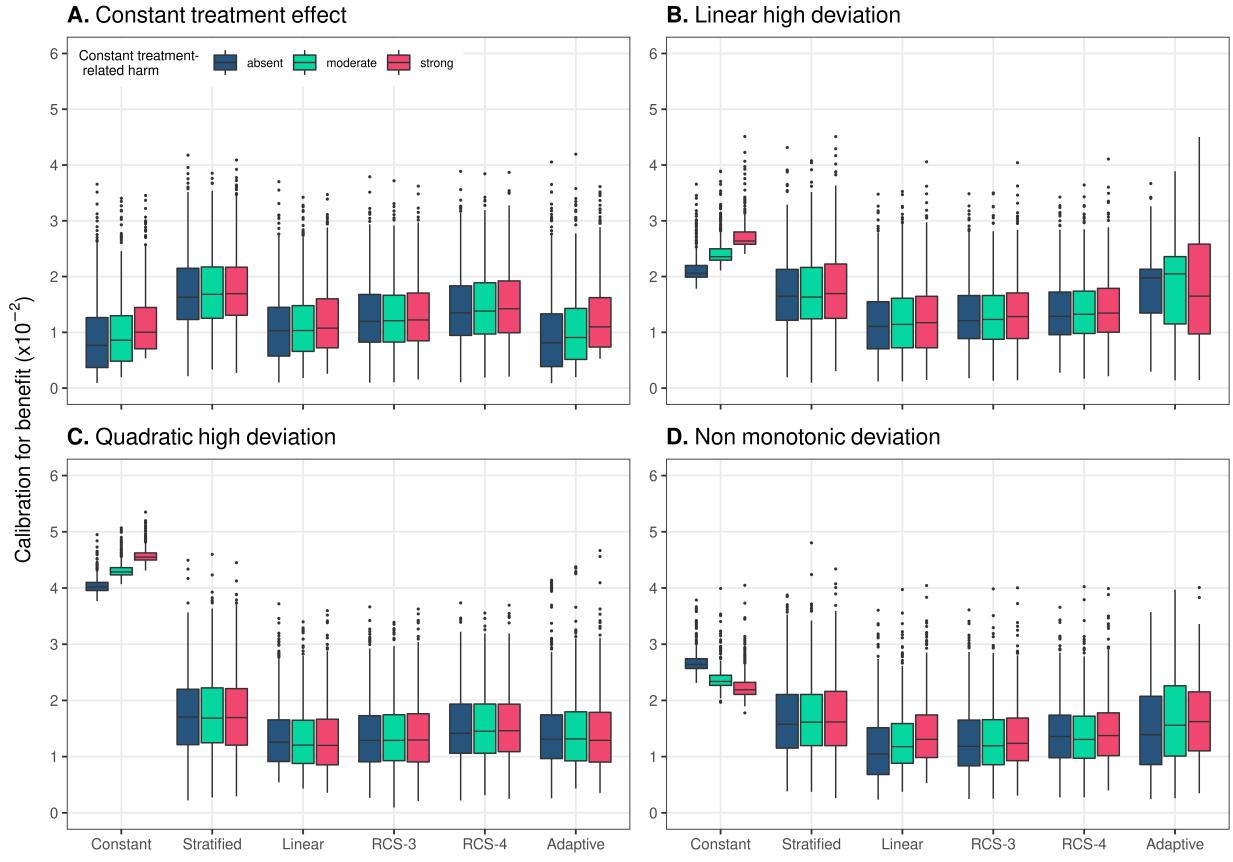


Figure 5: Calibration for benefit of the considered methods across 500 replications calculated in a simulated sample of size 500,000. True prediction AUC of 0.75 and sample size of 4,250.

152 viewer/. Additionally, all the code for the simulations can be found at https://github.com/rekkasa/arekkas_
 153 HteSimulation_XXXX_2021

154 3.2. Empirical illustration

155 We used the derived prognostic index to fit a constant treatment effect model, a linear interaction model
 156 and a RCS-3 model individualizing absolute benefit predictions. RCS-4 and RCS-5 models were excluded. In our
 157 simulations these methods were always outperformed by the simpler approaches and were often overfitted. Finally,
 158 an adaptive approach with only the 3 candidate models was also applied.

159 All considered methods provided similar fits, predicting increasing benefits for patients with higher baseline risk
 160 predictions. All models followed the evolution of the stratified estimates very closely. The adaptive approach based
 161 on AIC selected the constant treatment effect model. The constant treatment effect model had somewhat lower
 162 AIC compared to the linear interaction model slightly worse cross-validated discrimination (c-for-benefit 0.525 vs
 163 0.526) and better cross-validated calibration (ICI-for benefit 0.0104 vs 0.0115). In conclusion, a simpler constant
 164 treatment effect model is adequate for predicting absolute 30-day mortality benefits of treatment with tPA in

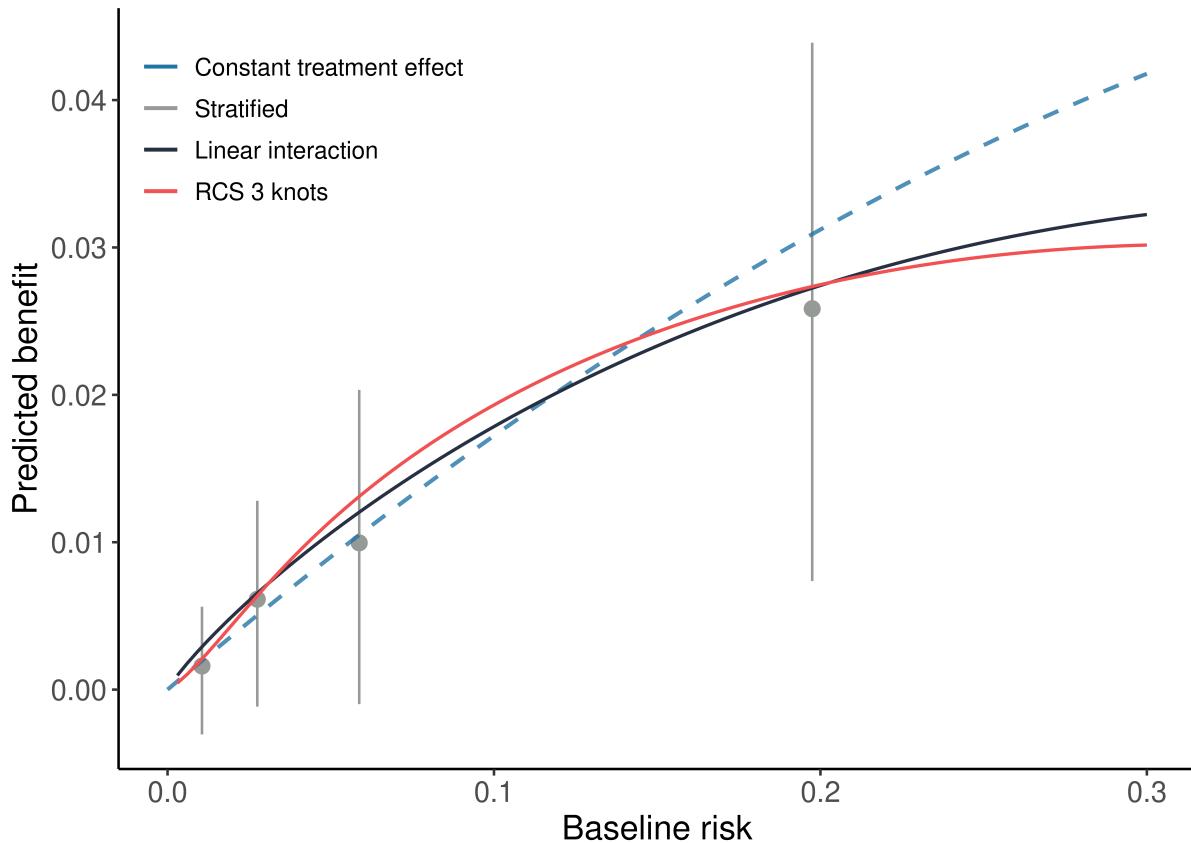


Figure 6: Individualized absolute benefit predictions based on baseline risk when using a constant treatment effect approach, a linear interaction approach and RCS smoothing using 3 knots. Risk stratified estimates of absolute benefit are presented within quartiles of baseline risk as reference.

¹⁶⁵ patients with acute MI.

¹⁶⁶ 4. Discussion

¹⁶⁷ The linear interaction model and the RCS-3 model both displayed very good performance under many of
¹⁶⁸ the considered simulation scenarios, in contrast with the constant relative treatment effect model. The linear
¹⁶⁹ interaction model was optimal in cases with smaller sample sizes and moderately performing baseline risk prediction
¹⁷⁰ models, that is, it had lower RMSE, was better calibrated for benefit and had better discrimination for benefit, even
¹⁷¹ in scenarios with strong quadratic deviations. In scenarios with true non-monotonic deviations, the linear interaction
¹⁷² model was outperformed by RCS-3, especially in the presence of true treatment-related harms. Increasing the sample
¹⁷³ size or the prediction model's discriminative ability favored RCS-3, especially in scenarios with non-monotonic
¹⁷⁴ deviations and in the presence of treatment-related harms.

¹⁷⁵ RCS-4 and RCS-5 proved to be too flexible in all considered scenarios, as indicated by higher RMSE, increased
¹⁷⁶ variability of discrimination for benefit and worse calibration of benefit predictions. Even with larger sample sizes

177 and strong quadratic or non-monotonic deviations from the base case scenario of constant relative treatment
178 effects, these more flexible restricted cubic splines did not outperform the simpler RCS-3. These approaches may
179 only be helpful if we expect more extreme patterns of heterogeneous treatment effects compared to the quadratic
180 deviations considered here. Considering interactions in RCS-3 models as the most complex approach often may be
181 reasonable.

182 The constant treatment effect model, despite having adequate performance in the presence of weak treatment
183 effect heterogeneity on the relative scale, quickly broke down with stronger deviations from constant relative
184 treatment effects. In these cases, the stratified approach generally had lower error rates compared to the constant
185 treatment effect model. Such stepwise treatment benefit estimates are useful for visually demonstrating treatment
186 effect heterogeneity but may be considered insufficient for making individualized benefit predictions.

187 Increasing the discriminative ability of the risk model—by increasing the predictor coefficients of the true risk
188 model—reduced RMSE for all methods. This increase in discriminative ability translates in higher variability of
189 predicted risks, which, in turn, allows the considered methods to better capture absolute treatment benefits. As
190 a consequence, the increase in discriminative ability of the risk model also led to higher discrimination between
191 those with low or high benefit (as reflected in values of c-for-benefit). Even though risk model performance is very
192 important for the ability of risk-based methods to predict treatment benefit, prediction model development was
193 outside the scope of this work and has already been studied extensively [5,8,9].

194 The adaptive approach had adequate performance, following closely on average the performance of the “true”
195 model in most scenarios. With smaller sample sizes it tended to miss the treatment-risk interactions and selected
196 simpler models (Supplement Section 4). This conservative behavior resulted in increased RMSE variability in these
197 scenarios, especially in the case of true strong linear or non-monotonic deviations from the base case scenario.
198 Therefore, in the case of smaller sample sizes the simpler linear interaction model may be a safer choice for
199 predicting absolute benefits, if a non-constant treatment effect is suspected.

200 Risk-based approaches to predictive HTE estimate treatment benefit as a function of baseline risk. A limitation
201 of our study is that we assumed treatment benefit to be a function of baseline risk in the majority of the simulation
202 scenarios. We also considered constant moderate and strong treatment-related harms, applied on the absolute scale
203 to expand the range of scenarios in line with previous work [15]. In a limited set of scenarios where we assumed
204 the existence of true treatment-covariate interactions, our conclusions remained unchanged. Even though the
205 average error rates increased for all the considered methods, due to the miss-specification of the outcome model,
206 the linear interaction model had the lowest error rates. RCS-3 had very comparable performance. The constant
207 treatment effect model often gave biased results, especially in the presence of moderate or strong treatment-related
208 harms. All the results of these simulations can be found in Supplement, Section 7. Future simulation studies could
209 explore the effect of more extensive deviations from risk-based treatment effects.

210 In our simulations we only focused on risk-based methods, using baseline risk as a reference in a two-stage
211 approach to individualizing benefit predictions. However, there is a plethora of different methods, ranging from
212 treatment effect modeling to tree-based approaches available in more recent literature [16–19]. Many of these
213 methods rely on incorporating treatment-covariate interactions in the prediction of benefit. An important caveat of
214 such approaches is that they may be prone to overfitting, thus exaggerating the magnitude of the predicted benefits.
215 In a wide range of simulation settings, a simpler risk modeling approach was consistently better calibrated for
216 benefit compared to more complex treatment effect modelling approaches [5]. Similarly, when SYNTAX score II, a
217 model developed for identifying patients with complex coronary artery disease that benefit more from percutaneous
218 coronary intervention or from coronary artery bypass grafting was redeveloped using fewer treatment-covariate
219 interactions had better external performance compared to its predecessor[20,21].

220 In conclusion, the linear interaction approach is a viable option with smaller sample sizes and/or moderately
221 performing risk prediction models if we consider a non-constant relative treatment effect plausible. RCS-3 is
222 a better option when non-monotonic deviations from a constant relative treatment effect and/or substantial
223 treatment-related harms are anticipated. Increasing the complexity of the RCS models by increasing the number
224 of knots does not translate to improved benefit prediction. Using AIC for model selection among the constant
225 treatment effect, the linear interaction and RCS-3 model is a viable option, especially with larger sample size.

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