ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

DOI: 10.5336/biostatic.2019-72402

Making Inference about a Biomarker by Using Information from Different Biomarkers in Time-Dependent ROC Estimation for Censored Data

Sansürlü Veriler için Zamana Bağlı ROC Tahmininde Farklı Biyobelirteçlerden Bilgi Kullanarak Biyobelirteç Hakkında Çıkarım Yapma

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ABSTRACT Objective: Time-dependent reciever operating characteristics (ROC) curves are statistical methods which can be used when the specified outcome is an event which can take place at any time after the diagnostic test has been measured and may be right censored. This work presents an approach for making inference related to the performance of prognostic biomarker which can be measured from smaller number of patients, by borrowing information from the other biomarker(s) which can be measured from larger number of patients for right censored survival data. **Material and Methods:** Simulation studies were performed to see the performance of the proposed modification. We evaluated estimators related to the time dependent ROC function and the area under the curve (AUC) in terms of efficiency and unbiasedness to see whether proposed modification provides benefit over the original method. **Results:** It is observed that proposed approach yielded smaller bias, mean square error and standard deviation values for most scenarios in the simulation studies. **Conclusion:** The proposed approach, which combines information from different samples with different biomarkers may be useful to make inference related to the biomarker of interest which is measured from sample with a smaller size.

Keywords: Biomarker; censored data; time dependent ROC curves

ÖZET Amaç: Zamana bağlı ROC eğrileri sonuç, tanı testinin ölçülmesinden sonra herhangi bir zamanda gerçekleşebilen ve sağdan sansürlü olay olarak tanımlandığında kullanılabilen istatistiksel yöntemlerdir. Bu çalışma, sağdan sansürlü sağkalım verileri için daha fazla sayıda hastadan ölçülebilen diğer biyobelirteçlerden bilgi alınarak az sayıda hasta için ölçülebilen prognostik biyobelirtecin performansı ile ilişkili çıkarım yapan bir yaklaşım sunmaktadır. **Gereç ve Yöntemler:** Önerilen modifikasyonun performansını görmek için simülasyon çalışmaları yapılmıştır. Önerilen yöntemin orijinal yönteme üstünlük sağlayıp sağlamadığını görmek için etkinlik ve yansızlık açısından eğri altında kalan alanla (AUC) ve zamana bağlı ROC fonksiyonuyla ilişkili tahmin ediciler değerlendirilmiştir. **Bulgular:** Önerilen yaklaşımın simülasyon çalışmalarındaki birçok senaryo için daha küçük yanlılık, hata kareler ortalaması ve standart sapma değerleri verdiği görülmüştür. **Sonuç:** Farklı biyobelirteçler ile farklı örneklemlerden elde edilen bilgiyi birleştiren önerilen yaklaşım, örneklemden daha küçük olan ilgilenilen biyobelirteçle ilgili çıkarım yapmak için yararlı olabilir.

Anahtar kelimeler: Biyobelirteç; sansürlü veri; zamana bağlı ROC eğrileri

Biomarkers are used in detection and diagnosis of a disease, provide information on the disease phase, and monitor its progression, to predict probable outcomes of a disease, to identify patients who are most likely to

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Peer review under responsibility of Turkiye Klinikleri Journal of Biostatistics.

Received: 15 Nov 2019 ***Received in revised form:*** 16 Dec 2019 ***Accepted:*** 30 Dec 2019 ***Available online:*** 06 Jan 2020

benefit from selected treatments and to guide clinical decision-making. Determining the biomarker's ability to accurately predict the probability of a specified outcome such as disease onset, disease progression or death is fundamental for their being used effectively in clinical practice. This encourages the development of new statistical methodologies to assess the relationship between biomarkers specific to a disease and the clinical outcomes.[1-7]

The diagnostic performance of a continuous biomarker X is often evaluated by receiver operating characteristics (ROC) curve analysis which displays the false positive rates (the probability that X be above given cut-off point for an healthy subject) versus the true positive rates (the probability that X be above given cut-off point for a diseased subject) for all possible cut-off points and the diagnostic accuracy is often summarized by the area under the ROC curve (AUC) which the statistical methods used to estimate these statistics need often large sample sizes.[8-12] In biomarker research, collecting large amounts of experimental data is crucial to process the data and draw conclusions. The studies conducted for evaluating the biomarkers can be expensive in terms of cost. Usually the power gained by a large sample size is being tried to be balanced against the cost of performing assays.[13] In addition, newly developed expensive biomarkers cannot be applied in most centers routinely to all patients due to financial constraints. For this reason, fewer patients can benefit from these newly developed biomarker.

Pooling and random sampling are two approaches commonly used by investigators to reduce overall cost. Due to high costs of evaluation the effectiveness of some biomarkers, several authors have proposed the pooling samples and statistical methods for ROC curve analysis when dealing with such data.[12,14-18] On the other hand many statistical approaches have been proposed to make inference about one population by combining information from other sources, especially when the sample size is small. Stein showed that precision could be "borrowed" from data drawn independently from populations other than the one which is inferential of interest.[19] Cox gave a general discussion for merging information from such data by using weighted means and pooling in the presence of over-dispersion.[20] Like the James-Stein estimator, Hu and Zidek suggested weighted likelihood (WL) estimator, which provides making inference on one sample by using the additional information from different populations.[21,22] Wang, Wang et al and Wang and Zidek proposed adaptive weights which were allowed to depend on data.[23,24] Plante has showed that WL can be derived from the entropy maximization principle using weighted empirical distribution function and he suggested minimum averaged mean squared error (MAMSE) weights.[25] Plante have used MAMSE weights for right censored data and proposed adaptively weighted Kaplan-Meier estimate, which borrows strength from different populations to make inference for just one population of interest.[26,27]

Models which are developed to predict patient survival using prognostic and predictive biomarkers are increasingly getting important in clinical research and practice. Various definitions and estimators of time-dependent ROC curves have been proposed which can be used when the specified outcome is an event which can take place at any time after the diagnostic test has been measured and may be right censored.[28] In their seminal work, Heagerty et al. defined cumulative sensitivity and dynamic specificity as time-dependent function at time point t as below:[29]

$$sens(t, c) = P(X > c \mid T \leq t) \tag{1}$$

$$spec(t, c) = P(X \leq c \mid T > t) \tag{2}$$

where T denotes the time from baseline to the occurrence of the disease or death, X be the continuous biomarker measured at baseline with the larger values are associated with higher probabilities of the event and c denotes the cut-off value. In this approach, let the sample size includes n independent and identically distributed subjects. So the i^{th} individual is considered as positive if $t_i \leq t$, and as negative if $t_i > t$ at time point t. When there is no censored data it is easy to calculate the estimators for these quantities. We have a complete information at time point t for the subjects who have experienced the event of interest before time t, or for the

subjects who haven't experienced the event yet and have a follow-up longer than t. The main complexity of the time-dependent ROC curve comes from those subjects who are censored before time point t.

Cumulative/dynamic, incident/static and incident/dynamic estimators for time-dependent sensitivity/specificity and related ROC curves were defined by Heagerty and Zheng and also discussed by Cai et al. and Pepe et al.[28,30,31] Etzioni et al. and Slate and Turnbull adopt an incident/static time dependent sensitivity/ specificity approach, in which cases are stratified according to the time at which the event occurs (incident) and controls are defined as those subjects who are event free through a fixed follow-up period.[32,33]

In the present paper we deal with the cumulative/dynamic type of the ROC curves. Heagerthy et al. proposed cumulative/dynamic versions of time-dependent estimation methods where i^{th} individual plays the role of control for times $t \leq t_i$, and then contributes as a case for times $t > t_i$.[29] They proposed two estimators which are based on traditional Kaplan-Meier survival function and based on bivariate distribution function provided by Akritas which uses nearest neighbor estimator.[34] Although the former gives good results when there is no dependence between the censoring time and biomarker, it does not guarantee monotonicity for sensitivity and specificity and can give values greater than 1. The second one needs a bandwidth since it uses a kernel function. Chambless and Diao also proposed two methods.[35] The first one estimates time-dependent ROC curves by using a recursive approach akin to the Kaplan-Meier method, again which does not guarantee the monotonicity. The second one uses Cox model to estimate conditional distribution of the survival time given the biomarker. Song and Zhou define the covariate specific time-dependent ROC curve using both the cumulative and the incident sensitivity.[36] Uno et al. and Hung and Chiang also have proposed estimators based on inverse probability of censoring weighting (IPCW).[37,38] Wolf et al. introduced a method for calculating sensitivity and specificity for censored data based on the Nelson-Aalen estimator and they used isotonic regression to achieve monotonicity for the ROC curve.[39] Blanche et al. proposed a conditional IPWC method which is the modified version of IPCW to obtain a nonparametric estimator robust to marker-dependent censoring.[40] They gave a detailed review of the time-dependent ROC curve estimators proposed in the literature and compare their properties. Li et al. and Martinez-Camblor et al. studied estimators where the missing status indicator is replaced by weights obtained from conditional survival functions.[41,42] Li et al. proposed a kernel weighting method to estimate cumulative/dynamic time-dependent sensitivity/specificity and related ROC curve nonparametrically.[41] They calculated a probability weight for being a case to those subjects who are censored before time point t, by proportioning the kernel-weighted Kaplan-Meier estimator for time t to follow-up time of the related subject. Again this method require a bandwidth parameter but the authors showed that their proposed methods was not sensitive to the bandwidth choice.[41] Martinez-Camblor et al. estimated cumulative/dynamic sensitivity/specificity by assigning a probability of belonging to the negative group to those subjects who are censored before time point t.[42] They proposed two methods to estimate this probability: the semi-parametric one which uses proportional hazard Cox regression model; and the non-parametric one using directly the Kaplan-Meier estimator. In the second one they noted that for the Kaplan-Meier method since X is a continuous variable, the probability was calculated, by proportioning the usual Kaplan-Meier estimator for time t to follow-up time of the related subject, for those subjects satisfying $X \leq x_i$. It has been shown that the proposed methods were monotone, ranges between 0 and 1, and also does not depend on any smoothing parameter.[42] Martinez-Camblor and Pardo-Fernandez used a bivariate kernel density estimator which accounts for censored observations in the sample and proposed smooth estimators of the cumulative/dynamic and incident/dynamic time-dependent ROC curves.[43]

In the present study we aimed to propose a method for making inference about a new prognostic biomarker that cannot be applied, to large samples, by using information obtained from other biomarkers routinely used in the same situation, measured in different samples with bigger sizes. As an example, consider the case where a newly investigated biomarker is evaluated for its performance in predicting prognosis in a group of patients of a certain disease or condition. Due to certain limitations, this biomarker can only be applied to a particular

portion of these patients. Thus, when measuring this biomarker from this small sample, another biomarker used routinely can be measured from the remaining patients, and the information to be obtained can be used to assess the performance of the new biomarker. Or a similar situation may be encountered when the biomarkers used to evaluate the prognosis of a disease may be change over time with advances in technology. In this case, in the evaluation of the performance of the newly developed biomarker the data of the samples that were obtained from the old biomarker/biomarkers used in a similar situation can be utilized. We evaluated the performance of the proposed method by simulation studies.

MATERIAL AND METHODS

METHODS

We will consider the case where there are k samples, there are n_i independent and identically distributed subjects in the i^{th} sample and the first sample is the sample of interest. Let T_{ij} denote the time from baseline to occurrence of disease or event of interest and C_{ij} denote the censoring time, $Y_{ij} = \min(T_{ij}, C_{ij})$ denote the observed time and $\delta_{ij} = I(T_{ij} \leq C_{ij})$ is the indicator function for $j = 1, 2, \ldots, n_i$ and $i = 1, \ldots, k$. So our observed data for the j^{th} subject in the i^{th} independent random sample with a marker value X_{ij} can be presented by $Z_{ij} = \{Y_{ij}, \delta_{ij}, X_{ij}\}$.

Let w_{1j} be the conditional probability of experiencing the event of interest at time t for the j^{th} subject in the 1^{st} sample, given z_{1j}:[42,43]

$$w_{1j} = P(t_{1j} \leq t | Z_{ij}) = 1 - \frac{S_T(t|X_{1j})}{S_T(Y_{1j}|X_{1j})} \quad (5)$$

Here we used the 0/1 symmetric nearest-neighbor kernel estimator of Akritas to calculate conditional survival functions with a span of $0.25(n^{-1/3})$ as suggested by Heagerthy et al.[29,35] Let $\hat{S}_1^*(t|X_{1j})$ be the Kaplan-Meier estimate of the first sample calculated using the subjects which are found in the neighborhood of X_{1j}. We calculated 1000 equally spaced quartile points for the biomarkers in each groups. Let the quartile order corresponding to the X_{1j} value be in the s^{th} order. For the markers found in the other groups, let the marker value corresponding to the same order be $X_{ij}(s)$ ($i \neq 1$; $s = 1, \ldots, 1000$). Then the Kaplan-Meier estimate for the i^{th} sample, calculated using the subjects which are found in the neighborhood of the $X_{ij}(s)$ can be presented by $\hat{S}_i^*(t|\, x_{ij(s)})$ where $i \neq 1$. We used MAMSE weights to combine the estimations of conditional survival functions of k ($i = 1, \ldots, k$) groups to obtain the estimates of $S_T(t|X_{1j})$ and $S_T(Y_{1j}|X_{1j})$ in equation-5 as follows:[28,44]

$$\hat{S}_T(t|X_{1j}) = \hat{S}_1^*(t|X_{1j}).\gamma_1 + \hat{S}_2^*(t|\, X_{2j(s)}).\gamma_2 + \ldots + \hat{S}_k^*(t|\, X_{kj(s)}).\gamma_k \quad (6)$$

$$\hat{S}_T(Y_{1j}|X_{1j}) = \hat{S}_1^*(Y_{1j}|X_{1j}).\gamma_1 + \hat{S}_2^*(Y_{1j}|\, X_{2j(s)}).\gamma_2 + \ldots + \hat{S}_k^*(Y_{1j}|\, X_{kj(s)}).\gamma_k \quad (7)$$

where γ_i ($i = 1, \ldots, k$) are the MAMSE weights which are calculated from the sub-samples of each sample, consisted of the survival data of the subjects which are found in the neighborhood of $X_{ij(s)}$ ($i = 1, \ldots, k$).

The empirical estimates of sensitivity and specificity can be written based on the $\hat{w}_{1j}$. Since we assume without loss of generality that a higher value of biomarker is associated with higher risk of disease, it is expected to be negative correlation between the real survival time and the biomarker value. The correlation between the observed survival time and biomarker, $cor(X, Y)$, would change depending on the $cor(X, C)$ and $cor(X, T)$. It is observed that the values of sensitivity and specificity are affected from the correlation between the observed survival time and the biomarker. We shifted the values of X so as to make a correction on sensitivity and specificity of the first population associated with $cor(X, Y)$ which can be given in Equation-8 and 9,

$$\widehat{Sens}_c = \frac{\sum_{j=1}^{n_1} \hat{w}_{1j} I(x_{1j} - \widehat{cor}(X,Y) * \varepsilon) > c}{\sum_{j=1}^{n_1} \hat{w}_{1j}} \quad (8)$$

$$\widehat{Spec}_c = \frac{\sum_{j=1}^{n_1} (1-\hat{w}_{1j}) I(x_{1j} + \widehat{cor}(X,Y) * \varepsilon) \leq c}{\sum_{j=1}^{n_1} (1-\hat{w}_{1j})} \quad (9)$$

,where $I(.)$ is the indicator function, $cor(X,Y)$ is the Pearson product-moment correlation coefficient and we take ε=0.00025.

SIMULATION

We conducted simulation studies to see whether proposed pooling modification provides benefit over the method which just uses the information from the sample of interest. For that propose we compared our proposed modification with the original method proposed by Li et al using tdROC() function from the R package tdROC with default arguments.[41,44] We choose this method because it guarantees monotonicity, it takes into consideration the structure which the censoring is dependent on the biomarker and the authors showed in the simulation studies that it is insensitive to bandwidth selection and gave better performance than the other time-dependent ROC curve methods in most cases. Simulations were performed for two groups (k = 2). Continuous biomarkers, survival times and censoring times were generated from multivariate normal distribution $[X, \log(T), \log(C)] \sim N(\mu_{3\times1}, \Sigma_{3\times3})$ for the both samples, where, a variety of sample sizes (n_1–n_2: 50-100, 100-200, 250-500, 500-1000; where n_1 is the sample size for the our sample of interest and n_2 is the sample size for the second sample which the different biomarker has been measured and we use to borrow information). Since in practice we evaluate the diagnostic performance of a biomarker on a specific disease, we simulated $\log(T)$ and $\log(C)$ from the same distribution in both groups $\{\mu_{logT1} = \mu_{logT2} = 0, \sigma_{logT1} = \sigma_{logT2} = 1; \mu_{logC1} = \mu_{logC2} = \mu_C, \sigma_{logC1} = \sigma_{logC2} = 1\}$. We took μ_C=–0.5 and μ_C=1 which yields censoring rates approximately 64% and 24% respectively. Since the biomarkers in Group 1 and in Group 2 are different, we simulated with different distribution parameters for each biomarker. Three different situations were taken into account for the biomarker values, where the difference between the measurements units of the two biomarkers were small, moderate and large. For a small difference we simulated with the parameters $\{\mu_{X1} = 0, \sigma_{X1} = 1; \mu_{X2} = 4, \sigma_{X2} = 0.8\}$, for a moderate difference we simulated with the parameters $\{\mu_{X1} = 0, \sigma_{X1} = 1; \mu_{X2} = 8, \sigma_{X2} = 1.6\}$ and for a large difference we simulated with the parameters $\{\mu_{X1} = 0, \sigma_{X1} = 1; \mu_{X2} = 16, \sigma_{X2} = 3.2\}$, by taking the coefficient of variation 5% for the second biomarker. We take $\rho_1 = -0.6$ to represent the correlation between the X and $\log(T)$; $\rho_2 = -0.4$, 0 or 0.4 to represent the correlation between the X and $\log(C)$, and $\rho_1\rho_2$ to represent the correlation between the $\log(T)$ and $\log(C)$ which gives conditional independence between $\log(T)$ and $\log(C)$ given X. ROC curve estimations were computed for $\log(t) = 0.8$. We performed 1000 repetitions for each simulation scenario and the results were given as percent bias and mean square error (MSE) for the AUC, for the sensitivity when the specificity is 0.9, 0.85 and 0.8 which are presented as $ROC(0.1)$, $ROC(0.15)$, $ROC(0.2)$ respectively, and for the specificity when the sensitivity is 0.9, 0.85 and 0.8 which hare presented as $ROC^{-1}(0.9)$, $ROC^{-1}(0.85)$, $ROC^{-1}(0.8)$ respectively. All the ROC curves are evaluated over a grid of 1000 equally spaced points on the specificity axis and all the AUC values are estimated by numerical integration. Simulations were performed in R version 3.4.2].[45]

RESULTS

In the tables we gave the results for the original method proposed by Li et al. in the single biomarker (SB) column.[41] The original method was implemented on the biomarker value measured from the first group which

is the biomarker of interest. The biomarker value measured from the first group (the biomarker of interest) was generated with $\mu_{X1}=0$, $\sigma_{X1}=1$ in all simulation scenarios. We gave the results of the combination method for three situations. In the first situation the second biomarker values measured from the second group were generated with $\mu_{X2}=4$, $\sigma_{X2}=0.8$, where the difference between the measurements units of the two biomarkers were small. In the second situation, the second biomarker values measured from the in the second group were generated with $\mu_{X2}=8$, $\sigma_{X2}=2.56$, where the difference between the measurements units of the two biomarkers were moderate. In the third situation, the second biomarker values measured from the second group were generated with $\mu_{X2}=16$, $\sigma_{X2}=19.23$, where the difference between the measurement units of the two biomarkers were large.

Tables 1-3 display the percent bias and MSE, for the estimate of $AUC(t)$, sensitivity at three points and specificity at three points at $\log(t)=0.8$, for the data generated with a 64% censoring rate and $\rho_1=-0.6$ at different sample sizes.

The simulation results for $\rho_2=0$ was given in Table 1. For $\rho_2=0$, percent bias and MSE values for all situations decreased with the increase in the sample sizes. Smaller percent bias and MSE values were obtained for the modified method in most cases except the $ROC^{-1}(0.9)$ and the $ROC^{-1}(0.8)$. For the AUC values, all the bias and MSE values were smaller than that of the original method. The difference between the proposed modification and the original method get smaller as the sample size get larger for AUC (t), $ROC(0.1)$, $ROC^{-1}(0.9)$ and $ROC(0.2)$ estimates and reached to minimum when the sample size was 500 for the sample of interest. Also it is observed that, the difference was the same for biomarkers derived from the different parameter values in the second group (Table 1).

TABLE 1: Percent bias and MSE values for AUC, sensitivity, specificity for $\mu_C=-0.5$ and $\rho_2=0$.

		Percent Bias				MSE			
	n_1-n_2	$\mu_{X_2}=4$	$\mu_{X_2}=8$	$\mu_{X_2}=16$	SB	$\mu_{X_2}=4$	$\mu_{X_2}=8$	$\mu_{X_2}=16$	SB
$AUC(t)$ (0.780)	50-100	-1.1869	-1.1869	-1.1865	-1.1919	0.008770	0.008770	0.008770	0.008771
	100-200	-1.1166	-1.1169	-1.1164	-1.1206	0.004251	0.004251	0.004252	0.004252
	250-500	-0.5617	-0.5617	-0.5610	-0.5639	0.001851	0.001851	0.001851	0.001852
	500-1000	-0.1741	-0.1731	-0.1733	-0.1742	0.000871	0.000871	0.000871	0.000872
ROC(0.1) (0.420)	50-100	-0.3655	-0.3657	-0.3646	-0.3735	0.035531	0.035530	0.035531	0.035532
	100-200	-3.0615	-3.0612	-3.0602	-3.0754	0.022335	0.022338	0.022338	0.022337
	250-500	-2.1473	-2.1483	-2.1448	-2.1507	0.010161	0.010158	0.010162	0.010164
	500-1000	-0.4282	-0.4286	-0.4286	-0.4279	0.004608	0.004606	0.004606	0.004607
$ROC^{-1}(0.9)$ (0.431)	50-100	4.6069	4.6005	4.5869	4.5906	0.039273	0.039271	0.039283	0.039267
	100-200	0.5522	0.5736	0.5733	0.5410	0.024451	0.024476	0.024463	0.024471
	250-500	0.7588	0.7724	0.7941	0.7763	0.011156	0.011164	0.011179	0.011175
	500-1000	0.5533	0.5559	0.5573	0.5490	0.005608	0.005602	0.005606	0.005608
$ROC(0.15)$ (0.517)	50-100	-2.5110	-2.5111	-2.5101	-2.5205	0.038376	0.038376	0.038376	0.038377
	100-200	-2.9892	-2.9912	-2.9884	-2.9906	0.022769	0.022768	0.022772	0.022774
	250-500	-1.7500	-1.7512	-1.7486	-1.7530	0.009611	0.009609	0.009610	0.009611
	500-1000	-0.2693	-0.2670	-0.2687	-0.2731	0.004692	0.004693	0.004692	0.004694
$ROC^{-1}(0.85)$ (0.525)	50-100	0.0154	0.0135	0.0143	0.0052	0.035813	0.035812	0.035810	0.035813
	100-200	-1.2012	-1.2029	-1.2007	-1.2124	0.022777	0.022770	0.022780	0.022783
	250-500	-0.6281	-0.6220	-0.6252	-0.6298	0.009655	0.009644	0.009641	0.009644
	500-1000	-0.0711	-0.0623	-0.0646	-0.0656	0.004974	0.004974	0.004972	0.004979
$ROC(0.20)$ (0.594)	50-100	-3.4945	-3.4942	-3.4933	-3.5067	0.038215	0.038215	0.038214	0.038220
	100-200	-2.2890	-2.2901	-2.2893	-2.2997	0.020242	0.020242	0.020244	0.020238
	250-500	-1.3722	-1.3717	-1.3691	-1.3734	0.009037	0.009032	0.009034	0.009035
	500-1000	-0.2330	-0.2294	-0.2311	-0.2325	0.004440	0.004442	0.004442	0.004440
$ROC^{-1}(0.8)$ (0.599)	50-100	-1.8475	-1.8473	-1.8467	-1.8377	0.032797	0.032797	0.032796	0.032791
	100-200	-1.9241	-1.9169	-1.9161	-1.9336	0.019880	0.019873	0.019874	0.019893
	250-500	-0.8786	-0.8702	-0.8747	-0.8739	0.008590	0.008585	0.008581	0.008591
	500-1000	-0.1651	-0.1628	-0.1575	-0.1607	0.004496	0.004504	0.004502	0.004504

The simulation results for $\rho_2 = -0.4$ was given in Table 2. For $\rho_2 = -0.4$, all the estimators were underestimated in all situations with both methods. But smaller percent bias and MSE values were obtained for the modified method in almost everywhere. The difference between the proposed modification and the original method get smaller as the sample size gets larger for almost all cases except $ROC^{-1}(0.9)$ and $ROC(0.2)$ estimates. This difference was the same for biomarkers derived from the different parameter values in the second group (Table 2).

The simulation results for $\rho_2 = 0.4$, which was the correlation between the X and $\log(C)$, was given in Table 3. For $\rho_2 = 0.4$ smaller percent bias and MSE values were obtained for the modified method in most cases regardless of the difference between the measurement units of the two biomarkers. The performance of both methods increased with the increase in the sample sizes (Table 3).

Table 4-6 displays the percent bias and MSE, for the estimate of AUC (t) , sensitivity at three points and specificity at three points at $\log(t) = 0.8$, for the data generated with a 24% censoring rate and $\rho_1 = -0.6$ at different sample sizes. Table 4, 5 and 6 display the results for $\rho_2 = 0$, $\rho_2 = -0.4$ and $\rho_2 = 0.4$ respectively. The

TABLE 2: Percent bias and MSE values for AUC, sensitivity, specificity for $\mu_C = -0.5$ and $\rho_2 = -0.4$.

		Percent Bias				MSE			
	$n_1 - n_2$	μ_{X_2}=4	μ_{X_2}=8	μ_{X_2}=16	SB	μ_{X_2}=4	μ_{X_2}=8	μ_{X_2}=16	SB
$AUC(t)$ (0.780)	50-100	-5.2634	-5.2634	-5.2727	0.011321	0.011321	0.011321	0.011330	0.011330
	100-200	-3.8129	-3.8130	-3.8212	0.005619	0.005620	0.005619	0.005623	0.005623
	250-500	-2.2648	-2.2647	-2.2711	0.00232	0.00232	0.002320	0.00232	0.00232
	500-1000	-1.2116	-1.2124	-1.2169	0.001070	0.001070	0.001070	0.001070	0.001070
ROC(0.1) (0.420)	50-100	-15.7891	-15.7892	-15.8120	0.046709	0.046709	0.046710	0.046711	0.046711
	100-200	-14.8793	-14.8796	-14.9139	0.032232	0.032233	0.032232	0.032250	0.032250
	250-500	-10.2092	-10.2097	-10.2379	0.015320	0.015318	0.015319	0.015336	0.015336
	500-1000	-5.9796	-5.9805	-6.0092	0.007913	0.007913	0.007913	0.007918	0.007918
$ROC^{-1}(0.9)$ (0.431)	50-100	-3.7925	-3.7908	-3.8323	0.034354	0.034354	0.034359	0.034385	0.034385
	100-200	-3.3816	-3.3468	-3.3750	0.019020	0.019046	0.019041	0.019030	0.019030
	250-500	-2.0132	-2.0075	-2.0228	0.008811	0.008812	0.008814	0.008821	0.008821
	500-1000	-0.6449	-0.6334	-0.6572	0.004549	0.004544	0.004550	0.004561	0.004561
$ROC(0.15)$ (0.517)	50-100	-15.9171	-15.9173	-15.9333	0.052416	0.052417	0.052416	0.052439	0.052439
	100-200	-13.2714	-13.2725	-13.2958	0.032129	0.032130	0.032129	0.032135	0.032135
	250-500	-8.3900	-8.3905	-8.4087	0.015172	0.015171	0.015171	0.015184	0.015184
	500-1000	-4.5582	-4.5591	-4.5720	0.007053	0.007054	0.007053	0.007055	0.007055
$ROC^{-1}(0.85)$ (0.525)	50-100	-6.8639	-6.8661	-6.9022	0.034618	0.034620	0.034631	0.034629	0.034629
	100-200	-5.0769	-5.0786	-5.0963	0.018982	0.018988	0.018986	0.018996	0.018996
	250-500	-2.2599	-2.2615	-2.2805	0.008308	0.008305	0.008305	0.008311	0.008311
	500-1000	-1.0157	-1.0308	-1.0339	0.004381	0.004380	0.004384	0.004385	0.004385
$ROC(0.20)$ (0.594)	50-100	-14.3317	-14.3322	-14.3467	0.051516	0.051516	0.051516	0.051534	0.051534
	100-200	-11.1606	-11.1537	-11.1677	0.029846	0.029847	0.029839	0.029849	0.029849
	250-500	-6.7316	-6.7321	-6.7541	0.013147	0.013146	0.013145	0.013153	0.013153
	500-1000	-3.1787	-3.1785	-3.1979	0.005819	0.005819	0.005818	0.005831	0.005831
$ROC^{-1}(0.8)$ (0.599)	50-100	-7.8688	-7.8338	-7.8936	0.033902	0.033903	0.033862	0.033925	0.033925
	100-200	-5.6822	-5.7017	-5.7114	0.019252	0.019243	0.019289	0.019266	0.019266
	250-500	-3.1799	-3.1801	-3.1933	0.007868	0.007874	0.007883	0.007890	0.007890
	500-1000	-1.3738	-1.3733	-1.3850	0.004246	0.004247	0.004247	0.004252	0.004252

TABLE 3: Percent bias and MSE values for AUC, sensitivity, specificity for μ_C = –0.5 and ρ_2 = 0.4.

		Percent Bias				MSE			
	n_1-n_2	μ_{X_2}=4	μ_{X_2}=8	μ_{X_2}=16	SB	μ_{X_2}=4	μ_{X_2}=8	μ_{X_2}=16	SB
$AUC(t)$ (0.780)	50-100	1.4130	1.4133	1.4131	1.4137	0.008322	0.008322	0.008321	0.008321
	100-200	0.7211	0.7214	0.7210	0.7217	0.004214	0.004214	0.004214	0.004214
	250-500	0.1404	0.1414	0.1412	0.1409	0.002036	0.002036	0.002036	0.002036
	500-1000	0.0054	0.0056	0.0056	0.0050	0.001049	0.001049	0.001049	0.001050
ROC(0.1) (0.420)	50-100	7.8905	7.8894	7.8904	7.8984	0.034915	0.034914	0.034915	0.034916
	100-200	3.5831	3.5875	3.5851	3.5942	0.019984	0.019984	0.019987	0.019971
	250-500	1.1670	1.1693	1.1715	1.1752	0.008071	0.008070	0.008071	0.008073
	500-1000	0.7137	0.7105	0.7081	0.7186	0.004013	0.004011	0.004013	0.004016
ROC^{-1}(0.9) (0.431)	50-100	12.6441	12.6447	12.6089	12.5995	0.045093	0.045092	0.044992	0.045012
	100-200	5.7889	5.7893	5.7890	5.7901	0.029499	0.029500	0.029500	0.029500
	250-500	1.8174	1.8213	1.8019	1.8194	0.016537	0.016534	0.016529	0.016539
	500-1000	-0.3249	-0.3227	-0.3342	-0.3289	0.008788	0.008786	0.008780	0.008791
ROC(0.15) (0.517)	50-100	4.9123	4.9135	4.9123	4.9149	0.035612	0.035612	0.035612	0.035615
	100-200	2.4535	2.4553	2.4537	2.4562	0.018490	0.018494	0.018495	0.018494
	250-500	0.7448	0.7495	0.7484	0.7484	0.008109	0.008108	0.008107	0.008113
	500-1000	0.5076	0.5068	0.5070	0.5113	0.004052	0.004050	0.004051	0.004054
ROC^{-1}(0.85) (0.525)	50-100	5.5945	5.5955	5.5947	5.5864	0.040949	0.040948	0.040948	0.040973
	100-200	1.9386	1.9373	1.9390	1.9436	0.026012	0.026012	0.026013	0.026022
	250-500	0.4837	0.4888	0.4832	0.4770	0.013028	0.013029	0.013028	0.013026
	500-1000	-0.4904	-0.4907	-0.4902	-0.4958	0.006840	0.006836	0.006840	0.006842
ROC(0.20) (0.594)	50-100	3.1741	3.1760	3.1744	3.1715	0.033539	0.033540	0.033538	0.033543
	100-200	1.8882	1.8894	1.8882	1.8939	0.018540	0.018540	0.018540	0.018538
	250-500	0.6576	0.6606	0.6595	0.6588	0.008004	0.008007	0.008010	0.008013
	500-1000	0.4057	0.4071	0.4071	0.4066	0.003906	0.003906	0.003906	0.003910
ROC^{-1}(0.8) (0.599)	50-100	2.5722	2.5736	2.5725	2.5731	0.035207	0.035204	0.035206	0.035201
	100-200	1.0110	1.0064	1.0059	1.0119	0.021791	0.021796	0.021797	0.021795
	250-500	-0.1859	-0.1832	-0.1836	-0.1880	0.010784	0.010784	0.010785	0.010787
	500-1000	-0.3502	-0.3428	-0.3405	-0.3454	0.005485	0.005477	0.005478	0.005483

TABLE 4: Percent bias and MSE values for AUC, sensitivity, specificity for μ_C = 1 and ρ_2 = 0.

		Percent Bias				MSE			
	n_1-n_2	μ_{X_2}=4	μ_{X_2}=8	μ_{X_2}=16	SB	μ_{X_2}=4	μ_{X_2}=8	μ_{X_2}=16	SB
$AUC(t)$ (0.780)	50-100	-0.9308	-0.9309	-0.9314	-0.9364	0.004624	0.004625	0.004624	0.004628
	100-200	-0.2743	-0.2742	-0.2741	-0.2787	0.002125	0.002125	0.002125	0.002127
	250-500	-0.1699	-0.1704	-0.1694	-0.1752	0.000895	0.000895	0.000895	0.000897
	500-1000	-0.0535	-0.0540	-0.0543	-0.0605	0.000453	0.000453	0.000453	0.000454
ROC(0.1) (0.420)	50-100	-1.3765	-1.3772	-1.3783	-1.3804	0.02260	0.02260	0.02259	0.02260
	100-200	-0.5747	-0.5730	-0.5774	-0.5794	0.01297	0.01298	0.01297	0.01299
	250-500	-0.2886	-0.2883	-0.2874	-0.3089	0.00571	0.00571	0.00571	0.00571
	500-1000	-0.1886	-0.1880	-0.1890	-0.2110	0.002692	0.002692	0.002693	0.002695
ROC^{-1}(0.9) (0.431)	50-100	0.3804	0.3745	0.3169	0.3521	0.02282	0.02291	0.02293	0.02274
	100-200	1.3318	1.3345	1.3393	1.2745	0.01184	0.01187	0.01186	0.01181
	250-500	0.6788	0.6658	0.6677	0.6614	0.00534	0.00535	0.00534	0.00535
	500-1000	0.5373	0.5319	0.5374	0.5216	0.00289	0.00288	0.00289	0.00289

(continue)

(continued)

TABLE 4: Percent bias and MSE values for AUC, sensitivity, specificity for μ_C = 1 and ρ_2 = 0.

		Percent Bias				MSE			
	n_1-n_2	μ_{X_2}=4	μ_{X_2}=8	μ_{X_2}=16	SB	μ_{X_2}=4	μ_{X_2}=8	μ_{X_2}=16	SB
ROC(0.15) (0.517)	50-100	-2.4409	-2.4418	-2.4423	-2.4530	0.02272	0.02272	0.02271	0.02272
	100-200	-0.8024	-0.8016	-0.8038	-0.8113	0.01215	0.01215	0.01215	0.01216
	250-500	-0.2295	-0.2297	-0.2287	-0.2475	0.00519	0.00520	0.00520	0.00519
	500-1000	0.0059	0.0057	0.0045	-0.0262	0.00262	0.00263	0.00263	0.00262
ROC^{-1}(0.85) (0.525)	50-100	-0.4043	-0.4347	-0.3931	-0.4677	0.021827	0.021870	0.021781	0.021736
	100-200	0.5208	0.5366	0.4853	0.4844	0.010952	0.010936	0.010976	0.010966
	250-500	0.0636	0.0666	0.0798	0.0486	0.004935	0.004931	0.004936	0.004946
	500-1000	0.3090	0.3099	0.3140	0.2949	0.002754	0.002753	0.002757	0.002761
ROC(0.20) (0.594)	50-100	-2.7875	-2.7894	-2.7908	-2.8019	0.021241	0.021243	0.021238	0.021248
	100-200	-0.6096	-0.6071	-0.6108	-0.6141	0.011093	0.011091	0.011092	0.011095
	250-500	-0.5156	-0.5159	-0.5148	-0.5278	0.004657	0.004657	0.004658	0.004660
	500-1000	-0.0731	-0.0749	-0.0747	-0.0895	0.002334	0.002334	0.002335	0.002331
ROC^{-1}(0.8) (0.599)	50-100	-1.4258	-1.4308	-1.4394	-1.4510	0.020341	0.020336	0.020360	0.020343
	100-200	-0.2795	-0.2725	-0.2822	-0.2946	0.010027	0.009980	0.009985	0.010002
	250-500	-0.1532	-0.1555	-0.1490	-0.1672	0.004437	0.004441	0.004440	0.004445
	500-1000	0.0719	0.0681	0.0684	0.0527	0.002372	0.002369	0.002374	0.002376

TABLE 5: Percent bias and MSE values for AUC, sensitivity, specificity for μ_C = 1 and ρ_2 = −0.4.

		Percent Bias				MSE			
	n_1-n_2	μ_{X_2}=4	μ_{X_2}=8	μ_{X_2}=16	SB	μ_{X_2}=4	μ_{X_2}=8	μ_{X_2}=16	SB
$AUC(t)$ (0.780)	50-100	-1.0320	-1.0323	-1.0328	-1.0413	0.004772	0.004773	0.004772	0.004774
	100-200	-0.3709	-0.3706	-0.3713	-0.3791	0.002251	0.002251	0.002250	0.002252
	250-500	-0.1616	-0.1609	-0.1612	-0.1705	0.000923	0.000923	0.000923	0.000924
	500-1000	-0.0676	-0.0679	-0.0678	-0.0773	0.000475	0.000475	0.000475	0.000476
ROC(0.1) (0.420)	50-100	-1.6536	-1.6534	-1.6551	-1.7100	0.025091	0.025091	0.025089	0.025106
	100-200	-0.7344	-0.7338	-0.7357	-0.7803	0.013389	0.013388	0.013385	0.013374
	250-500	-0.6283	-0.6280	-0.6283	-0.6829	0.006121	0.006121	0.006121	0.006124
	500-1000	-0.4073	-0.4081	-0.4080	-0.4283	0.003050	0.003050	0.003050	0.003049
ROC^{-1}(0.9) (0.431)	50-100	0.3409	0.3848	0.2895	0.3245	0.021861	0.021869	0.021846	0.021808
	100-200	1.2837	1.2398	1.2367	1.2301	0.012149	0.012141	0.012127	0.012139
	250-500	0.5886	0.6013	0.5890	0.5682	0.005316	0.005317	0.005316	0.005319
	500-1000	0.4948	0.4952	0.4982	0.4631	0.002839	0.002843	0.002839	0.002840
ROC(0.15) (0.517)	50-100	-3.0243	-3.0236	-3.0251	-3.0473	0.024011	0.024010	0.024007	0.024013
	100-200	-1.4197	-1.4188	-1.4205	-1.4467	0.013076	0.013074	0.013072	0.013079
	250-500	-0.2271	-0.2264	-0.2267	-0.2583	0.005656	0.005655	0.005655	0.005658
	500-1000	-0.2749	-0.2759	-0.2756	-0.2998	0.002827	0.002828	0.002828	0.002827
ROC^{-1}(0.85) (0.525)	50-100	-0.7726	-0.7733	-0.7599	-0.8218	0.020653	0.020669	0.020686	0.020676
	100-200	0.6084	0.5928	0.5914	0.5800	0.011361	0.011354	0.011374	0.011344
	250-500	0.5516	0.5504	0.5516	0.5266	0.004612	0.004607	0.004610	0.004605
	500-1000	0.4628	0.4611	0.4617	0.4331	0.002546	0.002545	0.002546	0.002543
ROC(0.20) (0.594)	50-100	-3.1257	-3.1262	-3.1272	-3.1358	0.023012	0.023012	0.023010	0.023046
	100-200	-1.1441	-1.1428	-1.1455	-1.1523	0.011668	0.011668	0.011664	0.011650
	250-500	-0.4634	-0.4628	-0.4640	-0.4855	0.004768	0.004766	0.004768	0.004768
	500-1000	-0.1365	-0.1368	-0.1368	-0.1602	0.002544	0.002544	0.002545	0.002546
ROC^{-1}(0.8) (0.599)	50-100	-1.2295	-1.2188	-1.2275	-1.2487	0.018861	0.018867	0.018861	0.018854
	100-200	-0.3038	-0.3060	-0.3089	-0.3246	0.010057	0.010069	0.010055	0.010067
	250-500	-0.2985	-0.2954	-0.2968	-0.3128	0.004103	0.004101	0.004100	0.004102
	500-1000	0.0668	0.0669	0.0678	0.0519	0.002332	0.002331	0.002332	0.002330

TABLE 6: Percent bias and MSE values for AUC, sensitivity, specificity for $\mu_C = 1$ and $\rho_2 = 0.4$.

		Percent Bias				MSE			
	$n_1 - n_2$	μ_{X_2}=4	μ_{X_2}=8	μ_{X_2}=16	SB	μ_{X_2}=4	μ_{X_2}=8	μ_{X_2}=16	SB
$AUC(t)$ (0.780)	50-100	-0.7169	-0.7165	-0.7161	-0.7217	0.004763	0.004762	0.004762	0.004765
	100-200	-0.2976	-0.2973	-0.2985	-0.3010	0.002213	0.002214	0.002214	0.002215
	250-500	-0.1691	-0.1687	-0.1685	-0.1712	0.000892	0.000893	0.000893	0.000894
	500-1000	-0.1008	-0.1013	-0.1021	-0.1053	0.000457	0.000457	0.000457	0.000458
ROC(0.1) (0.420)	50-100	0.2628	0.2632	0.2641	0.2559	0.021596	0.021594	0.021592	0.021596
	100-200	-0.0097	-0.0119	-0.0126	-0.0208	0.012704	0.012704	0.012703	0.012702
	250-500	-0.1494	-0.1521	-0.1502	-0.1649	0.005254	0.005255	0.005253	0.005256
	500-1000	-0.0426	-0.0443	-0.0435	-0.0563	0.002494	0.002494	0.002494	0.002495
$ROC^{-1}(0.9)$ (0.431)	50-100	0.1690	0.0966	0.0987	0.0921	0.024265	0.024280	0.024268	0.024202
	100-200	1.0216	0.9939	0.9777	1.0459	0.013293	0.013331	0.013323	0.013301
	250-500	0.5499	0.5385	0.5341	0.5562	0.005874	0.005882	0.005873	0.005884
	500-1000	0.0045	0.0131	0.0046	-0.0036	0.003015	0.003012	0.003015	0.003025
$ROC(0.15)$ (0.517)	50-100	-0.9013	-0.9014	-0.9007	-0.9121	0.022101	0.022099	0.022097	0.022092
	100-200	-0.5873	-0.5862	-0.5870	-0.5892	0.011457	0.011455	0.011455	0.011452
	250-500	-0.1657	-0.1665	-0.1627	-0.1702	0.004986	0.004986	0.004984	0.004988
	500-1000	0.0111	0.0085	0.0105	-0.0026	0.002501	0.002500	0.002502	0.002503
$ROC^{-1}(0.85)$ (0.525)	50-100	-0.5910	-0.5876	-0.5389	-0.6340	0.022442	0.022448	0.022427	0.022371
	100-200	-0.0006	-0.0069	0.0128	-0.0237	0.011555	0.011556	0.011537	0.011546
	250-500	-0.0276	-0.0224	-0.0296	-0.0258	0.005027	0.005035	0.005025	0.005035
	500-1000	0.0386	0.0335	0.0273	0.0166	0.002763	0.002765	0.002764	0.002772
$ROC(0.20)$ (0.594)	50-100	-1.5945	-1.5939	-1.5921	-1.6028	0.020500	0.020501	0.020502	0.020510
	100-200	-0.8599	-0.8581	-0.8609	-0.8594	0.010779	0.010779	0.010781	0.010780
	250-500	-0.2663	-0.2662	-0.2652	-0.2730	0.004465	0.004465	0.004465	0.004464
	500-1000	-0.0852	-0.0867	-0.0859	-0.0939	0.002324	0.002323	0.002324	0.002327
$ROC^{-1}(0.8)$ (0.599)	50-100	-1.2631	-1.2100	-1.1911	-1.2629	0.020372	0.020333	0.020377	0.020320
	100-200	-0.4368	-0.4296	-0.4403	-0.4260	0.010302	0.010307	0.010300	0.010297
	250-500	-0.2863	-0.2694	-0.2890	-0.2888	0.004571	0.004567	0.004576	0.004583
	500-1000	-0.2892	-0.2985	-0.2944	-0.2974	0.002405	0.002414	0.002409	0.002414

results for the $\rho_2 = 0$ and the $\rho_2 = -0.4$ were similar and smaller percent bias and MSE values were obtained for the modified method in most cases except the $ROC^{-1}(0.9)$ and the $ROC^{-1}(0.85)$. Percent bias and MSE of the $AUC(t)$ values were smaller for the combination method in all situations.

DISCUSSION

In this article, we introduce an approach which provides to make inference related to the diagnostic performance of a biomarker from population of interest, by pooling data from other sources which different biomarkers were measured, when the event of interest is right-censored. The simulation study demonstrates that the proposed approach provided an improvement in the performance of estimating the ROC curve.

The novel biomarkers may not be used in all medical centers since they are more expensive. Therefore fewer

patients can benefit from those markers. We consider the situations where there are additional populations from different medical centers or data from other studies for ROC curve estimation in the presence of right-censored data. We used MAMSE weights proposed by Plante et al. to combine the nearest-neighbor kernel weighted Kaplan-Meier functions calculated from the sub-samples we created based on the neighborhood of the biomarker values.[26] When the performance of this method has been compared with the classical method proposed by Li et al. via simulation studies, it is seen that the combination yielded smaller MSE and bias values in most cases.[41] The performance of the modified method was not affected by the difference between the measurements units of the biomarkers. Percent bias and MSE values did not changed for small, moderate and large difference between the measurements units of the biomarkers. This is an expected results since we used the quartiles to provide a matching between the two biomarker values by taking into account the order. We used biomarker values to obtain a subsample for calculating the conditional survival functions in both groups.

As expected, it is seen in most cases that performance of both methods increased as the sample size increased. The difference between the proposed modification and the original method gets smaller as the sample size gets larger and reached to minimum when the sample size was 500. The results show that it is not plausible to pool data when the sample size of the sample of interest is as large as 500. However despite that, bias and MSE values of the proposed method remained smaller than that of the original method's in most cases.

We follow the methodology proposed by Li et al. since the authors showed that the time-dependent ROC analysis method proposed by them demonstrated notable better performance compared the other methods in both dependent and independent censoring settings.[41] But it is possible that the other time-dependent ROC approaches can be used to estimate sensitivity and specificity values from the populations.

CONCLUSION

Specifically, we have proposed a pooling method for constructing time-dependent ROC curves related to target sample, borrowing information from additional sample where a different biomarker has been measured from more individuals, while our biomarker of interest is measured on a sample consisting of fewer units. The modified method gave smaller MSE and bias values, except when the sample size was 500 where there was no difference between the two methods. Percent bias and MSE values for the proposed combination method were not affected by the change in measurements units of the biomarkers. Although the simulation results which we are given in this study are promising, in the future studies theoretical properties of the presented methodology should be studied. Also the studies on the performance of the proposed modification should be investigated when the number of biomarkers is greater than two.

Source of Finance

This study was supported by Uludag University Scientific Research Project committee (KUAP(T)-2016/19).

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Deniz Sığırlı;* ***Design:*** *Deniz Sığırlı;* ***Control/Supervision:*** *Deniz Sığırlı, Fatma Ezgi Can;* ***Data Collection and/or Processing:*** *Deniz Sığırlı, Fatma Ezgi Can;* ***Analysis and/or Interpretation:*** *Deniz Sığırlı, Fatma Ezgi Can;* ***Literature Review:*** *Deniz Sığırlı;* ***Writing The Article:*** *Deniz Sığırlı, Fatma Ezgi Can;* ***Critical Review:*** *Deniz Sığırlı, Fatma Ezgi Can;* ***References and Fundings:*** *Deniz Sığırlı, Fatma Ezgi Can;* ***Materials:*** *Deniz Sığırlı, Fatma Ezgi Can.*

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