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GOODNESS–OF–FIT FOR THE COX MODEL FROM LEFT TRUNCATED AND RIGHT CENSORED DATA

Abstract. We propose a test for the proportional hazards (Cox) model which is oriented against wide classes of alternatives including monotone hazard ratios and crossings of survival functions and can be used when data are left truncated and right censored. The limit distribution of the test statistics is derived. The results are applied for statistical analysis of classical data considered by Stablein and Koutrouvelis [19], Klein and Moeschberger [12], Hosmer and Lemeshow [7], Hosmer, Lemeshow and May [8]

1. Introduction

The most known models for analysis of failure time regression data are the Cox and the accelerated failure time (AFT) and models. In reliability parametric versions of the AFT model are most applied. In survival analysis semiparametric Cox model is the most used.

General test statistics for the Cox model from right censored data were given by Cox [4], Moreau *et al* [15], Lin [14], Nagelkerke *et al* [16], Grambsch and Therneau [5], Quantin *et al* [17], Bagdonavičius *et al* [3].

We consider a test based on modified score functions obtained from left truncated and right censored data and oriented against wide classes of alternatives including monotone hazard ratios and crossings of survival functions.

2. Null hypothesis and the alternative

Let $S_z(t)$, $\lambda_z(t)$ and $\Lambda_z(t)$ be the survival, hazard rate and cumulative hazard functions under a m-dimensional explanatory variable z.

Key words and phrases. AFT model, Cox model, chemotherapy, crossings of survival functions, chemotherapy plus radiotherapy, chi-squared test, censored data, drug abuse, elderly, explanatory variable, gastric cancer patient, heroin addict, metadone treatment, left truncated data, modified score function, monotone hazard ratio, retirement community, right censored data.

The null hypothesis (the Cox model):

$$H_0: \ \lambda_z(t) = e^{\beta^T z} \lambda(t);$$

where $\lambda(t)$ is unknown baseline hazard function, the parameter β is m-dimensional.

Let us consider the following much wider model including the Cox model (Bagdonavičius and Nikulin [2]):

$$\lambda_z(t) = e^{\beta^T z} \{1 + e^{(\beta+\gamma)^T z} \Lambda(t)\}^{e^{-\gamma^T z} - 1} \lambda(t); \tag{1}$$

here

$$\Lambda(t) = \int_0^t \lambda(u) du.$$

The parameter γ is m-dimensional.

The Cox model is obtained taking $\gamma = 0$. So the alternative $\overline{H}$ is the model (1) with $\gamma \neq 0$.

Properties of the model (1): the ratios of the hazard rates increase, decrease or are constant, the hazard rates and the survival function do not intersect or intersect once in the interval $(0, \infty)$. So this model includes very wide class of alternatives to the Cox model.

3. The data and the modified score function

Let us consider left truncated and right censored failure time regression data:

$$(X_1, D_1, \delta_1, z_1), \cdots, (X_n, D_n, \delta_n, z_n),$$

where

$$X_i = T_i \wedge C_i, \quad \delta_i = \mathbf{1}_{\{T_i \leq C_i\}},$$

T_i being failure times, D_i – truncation times and C_i – censoring times.

Set

$$N_i(t) = \mathbf{1}_{\{X_i \leq t, \delta_i = 1\}}, \quad Y_i(t) = \mathbf{1}_{\{D_i < t \leq X_i\}},$$

$$N(t) = \sum_{i=1}^n N_i(t) \quad \text{and} \quad Y(t) = \sum_{i=1}^n Y_i(t);$$

$\mathbf{1}_A$ denotes the indicator of the event A.

Suppose that survival distributions of all n objects given x_i are absolutely continuous with the survival functions $S_i(t)$ and the hazard rates $\lambda_i(t)$.

Suppose that truncation and censoring are non informative (see Andersen *et al* [1], Huber *et al* [9–11], Solev [18], Turnbull [20]) and the multiplicative intensities model is verified: the compensators of the counting processes N_i with respect to the history of the observed processes are $\int Y_i \lambda_i du$.

In the parametric case with known λ the unknown finite-dimensional parameter θ contains the parameters β and γ. The parametric maximum likelihood (ML) estimator $\hat{\theta}$ of the parameter θ verifies the equation:

$$\dot{\ell}(\theta;\Lambda) = 0,$$

where $\dot{\ell}(\theta;\Lambda) = (\dot{\ell}_\beta(\theta;\Lambda), \dot{\ell}_\gamma(\theta;\Lambda))^T$ is the score function:

$$\dot{\ell}_\beta(\theta;\Lambda) = \sum_{i=1}^{n} \int_0^\infty \left(z_i + (e^{-\gamma^T z_i} - 1) \frac{z_i e^{(\beta+\gamma)^T z_i} \Lambda(t)}{1 + e^{(\beta+\gamma)^T z_i} \Lambda(t)} \right)$$

$$\times \{dN_i(t) - Y_i(t) e^{\beta^T z_i} \{1 + e^{(\beta+\gamma)^T z_i} \Lambda(t)\}^{e^{-\gamma^T z_i} - 1} \, d\Lambda(t)\},$$

$$\dot{\ell}_\gamma(\theta;\Lambda) = \sum_{i=1}^{n} \int_0^\infty \Bigg(- z_i e^{-\gamma^T z_i} \ln \left[1 + e^{(\beta+\gamma)^T z_i} \Lambda(t) \right]$$

$$+ \ (e^{-\gamma^T z_i} - 1) \frac{z_i e^{(\beta+\gamma)^T z_i} \Lambda(t)}{1 + e^{(\beta+\gamma)^T z_i} \Lambda(t)} \Bigg)$$

$$\times \{dN_i(t) - Y_i(t) e^{\beta^T z_i} \{1 + e^{(\beta+\gamma)^T z_i} \Lambda(t)\}^{e^{-\gamma^T z_i} - 1} \, d\Lambda(t)\}.$$

Let us consider the case of unknown baseline hazard λ.

The idea of test construction is very simple. In the expression of $\dot{\ell}(\theta;\Lambda)$ the parameter γ is replaced by 0, the parameter β – by it's estimator $\hat{\beta}$ obtained maximizing the partial likelihood function under the Cox model, i.e. $\hat{\beta}$ verifies the equation (see Andersen *et al* [1])

$$\dot{\tilde{\ell}}(\beta) = \sum_{i=1}^{n} \int_0^\infty \{z_i - E(t,\beta)\} dN_i(t) = 0,$$

where

$$E(t,\beta)=\frac{S^{(1)}(t,\beta)}{S^{(0)}(t,\beta)},\quad S^{(0)}(t,\beta)=\sum_{i=1}^{n}Y_i(t)e^{\beta^T z_i},$$
$$S^{(1)}(t,\beta)=\sum_{i=1}^{n}z_iY_i(t)e^{\beta^T z_i}.$$

The baseline cumulative intensity Λ is replaced by the Breslow estimator (see Andersen *et al* [1]):

$$\hat\Lambda(t)=\int_0^t\frac{dN(t)}{S^{(0)}(t,\hat\beta)}=\sum_{i=1}^{n}Y_i(t)e^{\hat\beta^T z_i}.$$

Note that

$$\dot\ell_\beta(\hat\beta,0;\hat\Lambda)=\sum_{i=1}^{n}\int_0^\infty z_i\{dN_i(t)-Y_i(t)e^{\hat\beta^T z_i}\,d\hat\Lambda(t)\}$$
$$=\sum_{i=1}^{n}\int_0^\infty\{z_i-E(t,\hat\beta)\}dN_i(t)=\dot{\tilde\ell}(\hat\beta)=0,$$

so we use only the statistic

$$U=\dot\ell_\gamma(\hat\beta,0;\hat\Lambda),$$

which can be written in the form $U=U(\infty)$, where

$$U(t)=-\sum_{i=1}^{n}\int_0^t z_i\ln\left[1+e^{\hat\beta^T z_i}\hat\Lambda(t)\right]\{dN_i(t)-Y_i(t)e^{\hat\beta^T z_i}\,d\hat\Lambda(t)\}$$
$$=\sum_{i=1}^{n}\int_0^\infty\{h(z_i,t,\hat\beta)-E_*(t,\hat\beta)\}dN_i(t);$$

here

$$h(z_i,t,\hat\beta)=-z_i\ln(1+e^{\hat\beta^T z_i}\hat\Lambda(t)),\quad E_*(t,\hat\beta)=\frac{S_*^{(1)}(t,\hat\beta)}{S^{(0)}(t,\hat\beta)},$$
$$S_*^{(1)}(t,\hat\beta)=-\sum_{i=1}^{n}z_iY_i(t)\,e^{\hat\beta^T z_i}\ln(1+e^{\hat\beta^T z_i}\hat\Lambda(t))$$

The statistic U is m-dimensional. The test is based on this modified score statistic and its asymptotic distribution.

4. Asymptotic distribution of the modified score statistic

Assumptions A:

a) $\sup\{t : Y(t) > 0\} \xrightarrow{P} \tau > 0$,

b) there exists a neighborhood Θ of β and the scalar, $m-$vector, and $m\times m$ matrix functions $s^{(0)}(v,b)$, $s^{(1)}(v,b)$ and $s^{(2)}(v,b)$ continuous in $b\in\Theta$, uniformly in $t\in[0,\tau]$ and bounded on $\Theta\times[0,\tau]$, such that $s^{(0)}(v,\beta) > 0$ for all $v\in[0,\tau]$,

$$\sup_{b\in\Theta, v\in[0,\tau]} \|\frac{1}{n}S^{(i)}(v,b) - s^{(i)}(v,b)\| \longrightarrow 0 \quad \text{as} \quad n\longrightarrow\infty,$$

c) $-\frac{\partial}{\partial b}s^{(0)}(t,b) = s^{(1)}(t,b)$ and $\frac{\partial^2}{\partial b^2}s^{(0)}(t,b) = s^{(2)}(t,b)$.

d) $\sup\limits_i ||z_i|| < \infty$.

e) $\Lambda(\tau) < \infty$.

f) the matrix

$$\Sigma(\beta) = -\int_0^\tau \left\{s^{(2)}(u,\beta) - e(u,\beta)(e(u,\beta))^T s^{(0)}(u,\beta)\right\} d\Lambda(u)$$

is positively definite; here $e(u,\beta) = s^{(1)}(u,\beta)/s^{(0)}(u,\beta)$.

Theorem 1. *Under Assumptions A*

$$T = n^{-1}U^T\widehat{D}^{-1}U \xrightarrow{\mathcal{D}} \chi^2(m),$$

where $\hat{D}$ is a consistent estimator of the limit covariance matrix of the random vector $n^{-1/2}U$ given in (2).

Proof. Under the Cox model

$$N_i(t) = \int_0^t Y_i(u)e^{\beta^T z_i}d\Lambda(u) + M_i(t),$$

where M_i are martingales with respect to the history generated by the data. So

$$U(t) = \sum_{i=1}^n \int_0^t \{h(z_i,u,\hat{\beta}) - E_*(u,\hat{\beta})\}Y_i(u)(e^{\beta^T z_i} - e^{\hat{\beta}^T z_i})d\Lambda(u)$$
$$+ \sum_{i=1}^n \int_0^t \{h(z_i,u,\hat{\beta}) - E_*(u,\hat{\beta})\}dM_i(u)$$

and

$$n^{-1/2}U(t) = -n^{-1}\sum_{i=1}^{n}\int_0^t \{h(z_i,u,\hat\beta)$$
$$- E_*(u,\hat\beta)\} z_i^T Y_i(u) e^{\hat\beta^T z_i} d\Lambda(u) n^{1/2}(\hat\beta - \beta)$$
$$+ n^{-1/2}\sum_{i=1}^{n}\int_0^t \{h(z_i,u,\hat\beta) - E_*(u,\hat\beta)\} dM_i(u) + o_P(1)$$

uniformly on $[0,\tau]$.

The first integral can be written in the form

$$n^{-1}\sum_{i=1}^{n}\int_0^t \{h(z_i,u,\hat\beta) - E_*(u,\hat\beta)\} z_i^T Y_i(u) e^{\hat\beta^T z_i} d\Lambda(u)$$
$$= n^{-1}\int_0^t V_*(u,\hat\beta) dN(u) + o_P(1);$$

here

$$V_*(u,\hat\beta) = \frac{S_*^{(2)}(u,\hat\beta)}{S^{(0)}(u,\hat\beta)} - E(u,\hat\beta) E_*^T(u,\hat\beta),$$
$$S_*^{(2)}(t,\hat\beta) = -\sum_{l=1}^{n} z_l^{\otimes 2} Y_l(t) e^{\hat\beta^T z_l} \ln(1 + e^{\hat\beta^T z_l}\hat\Lambda(t)).$$

Set

$$\hat\Sigma_*(t) = n^{-1}\int_0^t V_*(u,\hat\beta) dN(u), \quad \hat\Sigma_0(t) = n^{-1}\int_0^t V(u,\hat\beta) dN(u),$$

with

$$V(u,\hat\beta) = \frac{S^{(2)}(u,\hat\beta)}{S^{(0)}(u,\hat\beta)} - E^{\otimes 2}(u,\hat\beta), \quad S^{(2)}(t,\hat\beta) = \sum_{i=1}^{n} z_i^{\otimes 2} Y_i(t) e^{\hat\beta^T z_i};$$

$A^{\otimes 2}$ denotes AA^T for any matrix A.

The following development (see Andersen *et al* [1])

$$n^{1/2}(\hat\beta - \beta) = \hat\Sigma_0^{-1}(\tau)\sum_{i=1}^{n}\int_0^{\tau}\{z_i - E(u,\hat\beta)\}dM_i(u) + o_p(1)$$

implies:

$$n^{-1/2}U(t) = -\hat\Sigma_*(t)\hat\Sigma_0^{-1}(\tau)\,n^{-1/2}\sum_{i=1}^{n}\int_0^{t}\{z_i - E(u,\hat\beta)\}dM_i(u)$$
$$+\,n^{-1/2}\sum_{i=1}^{n}\int_0^{t}\{h(z_i,u,\hat\beta) - E_*(u,\hat\beta)\}dM_i(u) + o_p(1)$$

uniformly on $[0,\tau]$.

The predictable variation of the local martingale $n^{-1/2}U$ is

$$< n^{-1/2}U > (t)$$
$$= \hat\Sigma_*(t)\hat\Sigma_0^{-1}(\tau)\,n^{-1}\sum_{i=1}^{n}\int_0^{t}\{z_i - E(u,\hat\beta)\}^{\otimes 2}Y_i(u)e^{\beta^T z_i}d\Lambda(u)\hat\Sigma_0^{-1}(\tau)\hat\Sigma_*^T(t)$$
$$-\,\widehat\Sigma_*(t)\hat\Sigma_0^{-1}(\tau)\,n^{-1}\sum_{i=1}^{n}\int_0^{t}\{z_i - E(u,\hat\beta)\}\{h(z_i,u,\hat\beta)$$
$$-\,E_*(u,\hat\beta)\}^T Y_i(u)e^{\beta^T z_i}d\Lambda(u)$$
$$+\,n^{-1}\sum_{i=1}^{n}\int_0^{t}\{h(z_i,u,\hat\beta) - E_*(u,\hat\beta)\}\{z_i - E(u,\hat\beta)\}^T Y_i(u)e^{\beta^T z_i}d\Lambda(u)\hat\Sigma_0^{-1}\hat\Sigma_*^T$$
$$+\,n^{-1}\sum_{i=1}^{n}\int_0^{t}\{h(z_i,u,\hat\beta) - E_*(u,\hat\beta)\}^{\otimes 2}Y_i(u)e^{\beta^T z_i}d\Lambda(u) + o_P(1).$$

Note that

$$\sum_{i=1}^{n}\int_{0}^{t}\{z_i - E(u,\hat\beta)\}^{\otimes 2} Y_i(u) e^{\beta^T z_i} d\Lambda(u) = \hat\Sigma_0(t) + o_P(1),$$

$$n^{-1}\sum_{i=1}^{n}\int_{0}^{t}\{z_i - E(u,\hat\beta)\}\{h(z_i,u,\hat\beta) - E_*(u,\hat\beta)\}^T Y_i(u) e^{\beta^T z_i} d\Lambda(u)$$

$$= \hat\Sigma_*^T(t) + o_P(1),$$

$$n^{-1}\sum_{i=1}^{n}\int_{0}^{t}\{h(z_i,u,\hat\beta) - E_*(u,\hat\beta)\}^{\otimes 2} Y_i(u) e^{\beta^T z_i} d\Lambda(u) = \hat\Sigma_{**}(t) + o_P(1);$$

here

$$\widehat\Sigma_{**}(t) = n^{-1}\int_{0}^{t} V_{**}(u,\hat\beta) dN(u), \quad V_{**}(u,\hat\beta) = \frac{S_{**}^{(2)}(u,\hat\beta)}{S^{(0)}(u,\hat\beta)} - E_*^{\otimes 2}(u,\hat\beta),$$

$$S_{**}^{(2)}(u,\hat\beta) = -\sum_{i=1}^{n} z_i^{\otimes 2} Y_i(t) e^{\hat\beta^T z_i} \ln^2(1 + e^{\hat\beta^T z_i}\hat\Lambda(t)).$$

So the predictable variation is

$$< n^{-1/2} U > (t) = \widehat\Sigma_{**}(t) - \widehat\Sigma_*(t)\widehat\Sigma_0^{-1}(\tau)\widehat\Sigma_*^T(t) + o_P(1)$$

uniformly on $[0,\tau]$. Under conditions A the predictable variations converge in probability to non-random non-degenerated matrix and the Lindeberg conditions for the central limit theorem for martingales (see Andersen *et al* [1]) are verified.

Hence, the stochastic process $n^{-1/2}U(\cdot)$ converges in distribution to a zero mean Gaussian process on $[0,\tau]$, in particular

$$T = n^{-1} U^T \widehat D^{-1} U \xrightarrow{\mathcal{D}} \chi^2(m);$$

here

$$\hat D = \widehat\Sigma_{**}(\tau) - \widehat\Sigma_*(\tau)\widehat\Sigma_0^{-1}(\tau)\widehat\Sigma_*^T(\tau). \tag{2}$$

The proof is complete.

5. The test

The null hypothesis is rejected with the asymptotic significance level α if $T > \chi^2_\alpha(m)$; here $\chi^2_\alpha(m)$ is α critical value of the chi square distribution with m degrees of freedom. More about the construction of the chi-squared tests one can see, for example, in Greenwood and Nikulin [6].

6. Real data analysis

Example 1. Right censored data, one-dimensional dichotomous covariate; H_0 rejected. Stablein and Koutrouvelis [19] studied well known two-sample data of the Gastrointestinal Tumor Study Group concerning effects of chemotherapy ($z = 0$) and chemotherapy plus radiotherapy ($z = 1$) on the survival times of gastric cancer patients.

The number of patients $n = 90$. The estimate of parameter β under the Cox model is 0.10589. The proposed test statistic rejects the null hypothesis (the p-value is 0.000291, the value of the test statistic T is 13.1301), the Cox model is not appropriate. The result is natural because the Kaplan-Meier estimators of the survival functions of two patient groups intersect.

Example 2. Left truncated and right censored data, one-dimensional dichotomous covariate; H_0 not rejected. Klein and Moeschberger [12] analyse the data of death times of elderly residents ($z = 1$ – male, $z = 0$ – female) of a retirement community.

The number of individuals is 462 (97 males and 365 females). The data consists of age in months when member of the community died or left the center and the age when individuals entered the community. The life lengths are left truncated because an individual must survive to a sufficient age to enter the retirement community, all individuals who died earlier and not entered the center are considered left truncated. The estimate of parameter β is 0.31596 (due to missing values, the model is based on 458 of 462 objects).

The value of test statistic T is 1.43991, the p-value is 0.23015. The assumption of PH model is not rejected. The methods described by Kleinbaum and Klein [13] yield the same results: the plots of logarithm of cumulative hazard fuction looks reasonably parrallel, the test based on Schoenfeld residuals does not reject the Cox model assumption.

Example 3. Right censored data, 10 covariates; H_0 not rejected. To illustrate the application of the proposed test for models with more than one covariate we begin with right censored UIS data set given by Hosmer, Lemeshow and May [8].

UIS was a 5-year research project comprised of two concurrent randomized trials of residential treatment for drug abuse. The purpose of the study was to compare treatment programs of different planned durations designed to reduce drug abuse and to prevent high-risk HIV behavior. The UIS sought to determine whether alternative residential treatment approaches are variable in effectiveness and whether efficacy depends on planned program duration. The time variable is time to return to drug use (measured from admission). The individuals who did not returned to drug use are right censored. We use the model with 10 covariates (which support PH assumption) given by Hosmer, Lemeshow and May (2008). The covariates are: age (years); Beck depression score (becktota; 0 - 54); $NDRUGFP1 = ((NDRUGTX+1)/10)**(-1)$; $NDRUGFP2 = ((NDRUGTX+1)/10)**(-1)*log((NDRUGTX+1)/10)$; drug use history at admission (IVHX_3; 1 - recent, 0 - never or previous); race (0 - white, 1 - non-white); treatment randomization assigment (treat; 0 - short, 1 - Long); treatment site (site; 0 - A, 1 - B); interaction of age and treatment site (agexsite); interaction of race and treatment site (racexsite). The NDRUGTX denotes number of prior drug treatments (0 - 40). Due to missing data in covariates, the model is based on 575 of the 628 observations. The estimated coefficients β are given in table 1.

Table 1. The estimated coefficients.

Covariate	DF	Parameter Estimate	Standard Error	Chi-Square	Pr>ChiSq	Hazard Ratio
AGE	1	-0.04140	0.00991	17.4395	<.0001	0.959
becktota	1	0.00874	0.00497	3.0968	0.0784	1.009
NDRUGFP1	1	-0.57446	0.12519	21.0567	<.0001	0.563
NDRUGFP2	1	-0.21458	0.04859	19.5043	<.0001	0.807
IVHX_3	1	0.22775	0.10856	4.4009	0.0359	1.256
RACE	1	-0.46689	0.13476	12.0039	0.0005	0.627
TREAT	1	-0.24676	0.09434	6.8416	0.0089	0.781
SITE	1	-1.31699	0.53144	6.1412	0.0132	0.268
AGEXSITE	1	0.03240	0.01608	4.0596	0.0439	1.033
RACEXSITE	1	0.85028	0.24776	11.7778	0.0006	2.340

The value of the test statistic T is 13.3885, the p-value is 0.20276. The assumption of the Cox model is not rejected.

Example 4 (continuation of Example 3). Left truncated and right censored data, 10 covariates; H_0 not rejected. Suppose that in UIS following of subjects begins after they have completed the treatment program, but the drug free period (survival time) is defined as beginning at the time the subject entered the treatment program. In this case, only those subjects who completed the treatment program are included in the analysis, i.e. data are left truncated. Of the 628 subjects, 546 remained drug free for the duration of their treatment program. Due to missing data in covariates, the model is based on 504 of the 546 observations. The estimated coefficients are given in table 2.

Table 1. The estimated coefficients.

Covariate	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
AGE	1	-0.03319	0.01090	9.2714	0.0023	0.967
becktota	1	0.00455	0.00534	0.7246	0.3946	1.005
NDRUGFP1	1	-0.54606	0.14272	14.6401	0.0001	0.579
NDRUGFP2	1	-0.20381	0.05486	13.7995	0.0002	0.816
IVHX_3	1	0.21508	0.11852	3.2931	0.0696	1.240
RACE	1	-0.49450	0.14244	12.0514	0.0005	0.610
TREAT	1	0.13957	0.10501	1.7664	0.1838	1.150
SITE	1	-0.96014	0.55590	2.9831	0.0841	0.383
AGEXSITE	1	0.03985	0.01711	5.4253	0.0198	1.041
RACEXSITE	1	0.22033	0.28961	0.5788	0.4468	1.246

The value of test statistic T is 12.1233, the p-value is 0.2769217. The assumption of the Cox model is not rejected.

Example 5. Left truncated and right censored data, 4 covariates; H_0 rejected. The data given in Hosmer and Lemeshow (1998) are from The Worcester Heart Attack Study (WHAS). The main goal of this study is to describe trends over time in the incidence and survival rates following hospital admission for acute myocardial infarction (AMI). The time variable is total length of hospital stay (days between date of last follow up and hospital admission date). Censoring variable is the status of last follow-up (0 - alive, 1 - dead). Left truncation variable is the length of hospital stay (days between hospital discharge and hospital admission), subjects who died in the hospital are not included in the analysis. The covariates are sex (0 - male, 1 - female), left heart failure complications (CHF; 0 - no, 1 - yes), MI order (MIORD; 0 - first, 1 - recurrent), MI type (MITYPE; 1 - jei Q-wave, 0 - Not Q-wave). Due to missing data in covariates, the model is based on 392 observations. The estimated coefficients are given in table 3.

Table 3. The estimated coefficients.

Covariate	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
SEX	1	0.15246	0.16234	0.8820	0.3477	1.165
CHF	1	0.88820	0.15921	31.1244	<.0001	2.431
MI ORDER	1	0.42266	0.16237	6.7759	0.0092	1.526
MITYPE	1	-0.07956	0.16424	0.2346	0.6281	0.924

The value of the test statistic T is 12.66, the p-value is 0.01306. The assumption of the Cox model is rejected. The method based on Schoenfeld residuals yields the same result.

Example 6. Right censored data, 4 covariates; H_0 rejected. The data given in Kleinbaum and Klein (2005) are from study where two methadone treatment clinics for heroin addicts were compared to assess patient time remaining under methadone treatment.

The time variable is time (in days), until the person dropped out of the clinic or was censored. The data are right censored. The covariates are prison – indicates whether the patient had a prison record (coded 1) or nor (coded 0); dose – the continuous variable for the patient maximum methadone dose (mg/day); clinic – indicates which methadone treatment clinic the patient attended (coded 1 or 2).

The value of test statistic T is 13.016, the p-value is 0.0046. The assumption of the Cox model is rejected. The method based on Schoenfeld residuals yields the same result.

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