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Simultaneous modelling of operative mortality and long-term survival after coronary artery bypass surgery

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SUMMARY

Typical analyses of lifetime data treat the time to death or failure as the response variable and use a variety of modelling strategies such as proportional hazards or fully parametric, to investigate the relationship between the response and covariates. In certain circumstances it may be more natural to view the distribution of the response variable as consisting of two or more parts since the survival curve appears segmented. This article addresses such a scenario and we propose a model for simultaneously investigating the effects of covariates over the two segments. The model is an analogue of that proposed by Lambert for zero-inflated Poisson regression. The application is central to the model development and is concerned with survival after coronary artery bypass surgery. Here operative mortality, defined as death within 30 days after surgery, and long-term mortality, are viewed as distinct outcomes. For the application considered, the survivor function displays much steeper descent during the first 30 days after surgery, that is, for operative mortality, than after this period. An investigation of the effects of covariates on operative and long-term mortality after coronary artery bypass surgery illustrates the usefulness of the proposed model. Copyright © 2001 John Wiley & Sons, Ltd.

1. INTRODUCTION

Standard lifetime analysis models time to failure, usually as a function of covariates, employing parametric models such as the Weibull or exponential, or semi-parametric methods such as the Cox proportional hazards model. Sometimes, however, preliminary analysis of lifetime data indicates that the survival curve appears segmented with a steep initial descent followed by a less drastic mortality rate. This is not uncommon in situations where treatment is harsh,

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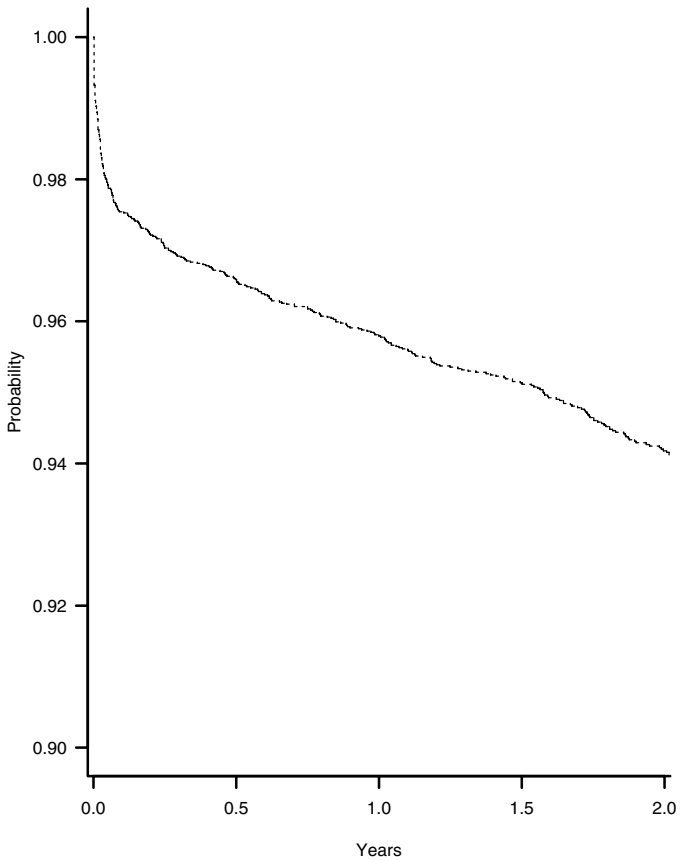

Figure 1. Estimated survivor function for the coronary artery bypass data.

and lifetime is measured from the start of such treatment. For example, our motivating application considers mortality after coronary artery bypass (CAB) surgery. CAB surgery is the most commonly performed open heart surgical procedure, and is used for the treatment of serious ischaemic heart disease. Ischaemic heart disease is reduced or non-existent blood flow to the heart resulting from the clogging of one or more arteries. In bypass surgery, another vein or artery is used to bring blood directly to the vessel below the obstruction. CAB carries a high risk of operative mortality, defined as death within 30 days after surgery. Figure 1 presents the Kaplan–Meier survivor function for CAB data from British Columbia and illustrates steep initial descent. Note that this estimated survivor function does not take into account covariate effects. Prediction of operative mortality after CAB surgery has been extensively studied and recently reviewed [1, 2]. There have also been many studies examining predictors of long-term survival, for example, references [3–5].

This article introduces a new approach to the modelling of survival data after bypass surgery. Operative mortality, a binary endpoint, and long-term survival, a continuous lifetime variable, are studied simultaneously using data from a population-based cardiac surgery

database in British Columbia, Canada. This new technique for simultaneously assessing the effects of covariates on both of these outcomes permits an exploration of structure in the effects of the covariates which may not be apparent from fitting separate models to these two outcomes. It is an adaptation of a model developed by Lambert [6] for a manufacturing scenario involving count data where there are many more zero counts than expected. Another model [7, 8] relating time to early death and a binary variable for long-term survivorship shares the similarity with the model developed herein that it is a mixture model dealing with a continuous variable and binary endpoint. However, here it is early death or operative mortality which is the binary endpoint. This translates into a distinct formulation of the parts contributing to the mixture, so the resulting likelihood is quite different. Although the development of the likelihood and inference for the model parameters is framed in the context of our particular application to survival after cardiac surgery, it should be noted that the model can be applied more generally to situations where initial treatment is harsh enough that the Kaplan–Meier survival curve exhibits the form in Figure 1.

In Section 2 we develop the model for simultaneously investigating the effects of covariates on operative and long-term mortality and discuss inference for this model. In Section 3 we illustrate the model using the British Columbia Cardiac Registries data and examine its goodness-of-fit. The article closes with a discussion of extensions to the model.

2. SIMULTANEOUS MODELLING OF SHORT- AND LONG-TERM SURVIVAL

2.1. Introduction and model assumptions

Traditional survival analysis involves fitting a model to a single response, lifetime. For our application, this assumes both operative mortality (or short-term survival) and long-term survival are influenced by the same set of covariates. Although this may be a reasonable assumption, we wish to develop a model which will view these two outcomes separately, and allow predictions for them.

A natural approach to fitting two separate models would be to fit a logistic regression model to predict operative mortality and a proportional hazards model or a parametric regression model to predict long-term survival, that is, survival after 30 days. Since the Weibull regression model is a proportional hazards model and is a flexible one, we use this model to describe the distribution of long-term survival. The PDF of lifetime, t, under the Weibull assumption given a vector $\mathbf{x}$ of regressor variables, is

$$\frac{\delta}{\alpha(\mathbf{x})}\left(\frac{t}{\alpha(\mathbf{x})}\right)^{\delta-1}\exp\left[-\left(\frac{t}{\alpha(\mathbf{x})}\right)^{\delta}\right], \quad t \geqslant 0 \tag{1}$$

where δ and α are the parameters of the Weibull regression model. Here, only the scale parameter α depends on $\mathbf{x}$, which implies proportional hazards for lifetimes and constant variance for log-lifetimes of individuals (Lawless [9]). More precisely, for $i = 1, \ldots, n$ let

$$z_i = \begin{cases} 1 & \text{if the } i\text{th individual died within the first 30 days after surgery} \\ 0 & \text{otherwise} \end{cases}$$

Let $p_i = P(z_i = 1)$ be the probability that the ith individual dies within the first 30 days after surgery, $\mathbf{p} = (p_1, \ldots, p_n)$. Furthermore, let T_i denote the ith lifetime, L_i denote the ith censoring

time for the individual who has survived beyond 30 days after surgery and $t_i = \min\{T_i, L_i\}$. Here, lifetime is defined as the interval between date of surgery and death date, for our application. Then let

$$Y_i = \begin{cases} t_i - 30 & \text{if } z_i = 0 \\ 0 & \text{otherwise} \end{cases}$$

We will work with log-lifetimes since the resulting model is a linear regression model and is notationally simpler to describe than the Weibull regression model. The distribution of $W = \log(Y)$, given the covariate vector $\mathbf{x}$ and $z = 0$, is the extreme-value distribution whose PDF is the following:

$$g(w|z=0,\mathbf{x}) = \frac{1}{\sigma}\exp\left[\frac{w-\mu(\mathbf{x})}{\sigma} - \exp\left(\frac{w-\mu(\mathbf{x})}{\sigma}\right)\right], \quad -\infty < w < \infty \tag{2}$$

where $\mu(\mathbf{x}) = \log\alpha(\mathbf{x})$ and $\sigma = 1/\delta$. The most frequently used model is the linear one, with

$$\mu(\mathbf{x}) = \mathbf{x}\beta$$

Thus, fitting two separate models, a logistic regression model to the binary response and an extreme-value regression model to the lifetimes conditional on $z_i = 0$ gives

$$\begin{aligned} \text{logit}(\mathbf{p}) &= \mathbf{G}\gamma \\ \log(\mathbf{Y}) &= \mathbf{X}^{\star}\beta + \sigma\varepsilon \end{aligned} \tag{3}$$

for covariate matrices $\mathbf{G}$ and $\mathbf{X}^{\star}$. Here, ε follows a standard extreme-value distribution and σ is the scale parameter of the extreme-value regression model.

In order to tackle the problem of simultaneous estimation of covariate effects on operative mortality and long-term survival, we use a model analogous to that derived by Lambert [6]. Here we pool information from the model predicting operative mortality with that which predicts long-term survival. If the same covariates affect logit($\mathbf{p}$) and log($\mathbf{Y}$) so that as operative mortality decreases, long-term survival increases, we may have

$$\begin{aligned} \text{logit}(\mathbf{p}) &= -\tau\mathbf{X}\beta \\ \log(\mathbf{Y}) &= \mathbf{X}^{\star}\beta + \sigma\varepsilon \end{aligned} \tag{4}$$

for covariate matrices $\mathbf{X}$, $\mathbf{X}^{\star}$, and unknown real-valued shape parameter τ. Note that the covariate matrices $\mathbf{X}$ and $\mathbf{X}^{\star}$ contain the same set of covariates but differ in their number of rows since $\mathbf{X}$ contains data from all cases, while $\mathbf{X}^{\star}$ contains information only from those cases who survived the first 30 days. When $\tau > 0$, the risk of operative mortality decreases as long-term survival increases, and as $\tau \to \infty$, the risk of operative mortality diminishes. As $\tau \to -\infty$, the risk of operative mortality becomes certain.

The parameterization in (4) however, assumes that the same set of covariates influence both operative mortality and long-term survival. In order to provide a bit more flexibility to accommodate those covariates whose effects on the two outcomes may differ, model 4 is

reformulated as

$$\begin{aligned} \text{logit}(\mathbf{p}) &= -\tau\mathbf{X}\beta + \mathbf{Z}\gamma \\ \log(\mathbf{Y}) &= \mathbf{X}^{\star}\beta + \sigma\varepsilon \end{aligned} \tag{5}$$

where γ contains the parameters corresponding to those covariates whose effects on operative mortality and long-term survival differ. In order to avoid overparameterizing, while $\mathbf{X}$ and $\mathbf{X}^{*}$ contain a general constant term represented by a column of ones, $\mathbf{Z}$ does not. What is envisioned is that $\mathbf{X}$ and $\mathbf{Z}$ should contain different sets of covariates, or, perhaps, just a few in common. The focus of fitting the simultaneous model (5) is to explore commonalities which lead to simple structures for covariate effects. For example, in the application discussed in Section 3, only one covariate is common to $\mathbf{X}$ and $\mathbf{Z}$, and τ is estimated as unity. If no such simple structure exists, as happens when there are many common covariates in $\mathbf{X}$ and $\mathbf{Z}$, a model allowing all covariates to have different parameters for short versus long-term survival, as in (3), is preferable.

2.2. *Likelihood development and maximum likelihood estimation*

The likelihood functions under the three different model formulations (3), (4) and (5) are very similar and only the likelihood function for the model (5) will be presented. Let $\mathbf{z} = (z_1, \ldots, z_n)$ be the vector of indicators for operative mortality and let $\mathbf{W} = \log(\mathbf{Y})$ where $\mathbf{Y} = (Y_1, \ldots, Y_n)$. Then $f(\mathbf{z}, \mathbf{w})$, the joint probability of $\mathbf{z}$ and $\mathbf{w}$ is given by $f(\mathbf{z}, \mathbf{w}) = f(\mathbf{w}|\mathbf{z})f(\mathbf{z})$ and the likelihood $\mathscr{L}(\gamma, \beta, \tau, \sigma; \mathbf{z}, \mathbf{w})$ is given by

$$\prod_{i=1}^{n} f(z_i; \tau, \beta, \gamma) \prod_{i \in D} g(w_i | z_i = 0; \beta, \sigma) \prod_{i \in C} S(w_i | z_i = 0; \beta, \sigma)$$

where $f(.)$ is the PDF of z_i, $S(.)$ is the survivor function corresponding to $g(.)$, D is the set of individuals who survived the first 30 days after CAB surgery and whose lifetime is observed and C is the set of individuals who survived the first 30 days after CAB surgery and whose lifetime is censored. Let $\mathbf{X}_i^{\star}$ and $\mathbf{Z}_i$ denote the ith row of $\mathbf{X}^{\star}$ and $\mathbf{Z}$, respectively, and let r be the number of individuals in D. Then, since

$$f(z_i) = p_i^{z_i}(1 - p_i)^{1 - z_i} \tag{6}$$

$$g(w_i | z_i = 0; \beta, \sigma) = \frac{1}{\sigma} \exp\left[\frac{w_i - \mathbf{X}_i^{\star}\beta}{\sigma} - \exp\left(\frac{w_i - \mathbf{X}_i^{\star}\beta}{\sigma} \right) \right] \tag{7}$$

$$S(w_i | z_i = 0; \beta, \sigma) = \exp\left(- \exp\left(\frac{w_i - \mathbf{X}_i^{\star}\beta}{\sigma} \right) \right) \tag{8}$$

the log of the likelihood becomes

$$\begin{aligned} \log \mathscr{L}(\gamma, \beta, \tau, \sigma; \mathbf{z}, \mathbf{w}) = & \sum_{i=1}^{n} \{ z_i[-\tau\mathbf{X}_i\beta + \mathbf{Z}_i\gamma] - \log(1 + \exp(-\tau\mathbf{X}_i\beta + \mathbf{Z}_i\gamma)) \} \\ & + \sum_{i \in D} \frac{w_i - \mathbf{X}_i^{\star}\beta}{\sigma} - \sum_{i \in D, C} \exp\left(\frac{w_i - \mathbf{X}_i^{\star}\beta}{\sigma} \right) - r \log \sigma \end{aligned} \tag{9}$$

The maximum likelihood estimates of β, γ, τ and σ are obtained from (9); we have experienced no difficulties implementing a Newton–Raphson algorithm, for example. First and second partial derivatives are required for the algorithm. For ease of presentation, the components of the score vector

$$\mathbf{U} = \left(\frac{\partial \log \mathscr{L}}{\partial \gamma_1}, \ldots, \frac{\partial \log \mathscr{L}}{\partial \gamma_q}, \frac{\partial \log \mathscr{L}}{\partial \beta_1}, \ldots, \frac{\partial \log \mathscr{L}}{\partial \beta_p}, \frac{\partial \log \mathscr{L}}{\partial \tau}, \frac{\partial \log \mathscr{L}}{\partial \sigma} \right)$$

and the observed Fisher information matrix $\mathbf{I}_0$ have been relegated to Appendix A.

In the model fitting process, to test the hypothesis $H_0: \beta_i = 0$ versus the alternative $H_1: \beta_i \neq 0$ or $H_0: \gamma_i = 0$ versus $H_1: \gamma_i \neq 0$, the standard large-sample likelihood ratio test may be employed. The significance of the covariate effects should be assessed in the presence of τ before testing hypotheses concerning τ. Profile plots for τ and σ should be examined in order to evaluate whether it is reasonable to assume that $\tau = 1$ or $\sigma = 1$. If we fail to reject the null hypothesis that σ equals one, the model reduces to an exponential regression model.

From a clinical point of view, it is of interest to view the effects of the covariates via odds ratios and relative risks. Odds ratios of predictors of operative mortality are found by exponentiating the parameter estimates in the logistic regression model. For an extreme-value regression model, the estimated relative risk of the jth risk factor relative to the baseline is $\exp(-\hat{\beta}_j/\hat{\sigma})$. For a categorical variable, x_j, this is interpreted as the ratio of hazard functions when $x_j = 1$ versus when $x_j = 0$, given all other covariates are fixed. The relative risk for a continuous variable measures the risk ratio when x_j is increased by unity. Note that for the simultaneous model, when there are common covariates in $\mathbf{X}$ and $\mathbf{Z}$, the estimated odds ratios of the corresponding predictors of operative mortality will be found by combining two estimates, one a component of β, the other a component of γ. Hence, standard errors for such estimates will need to take into account estimated covariances of these estimated components. If τ is not unity, estimated odds ratios for operative mortality will also need to account for this factor both in the estimated effects and in their estimated variances, through the delta approximation for the latter.

3. APPLICATION TO THE BRITISH COLUMBIA CARDIAC REGISTRIES DATA

The British Columbia Cardiac Registries (BCCR) maintains a population-based database containing prognostic information on all open-heart surgery performed in the province of British Columbia. Data collection began in January 1991, and the analysis which follows is an examination of data collected on all isolated coronary artery bypass (CAB) surgery performed before 31 December 1994. The data come primarily from the Operative report which is completed by the surgeon immediately after surgery. Prognostic information can be grouped as belonging to a number of different categories including demographic information, information on previous cardiac surgery, diagnosis information, other diseases co-existent at the time of cardiac surgery, urgency of surgery and measures of severity of disease. Based on discussions with clinicians and previous work published on predicting operative mortality, a list of potential prognostic factors was developed. Data on most of these are recorded on the operative report, however, for some variables these data were obtained from other sources. Altogether, there were 33 prognostic factors examined.

Table I. Significant and potentially significant predictors.

Operative mortality	Long-term survival
Significant predictor	Significant predictor
Gender★†	Re-operation★†
Urgency of surgery★†	Diabetes★
Pre-op iv nitroglycerine★†	Peripheral vascular disease★†
Peripheral vascular disease	Dialysis/elevated creatinine★†
Urban/rural residence★†	Congestive heart failure★†
Age★†	Number of diseased vessels★†
Ejection fraction★†	Year of surgery★
Diabetes★	Ejection fraction★†
Dialysis/elevated creatinine★	Age★†
Congestive heart failure★	
Year of surgery	
Potentially significant predictor	Potentially significant predictor
Re-operation★†	ASA within 5 days
Number of diseased vessels★†	Pre-op ventilation/intubation★
ASA within 5 days	Cerebrovascular disease★
Pre-op ventilation/intubation★†	Pulmonary hypertension
Cerebrovascular disease★	Pre-op diuretic★†
Pulmonary hypertension†	Urgency of surgery
Pre-op diuretic ★†	

Since the list of potential risk factors is large, several variable selection procedures were implemented in the model fitting process in order to make the model parsimonious. These included backward elimination, simultaneously dropping several variables, and stepwise procedures. No matter which model fitting procedure was used, one set of covariates was consistently identified as important in predicting operative mortality and long-term survival; Table I lists these as 'significant predictors'. There were a few other covariates which appeared as predictors in some model fitting procedures and not in others; these are identified in Table I as 'potentially significant predictors'.

Examination of the estimates for the year of surgery effect indicated that cases undergoing surgery in 1993 tended to have lower operative mortality and longer long-term survival than those corresponding to 1991, 1992 and 1994. Since there was no clinical evidence to support inclusion of this variable for future predictions, we decided to exclude year of surgery as a covariate. It was also decided that a model without urgency of surgery and ASA within 5 days of surgery as predictors of long-term survival would be more clinically interpretable. Covariate selection was next performed on a model which included all the variables listed in Table I excluding year of surgery, and excluding ASA within 5 days and urgency of surgery as predictors of long-term survival. Significant predictors from the non-simultaneous model (3) are identified with a † sign in Table I. Interaction terms with sex and age were also considered as well as a quadratic term with age. None of these was significant. For exploring model structure, we consider the simultaneous fit (5) in the following paragraphs. Significant predictors included in this simultaneous model are identified in Table I with a ★ sign.

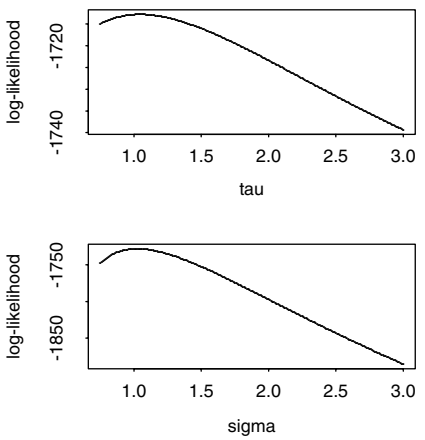

Figure 2. Profile plots for τ and σ.

For the simultaneous model, the estimate of τ is 1.2 with a standard error of 0.16. A profile plot of τ is shown in Figure 2. Visual inspection reveals that τ may be set to one. Ninety-five per cent confidence intervals for τ based on the large sample normal approximation to the distribution of $\hat{\tau}$ and based on the profile plot are (0.9,1.5) and (0.8,1.6), respectively. Since there is no evidence against the hypothesis that $\tau = 1$, we refit the model with τ set at unity.

It is also of interest to test the hypothesis that σ is one since this indicates that the simpler exponential regression model provides a reasonable fit to the data. The estimate of σ is 1.02 with a standard error of 0.05. The profile plot for σ is also given in Figure 2. A 95 per cent confidence interval for σ based on the asymptotic normality of $\hat{\sigma}$ is (0.9,1.1) while a 95 per cent confidence interval based on the profile plot of σ is (0.9,1.2). Note that these are obtained under the reduced model with $\tau = 1$. It seems that the exponential regression model gives a fair fit to the data.

A half-normal plot of the logistic residuals together with their simulated envelope proposed by Atkinson [10] showed no obvious discrepancy with the logistic fit. Residuals for the Weibull fit, are of course, difficult to interpret since 94 per cent of the observations were censored. Model assessment is ongoing for this project as data for several more years becomes accessible. The parameter estimates corresponding to the fitted model with both τ and σ equal to one are reported in Table II, while Appendix B provides the estimated covariances. Estimated odds ratios for operative mortality corresponding to this fit are given in Table III. The estimated relative risks for long-term mortality are reported in Table IV.

To interpret the simultaneous model in the current context, note that gender, urgency of surgery and place of residence are significant predictors of operative mortality but not long-term survival. The increased operative mortality for women and more urgent surgery is well established [1, 2]. The estimated rural versus urban effect is possibly explained by the distance of the patients to the centres and specialists performing surgery. Interpretation of covariates which affect both operative and long-term mortality is similarly straightforward. For example, being a diabetic increases risks corresponding to both operative and long-term mortality. In this case, the odds ratio for operative mortality and the ratio of instantaneous probability of mortality given survival to date, for a diabetic versus a non-diabetic is about 1.3, given all

Table II. Parameter estimates and their standard errors for the simultaneous fit with both $\tau = 1$ and $\sigma = 1$. Covariates identified with an asterisk are indicator variables for the presence of the named condition or status.

Factor	Label	$\hat{\gamma}$	SE($\hat{\gamma}$)
Female gender★		0.51	0.21
Urgency of surgery	elective		
	urgent	0.43	0.21
	emergency	1.37	0.36
Rural residence★ (baseline in urban residence)		0.57	0.21
Peripheral vascular disease★		−0.86	0.32
Factor	**Label**	$\hat{\beta}$	SE($\hat{\beta}$)
Age		−0.06	0.01
Ejection fraction	>50%		
	35–50%	−0.28	0.12
	<35%	−0.94	0.15
Re-operation★		−0.58	0.15
Diabetes★		−0.25	0.13
Pre-op diuretic★		−0.43	0.15
Pre-op ventilation/intubation★		−1.06	0.45
Peripheral vascular disease★		−0.61	0.15
Cerebrovascular disease★		−0.32	0.16
Dialysis/elevated creatinine★		−0.32	0.16
Congestive heart failure★		−0.53	0.14
Number of diseased vessels	1–2		
	⩾ 3	−0.30	0.18
	main left stenosis	−0.56	0.19

other covariates are the same.

The only striking difference between the parameter estimates and their standard errors for the non-simultaneous (3) and simultaneous (5) fits relates to the estimated effects of pre-op ventilation and congestive heart failure. For the simultaneous fit, both of these variables are included and are highly significant, while for the non-simultaneous fit, of these two variables, only pre-op ventilation remains in the final fitted model, also being highly significant. If the estimated effects of pre-op ventilation (−1.06) and congestive heart failure (−0.53) from the fitted simultaneous model are added, the estimated joint effect is close to that of pre-op ventilation (−1.85) in the non-simultaneous fit. Pre-op ventilation is often needed because of congestive heart failure. Hence, in the simultaneous model, it may be the joint effect of these two variables which better reflects either of their effects. It may have been better to combine these variables in the analyses, or to isolate those individuals who fell into both these categories as a separate higher risk congestive heart failure category. The other differences between these two fitted models relate to the weakest predictors, those which are only marginally significant in either of the models. For example, diabetes, cerebrovascular disease and dialysis are all included as marginally significant predictors in the simultaneous model (see Table II), but not in the non-simultaneous model.

With small or moderately sized samples, rather than rely on maximum likelihood asymptotic

Table III. Odds ratios for operative mortality and their confidence intervals for the simultaneous fit with $\tau = 1$ and $\sigma = 1$. Covariates identified with an asterisk are indicator variables for the presence of the named condition or status.

Factor	Label	OR	95 per cent CI
Female gender★		1.67	(1.11, 2.5)
Urgency of surgery	elective	1.00	
	urgent	1.53	(1.02, 2.29)
	emergency	3.92	(1.95, 7.87)
Rural residence★ (baseline is urban residence)		1.77	(1.18, 2.65)
Peripheral vascular disease★		0.77	(0.44, 1.37)
Age		1.06	(1.05, 1.07)
Ejection fraction	$>50\%$	1.00	
	35–50%	1.32	(1.05, 1.67)
	$<35\%$	2.56	(1.92, 3.40)
Re-operation★		1.79	(1.32, 2.41)
Diabetes★		1.29	(1.00, 1.66)
Pre-op diuretic★		1.53	(1.14, 2.05)
Pre-op ventilation/intubation★		2.90	(1.19, 7.05)
Cerebrovascular disease★		1.37	(1.01, 1.87)
Dialysis/elevated creatinine★		1.37	(1.04, 1.80)
Congestive heart failure★		1.71	(1.29, 2.26)
Number of diseased vessels	1–2	1.00	
	$\geqslant 3$	1.35	(1.00, 1.91)
	main left stenosis	1.74	(1.19, 2.55)

Table IV. Relative risks for long-term mortality and their confidence intervals for the simultaneous fit with $\tau = 1$ and $\sigma = 1$. Covariates identified with an asterisk are indicator variables for the presence of the named condition or status.

Factor	Label	RR	95 per cent CI
Age		1.06	(1.05, 1.07)
Ejection fraction	$>50\%$	1.00	
	35–50%	1.32	(1.05, 1.67)
	$<35\%$	2.56	(1.92, 3.40)
Re-operation★		1.79	(1.32, 2.41)
Diabetes★		1.29	(1.00, 1.66)
Pre-op diuretic★		1.53	(1.14, 2.05)
Pre-op ventilation/intubation★		2.90	(1.19, 7.05)
Peripheral vascular disease★		1.83	(1.37, 2.44)
Cerebrovascular disease★		1.37	(1.01, 1.87)
Dialysis/elevated creatinine★		1.37	(1.04, 1.80)
Congestive heart failure★		1.71	(1.29, 2.26)
Number of diseased vessels	1–2	1.00	
	$\geqslant 3$	1.35	(1.00, 1.91)
	main left stenosis	1.74	(1.19, 2.55)

Table V. Maximum likelihood estimates, their estimated standard errors, jack-knifed estimates of bias and jack-knifed estimates of standard errors. Covariates identified with an asterisk are indicator variables for the presence of the named condition or status.

Factor	Estimate	Bias	Standard error	
			Model-based	Jack-knife
γ_0	5.339	−0.026	0.224	0.230
Female gender*	0.510	−0.004	0.208	0.208
Urgency of surgery: urgent	0.426	0.003	0.207	0.208
Urgency of surgery: emergency	1.366	−0.028	0.356	0.342
Rural residence*	0.571	0.009	0.207	0.210
Peripheral vascular disease*	−0.861	−0.024	0.317	0.326
β_0	10.800	0.023	0.175	0.178
Age	−0.059	−0.000	0.007	0.007
Ejection fraction: 35–50%	−0.279	−0.001	0.119	0.119
Ejection fraction: $<35\%$	−0.938	−0.005	0.146	0.151
Reoperation*	−0.581	0.001	0.153	0.167
Diabetes*	−0.254	0.001	0.128	0.132
Pre-op diuretic*	−0.426	0.002	0.148	0.155
Pre-op ventilation*	−1.063	0.009	0.454	0.543
Peripheral vascular disease*	−0.606	0.003	0.147	0.155
Cerebrovascular disease*	−0.316	0.003	0.158	0.163
Dialysis/elevated creatinine*	−0.315	0.001	0.140	0.142
Congestive heart failure*	−0.535	−0.002	0.143	0.151
Number of diseased vessels: $\geqslant 3$	−0.304	−0.010	0.176	0.181
Number of diseased vessels: main left stenosis	−0.556	−0.010	0.194	0.196

theory, it may be preferable to use a resampling variance estimate, such as the bootstrap or its approximation the jack-knife [11]. Both are convenient with the usual availability of good computing facilities. Though the sample size is quite large here, we discuss jack-knife procedures because of their robustness and their diagnostic benefit. Table V provides jack-knifed estimates of the bias in the estimated parameters from the fitted simultaneous model (5) and jack-knifed estimates of their standard errors. It is apparent that maximum likelihood asymptotic theory works quite well here, as biases are negligible, and the likelihood-based standard errors are quite close to the jack-knifed ones. Plots of the jack-knifed estimates, for each covariate, versus the case deleted, are useful for case-deletion diagnostics, in that they can pinpoint observations which have undue influence on covariate estimates. In this example, these plots, not shown here, provide no striking evidence of influential cases.

4. DISCUSSION

The model discussed here provides a straightforward way of separating mortality after surgery into two outcomes to reflect severity of response to a surgical treatment. It provides for parsimony in representation and we have had no difficulties implementing its fit. In general, the non-simultaneous fitting offers greater flexibility. However, the simultaneous model is a tool which aids in understanding the nature of the joint effects on short- and long-term survival, to see whether the parameters from the long-term model are modulated in the same

fashion as the short-term, for example. There is ease of interpretation afforded when τ and σ are unity.

Other forms than the logistic regression model can be used for modelling the probability of operative mortality as a function of covariates; for example, the log–log link defined by $\log(-\log(\mathbf{p})) = \tau\mathbf{X}\beta$ or the complementary log–log link defined by $\log(-\log(1-\mathbf{p})) = -\tau\mathbf{X}\beta$. In addition, an interesting and logical extension of the simultaneous model discussed here is one which fits a logistic regression model to operative mortality together with Cox's proportional hazards model for long-term survival. This may be more robust than the use of the Weibull model for long-term survival. In a recent publication, Chevret *et al.* [12] used a Markov process approach to address a similar issue of modelling two endpoints; further exploration of this approach in the current context would also be useful.

APPENDIX A

Let

$$a_i = \exp(-\tau\mathbf{X}_i\beta + \mathbf{Z}_i\gamma)$$

$$V_i = \left(\frac{w_i - \mathbf{X}_i^{\star}}{\sigma}\right)$$

For the model discussed in Section 3.3, the components of the score vector and the information matrix are the following:

$$\frac{\partial \log \mathscr{L}}{\partial \gamma_l} = \sum_{i=1}^{n}\left(z_i - \frac{a_i}{1+a_i}\right)Z_{il}$$

$$\frac{\partial \log \mathscr{L}}{\partial \beta_l} = -\tau\sum_{i=1}^{n}\left(z_i - \frac{a_i}{1+a_i}\right)X_{il} - \frac{1}{\sigma}\sum_{i\in D}X_{il}^{\star} + \frac{1}{\sigma}\sum_{i\in D,C}X_{il}^{\star}\exp(V_i)$$

$$\frac{\partial \log \mathscr{L}}{\partial \tau} = -\sum_{i=1}^{n}\left(z_i - \frac{a_i}{1+a_i}\right)\mathbf{X}_i\beta$$

$$\frac{\partial \log \mathscr{L}}{\partial \sigma} = -\frac{r}{\sigma} - \frac{1}{\sigma}\sum_{i\in D}V_i + \frac{1}{\sigma}\sum_{i\in D,C}V_i\exp(V_i)$$

$$\frac{\partial^2 \log \mathscr{L}}{\partial \gamma_l \partial \gamma_m} = -\sum_{i=1}^{n}\frac{a_i}{(1+a_i)^2}Z_{il}Z_{im}$$

$$\frac{\partial^2 \log \mathscr{L}}{\partial \gamma_l \partial \beta_m} = \tau\sum_{i=1}^{n}\frac{a_i}{(1+a_i)^2}Z_{il}X_{im}$$

$$\frac{\partial^2 \log \mathscr{L}}{\partial \gamma_l \partial \tau} = \sum_{i=1}^{n}(\mathbf{X}_i\beta)\frac{a_i}{(1+a_i)^2}Z_{il}$$

$$\frac{\partial^2 \log \mathscr{L}}{\partial \gamma_l \partial \sigma} = 0$$

$$\frac{\partial^2 \log \mathscr{L}}{\partial \beta_l \partial \beta_m} = -\tau^2 \sum_{i=1}^{n} \frac{a_i}{(1+a_i)^2} X_{il} X_{im} - \frac{1}{\sigma^2} \sum_{i \in D,C} X_{il}^{\star} X_{im}^{\star} \exp(V_i)$$

$$\frac{\partial^2 \log \mathscr{L}}{\partial \beta_l \partial \tau} = -\sum_{i=1}^{n} \left(z_i - \frac{a_i}{1+a_i} \right) X_{il} - \tau \sum_{i=1}^{n} \mathbf{X}_i \beta \frac{a_i}{(1+a_i)^2} X_{il}$$

$$\frac{\partial^2 \log \mathscr{L}}{\partial \beta_l \partial \sigma} = \frac{1}{\sigma^2} \sum_{i \in D} X_{il}^{\star} - \frac{1}{\sigma^2} \sum_{i \in D,C} X_{il}^{\star} \exp(V_i) - \frac{1}{\sigma^2} \sum_{i \in D,C} X_{il}^{\star} V_i \exp(V_i)$$

$$\frac{\partial^2 \log \mathscr{L}}{\partial \tau^2} = -\sum_{i=1}^{n} (\mathbf{X}_i \beta)^2 \frac{a_i}{(1+a_i)^2}$$

$$\frac{\partial^2 \log \mathscr{L}}{\partial \tau \partial \sigma} = 0$$

$$\frac{\partial^2 \log \mathscr{L}}{\partial \sigma^2} = \frac{r}{\sigma^2} + \frac{2}{\sigma^2} \sum_{i \in D} V_i - \frac{2}{\sigma^2} \sum_{i \in D,C} V_i \exp(V_i) - \frac{1}{\sigma^2} \sum_{i \in D,C} V_i^2 \exp(V_i)$$

The partitioned form of the observed information matrix $\mathbf{I}_0$ is of the form

$$- \begin{bmatrix} \frac{\partial^2 \log \mathscr{L}}{\partial \gamma \partial \gamma'} & \frac{\partial^2 \log \mathscr{L}}{\partial \gamma \partial \beta'} & \frac{\partial^2 \log \mathscr{L}}{\partial \gamma \partial \tau} & \frac{\partial^2 \log \mathscr{L}}{\partial \gamma \partial \sigma} \\ \frac{\partial^2 \log \mathscr{L}}{\partial \beta \partial \gamma'} & \frac{\partial^2 \log \mathscr{L}}{\partial \beta \partial \beta'} & \frac{\partial^2 \log \mathscr{L}}{\partial \beta \partial \tau} & \frac{\partial^2 \log \mathscr{L}}{\partial \beta \partial \sigma} \\ \frac{\partial^2 \log \mathscr{L}}{\partial \tau \partial \gamma'} & \frac{\partial^2 \log \mathscr{L}}{\partial \tau \partial \beta'} & \frac{\partial^2 \log \mathscr{L}}{\partial \tau^2} & \frac{\partial^2 \log \mathscr{L}}{\partial \tau \partial \sigma} \\ \frac{\partial^2 \log \mathscr{L}}{\partial \sigma \partial \gamma'} & \frac{\partial^2 \log \mathscr{L}}{\partial \sigma \partial \beta'} & \frac{\partial^2 \log \mathscr{L}}{\partial \sigma \partial \tau} & \frac{\partial^2 \log \mathscr{L}}{\partial \sigma^2} \end{bmatrix}_{(\hat{\gamma},\hat{\beta},\hat{\tau},\hat{\sigma})}$$

In the iteration process, let ξ_0 be the initial estimate of the parameter vector $\xi = (\beta, \gamma, \tau, \sigma)$. Calculate $\mathbf{U}(\xi_0)$ and $\mathbf{I}(\xi_0)$. The next approximation ξ_1 to ξ is given by

$$\xi_1 = \xi_0 - \mathbf{I}(\xi_0)^{-1} \mathbf{U}(\xi_0)$$

For fitting models (4) and (5), an initial value of ξ can be obtained by manipulation of the estimates from (3).

APPENDIX B

Estimated covariances of the parameter estimates from the fitted simultaneous model (5).

Parameter	Definition
γ_0	Constant in operative mortality model
γ_1	Indicator for female gender
γ_2	Indicator for urgent surgery
γ_3	Indicator for emergency surgery
γ_4	Indicator for periph. vasc. disease in operative mortality
γ_5	Indicator for rural residence
β_0	Constant in long-term survival model
β_1	Age-65
β_2	Indicator for ejection fraction: 35–50%
β_3	Indicator for ejection fraction $<35\%$
β_4	Indicator for reoperation
β_5	Indicator for diabetes
β_6	Indicator for pre-op diuretic use
β_7	Indicator for pre-op ventilation/intubation
β_8	Indicator for periph. vasc. disease in long-term model
β_9	Indicator for cerebrovascular disease
β_{10}	Indicator for dialysis/elevated creatinine
β_{11}	Indicator for congestive heart failure
β_{12}	Indicator for three diseased vessels
β_{13}	Indicator for main left stenosis

	γ_0	γ_1	γ_2	γ_3	γ_4	γ_5
γ_0	0.0501	−0.0139	−0.0198	−0.0218	−0.0161	−0.0279
γ_1		0.0431	−0.0016	−0.0026	0.0015	0.0008
γ_2			0.0429	0.0221	−0.0017	−0.0022
γ_3				0.1265	0.0029	0.0004
γ_4					0.1005	0.0008
γ_5						0.0427

	γ_0	γ_1	γ_2	γ_3	γ_4	γ_5
β_0	0.0046	0.0010	−0.0014	0.0034	−0.0047	0.0005
β_1	0.0000	0.0001	0.0001	0.0000	0.0000	0.0000
β_2	−0.0001	−0.0005	0.0003	0.0011	0.0003	0.0000
β_3	0.0007	−0.0016	0.0001	−0.0003	−0.0003	−0.0007
β_4	−0.0001	−0.0015	0.0003	−0.0001	0.0005	0.0003
β_5	0.0002	0.0007	0.0000	−0.0003	−0.0007	−0.0004
β_6	−0.0007	0.0012	0.0008	0.0008	−0.0001	0.0001
β_7	−0.0010	−0.0001	0.0009	0.0342	0.0013	−0.0010
β_8	−0.0047	−0.0003	−0.0004	0.0003	0.0182	0.0002
β_9	0.0005	0.0004	−0.0001	−0.0008	−0.0004	−0.0007
β_{10}	−0.0004	−0.0007	−0.0004	−0.0011	0.0007	0.0012
β_{11}	−0.0003	0.0006	0.0006	0.0021	0.0002	−0.0001
β_{12}	0.0004	−0.0008	0.0001	−0.0051	0.0000	−0.0001
β_{13}	−0.0001	−0.0011	0.0033	−0.0035	−0.0002	−0.0013

	β_0	β_1	β_2	β_3	β_4	β_5	β_6	β_7	β_8	β_9	β_{10}	β_{11}	β_{12}	β_{13}
β_0	0.0307	−0.0001	−0.0048	−0.0046	−0.0020	−0.0020	0.0003	−0.0020	−0.0022	−0.0010	−0.0005	0.0007	−0.0252	−0.0255
β_1		0.0000	0.0000	0.0001	0.0000	0.0001	0.0000	0.0001	0.0000	−0.0001	0.0000	−0.0001	−0.0001	−0.0001
β_2			0.0141	0.0070	−0.0010	0.0002	0.0003	−0.0015	−0.0006	−0.0001	0.0003	−0.0023	−0.0011	−0.0004
β_3				0.0212	−0.0020	−0.0005	−0.0020	−0.0049	−0.0006	0.0009	0.0003	−0.0076	−0.0009	−0.0004
β_4					0.0235	0.0014	−0.0012	0.0018	0.0001	0.0015	−0.0017	0.0011	−0.0008	0.0000
β_5						0.0165	−0.0028	0.0003	−0.0016	−0.0007	−0.0013	−0.0001	−0.0011	0.0002
β_6							0.0220	0.0042	−0.0015	0.0001	−0.0037	−0.0062	−0.0013	−0.0003
β_7								0.2062	0.0008	−0.0008	−0.0006	−0.0040	0.0018	−0.0003
β_8									0.0215	−0.0076	−0.0016	−0.0010	−0.0006	−0.0013
β_9										0.0249	−0.0017	0.0004	−0.0005	−0.0013
β_{10}											0.0196	−0.0022	−0.0009	−0.0010
β_{11}												0.0206	−0.0007	−0.0011
β_{12}													0.0311	0.0270
β_{13}														0.0375

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