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Efficient and Robust Estimation of τ-year Risk Prediction Models Leveraging Time Varying Intermediate Outcomes

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Abstract:

Accurate risk prediction models play a key role in precision medicine, where optimal individualized disease prevention and treatment strategies can be formed based on predicted risks. In many clinical settings, it is of great interest to predict the τ-year risk of developing a clinical event using baseline covariates. Such τ-year risk models can be estimated by fitting standard survival models, including the Cox proportional hazards model and the more flexible τ-year specific generalized linear model (τ-GLM). However, an efficient and robust estimation of the risk model is challenging under heavy censoring and potential model misspecification. Intermediate outcomes observed prior to censoring can be highly predictive of the outcome and, thus, may be used to improve the efficiency of the model estimation. However, existing augmentation methods either do not allow intermediate outcomes to be subject to censoring, or exhibit limited efficiency gains. Here, we propose a two-step augmentation method to improve the estimation of the τ-year risk model by leveraging longitudinally collected inter-

Statistica Sinica: Preprint
doi:10.5705/ss.202019.0066

mediate outcome information that is subject to censoring. Our method allows for the easy incorporation of regularization to accommodate moderate covariate sizes and rare events. We also propose resampling methods to assess the variability of our proposed estimators. Our numerical studies show that the proposed point and interval estimation procedures perform well in a finite sample. We also demonstrate that our proposed estimators are substantially more efficient than existing methods. Finally, we illustrate the proposed methods using data from the Diabetes Prevention Program, a randomized clinical trial on high-risk subjects.

Key words and phrases: Efficiency augmentation, Intermediate outcomes, Model misspecification, Risk prediction, Robustness, Survival.

1. Introduction

Developing accurate risk prediction models is an important task in translational medicine research. Disease prevention and treatment strategies can be tailored to individual patients based on the risks predicted by such models. For disease prognosis and prevention, it is often of interest to predict the τ-year risk of experiencing a clinical event using baseline clinical and biomarker information. Such τ-year risk models can be estimated by fitting a wide range of survival models, including the Cox proportional hazards model (Cox, 1972) and the more flexible τ-year specific generalized linear model (τ-GLM) (Uno et al., 2007). However, an efficient and

Statistica Sinica: Preprint
doi:10.5705/ss.202019.0066

robust estimation of the risk model is challenging under heavy censoring and possible model misspecification. Under a model misspecification, the partial likelihood estimator for the Cox model converges to a quantity that depends on the censoring distribution (Van Houwelingen, 2007; Cai and Cheng, 2008). This leads to reproducibility issues because the censoring distribution is almost always study dependent. To derive a robust risk model, Uno et al. (2007) proposed an inverse probability weighted (IPW) estimator for τ-GLM, such that the model parameters are always convergent to meaningful quantities that are free of the censoring distribution. However, the IPW estimator suffers from low efficiency in heavy censoring settings because it discards information from subjects who are censored before τ .

To improve the estimation efficiency under general survival settings, various augmentation procedures have been proposed in the literature that leverage auxiliary baseline covariates or intermediate outcomes. For example, Robins, Rotnitzky, and Zhao (1994) employed alternative estimators for the censoring weights to improve the efficiency of the IPW estimators. The doubly robust augmented IPW (AIPW) method provides protection against misspecification of the weights, and could potentially improve the estimation efficiency by further employing outcome imputations (Scharf-

Statistica Sinica: Preprint
doi:10.5705/ss.202019.0066

stein, Rotnitzky, and Robins, 1999; Bang, 2005; Tsiatis, 2006). DiRienzo (2009) incorporated the AIPW method to estimate the τ-GLM, augmenting an estimating function involving outcome imputation to achieve double robustness. However, the AIPW estimators may attain little, or even a negative efficiency gain when the outcome model is misspecified. In addition, these existing methods tend to perform poorly when the number of baseline covariates and intermediate outcomes is not small. Zhang and Cai (2017) proposed a two-step imputation-based procedure that incorporates auxiliary information, including post-baseline outcomes, to improve the efficiency. The method requires that the auxiliary predictors be fully observed. However, in cohort studies or clinical trials, post-baseline intermediate outcomes are often not observable after subjects experience either the primary outcome or censoring. It is not straightforward to adapt the method to the present setting of a τ-GLM estimation, with the additional complication of intermediate outcomes being missing for those who are no longer at risk.

In this paper, we propose robust imputation-based methods to improve the estimation of τ-GLM model parameters. These methods effectively incorporate intermediate outcomes that are subject to censoring, while allowing both the τ-GLM and the imputation models to be misspecified. Our

Statistica Sinica: Preprint
doi:10.5705/ss.202019.0066

method can also easily employ regularization to control for overfitting when the number of augmentation variables is not small. When the post-baseline covariates are measured at multiple time points, we further develop a systematic approach to optimally combine several estimators in order to maximize efficiency. The rest of the manuscript is organized as follows. Section 2 describes the estimation and inference procedure. Section 3 presents our simulation results, demonstrating the consistency and efficiency gain of the proposed estimator. Section 4 illustrates the proposed method using data from the Diabetes Prevention Program, a placebo-controlled randomized clinical trial investigating whether a change of lifestyle or taking metformin prevents type 2 diabetes among high-risk adults. Concluding remarks are given in Section 5.

2 Methods

Let $T^\dagger$ be a continuous failure time, and $\mathbf{X} = (X_1 = 1, X_2, ..., X_p)^\intercal$ be a $p \times 1$ vector of bounded baseline predictors. Our goal is to develop an accurate and robust risk prediction model for $Y_\tau = I(T^\dagger \leq \tau)$ at some prespecified time τ, based on $\mathbf{X}$. We propose constructing the prediction model for Y_τ by fitting the following τ-GLM *working* model:

$$\Pr(T^\dagger \leq \tau|\mathbf{X}) = \Pr(Y_\tau = 1|\mathbf{X}) = g(\boldsymbol{\beta}^\intercal \mathbf{X}), \tag{2.1}$$

Statistica Sinica: Preprint
doi:10.5705/ss.202019.0066

where $g(\cdot)$ is a known smooth probability distribution function, and $\boldsymbol{\beta}$ is a p-dimensional vector of unknown parameters. For simplicity, we focus on the logistic link with $g(x) = e^x/(1+e^x)$ throughout, although the procedure can be modified easily to accommodate other link functions. We allow $\boldsymbol{\beta}$ to depend on τ, but suppress τ for notational ease.

In addition to the event time and baseline covariates, q-dimensional intermediate outcomes, denoted by $\mathbf{S}$, are collected over time. Without loss of generality, we assume that $\mathbf{S}$ is measured at K visit times, for $0 < t_1 < \cdots < t_K < \tau$, and let $\vec{\mathbf{S}} = (\mathbf{S}_{t_1}^\intercal, ..., \mathbf{S}_{t_K}^\intercal)^\intercal$, where $\mathbf{S}_t$ denotes $\mathbf{S}$ measured at time t. Owing to censoring, for $T^\dagger$, we only observe $T = \min(T^\dagger, C)$ and $\delta = I(T^\dagger \leq C)$, where C is the censoring time, assumed to be independent of $(T^\dagger, \vec{\mathbf{S}}^\intercal, \mathbf{X}^\intercal)$ with a common survival function $G(\cdot)$. We allow $\mathbf{S}_t$ to be missing for those who have censored or experienced the event by t, but assume that $\mathbf{S}_t$ is observable when $T > t$. The underlying data consist of n independent and identically distributed (i.i.d.) random vectors, $\mathscr{F} = \{(T_i^\dagger, C_i, \mathbf{X}_i^\intercal, \vec{\mathbf{S}}_i^\intercal), i = 1, ...,\text{n}\}$. The observed data consist of $\mathscr{D} = \{(T_i, \delta_i, \mathbf{X}_i^\intercal, \vec{\mathbf{S}}_{T_i-}^\intercal), i = 1, ...,\text{n}\}$, where $\vec{\mathbf{S}}_{T_i-}$ is a subvector of $\vec{\mathbf{S}}_i$, measured prior to T_i.

Statistica Sinica: Preprint
doi:10.5705/ss.202019.0066

2.1 Estimation procedure

To estimate $\boldsymbol{\beta}$ under the τ-GLM given in (2.1), we let $\bar{\boldsymbol{\beta}}$ denote the unique solution to

$$\mathbf{U}_0(\boldsymbol{\beta}) = E[\mathbf{X}\{Y_\tau - g(\boldsymbol{\beta}^\mathsf{T}\mathbf{X})\}] = 0.$$

When (2.1) is correctly specified, $\bar{\boldsymbol{\beta}}$ is the true model parameter. Under a mild model misspecification, the resulting risk score $\bar{\boldsymbol{\beta}}^\mathsf{T}\mathbf{X}$ is shown to approximately maximize a weighted area under the receiver operating characteristic curve among all functions of $\mathbf{X}$ for classifying Y_τ (Eguchi and Copas, 2002). Thus, $\bar{\boldsymbol{\beta}}$ is a sensible target parameter, regardless of the adequacy of the τ-GLM. We aim to derive a τ-year risk model by constructing a consistent estimator of $\bar{\boldsymbol{\beta}}$.

To account for censoring, Uno et al. (2007) proposed an IPW estimator, $\widetilde{\boldsymbol{\beta}}$, as the solution to

$$\tilde{\mathbf{U}}_n(\boldsymbol{\beta}) = n^{-1}\sum_{i=1}^{n} \widehat{w}_{\tau i}\mathbf{X}_i\{Y_{\tau i} - g(\boldsymbol{\beta}^\mathsf{T}\mathbf{X}_i)\}, \tag{2.2}$$

where $\widehat{w}_{\tau i} = I(T_i \le \tau)\delta_i + I(T_i > \tau)/\widehat{G}(T_i \wedge \tau)$, and $\widehat{G}(\cdot)$ is the KaplanMeier estimator of $G(\cdot)$. For the logistic link $g(\cdot)$, $\widetilde{\boldsymbol{\beta}}$ is also the minimizer of the weighted negative logistic log-likelihood

$$\sum_{i=1}^{n} \widehat{w}_{\tau i}\ell(Y_{\tau i}, \boldsymbol{\beta}^\mathsf{T}\mathbf{X}_i), \quad \text{where} \quad \ell(y,x) = -y\log\{g(x)\} - (1-y)\log\{1-g(x)\}.$$

Statistica Sinica: Preprint
doi:10.5705/ss.202019.0066

Although $\widetilde{\boldsymbol{\beta}} \to \bar{\boldsymbol{\beta}}$ in probability, regardless of the adequacy of (2.1), it suffers from low efficiency in settings with heavy censoring because it discards information from subjects censored before τ. We derive a more efficient estimator of $\bar{\boldsymbol{\beta}}$ by leveraging the observed information on $\vec{\mathbf{S}}$.

S measured at a single visit We first consider $\mathbf{S}$ measured at a single time point $t_s < \tau$, $\mathbf{S}_{t_s}$, and write

$$Y_\tau = I(T^\dagger \leq t_s) + I(t_s < T^\dagger \leq \tau) = Y_{t_s} + I(T^\dagger > t_s)Y_\tau.$$

We propose estimating $\bar{\boldsymbol{\beta}}$ by separately imputing the missing Y_{t_s} and $I(T^\dagger > t_s)Y_\tau$. To this end, let $\mathbf{Z} = (\mathbf{X}^\intercal, \mathbf{S}_{t_s}^\intercal)^\intercal$ where we suppress t_s from $\mathbf{Z}$ for notational ease. For both $\mathbf{X}$ and $\mathbf{Z}$, we consider their possibly nonlinear basis functions, $\boldsymbol{\Phi}(\mathbf{X})$ and $\boldsymbol{\Psi}(\mathbf{Z})$, respectively, to account for potential nonlinear effects, where we let the first p elements of $\boldsymbol{\Phi}(\mathbf{X})$ and $\boldsymbol{\Psi}(\mathbf{Z})$ be $\mathbf{X}$.

To impute Y_{t_s}, we fit a working model $P(Y_{t_s} = 1 \mid \mathbf{X}) = g\{\boldsymbol{\theta}_{t_s}^\intercal \boldsymbol{\Phi}(\mathbf{X})\}$ and estimate $\boldsymbol{\theta}_{t_s}$ as $\widehat{\boldsymbol{\theta}}_{t_s}$, the minimizer of the penalized IPW likelihood,

$$\widehat{\mathbf{Q}}_n(\boldsymbol{\theta}) = n^{-1} \sum_{i=1}^{n} \widehat{w}_{t_s i} \ell \left\{ Y_{t_s i}, \boldsymbol{\theta}^\intercal \boldsymbol{\Phi}_i \right\} + \lambda_1 \mathcal{Q}(|\boldsymbol{\theta}_{[-1]}|), \tag{2.3}$$

where $\boldsymbol{\Phi}_i = \boldsymbol{\Phi}(\mathbf{X}_i)$, $\mathcal{Q}(\cdot)$ is a penalty function, such as the ridge or LASSO (Friedman, Hatie, and Tibshirani, 2001), that allows the dimension of $\boldsymbol{\Phi}(\mathbf{X})$

Statistica Sinica: Preprint
doi:10.5705/ss.202019.0066

not to be small relative to n, $\lambda_1 = o(n^{-\frac{1}{2}})$ is a nonnegative penalty parameter that controls the degree of regularization, and for any vector $\boldsymbol{a}$, $\boldsymbol{a}_{[-1]}$ represents the subvector of $\boldsymbol{a}$ with its first element removed. We choose a small penalty parameter to reduce the potential bias in the estimated $\widehat{\boldsymbol{\theta}}_{t_s}$.

For $I(T^\dagger > t_s)Y_\tau$, we impose the working model

$$P(Y_\tau = 1 \mid \mathbf{Z}, T^\dagger > t_s) = g\{\boldsymbol{\gamma}_{\tau|t_s}^\intercal \boldsymbol{\Psi}(\mathbf{Z})\}.$$

We use those with $T > t_s$ to estimate $\boldsymbol{\gamma}_{\tau|t_s}$ because $P(Y_\tau = 1 \mid \mathbf{Z}, T^\dagger > t_s) = P(Y_\tau = 1 \mid \mathbf{Z}, T > t_s)$ under independent censoring. For subjects with $T > t_s$, their intermediate outcome information $\mathbf{S}_{t_s}$, and hence $\mathbf{Z}$, are fully observed. We estimate $\boldsymbol{\gamma}_{\tau|t_s}$ as $\widehat{\boldsymbol{\gamma}}_{\tau|t_s}$, the minimizer of an IPW penalized log-likelihood associated with Y_τ among $T_i > t_s$:

$$\widehat{\mathbf{D}}_n(\boldsymbol{\gamma}) = n^{-1} \sum_{i=1}^{n} I(T_i > t_s) \widehat{w}_{\tau i} \ell\left(Y_{t_s i}, \boldsymbol{\gamma}^\intercal \boldsymbol{\Psi}_i\right) + \lambda_2 \mathcal{Q}(|\boldsymbol{\gamma}_{[-1]}|), \tag{2.4}$$

where $\boldsymbol{\Psi}_i = \boldsymbol{\Psi}(\mathbf{Z}_i)$ and $\lambda_2 = o(n^{-\frac{1}{2}})$ is a nonnegative penalty parameter.

Combining the estimates from these two working models, and noting that the expectation of $\varpi_{t_s i} = I(T_i > t_s)/G(t_s)$, given $\mathbf{Z}_i$ and $T_i^\dagger$, is $I(T_i^\dagger > t_s)$, we impute Y_τ as

$$\widehat{Y}_{\tau i}^{t_s} = g(\widehat{\boldsymbol{\theta}}_{t_s}^\intercal \boldsymbol{\Phi}_i) + \widehat{\varpi}_{t_s i}\, g(\widehat{\boldsymbol{\gamma}}_{\tau|t_s}^\intercal \boldsymbol{\Psi}_i), \quad \text{where} \quad \widehat{\varpi}_{t_s i} = \frac{I(T_i > t_s)}{\widehat{G}(t_s)}.$$

With the imputed outcome, we now use all subjects in the data set to

Statistica Sinica: Preprint
doi:10.5705/ss.202019.0066

estimate $\bar{\boldsymbol{\beta}}$ as $\widehat{\boldsymbol{\beta}}$, the solution to the estimating equation

$$\widehat{\mathbf{U}}_n(\boldsymbol{\beta}) \equiv n^{-1} \sum_{i=1}^{n} \mathbf{X}_i \left\{ \widehat{Y}_{\tau i}^{t_s} - g(\boldsymbol{\beta}^{\mathsf{T}} \mathbf{X}_i) \right\} = 0. \tag{2.5}$$

We show in Supplementary Material Appendix A that $\widehat{\boldsymbol{\beta}}$ is a consistent estimator of $\bar{\boldsymbol{\beta}}$, regardless of the adequacy of the τ-GLM or the imputation models. This demonstrates the robustness of the proposed imputation-based procedure, in that $\widehat{\boldsymbol{\beta}}$ is valid even if both the imputation model and the τ-GLM are misspecified. In contrast, under a misspecification of the τ-GLM, separately fitting the GLM to Y_τ and Y_{t_s} will likely yield different estimates of the covariate effects. In the Supplementary Material Appendix B, we show that $n^{\frac{1}{2}}(\widehat{\boldsymbol{\beta}} - \bar{\boldsymbol{\beta}})$ converges in distribution to a multivariate normal with mean zero and covariance matrix

$$\begin{aligned}\boldsymbol{\Sigma}_{t_s} = \mathrm{var}(\mathbf{F}_{1i}) &+ \int_0^{t_s} \mathrm{var}(\mathbf{F}_{2i} + \mathbf{L}_i | T_i^{\dagger} > s) \frac{S(s)^2 d\Lambda_c(s)}{\pi(s)} \\ &+ \int_{t_s}^{\tau} \mathrm{var}(\mathbf{F}_{3i} | T_i^{\dagger} > s) \frac{S(s)^2 d\Lambda_c(s)}{\pi(s)},\end{aligned}$$

where $\mathbf{F}_{1i} = \mathbb{J}^{-1}\mathbf{X}_i\{Y_{\tau i} - g(\bar{\boldsymbol{\beta}}^{\mathsf{T}}\mathbf{X}_i)\}$, $\mathbf{F}_{2i} = \mathbb{J}^{-1}\mathbf{X}_i\{Y_{t_s i} - g(\bar{\boldsymbol{\theta}}_{t_s}^{\mathsf{T}}\boldsymbol{\Phi}_i)\}$, $\mathbf{F}_{3i} = \mathbb{J}^{-1}\mathbf{X}_i\{Y_{\tau i} - g(\bar{\boldsymbol{\gamma}}_{\tau|t_s}^{\mathsf{T}}\boldsymbol{\Psi}_i)\}$, $\mathbf{L}_i = \mathbb{J}^{-1}\mathbf{X}_i^{\mathsf{T}} g(\bar{\boldsymbol{\gamma}}_{\tau|t_s}^{\mathsf{T}}\boldsymbol{\Psi}_i) I(T_i^{\dagger} > t_s)$, $\pi(t) = P(T_i \geq t)$, $\mathbb{J} = E\{\mathbf{X}_i^{\otimes 2}\dot{g}(\bar{\boldsymbol{\beta}}^{\mathsf{T}}\mathbf{X}_i)\}$, $\bar{\boldsymbol{\theta}}_{t_s}$ and $\bar{\boldsymbol{\gamma}}_{\tau|t_s}$ are the respective limits of $\widehat{\boldsymbol{\theta}}_{t_s}$ and $\widehat{\boldsymbol{\gamma}}_{\tau|t_s}$, $S(t) = P(T_i^{\dagger} \geq t)$, and $\Lambda_c(\cdot) = -\log\{G(s)\}$.

To evaluate the potential efficiency gain of $\widehat{\boldsymbol{\beta}}$ over $\widetilde{\boldsymbol{\beta}}$, we note that the

Statistica Sinica: Preprint
doi:10.5705/ss.202019.0066

asymptotic variance of $n^{\frac{1}{2}}(\widetilde{\boldsymbol{\beta}} - \bar{\boldsymbol{\beta}})$ is

$$\boldsymbol{\Sigma}_{\text{IPW}} = \text{var}(\mathbf{F}_{1i}) + \int_0^{\tau} \text{var}(\mathbf{F}_{1i}|T_i^{\dagger} > s)\frac{S(s)^2 d\Lambda_c(s)}{\pi(s)}.$$

It follows that the variance reduction is

$$\begin{aligned}\boldsymbol{\Sigma}_{\text{IPW}} - \boldsymbol{\Sigma}_{t_s} = &\int_0^{t_s} \{\text{var}(\mathbf{F}_{1i}|T_i^{\dagger} > s) - \text{var}(\mathbf{F}_{2i} + \mathbf{L}_i|T_i^{\dagger} > s)\}\frac{S(s)^2 d\Lambda_c(s)}{\pi(s)} \\ &+ \int_{t_s}^{\tau} \{\text{var}(\mathbf{F}_{1i}|T_i^{\dagger} > s) - \text{var}(\mathbf{F}_{3i}|T_i^{\dagger} > s)\}\frac{S(s)^2 d\Lambda_c(s)}{\pi(s)}.\end{aligned}$$

Although it is difficult, if not impossible, to provide conditions under which $\boldsymbol{\Sigma}_{\text{IPW}} - \boldsymbol{\Sigma}_{t_s}$ is positive definite, we expect the variance of $\widehat{\boldsymbol{\beta}}$ to be smaller than that of $\widetilde{\boldsymbol{\beta}}$ because $\{Y_{t_s i} - g(\bar{\boldsymbol{\theta}}_{t_s}^{\mathsf{T}}\boldsymbol{\Phi}_i)\} + I(T_i^{\dagger} > t_s)\{Y_{\tau i} - g(\bar{\boldsymbol{\gamma}}_{\tau|t_s}^{\mathsf{T}}\boldsymbol{\Psi}_i)\}$ is expected to have a smaller variance than that of $Y_{\tau i} - g(\bar{\boldsymbol{\beta}}^{\mathsf{T}}\mathbf{X}_i)$ when the τ-GLM model is misspecified and/or $\mathbf{S}_{t_s}$ is highly predictive of Y_{τ}. To further improve the robustness and efficiency of the proposed procedure, we next describe our final combined estimator, which combines information across all $\vec{\mathbf{S}}$ and $\widetilde{\boldsymbol{\beta}}$.

S measured at multiple visits When $\mathbf{S}$ is collected over multiple time points, leveraging all measurements to maximally improve the estimation efficiency is challenging because of the unknown trade-off between the missing rates and the predictiveness of $\mathbf{S}$ at different time points. While the measurements of $\mathbf{S}$ may be more complete at earlier time points, the

Statistica Sinica: Preprint
doi:10.5705/ss.202019.0066

latter measurements might be more predictive of Y_τ. We propose combining all available $\vec{\mathbf{S}}$ by first constructing K estimators, $\widehat{\mathbb{B}} = [\widehat{\boldsymbol{\beta}}_{t_1}, \ldots, \widehat{\boldsymbol{\beta}}_{t_K}]_{p\times K}$, with the kth estimator obtained as $\widehat{\boldsymbol{\beta}}$ using $\mathbf{S}_{t_k}$. Using similar arguments to those given in Appendix A and B, we can show that $n^{\frac{1}{2}}\{(\widetilde{\boldsymbol{\beta}} - \bar{\boldsymbol{\beta}})^\intercal, (\widehat{\boldsymbol{\beta}}_{t_1} - \bar{\boldsymbol{\beta}})^\intercal, \ldots, (\widehat{\boldsymbol{\beta}}_{t_K} - \bar{\boldsymbol{\beta}})^\intercal\}^\intercal$ converges jointly to a zero mean multivariate normal. This enables us to construct a combined estimator of $\bar{\boldsymbol{\beta}}$ by deriving an optimal linear combination of $\widetilde{\boldsymbol{\beta}}$, $\widehat{\boldsymbol{\beta}}_{t_1}$, ..., $\widehat{\boldsymbol{\beta}}_{t_K}$. For simplicity, we focus on an element-wise combination. For $j = 1, \ldots, p$, we identify the combined estimator

$$\widehat{\beta}_{\mathrm{CMB},j} = \widetilde{\beta}_j - \widehat{\mathbf{W}}_j^\intercal \widehat{\boldsymbol{\Delta}}_j$$

, with $\widehat{\mathbf{W}}_j$ a consistent estimator of

$$\overline{\mathbf{W}}_j = \underset{\mathbf{W}_j}{\operatorname{argmin}} \left\{ \operatorname{var}(\widetilde{\beta}_j - \alpha_j - \mathbf{W}_j^\intercal \widehat{\boldsymbol{\Delta}}_j) \right\},$$

where $\widehat{\boldsymbol{\Delta}}_j = \widetilde{\beta}_j - \widehat{\mathbb{B}}_j$, and for any matrix $\mathbb{B}$, $\mathbb{B}_j$ represents the jth row vector. To obtain $\widehat{\mathbf{W}}_j$ in practice, we approximate the joint distribution of $\widetilde{\boldsymbol{\beta}}$ and $\widehat{\mathbb{B}}$ using a perturbation resampling procedure, see section 2.2. For $b = 1, \ldots, B$, let $\widetilde{\boldsymbol{\beta}}^{(b)}$ and $\widehat{\mathbb{B}}^{(b)}$ denote the bth realization of the resampled estimate of $\widetilde{\boldsymbol{\beta}}$ and $\widehat{\mathbb{B}}$, respectively, and let $\widehat{\boldsymbol{\Delta}}_j^{(b)} = \widetilde{\beta}_j^{(b)} - \widehat{\mathbb{B}}_{j,}^{(b)}$. Then, we obtain

$$\widehat{\mathbf{W}}_j = \underset{\mathbf{W}_j}{\operatorname{argmin}} \left\{ \sum_{b=1}^{B} \left(\widetilde{\beta}_j^{(b)} - \alpha_j - \mathbf{W}_j^\intercal \widehat{\boldsymbol{\Delta}}_j^{(b)} \right)^2 + \upsilon \|\mathbf{W}_j\|_1 \right\},$$

Statistica Sinica: Preprint
doi:10.5705/ss.202019.0066

where $\alpha_j = E(\widetilde{\beta}_j)$ is a nuisance parameter, υ is the tuning parameter, and $\|\cdot\|_1$ denotes the L_1 norm.

Regularization can be used to estimate $\boldsymbol{\beta}$ when p is not small relative to the number of events by first noting that $\widetilde{\boldsymbol{\beta}}$ and the proposed augmented estimator $\widehat{\boldsymbol{\beta}}_{t_s}$ are the respective minimizers of $\widetilde{L}_n(\boldsymbol{\beta}) = -\sum_{i=1}^n \widehat{w}_i \ell(Y_{\tau i}, \boldsymbol{\beta}^\intercal \mathbf{X}_i)$ and $\widehat{L}_n(\boldsymbol{\beta}) = -\sum_{i=1}^n \ell(\widehat{Y}_{\tau i}^{t_s}, \boldsymbol{\beta}^\intercal \mathbf{X}_i)$. To adopt a regularization method, such as the adaptive LASSO (Zhang and Lu, 2007), we estimate $\boldsymbol{\beta}$ as $\widetilde{\mathscr{B}}$, the minimizer of the penalized objective function

$$\widetilde{L}_n(\boldsymbol{\beta}) + \widetilde{\nu}_n \sum_{j=2}^{p} \left| \beta_j / \widetilde{\beta}_j \right|, \tag{2.6}$$

where $0 \leq \widetilde{\nu}_n \to \infty$ as and $\widetilde{\nu}_n n^{-\frac{1}{2}} \to 0$ as $n \to \infty$. The regularized counterpart of $\widehat{\boldsymbol{\beta}}$, $\widehat{\mathscr{B}}$, can be obtained as the minimizer of $\widehat{L}_n(\boldsymbol{\beta}) + \widehat{\nu}_n \sum_{j=2}^p |\beta_j / \widehat{\beta}_j|$ with similarly chosen $\widehat{\nu}_n$. The resampling procedure discussed in Section 2.2 can be similarly used to estimate the variability of $\widetilde{\mathscr{B}}$ and $\widehat{\mathscr{B}}$, as well as to construct the final combined estimator that synthesizes information on $\mathbf{S}$ across multiple visits.

2.2 Inference via resampling

To construct $\widehat{\boldsymbol{\beta}}_{\text{CMB}} = (\widehat{\beta}_{\text{CMB},1}, \ldots, \widehat{\boldsymbol{\beta}}_{\text{CMB},p})^\intercal$ and estimate its variance, we propose a perturbation resampling procedure. Specifically, let $\mathbf{V} = (V_1, ..., V_n)^\intercal$ be a vector of i.i.d. nonnegative random variables with mean and variance

Statistica Sinica: Preprint
doi:10.5705/ss.202019.0066

both one, generated independently of $\mathscr{D}$. Then, for $t_s = t_1, \ldots, t_K$, we obtain a perturbed version of $\widehat{\boldsymbol{\beta}}$ with $\mathbf{Z} = (\mathbf{X}^\intercal, \mathbf{S}_{t_s}^\intercal)^\intercal$, namely $\widehat{\boldsymbol{\beta}}_{t_s}^*$, as the solution to $\widehat{\mathbf{U}}_n^*(\boldsymbol{\beta}) \equiv n^{-1}\sum_{i=1}^n V_i\mathbf{X}_i\{\widehat{Y}_\tau^* - g(\boldsymbol{\beta}^\intercal\mathbf{X}_i)\} = 0$, where

$$\widehat{Y}_\tau^* = g(\boldsymbol{\Phi}_i^\intercal\widehat{\boldsymbol{\theta}}_{t_s}^*) + I(T_i > t_s)\widehat{G}^*(t_s)^{-1}g(\boldsymbol{\Psi}_i^\intercal\widehat{\boldsymbol{\gamma}}_{\tau|t_s}^*),$$

with $\widehat{\boldsymbol{\theta}}_{t_s}^*$ and $\widehat{\boldsymbol{\gamma}}_{\tau|t_s}^*$ as the respective minimizers of

$$\widehat{\mathbf{Q}}_n^*(\boldsymbol{\theta}) = n^{-1}\sum_{n}^{i=1}\widehat{w}_{t_si}^*\ell(Y_{t_si}, \boldsymbol{\theta}^\intercal\boldsymbol{\Phi}_i) + \lambda_1\mathcal{Q}(|\boldsymbol{\theta}_{[-1]}|),$$

$$\widehat{\mathbf{D}}_n^*(\boldsymbol{\gamma}) = n^{-1}\sum_{i=1}^{n} I(T_i > t_s)\widehat{w}_{\tau i}^*\ell(Y_{t_si}, \boldsymbol{\gamma}^\intercal\boldsymbol{\Psi}_i) + \lambda_2\mathcal{Q}(|\boldsymbol{\gamma}_{[-1]}|).$$

Here, $\widehat{w}_{ti}^* = \{I(T_i \le t)\delta_i + I(T_i > t)\}\widehat{G}^*(T_i \wedge t)^{-1}$, and $\widehat{G}^*(\cdot)$ is the weighted Kaplan-Meier estimator of $G(t)$, with $\mathbf{V}$ being the weights. Similarly, we may perturb the IPW estimator $\widetilde{\boldsymbol{\beta}}$ as $\widetilde{\boldsymbol{\beta}}^*$, the solution to the weighted estimating equation

$$\widetilde{\mathbf{U}}_n^*(\boldsymbol{\beta}) = n^{-1}\sum_{i=1}^{n}\widehat{w}_{\tau i}^* V_i\mathbf{X}_i\{\widehat{Y}_\tau - g(\boldsymbol{\beta}^\intercal\mathbf{X}_i)\}.$$

In practice, one can generate B random samples of $\mathbf{V}$ to obtain B realizations of the perturbed estimators $\widetilde{\boldsymbol{\beta}}^*, \widehat{\boldsymbol{\beta}}_{t_1}^*, \ldots, \widehat{\boldsymbol{\beta}}_{t_K}^*$. These estimators can then be used to construct the combined estimator $\widehat{\boldsymbol{\beta}}_{\text{CMB}}$, as described in Section 2.1. In addition, it is straightforward to see that the variability in $\widehat{\mathbf{W}}_j$ does not contribute to the variability of $\widehat{\boldsymbol{\beta}}_{\text{CMB}}$ at the first order. Thus, these perturbed samples can also be used to estimate the final variance of $\widehat{\boldsymbol{\beta}}_{\text{CMB}}$ and construct associated confidence intervals.

Statistica Sinica: Preprint
doi:10.5705/ss.202019.0066

3 Simulation

We conducted extensive simulation studies to evaluate the finite-sample performance of the proposed estimation and inference procedures, and then compared this performance with that of existing methods. Throughout, we generated 500 data sets under each configuration at sample size $n = 500$, and $B = 500$ replications were used for the perturbation resampling procedure. For each setting, we obtain the "true value" $\bar{\boldsymbol{\beta}}$ using the Monte Carlo method by averaging over the logistic regression estimates obtained from fitting Y_τ against $\mathbf{X}$ using 500 sets of simulated uncensored data at sample size $N = 10000$. For the proposed estimator, natural spline bases with three prespecified 3 knots for each covariate are used as $\boldsymbol{\Phi}(\cdot)$ and $\boldsymbol{\Psi}(\cdot)$ in the imputation models. In Section 3.1, we consider the scenario with $p = 4$ and let $\mathcal{Q}(\cdot) = \|\cdot\|_2$; while in Section 3.2, we consider the case with $p = 11$ covariates, of seven are noise predictors unrelated to the risk, and let $\mathcal{Q}(\cdot) = \|\cdot\|_1$. For both settings, we let $\tau = 0.8$ and generate a single intermediate outcome S measured at $K = 4$ different time points, with $t_1 = 0.05$, $t_2 = 0.1$, $t_3 = 0.15$, and $t_4 = 0.2$. The surrogate marker S has an increasing correlation with the outcome over time, but also has an increasing proportion of missing values due to censoring or failure. We also consider an additional simulation in which $\mathbf{S}$ has a constant correlation

Statistica Sinica: Preprint
doi:10.5705/ss.202019.0066

with the outcome over time. To evaluate the improvement in efficiency of S, we obtained our combination estimator $\widehat{\boldsymbol{\beta}}_{\text{CMB}}$ using $\mathbf{Z} = (\mathbf{X}^\intercal, \mathbf{S}^\intercal)^\intercal$ and $\mathbf{Z} = \mathbf{X}$, denoted respectively by $\widehat{\boldsymbol{\beta}}_{\text{CMB}}^{\text{KM},\mathbf{Z}}$ and $\widehat{\boldsymbol{\beta}}_{\text{CMB}}^{\text{KM},\mathbf{X}}$. The percentage efficiency gain of $\widehat{\boldsymbol{\beta}}$ over $\widetilde{\boldsymbol{\beta}}$ is calculated as $\{\text{MSE}(\widetilde{\boldsymbol{\beta}})/\,\text{MSE}(\widehat{\boldsymbol{\beta}}) - 1\} \times 100$.

In addition to the comparison with $\widetilde{\boldsymbol{\beta}}$ (IPW_{KM}, Uno et al., 2007), we obtained (i) the IPW estimator, with censoring weights estimated from fitting a Cox model to the data $\{(T_i, 1-\delta_i, \mathbf{X}_i), i = 1, ..., n\}$ ($\text{IPW}_{\text{Cox},\mathbf{X}}$), and (ii) the AIPW estimator (AIPW_{KM}, DiRienzo, 2009), with censoring weights estimated using the KaplanMeier estimator and the outcome imputed from the model based on $\Phi(\mathbf{X})$.

3.1 Low-dimension setting with $p = 4$

In this setting, we generated $\mathbf{X}_{-1}$, C, and $T^\dagger$ from

$$\mathbf{X}_{-1} = (X_2, X_3, X_4)^\intercal \sim N(\mathbf{0}, 0.3 + 0.7\mathbb{I}_3), \quad C \sim \text{exponential}(\lambda),$$

$$\log(T^\dagger) = 0.5(X_2 + X_3 + X_4) + 0.5X_2^2 + X_3^2 + 0.5X_4^2 - 3 + \text{logit}(U) + \log(\alpha),$$

where $\mathbb{I}_d$ is a $d \times d$ diagonal matrix, and $U \sim$ Uniform(0,1). We considered two settings: (i) a low event rate (12−18% by τ) and heavy censoring rate (65−74% before τ) with $\{\alpha = 12, \lambda = 0.5\}$, where the "true" $\boldsymbol{\beta}$ is estimated as (-1.05,-0.25,-0.13,-0.24); and (ii) a moderate event rate (25−34% by τ) and moderate censoring rate (37−50% by τ) with $\{\alpha = 6, \lambda = 1\}$, where

Statistica Sinica: Preprint
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the "true" $\boldsymbol{\beta}$ is estimated as (-0.50,-0.27,-0.16,-0.27). We generated $\vec{\mathbf{S}} = (S_{t_1}, S_{t_2}, S_{t_3}, S_{t_4})^\intercal$ from

$$S_t = \text{logit}(U) + 0.1(X_1 + X_2) + (10t^{1.5})^{-1}\varepsilon_t \quad \text{with } \varepsilon_t \sim N(0,1),$$

where ε_t is generated independently across different time points. Under this setting, the Pearson correlation coefficient between $log(T^\dagger)$ and $\vec{\mathbf{S}}$ is about $(13\%, 34\%, 55\%, 65\%)^\intercal$, and approximately 87%, 76%, 67%, and 60% of patients are at risk at t_1, t_2, t_3, and t_4, respectively. We use an additional simulation in which the correlation between S_t and outcome is constant over time (about 65%) to evaluate how the proportion of partially observed subjects affects the efficiency gain.

As shown in Table 1, the proposed estimator has negligible bias and gains substantial efficiency relative to IPW_{KM}. Compared with IPW_{KM}, IPW_{Cox} and AIPW_{KM} attained limited efficiency gains, especially in the low event and high censoring setting. Even in the absence of $\vec{\mathbf{S}}$, $\widehat{\boldsymbol{\beta}}_{\text{CMB}}^{\text{KM},\mathbf{X}}$ is much more efficient than IPW_{KM} because the imputation model using a basis expansion captures the nonlinear effects. The proposed estimator $\widehat{\boldsymbol{\beta}}_{\text{CMB}}^{\text{KM},\mathbf{Z}}$ gains further efficiency by additionally incorporating $\vec{\mathbf{S}}$. Figure 1 shows that the efficiency of the proposed estimator $\widehat{\boldsymbol{\beta}}_{t_s}^{\text{KM},\mathbf{Z}}$ relative to $\widetilde{\boldsymbol{\beta}}$ varies substantially across t_s. Furthermore, the final estimator $\widehat{\boldsymbol{\beta}}_{\text{CMB}}^{\text{KM},\mathbf{Z}}$, the optimal combination of them, has the highest efficiency gain, as expected. The results from Ta-

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Figure 1: The percentage of efficiency gain (%EffG) from the IPW estimator $\widetilde{\boldsymbol{\beta}}$ and the coverage percentage for the 95% confidence interval for the proposed estimators $\{\widehat{\boldsymbol{\beta}}_{t_k}^{\mathrm{KM},\mathbf{Z}}, k = 1,2,3,4\}$, as well as the combined estimator $\widehat{\boldsymbol{\beta}}_{\mathrm{CMB}}^{\mathrm{KM},\mathbf{Z}}$ under the low-dimension baseline model.

low_dimension.pdf

ble 1 and Figure 1 suggest that the proposed interval estimation procedure based on resampling works well, with empirical coverage levels close to the nominal level of 95%. Note that in the setting where S_t has a similar correlation with the outcome across t_s, the efficiency gain of $\widehat{\boldsymbol{\beta}}_{t_s}^{\mathrm{KM},\mathbf{Z}}$ tends to decrease over time (especially in the heavy censoring setting), owing to the decreasing proportion of partially observed subjects (i.e., censored between t_s and τ), as shown in Figure 2.

3.2 Moderate p with regularization

For the setting with $p = 11$, we generated $\mathbf{X}_{-1}$ from an independent standard normal distribution, and $T^{\dagger}$ from

$$\log(T^{\dagger}) = X_2 + X_3 + X_4 + 0.5X_2^2 + X_3^2 + 0.5X_4^2 - 3 + \mathrm{logit}(U) + \log(6).$$

The surrogate markers $\vec{\mathbf{S}}$ were generated in the same way as in the low-dimensional setting, and $C \sim$ exponential(1). Under this setting, the ob-

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doi:10.5705/ss.202019.0066

Table 1: Empirical bias, SE (ESE), and average of the estimated SE (ASE) for the low-dimensional setting, as well as the percentage efficiency gain (%EffG) relative to the IPW_{KM} estimator.

	Bias × 100				ESE × 100				%EffG			
	β_0	β_1	β_2	β_3	β_0	β_1	β_2	β_3	β_0	β_1	β_2	β_3
Low Event Rate												
IPW_{KM}	0.58	-2.48	-2.01	-2.39	15.23	20.35	20.50	20.44	0.00	0.00	0.00	
$\text{IPW}_{\text{Cox},\mathbf{X}}$	-1.01	-2.17	-2.26	-2.34	15.17	18.86	18.42	18.62	0.53	16.56	23.17	20.16
AIPW_{KM}	2.01	-2.58	-1.16	-2.32	16.68	22.77	20.00	22.22	-17.75	-20.01	5.69	-15.17
$\text{AUG}_{\text{CMB}}^{\text{KM},\mathbf{X}}$	-0.17	-0.59	-3.41	-0.97	14.76	16.20	14.68	15.29	6.52	59.78	86.67	80.32
$\text{AUG}_{\text{CMB}}^{\text{KM},\mathbf{Z}}$	1.79	0.07	-3.47	-0.22	14.31	14.51	12.95	13.68	11.59	99.51	135.88	126.06
Moderate Event Rate												
IPW_{KM}	0.28	-1.21	-1.06	-0.59	10.87	14.26	13.98	14.19	-	-	-	-
$\text{IPW}_{\text{Cox},\mathbf{X}}$	-0.37	-0.91	-1.07	-0.46	10.78	13.52	12.96	13.41	1.54	11.60	16.25	12.13
AIPW_{KM}	0.73	-1.37	-0.60	-0.63	11.03	13.54	12.11	13.27	-3.21	10.55	33.88	14.28
$\text{AUG}_{\text{CMB}}^{\text{KM},\mathbf{X}}$	-0.50	-0.50	-1.76	0.03	10.61	12.20	11.04	12.09	4.77	37.38	57.34	38.04
$\text{AUG}_{\text{CMB}}^{\text{KM},\mathbf{Z}}$	-0.26	0.44	-1.02	0.33	10.19	11.35	10.34	11.51	13.80	58.77	82.33	52.35

Statistica Sinica: Preprint
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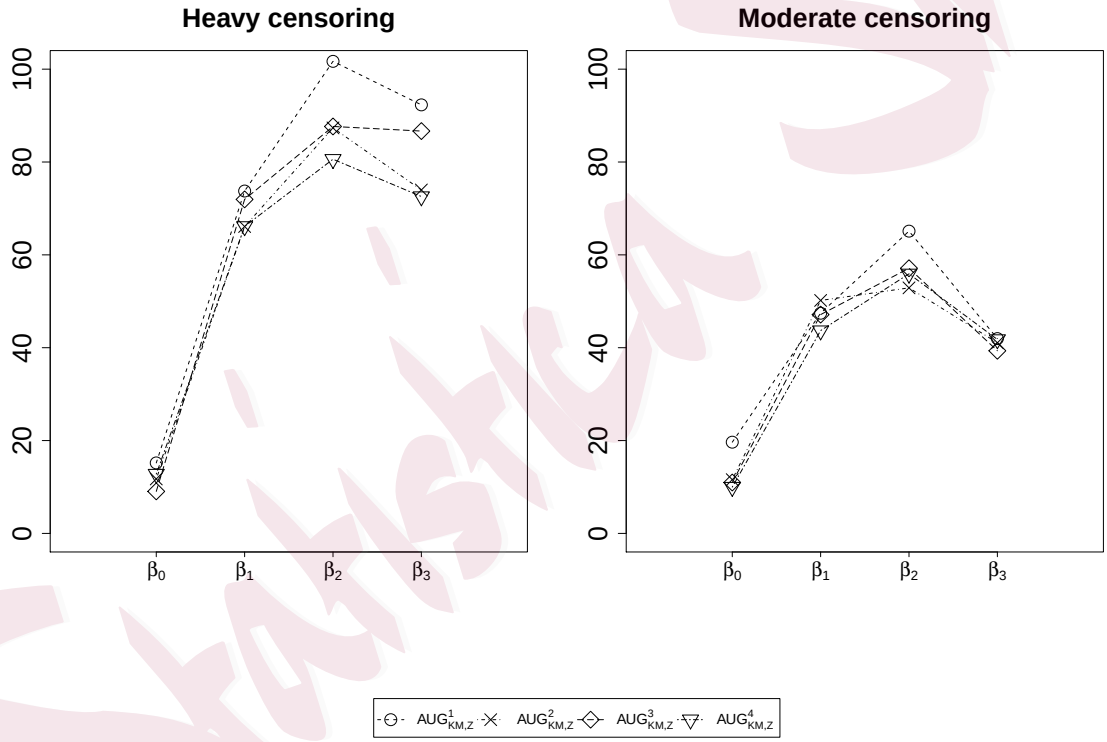
Figure 2: The percentage of efficiency gain (%EffG) for the proposed estimators $\{\widehat{\boldsymbol{\beta}}_{t_k}^{\mathrm{KM},\mathbf{Z}}, k = 1, 2, 3, 4\}$, assuming a constant correlation between S and the outcome over time under the low dimension baseline model.



Statistica Sinica: Preprint
doi:10.5705/ss.202019.0066

served event rate by τ is about $26-38\%$, leading to an effective sample size of around 100 - 200, which is not large relative to $p=11$. We use the adaptive LASSO in (2.6) to regularize the baseline prediction model in all methods. The "true" $\boldsymbol{\beta}$ for the working model estimated from the complete data is (-0.49, -0.66, -0.52, -0.66, 0.00,0.00, 0.00, 0.00, 0.00, 0.00, 0.00).

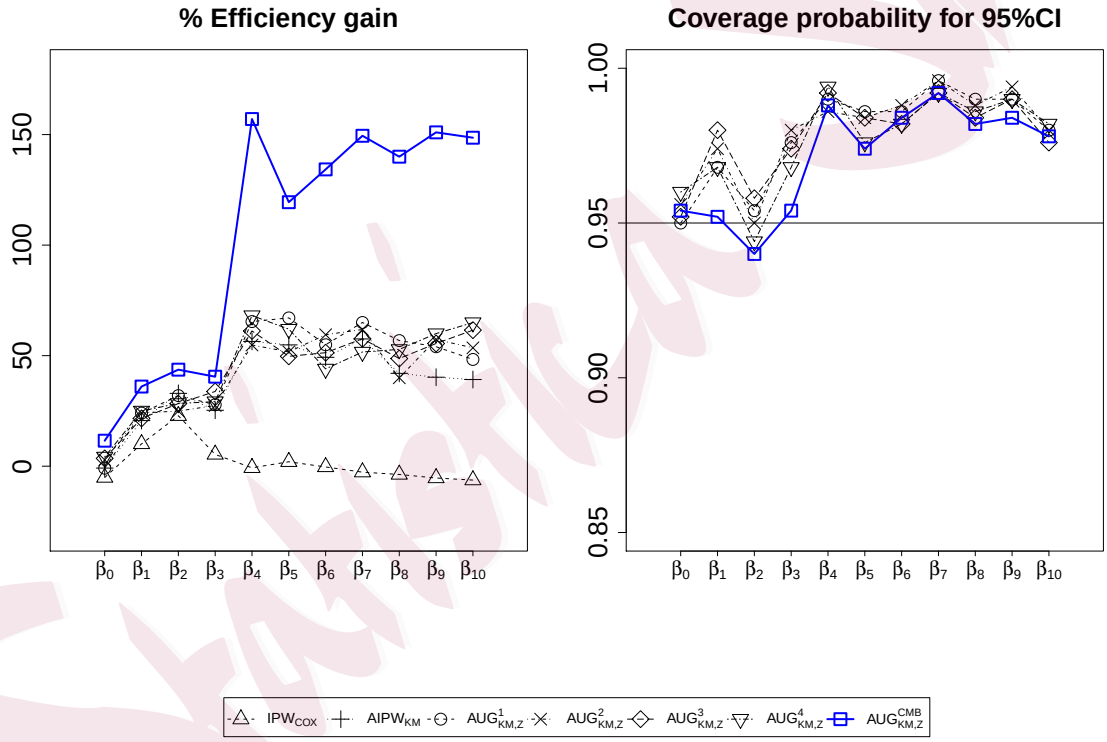
Figure 3 summarizes the results for $\{\widehat{\boldsymbol{\beta}}_{t_k}^{\mathrm{KM},\mathbf{Z}}, k=1,2,3,4\}$, the final combined linear optimal estimator $\widehat{\boldsymbol{\beta}}_{\mathrm{CMB}}^{\mathrm{KM},\mathbf{Z}}$, and $\mathrm{IPW}_{\mathrm{KM}}$ and $\mathrm{IPW}_{\mathrm{Cox}}$ as benchmarks for the efficiency assessment. The AIPW methods are not included because no associated regularization procedures were available. In general, $\widehat{\boldsymbol{\beta}}_{t_k}^{\mathrm{KM},\mathbf{Z}}$ is more efficient than $\mathrm{IPW}_{\mathrm{Cox}}$, and the combined estimator $\widehat{\boldsymbol{\beta}}_{\mathrm{CMB}}^{\mathrm{KM},\mathbf{Z}}$ outperforms all other estimators, with a substantial efficiency gain over existing methods. The resampling procedures also perform well, with the empirical coverage percentage ranging from 92 - 95% for informative signals. The coverage percentage for the zero signals ranges from 96% - 98%, which is expected owing to the oracle properties.

4 Example

We illustrate the proposed procedures using a data set from the Diabetes Prevention Program (DPP) (DPPG, 2002). The DPP is a placebo-controlled randomized clinical trial that investigates whether changes in

Statistica Sinica: Preprint
doi:10.5705/ss.202019.0066

Figure 3: The percentage of efficiency gain (%EffG) and the coverage percentage for the 95% confidence interval for the proposed estimator of the regularized baseline model.



Statistica Sinica: Preprint
doi:10.5705/ss.202019.0066

lifestyle or taking metformin prevent type 2 diabetes among high-risk adults. The primary outcome, type 2 diabetes, is defined as fasting glucose $\geq$ 140mg/dL for visits through 6/23/1997, $\geq$ 126 mg/dL for visits on or after 6/24/1997, or 2-h post challenge glucose $\geq$ 200 mg/dL. The study found that the both lifestyle changes andn metformin significantly prevent or delay the development of type 2 diabetes.

Suppose we are interested in constructing a time-specific risk prediction model for $\tau = 4$ years for the lifestyle intervention group (N=1024) and the placebo group (N=1030), respectively. The event rate was 13.5% for lifestyle intervention group and 27.5% for placebo group by year four, with 74% and 62%, respectively, censored before year four. The working baseline prediction model includes three predictors: age in ordinal scale, body mass index (BMI) in ordinal scale, and hemoglobin A1c (HBA1C). There are two intermediate outcomes, namely fasting plasma glucose and HBA1C, measured in each of the first three years.

All covariates are standardized to have mean zero and standard deviation one. For the imputation modeling in AIPW_{KM} and our approach, we use spline bases with three knots for all variables. Resampling with 500 replications is used to generate the variance of the IPW_{KM} method and our proposed methods, and the bootstrap is used for the other methods. As

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Table 2: Estimated prediction models for diabetes by year 3.5 in DPP study

	Coefficient$_{SE}$				Efficiency gain			
	Int	age	BMI	HA1C	Int	age	BMI	HA1C
	Lifestyle group							
IPW_{KM}	$-1.41_{.123}$	$-0.21_{.146}$	$0.15_{.120}$	$0.41_{.146}$	-	-	-	-
$\text{IPW}_{\text{Cox},\mathbf{x}}$	$-1.41_{.123}$	$-0.26_{.127}$	$0.21_{.105}$	$0.42_{.148}$	-2.03	32.67	29.61	-2.20
AIPW_{KM}	$-1.28_{.145}$	$-0.17_{.221}$	$0.00_{.202}$	$0.41_{.229}$	-28.25	-56.23	-64.87	-59.08
$\text{AUG}^1_{\text{KM},\mathbf{x}}$	$-1.36_{.128}$	$-0.23_{.123}$	$0.14_{.096}$	$0.39_{.133}$	-7.66	41.18	55.38	21.46
$\text{AUG}^1_{\text{KM},\mathbf{Z}}$	$-1.42_{.127}$	$-0.28_{.116}$	$0.10_{.088}$	$0.38_{.122}$	-7.13	58.31	85.66	44.48
$\text{AUG}^2_{\text{KM},\mathbf{x}}$	$-1.36_{.125}$	$-0.24_{.114}$	$0.17_{.090}$	$0.35_{.128}$	-3.46	64.12	76.26	29.85
$\text{AUG}^2_{\text{KM},\mathbf{Z}}$	$-1.29_{.133}$	$-0.22_{.116}$	$0.13_{.086}$	$0.34_{.113}$	-15.14	59.29	92.36	69.85
$\text{AUG}^3_{\text{KM},\mathbf{x}}$	$-1.37_{.123}$	$-0.23_{.101}$	$0.16_{.083}$	$0.31_{.116}$	-1.45	110.49	106.11	59.16
$\text{AUG}^3_{\text{KM},\mathbf{Z}}$	$-1.43_{.119}$	$-0.22_{.103}$	$0.16_{.083}$	$0.35_{.108}$	5.22	101.59	107.57	85.03
$\text{AUG}^{\text{KM},\mathbf{x}}_{\text{CMB}}$	$-1.39_{.121}$	$-0.24_{.099}$	$0.15_{.073}$	$0.29_{.109}$	2.12	119.86	169.57	81.18
$\text{AUG}^{\text{KM},\mathbf{Z}}_{\text{CMB}}$	$-1.41_{.119}$	$-0.25_{.095}$	$0.10_{.067}$	$0.31_{.094}$	6.39	137.98	217.79	144.82
	Placebo group							
IPW_{KM}	$-0.58_{.097}$	$0.01_{.134}$	$0.13_{.138}$	$0.34_{.128}$	-	-	-	-
$\text{IPW}_{\text{Cox},\mathbf{x}}$	$-0.58_{.098}$	$-0.04_{.120}$	$0.19_{.130}$	$0.37_{.135}$	-1.79	24.24	11.37	-8.98
AIPW_{KM}	$-0.54_{.099}$	$0.09_{.203}$	$0.02_{.210}$	$0.32_{.205}$	-4.25	-56.60	-56.90	-60.74
$\text{AUG}^1_{\text{KM},\mathbf{x}}$	$-0.58_{.095}$	$-0.02_{.102}$	$0.13_{.113}$	$0.34_{.101}$	4.35	72.02	49.51	60.44
$\text{AUG}^1_{\text{KM},\mathbf{Z}}$	$-0.54_{.091}$	$0.01_{.091}$	$0.15_{.097}$	$0.39_{.097}$	13.28	117.05	99.78	74.44
$\text{AUG}^2_{\text{KM},\mathbf{x}}$	$-0.59_{.095}$	$-0.03_{.089}$	$0.15_{.096}$	$0.38_{.093}$	4.34	127.23	105.28	89.12
$\text{AUG}^2_{\text{KM},\mathbf{Z}}$	$-0.58_{.095}$	$-0.03_{.086}$	$0.15_{.087}$	$0.45_{.093}$	4.72	142.87	147.97	90.12
$\text{AUG}^3_{\text{KM},\mathbf{x}}$	$-0.59_{.097}$	$-0.04_{.080}$	$0.14_{.081}$	$0.47_{.087}$	0.54	183.43	192.25	118.48
$\text{AUG}^3_{\text{KM},\mathbf{Z}}$	$-0.63_{.093}$	$-0.03_{.077}$	$0.13_{.076}$	$0.50_{.088}$	9.27	202.67	224.08	137.77
$\text{AUG}^{\text{KM},\mathbf{x}}_{\text{CMB}}$	$-0.58_{.095}$	$-0.06_{.070}$	$0.15_{.067}$	$0.45_{.069}$	5.11	267.02	325.85	242.39
$\text{AUG}^{\text{KM},\mathbf{Z}}_{\text{CMB}}$	$-0.59_{.088}$	$-0.03_{.065}$	$0.15_{.062}$	$0.45_{.067}$	21.11	327.89	395.28	263.68

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shown in Table 2, the point estimates from IPW_{KM} and IPW_{Cox} are quite similar, supporting that censoring may be independent of the baseline predictors. The proposed method also provides point estimates similar to those of IPW_{KM} and IPW_{Cox}, but have substantially smaller standard errors. For example, in the lifestyle intervention group, the coefficient estimation for age is -0.21 with standard error 0.15 using the IPW_{KM} method, while our estimation is -0.25 with standard error 0.095, making age a significant predictor. Similarly, in the placebo group, the coefficient estimation for BMI is 0.13 with standard error 0.138 using the IPW_{KM} method, while our estimation is 0.15 with standard error 0.062, making BMI a significant predictor.

5 Conclusion

Deriving a robust and efficient estimator for a τ-year risk prediction model is challenging in the presence of heavy censoring prior to τ and potential model misspecification. The proposed approach adds to the literature as follows. First, unlike most existing imputation based estimators, the proposed method is robust to model misspecifications in both the underlying risk model and the imputation model. Second, our method is able to incorporate information from longitudinal intermediate outcomes that are subject to missingness due to censoring or failure. Third, the pro-

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doi:10.5705/ss.202019.0066

posed efficient data-adaptive combination strategy allows us to effectively combine information from $\mathbf{S}$ measured at different visits along with other consistent estimators (e.g., $\tilde{\boldsymbol{\beta}}$) to achieve maximal efficiency. Analogous to overfitting in a regression, our regularization-based combination strategy can effectively overcome both the correlation between the estimators and the potentially large number of candidate estimators.

The degree of efficiency gain from incorporating $\mathbf{S}$ in our proposed estimator depends on the censoring distribution prior to τ, how well the τ-GLM approximates the true conditional risk, the censoring rate for $\mathbf{S}$, and the predictiveness of $\mathbf{S}$ for Y_τ above and beyond $\mathbf{X}$. The proposed method could be particularly useful in settings in where a prediction model with a long-term outcome involves heavy censoring because of administrative reasons (e.g., study closure, etc.), but intermediate covariates that are predictive of the outcome are collected for a large proportion of the patients.

We assume that C is independent of the baseline covariates covariates $\mathbf{X}$, for simplicity. However, similarly to existing IPW estimators, we can allow C to depend on $\mathbf{X}$ by calculating the censoring weights $\widehat{w}_i$ by fitting a Cox or other semi-parametric model for $C \mid \mathbf{X}$. When C depends on $\mathbf{X}$, but cannot be correctly modeled, Zhang and Cai (2017) demonstrated using simulation studies that the imputation-based approach tends to be

Statistica Sinica: Preprint
doi:10.5705/ss.202019.0066

more robust than the simple IPW approach. When p is not small, our approach also has advantages over the augmentation method that uses the Cox model to estimate the censoring weights. This is because employing a regularization in the estimation of the censoring model diminishes its potential efficiency gain. In contrast, our imputation-based method naturally allows for variable selection.

Throughout, we assume that the intermediate outcomes are potentially measured at the same time points across subjects. This is a reasonable assumption for clinical trials because study visit times are typically prescheduled according to the study protocol. For settings in which these times vary across patients, we can choose a set $\{t_s, s = 1..., K\}$ as landmark time points, and summarize $\mathbf{S}$ information up to t_s as the intermediate outcome associated with t_s for each patient.

Supplementary Material

All technical proofs are available in the online Supplementary Material.

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