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Estimation of Covariate-Specific Time-Dependent ROC Curves in the Presence of Missing Biomarkers

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Summary. Covariate-specific time-dependent ROC curves are often used to evaluate the diagnostic accuracy of a biomarker with time-to-event outcomes, when certain covariates have an impact on the test accuracy. In many medical studies, measurements of biomarkers are subject to missingness due to high cost or limitation of technology. This article considers estimation of covariate-specific time-dependent ROC curves in the presence of missing biomarkers. To incorporate the covariate effect, we assume a proportional hazards model for the failure time given the biomarker and the covariates, and a semiparametric location model for the biomarker given the covariates. In the presence of missing biomarkers, we propose a simple weighted estimator for the ROC curves where the weights are inversely proportional to the selection probability. We also propose an augmented weighted estimator which utilizes information from the subjects with missing biomarkers. The augmented weighted estimator enjoys the double-robustness property in the sense that the estimator remains consistent if either the missing data process or the conditional distribution of the missing data given the observed data is correctly specified. We derive the large sample properties of the proposed estimators and evaluate their finite sample performance using numerical studies. The proposed approaches are illustrated using the US Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset.

Key words: Augmented estimator; Location model; Missing data; Proportional hazards model; Survival analysis; Weighted estimating equation.

1. Introduction

Receiver Operating Characteristic (ROC) curve is a common tool for evaluating diagnostic accuracy of a continuous biomarker by plotting true positive rate (TPR) against false positive rate (FPR) at various threshold values (Metz, 1978). When covariates have an impact on the predictive accuracy of a biomarker, it is important to adjust for the covariate effects to ensure generalizability of the results to other different populations. Therefore, covariate-specific ROC curves are widely used for evaluation of diagnostic accuracy of biomarkers within specific subgroups (Liu and Zhou, 2011).

In prospective cohort studies, information on biomarkers and disease status is often collected over time. Therefore, evaluation of biomarker accuracy with event time outcomes has attracted much interest, see Pepe, Zheng, and Jin (2008) for comprehensive reviews. With event time outcomes, subjects are classified as cases or controls depending on their survival status, and the biomarker accuracy can be evaluated at various time points of interest. Heagerty and Zheng (2005) discussed several definitions of time-dependent TPR and FPR, where instantaneous failures or cumulative failures are considered to define the cases, and dynamic survivors or a fixed group of survivors are considered to define the controls.

In this manuscript, we consider two types of covariate-specific time-dependent ROC curves: the Incident/Dynamic ($\mathbb{I}/\mathbb{D}$) ROC and the Cumulative/Dynamic ($\mathbb{C}/\mathbb{D}$) ROC (Heagerty and Zheng, 2005). Let Z be a single marker or a combination of multiple markers, and X be a vector of covariates that affect the failure time T. Without loss of generality, we assume larger values of Z are associated with greater risks. The covariate-specific incident TPR, cumulative TPR and dynamic FPR at cutoff point c are defined respectively as

$$\begin{aligned}\mathrm{TPR}_{\mathbb{I}}(c;t,x) &= P(Z>c|T=t,X=x),\\ \mathrm{TPR}_{\mathbb{C}}(c;t,x) &= P(Z>c|T\le t,X=x),\\ \mathrm{FPR}_{\mathbb{D}}(c;t,x) &= P(Z>c|T>t,X=x).\end{aligned}$$

The $\mathbb{I}/\mathbb{D}$ ROC curve and the $\mathbb{C}/\mathbb{D}$ ROC curve are defined as

$$\begin{aligned}\mathrm{ROC}_{\mathbb{I}/\mathbb{D}}(p;t,x) &= \mathrm{TPR}_{\mathbb{I}}\{[\mathrm{FPR}_{\mathbb{D}}]^{-1}(p;t,x);t,x\}, \quad \text{and}\\ \mathrm{ROC}_{\mathbb{C}/\mathbb{D}}(p;t,x) &= \mathrm{TPR}_{\mathbb{C}}\{[\mathrm{FPR}_{\mathbb{D}}]^{-1}(p;t,x);t,x\},\end{aligned}$$

where $p\in(0,1)$. The $\mathbb{I}/\mathbb{D}$ ROC curve is used to distinguish subjects failing at time t from those failing after time t, whereas the $\mathbb{C}/\mathbb{D}$ ROC is used to distinguish subjects failing by time t from those failing after time t. Various approaches have been proposed to estimate the covariate-specific time-dependent ROC curves in the literature. For example, Cai et al. (2006) used generalized linear model concepts to characterize the shape of the ROC curve, allowing covariates to impact accuracy directly. Zheng and Heagerty (2004) modeled the marker distribution for cases and controls as a function of

disease status, covariates and disease onset time (cases only), and calculated the induced covariate-specific ROC curves. Song and Zhou (2008) adopted a joint model which assumes that the failure time depends on the biomarker and the covariates through a regression model, and that the biomarker depends on the covariates through a location model.

The existing methods on estimating time-dependent ROC functions, with or without covariate adjustment, are mostly developed for settings with complete observations. However, in practice, values of biomarkers are not always observed due to limitations in measuring technology or inhibitive measuring cost. Despite the popularity of the time-dependent ROC modeling, the problem of missing biomarkers has not been well studied. In a related but different setting, Liu, Cai, and Zheng (2012) proposed an inverse probability weighting approach to estimate the predictive values of biomarkers under the case-cohort sampling design, where all cases and a random subset of the full cohort are selected (Prentice, 1986). They evaluated the accuracy of biomarkers in the absence of covariates. In addition, the weight used to adjust for the selection bias is proportional to the sampling fraction, which is assumed known.

To complement the existing work, we consider estimation of covariate-specific time-dependent ROC curves when the missingness process needs to be estimated. To incorporate covariate effects, we consider a joint modeling approach where the failure time depends on the biomarker and the covariates through a proportional hazards model, and the biomarker depends on the covariates through a semiparametric location model (Song and Zhou, 2008). To handle the missing biomarkers, we propose an inverse probability weighted estimator, where individual contributions are weighted inversely proportional to their selection probabilities. In real data applications, the missingness process is rarely known. To implement the inverse probability weighted estimator, we suggest a parametric approach for the estimation of the missingness process. However, the estimator may result in a large bias, if the model for the missingness process is misspecified. Using the projection method proposed by Robins, Rotnitzky, and Zhao (1994), we further propose a fully augmented weighted estimator, in which both the proportional hazards model and the semiparametric location model are augmented. The resulting augmented estimator enjoys the so-called "double robustness" property Robins et al. (1994) in the sense that the estimator remains consistent if either the missing data process or the conditional distribution of the biomarkers given the observed data is correctly specified.

The rest of this article is organized as follows. In Section 2, we propose the simple weighted estimators, which require correct specification of the missing data process. In Section 3, we describe the fully augmented estimators, which incorporate information from subjects with incomplete data. In Section 4, we develop large sample properties of the proposed estimators. An extensive simulation study is conducted in Section 5. We illustrate the proposed approach using an Alzheimer's disease study in Section 6. General discussion is included in Section 7.

2. Simple Weighted Estimators

For subject $i = 1, \ldots, n$, let T_i, C_i, and $R_i = \min(T_i, C_i)$ denote the failure time, censoring time, and observed time. Let $\delta_i = I(T_i \le C_i)$ denote the censoring indicator. Let X_i be a p-dimensional vector of covariates and Z_i a biomarker value for subject i. We write $Q_i = (Z_i, X_i^T)^T$. For simplicity, we assume that C_i and T_i are independent given Q_i. When multiple biomarkers are available, we combine them into a composite score for disease prediction, and thus Z_i could represent a combination of multiple markers. We assume the combination is pre-specified and if one component is missing, the composite score Z_i is considered as missing.

We assume the failure time T_i satisfies the proportional hazards model

$$\lambda_i(t) = \lambda_0(t) \exp(\beta_0 Z_i + \gamma_0{}^T X_i), \tag{1}$$

where $\lambda_0(t)$ is an unspecified baseline hazard function, and $\theta_0 = (\beta_0, \gamma_0{}^T)^T$ is a $(p+1)$-dimensional parameter. Let V_i be the missingness indicator taking 1 if Z_i is observed and 0 otherwise. Let $W_i = (R_i, X_i, \delta_i)$ denote the observed data. We assume Z_i is missing at random in that $\pi(W_i) = P(V_i = 1 \mid W_i) = P(V_i = 1 \mid R_i, X_i, Z_i, \delta_i)$. That is, given the observed data W_i, the probability of observing Z_i is conditionally independent of Z_i.

Following the Bayes' theorem, we write TPR and FPR as

$$\mathrm{TPR}_{\mathbb{C}}(c;t,x) = \frac{\int_c^\infty \{1 - S(t|u,x)\} \mathrm{d}P(Z \le u | X = x)}{\int_{-\infty}^\infty \{1 - S(t|u,x)\} \mathrm{d}P(Z \le u | X = x)}, \tag{2}$$

$$\mathrm{TPR}_{\mathbb{I}}(c;t,x) = \frac{\int_c^\infty \{f(t|u,x)\} \mathrm{d}P(Z \le u | X = x)}{\int_{-\infty}^\infty \{f(t|u,x)\} \mathrm{d}P(Z \le u | X = x)}, \tag{3}$$

$$\mathrm{FPR}_{\mathbb{D}}(c;t,x) = \frac{\int_c^\infty \{S(t|u,x)\} \mathrm{d}P(Z \le u | X = x)}{\int_{-\infty}^\infty \{S(t|u,x)\} \mathrm{d}P(Z \le u | X = x)}, \tag{4}$$

where $S(t|u,x) = P(T > t | Z = u, X = x)$ is the conditional survival function, and $f(t|u,x) = -\mathrm{d}S(t|u,x)/\mathrm{d}t$ is the conditional density function. To estimate TPR and FPR, we need estimators for $S(t|z,x)$, $f(t|z,x)$ and $P(Z \le z \mid X = x)$. Under the proportional hazards model, the survival function is $S(t \mid z, x) = \exp\{-\Lambda_0(t) \exp(\beta_0 z + \gamma_0{}^T x)\}$, where $\Lambda_0(t) = \int_0^t \lambda_0(s)\mathrm{d}s$, and the density function is $f(t|z,x) = \lambda_0(t) \exp(\beta_0 z + \gamma_0{}^T x) S(t \mid z, x)$.

A variety of methods have been proposed to handle missing covariates in the proportional hazards model, see Paik and Tsai (1997), Chen and Little (1999), Wang and Chen (2001), Wang, Xie, and Prentice (2001), Qi, Wang, and Prentice (2005), Luo, Tsai, and Xu (2009), Xu et al. (2009). To fix the idea, we focus on the inverse probability weighted estimating equation approach proposed by Qi et al. (2005), and indicate that other approaches can be applied as well. Let $N_i(t) = \delta_i I(R_i \le t)$ and $Y_i(t) = I(R_i \ge t)$ be the counting process and the at-risk process for subject i. The simple weighted estimating equation in Qi et al. (2005) is given as

$$U_\theta(\theta) = \frac{1}{n} \sum_{i=1}^n \frac{V_i}{\pi(W_i)} \int_0^\tau \left\{ Q_i - \frac{S^{(1)}(\theta,t)}{S^{(0)}(\theta,t)} \right\} \mathrm{d}N_i(t),$$

where for k=0, 1, 2, $S^{(k)}(\theta,t) = n^{-1} \sum_{i=1}^n \frac{V_i}{\pi(W_i)} Y_i(t) Q_i^{\otimes k} \exp(\theta^T Q_i)$, with $a^{\otimes 0} = 1$, $a^{\otimes 1} = a$ and $a^{\otimes 2} = aa^T$, and τ is the end of

the study period. The simple weighted estimator $\widehat{\theta}$ can be obtained by solving $U_\theta(\theta) = 0$.

Since $S(t|z,x)$ and $f(t|z,x)$ are functions of both θ and $\Lambda_0(t)$, we also need to estimate $\Lambda_0(t)$. By the property of the counting process, we have $E(\mathrm{d}N_i(t) \mid \mathcal{F}_{t-}) = Y_i(t)\exp(\theta_0^T Q_i)\lambda_0(t)\mathrm{d}t$, where $\mathcal{F}_t$ is the σ-field generated by $\{(N_i(u), Y_i(u)) : 0 \le u \le t, i = 1, \ldots, n\}$. Therefore, the weighted estimator for $\lambda_0(t)\mathrm{d}t = \mathrm{d}\Lambda_0(t)$ with the plug-in estimator $\widehat{\theta}$ is given by

$$\mathrm{d}\widehat{\Lambda}_0(t;\widehat{\theta}) = \frac{1}{n}\frac{\sum_{i=1}^n \{V_i/\pi(W_i)\}\mathrm{d}N_i(t)}{S^{(0)}(\widehat{\theta}, t)}. \tag{5}$$

With the plug-in estimators $\widehat{\theta}$ and $\mathrm{d}\widehat{\Lambda}_0(t;\widehat{\theta})$, we can estimate $S(t|z,x)$ and $f(t|z,x)$ by $\widehat{S}(t|z,x) = \exp\{-\widehat{\Lambda}_0(t)\exp(\widehat{\beta}z + \widehat{\gamma}^T x)\}$, and $\widehat{f}(t|z,x)\mathrm{d}t = \mathrm{d}\widehat{\Lambda}_0(t)\exp(\widehat{\beta}z + \widehat{\gamma}^T x)\widehat{S}(t|z,x)$.

To estimate $P(Z \le z \mid X = x)$, we further assume a linear regression model,

$$Z_i = {\alpha_0}^T X_i + \epsilon_i, \tag{6}$$

where ϵ_i is a zero-mean random variable with unknown distribution function $H(\cdot)$ and α_0 is a p-dimensional parameter. The model is equivalent to the semiparametric location model $P(Z_i \le z|X_i = x) = H(z - {\alpha_0}^T x)$ considered by Song and Zhou (2008). The estimator $\widehat{\alpha}$ can be obtained by solving the estimating equation $U_\alpha(\alpha) = 0$, where

$$U_\alpha(\alpha) = \frac{1}{n}\sum_{i=1}^n \frac{V_i}{\pi(W_i)}(Z_i - \alpha^T X_i)X_i.$$

The unknown distribution function $H(z)$ is estimated by the weighted estimator

$$\widehat{H}(z) = \frac{1}{n}\sum_{i=1}^n \frac{V_i I(Z_i - \widehat{\alpha}^T X_i \le z)}{\pi(W_i)},$$

and thus $P(Z \le z \mid X = x)$ is estimated by $\widehat{H}(z - \widehat{\alpha}^T x)$.

Plugging the estimators for $S(t|z,x)$, $f(t|z,x)$ and $P(Z \le z \mid X = x)$ into equations (2)–(4) leads to estimators $\widehat{\mathrm{TPR}_{\mathbb{C}}}(c;t,x)$, $\widehat{\mathrm{TPR}_{\mathbb{I}}}(c;t,x)$, $\widehat{\mathrm{FPR}_{\mathbb{D}}}(c;t,x)$. For example,

$$\widehat{\mathrm{TPR}_{\mathbb{C}}}(c;t,x) = \frac{\sum_{i=1}^n V_i/\pi(W_i)\left[1 - \widehat{S}\{t|Z_i - \widehat{\alpha}^T(X_i - x), x\}\right] I\{Z_i - \widehat{\alpha}^T(X_i - x) > c\}}{\sum_{i=1}^n V_i/\pi(W_i)\left[1 - \widehat{S}\{t|Z_i - \widehat{\alpha}^T(X_i - x), x\}\right]}.$$

The resulting ROC estimators are denoted by $\widehat{\mathrm{ROC}}_{\mathbb{I}/\mathbb{D}}(p;t,x)$ and $\widehat{\mathrm{ROC}}_{\mathbb{C}/\mathbb{D}}(p;t,x)$.

In practice, the selection probability $\pi(W_i)$ is often unknown. To implement the simple weighted estimators, we postulate a parametric model, say $\pi_i(\phi_0) = \pi(W_i;\phi_0)$, to characterize the missing data process, where ϕ_0 is a finite dimensional parameter. Let $\ell(\phi)$ denote the resulting log likelihood, that is, $\ell(\phi) = \sum_{i=1}^n V_i \log \pi_i(\phi) + (1 - V_i)\log\{1 - \pi_i(\phi)\}$. Then the score function for ϕ is $U_\phi(\phi) = n^{-1}\sum_{i=1}^n U_{\phi,i}(\phi)$, where

$$U_{\phi,i}(\phi) = \frac{V_i - \pi_i(\phi)}{\pi_i(\phi)\{1 - \pi_i(\phi)\}}\frac{\partial \pi_i(\phi)}{\partial \phi}.$$

Let $S^{(k)}(\theta,\phi,t) = \frac{1}{n}\sum_{i=1}^n \frac{V_i}{\pi_i(\phi)} Y_i(t) Q_i^{\otimes k}\exp(\theta^T Q_i)$, $k = 0, 1, 2$. The estimators $(\widehat{\theta}_P, \widehat{\phi})$ can be obtained by simultaneously solving the estimating equations $(U_\theta(\theta,\phi)^T, U_\phi(\phi)^T)^T = 0$, where

$$U_\theta(\theta,\phi) = \frac{1}{n}\sum_{i=1}^n \frac{V_i}{\pi(W_i;\phi)}\int_0^\tau \left\{Q_i - \frac{S^{(1)}(\theta,\phi,t)}{S^{(0)}(\theta,\phi,t)}\right\}\mathrm{d}N_i(t).$$

The corresponding estimator for $\mathrm{d}\Lambda_0(t)$ is given by

$$\mathrm{d}\widehat{\Lambda}_0^P(t;\widehat{\theta}_P,\widehat{\phi}) = \frac{1}{n}\frac{\sum_{i=1}^n \{V_i/\pi(W_i,\widehat{\phi})\}\mathrm{d}N_i(t)}{S^{(0)}(\widehat{\theta}_P,\widehat{\phi},t)}. \tag{7}$$

The resulting estimators of $S(t|z,x)$, $f(t|z,x)$ are denoted by $\widehat{S}_P(t|z,x)$ and $\widehat{f}_P(t|z,x)$.

Similarly, $\widehat{\alpha}_P$ can be obtained by solving $(U_\alpha(\alpha,\phi)^T, U_\phi(\phi)^T)^T = 0$, where

$$U_\alpha(\alpha,\phi) = \frac{1}{n}\sum_{i=1}^n \frac{V_i}{\pi_i(\phi)}(Z_i - \alpha^T X_i)X_i,$$

and the resulting estimator for $H(z)$ is denoted by $\widehat{H}_P(z)$. Plugging $\widehat{S}_P(t|z,x)$, $\widehat{f}_P(t|z,x)$ and $\widehat{H}_P(z)$ into equations (2)–(4) leads to estimators $\widehat{\mathrm{TPR}_{\mathbb{C}}}^{\mathrm{P}}$, $\widehat{\mathrm{TPR}_{\mathbb{I}}}^{\mathrm{P}}$, and $\widehat{\mathrm{FPR}_{\mathbb{D}}}^{\mathrm{P}}$. For example, $\widehat{\mathrm{TPR}_{\mathbb{C}}}^{\mathrm{P}}$ can be written as

$$\widehat{\mathrm{TPR}_{\mathbb{C}}}^{\mathrm{P}}(c;t,x) = \frac{\sum_{i=1}^n V_i/\pi_i(\widehat{\phi})\left[1 - \widehat{S}_P\{t|Z_i - \widehat{\alpha}_P^T(X_i - x), x\}\right] I\{Z_i - \widehat{\alpha}_P^T(X_i - x) > c\}}{\sum_{i=1}^n V_i/\pi_i(\widehat{\phi})\left[1 - \widehat{S}_P\{t|Z_i - \widehat{\alpha}_P^T(X_i - x), x\}\right]}.$$

The resulting estimators for ROC functions are denoted by $\widehat{\mathrm{ROC}}_{\mathbb{I}/\mathbb{D}}^{\mathrm{P}}(p;t,x)$ and $\widehat{\mathrm{ROC}}_{\mathbb{C}/\mathbb{D}}^{\mathrm{P}}(p;t,x)$.

3. Fully Augmented Weighted Estimators

While the parametric method in Section 2 provides a flexible scheme for modeling the missing data process, the consistency of the ROC estimators still hinges on the correct specification of the model for $\pi(W_i)$. Moreover, the weighted estimating equation approach in Section 2 only utilizes the subjects with complete measurements, which may result in a loss of information. To address these issues, we develop fully augmented

weighted estimators of ROC. The key idea is to project the corresponding estimating equations constructed in Section 2 onto the orthogonal complement of the tangent space for the nuisance missing data process, and then construct new estimating equations by removing redundant information Robins et al. (1994).

For theoretical presentation, for now we assume $\pi(W_i)$ and $f(Z_i|X_i)$ are given. Following Qi et al. (2005), we estimate θ by solving the following augmented estimating equations

$$U_{\mathrm{A}}(\theta) = \frac{1}{n}\sum_{i=1}^{n}\frac{V_i}{\pi(W_i)}\int_0^{\tau}\left\{Q_i - \frac{S_{\mathrm{A}}^{(1)}(\theta,t)}{S_{\mathrm{A}}^{(0)}(\theta,t)}\right\}\mathrm{d}N_i(t) + \frac{1}{n}\sum_{i=1}^{n}A_i^{\mathrm{A}}(\theta), \tag{8}$$

where for $k = 0, 1, 2$,

$$S_{\mathrm{A}}^{(k)}(\theta,t) = \frac{1}{n}\sum_{i=1}^{n}\left[\frac{V_i}{\pi(W_i)}Y_i(t)Q_i^{\otimes k}\exp(\theta^T Q_i) + \left(1-\frac{V_i}{\pi(W_i)}\right)Y_i(t)E\{Q_i^{\otimes k}\exp(\theta^T Q_i)\mid W_i\}\right], \tag{9}$$

$$A_i^{\mathrm{A}}(\theta) = \left(1-\frac{V_i}{\pi(W_i)}\right)\int_0^{\tau}\left[E\{Q_i\mathrm{d}N_i(t)\mid W_i\} - \frac{S_{\mathrm{A}}^{(1)}(\theta,t)}{S_{\mathrm{A}}^{(0)}(\theta,t)}E\{\mathrm{d}N_i(t)\mid W_i\}\right]. \tag{10}$$

Note that the subjects with missing biomarkers contribute to $U_{\mathrm{A}}(\theta)$ in two ways, one through the augmentation term $A_i^{\mathrm{A}}(\theta)$ and the other through the risk set weighted average $S_{\mathrm{A}}^{(k)}(\theta,t)$. It is easily seen that, if π is correctly specified, equation (8) is unbiased even if $f(Z_i|W_i)$ is mis-specified. On the other hand, if $f(Z_i|W_i)$ is mis-specified, equation (8) is also unbiased even if π is incorrectly specified. Therefore, the augmented estimator $\widehat{\theta}_{\mathrm{A}}$, obtained by solving $U_{\mathrm{A}}(\theta) = 0$, enjoys the so-called "double robustness" property (Robins et al., 1994; Wang and Chen, 2001). In addition, under proportional hazards model, it can be shown that

$$f(Z_i|W_i) = \frac{\exp\{\delta_i(\beta_0 Z_i + \gamma_0^T X_i)\}\exp\{-\Lambda_0(R_i)\exp(\beta_0 Z_i + \gamma_0^T X_i)\}f(Z_i|X_i)}{\int[\exp\{\delta_i(\beta_0 Z_i + \gamma_0^T X_i)\}\exp\{-\Lambda_0(R_i)\exp(\beta_0 Z_i + \gamma_0^T X_i)\}f(Z_i|X_i)]dZ_i},$$

where $f(Z_i|X_i)$ follows the semiparametric location model (6). We assume validity of the proportional hazards model and allow for arbitrary error distribution in the location model. Therefore, in our context, $\widehat{\theta}_{\mathrm{A}}$ is doubly robust in the sense that it is consistent if either $\pi(W_i)$ or $f(Z_i|X_i)$ is correctly specified.

To construct doubly robust estimators of ROC functions, we develop augmented weighted estimators of $\mathrm{d}\Lambda_0(t)$, α and $H(z)$, respectively. Following the same principle, we give the following augmented estimator of $\mathrm{d}\Lambda_0(t)$:

$$\mathrm{d}\widehat{\Lambda}_0^{\mathrm{A}}(t;\widehat{\theta}_{\mathrm{A}}) = \frac{1}{n}\frac{\sum_{i=1}^{n}\mathrm{d}N_i(t)}{S_{\mathrm{A}}^{(0)}(\widehat{\theta}_{\mathrm{A}},t)}. \tag{11}$$

In contrast to the simple weighted estimator $\mathrm{d}\widehat{\Lambda}_0(t;\widehat{\theta})$ in (5), $\mathrm{d}\widehat{\Lambda}_0^{\mathrm{A}}(t;\widehat{\theta}_{\mathrm{A}})$ has an augmentation term $S_{\mathrm{A}}^{(k)}(\theta,t)$ that incorporates information from incomplete observations. In addition, in (11), the counting processes $\mathrm{d}N_i(t)$ are averaged over all subjects, whereas in (5), $\mathrm{d}N_i(t)$ are averaged over subjects with complete observations. In Web Appendix B, we show that $\mathrm{d}\widehat{\Lambda}_0^{\mathrm{A}}(t;\widehat{\theta}_{\mathrm{A}})$ also has the double robustness property. By plugging in $\mathrm{d}\widehat{\Lambda}_0^{\mathrm{A}}(t;\widehat{\theta}_{\mathrm{A}})$ and $\widehat{\theta}_{\mathrm{A}}$, the resulting estimators of $S(t|z,x)$ and $f(t|z,x)dt$ are denoted by $\widehat{S}_{\mathrm{A}}(t|z,x)$ and $\widehat{f}_{\mathrm{A}}(t|z,x)dt$.

Similarly, the augmented weighted estimating equation for α is

$$U_{\alpha}^{\mathrm{A}}(\alpha) = \frac{1}{n}\sum_{i=1}^{n}\left[\frac{V_i}{\pi(W_i)}(Z_i - \alpha^T X_i)X_i + \left(1-\frac{V_i}{\pi(W_i)}\right)E\{(Z_i-\alpha^T X_i)X_i\mid W_i\}\right]. \tag{12}$$

Let $\widehat{\alpha}_{\mathrm{A}}$ denote the root of $U_{\alpha}^{\mathrm{A}}(\alpha) = 0$, and $F_Z(z\mid W_i) = E\{I(Z_i \le z)\mid W_i\}$. The distribution function $H(z)$ is estimated by the augmented estimator

$$\widehat{H}_{\mathrm{A}}(z) = \frac{1}{n}\sum_{i=1}^{n}\left\{\frac{V_i}{\pi(W_i)}I(Z_i - \widehat{\alpha}_{\mathrm{A}}^T X_i \le z) + \left(1-\frac{V_i}{\pi(W_i)}\right)F_Z(z+\widehat{\alpha}_{\mathrm{A}}^T X_i\mid W_i)\right\}. \tag{13}$$

Plugging $\widehat{S}_{\mathrm{A}}(t|z,x)$, $\widehat{f}_{\mathrm{A}}(t|z,x)$ and $\widehat{H}_{\mathrm{A}}(z)$ into equations (2)–(4) leads to estimators $\widetilde{\mathrm{TPR}}_{\mathbb{C}}(c;t,x)$, $\widetilde{\mathrm{TPR}}_{\mathbb{I}}(c;t,x)$ and $\widetilde{\mathrm{FPR}}_{\mathbb{D}}(c;t,x)$. For example, letting $L_i = Z_i - \widehat{\alpha}_A^T(X_i - x)$, we write $\widetilde{\mathrm{FPR}}_{\mathbb{D}}(c;t,x)$ as

$$\frac{\sum_{i=1}^{n}\frac{V_i}{\pi(W_i)}\widehat{S}_A(t|L_i,x)I(L_i>c) + \sum_{i=1}^{n}\left\{1-\frac{V_i}{\pi(W_i)}\right\}\int_c^{\infty}\widehat{S}_A(t|u,x)\mathrm{d}F_Z\{u-\widehat{\alpha}_A^T(x-X_i)\mid W_i\}}{\sum_{i=1}^{n}\frac{V_i}{\pi(W_i)}\widehat{S}_A(t|L_i,x) + \sum_{i=1}^{n}\left\{1-\frac{V_i}{\pi(W_i)}\right\}\int_{-\infty}^{\infty}\widehat{S}_A(t|u,x)\mathrm{d}F_Z\{u-\widehat{\alpha}_A^T(x-X_i)\mid W_i\}}.$$

The resulting estimators for ROC functions are denoted by $\widetilde{\mathrm{ROC}}_{\mathbb{I}/\mathbb{D}}(p;t,x)$ and $\widetilde{\mathrm{ROC}}_{\mathbb{C}/\mathbb{D}}(p;t,x)$.

Our estimation procedures are fully augmented in the sense that the estimating equations and estimators $U_{\mathrm{A}}(\theta)$, $\mathrm{d}\widehat{\Lambda}_0^{\mathrm{A}}(t;\widehat{\theta}_{\mathrm{A}})$, $U_{\alpha}^{\mathrm{A}}(\alpha)$, $\widehat{H}_{\mathrm{A}}(z)$ are all augmented. This ensures the

double robustness of $\{\widehat{\theta}_{\mathrm{A}}, \widehat{\alpha}_{\mathrm{A}}, \widehat{H}_{\mathrm{A}}(z), \widehat{\Lambda}_0^{\mathrm{A}}(t;\widehat{\theta}_{\mathrm{A}})\}$. Therefore the resulting estimators of ROC functions are also doubly robust. One problem with the augmented estimators is that it does not guarantee the TPR and FPR functions are monotone, because of some negative weighting of the data points induced by the $(1 - V_i/\pi_i)$ term (Alonzo and Pepe, 2005). Our numerical studies show that the augmented estimators do not show dramatic deviation from monotonicity, therefore, the non-monotonicity is not a major concern in this manuscript.

The above augmented estimation approach assumes $\pi(W_i)$, $\Lambda_0(t)$ and $f(Z_i|X_i)$ are given, while all of them are usually unknown in practice. Qi et al. (2005) proposed a nonparametric approach to estimate the unknown functions. However, their approach is not applicable in the presence of high dimensional X_i due to the curse of dimensionality. In this manuscript, we consider a parametric approach to estimate those functions. As illustrated in Section 2, we can postulate a parametric model for $\pi(W_i)$, say $\pi_i(\phi_0) = \pi(W_i;\phi_0)$. Similarly, we assume a parametric distribution for the error term ϵ_i in the semiparametric location model for $Z_i|X_i$. Note that this assumption is not needed for the simple weighted estimator $\widehat{H}_P$, because it has the form of a weighted empirical estimator. On the contrary, the augmented estimator $\widehat{H}_{\mathrm{A}}$ involves estimation of $f(Z_i|W_i)$, thus further assumption is required. $\widehat{H}_{\mathrm{A}}$ remains consistent if either one of the two parametric models for π and $f(Z_i \mid X_i)$ is correctly specified.

Assume that the parametric distribution for ϵ_i is indexed by η_0, and let $Sc(Z_i|X_i;\eta,\alpha) = \frac{\partial}{\partial\eta}\log f(Z_i|X_i;\eta,\alpha)$ denote the score function for η. The expression of the augmented estimator also requires an estimator for $\mathrm{d}\Lambda_0(t)$, and we denote it by $\mathrm{d}\widetilde{\Lambda}_0(t,\phi)$. The choice of $\mathrm{d}\widetilde{\Lambda}_0(t,\phi)$ will be discussed later. Let $\chi_0 = (\theta_0, \alpha_0, \phi_0, \eta_0)$. As a result of replacing $\Lambda_0(t)$ with $\widetilde{\Lambda}_0(t,\phi)$, $E(\cdot \mid W_i)$ in (9), (10), and (12) is denoted by $\widetilde{E}(\cdot \mid W_i;\chi)$, and the estimated $S_{\mathrm{A}}^{(k)}(\theta,t)$ in (9) is denoted by $\widetilde{S}_A^{(k)}(\chi,t)$. Details about calculation of $\widetilde{E}(\cdot \mid W_i;\chi)$ can be found in Web Appendix E. Let $U^{\mathrm{AP}}(\chi) = (U_\theta^{\mathrm{AP}}(\chi)^T, U_\alpha^{\mathrm{AP}}(\alpha,\phi,\eta)^T, U_\eta^{\mathrm{AP}}(\alpha,\phi,\eta)^T, U_\phi(\phi)^T)^T$, where

$$
\begin{aligned}
U_\theta^{\mathrm{AP}}(\chi) = {} & \frac{1}{n}\sum_{i=1}^{n}\frac{V_i}{\pi(W_i,\phi)}\int_0^\tau\left\{Q_i - \frac{\widetilde{S}_{\mathrm{A}}^{(1)}(\chi,t)}{\widetilde{S}_{\mathrm{A}}^{(0)}(\chi,t)}\right\}\mathrm{d}N_i(t) \\
& + \frac{1}{n}\sum_{i=1}^{n}\left(1 - \frac{V_i}{\pi(W_i,\phi)}\right)\int_0^\tau\left\{\widetilde{E}\{Q_i\mathrm{d}N_i(t)|W_i;\chi\}\right. \\
& \left. - \frac{\widetilde{S}_{\mathrm{A}}^{(1)}(\chi,t)}{\widetilde{S}_{\mathrm{A}}^{(0)}(\chi,t)}\widetilde{E}\{\mathrm{d}N_i(t) \mid W_i;\chi\}\right\}, \\
U_\alpha^{\mathrm{AP}}(\alpha,\phi,\eta) = {} & \frac{1}{n}\sum_{i=1}^{n}\left[\frac{V_i}{\pi(W_i,\phi)}(Z_i - \alpha^T X_i)X_i\right. \\
& \left. + \left(1 - \frac{V_i}{\pi(W_i,\phi)}\right)\widetilde{E}\{(Z_i - \alpha^T X_i)X_i \mid W_i;\chi\}\right], \\
U_\eta^{\mathrm{AP}}(\alpha,\phi,\eta) = {} & \frac{1}{n}\sum_{i=1}^{n}\left\{\frac{V_i}{\pi(W_i,\phi)}Sc(Z_i|X_i;\eta,\alpha)\right. \\
& \left. + \left(1 - \frac{V_i}{\pi(W_i,\phi)}\right)\widetilde{E}\{Sc(Z_i|X_i;\eta,\alpha) \mid W_i\}\right\}.
\end{aligned}
$$

The parameters χ can be estimated by solving $U^{\mathrm{AP}}(\chi) = 0$, and the resulting estimators are denoted by $(\widehat{\theta}_{\mathrm{AP}}, \widehat{\alpha}_{\mathrm{AP}}, \widehat{\phi}, \widehat{\eta})$. Similarly, the augmented estimator of $\mathrm{d}\Lambda_0(t)$ is given by

$$
\mathrm{d}\widehat{\Lambda}_0^{\mathrm{AP}}(t;\widehat{\theta}_{\mathrm{AP}},\widehat{\phi},\widehat{\eta}) = \frac{1}{n}\frac{\sum_{i=1}^{n}\mathrm{d}N_i(t)}{S_{\mathrm{A}}^{(0)}(\widehat{\theta}_{\mathrm{AP}},\widehat{\phi},\widehat{\eta},t)}.
$$

where $S_{\mathrm{A}}^{(0)}(\theta,\phi,\eta,t)$ is given in equation (9) with parameterized $\pi(W_i)$ and $f(Z_i|X_i)$. Let $\widehat{F}_Z(z \mid W_i;\chi) = \widehat{E}\{I(Z_i < z) \mid W_i;\chi\}$, which is obtained with the plug-in estimator $\widehat{\eta}$. The augmented estimator of $H(z)$ is given by

$$
\begin{aligned}
\widehat{H}_{\mathrm{AP}}(z) = {} & \frac{1}{n}\sum_{i=1}^{n}\left\{\frac{V_i}{\pi(W_i,\widehat{\phi})}I(Z_i - \widehat{\alpha}_{\mathrm{AP}}^T X_i \le z)\right. \\
& \left. + \left(1 - \frac{V_i}{\pi(W_i,\widehat{\phi})}\right)\widehat{F}_Z(z + \widehat{\alpha}_{\mathrm{AP}}^T X_i \mid W_i;\chi)\right\}.
\end{aligned}
$$

Recall that the estimators $\widehat{\Lambda}_0^{\mathrm{AP}}$, $\widehat{H}_{\mathrm{AP}}$, and $\widehat{\phi}$, $\widehat{\eta}$ depend on the choice of $\mathrm{d}\widetilde{\Lambda}_0$ in $\widetilde{E}(\cdot \mid W_i;\chi)$. One choice is the simple weighted estimator given in (7). However, if $\pi(W_i,\phi)$ is misspecified, the simple weighted estimator can deviate from the truth, which leads to incorrect estimation of $\widetilde{E}$ and biased estimation of $(\Lambda_0, H, \phi, \eta)$. To address this issue, we estimate the parameters based on an EM-type iterative algorithm following similar ideas of Wang and Chen (2001) and Zheng, Barlow, and Cutter (2005). First, we calculate the estimators $\widehat{\Lambda}_0^{\mathrm{AP}}$, $\widehat{H}_{\mathrm{AP}}$, $\widehat{\phi}$ and $\widehat{\eta}$ with the initial estimator $\mathrm{d}\widetilde{\Lambda}_0(t)$ in (7). Second, we update $\widetilde{\Lambda}_0(t)$ using $\widehat{\Lambda}_0^{\mathrm{AP}}(t)$ obtained from the previous iteration and recalculate all the estimators with $\widetilde{\Lambda}_0(t) = \widehat{\Lambda}_0^{\mathrm{AP}}(t)$. Third, repeat the second step until certain convergence criterion is met. With a slight abuse of notation, we still denote the estimators obtained from this iterative algorithm by $\widehat{\Lambda}_0^{\mathrm{AP}}$, $\widehat{H}_{\mathrm{AP}}$, $\widehat{\phi}$ and $\widehat{\eta}$.

With the plug-in estimators $\widehat{\Lambda}_0^{\mathrm{AP}}$, $\widehat{H}_{\mathrm{AP}}$, $\widehat{\phi}$, and $\widehat{\eta}$, we denote the corresponding ROC estimators by $\widetilde{\mathrm{ROC}}_{\mathbb{I}/\mathbb{D}}^{\mathrm{P}}(p;t,x,\pi(\widehat{\phi}),\widehat{\eta})$ and $\widetilde{\mathrm{ROC}}_{\mathbb{C}/\mathbb{D}}^{\mathrm{P}}(p;t,x,\pi(\widehat{\phi}),\widehat{\eta})$. We show in the next section that $\widetilde{\mathrm{ROC}}_{\mathbb{I}/\mathbb{D}}^{\mathrm{P}}$ and $\widetilde{\mathrm{ROC}}_{\mathbb{C}/\mathbb{D}}^{\mathrm{P}}$ are doubly robust, and they are asymptotically equivalent to $\widetilde{\mathrm{ROC}}_{\mathbb{I}/\mathbb{D}}$ and $\widetilde{\mathrm{ROC}}_{\mathbb{C}/\mathbb{D}}$ respectively. This implies that estimation of $\pi(W_i)$ and $f(Z_i|X_i)$ does not affect the asymptotic distribution of $\widetilde{\mathrm{ROC}}_{\mathbb{I}/\mathbb{D}}^{\mathrm{P}}$ and $\widetilde{\mathrm{ROC}}_{\mathbb{C}/\mathbb{D}}^{\mathrm{P}}$.

4. Inference in Large Samples

In this section, we outline theoretical results for the proposed estimators. As shown in Section 2, the ROC functions depend on both θ and $\Lambda_0(t)$. The asymptotics of the estimators for θ have been established under various missing data processes (Wang and Chen, 2001; Qi et al., 2005; Luo et al., 2009; Xu et al., 2009). However, to the best of our knowledge, the asymptotics of $\Lambda_0(t)$ in the presence of missing data remain largely unexplored. As a byproduct of our asymptotic results, we derive the limiting distributions of a variety of estimators for $\Lambda_0(t)$. Therefore, our results complement the existing works in the literature.

In Lemmas 1 and 3 in Web Appendix B, we establish the large sample properties of $\widehat{\Lambda}_0(t;\widehat{\theta})$ and $\widehat{\Lambda}_0^P(t;\widehat{\theta}_P,\widehat{\phi})$. In Lemmas 2 and 4, we establish the large sample properties of $\widehat{\alpha}$, $\widehat{H}(z-\widehat{\alpha}^T x)$ and $\widehat{\alpha}_P$, $\widehat{H}_P(z-\widehat{\alpha}_P^T x)$. Let $\mathcal{Z}$ and $\mathcal{X}$ be the supports of Z and X, respectively. The following theorems establish the asymptotic properties of the simple weighted estimators.

THEOREM 1. *Under conditions (A1)–(A9) in Web Appendix A, given* $(x,t)\in\mathcal{X}\times[0,\tau]$, $n^{1/2}\{\widehat{\mathrm{TPR}}_{\mathbb{C}}(\cdot;t,x)-\mathrm{TPR}_{\mathbb{C}}(\cdot;t,x)\}$, $n^{1/2}\{\widehat{\mathrm{TPR}}_{\mathbb{I}}(\cdot;t,x)-\mathrm{TPR}_{\mathbb{I}}(\cdot;t,x)\}$ *and* $n^{1/2}\{\widehat{\mathrm{FPR}}_{\mathbb{D}}(\cdot;t,x)-\mathrm{FPR}_{\mathbb{D}}(\cdot;t,x)\}$ *converge weakly to zero-mean Gaussian processes on* $\mathcal{Z}$ *with covariances given in Web Appendix C. Moreover,* $n^{1/2}\{\widehat{\mathrm{ROC}}_{\mathbb{I}/\mathbb{D}}(\cdot;t,x)-\mathrm{ROC}_{\mathbb{I}/\mathbb{D}}(\cdot;t,x)\}$ *and* $n^{1/2}\{\widehat{\mathrm{ROC}}_{\mathbb{C}/\mathbb{D}}(\cdot;t,x)-\mathrm{ROC}_{\mathbb{C}/\mathbb{D}}(\cdot;t,x)\}$ *converge weakly to zero-mean Gaussian processes on* $[p,q]$ *with covariances given in Web Appendix C and* p,q *defined in Web Appendix A.*

THEOREM 2. *Under conditions (A1)–(A10) in Web Appendix A, if* $\pi(W;\phi_0)$ *is correctly specified, then given* $(x,t)\in\mathcal{X}\times[0,\tau]$, $n^{1/2}\{\widehat{\mathrm{TPR}}_{\mathbb{C}}^{\mathrm{P}}(\cdot;t,x)-\mathrm{TPR}_{\mathbb{C}}(\cdot;t,x)\}$, $n^{1/2}\{\widehat{\mathrm{TPR}}_{\mathbb{I}}^{\mathrm{P}}(\cdot;t,x)-\mathrm{TPR}_{\mathbb{I}}(\cdot;t,x)\}$ *and* $n^{1/2}\{\widehat{\mathrm{FPR}}_{\mathbb{D}}^{\mathrm{P}}(\cdot;t,x)-\mathrm{FPR}_{\mathbb{D}}(\cdot;t,x)\}$ *converge weakly to zero-mean Gaussian processes with covariances given in Web Appendix C.* $n^{1/2}\{\widehat{\mathrm{ROC}}_{\mathbb{I}/\mathbb{D}}^{\mathrm{P}}(\cdot;t,x)-\mathrm{ROC}_{\mathbb{I}/\mathbb{D}}(\cdot;t,x)\}$ *and* $n^{1/2}\{\widehat{\mathrm{ROC}}_{\mathbb{C}/\mathbb{D}}^{\mathrm{P}}(\cdot;t,x)-\mathrm{ROC}_{\mathbb{C}/\mathbb{D}}(\cdot;t,x)\}$ *converge weakly to zero-mean Gaussian processes on* $[p,q]$ *with covariances given in Web Appendix C and* p,q *defined in Web Appendix A.*

Theorem 2 shows that simple weighted ROC estimators with estimated selection probabilities remain consistent, provided the selection probability model $\pi_i(\phi_0)$ is correctly specified.

In Lemmas 5 and 6 in Web Appendix B, we establish the asymptotic properties and the double robustness properties of the augmented estimators $\widehat{\Lambda}_{\mathrm{A}}(t;\widehat{\theta}_{\mathrm{A}})$, $\widehat{\alpha}_{\mathrm{A}}$ and $\widehat{H}_{\mathrm{A}}(z)$. The following theorem establishes the asymptotic properties of the resulting ROC estimators. For theoretical presentation, we assume π and $f(Z_i|W_i)$ are known.

THEOREM 3. *Under conditions (A1)–(A9) in Web Appendix A, given* $(x,t)\in\mathcal{X}\times[0,\tau]$, $n^{1/2}\{\widetilde{\mathrm{TPR}}_{\mathbb{C}}(\cdot;t,x)-\mathrm{TPR}_{\mathbb{C}}(\cdot;t,x)\}$, $n^{1/2}\{\widetilde{\mathrm{TPR}}_{\mathbb{I}}(\cdot;t,x)-\mathrm{TPR}_{\mathbb{I}}(\cdot;t,x)\}$ *and* $n^{1/2}\{\widetilde{\mathrm{FPR}}_{\mathbb{D}}(\cdot;t,x)-\mathrm{FPR}_{\mathbb{D}}(\cdot;t,x)\}$ *converge weakly to zero-mean Gaussian processes on* $\mathcal{Z}$ *with covariances given in Web Appendix C. As a result, given* $(x,t)\in\mathcal{X}\times[0,\tau]$, $n^{1/2}\{\widetilde{\mathrm{ROC}}_{\mathbb{I}/\mathbb{D}}(\cdot;t,x)-\mathrm{ROC}_{\mathbb{I}/\mathbb{D}}(\cdot;t,x)\}$ *and* $n^{1/2}\{\widetilde{\mathrm{ROC}}_{\mathbb{C}/\mathbb{D}}(\cdot;t,x)-\mathrm{ROC}_{\mathbb{C}/\mathbb{D}}(\cdot;t,x)\}$ *converge weakly to zero-mean Gaussian processes on* $[p,q]$ *with covariances given in Web Appendix C and* p,q *defined in Web Appendix A.*

In Web Appendix B, we show that $\widehat{\Lambda}_0^{\mathrm{AP}}(t;\widehat{\theta}_{\mathrm{AP}},\widehat{\phi},\widehat{\eta})$ and $\widehat{H}_{\mathrm{AP}}(z-\widehat{\alpha}_{\mathrm{AP}}^T x;\widehat{\phi},\widehat{\eta})$ are asymptotically equivalent to $\widehat{\Lambda}_0^{\mathrm{A}}(t;\widehat{\theta}_{\mathrm{A}})$ and $\widehat{H}_{\mathrm{A}}(z-\widehat{\alpha}_{\mathrm{A}}^T x)$ respectively. The following theorem summarizes the asymptotic properties of the augmented ROC estimators with estimated π and $f(Z_i|X_i)$.

THEOREM 4. *Under conditions (A1)–(A14) in Web Appendix A, given* $(x,t)\in\mathcal{X}\times[0,\tau]$, *if both* $\pi(W_i)$ *and* $f(Z_i|X_i)$ *are correctly specified,* $\widetilde{\mathrm{TPR}}_{\mathbb{C}}^{\mathrm{P}}(\cdot;t,x,\pi(\widehat{\phi}),\widehat{\eta})$, $\widetilde{\mathrm{TPR}}_{\mathbb{I}}^{\mathrm{P}}(\cdot;t,x,\pi(\widehat{\phi}),\widehat{\eta})$ *and* $\widetilde{\mathrm{FPR}}_{\mathbb{D}}^{\mathrm{P}}(\cdot;t,x,\pi(\widehat{\phi}),\widehat{\eta})$ *are asymptotically equivalent to* $\widetilde{\mathrm{TPR}}_{\mathbb{C}}(\cdot;t,x)$, $\widetilde{\mathrm{TPR}}_{\mathbb{I}}(\cdot;t,x)$ *and* $\widetilde{\mathrm{FPR}}_{\mathbb{D}}(\cdot;t,x)$ *on* $\mathcal{Z}$, *respectively. In addition,* $\widetilde{\mathrm{ROC}}_{\mathbb{I}/\mathbb{D}}^{\mathrm{P}}(\cdot;t,x,\pi(\widehat{\phi}),\widehat{\eta})$ *and* $\widetilde{\mathrm{ROC}}_{\mathbb{C}/\mathbb{D}}^{\mathrm{P}}(\cdot;t,x,\pi(\widehat{\phi}),\widehat{\eta})$ *are asymptotically equivalent to* $\widetilde{\mathrm{ROC}}_{\mathbb{I}/\mathbb{D}}(\cdot;t,x)$ *and* $\widetilde{\mathrm{ROC}}_{\mathbb{C}/\mathbb{D}}(\cdot;t,x)$ *on* $[p,q]$, *respectively.*

Theorem 4 implies that estimation of $\pi(W_i)$ and $f(Z_i\mid X_i)$ does not affect the asymptotic properties of the augmented estimators. This is because the derivatives of the estimating equations such as $U_\theta^{\mathrm{AP}}(\chi)$ with respective to η and ϕ converge to zero in probability. By the Taylor expansion, the error of estimating η and ϕ is asymptotically ignorable. Note that, this property requires correct specification of both $\pi(W_i)$ and $f(Z_i\mid X_i)$. In practice, it is of interest to study the variance formula when one component is misspecified. In Web Appendix D, we briefly discuss the asymptotics of the augmented estimators under misspecified models.

Although we have derived the asymptotic distributions of the proposed estimators, it is intractable to obtain the explicit analytic expressions for the variance-covariance processes. To alleviate this difficulty, we approximate the limiting distributions using resampling techniques, as proposed and used by Parzen, Wei, and Ying (1994), Cai and Pepe (2002), and others. Details about the variance estimation procedure can be found in Web Appendix E.

5. Simulation Study

We conduct extensive simulation studies to compare the performance of the augmented weighted estimators with that of the simple weighted estimators and the estimators from the complete-case analysis. The sample size is $n=500$ and the number of simulation replications is 300. The covariate X_{i1} is generated from uniform $(-1,1)$, and X_{i2} is generated from a Bernoulli distribution with mean 0.5. The biomarker Z_i is generated from a normal distribution with mean $-X_{i1}-0.5X_{i2}$ and variance 1, that is, $\alpha_0^T=(-1,-0.5)$. The failure time T_i is generated according to the proportional hazards model, with $\theta_0^T=(1.5,1.5,1.5)$, and $\lambda_0(t)=0.1$, which results in a median survival time of 4. The censoring time C_i followed a uniform distribution with the upper limit selected to yield a censoring rate of 40%.

We evaluate the following estimators for the ROC functions: (1) the estimators based on the full-cohort, (2) the estimators from the complete-case analysis (CC), (3) the simple weighted estimator with the true π, denoted as SWE-π, (4) the simple weighted estimator with the estimated π, denoted as SWE-$\widehat{\pi}$, (5) the augmented weighted estimator with true π and true $f(Z|X)$, denoted as AWE-π-$f_{Z|X}$, (6) the augmented weighted estimator with estimated π and estimated $f(Z|X)$, denoted as AWE-$\widehat{\pi}$-$\widehat{f}_{Z|X}$, and (7) the augmented weighted estimator with misspecified $f(Z|X)$, denoted as AWE-$\widehat{\pi}$-$\widehat{f}_{Z|X_1}$, where a misspecified model $Z_i=\alpha X_{i1}+\epsilon_i$, $\epsilon_i\sim N(0,\sigma^2)$ is used to model $Z_i|X_i$. Both cumulative and incident ROC curves are evaluated at $t=5$, $X_1=0$, $X_2=1$, and FPR $=0.1,0.3,0.5$. We consider two sets of simulation scenarios, with different missingness probabilities for the biomarker Z_i.

Under the first simulation setting, the selection probability is $\pi_i=0.7\delta_i+0.3(1-\delta_i)$, which results in 46% of missingness.

Table 1

Simulation results for ROC estimators evaluated at $t = 5$, $X_1 = 0$, and $X_2 = 1$ under the first scenario. B is the empirical bias (×1000); SE is the sample standard error (×1000); ASE is the average theoretical standard errors (×1000); CP is the coverage probability of the 95% confidence interval (×100).

	Incident ROC				Cumulative ROC			
Approach	B	SE	ASE	CP	B	SE	ASE	CP
$v = 0.1$								
Full cohort	0	17	17	96.7	−1	24	24	94.0
CC	−46	18	19	31.5	−4	34	32	93.2
SWE-π	2	24	25	94.9	2	32	34	96.2
SWE-$\widehat{\pi}$	1	23	25	96.9	1	32	33	96.9
AWE-π-$f_{Z\|X}$	3	25	23	95.3	4	34	33	93.6
AWE-$\widehat{\pi}$-$\widehat{f}_{Z\|X}$	3	24	23	95.3	4	33	32	94.3
AWE-$\widehat{\pi}$-$\widehat{f}_{Z\|X_1}$	3	24	23	93.6	4	33	33	93.2
$v = 0.3$								
Full cohort	−1	19	19	96.2	0	14	14	94.9
CC	−53	24	25	42.3	−6	20	19	92.6
SWE-π	−1	29	29	95.6	0	19	21	95.6
SWE-$\widehat{\pi}$	−2	27	29	96.9	0	18	20	96.3
AWE-π-$f_{Z\|X}$	1	29	28	94.3	3	21	20	93.1
AWE-$\widehat{\pi}$-$\widehat{f}_{Z\|X}$	1	29	28	95.0	2	21	20	93.1
AWE-$\widehat{\pi}$-$\widehat{f}_{Z\|X_1}$	2	30	28	93.2	3	21	21	92.9
$v = 0.5$								
Full cohort	0	13	14	97.1	0	8	8	95.3
CC	−38	20	20	55.2	−5	11	11	93.4
SWE-π	−1	21	22	94.0	0	10	13	96.9
SWE-$\widehat{\pi}$	−1	20	22	95.3	0	10	11	95.9
AWE-π-$f_{Z\|X}$	1	22	21	93.2	2	12	12	94.0
AWE-$\widehat{\pi}$-$\widehat{f}_{Z\|X}$	1	21	21	94.3	1	12	11	92.3
AWE-$\widehat{\pi}$-$\widehat{f}_{Z\|X_1}$	0	23	21	92.2	1	12	12	94.3

Table 2

Simulation results for ROC estimators evaluated at $t = 5$, $X_1 = 0$, and $X_2 = 1$ under the second scenario. G denotes (R, X_1, X_1^2, δ). B is the empirical bias (×1000); SE is the sample standard error (×1000); ASE is the average theoretical standard errors (×1000); CP is the coverage probability of the 95% confidence interval (×100).

	Incident ROC				Cumulative ROC			
Approach	B	SE	ASE	CP	B	SE	ASE	CP
$v = 0.1$								
Full cohort	0	17	17	97.1	−1	25	24	93.2
CC	61	28	29	46.6	−112	40	43	20.8
SWE-π	−2	30	31	95.6	−5	56	52	91.3
SWE-$\widehat{\pi}(\delta)$	−12	22	24	95.1	−165	43	46	5.3
SWE-$\widehat{\pi}(G)$	1	28	30	96.1	−5	55	47	90.3
AWE-π-$f_{Z\|X}$	6	32	31	95.1	7	57	57	93.7
AWE-$\widehat{\pi}(\delta)$-$\widehat{f}_{Z\|X}$	4	25	21	90.8	2	34	36	94.6
AWE-$\widehat{\pi}(G)$-$\widehat{f}_{Z\|X}$	2	30	31	97.6	4	54	57	93.2
AWE-$\widehat{\pi}(G)$-$\widehat{f}_{Z\|X_1}$	7	33	32	92.1	8	60	57	90.7
$v = 0.3$								
Full cohort	−1	19	19	96.1	0	14	14	95.1
CC	59	27	28	40.2	−46	26	27	61.7
SWE-π	−1	33	34	92.2	−2	31	32	94.2
SWE-$\widehat{\pi}(\delta)$	−13	25	27	97.5	−87	29	31	12.6
SWE-$\widehat{\pi}(G)$	1	31	34	94.6	−1	30	27	91.7
AWE-π-$f_{Z\|X}$	6	33	35	96.6	5	31	31	94.2
AWE-$\widehat{\pi}(\delta)$-$\widehat{f}_{Z\|X}$	4	27	26	91.8	4	20	22	96.1
AWE-$\widehat{\pi}(G)$-$\widehat{f}_{Z\|X}$	3	34	35	96.6	3	29	32	92.7
AWE-$\widehat{\pi}(G)$-$\widehat{f}_{Z\|X_1}$	6	35	36	93.1	7	33	33	92.6
$v = 0.5$								
Full cohort	0	13	14	98.5	0	7	8	96.6
CC	39	18	18	84.5	−18	15	15	84.5
SWE-π	1	24	25	92.7	−1	16	21	95.1
SWE-$\widehat{\pi}(\delta)$	−8	19	21	96.6	−42	17	18	34.5
SWE-$\widehat{\pi}(G)$	1	23	24	95.1	0	16	16	94.2
AWE-π-$f_{Z\|X}$	5	25	26	95.1	3	17	19	95.1
AWE-$\widehat{\pi}(\delta)$-$\widehat{f}_{Z\|X}$	3	19	18	91.3	2	10	12	97.1
AWE-$\widehat{\pi}(G)$-$\widehat{f}_{Z\|X}$	3	26	27	94.2	3	16	18	94.7
AWE-$\widehat{\pi}(G)$-$\widehat{f}_{Z\|X_1}$	4	26	26	90.2	4	18	20	94.0

Table 1 exhibits the results for the various estimators under the first simulation scenario. Bias is the empirical bias. SE denotes the square root of the sample variance of the estimates. ASE denotes the average of the standard error estimates using methods discussed in Web Appendix E. The 95% coverage probability is constructed using ASE. For the estimators with $\widehat{\pi}$, π is estimated as a function of W by fitting the logistic regression, thus the missing data process is correctly specified. The complete-case analysis yields large bias because the selection probability is strongly associated with the outcome variable δ. All remaining estimators show negligible bias, which agrees with the consistency properties of SWE and AWE under the correctly specified missing data model. Comparing the efficiency of the proposed estimators, we find that SWE-$\widehat{\pi}$, AWE-$\widehat{\pi}$-$\widehat{f}_{Z|X}$, and AWE-π-$f_{Z|X}$ have comparable efficiency with SWE-π. Note that, although it can be shown that $(\widehat{\theta}_{\mathrm{P}}, \widehat{\alpha}_{\mathrm{P}}, \widehat{\Lambda}_0^{\mathrm{P}}, \widehat{H}_{\mathrm{P}})$ and $(\widehat{\theta}_{\mathrm{A}}, \widehat{\alpha}_{\mathrm{A}}, \widehat{\Lambda}_0^{\mathrm{A}}, \widehat{H}_{\mathrm{A}})$ have higher efficiency than $(\widehat{\theta}, \widehat{\alpha}, \widehat{\Lambda}, \widehat{H})$, this result may not be generalizable to the ROC estimators, because TPR and FPR are nonlinear functions of $(\theta, \alpha, \Lambda_0, H)$, and the correlation among the estimators of $(\theta, \alpha, \Lambda_0, H)$ is difficult to characterize. This explains why we do not observe a substantial efficiency gain of AWE-π-$f_{Z|X}$ over SWE-π. The augmented estimator with misspecified $Z|X$, AWE-$\widehat{\pi}$-$\widehat{f}_{Z|X_1}$, is also unbiased due to its double robustness property, but it shows larger SE than its competitors. For unbiased estimators, the estimated standard errors track the empirical standard errors well, and the coverage probabilities are close to the nominal level.

Under the second simulation setting, the selection probability is given by $\pi_i = 1/\{1 + \exp(3 - 0.8R_i - 0.5X_{1i}^2 - X_{1i} - 0.5\delta_i)\}$, which results in 42% of missingness. For the purpose of comparison, we report estimators with misspecified $\widehat{\pi}_i$, where π_i is estimated using logistic regression with δ_i as covariate only, and also estimators with correctly specified $\widehat{\pi}_i$, where π_i is estimated using logistic regression with covariates $G_i = (R_i, X_{i1}^2, X_{i1}, \delta_i)$. The simulation results are summarized in Table 2. Similar to the first setting, the complete-case analysis leads to biased results. In addition, SWE-$\widehat{\pi}(\delta)$ also

Table 3

Simulation results for TPR and FPR estimators evaluated at $t = 5$, $(X_1, X_2) = (0, 1)$ under the second scenario. G denotes (R, X_1, X_1^2, δ). B is the empirical bias (×1000); SE is the sample standard error (×1000); ASE is the average theoretical standard errors (×1000); CP is the coverage probability of the 95% confidence interval (×100).

	Incident TPR				Cumulative TPR				FPR			
Approach	B	SE	ASE	CP	B	SE	ASE	CP	B	SE	ASE	CP
$z = -1.4$												
Full cohort	0	20	19	96.1	0	8	7	94.6	0	37	40	96.7
CC	−12	25	23	92.9	−39	19	16	28.8	−90	39	38	40.2
SWE-π	−1	32	28	93.4	−2	17	20	95.6	−3	49	53	96.7
SWE-$\widehat{\pi}(\delta)$	10	23	21	88.5	−20	16	13	70.1	25	39	40	92.9
SWE-$\widehat{\pi}(G)$	−1	32	27	94.0	−1	18	15	93.4	−4	49	53	93.8
AWE-π-$f_{Z\|X}$	3	32	33	94.0	2	16	21	96.9	−4	49	51	96.1
AWE-$\widehat{\pi}(\delta)$-$\widehat{f}_{Z\|X}$	1	26	28	95.6	0	11	14	93.4	−5	47	46	94.0
AWE-$\widehat{\pi}(G)$-$\widehat{f}_{Z\|X}$	1	32	32	95.6	1	16	17	96.1	−4	50	50	95.1
AWE-$\widehat{\pi}(G)$-$\widehat{f}_{Z\|X_1}$	5	33	23	92.6	2	17	20	95.8	−3	45	50	97.6
$z = -1.1$												
Full cohort	0	30	28	94.0	0	13	11	92.6	2	38	38	94.6
CC	−17	39	34	88.0	−70	31	25	23.3	−83	38	34	34.7
SWE-π	−1	48	42	91.8	−3	30	26	91.8	−2	51	51	95.1
SWE-$\widehat{\pi}(\delta)$	15	38	33	88.5	−42	29	21	57.6	30	41	41	90.7
SWE-$\widehat{\pi}(G)$	0	47	42	90.7	−2	29	24	90.6	−2	49	51	91.3
AWE-π-$f_{Z\|X}$	4	50	50	93.4	3	29	31	94.0	−3	51	49	92.5
AWE-$\widehat{\pi}(\delta)$-$\widehat{f}_{Z\|X}$	1	42	44	96.7	2	20	24	97.2	−5	48	45	93.5
AWE-$\widehat{\pi}(G)$-$\widehat{f}_{Z\|X}$	2	49	50	94.6	2	26	26	93.5	−3	51	48	91.8
AWE-$\widehat{\pi}(G)$-$\widehat{f}_{Z\|X_1}$	7	49	49	95.3	5	28	29	93.0	0	47	48	95.3
$z = -0.8$												
Full cohort	1	37	37	95.1	1	19	17	91.8	2	29	30	96.1
CC	−18	48	44	97.5	−115	43	35	10.8	−63	30	26	35.8
SWE-π	1	58	55	92.4	−4	44	39	90.4	1	43	42	95.1
SWE-$\widehat{\pi}(\delta)$	25	49	45	91.3	−75	42	31	38.5	30	37	37	91.8
SWE-$\widehat{\pi}(G)$	0	58	55	92.4	−4	43	37	89.6	−2	40	41	92.3
AWE-π-$f_{Z\|X}$	3	61	61	92.4	4	44	43	92.9	−3	43	39	92.4
AWE-$\widehat{\pi}(\delta)$-$\widehat{f}_{Z\|X}$	−3	52	58	97.2	0	30	37	98.3	−7	37	37	92.9
AWE-$\widehat{\pi}(G)$-$\widehat{f}_{Z\|X}$	−1	59	60	92.9	3	41	41	94.0	−5	41	38	90.9
AWE-$\widehat{\pi}(G)$-$\widehat{f}_{Z\|X_1}$	5	61	60	94.4	7	44	41	91.2	−4	40	38	92.1

yields substantial bias, while AWE-$\widehat{\pi}(\delta)$-$\widehat{f}_{Z|X}$ remains consistent. This agrees with our theoretical results that the simple weighted estimators rely on the correct specification of the missing data process, whereas the augmented weighted estimators are doubly robust. Similar to the first setting, the estimators with correctly specified $\widehat{\pi}$, SWE-$\widehat{\pi}(G)$ and AWE-$\widehat{\pi}(G)$-$\widehat{f}_{Z|X}$, have comparable efficiency as SWE-π. The augmented estimator with misspecified $Z|X$, AWE-$\widehat{\pi}(G)$-$\widehat{f}_{Z|X_1}$, is consistent and has slightly larger SE than its competitors. To further explore the performances of the SWE and AWE, we compare the estimated TPR and FPR using different approaches in Table 3. The same conclusion is drawn. In particular, SWE-$\widehat{\pi}(\delta)$ yields substantial bias in $\text{TPR}_{\mathbb{I}}$, $\text{TPR}_{\mathbb{C}}$ and FPR, while the augmented estimators show small bias for all these quantities.

Additional simulation results with varying sample sizes, censoring rates, missing proportions, and a nonconstant baseline hazard rate can be found in Web Appendix F.

In summary, we find that the AWE is consistent provided one of the models for π and $Z|X$ is correctly specified. In addition, AWE achieves similar or higher efficiency than SWE-π, and its standard errors and confidence intervals can be well approximated using the resampling methods. These observations hold for both ROC and TPR, FPR estimation. Based on our simulation results, we recommend the use of the augmented estimators in practice.

6. Application to the Alzheimers Disease Neuroimaging Initiative Study

The Alzheimer's Disease Neuroimaging Initiative (ADNI) study is a research investigation designed to develop clinical, imaging, genetic, and biochemical biomarkers for the early detection and tracking of Alzheimer's disease (AD) (quoted from http://adni.loni.ucla.edu/). The study is supported by the NIH, private pharmaceutical companies, and nonprofit organizations. Enrollment target was 800 participants, including 400 subjects diagnosed with mild cognitive impairment (MCI), 200 subjects with early AD and 200 elderly control subjects. Participants were enrolled on a rolling basis, and were evaluated every 6 months. One of the major goals of

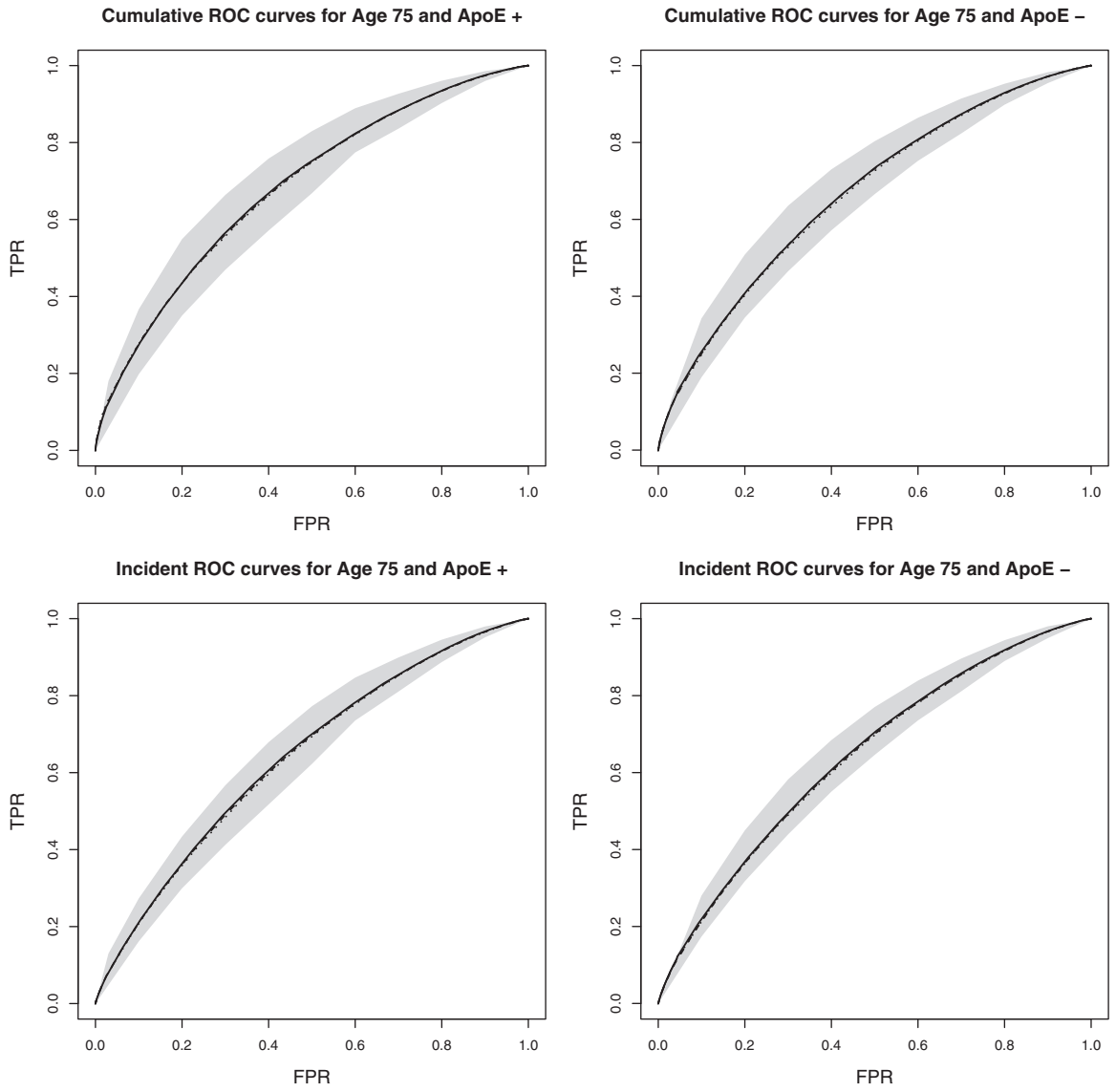

Figure 1. Time-dependent ROC curves for neuroimaging biomarkers in the ADNI study. The upper panels are cumulative ROC curves at t =24, for individuals with $X_1 = 75, X_2 = 1$ and $X_1 = 75, X_2 = 0$ respectively. The lower panels are incidence ROC curves at $t = 24$, for individuals with $X_1 = 75, X_2 = 1$ and $X_1 = 75, X_2 = 0$ respectively. Solid lines represent the fully augmented estimator, with 95% point-wise confidence interval in shaded areas. Dashed lines represent the simple weighted estimator. Dotted lines represent the complete-case estimator.

the ADNI study is to identify biomarkers that are associated with progression from MCI to AD. Sensitivity and specificity were considered important statistical techniques for assessing biomarkers in the disease progression.

We analyze the dataset for the 393 MCI patients, using onset of AD as the event outcome. The biomarkers include cognition, genetics, neuroimaging, and cerebrospinal fluid measures, which are subject to missing values. Patient demographics, such as age, gender, education and Apolipoprotein E (ApoE), are completely observed. To illustrate our approach, we evaluate the diagnostic accuracy of the neuroimaging biomarkers, while adjusting for age and ApoE. We consider two neuroimaging biomarkers: hippocampus volume and ventricular volume, because both hippocampus and ventricle are primary brain regions that modulate cognitive function. To avoid overestimation, we use a predefined rule (take the difference) to combine the two biomarkers after standardization. Using the previously introduced notations, Z_i is the composite score of the baseline neuroimaging biomarkers, X_{1i} is the baseline age, X_{2i} is the ApoE status, and T_i is the time to AD since enrollment. Among these 393 MCI patients, 118 had missing neuroimaging biomarkers, resulting in about 30% of missingness.

We fit logistic regression models to the selection indicator V_i. A model selection procedure is performed with T_i, δ_i, X_{1i}, X_{2i} and the quadratic and interaction terms of these vari-

Table 4
Estimates and SEs for time-dependent TPR and FPR in the ADNI study, evaluated at $t = 24$, $X_1 = 75$, and $X_2 = 0, 1$

	$X_1 = 75, X_2 = 0$			$X_1 = 75, X_2 = 1$		
Approach	$z = -0.3$	$z = 0.1$	$z = 0.5$	$z = -0.3$	$z = 0.1$	$z = 0.5$
Incident TPR						
CC	0.78 (0.04)	0.49 (0.06)	0.20 (0.04)	0.83 (0.03)	0.54 (0.05)	0.22 (0.03)
SWE-$\widehat{\pi}$	0.82 (0.03)	0.52 (0.04)	0.23 (0.04)	0.85 (0.03)	0.56 (0.05)	0.24 (0.04)
AWE-$\widehat{\pi}$-$\widehat{f}_{Z\|X}$	0.82 (0.03)	0.53 (0.04)	0.24 (0.04)	0.87 (0.03)	0.57 (0.05)	0.24 (0.04)
Cumulative TPR						
CC	0.81 (0.03)	0.53 (0.06)	0.22 (0.04)	0.85 (0.02)	0.62 (0.05)	0.26 (0.04)
SWE-$\widehat{\pi}$	0.84 (0.02)	0.56 (0.04)	0.26 (0.04)	0.87 (0.03)	0.63 (0.05)	0.29 (0.04)
AWE-$\widehat{\pi}$-$\widehat{f}_{Z\|X}$	0.84 (0.02)	0.56 (0.04)	0.26 (0.04)	0.87 (0.03)	0.64 (0.05)	0.30 (0.04)
FPR						
CC	0.66 (0.04)	0.31 (0.03)	0.11 (0.02)	0.67 (0.03)	0.35 (0.05)	0.11 (0.03)
SWE-$\widehat{\pi}$	0.69 (0.02)	0.34 (0.02)	0.12 (0.02)	0.69 (0.03)	0.36 (0.05)	0.12 (0.02)
AWE-$\widehat{\pi}$-$\widehat{f}_{Z\|X}$	0.69 (0.03)	0.34 (0.02)	0.12 (0.02)	0.70 (0.03)	0.38 (0.05)	0.12 (0.02)

ables as candidate predictors. The best model is selected using Akaike information criterion, which includes T_i, δ_i and their interaction as predictors. We then estimate the ROC curves using the simple weighted estimator, the augmented weighted estimator as well as the complete-case analysis, with $\widehat{\pi}$ estimated from the selected logistic regression model.

The upper panels of Figure 1 exhibit the estimated cumulative ROC curves evaluated at $t = 24$ months, for individuals of 75 years old with ApoE4 positive and ApoE4 negative respectively. The lower panels of Figure 1 present the corresponding incident ROC curves. It appears that the estimated ROC curves and the 95% pointwise confidence intervals (CIs) using three approaches are very close. For clarity of presentation, we only show the CIs of the augmented estimator. Though the estimated ROC curves are similar using all three approaches, the estimated TPR and FPR show some differences. Specifically, as shown in Table 4, the complete-case estimator yields lower TPR and FPR than the other two estimators. Because sensitivity (TPR) and specificity (1 − FPR) are the most clinically relevant quantities in AD research, it is important to find an estimator that is unbiased in these quantities. We advocate the use of the augmented weighted estimator, because it is more robust to model misspecification.

In the following, we summarize the analytical results obtained from the augmented estimator. The cumulative ROC curves show that the combined marker has moderate capacity for discriminating 75 years old MCI individuals who would experience AD in the next 24 months from those who would not. In particular, the estimated AUC is 0.69 (CI: 0.63–0.75) for the ApoE4 positive group, and 0.66 (CI: 0.61–0.70) for the ApoE4 negative group. For the incident ROC curves, the estimated AUC is 0.64 (CI: 0.60–0.68) for the ApoE4 positive group, and 0.63 (CI: 0.59–0.67) for the ApoE4 negative group. Figure 2 shows the AUC as a function of time using different estimators. The $\mathbb{C}/\mathbb{D}$ AUC is slightly increasing over time, suggesting that the combined marker has higher accuracy in predicting late onset of AD. The difference of $\mathbb{C}/\mathbb{D}$ AUC in the two ApoE groups shows the impact of ApoE4 on the classification accuracy of the biomarkers.

7. Discussion

Missing biomarker problem is commonly encountered in time-to-event data. Existing methods on estimating the time-dependent accuracy measures of biomarkers are mainly developed for complete data. In the presence of missing biomarkers,

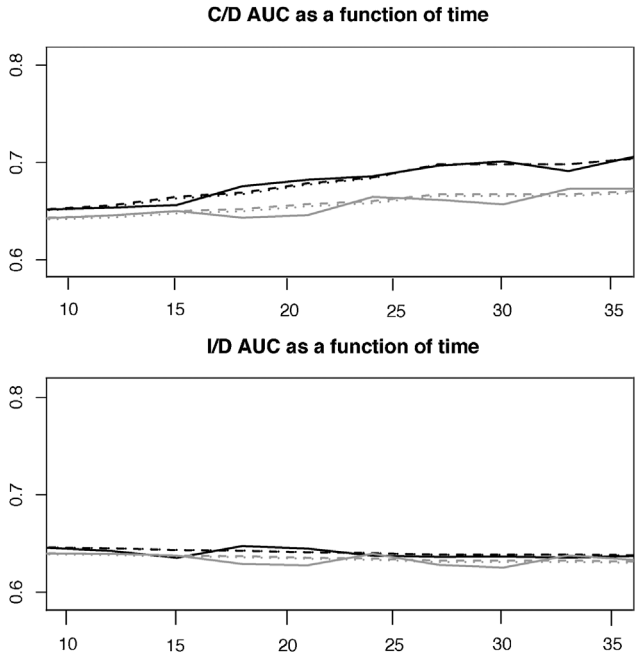

Figure 2. AUC as a function of time for neuroimaging biomarkers in the ADNI study. The upper panel shows the AUCs for the cumulative ROCs and the lower panel shows the AUCs for the incidence ROCs. For both panels, the black curves pertain to individuals with $X_1 = 75, X_2 = 1$ and the gray curves pertain to individuals with $X_1 = 75, X_2 = 0$. Solid lines represent the fully augmented estimator. Dashed lines represent the simple weighted estimator. Dotted lines represent the complete-case estimator.

the naive complete-case analysis may lead to inconsistent and inefficient estimation. Therefore, it is urgent to develop estimation procedures that account for the missingness effect. The proposed simple weighted estimators correct the bias by inversely weighting each completely observed subject by its selection probability, and they are shown to be consistent when the selection probability is correctly specified. Furthermore, we propose augmented weighted estimators which are robust against misspecification of the selection probability. Both theoretical and numerical results suggest that the augmented weighted estimator outperforms the complete-case analysis and the simple weighted estimator, because it remains consistent if either the selection probability or the missing data given the observed data is correctly specified, and it often has comparable or improved efficiency than the other estimators. We suggest the use of the augmented weighted estimators, especially when the selection probability is unknown.

In addition to studying biomarker accuracy at a given time point t, it is often of interest to evaluate the biomarker's overall predictive accuracy. Heagerty and Zheng (2005) proposed a global summary measure for the time-dependent ROC curve, which is defined as: $C = P(Z_j > Z_k | T_j < T_k)$. To incorporate covariate effect, we extend their definition to a covariate-specific summary measure: $C_x = P(Z_j > Z_k | T_j < T_k, X_j = X_k = x)$. C_x characterizes the probability that, among subjects with covariate values x, those who fail at an earlier time have larger marker values. To estimate this summary measure, we write it as $C_x = 2\int_t \mathrm{AUC}_{\mathbb{I}/\mathbb{D}}(t \mid x) f(t \mid x) S(t \mid x) dt$, where $\mathrm{AUC}_{\mathbb{I}/\mathbb{D}}$ can be estimated by numerical integration under the $\mathbb{I}/\mathbb{D}$ ROC curves, and $f(t \mid x)$, $S(t \mid x)$ can be estimated under both the location model and the proportional hazards model. We have established augmented estimators for each component, thus the resulting estimator for C_x also inherits the double robustness property.

There are several directions for future research. First, in this manuscript, we assume the covariates are fully observed. It would be of interest to extend our method to accommodate missingness in both biomarkers Z_i and covariates X_i, where X_i can be partitioned into fully observed covariates X_i^c and covariates subject to missingness X_i^m. Second, we have confined our attention to right censored survival data. In practice, it might be challenging for clinicians to identify exact time of disease onset, thus the survival outcomes might be subject to interval censoring. It is an important extension to study biomarker accuracy under both missingness in biomarkers and interval censoring in survival outcomes. Finally, the proposed ROC estimation approaches are built on the proportional hazards model. To relax the model assumption, one can consider more flexible models such as the semiparametric transformation model. Further investigation is warranted.

8. Supplementary Materials

Web Appendices, Tables referenced in Sections 3, 4, 5, and the R code implementing the new methods are available with this paper at the *Biometrics* website on Wiley Online Library.

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