Journal of Statistical Planning and Inference 156 (2015) 90–102

Contents lists available at ScienceDirect

Journal of Statistical Planning and Inference

journal homepage: www.elsevier.com/locate/jspi

Time-dependent diagnostic accuracy analysis with censored outcome and censored predictor

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ARTICLE INFO

Article history:
Received 20 April 2012
Received in revised form 14 May 2014
Accepted 18 August 2014
Available online 27 August 2014

Keywords:
Area under the ROC curve
Bivariate survival functions
Bootstrap
Empirical processes
Time-dependent ROC analysis

ABSTRACT

We consider a unified approach for estimating time-dependent diagnostic accuracy measures, including time-dependent sensitivity, specificity, positive predictive value, negative predictive value, receiver operating characteristic (ROC) curve, area under the ROC curve (AUC) and integrated AUC across time. In particular, our estimation method incorporates the double censoring setting, i.e. a censored outcome and a censored marker. Our unified approach greatly broadens the application of time-dependent diagnostic measures and allows for comparison between event-type predictors and/or completely observed continuous markers. More specifically, we express these time-dependent diagnostic accuracy measures in terms of bivariate and univariate survival functions. Hence they can be estimated by simply plugging in the Kaplan–Meier estimator for univariate survival functions and the Dabrowska estimator for the bivariate survival function. Asymptotic properties for our proposed estimators and bootstrap validity are established by using empirical processes techniques. Our simulation studies show that our proposed estimators and test procedures perform well for samples of moderate size. We apply our methods to an econometric example as well as a diabetic study.

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1. Introduction

Quantifying the classification and prediction accuracy of biomarkers for time-dependent diagnostic outcomes has interested statistical researchers in the past decade. Heagerty et al. (2000) proposed a statistical framework for time-dependent Receiver Operating Characteristic (ROC) analysis and pointed out that traditional accuracy studies for dichotomous outcomes could be extended and adapted to survival outcomes by properly modifying the definitions of key building components of the ROC curve. Besides borrowing from existing methodology for this new field of application, investigators were also making technical advancements to rectify the involved difficulties such as numerically handling incompleteness of survival data and establishing large sample properties of the estimators. Among many other works, Heagerty and Zheng (2005) considered constructing predictive accuracy measures for survival outcomes from fitted Cox regression models; Cai et al. (2006) evaluated the sensitivity and the specificity of biomarkers for censored event times by using a semiparametric model; Song

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http://dx.doi.org/10.1016/j.jspi.2014.08.002
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and Zhou (2008) considered a covariate-specific ROC curve with a survival outcome; Li and Ma (2011) developed an ROC analysis procedure for diverse censoring patterns; Cai and Zheng (2011) considered the inference procedure of marker accuracy under nested case-control studies.

Existing methods for time-dependent ROC analysis all have necessary procedures to deal with censored outcomes. They differ in their implementation complexity and estimation efficiency, but share the common feature that the continuous marker has been considered fully observable in the sample (Cai et al., 2011). In this paper, we are interested in studying a more general situation where both the marker and the outcome are censored. Examples of a censored marker can be a marker that is subject to a detection limit, or a marker of previous history of episodes that may have too many to recall, or a short-term event time as a marker for a long-term event. Diagnostic accuracy analysis with both the censored marker and the censored outcome has not been considered until recently by Parast et al. (2011) and Parast et al. (2012). They focused on predicting long-term survival by incorporating a short-term event time along with a discrete baseline biomarker (Parast et al., 2011) or with one or more continuous time-independent covariates (Parast et al., 2012). Their estimation procedures were constructed based on inverse-probability-weighting which requires the estimation of survival function of random censoring.

We consider a more general definition of censored biomarkers including those non-event type of variables. For example, in an economic dataset the years of education for any subjects with the college degree or above were coded as 16. The year of education here is not an event. However, those with more than 16 years of education were censored at 16. In this case the survival function of censoring may not be well estimated, hence the methods considered by Parast et al. (2011) and Parast et al. (2012) are not directly applicable. Moreover, the outcome may not be an event time, either. In the economic example, the outcome is wage level which is censored at $80,000. In this manuscript, we adopt the extended definitions of sensitivity, specificity, positive and negative predictive values, and the outcome-specific ROC for a right-censored outcome (Heagerty et al., 2000), and propose estimation procedures that can handle different types of censored markers. Observing that there is a close relationship between the bivariate distribution of the marker and the outcome, and the diagnostic accuracy measures, we propose inference procedures for the censored marker and the censored outcome by borrowing some existing methods from the literature on bivariate survival data. Our construction automatically provides solutions for uncensored marker accuracy as well as for censored continuous marker, and therefore unifies time-dependent ROC analysis. Some numerical studies suggest that our estimators of the accuracy measures have good practical performance as expected, since we are using some well-studied estimators for the univariate distributions and bivariate joint distribution of the marker and the outcome.

An inherent feature associated with a censored marker is that the ROC curve may not be complete, if the largest observed marker value is censored. Partial area under the ROC curve (PAUC) is often used for a restricted range of specificity (Thompson and Zucchini, 1989; Pepe et al., 2003). In our work we will use the scaled PAUC (Walter, 2005). The remaining paper is organized as follows. In Section 2, we present the estimation methods and inference procedures for the diagnostic accuracy measures. In Section 3, we include the asymptotic properties of the estimators and the bootstrap validity of the estimators, justified by using empirical processes theory. The succinct argument via functional space enables us to conclude weak convergence of the stochastic processes under consideration without referring to complicated Martingale constructions. In Section 4, simulations are included to assess the finite-sample performance of our procedure. Two examples are included to illustrate our methods in Section 5. Section 6 concludes with a discussion.

2. Methods

2.1. A general setting

Existing classification measures for binary outcomes were extended to incorporate the more general survival time outcomes by dichotomizing the continuous event time into two disease states at any given time point of interest (Heagerty et al., 2000). Let $T \in \mathcal{T}$ be the time to a definitive event where $\mathcal{T} \subset \mathbb{R}^+$. Note that the outcome does not have to be an event time. However, to be consistent with the literature on time-dependent diagnostic analysis, in the following we refer to T as the failure time. We denote the continuous marker to be $Y \in \mathcal{Y} \subset \mathbb{R}^+$. We assume T and Y are random variables defined on proper measurable spaces. Their distributions can be continuous, discrete or a mixture of continuous and discrete components.

As is the convention in diagnostic medicine, we assume that a high value of Y leads to a positive diagnosis. For a specific event time t, the time-dependent sensitivity and specificity for the marker Y at a decision threshold y can be defined as

$$\mathtt{se}_t(y) = P(Y \geq y | T \leq t), \tag{1}$$

$$\mathtt{sp}_t(y) = P(Y < y | T > t). \tag{2}$$

The event $T \leq t$ indicates the failure outcome occurs at or before t and corresponds to a disease-present status while $T > t$ corresponds to a disease-free status. The event $Y \geq y$ indicates that a positive diagnosis has been made and the subject is declared to be "diseased" while $Y < y$ indicates a negative diagnosis. We note that in the event where lower marker value Y corresponds to a positive diagnosis we can take a transformation of $\tilde{Y} = -Y$ and re-define (1) and (2) using $\tilde{Y}$. In this paper, we focus on the definitions (1) and (2) as they are more commonly accepted for uncensored diagnostic tests.

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