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Emory University and Georgia State University

Comparative Step-Up and Composite Tests for Selecting Prognostic Indicators Associated with Survival

A. A. BARTOLUCCI[1] and M. D. FRASER

1.0 Introduction

The exponential distribution has often been applied as that parametric probability model which describes patient survival, FEIGL and ZELEN (1965), ZELEN (1966). FEIGL and ZELEN (1965) discussed methods of parametrizing the exponential model so that concomitant variables could be included in the analysis. ZIPPIN and ARMITAGE (1966) discussed exponential survival analysis and covariate values in the light of incomplete or censored survival times. COX (1972) and PRENTICE (1973) carried on this work with emphasis on the exponential hazard function. BARTOLUCCI and DICKEY (1975) presented a BAYESian methodology for meeting the challenge of analyzing exponential survival data with censored observations and describe how their results can easily be generalized to include concomitant variables. KRALL et al. (1975) adopted a model with the inverse hazard expressed as a linear function of concomitant variables. A step-up procedure is then applied to select the most important concomitant variables.

This paper adopts a model similar to COX (1972). The exponential parametrization (see equation (2.2) below) has specific advantages in that convergence to final maximum likelihood solutions occurs without active boundary conditions in the computing algorithm. Such statements that expected survival times must be positive may be omitted. This condition is deducible from the present model which obviates the auxiliary constraint on the coefficients that KRALL et al. (1975) suggested to ensure meaningful solutions.

Concomitant variables are considered for inclusion by a forward selection procedure based on the likelihood function. Step-up tests are performed using the three test statistics of RAO (1948), WALD (1943) and the usual $-2 \log \Lambda$ used by KRALL et al. (1975), where Λ is the likelihood ratio criterion of NEYMAN and PEARSON (1928). Prompted by a statement by RAO (1973, p. 418), we further compare the relative merits of these three statistics in detecting departures from the null hypothesis on the basis of their respective powers.

To obtain a check for consistency in the selection of the most important prognostic indicators, the survival times are transformed to a log scale and beta

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weights are discussed as a basis for two additional forward selection procedures. Three composite step-up tests are proposed, each test using one of the RAO, WALD and $-2 \log \Lambda$ statistics. Again, we compare the relative merits of the test statistics in terms of power. For a discussion of beta weights see LAND (1969) and BLALOCK (1972).

An example using HODGKIN's disease patient data is given and all techniques introduced in the paper are applied and discussed.

2.0 The Exponential Model

We consider the case of independent sampling from an exponential distribution in which the log scale parameter (log hazard function) associated with each individual is expressed as a linear function of covariate values. Let $t_1, \ldots, t_{n_1}$ be a sample of n_1 independent failure times and $t_{n_1+1}, \ldots, t_n$ $(n=n_1+n_2)$ be a sample of n_2 independent times of patients still alive at time $t_j; j=n_1+1, \ldots, n$. (Note that merely for the sake of notational convenience we have subscripted the censored times or incomplete observations with the last n_2 subscripts. The censoring can in fact be arbitrary and the subscripting scheme is not meant to imply that censoring occurs only after the last observed failure time.) The density function associated with the i^{th} failure time is

$$f_i(t) = \begin{cases} \lambda_i \exp(-\lambda_i t) & t \geqq 0 \\ 0 & t < 0 \end{cases} \tag{2.1}$$

with

$$\lambda_i = e^{\sum_{j=0}^{q} \beta_j x_{ij}} \tag{2.2}$$

where $x_{i1}, \ldots, x_{iq}$ are the q covariate values and x_{i0} is taken equal to one. We do not assume the hazard, λ_i, to be a function of t as described by Cox (1972). The likelihood function of the β_i's is then written

$$l(\underset{\sim}{\beta}) = \left\{ \prod_{i=1}^{n_1} e^{\sum_{j=0}^{k} \beta_j x_{ij}} \exp\left[-e^{\sum_{j=0}^{q} \beta_j x_{ij}} t_i\right] \right\} \left\{ \prod_{h=n_1+1}^{n_2} \exp\left(-e^{\sum_{j=0}^{q} \beta_j x_{ij}} t_h\right) \right\} \tag{2.3}$$

$$\underset{\sim}{\beta} = (\beta_1, \ldots, \beta_q) .$$

Maximum likelihood estimates (m.l.e.'s) of the β_j's are computed in the usual manner by differentiating the log likelihood function,

$$\log l(\underset{\sim}{\beta}) = L = \sum_{i=1}^{n_1} \sum_{j=0}^{q} \beta_j x_{ij} - \sum_{i=1}^{n} e^{\sum_{j=0}^{q} \beta_j x_{ij}} t_j , \tag{2.4}$$

with respect to each β_r, $r=0, \ldots, q$ and solving the $q+1$ nonlinear equations

$$L'_r = \sum_{i=1}^{n_1} x_{ir} - \sum_{i=1}^{n} x_{ir} e^{\sum_{j=0}^{q} \beta_j x_{ij}} t_i = 0 . \tag{2.5}$$

MANTEL and MYERS (1971) describe these iterative procedures in detail. Such results also give rise to an asymptotic variance-covariance matrix for the m.l.e.'s, $\hat{\beta}_r$, as the inverse of the matrix having elements $-E(L''_{rs})$ for

$$E(L''_{rs}) = -\sum_{i=1}^{n} x_{ir}x_{is}\left[1-\exp\left(e^{\sum_{j=0}^{q}\beta_j x_{ij}} t_i\right)\right] \tag{2.6}$$

where t'_i = maximum observable time associated with the i^{th} patient, i.e.,

$$\begin{aligned} &t_i < t'_i \quad i = 1, 2, \ldots, n_1 \\ &t_i = t'_i \quad i = n_1+1, \ldots, n \end{aligned} \tag{2.7}$$

and is defined as the time between the i^{th} patient's entry date on study and the last date of the study. The quantities t'_i permit computing the $E(L''_{rs})$ when censored observations are utilized in the model.

3.0 The Selection Procedure and the Alternative Test Statistics

NEYMAN and PEARSON (1928), WALD (1943), and RAO (1948) have all proposed statistics for testing simple or composite hypotheses on a parameter space given that the actual observations are independently and identically distributed. All results have led to tractable asymptotic chi square distributions. In our case we have nonidentically distributed random variables. Therefore in what follows we simulate the distributions of all required statistics and compare the outcome of the selection process and simulated powers of each test. Because of the simulations involved we have performed a step-up procedure for considering variables in the model as opposed to a step-back or backward selection procedure. A backward method is not practical in view of computing time and cost especially if many variables are considered in the analysis.

We first compute the log likelihood function, L_{β_0}, when the scale parameters λ_i, $i = 1, \ldots, n$ are each expressed in terms of the common constant, β_0, i.e. $\lambda_i = e^{\beta_0}$. The notation, L_{β_r}, $(r = 1, \ldots, q)$ denotes the log likelihood function when only the explanatory variable, x_{ir}, is considered, i.e., $\lambda_i = e^{\beta_0+\beta_r x_{ir}}$. We follow the usual methodology of finding the maximum likelihood solutions for each β_r, $r = 1, \ldots, q$ entered singularly in the model as well as computing the actual max $(L_{\beta_r}) = L_{\hat{\beta}_r}$ for each $r = 1, \ldots, q$. If we rank the $L_{\hat{\beta}_r}$'s in ascending order we write in new notation

$$L_{(q)} \leqq L_{(q-1)} \leqq \cdots \leqq L_{(2)} \leqq L_{(1)} \tag{3.1}$$

where

$$\begin{aligned} L_{(1)} &= \max\left[L_{\hat{\beta}_1}, \ldots, L_{\hat{\beta}_{r-1}}, L_{\hat{\beta}_r}, L_{\hat{\beta}_{r+1}}, \ldots, L_{\hat{\beta}_q}\right] \\ L_{(q)} &= \min\left[L_{\hat{\beta}_1}, \ldots, L_{\hat{\beta}_{r-1}}, L_{\hat{\beta}_r}, L_{\hat{\beta}_{r+1}}, \ldots, L_{\hat{\beta}_q}\right]. \end{aligned} \tag{3.2}$$

The variable associated with $L_{(1)}$, say $x_{i(1)}$, is selected as the first variable to be considered as a significant covariate.

A common procedure for testing the hypothesis $H_0: \beta_{(1)}=0$ given β_0 in the initial model is to compute the statistic

$$S=-2\delta \tag{3.3}$$

for $\delta=L_{\beta_0}-L_{(1)}$. The distribution of S is then simulated and if $S>S_{1-\alpha}$ where $S_{1-\alpha}$ is the appropriate $(1-\alpha)^{\text{th}}$ percentile, the hypothesis is rejected and $x_{i(1)}$ enters the model. Next the statistic S is computed for $\delta=L_{(1)}-L_{(1,2)}$ where $L_{(1,2)}$ is the log likelihood maximized by a second variable, say $\beta_{(2)}$, given $x_{i(1)}$ is in the model, and the hypothesis $H_0: \beta_{(2)}=0$ is tested. The method is repeated for each succeeding $\beta_{(r)}$ until $S=-2\delta \leqq S_{1-\alpha}$, i.e. the test fails to reject the hypothesis $H_0: \beta_{(r)}=0$ for $1 \leqq r \leqq q$. The resulting model is

$$\log \hat{\lambda}_i=\hat{\beta}_0+\hat{\beta}_{(1)}x_{i(1)}+\hat{\beta}_{(2)}x_{i(2)}+\cdots+\hat{\beta}_{(h)}x_{i(h)} \quad 1 \leqq h \leqq q \tag{3.4}$$

which constitutes the final solution of the step-up procedure.

RAO (1948) proposed a test statistic which when applied to the r^{th} entry of the step-up procedure takes the form

$$R=(L_r')^2/\bar{s}^2_{(r)} \tag{3.5}$$

for which L_r' is exactly (2.5) evaluated at the restricted m.l.e.'s of the first r coefficients entered into the model; restricted in the sense that they are computed given the remaining $q-r$ coefficients are set equal to zero. The value $\bar{s}^2_{(r)}$ is the asymptotic variance of $\hat{\beta}_{(r)}$ in the restricted setting; the asymptotic variance-covariance matrix has dimension $(r+1)\times(r+1)$ and is evaluated at $\hat{\beta}_0, \hat{\beta}_{(1)}, \ldots, \hat{\beta}_{(r-1)}$ and $\hat{\beta}_{(r)}=0$. Following the procedure for the S statistic the hypothesis $H_0: \beta_{(r)}=0$ is rejected at the r^{th} step if $R>R_{1-\alpha}$ where $R_{1-\alpha}$ is the $(1-\alpha)^{\text{th}}$ percentile of the simulated distribution of R.

The third statistic we adapt to our step-up procedure was proposed by WALD (1943). The statistic when applied for testing $H_0: \beta_{(r)}=0$ conveniently reduces to the form

$$W=\hat{\beta}^2_{(r)}/s^2_{(r)} \tag{3.6}$$

where $\hat{\beta}_{(r)}$ is the unrestricted m.l.e. of $\beta_{(r)}$ and $s^2_{(r)}$ is the asymptotic variance of $\hat{\beta}_{(r)}$ is the full $(r+1)\times(r+1)$ asymptotic variance-covariance matrix of the maximum likelihood estimates $\hat{\beta}_0, \ldots, \hat{\beta}_{(r)}$.

Results of all three statistics for hypothesis testing in the step-up setting are given in section 6.0.

If computing is a practical consideration, we note that the S (3.3) calculation requires execution of approximately twice as many machine instructions as does either the R (3.5) or the W (3.6) calculations. Moreover, S will generally require a total of slightly more than twice the number of iterations for the final maximum likelihood solutions than does the R calculation and slightly less than twice the number than does the W statistic. This is because the S uses both the restricted and unrestricted solutions which the R and W statistics require only the former and latter, respectively.

4.0 A Beta Weight Selection Procedure

We have been discussing the step-up procedure which is dependent on the contribution of each variable to the likelihood function. However, it is often the case that independent variables are presented with different units of measurement and some of these variables will vary more than others. It may be desirable to obtain a measure of the direct effect of each independent variable on the dependent variable without regard to the units of measurement. LAND (1969, Ch. 1) and BLALOCK (1972, Ch. 19) discuss the beta weight technique for linear models which assures the same variability of each independent variable so that the relative sizes of such weights provides a ranking of the variables in order of their direct contribution to the predicted variable.

To apply such a technique to our model it is convenient to express the mean $1/\lambda_i$, as mathematically independent of the variance. Consider the transformation $V_i = \ln t_i$ for which

$$E(V_i) = \mu_i = -\ln \lambda_i + \gamma \tag{4.1}$$
$$\text{Var}\,(V_i) = \zeta(2) = \Pi^2/6$$

where γ is EULER's constant and ζ is RIEMANN's Zeta function. Note the mean and variance are mathematically independent. Also as a result of the log transformation,

$$\mu_i = -\sum_{j=0}^{q} \beta_j x_{ij} + \gamma\,, \tag{4.2}$$

which is seen to be a linear parametrization of the mean. Standardize each dependent and explanatory variable

$$V_i^* = V_i/\sqrt{(\Pi^2/6)}\,, \quad x_{ij}^* = x_{ij}/\hat{\sigma}_j \tag{4.3}$$

for $\hat{\sigma}_j^2 = (n-1)^{-1} \sum_{i=1}^{n} (x_{ij} - \bar{x}_{\cdot j})^2$, $\bar{x}_{\cdot j} = n^{-1} \sum_{i=1}^{n} x_{ij}$. Thus (4.2) becomes

$$\mu_i = -\sum_{j=0}^{q} \beta_j^* x_{ij}^* + \gamma^* \tag{4.4}$$
$$\beta_j^* = \beta_j \hat{\sigma}_j/\sqrt{(\Pi^2/6)}\,, \quad \gamma^* = \gamma/\sqrt{(\Pi^2/6)}\,.$$

The β_j^*'s are called the beta weights. A step-up procedure based on beta weights is easy to establish. Compute the new log likelihood function $L_{\bar{\beta}}$ in the usual way with the single constant variable $\bar{\beta} = \gamma^* - \beta_0^*$. Next compute each $L_{\beta_r^*}$ singularly as in section 2.0, $r = 1, \ldots, q$; in each case computing the m.l.e. β_r^*. Whichever of the q β_r^*'s yields the largest absolute value of the beta weight, β_r^*, according to (4.4), call the associated variable $x_{i(1)}$, enter it next into the model and test $H_0 : \beta_{(1)} = 0$ according to each of the three statistics, S, R, or W. If H_0 is rejected recompute the β_r^*'s for each of the remaining $q-1$ variables one at a time with the constant $\bar{\beta}$ and $x_{i(1)}^*$ included. Select the variable $x_{i(2)}$ with the largest $|\beta_r^*|$ and test $H_0 : \beta_{(2)} = 0$. In general the procedure continues r times until $H_0 : \beta_{(r)} = 0$ is accepted, $1 \leqq r \leqq q$.

5.0 A Composite Step-Up Method

A second method of ranking by the β_r^*'s is to compute all q of the β_r^*'s simultaneously in the complete unrestricted likelihood function and rank the x_{ij} by the absolute values of their beta weights. Once the rankings are established one can proceed to test composite hypotheses in a step-up fashion. Given that $\beta_{(1)}^*$ is the beta weight with the largest absolute value we include $x_{i(1)}$ in the model and test $H_0: (\beta_{(2)}, \ldots, \beta_{(q)}) = \underset{\sim}{0}$ vs. $H_1: (\beta_{(2)}, \ldots, \beta_{(q)}) \neq \underset{\sim}{0}$. The S statistic for this test takes the form

$$S_c = -2 \log \Lambda_c, \quad \Lambda_c = \sup_{R_i(\underset{\sim}{\beta})} l(\underset{\sim}{\beta}) / \sup l(\underset{\sim}{\beta}) \tag{5.1}$$

where the numerator of Λ_c is the likelihood maximized under the restrictions $R_i(\underset{\sim}{\beta}) = \beta_{(r_j)} = 0$, $i = 1, \ldots, q-1$, $\beta_{(r_j)}$ being the coefficient of the i^{th} variable not included in the model, and the denominator is the usual unrestricted maximum likelihood.

The composite R statistic due to RAO (1948) is

$$R_c = \boldsymbol{G}' \boldsymbol{I}^{-1}(\underset{\sim}{\hat{\beta}})\, \boldsymbol{G} \tag{5.2}$$

where $\boldsymbol{G}' = (\varphi_0(\underset{\sim}{\hat{\beta}}), \ldots, \varphi_q(\underset{\sim}{\hat{\beta}}))\,|_{R_i(\underset{\sim}{\beta})}$, $\varphi_i(\underset{\sim}{\beta}) = (\partial/\partial\beta_i) \log l(\underset{\sim}{\beta})$, and the matrix $\boldsymbol{I}(\underset{\sim}{\hat{\beta}})$ is the usual information matrix evaluated at the m.l.e. $\underset{\sim}{\hat{\beta}}$ of $\underset{\sim}{\beta}$ calculated with the restriction $R_i(\underset{\sim}{\beta}) = 0$, $i = 1, \ldots, q-1$.

The composite W statistic of WALD (1943) is

$$W_c = \sum_{i=1}^{q-1} \sum_{j=1}^{q-1} \lambda_{ij} R_i(\underset{\sim}{\hat{\beta}}) R_j(\underset{\sim}{\hat{\beta}}) \tag{5.3}$$

where λ_{ij} is the ij^{th} element of the matrix $(\lambda_{ij}) = \left(\sum_{r=0}^{q} \sum_{s=0}^{q} (\partial R_i(\underset{\sim}{\beta})/\partial\beta_r) \cdot (\partial R_j(\underset{\sim}{\beta})/\partial\beta_s)\, c_{rs} \right)^{-1}$ and (c_{rs}) is the inverse of the information matrix $\boldsymbol{I}(\underset{\sim}{\hat{\beta}})$ and evaluated at the unrestricted m.l.e. $\underset{\sim}{\hat{\beta}}$ of $\underset{\sim}{\beta}$.

In any case of the hypothesis H_0 is rejected then $x_{i(2)}$ is included in the model and the procedure repeats for the $q-2$ restrictions $R_i(\underset{\sim}{\beta}) = \beta_{(r_i)} = 0$. In general the test procedure is performed r times $1 \leqq r \leqq q$ until H_0 is accepted. RAO (1973, p. 418) discusses all three statistics (5.1), (5.2), and (5.3) as well as their asymptotic distributions for the case of identically distributed random variables. In section 6.0 we present results for the simulated distributions in the nonidentically distributed case. The powers of the tests are of particular interest.

6.0 Numerical Illustration and Discussion

In Table 1 is listed data (Courtesy of the Southeastern Cancer Study Group) on 60 HODGKIN's disease patients receiving a standard therapy. In Table 2 we have the coding pattern used for each variable; stage, sex, and disease histology were

Table 1
Characteristics of HODGKIN's Disease Patients Receiving A Standard Therapy

Patient No.	Survival Time Mos. t	t'	Censoring Status*	Age	Sex**	Stage	Histology***
1	56.30	64.83	1	45	M	3B	NS
2	0.53	49.10	1	78	M	3A	UD
3	12.40	44.63	1	27	M	4B	NS
4	10.47	46.83	1	22	F	4B	NS
5	3.50	36.03	1	67	M	4B	MC
6	33.63	33.63	0	37	M	4A	NS
7	30.07	30.07	0	14	F	3A	NS
8	58.80	58.80	0	39	M	3B	MC
9	58.33	58.33	0	38	M	4B	MC
10	5.60	49.20	1	37	M	4B	LD
11	29.77	35.93	1	57	M	3B	NS
12	30.30	30.30	0	39	M	3B	NS
13	63.77	63.77	0	17	M	4B	NS
14	49.47	49.47	0	40	F	3A	MC
15	16.90	45.70	1	27	M	4B	MC
16	24.97	54.33	1	60	F	4B	UD
17	2.37	39.43	1	30	M	4B	LD
18	26.83	26.83	0	64	M	3B	MC
19	12.03	28.53	1	29	M	3B	NS
20	31.97	31.97	0	26	M	3A	NS
21	32.73	32.73	0	57	F	3B	MC
22	57.70	57.70	0	50	M	4B	MC
23	50.53	50.53	0	35	F	3B	NS
24	27.00	40.33	1	37	F	4B	NS
25	34.97	34.97	0	30	F	3B	NS
26	32.07	32.07	0	58	M	4B	NS
27	26.63	26.63	0	47	M	4B	NS
28	14.70	33.17	1	51	M	4B	MC
29	3.30	61.27	1	60	M	4A	LD
30	21.57	46.47	1	59	F	4B	MC
31	6.47	44.83	1	43	M	4B	NS
32	26.60	41.87	1	20	M	4B	NS
33	33.87	33.87	0	43	M	3B	NS
34	1.17	30.57	1	34	F	4B	MC
35	30.83	30.83	0	12	F	3B	NS
36	11.90	53.43	1	67	M	3B	NS
37	66.13	66.13	0	26	M	3B	MC
38	56.03	56.03	0	28	M	4B	MC
39	24.80	26.37	1	28	F	3B	NS
40	28.03	28.03	0	35	M	4B	MC
41	4.00	51.80	1	48	F	3B	LD
42	42.33	42.33	0	42	F	4B	NS
43	5.97	29.97	1	64	M	3B	MC
44	42.00	42.00	0	66	M	3B	NS
45	38.50	38.50	0	24	M	4B	MC
46	30.37	30.37	0	15	F	3B	LD
47	14.43	49.20	1	40	M	4B	MC
48	38.60	38.60	0	24	M	3B	NS
49	31.10	31.10	0	15	M	3B	NS

Continued Table 1

Patient No.	Survival Time Mos. t	t'	Censoring Status*	Age	Sex**	Stage	Histology***
50	28.47	28.47	0	24	M	4A	NS
51	21.13	31.03	1	66	M	3B	MC
52	0.37	49.10	1	63	F	4A	NS
53	17.20	48.30	1	25	M	4B	NS
54	33.07	46.07	1	22	M	4A	NS
55	30.70	30.70	0	38	M	3B	NS
56	11.73	63.50	1	59	F	4B	MC
57	39.73	42.07	1	18	M	4B	NS
58	0.70	41.20	1	24	M	4B	MC
59	34.67	34.67	0	21	F	4B	NS
60	30.83	30.83	0	13	M	4B	MC

* 1 – denotes a failure, 0 – denotes censored
** M – male, F – female
*** NS – Nodular Sclerosis
MC – Mixed Cellular
LD – Lymphocyte Depletion
UD – Undefined Disease

Table 2
Variables In The Model

Coefficient	Variable Name	Coding Pattern
β_1	Age	age (yrs.)
β_2	Sex	1/0*
β_3	Stage 3B	1/0**
β_4	Stage 4A	1/0
β_5	Stage 4B	1/0
β_6	Histology NS	1/0
β_7	Histology MC	1/0
β_8	Histology LD	1/0

* 1 – denotes female, 0 – denotes male
** 1 – denotes presence, 0 – denotes absence

Table 3
Three Procedures For Ranking Concomitant Variables And M.L.E. Coefficients For All Variables

Variable	Step-Up Max L	Step-Up β Weights	Joint β Weights	Full Model Fit
AGE	−146.136 (1)	0.561 (1)	0.687 (1)	0.040
SEX	−138.138 (4v)	0.0004 (4v)	0.008 (8)	−0.017
3B	−138.138 (3)	0.500 (3)	0.222 (5)	−0.457
4A	−138.137 (4iv)	0.009 (4iv)	0.152 (6)	0.546
4B	−138.047 (4iii)	0.120 (4iii)	0.314 (3)	0.624
NS	−137.967 (4ii)	0.121 (4ii)	0.135 (7)	−0.268
MC	−137.802 (4i)	0.159 (4i)	0.265 (4)	−0.550
LD	−141.594 (2)	0.581 (2)	0.496 (2)	1.781

treated as indicator variables (see NETER and WASSERMAN (1974), Ch. 9). Therefore in the model each individual's survival time is associated with eight variables.

The maximum log likelihoods for the step-up procedure of section 3.0 are listed in Table 3, column two. The numbers in parentheses are the ranks of the variables as listed in the first column. Column three of Table 3 contains the m.l.e.'s of the beta weights for the step-up procedure of section 4.0 together with the ranks, in parentheses, resulting from that procedure. In both cases all three step-up methods S, R, and W gave identical models. When acceptance of the null hypothesis is realized we have five variables remaining. Their order of rank with the included model variables are denoted by the Roman numerals. In Table 4 is listed the percentiles at each step of the procedure for all three statistics. The triple row entries in columns three and four correspond to S, R, and W. The percentiles in column three are based on 100 simulations. The observed values of S, R, and W in column four are computed from the actual data given in Table 1. Note that all three statistics include the variables age, LD, and 3B.

Table 4
Step-Up Tests Of AGE, LD, 3B

Variable	Coefficients H_0	Coefficients H_1	H_0 Percentiles	.1	.5	.9	Observed Values	
β_0	−4.004	−5.302	S	.010	.460	2.241	S	7.947
AGE	0.0	0.033	R	.010	.443	2.062	R	6.409
			W	.010	.461	2.392	W	9.669
β_0	−5.302	−5.624	S	.017	.391	2.276	S	9.085
AGE	0.033	0.037	R	.017	.392	2.030	R	4.577
LD	0.0	2.085	W	.016	.377	2.345	W	17.135
β_0	−5.624	−5.420	S	.014	.455	2.750	S	6.910
AGE	0.037	0.041	R	.014	.451	2.805	R	6.709
LD	2.086	2.161	W	.014	.448	2.886	W	6.181
3B	0.0	1.029						

Table 5 permits comparisons of the performance of S, R, and W with respect to powers. The numbers in parentheses below the variables in column one are the m.l.e.'s of the coefficients at which the powers have been simulated. Generally, the powers appearing in the last column are low. Even though the maximum power for W is the highest (.34 at MC), the R statistic is preferable in that it never produced a biased test; S is biased for 4A (.08) and W is biased for 4B (.07). A general criticism of the step-up procedure for this example is that the individual contribution of a variable is difficult to assess as indicated by the low maximum powers of all three statistics.

Table 6 gives the composite step-up test results. The joint beta weight ranking of Table 3, column four was used for the test sequence. The triple row entries in each block of Table 6 correspond to S_c (5.1), R_c (5.2), and W_c (5.3). The powers

Table 5
Step-Up Tests Of AGE, LD, 3B vs. Possible Fourth Variables

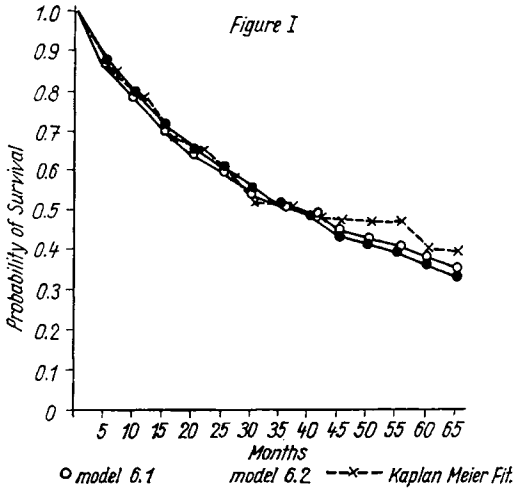
Fourth Variable		Percentiles H_0 .5	H_0 .9	H_1 .5	H_1 .9	Observed Values	Powers
SEX	S	0.348	2.303	0.350	2.299	0.000006	.10
(0.001)	R	0.331	2.043	0.332	2.048	0.000005	.10
	W	0.358	2.243	0.359	2.248	0.000006	.10
4A	S	0.604	2.337	0.648	2.285	0.002	.08
(0.033)	R	0.505	2.164	0.526	2.275	0.002	.10
	W	0.695	2.527	0.696	2.525	0.003	.10
4B	S	0.626	3.340	0.624	3.378	0.183	.11
(0.239)	R	0.613	3.084	0.590	3.314	0.159	.12
	W	0.635	3.682	0.645	3.441	0.207	.07
NS	S	0.538	2.681	0.736	4.146	0.343	.17
(0.240)	R	0.480	2.379	0.732	3.624	0.348	.19
	W	0.518	2.862	0.726	4.195	0.335	.15
MC	S	0.482	2.008	0.965	4.857	0.674	.32
(−0.331)	R	0.473	2.019	0.971	4.569	0.652	.31
	W	0.493	1.868	0.955	4.742	0.682	.34

Table 6
Composite Step-Up Tests Of AGE And LD

H_0 Models Rejected ($\alpha = 0.1$)						H_0 Model Accepted: β_0, AGE, LD			
Variables		H_0 Percentiles .1	.5	.9	Observed Values		H_0 Percentiles .5	.9	Observed Values
β_0	S_c	3.271	8.421	13.189	25.166	S_c	5.174	10.664	8.134
	R_c	3.079	7.513	11.338	17.266	R_c	4.557	9.288	8.378
	W_c	2.928	7.374	13.990	31.689	W_c	5.503	11.865	6.968
							H_1 Percentiles .1	.5	Powers
β_0	S_c	2.348	6.474	11.833	17.219				
AGE	R_c	2.338	5.883	10.796	11.886	S_c	6.363	13.819	.64
	W_c	2.176	6.758	13.498	23.156	R_c	5.496	11.263	.66
						W_c	6.627	13.248	.58

have been simulated at the m.l.e.'s of the coefficients in the full model $\lambda_i = e^{\sum_{j=0}^{8} \beta_j x_{ij}}$ listed in Table 3, column five, $\hat{\beta}_0 = 5.567$. The H_0 model coefficients would be the same as given in Table 4, column two. Note that by this procedure the powers are nearly twice as high for S_c and R_c and over 1.5 times higher for W_c compared to those seen for MC in Table 5. This procedure answers the criticism posed above by considering simultaneously *all* variables *not included* in the model in the H_0 hypothesis. Again, R_c is preferable on the basis that it produced the highest power.

Note that in the composite procedure all three statistics yielded a model requiring one less variable than that found by the step-up procedure, Table 4.



Note in Figure 1 the three variable step-up model

$$\log \lambda_i = -5.420 + 0.0413(\text{age}) + 2.161(\text{LD}) - 1.029(\text{3B}) \tag{6.1}$$

and the model based on the composite test,

$$\log \lambda_i = -5.624 + 0.0373(\text{age}) + 2.085(\text{LD}) \tag{6.2}$$

fit fairly well to the KAPLAN-MEIER plot (1958). The largest deviations are 0.083 for the three variable model (6.1) and 0.089 for the two variable model (6.2), both at 55 months.

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Summary

Prognostic indicators (concomitant variables, covariates) are relevant to patient performance on most cancer therapy trials. Lately, the emphasis has been directed to developing procedures for choosing those indicators which have the greatest influence on survival or duration of response (KRALL et al. 1975, LEE, 1974). Assuming each patient's survival time, measured from time on initial therapy until failure, is exponentially distributed, this paper examines several step-up and composite step-up procedures based on three statistics and in turn these statistics are compared for preference based on the power of the test procedures as well as computing considerations required to complete the selection process. A discussion of HODGKIN's disease survival data with ten covariate values follows in which three covariates are chosen by the step-up procedure as having greatest influence on survival while two covariates are chosen for the same purpose by the composite step-up method.

References

BARTOLUCCI, Alfred A., and James M. DICKEY, 1975: Comparative BAYESian and traditional inferences for gamma-modeled survival data. To be published in *Biometrics*.

BLALOCK, Hubert M., 1972: Social Statistics, Chapter 19. McGraw Hill, New York.

COX, D. R., 1972: Regression models and life tables (with discussion). J. R. Statist. Soc. B. **34**, 187–220.

FEIGL, P., and M. ZELEN, 1965: Estimation of exponential survival probabilities with concomitant information. Biometrics **21**, 826–838.

KAPLAN, E. L., and P. MEIER, 1958: Non parametric estimation from incomplete observations. J. Am. Statist. Assoc. **53**, 457–481.

KRALL et al., 1975: A step-up procedure for selecting variables associated with survival. Biometrics **31**, 49–57.

LAND, K. C., 1969: Principles of Path Analysis. Sociological Methodology, Ch. 1, Jossey Bass. Inc., San Francisco.

LEE, E. T., 1974: A computer program for linear logistic regression analysis. Computer programs in biomedicine **4**, 80–92.

NETER, John, and W. WASSERMAN, 1974: Applied Linear Statistical Models, Chapter 9. Richard D. Irwin Inc., Illinois.

NEYMAN, J., and E. S. PEARSON, 1928: On the use and interpretation of certain test criteria for purposes of statistical inference. Biometrika **20A**, 175–240 and 263–294.

PRENTICE, R. L., 1973: Exponential survivals with censoring and explanatory variables. Biometrika **60**, 279–288.

RAO, C. R., 1948: Large sample tests of statistical hypotheses concerning several parameters with applications to problems of estimation. Proc. Cam. Phil. Soc. **44**, 50–57.

RAO, C. R., 1973: Linear Statistical Inference and Its Applications, Chapter 6. John Wiley & Sons Inc., New York.

WALD, A., 1943: Tests of statistical hypotheses concerning several parameters when the number of observations is large. Trans. Am. Math. Soc. **54**, 426–482.

ZELEN, M., 1966: Applications of exponential models to problems in cancer research. J. R. Statist. Soc. A. **129**, 368–398.

ZIPPIN, C., and P. ARMITAGE, 1966: Use of concomitant variables and incomplete survival information in the estimation of an exponential survival parameter. Biometrics **22**, 665–672.

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