Confidence bands for the difference of two s rvival c rves nder proportional hazards model

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Technical Report 29

February 1998

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A stract.

A common approach to testing for differences between the survival rates of two therapies is to use a proportional hazards regression model which allows for an adjustment of the two survival functions for any imbalance in prognostic factors in the comparison. An alternative approach to this problem is to plot the difference between the two predicted survival functions with a confidence band that provides information about when these two treatments differ. Such a band will depend on the covariate values of a given patient. In this paper we show how to construct a confidence band for the difference of two survival functions based on the proportional hazards model. A simulation approach is used to generate the bands. This approach is used to compare the survival probabilities of chemotherapy and allogeneic bone marrow transplants for chronic leukemia.

1. Introduction

A common probl m ncount r d in biom dical applications is t comparison of t survival rat s of t o tr atm nts. In t is comparison on t sts t r t t o tr atm nts av t sam survival function or quival ntly t sam azard function ov r a giv n tim p riod. W n t r ar additional covariat s associat d it survival t n t is t sting is typically p rform d in t fram ork of a ox (1972) proportional azards mod l.

W n t t sting r sults indicat t at t o survival functions ar diff r nt, pati nts and p ysicians oft n ant to kno n "at at tim s ar t s t o tr atm nts diff r nt?". T is is p a (n al Tm 48 0 0 48 0 0 cm BT /F1 12 9 rf -3 0 0 -3 0 0 Tm (Pvalu nts's 4f(W9621DM(ranJ71.marrojm12)'167 TDm(o)T1)6jm-3765j999p1TDm(t)59nal n

plots and comparing t confid nc bands it t z ro lin summariz s o t diff r nc b t n t t o survival functions c ang it tim . R c ntly, Parz n *et a* (1997) us d t Kaplan-M i r (1958) stimators of t t o survival functions, $\hat{F}_1(\cdot)$ and $\hat{F}_2(\cdot)$, to stimat t diff r nc b t n t survival functions and t y propos d a simulation m t od to construct a confid nc band for t is diff r nc .

In many applications t r is a n d, n comparing t o tr atm nts, to mak adjust-

H r , β can b stimat d by maximizing t stratifi d ox partial log lik li ood function

$$C(\beta,t)=\sum_{i=1}^{2}\sum_{j=1}^{n_i}\int_0^t \beta' Z_{ij}\, d\ _{ij}(u)-\sum_{i=1}^{2}\int_0^t \log\left(\sum_{j=1}^{n_i} Y_{ij}(u)e^{\beta' Z_{ij}}\right) d\ ^{-}_{i}(u),$$

r $_{ij}(u)=I\{X_{ij}\le T_{ij}\le u, D_{ij}=1\}$, $^{-}_{i}=\sum_i$ $_{ij}$, and $Y_{ij}(u)=I\{X_{ij}\le u\le T_{ij}\}$ is t indicator of t r t jt individual is at risk at tim u and is in t it tr atm nt group. Not t at an individual is at risk only sinc is or r truncation tim , so t at t siz of t risk s t is initally incr asing and t n d cr as s.

To compar t o pr dict d survival curv s, stimat t conditional survival functions for t t o tr atm nts for a pati nt it a particular s t of covariat s z_0,

$$F_i(t;z_0)=P(T>t|z_0,\ \text{Tr atm nt } i)=e^{-\Lambda_i(t;z_0)},$$

r $\Lambda_i(t|z_0)=e^{\beta' z_0}\int_0^t \lambda_{i0}(u)du$. An stimator of t cumulativ bas lin azard rat for tr atm nt $i, i=1,2$ is giv n by Br slo 's (1975) stimator

$$\hat{\Lambda}_{i0}(t)=\int_0^t \frac{d\ ^{-}_{i}(u)}{\sum_{j=1}^{n_i} Y_{ij}(u)\ \exp(\hat{\beta}' Z_{ij})}.$$

For conv ni nc introduc t notations

$$\begin{aligned}
S_i^{(k)}(\beta,t) &= \frac{1}{n_i}\sum_{j=1}^{n_i} Y_{ij}(t) Z_{ij}^{\otimes k} e^{\beta' Z_{ij}},\\
_i(\beta,t) &= S_i^{(1)}(\beta,t)/S_i^{(0)}(\beta,t),\\
V_i(\beta,t) &= S_i^{(2)}(\beta,t)/S_i^{(0)}(\beta,t)-\ _i(\beta,t),\\
s_i^{(k)}(\beta,t) &= \{S_i^{(k)}(\beta,t)\},\\
e_i(\beta,t) &= s_i^{(1)}(\beta,t)/s_i^{(0)}(\beta,t),\\
v_i(\beta,t) &= s_i^{(2)}(\beta,t)/s_i^{(0)}(\beta,t)-e_i(\beta,t),
\end{aligned}$$

for $i=1,2$, and $k=\ ,1,2,$ r for a column v ctor a, $a^{\otimes 0}=1$, $a^{\otimes 1}=a$, and $a^{\otimes 2}=aa'$.

For simplicity of pr s ntation, assum $\{X_{ij},T_{ij},D_{ij},Z_{ij}\}$, $(j=1,\cdots,n_i)$ ar ind p nd nt and id ntically distribut d, $P(T_{ij}\ge X_{ij})>\ $, and $\{Z_{ij}\}$ is bound d. L ft-truncat d and rig t-c nsor d survival data as b n studi d xt nsiv ly. T mor g n ral conditions r quir d to obtain larg sampl r sults for t is typ of data can b found in Woodroof (1985), Lai and Ying (1991) and And rs n *et a* (1993). And rs n *et a* (1993) argu d t at t martingal c ntral limit t ory can b appli d to t l ft-truncat d data, so t at t asymptotic r sults bas d on rig t c nsor d data can b xt nd d to t l ft-truncat d and rig t c nsor d data. Also assum t at t o sampl s ar ind p nd nt. L t $n=n_1+n_2$. T n, if $n_i/n\longrightarrow p_i>\ $, for $i=1,2$, $\hat{\beta}$ is an consist nt stimat of β, and

$$\sqrt{n}(\hat{\beta}-\beta)\xrightarrow{\mathcal{D}}\ (\ ,\Sigma^{-1}),$$

r

$$\Sigma = \sum_{i=1}^{2} p_i \int_0^{\infty} v_i(\beta, t) s^{(0)}(\beta, t) \lambda_{i0}(t) dt,$$

ic is assum d to b positiv d finit and can b consist ntly stimat d by t obs rv d information matrix

$$\widehat{\Sigma} = {}^{1}$$

It follo s t at t varianc of $W(t; z_0$

T transplant co ort includ d 548 pati nts r c iving ydroxyur a or int rf ron pr - tr atm nt and a HLA-id ntical sibling bon marro transplant (BMT). All pati nts r r port d to t Int rnational Bon Marro Transplant R gistry (IBMTR). IBMTR is a voluntary orking group of ov r 3 transplant c nt rs orld id t at contribut data on t ir allog n ic bon marro transplants to a Statistical nt r at t M dical oll g of Wisconsin. Pati nts in t is arm r diagnos d b t n 1983 and 1991, and r b t n 15 and 55 y ars of ag . For d tail d pati nt c aract ristics s Gal *et a* c3

t at

Figur 1a s o s t stimat d survival curv s for a r c ntly diagnos d ($\geq$ 1988) old r ($\geq$ 35 y ars) mal pati nt it larg spl n siz ≥ 1 cm. Figur 1b s o s t stimat d diff r nc (BMT- mot rapy) b t n t t o survival curv s it a 95% point is confid nc int rval and 95% confid nc band for suc a pati nt. A similar plot for a pati nt diagnos d prior to 1988 it t sam c aract ristics is giv n in Figur 2.

T s confid nc band plots indicat d t at t c mot rapy tr atm nt as an arly survival advantag du , p r aps, to t toxicity of t bon marro transplant. T r is a significant lat survival advantag for transplant pati nt du to a lo r r laps rat . Also for t r c ntly tr at d cas s (Figur 1) BMT ad a survival advantag (95% confid nc band is >) starting at 5.5 y ars aft r diagnosis. T is is in contrast to pati nts tr at d prior to 1988 (Figur 2) r BMT start d to s o an advantag only aft r 8.29 y ars sinc diagnosis. T is may b du to t improv m nt of bon marro transplant t c niqu s ov r t y ars.

In t is xampl , t r ar 16 s ts of possibl covariat s valu s. T tim points sinc diagnosis r BMT starts to av a survival advantag ar pr s nt d in Tabl 2. T s tim points rang d from 5.5 y ars to 8.29 y ars sinc diagnosis d p nding on t giv n pati nt c aract ristics. By contrast to t comparison of t o Kaplan-M i r survival curv s, t is comparison of t o pr dict d survival curv s bas d on t ox mod l provid s mor information to bot t p ysicians and pati nts.

Table 2. Tim points t_0 sinc diagnosis (DX) in y ars r BMT starts to av survival advantag .

ovariat Valu s					
S x	Spl n Siz	Ag	Y ar of DX	C_α	t_0
M	< 1 cm	< 35	< 88	2.96	7.84
M	< 1 cm	< 35	≥ 88	2.97	5.97
M	≥ 1 cm	< 35	< 88	2.96	7.84
M	≥ 1 cm	< 35	≥ 88	2.99	5.88
M	< 1 cm	≥ 35	< 88	2.99	7.84
M	< 1 cm	≥ 35	≥ 88	2.95	5.88
M	≥ 1 cm	≥ 35	< 88	2.96	8.29
M	≥ 1 cm	≥ 35	≥ 88	2.94	5.5
F	< 1 cm	< 35	< 88	2.96	8.29
F	< 1 cm	< 35	≥ 88	2.93	5.97
F	≥ 1 cm	< 35	< 88	2.99	7.84
F	≥ 1 cm	< 35	≥ 88	2.98	6.24
F	< 1 cm	≥ 35	< 88	2.92	7.84
F	< 1 cm	≥ 35	≥ 88	2.89	5.97
F	≥ 1 cm	≥ 35	< 88	2.9	7.84
F	≥ 1 cm	≥ 35	≥ 88	2.92	5.88

. emar s

Plotting t confid nc band for t diff r nc of t o pr dict d survival functions provid s a valuabl d cision making tool for p ysicians and pati nts. T propos d simulation m t od is asy to program, and off rs a fl xibl ay to construct suc confid nc bands, particularly n t limiting distributions cannot b valuat d analytically. T propos d simulation m t od can b xt nd d to compar t diff r nc of t o survival curv s bas d on ot r mod ls, suc as Aal n's (1989) additiv mod l or ot r mor g n ral mod ls.

T stimat d critical valu , C_α, d p nds on t numb r of r alizations . It is important to kno at is t appropriat . In our xampl for an arly diagnos d young (< 35 yr) mal pati nt it small spl n siz (< 1 cm), t stimat d C'_αs r 3. 1, 2.98, 2.97, 3. 1, 2.97, and 3. 1 for $= 5$, 15 , 3 , 5 , 8 and 1 , r sp ctiv ly. It app ars t at t stimat of C_α is r sonably stabl aft r only 5 r plications.

Acknowledgments

T is r s arc as support d by Grant 2 RO1 A547 6- 6 from t National anc r Institut , and PO1- A-4 53 from t National anc r Institut , t National Institut of All rgy and Inf ctious Dis as s and T National H art, Lung and Blood Institut . Wsa nadnNdlalyi i