Supplementary Materials for
Optimizing Precision and Power by Machine Learning in Randomized Trials with Ordinal and Time-to-Event Outcomes, with an Application to COVID-19.

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A Auxiliary covariates for estimation algorithm

Denote the survival function for Y at time $k \in \{1, \dots, K\}$ conditioned on study arm a and baseline variables w by

$$S(k, a, w) = P(Y > k \mid A = a, W = w). \tag{2}$$

Similarly, define the following function of the censoring distribution:

$$G(k, a, w) = P(C \geq k \mid A = a, W = w). \tag{3}$$

Under the assumption $C \perp\!\!\!\perp (Y, W) \mid A = a$ for each treatment arm a, we have $Y \perp\!\!\!\perp C \mid A, W$ and therefore $S(k, a, w)$ and $G(k, a, w)$ have the following product formula representations:

$$S(k, a, w) = \prod_{u=1}^{k} \{1 - m(u, a, w)\}; \qquad \Pi_C(k, a, w) = \prod_{u=0}^{k-1} \{1 - \pi_C(u, a, w)\}. \tag{4}$$

At each iteration of the estimation algorithm, the auxiliary covariates fr $\tilde{S}_{\mathrm{TMLE}}$ and $\tilde{S}_{\mathrm{IE-TMLE}}$ are constructed as follows:

$$\begin{aligned} H_{Y,k,u} &= -\frac{\mathbb{1}\{A = a\}}{\widehat{\pi}_A(a, W)\widehat{\Pi}_C(u, a, W)} \frac{\widehat{S}(k, a, W)}{\widehat{S}(u, a, W)} \\ H_A &= \frac{S(k, a, W)}{\pi_A(a, W)}, \\ H_{C,k,u} &= -\frac{\mathbb{1}\{A = a\}}{\widehat{\pi}_A(a, W)} \frac{\widehat{S}(k, a, W)}{\widehat{S}(u, a, W)} \frac{1}{\widehat{\Pi}_C(u + 1, a, W)}, \end{aligned}$$

where $\widehat{\pi}_A$, $\widehat{S}$, and $\widehat{\Pi}_C$ are the estimates in the current step of the iteration.

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B Efficiency theory

Before proving Theorem 1 given in the paper, we introduce some notation and efficiency theory for estimation of $S(k, a)$. We will use the notation of Díaz et al. (2019). First, we encode a single participant's data vector $O = (W, A, \Delta = \mathbb{1}\{Y \leq C\}, \widetilde{Y} = \min(C, Y))$ using the following longitudinal data structure:

$$O = (W, A, R_0, L_1, R_1, L_2 \ldots, R_{K-1}, L_K), \tag{5}$$

where $R_u = \mathbb{1}\{\widetilde{Y} = u, \Delta = 0\}$ and $L_u = \mathbb{1}\{\widetilde{Y} = u, \Delta = 1\}$, for $u \in \{0, \ldots, K\}$. The sequence $R_0, L_1, R_1, L_2 \ldots, R_{K-1}, L_K$ in the above display consists of all 0's until the first time that either the event is observed or censoring occurs, i.e., time $u = \widetilde{Y}$. In the former case $L_u = 1$; otherwise $R_u = 1$. For a random variable X, we denote its history through time u as $\bar{X}_u = (X_0, \ldots, X_u)$. For a given scalar x, the expression $\bar{X}_u = x$ denotes element-wise equality. The corresponding vector (5) for participant i is denoted by $(W_i, A_i, R_{0,i}, L_{1,i}, R_{1,i}, L_{2,i} \ldots, R_{K-1,i}, L_{K,i})$.

Define the following indicator variables for each $u \geq 1$:

$$I_u = \mathbb{1}\{\bar{R}_{u-1} = 0, \bar{L}_{u-1} = 0\}, \qquad J_u = \mathbb{1}\{\bar{R}_{u-1} = 0, \bar{L}_u = 0\}.$$

The variable I_u is the indicator based on the data through time $u - 1$ that a participant is at risk of the event being observed at time u; in other words, $I_u = 1$ means that all the variables $R_0, L_1, R_1, L_2..., L_{u-1}, R_{u-1}$ in the data vector (5) equal 0, which makes it possible that $L_u = 1$. Analogously, J_u is the indicator based on the outcome data through time u and censoring data before time u that a participant is at risk of censoring at time u. By convention we let $J_0 = 1$.

The efficient influence function for estimation of $S(k, a)$ (see Moore and van der Laan 2009) is equal to:

$$D_\eta(O) = \sum_{u=1}^{k} I_u \times H_Y(u, A, W)\{L_u - m(u, a, W)\} + S(k, a, W) - S(k, a), \tag{6}$$

where we have explicitly added the dependence of the auxiliary covariate H_Y on (u, A, W) to the notation, and have denoted the nuisance parameters with $\eta = (m, \pi_A, \pi_C)$. In what follows we will use $\theta = S(k, a)$, and will use $\theta(\eta_1)$ to refer to the target parameter evaluated at a specific distribution implied by η_1. We will denote $\mathsf{P}f = \int f(o)\mathrm{d}\mathsf{P}(o)$, and $\mathsf{P}h(t, a, W) = \int h(t, a, w)\mathrm{d}\mathsf{P}(w)$ for functions f and h. The efficient influence function has important implications for estimation of $S(k, a)$. First, the variance of $D_\eta(O)$ is the non-parametric efficiency bound, meaning that it is the smallest possible variance achievable by any regular estimator (Bickel et al. 1997). Second, the efficient influence function characterizes the first order bias of a plug-in estimator based on data-adaptive regression. Correction for this first order bias will allow us to establish normality of the estimators. Specifically, for any estimate $\widehat{\eta}$ we have the following first order expansion around the true parameter value $\theta(\eta)$, proved in Lemma 1 in the Supplementary materials of Díaz et al. (2018):

$$\theta(\widehat{\eta}) - \theta(\eta) = -\mathsf{P}D_{\widehat{\eta}} + \mathsf{Rem}_1(\widehat{\eta}), \tag{7}$$

where Rem_1 is a second order remainder term given by

$$\mathsf{Rem}_1(\widehat{\eta}) = -\sum_{u=1}^{k} \int \frac{\widehat{S}(k, a, w)}{\widehat{S}(u, a, w)} S(u-1, a, w)\{m(u, a, w) - \widehat{m}(u, a, w)\}\left\{\frac{\pi_A(a, w)\Pi_C(u, a, w)}{\widehat{\pi}_A(a, w)\widehat{\Pi}_C(u, a, w)} - 1\right\}\mathrm{d}\mathsf{P}(w),$$

and $\theta(\widehat{\eta})$ is the substitution estimator

$$\theta(\widehat{\eta}) = \frac{1}{n}\sum_{i=1}^{n}\prod_{u=1}^{k}\{1-\widehat{m}(u,a,W_i)\}.$$

The following proposition establishing the robustness of D_η to misspecification of the model m will be useful to prove consistency of the estimator.

Proposition 1. *Let $\eta_1 = (m_1, \pi_{A,1}, \pi_{C,1})$ be such that either $m_1 = m$ or $(\pi_{A,1}, \pi_{C,1}) = (\pi_A, \pi_C)$. Then $\mathsf{P}D_{\eta_1} = 0$.*

Recall the cross-fitting procedure described in the main document as follows. Let $\mathcal{V}_1, \ldots, \mathcal{V}_J$ denote a random partition of the index set $\{1, \ldots, n\}$ into J prediction sets of approximately the same size. That is, $\mathcal{V}_j \subset \{1, \ldots, n\}$; $\bigcup_{j=1}^{J}\mathcal{V}_j = \{1, \ldots, n\}$; and $\mathcal{V}_j \cap \mathcal{V}_{j'} = \emptyset$. In addition, for each j, the associated training sample is given by $\mathcal{T}_j = \{1, \ldots, n\} \setminus \mathcal{V}_j$. Let $\widehat{m}_j$ denote the prediction algorithm trained in $\mathcal{T}_j$. Letting $j(i)$ denote the index of the validation set which contains observation i, cross-fitting entails using only observations in $\mathcal{T}_{j(i)}$ for fitting models when making predictions about observation i. That is, the outcome predictions for each subject i are given by $\widehat{m}_{j(i)}(u, a, W_i)$. Since only $\widehat{m}$ and not $(\widehat{\pi}_A, \widehat{\pi}_C)$ is cross-fitted, we let $\widehat{\eta}_{j(i)} = (\widehat{m}_{j(i)}, \widehat{\pi}_A, \widehat{\pi}_C)$ and $\widetilde{\eta}_{j(i)} = (\widetilde{m}_{j(i)}, \widehat{\pi}_A, \widehat{\pi}_C)$.

C Proof of Theorem 1

In what follows we let $\mathsf{P}_{n,j}$ denote the empirical distribution of the prediction set $\mathcal{V}_j$, and let $\mathsf{G}_{n,j}$ denote the associated empirical process $\sqrt{n/J}(\mathsf{P}_{n,j} - \mathsf{P})$. Let G_n denote the empirical process $\sqrt{n}(\mathsf{P}_n - \mathsf{P})$. We use $E(g(O_1, \ldots, O_n))$ to denote expectation with respect to the joint distribution of $(O_1, \ldots, O_n)$, and use $a_n \lesssim b_n$ to mean $a_n \leq c b_n$ for universal constants c. The following lemmas will be useful in the proof of the theorem.

Lemma 1. *Assume A1, A4, and A5 . Then we have $\Pi_C(k, a, w)$ does not depend on w, and $\pi_A(a, w)$ does not depend on w. Furthermore, we have*

$$\begin{aligned}\sqrt{n}\{\widehat{\Pi}_C(k,a) - \Pi_C(k,a)\} &= \mathsf{G}_n\Delta_{k,a} + o_P(1),\\ \sqrt{n}\{\widehat{\pi}_A(a) - \pi_A(a)\} &= \mathsf{G}_n\Lambda_a + o_P(1),\end{aligned}$$

for mean-zero functions $\Delta_{k,a}(O_i)$ and $\Lambda_a(O_i)$ of (k, a) and O_i that do not depend on W_i.

Proof. This lemma follows by application of the Delta method to the non-parametric maximum likelihood estimators $\widehat{\pi}_A$ and $\widehat{\Pi}_C$. □

Lemma 2. *For two sequences $a_1, \ldots, a_m$ and $b_1, \ldots, b_m$ we have*

$$\prod_{t=1}^{m}(1-a_t) - \prod_{t=1}^{m}(1-b_t) = \sum_{t=1}^{m}\left\{\left[\prod_{k=1}^{t-1}(1-a_k)\right](b_t - a_t)\left[\prod_{k=t+1}^{m}(1-b_k)\right]\right\}.$$

Proof. Replace $(b_t - a_t)$ by $(1 - a_t) - (1 - b_t)$ in the right hand side and expand the sum to notice it is a telescoping sum. □

The proof of Theorem 1 proceeds as follows.

Proof. Since censoring is completely at random by A1, we have $\theta = S(k,a) = \int S(k,a,w)\mathrm{d}\mathsf{P}(w)$. Let $\widetilde{\theta} = \tilde{S}_{\mathrm{TMLE}}(k,a)$. Define $\sigma^2 = \mathrm{Var}[D_{\eta_1}(O)]$, where $\eta_1 = (m_1, \pi_A, \pi_C)$, and let

$$\widetilde{\Theta}_n = \sqrt{n}(\widetilde{\theta} - \theta)/\widetilde{\sigma}$$
$$\check{\Theta}_n = \sqrt{n}(\widetilde{\theta} - \theta)/\sigma$$
$$\Theta_n = \mathsf{G}_n D_{\eta_1}/\sigma.$$

First, note that $\Theta_n \rightsquigarrow N(0,1)$ by the central limit theorem. We will now show that $|\widetilde{\Theta}_n - \Theta_n| = o_P(1)$, which would yield the result in the theorem. First, note that

$$\begin{aligned} |\widetilde{\Theta}_n - \Theta_n| &= |(\check{\Theta}_n - \Theta_n)(\sigma/\widetilde{\sigma}) + \Theta_n(\sigma - \widetilde{\sigma})/\widetilde{\sigma}| \\ &\leq |\check{\Theta}_n - \Theta_n|\,|\sigma/\widetilde{\sigma}| + |\Theta_n|\,|\sigma/\widetilde{\sigma} - 1| \\ &\lesssim |\check{\Theta}_n - \Theta_n| + o_P(1), \end{aligned}$$

where the last inequality follows because $|\sigma/\widetilde{\sigma} - 1| = o_P(1)$ (which follows by Lemma 1 and A3) and because $|\Theta_n| = O_P(1)$ by the central limit theorem. We will now show that $|\check{\Theta}_n - \Theta_n| = o_P(1)$.

An application of (7) with $\widehat{\eta} = \widetilde{\eta}$ yields

$$\begin{aligned} \sqrt{n}(\widetilde{\theta} - \theta) &= -\sqrt{n}\mathsf{P}D_{\widetilde{\eta}} + \sqrt{n}\mathsf{Rem}_1(\widetilde{\eta}) \\ &= \sqrt{n}(\mathsf{P}_n - \mathsf{P})D_{\widetilde{\eta}} + \sqrt{n}\mathsf{Rem}_1(\widetilde{\eta}) \\ &= \mathsf{G}_n D_{\eta_1} + \mathsf{G}_n(D_{\widetilde{\eta}} - D_{\eta_1}) + \sqrt{n}\mathsf{Rem}_1(\widetilde{\eta}), \end{aligned}$$

where the second equality follows because $\mathsf{P}_n D_{\widetilde{\eta}} = 0$ by definition of $\widetilde{\eta}$ (see Díaz et al. 2019). This implies

$$\check{\Theta}_n - \Theta_n = B_{n,2} + B_{n,1},$$

where $B_{n,2} = \mathsf{G}_n(D_{\widetilde{\eta}} - D_{\eta_1})$ and $B_{n,1} = \sqrt{n}\mathsf{Rem}_1(\widetilde{\eta})$.

We first tackle the case of A6.2, where the estimators for m are cross-fitted. Note that

$$B_{n,2} = \frac{1}{\sqrt{J}}\sum_{j=1}^{J} \mathsf{G}_{n,j}(D_{\widetilde{\eta}_j} - D_{\eta_1}),$$

and that $D_{\widetilde{\eta}_j}$ depends on the full sample through the estimate of the parameter ε of the logistic tilting model. To make this dependence explicit, we introduce the notation $D_{\widehat{\eta}_j,\widehat{\varepsilon}} = D_{\widetilde{\eta}_j}$. Let ε_1 denote the probability limit of $\widehat{\varepsilon}$, which exists and is finite by Assumption A7. We can find a deterministic sequence $\delta_n \to 0$ satisfying $P(|\widehat{\varepsilon} - \varepsilon_1| < \delta_n) \to 1$. Let $\mathcal{F}_n^j = \{D_{\widehat{\eta}_j,\varepsilon} - D_{\eta_1} : |\varepsilon - \varepsilon_1| < \delta_n\}$. Because the function $\widehat{\eta}_j$ is fixed given the training data, we can apply Theorem 2.14.2 of van der Vaart and Wellner (1996) to obtain

$$E\left\{\sup_{f \in \mathcal{F}_n^j} |\mathsf{G}_{n,j} f| \;\middle|\; \mathcal{T}_j\right\} \lesssim \|F_n^j\| \int_0^1 \sqrt{1 + N_{[\,]}(\alpha\|F_n^j\|, \mathcal{F}_n^j, L_2(\mathsf{P}))}\mathrm{d}\alpha, \tag{8}$$

where $N_{[\,]}(\alpha\|F_n^j\|, \mathcal{F}_n^j, L_2(\mathsf{P}))$ is the bracketing number and we take $F_n^j = \sup_{\varepsilon:|\varepsilon-\varepsilon_1|<\delta_n} |D_{\widehat{\eta}_j,\varepsilon} - D_{\eta_1}|$ as an envelope for the class $\mathcal{F}_n^j$. Theorem 2.7.2 of van der Vaart and Wellner (1996) shows

$$\log N_{[\,]}(\alpha\|F_n^j\|, \mathcal{F}_n^j, L_2(\mathsf{P})) \lesssim \frac{1}{\alpha\|F_n^j\|}.$$

This shows

$$\begin{aligned}\|F_n^j\| \int_0^1 \sqrt{1 + N_{[\,]}(\alpha \|F_n^j\|, \mathcal{F}_n^j, L_2(\mathsf{P}))} \mathrm{d}\alpha &\lesssim \int_0^1 \sqrt{\|F_n^j\|^2 + \frac{\|F_n^j\|}{\alpha}} \mathrm{d}\alpha \\ &\leq \|F_n^j\| + \|F_n^j\|^{1/2} \int_0^1 \frac{1}{\alpha^{1/2}} \mathrm{d}\alpha \\ &\leq \|F_n^j\| + 2\|F_n^j\|^{1/2}.\end{aligned}$$

Since $D_{\widehat{\eta}_j, \widehat{\varepsilon}} \to D_{\eta_1}$ and $\delta_n \to 0$, $\|F_n^j\| = o_P(1)$. The above argument shows that $\sup_{f \in \mathcal{F}_n^j} |\mathsf{G}_{n,j} f| = o_P(1)$ for each j, conditional on $\mathcal{T}_j$. Thus $|B_{n,2}| = o_P(1)$.

In the case of A6.1, where the estimators for m are *not* cross-fitted but belong in a parametric family, standard empirical process theory such as Example 19.7 of van der Vaart (1998) shows that $D_{\widetilde{\eta}}$ takes values in a Donsker class. Therefore, an application of Theorem 19.24 of van der Vaart (1998) yields $|B_{n,2}| = o_P(1)$.

We now show that $|B_{n,1}| = o_P(1)$. First, Lemma 1 along with the Delta method show that

$$\sqrt{n} \left\{ \frac{\pi_A(a,w)\Pi_C(u,a,w)}{\widetilde{\pi}_A(a,w)\widetilde{\Pi}_C(u,a,w)} - 1 \right\} = \mathsf{G}_n \Gamma_{k,a} + o_P(1),$$

for some function $\Gamma_{k,a}(O)$ not depending on W. Thus

$$\begin{aligned}B_{n,1} &= -\sum_{u=1}^{k} \int \frac{\widetilde{S}(k,a,w)}{\widetilde{S}(u,a,w)} S(u-1,a,w)\{m(u,a,w) - \widetilde{m}(u,a,w)\} \left\{\mathsf{G}_n \Gamma_{k,a} + o_P(1)\right\} \mathrm{d}\mathsf{P}(w) \qquad (9) \\ &= -\mathsf{G}_n \Gamma_{k,a} \sum_{u=1}^{k} \int \frac{\widetilde{S}(k,a,w)}{\widetilde{S}(u,a,w)} S(u-1,a,w)\{m(u,a,w) - \widetilde{m}(u,a,w)\} \mathrm{d}\mathsf{P}(w) + o_P(1) \\ &= \mathsf{G}_n \Gamma_{k,a} \int \{S(k,a,w) - \widetilde{S}(k,a,w)\} \mathrm{d}\mathsf{P}(w) + o_P(1),\end{aligned}$$

where the last equality follows from Lemma 2. Expression (7) together with the assumptions of the theorem and Proposition 1 show that the estimator $\widetilde{\theta}$ is consistent, and thus

$$\int \{S(k,a,w) - \widetilde{S}(k,a,w)\} \mathrm{d}\mathsf{P}(w) = o_P(1).$$

The central limit theorem shows that $\mathsf{G}_n \Gamma_{k,a} = O_P(1)$, which yields $|B_{n,1}| = o_P(1)$, concluding the proof of the theorem. □

Remark 1. *If any one of Assumptions A1, A4, or A5 were incorrect, then it would not be possible to take $\mathsf{G}_n \Gamma_{k,a}$ out of the integral in (9). This would mean that, in general $B_{n,1}$ would fail to be $o_P(1)$ and our proof would fail. In these cases, it would generally be true that $B_{n,1}$ is asymptotically linear. If the influence function $B_{n,1}$ is equal to $-C_{\eta_1}(O)$, then the asymptotic variance would be equal to the variance of $D_{\eta_1}(O) - C_{\eta_1}(O)$. See §4.1.3 of Moore and van der Laan (2009) for more discussion on this point.*

D Tables with simulation results

D.1 Results for simulations with a positive effect and where the covariates are prognostic of the outcome

Estimator	n	Effect size	P(Reject H_0)	$n \times$ MSE	$n \times$ Var	Bias	Rel. eff.
CF-MARS	100	1.04	0.26	83	83	0.04	1.29
CF-RF	100	1.04	0.24	71	71	0.00	1.10
CF-XGBoost	100	1.04	0.23	70	70	0.00	1.09
ℓ_1-LR	100	1.04	0.28	58	58	-0.02	0.90
LR	100	1.04	0.34	67	67	0.00	1.03
MARS	100	1.04	0.27	70	69	-0.09	1.09
RF	100	1.04	0.62	51	45	-0.25	0.79
Unadjusted	100	1.04	0.25	65	65	0.01	1.00
XGBoost	100	1.04	0.27	64	64	-0.01	0.99
max MC error			0.01	1.77	1.66	0.01	0.04
CF-MARS	500	1.04	0.85	61	61	0.00	0.93
CF-RF	500	1.04	0.85	60	60	0.00	0.91
CF-XGBoost	500	1.04	0.82	65	65	0.01	0.98
ℓ_1-LR	500	1.04	0.87	58	58	0.00	0.88
LR	500	1.04	0.87	60	60	0.00	0.92
MARS	500	1.04	0.86	58	58	-0.01	0.88
RF	500	1.04	0.97	66	56	-0.14	1.00
Unadjusted	500	1.04	0.82	66	66	0.00	1.00
XGBoost	500	1.04	0.88	58	58	-0.01	0.88
			0.01	1.35	1.32	0.01	0.03
CF-MARS	1500	1.04	1.00	61	60	0.00	0.93
CF-RF	1500	1.04	1.00	48	48	0.00	0.74
CF-XGBoost	1500	1.04	1.00	62	62	0.00	0.95
ℓ_1-LR	1500	1.04	1.00	58	58	0.00	0.89
LR	1500	1.04	1.00	57	57	0.00	0.88
MARS	1500	1.04	1.00	60	60	0.00	0.92
RF	1500	1.04	1.00	61	51	-0.08	0.94
Unadjusted	1500	1.04	1.00	65	65	0.00	1.00
XGBoost	1500	1.04	1.00	56	56	-0.01	0.86
			<0.01	1.27	1.30	<0.01	0.03

Table A1: Simulation results for the RMST of time to intubation or death at day 14 under a positive effect and covariates with prognostic power.

Estimator	n	Effect size	P(Reject H_0)	$n \times$ MSE	$n \times$ Var	Bias	Rel. eff.
CF-MARS	100	0.10	0.27	0.74	0.73	0.00	1.23
CF-RF	100	0.10	0.25	0.64	0.64	0.00	1.08
CF-XGBoost	100	0.10	0.25	0.64	0.64	0.00	1.07
ℓ_1-LR	100	0.10	0.28	0.55	0.55	0.00	0.92
LR	100	0.10	0.32	0.60	0.60	0.00	1.01
MARS	100	0.10	0.28	0.64	0.63	-0.01	1.07
RF	100	0.10	0.50	0.56	0.52	-0.02	0.94
Unadjusted	100	0.10	0.26	0.60	0.60	0.00	1.00
XGBoost	100	0.10	0.28	0.60	0.60	0.00	1.01
max MC error			<0.01	0.02	0.01	<0.01	0.03
CF-MARS	500	0.10	0.85	0.57	0.57	0.00	0.92
CF-RF	500	0.10	0.85	0.56	0.56	0.00	0.91
CF-XGBoost	500	0.10	0.84	0.59	0.59	0.00	0.96
ℓ_1-LR	500	0.10	0.87	0.54	0.54	0.00	0.89
LR	500	0.10	0.86	0.57	0.57	0.00	0.92
MARS	500	0.10	0.85	0.56	0.55	0.00	0.90
RF	500	0.10	0.94	0.66	0.58	-0.01	1.07
Unadjusted	500	0.10	0.83	0.61	0.61	0.00	1.00
XGBoost	500	0.10	0.87	0.55	0.55	0.00	0.90
			<0.01	0.01	0.01	<0.01	0.03
CF-MARS	1500	0.10	1.00	0.58	0.58	0.00	0.96
CF-RF	1500	0.10	1.00	0.47	0.47	0.00	0.77
CF-XGBoost	1500	0.10	1.00	0.56	0.56	0.00	0.94
ℓ_1-LR	1500	0.10	1.00	0.56	0.56	0.00	0.93
LR	1500	0.10	1.00	0.55	0.55	0.00	0.92
MARS	1500	0.10	1.00	0.57	0.57	0.00	0.94
RF	1500	0.10	1.00	0.61	0.54	-0.01	1.01
Unadjusted	1500	0.10	1.00	0.60	0.60	0.00	1.00
XGBoost	1500	0.10	1.00	0.54	0.53	0.00	0.89
			<0.01	0.01	0.01	<0.01	0.03

Table A2: Simulation results for the RD of time to intubation or death at day 7 under a positive effect and covariates with prognostic power.

Estimator	n	Effect size	P(Reject H_0)	$n \times$ MSE	$n \times$ Var	Bias	Rel. eff.
CF-MARS	100	0.60	0.35	73	70	0.17	0.13
CF-RF	100	0.60	0.36	38	37	0.11	0.07
CF-XGBoost	100	0.60	0.36	35	34	0.07	0.06
ℓ_1-LR	100	0.60	0.45	57	55	0.16	0.10
LR	100	0.60	0.48	472	393	0.89	0.81
MARS	100	0.60	0.45	192	176	0.40	0.33
RF	100	0.60	0.48	32	32	0.01	0.05
Unadjusted	100	0.60	0.42	582	441	1.19	1.00
XGBoost	100	0.60	0.41	50	49	0.06	0.09
max MC error			<0.01	21.59	8.83	0.03	0.01
CF-MARS	500	0.60	0.90	30	30	0.02	0.54
CF-RF	500	0.60	0.93	16	16	-0.01	0.29
CF-XGBoost	500	0.60	0.92	19	19	0.01	0.34
ℓ_1-LR	500	0.60	0.93	19	19	0.01	0.33
LR	500	0.60	0.92	33	33	0.03	0.59
MARS	500	0.60	0.93	32	32	0.01	0.57
RF	500	0.60	0.99	16	15	-0.04	0.28
Unadjusted	500	0.60	0.86	56	56	0.02	1.00
XGBoost	500	0.60	0.95	16	15	-0.04	0.29
			<0.01	8.25	1.12	<0.01	0.02
CF-MARS	1500	0.60	1.00	18	18	0.00	0.88
CF-RF	1500	0.60	1.00	12	12	-0.01	0.61
CF-XGBoost	1500	0.60	1.00	15	15	0.00	0.76
ℓ_1-LR	1500	0.60	1.00	18	18	0.00	0.89
LR	1500	0.60	1.00	17	17	0.01	0.85
MARS	1500	0.60	1.00	17	17	0.00	0.83
RF	1500	0.60	1.00	10	9	-0.02	0.49
Unadjusted	1500	0.60	1.00	20	20	0.00	1.00
XGBoost	1500	0.60	1.00	11	11	-0.02	0.55
			<0.01	0.41	0.40	<0.01	0.03

Table A3: Simulation results for the LOR of the modified WHO scale at day 14 under a positive effect and covariates with prognostic power.

Estimator	n	Effect size	P(Reject H_0)	$n \times$ MSE	$n \times$ Var	Bias	Rel. eff.
CF-MARS	100	0.46	0.24	0.66	0.66	0.00	2.52
CF-RF	100	0.46	0.17	0.24	0.24	0.00	0.90
CF-XGBoost	100	0.46	0.15	0.24	0.24	0.00	0.92
ℓ_1-LR	100	0.46	0.18	0.23	0.23	0.00	0.86
LR	100	0.46	0.45	1.68	1.66	0.01	6.40
MARS	100	0.46	0.23	0.49	0.49	0.00	1.85
RF	100	0.46	0.22	0.20	0.19	0.01	0.76
Unadjusted	100	0.46	0.14	0.26	0.26	0.00	1.00
XGBoost	100	0.46	0.19	0.21	0.21	0.00	0.81
max MC error			<0.01	0.03	0.03	<0.01	0.09
CF-MARS	500	0.46	0.51	0.52	0.51	-0.01	2.01
CF-RF	500	0.46	0.56	0.20	0.20	0.00	0.79
CF-XGBoost	500	0.46	0.53	0.23	0.22	0.00	0.87
ℓ_1-LR	500	0.46	0.53	0.21	0.21	0.00	0.82
LR	500	0.46	0.54	0.24	0.24	0.00	0.92
MARS	500	0.46	0.51	0.26	0.26	0.00	1.02
RF	500	0.46	0.76	0.14	0.14	0.00	0.55
Unadjusted	500	0.46	0.44	0.26	0.26	0.00	1.00
XGBoost	500	0.46	0.59	0.20	0.20	0.00	0.76
			<0.01	0.03	0.01	<0.01	0.06
CF-MARS	1500	0.46	0.93	0.23	0.22	0.00	0.86
CF-RF	1500	0.46	0.99	0.15	0.14	0.00	0.57
CF-XGBoost	1500	0.46	0.97	0.19	0.18	0.00	0.73
ℓ_1-LR	1500	0.46	0.93	0.23	0.22	0.00	0.86
LR	1500	0.46	0.94	0.23	0.21	0.00	0.85
MARS	1500	0.46	0.94	0.21	0.21	0.00	0.80
RF	1500	0.46	1.00	0.11	0.11	0.00	0.40
Unadjusted	1500	0.46	0.88	0.27	0.26	0.00	1.00
XGBoost	1500	0.46	0.99	0.14	0.13	0.00	0.52
			<0.01	0.01	<0.01	<0.01	0.02

Table A4: Simulation results for the MW estimand of the modified WHO scale at day 14 under a positive effect and covariates with prognostic power.

D.2 Results for simulations with null treatment effect and where the covariates are prognostic of the outcome

Estimator	n	Effect size	P(Reject H_0)	$n \times$ MSE	$n \times$ Var	Bias	Rel. eff.
CF-MARS	100	0.00	0.10	127	122	-0.23	1.44
CF-RF	100	0.00	0.05	89	89	0.02	1.01
CF-XGBoost	100	0.00	0.05	91	91	0.02	1.03
ℓ_1-LR	100	0.00	0.07	82	82	0.01	0.93
LR	100	0.00	0.09	87	87	0.01	0.99
MARS	100	0.00	0.09	88	88	-0.07	1.00
RF	100	0.00	0.30	52	52	-0.01	0.59
Unadjusted	100	0.00	0.06	88	88	-0.03	1.00
XGBoost	100	0.00	0.05	78	78	-0.01	0.89
max MC error			<0.01	2.55	2.43	0.02	0.10
CF-MARS	500	0.00	0.05	81	81	-0.01	0.95
CF-RF	500	0.00	0.05	76	76	0.00	0.89
CF-XGBoost	500	0.00	0.05	84	84	0.00	0.98
ℓ_1-LR	500	0.00	0.05	73	73	-0.01	0.86
LR	500	0.00	0.06	80	80	0.00	0.94
MARS	500	0.00	0.05	78	78	0.00	0.92
RF	500	0.00	0.29	48	48	0.00	0.57
Unadjusted	500	0.00	0.05	85	85	-0.01	1.00
XGBoost	500	0.00	0.07	73	73	0.00	0.86
			<0.01	1.77	1.70	<0.01	0.03
CF-MARS	1500	0.00	0.05	73	73	0.00	0.85
CF-RF	1500	0.00	0.05	56	56	0.00	0.66
CF-XGBoost	1500	0.00	0.05	80	80	0.00	0.94
ℓ_1-LR	1500	0.00	0.05	76	76	0.00	0.88
LR	1500	0.00	0.06	75	75	0.00	0.88
MARS	1500	0.00	0.05	77	77	0.00	0.89
RF	1500	0.00	0.30	28	28	0.00	0.32
Unadjusted	1500	0.00	0.05	86	86	0.00	1.00
XGBoost	1500	0.00	0.07	64	64	0.00	0.75
			<0.01	1.73	1.72	<0.01	0.03

Table A5: Simulation results for the RMST of time to intubation or death at day 14 under null treatment effect and covariates with prognostic power.

Estimator	n	Effect size	P(Reject H_0)	$n \times$ MSE	$n \times$ Var	Bias	Rel. eff.
CF-MARS	100	0.00	0.09	1.00	0.96	-0.02	1.36
CF-RF	100	0.00	0.05	0.75	0.75	0.00	1.02
CF-XGBoost	100	0.00	0.05	0.75	0.75	0.00	1.03
ℓ_1-LR	100	0.00	0.07	0.69	0.69	0.00	0.95
LR	100	0.00	0.09	0.72	0.72	0.00	0.98
MARS	100	0.00	0.08	0.72	0.72	-0.01	0.99
RF	100	0.00	0.26	0.51	0.51	0.00	0.70
Unadjusted	100	0.00	0.06	0.73	0.73	0.00	1.00
XGBoost	100	0.00	0.05	0.66	0.66	0.00	0.90
max MC error			$<$0.01	0.02	0.02	$<$0.01	0.11
CF-MARS	500	0.00	0.05	0.69	0.68	0.00	0.95
CF-RF	500	0.00	0.04	0.63	0.63	0.00	0.88
CF-XGBoost	500	0.00	0.04	0.70	0.70	0.00	0.98
ℓ_1-LR	500	0.00	0.05	0.63	0.63	0.00	0.88
LR	500	0.00	0.06	0.69	0.69	0.00	0.95
MARS	500	0.00	0.06	0.68	0.68	0.00	0.94
RF	500	0.00	0.25	0.45	0.45	0.00	0.62
Unadjusted	500	0.00	0.05	0.72	0.72	0.00	1.00
XGBoost	500	0.00	0.06	0.62	0.62	0.00	0.86
			$<$0.01	0.02	0.01	$<$0.01	0.03
CF-MARS	1500	0.00	0.04	0.62	0.62	0.00	0.86
CF-RF	1500	0.00	0.05	0.49	0.49	0.00	0.67
CF-XGBoost	1500	0.00	0.05	0.68	0.68	0.00	0.94
ℓ_1-LR	1500	0.00	0.05	0.64	0.64	0.00	0.89
LR	1500	0.00	0.05	0.65	0.65	0.00	0.90
MARS	1500	0.00	0.05	0.65	0.65	0.00	0.90
RF	1500	0.00	0.25	0.26	0.26	0.00	0.36
Unadjusted	1500	0.00	0.05	0.72	0.72	0.00	1.00
XGBoost	1500	0.00	0.07	0.56	0.56	0.00	0.78
			$<$0.01	0.01	0.01	$<$0.01	0.03

Table A6: Simulation results for the RD of time to intubation or death at day 7 under null treatment effect and covariates with prognostic power.

Estimator	n	Effect size	P(Reject H_0)	$n \times$ MSE	$n \times$ Var	Bias	Rel. eff.
CF-MARS	100	0.00	0.07	21	21	0.00	0.55
CF-RF	100	0.00	0.06	17	17	0.01	0.44
CF-XGBoost	100	0.00	0.07	18	18	0.00	0.47
ℓ_1-LR	100	0.00	0.09	28	28	0.00	0.73
LR	100	0.00	0.11	112	112	0.03	2.89
MARS	100	0.00	0.09	60	60	0.01	1.56
RF	100	0.00	0.13	22	22	-0.01	0.57
Unadjusted	100	0.00	0.06	39	39	0.00	1.00
XGBoost	100	0.00	0.10	19	19	0.01	0.49
max MC error			<0.01	40.73	2.25	0.02	0.94
CF-MARS	500	0.00	0.05	15	15	0.00	0.88
CF-RF	500	0.00	0.05	13	13	0.00	0.75
CF-XGBoost	500	0.00	0.06	14	14	0.00	0.84
ℓ_1-LR	500	0.00	0.06	14	14	0.00	0.81
LR	500	0.00	0.06	14	14	0.00	0.82
MARS	500	0.00	0.05	13	13	0.00	0.76
RF	500	0.00	0.14	7	7	0.00	0.44
Unadjusted	500	0.00	0.05	17	17	0.00	1.00
XGBoost	500	0.00	0.08	11	11	0.00	0.66
			<0.01	0.33	0.33	<0.01	0.02
CF-MARS	1500	0.00	0.05	13	13	0.00	0.82
CF-RF	1500	0.00	0.05	8	8	0.00	0.51
CF-XGBoost	1500	0.00	0.05	11	11	0.00	0.68
ℓ_1-LR	1500	0.00	0.05	13	13	0.00	0.79
LR	1500	0.00	0.05	13	13	0.00	0.81
MARS	1500	0.00	0.05	13	13	0.00	0.77
RF	1500	0.00	0.15	5	5	0.00	0.28
Unadjusted	1500	0.00	0.05	16	16	0.00	1.00
XGBoost	1500	0.00	0.16	6	6	0.00	0.39
			<0.01	0.33	0.33	<0.01	0.02

Table A7: Simulation results for the LOR of the modified WHO scale at day 14 under null treatment effect and covariates with prognostic power.

Estimator	n	Effect size	P(Reject H_0)	$n \times$ MSE	$n \times$ Var	Bias	Rel. eff.
CF-MARS	100	0.50	0.11	0.54	0.54	0.00	1.95
CF-RF	100	0.50	0.07	0.23	0.23	0.00	0.84
CF-XGBoost	100	0.50	0.07	0.25	0.25	0.00	0.92
ℓ_1-LR	100	0.50	0.07	0.22	0.22	0.00	0.80
LR	100	0.50	0.48	2.14	2.14	0.00	7.77
MARS	100	0.50	0.12	0.43	0.43	0.00	1.58
RF	100	0.50	0.13	0.16	0.16	0.00	0.57
Unadjusted	100	0.50	0.06	0.28	0.28	0.00	1.00
XGBoost	100	0.50	0.09	0.21	0.21	0.00	0.75
max MC error			<0.01	0.03	0.04	<0.01	0.78
CF-MARS	500	0.50	0.06	0.28	0.28	0.00	1.07
CF-RF	500	0.50	0.05	0.20	0.20	0.00	0.74
CF-XGBoost	500	0.50	0.06	0.22	0.22	0.00	0.85
ℓ_1-LR	500	0.50	0.05	0.21	0.21	0.00	0.80
LR	500	0.50	0.08	0.79	0.79	0.00	2.98
MARS	500	0.50	0.06	0.27	0.27	0.00	1.01
RF	500	0.50	0.14	0.13	0.13	0.00	0.48
Unadjusted	500	0.50	0.05	0.27	0.27	0.00	1.00
XGBoost	500	0.50	0.08	0.18	0.18	0.00	0.69
			<0.01	0.05	0.02	<0.01	0.03
CF-MARS	1500	0.50	0.05	0.22	0.22	0.00	0.84
CF-RF	1500	0.50	0.05	0.13	0.13	0.00	0.52
CF-XGBoost	1500	0.50	0.06	0.18	0.18	0.00	0.71
ℓ_1-LR	1500	0.50	0.05	0.21	0.21	0.00	0.81
LR	1500	0.50	0.06	0.22	0.22	0.00	0.84
MARS	1500	0.50	0.05	0.22	0.22	0.00	0.84
RF	1500	0.50	0.16	0.20	0.20	0.00	0.78
Unadjusted	1500	0.50	0.05	0.26	0.26	0.00	1.00
XGBoost	1500	0.50	0.15	0.11	0.11	0.00	0.43
			<0.01	0.04	<0.01	<0.01	0.02

Table A8: Simulation results for the MW estimand of the modified WHO scale at day 14 under null treatment effect and covariates with prognostic power.

D.3 Results for simulations with a positive effect and where the covariates are not prognostic of the outcome

Estimator	n	Effect size	P(Reject H_0)	$n \times$ MSE	$n \times$ Var	Bias	Rel. eff.
CF-MARS	100	1.04	0.25	95	95	0.01	1.46
CF-RF	100	1.04	0.21	77	77	0.00	1.19
CF-XGBoost	100	1.04	0.23	77	77	0.01	1.20
ℓ_1-LR	100	1.04	0.24	64	64	-0.01	0.99
LR	100	1.04	0.30	76	76	0.02	1.17
MARS	100	1.04	0.25	73	73	-0.09	1.14
RF	100	1.04	0.58	68	64	-0.20	1.06
Unadjusted	100	1.04	0.25	65	65	0.01	1.00
XGBoost	100	1.04	0.26	67	67	0.01	1.03
max MC error			<0.01	2.03	1.89	0.01	0.04
CF-MARS	500	1.04	0.81	67	67	0.00	1.02
CF-RF	500	1.04	0.77	74	74	0.01	1.12
CF-XGBoost	500	1.04	0.77	73	73	0.00	1.11
ℓ_1-LR	500	1.04	0.83	67	67	0.00	1.01
LR	500	1.04	0.83	68	68	0.01	1.03
MARS	500	1.04	0.82	65	65	-0.01	0.98
RF	500	1.04	0.91	82	80	-0.06	1.24
Unadjusted	500	1.04	0.82	66	66	0.00	1.00
XGBoost	500	1.04	0.83	64	64	-0.01	0.97
			<0.01	1.60	1.59	<0.01	0.03
CF-MARS	1500	1.04	1.00	66	66	0.00	1.01
CF-RF	1500	1.04	1.00	74	74	0.00	1.14
CF-XGBoost	1500	1.04	1.00	71	71	0.00	1.08
ℓ_1-LR	1500	1.04	1.00	66	66	0.00	1.01
LR	1500	1.04	1.00	66	66	0.00	1.01
MARS	1500	1.04	1.00	66	66	0.00	1.01
RF	1500	1.04	1.00	75	75	0.00	1.15
Unadjusted	1500	1.04	1.00	65	65	0.00	1.00
XGBoost	1500	1.04	1.00	67	67	0.00	1.03
			<0.01	1.57	1.55	<0.01	0.03

Table A9: Simulation results for the RMST of the time to intubation or death at day 14 under a positive effect and covariates with no prognostic power.

Estimator	n	Effect size	P(Reject H_0)	$n \times$ MSE	$n \times$ Var	Bias	Rel. eff.
CF-MARS	100	0.10	0.26	0.83	0.83	0.00	1.39
CF-RF	100	0.10	0.22	0.68	0.68	0.00	1.14
CF-XGBoost	100	0.10	0.26	0.70	0.70	0.00	1.17
ℓ_1-LR	100	0.10	0.26	0.60	0.60	0.00	1.00
LR	100	0.10	0.30	0.67	0.67	0.00	1.13
MARS	100	0.10	0.27	0.67	0.67	-0.01	1.13
RF	100	0.10	0.51	0.71	0.68	-0.02	1.18
Unadjusted	100	0.10	0.26	0.60	0.60	0.00	1.00
XGBoost	100	0.10	0.27	0.62	0.62	0.00	1.03
max MC error			$<$0.01	0.02	0.02	$<$0.01	0.04
CF-MARS	500	0.10	0.82	0.61	0.61	0.00	1.00
CF-RF	500	0.10	0.79	0.66	0.66	0.00	1.08
CF-XGBoost	500	0.10	0.79	0.66	0.66	0.00	1.07
ℓ_1-LR	500	0.10	0.83	0.61	0.61	0.00	0.99
LR	500	0.10	0.83	0.62	0.62	0.00	1.02
MARS	500	0.10	0.83	0.59	0.59	0.00	0.96
RF	500	0.10	0.89	0.79	0.77	-0.01	1.28
Unadjusted	500	0.10	0.83	0.61	0.61	0.00	1.00
XGBoost	500	0.10	0.83	0.60	0.59	0.00	0.97
			$<$0.01	0.02	0.02	$<$0.01	0.04
CF-MARS	1500	0.10	1.00	0.61	0.61	0.00	1.01
CF-RF	1500	0.10	1.00	0.67	0.67	0.00	1.11
CF-XGBoost	1500	0.10	1.00	0.63	0.63	0.00	1.05
ℓ_1-LR	1500	0.10	1.00	0.60	0.60	0.00	0.99
LR	1500	0.10	1.00	0.60	0.60	0.00	0.99
MARS	1500	0.10	1.00	0.60	0.60	0.00	0.99
RF	1500	0.10	1.00	0.69	0.69	0.00	1.14
Unadjusted	1500	0.10	1.00	0.60	0.60	0.00	1.00
XGBoost	1500	0.10	1.00	0.61	0.61	0.00	1.01
			$<$0.01	0.01	0.01	$<$0.01	0.03

Table A10: Simulation results for the RD of the time to intubation or death at day 7 under a positive effect and covariates with no prognostic power.

Estimator	n	Effect size	P(Reject H_0)	$n \times$ MSE	$n \times$ Var	Bias	Rel. eff.
CF-MARS	100	0.60	0.35	67	65	0.16	0.12
CF-RF	100	0.60	0.37	62	59	0.19	0.11
CF-XGBoost	100	0.60	0.40	76	72	0.19	0.13
ℓ_1-LR	100	0.60	0.44	96	90	0.23	0.16
LR	100	0.60	0.41	393	331	0.79	0.67
MARS	100	0.60	0.41	188	168	0.45	0.32
RF	100	0.60	0.45	61	60	0.12	0.10
Unadjusted	100	0.60	0.42	582	441	1.19	1.00
XGBoost	100	0.60	0.43	133	125	0.29	0.23
max MC error			<0.01	12.80	8.83	0.03	0.02
CF-MARS	500	0.60	0.87	31	31	0.02	0.56
CF-RF	500	0.60	0.87	23	23	0.00	0.41
CF-XGBoost	500	0.60	0.88	26	26	0.02	0.46
ℓ_1-LR	500	0.60	0.87	24	24	0.01	0.43
LR	500	0.60	0.86	54	53	0.03	0.96
MARS	500	0.60	0.87	39	39	0.02	0.70
RF	500	0.60	0.91	34	34	0.00	0.60
Unadjusted	500	0.60	0.86	56	56	0.02	1.00
XGBoost	500	0.60	0.89	23	23	0.00	0.40
			<0.01	8.25	1.12	<0.01	0.03
CF-MARS	1500	0.60	1.00	21	21	0.00	1.04
CF-RF	1500	0.60	1.00	21	21	0.00	1.04
CF-XGBoost	1500	0.60	1.00	22	22	0.01	1.10
ℓ_1-LR	1500	0.60	1.00	21	21	0.00	1.03
LR	1500	0.60	1.00	20	20	0.00	1.00
MARS	1500	0.60	1.00	20	20	0.00	1.00
RF	1500	0.60	1.00	21	20	0.00	1.02
Unadjusted	1500	0.60	1.00	20	20	0.00	1.00
XGBoost	1500	0.60	1.00	20	20	-0.01	1.01
			<0.01	0.44	0.44	<0.01	0.03

Table A11: Simulation results for the LOR of the modified WHO scale at day 14 under a positive effect and covariates with no prognostic power.

Estimator	n	Effect size	P(Reject H_0)	$n \times$ MSE	$n \times$ Var	Bias	Rel. eff.
CF-MARS	100	0.46	0.18	0.54	0.54	0.00	2.05
CF-RF	100	0.46	0.15	0.29	0.29	0.00	1.11
CF-XGBoost	100	0.46	0.15	0.29	0.29	0.00	1.10
ℓ_1-LR	100	0.46	0.16	0.26	0.26	0.00	1.00
LR	100	0.46	0.44	1.69	1.67	0.01	6.43
MARS	100	0.46	0.18	0.43	0.43	0.00	1.63
RF	100	0.46	0.19	0.24	0.23	0.01	0.91
Unadjusted	100	0.46	0.14	0.26	0.26	0.00	1.00
XGBoost	100	0.46	0.18	0.26	0.26	0.00	1.00
max MC error			<0.01	0.03	0.03	<0.01	0.18
CF-MARS	500	0.46	0.44	0.50	0.49	0.00	1.93
CF-RF	500	0.46	0.44	0.28	0.28	0.00	1.09
CF-XGBoost	500	0.46	0.46	0.27	0.27	0.00	1.04
ℓ_1-LR	500	0.46	0.46	0.26	0.26	0.00	1.02
LR	500	0.46	0.46	0.29	0.28	0.00	1.10
MARS	500	0.46	0.44	0.30	0.30	0.00	1.16
RF	500	0.46	0.51	0.24	0.24	0.00	0.93
Unadjusted	500	0.46	0.44	0.26	0.26	0.00	1.00
XGBoost	500	0.46	0.47	0.26	0.25	0.00	0.98
			<0.01	0.03	<0.01	<0.01	0.05
CF-MARS	1500	0.46	0.87	0.28	0.27	0.00	1.04
CF-RF	1500	0.46	0.88	0.27	0.27	0.00	1.03
CF-XGBoost	1500	0.46	0.88	0.28	0.27	0.00	1.06
ℓ_1-LR	1500	0.46	0.88	0.27	0.26	0.00	1.00
LR	1500	0.46	0.89	0.26	0.25	0.00	0.98
MARS	1500	0.46	0.88	0.27	0.26	0.00	1.03
RF	1500	0.46	0.91	0.26	0.26	0.00	0.98
Unadjusted	1500	0.46	0.88	0.27	0.26	0.00	1.00
XGBoost	1500	0.46	0.89	0.27	0.26	0.00	1.01
			<0.01	<0.01	<0.01	<0.01	0.03

Table A12: Simulation results for the MW of the modified WHO scale at day 14 under a positive effect and covariates with no prognostic power.

D.4 Results for simulations with null treatment effect and where the covariates are not prognostic of the outcome

Estimator	n	Effect size	P(Reject H_0)	$n \times$ MSE	$n \times$ Var	Bias	Rel. eff.
CF-MARS	100	0.00	0.11	142	136	-0.25	1.62
CF-RF	100	0.00	0.05	103	103	0.02	1.17
CF-XGBoost	100	0.00	0.05	96	96	0.00	1.09
ℓ_1-LR	100	0.00	0.06	87	87	-0.03	0.99
LR	100	0.00	0.09	100	100	0.02	1.14
MARS	100	0.00	0.08	98	97	-0.07	1.11
RF	100	0.00	0.31	71	71	-0.02	0.80
Unadjusted	100	0.00	0.06	88	88	-0.03	1.00
XGBoost	100	0.00	0.06	88	88	-0.01	1.00
max MC error			<0.01	3.02	2.72	0.02	0.04
CF-MARS	500	0.00	0.06	92	92	-0.02	1.08
CF-RF	500	0.00	0.05	98	98	0.00	1.16
CF-XGBoost	500	0.00	0.05	98	98	0.00	1.15
ℓ_1-LR	500	0.00	0.05	87	87	0.01	1.03
LR	500	0.00	0.06	93	93	0.00	1.09
MARS	500	0.00	0.05	88	88	0.00	1.04
RF	500	0.00	0.17	86	86	0.00	1.01
Unadjusted	500	0.00	0.05	85	85	-0.01	1.00
XGBoost	500	0.00	0.06	87	87	0.00	1.02
			<0.01	1.98	1.97	<0.01	0.03
CF-MARS	1500	0.00	0.05	86	86	0.00	1.00
CF-RF	1500	0.00	0.05	95	95	0.00	1.10
CF-XGBoost	1500	0.00	0.04	93	93	0.00	1.09
ℓ_1-LR	1500	0.00	0.05	86	86	0.00	1.00
LR	1500	0.00	0.06	90	90	0.00	1.05
MARS	1500	0.00	0.05	89	89	0.00	1.04
RF	1500	0.00	0.11	89	89	0.00	1.04
Unadjusted	1500	0.00	0.05	86	86	0.00	1.00
XGBoost	1500	0.00	0.07	90	90	0.00	1.04
			<0.01	1.93	1.89	<0.01	0.03

Table A13: Simulation results for the RMST of the time to intubation or death at day 14 under null treatment effect and covariates with no prognostic power.

Estimator	n	Effect size	P(Reject H_0)	$n \times$ MSE	$n \times$ Var	Bias	Rel. eff.
CF-MARS	100	0.00	0.10	1.11	1.07	-0.02	1.52
CF-RF	100	0.00	0.05	0.85	0.85	0.00	1.17
CF-XGBoost	100	0.00	0.05	0.80	0.80	0.00	1.09
ℓ_1-LR	100	0.00	0.06	0.72	0.72	0.00	0.99
LR	100	0.00	0.08	0.82	0.82	0.00	1.12
MARS	100	0.00	0.07	0.79	0.79	0.00	1.09
RF	100	0.00	0.27	0.66	0.66	0.00	0.90
Unadjusted	100	0.00	0.06	0.73	0.73	0.00	1.00
XGBoost	100	0.00	0.06	0.73	0.73	0.00	1.00
max MC error			<0.01	0.02	0.02	<0.01	0.04
CF-MARS	500	0.00	0.05	0.76	0.76	0.00	1.06
CF-RF	500	0.00	0.05	0.82	0.82	0.00	1.13
CF-XGBoost	500	0.00	0.05	0.80	0.80	0.00	1.11
ℓ_1-LR	500	0.00	0.05	0.72	0.72	0.00	1.00
LR	500	0.00	0.06	0.78	0.78	0.00	1.08
MARS	500	0.00	0.05	0.74	0.74	0.00	1.03
RF	500	0.00	0.16	0.73	0.73	0.00	1.02
Unadjusted	500	0.00	0.05	0.72	0.72	0.00	1.00
XGBoost	500	0.00	0.06	0.72	0.72	0.00	1.00
			<0.01	0.02	0.02	<0.01	0.03
CF-MARS	1500	0.00	0.05	0.71	0.71	0.00	0.99
CF-RF	1500	0.00	0.05	0.79	0.79	0.00	1.09
CF-XGBoost	1500	0.00	0.04	0.77	0.77	0.00	1.07
ℓ_1-LR	1500	0.00	0.05	0.72	0.72	0.00	0.99
LR	1500	0.00	0.06	0.74	0.74	0.00	1.03
MARS	1500	0.00	0.05	0.74	0.74	0.00	1.03
RF	1500	0.00	0.10	0.74	0.74	0.00	1.03
Unadjusted	1500	0.00	0.05	0.72	0.72	0.00	1.00
XGBoost	1500	0.00	0.06	0.75	0.75	0.00	1.05
			<0.01	0.02	0.02	<0.01	0.03

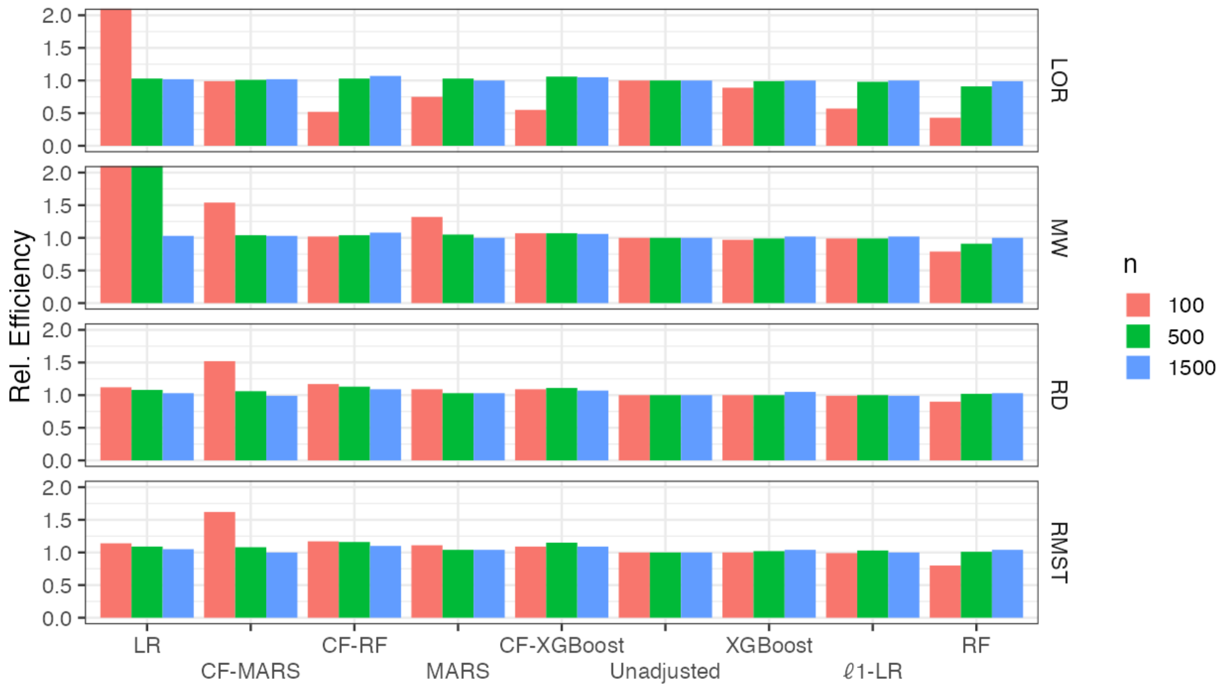
Table A14: Simulation results for the RD of the time to intubation or death at day 7 under null treatment effect and covariates with no prognostic power.

Estimator	n	Effect size	P(Reject H_0)	$n \times$ MSE	$n \times$ Var	Bias	Rel. eff.
CF-MARS	100	0.00	0.07	38	38	0.01	0.99
CF-RF	100	0.00	0.06	20	20	-0.01	0.52
CF-XGBoost	100	0.00	0.07	21	21	0.00	0.55
ℓ_1-LR	100	0.00	0.09	22	22	0.01	0.57
LR	100	0.00	0.08	96	96	0.00	2.49
MARS	100	0.00	0.07	29	29	0.01	0.75
RF	100	0.00	0.11	17	17	-0.01	0.43
Unadjusted	100	0.00	0.06	39	39	0.00	1.00
XGBoost	100	0.00	0.10	34	34	0.01	0.89
max MC error			<0.01	23.34	1.92	0.01	0.07
CF-MARS	500	0.00	0.05	17	17	0.00	1.01
CF-RF	500	0.00	0.05	17	17	0.00	1.03
CF-XGBoost	500	0.00	0.06	18	18	0.00	1.06
ℓ_1-LR	500	0.00	0.06	16	16	0.00	0.98
LR	500	0.00	0.06	17	17	0.00	1.03
MARS	500	0.00	0.06	17	17	0.00	1.03
RF	500	0.00	0.09	15	15	0.00	0.91
Unadjusted	500	0.00	0.05	17	17	0.00	1.00
XGBoost	500	0.00	0.07	17	17	0.00	0.99
			<0.01	0.36	0.35	<0.01	0.03
CF-MARS	1500	0.00	0.05	17	17	0.00	1.02
CF-RF	1500	0.00	0.06	17	17	0.00	1.07
CF-XGBoost	1500	0.00	0.06	17	17	0.00	1.05
ℓ_1-LR	1500	0.00	0.05	16	16	-0.01	1.00
LR	1500	0.00	0.05	17	17	0.00	1.02
MARS	1500	0.00	0.05	16	16	0.00	1.00
RF	1500	0.00	0.08	16	16	0.00	0.99
Unadjusted	1500	0.00	0.05	16	16	0.00	1.00
XGBoost	1500	0.00	0.06	16	16	0.00	1.00
			<0.01	0.36	0.35	<0.01	0.03

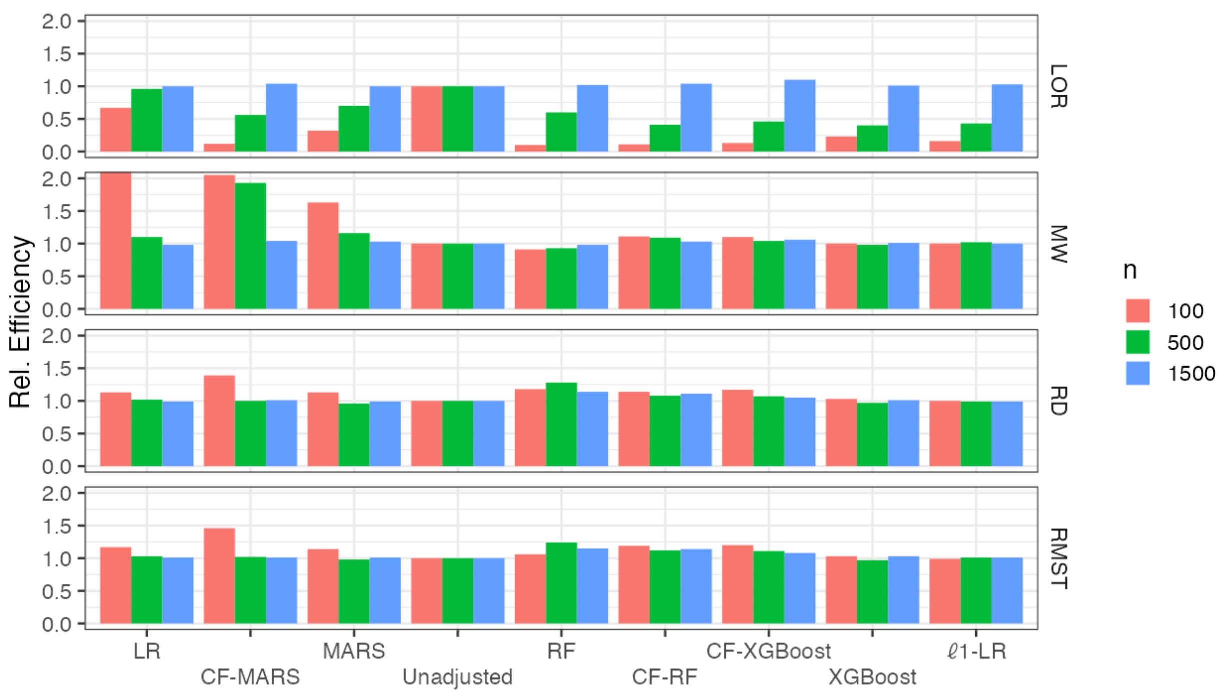
Table A15: Simulation results for the LOR of the modified WHO scale at day 14 under null treatment effect and covariates with no prognostic power.

Estimator	n	Effect size	P(Reject H_0)	$n \times$ MSE	$n \times$ Var	Bias	Rel. eff.
CF-MARS	100	0.50	0.08	0.42	0.42	0.00	1.54
CF-RF	100	0.50	0.06	0.28	0.28	0.00	1.02
CF-XGBoost	100	0.50	0.07	0.29	0.29	0.00	1.07
ℓ_1-LR	100	0.50	0.07	0.27	0.27	0.00	0.99
LR	100	0.50	0.47	2.09	2.09	0.00	7.57
MARS	100	0.50	0.08	0.36	0.36	0.00	1.32
RF	100	0.50	0.11	0.22	0.22	0.00	0.79
Unadjusted	100	0.50	0.06	0.28	0.28	0.00	1.00
XGBoost	100	0.50	0.09	0.27	0.27	0.00	0.97
max MC error			<0.01	0.03	0.04	<0.01	0.21
CF-MARS	500	0.50	0.05	0.28	0.28	0.00	1.04
CF-RF	500	0.50	0.06	0.28	0.28	0.00	1.04
CF-XGBoost	500	0.50	0.06	0.29	0.29	0.00	1.07
ℓ_1-LR	500	0.50	0.05	0.26	0.26	0.00	0.99
LR	500	0.50	0.08	0.72	0.72	0.00	2.69
MARS	500	0.50	0.06	0.28	0.28	0.00	1.05
RF	500	0.50	0.09	0.24	0.24	0.00	0.91
Unadjusted	500	0.50	0.05	0.27	0.27	0.00	1.00
XGBoost	500	0.50	0.07	0.26	0.26	0.00	0.99
			<0.01	0.04	0.01	<0.01	0.08
CF-MARS	1500	0.50	0.05	0.27	0.27	0.00	1.03
CF-RF	1500	0.50	0.06	0.28	0.28	0.00	1.08
CF-XGBoost	1500	0.50	0.06	0.28	0.28	0.00	1.06
ℓ_1-LR	1500	0.50	0.05	0.26	0.26	0.00	1.02
LR	1500	0.50	0.05	0.27	0.27	0.00	1.03
MARS	1500	0.50	0.05	0.26	0.26	0.00	1.00
RF	1500	0.50	0.08	0.26	0.26	0.00	1.00
Unadjusted	1500	0.50	0.05	0.26	0.26	0.00	1.00
XGBoost	1500	0.50	0.06	0.27	0.27	0.00	1.02
			<0.01	<0.01	<0.01	<0.01	0.03

Table A16: Simulation results for the MW of the modified WHO scale at day 14 under null treatment effect and covariates with no prognostic power.

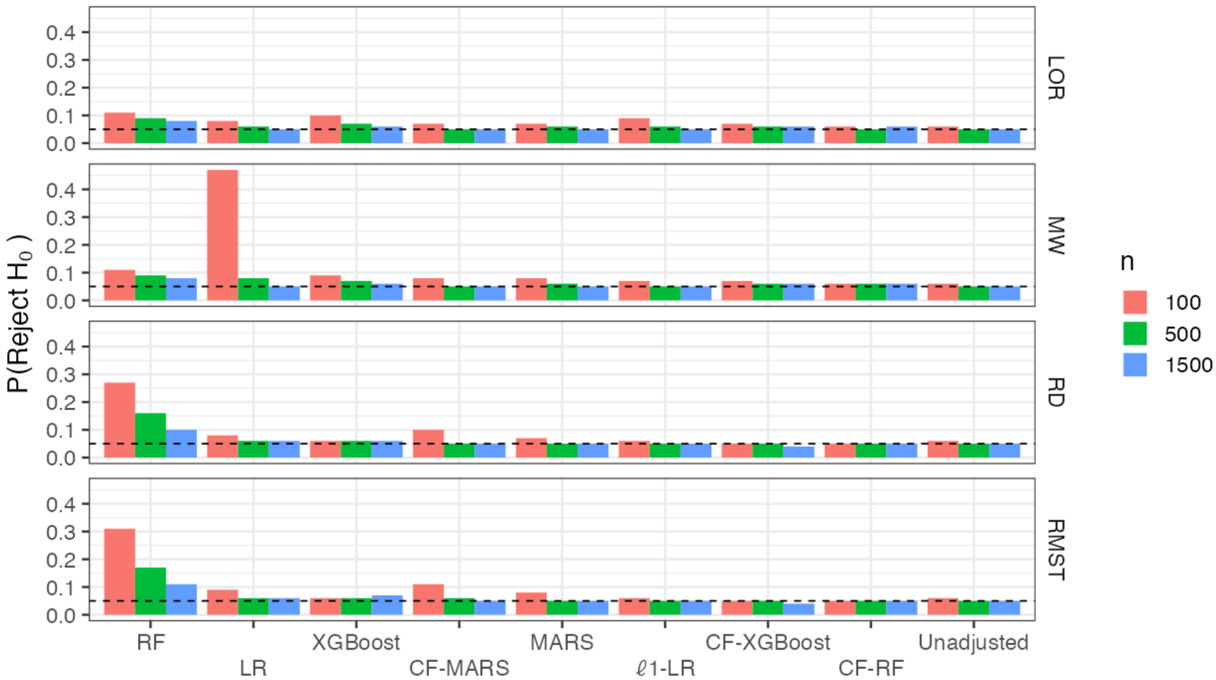


(a)

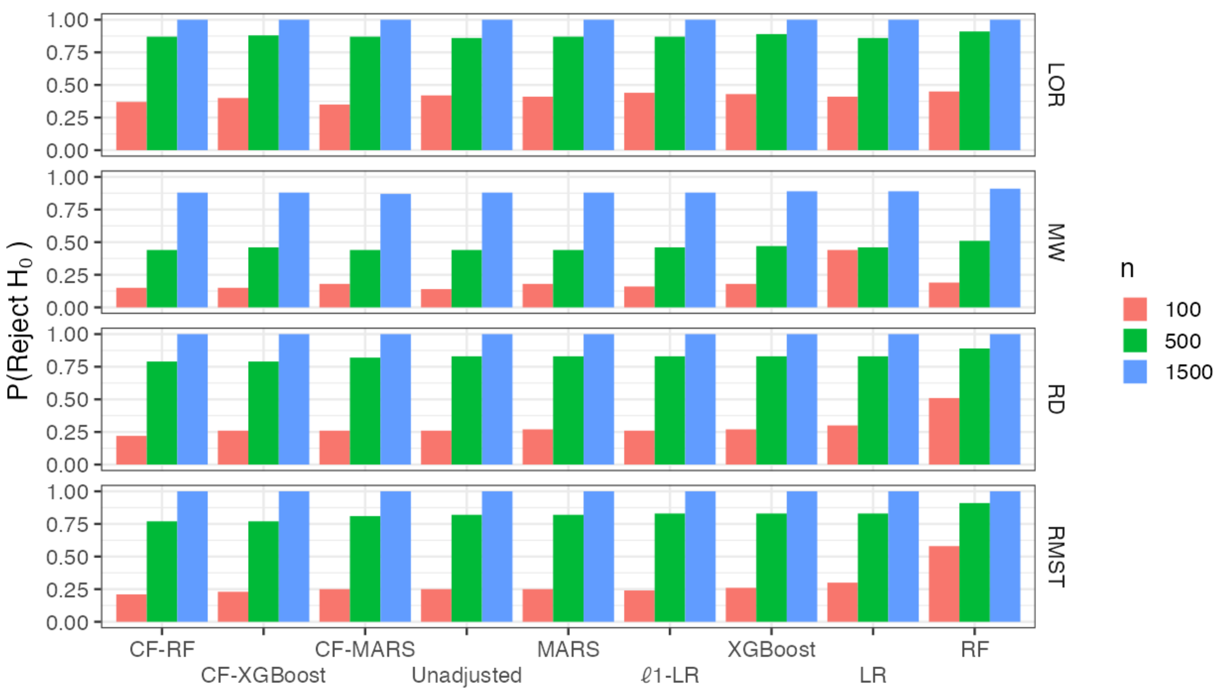


(b)

Figure A1: Efficiency of adjusted estimators relative to an unadjusted estimator for LOR, MW, RD, and RMST when there is (a) no effect of the exposure on the outcome and (b) when there is a positive effect of the exposure on the outcome and covariates are not prognostic of the outcome. Estimators are ordered by decreasing order of efficiency and efficiency is truncated at two.



(a)



(b)

Figure A2: Probability of rejecting H_0 for LOR, MW, RD, and RMST when covariates are not prognostic of the outcome and there is (a) no effect of the exposure on the outcome–estimators ordered by decreasing probability–and (b) when there is a positive effect of the exposure on the outcome–estimators ordered by increasing probability.

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