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Predicting Clustered Dental Implant Survival Using Frailty Methods

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Abstract

The purpose of this study was to predict future implant survival using information on risk factors and on the survival status of an individual's existing implant(s). We considered a retrospective cohort study with 677 individuals having 2349 implants placed. We proposed to predict the survival probabilities using the Cox proportional hazards frailty model, with three important risk factors: smoking status, timing of placement, and implant staging. For a non-smoking individual with 2 implants placed, an immediate implant and in one stage, the marginal probability that 1 implant would survive 12 months was 85.8% (95%CI: 77%, 91.7%), and the predicted joint probability of surviving for 12 months was 75.1% (95%CI: 62.1%, 84.7%). If 1 implant was placed earlier and had survived for 12 months, then the second implant had an 87.5% (95%CI: 80.3%, 92.4%) chance of surviving 12 months. Such conditional and joint predictions can assist in clinical decision-making for individuals.

Keywords

clustered data; survival predictions; frailty; correlated survival analysis; proportional hazards model; dental implants

INTRODUCTION

In clinical dental research, each participant often contributes multiple, potentially clustered observations to a database. For example, in dental implants, multiple implants placed within the same individual will be clustered or correlated. It is common practice for those conducting dental research to assume independent outcome observations in survival analyses (Higuchi *et al.*, 1995; Wheeler, 1996; Buser *et al.*, 1997; Brocard *et al.*, 2000; Testori *et al.*, 2001). These approaches tend to underestimate the variability of the estimated covariate effects or survival probabilities, because the possible within-cluster correlations are overlooked. To account for correlation, many authors have recommended randomly selecting 1 implant *per* person, and the use of only the subset for analysis (Lekholm *et al.*, 1999; Herrmann *et al.*, 1999, 2005; Gomez-Roman *et al.*, 2001; Weibrich *et al.*, 2001). However, this approach does not fully utilize all the available information, and thus may be inefficient. This gives rise to the need for the application of novel survival methods that can efficiently analyze clustered dental survival data.

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There have been considerable statistical methods reported for the analysis of clustered survival data (Klein, 1992; Lee *et al.*, 1992; Lin, 1994; Hougard, 1995, 2000; Parner, 1998; Spiekerman and Lin, 1998; Cai *et al.*, 2000, 2002; Fine *et al.*, 2003; Yin and Cai, 2005). Among these, two types of models have been proposed: frailty models and marginal models. Frailty models explicitly specify the within-cluster correlation structure, which allows for joint inference about the survival times within the same cluster. Marginal models leave the correlation structure completely unspecified, but adjust for the correlation by using robust sandwich-type estimators for the variance. Applications of these important methodologies to dental research have not yet been adequately explored.

We have previously applied the marginal approach (Chuang *et al*., 2002b) to predict covariate specific implant failure. The marginal approach, while effective, can predict only marginal survival probabilities of a single implant. In this research, we proposed to apply the frailty approach to predict implant survival accounting for within-individual correlation. In contrast to the marginal approach, the frailty approach allowed us to make joint predictions for several implants in the same individual. The primary purpose of this research was to predict the joint survival probability of multiple implants within the same individual, given their covariate information, and to predict the conditional survival probability of a future implant, given the survival status of an existing implant. The secondary aim was to compare and contrast the marginal and frailty approaches by comparing the point and interval estimates of the survival probabilities obtained based on the 2 methods.

MATERIALS & METHODS

Methods

The research methods have been described in detail in other studies (Chuang *et al.*, 2002a; Vehemente *et al.*, 2002). We conducted a retrospective cohort study design composed of individuals who had at least 1 Bicon® implant placed between May 20, 1992, and July 6, 2000, at the Implant Dentistry Center based at Faulkner Hospital (IDC-FH), Boston, MA, USA. We reviewed the participants' records to collect information regarding exposures associated with implant failures grouped into the following main categories: demographic, health status, anatomic, implant- and abutment-specific, anticipated restoration, peri-operative chemotherapy, reconstructive, and operator. The major outcome variable of interest was implant failure, which was defined as the removal of the implant for any reason (Dental Implant Clinical Research Group, 1997). We estimated survival time by computing the difference in time (mos) between implant placement and implant explantation, or the date of the last follow-up visit, for individuals whose implants had not been removed. The use of human participants in this study followed a protocol approved by the human research committee.

Statistical Issues

In this report, our interest focused on survival prediction for multiple implants under the Cox proportional hazards frailty model (Hougaard, 1995, 2000). Specifically, we assumed that, conditional on some unobserved frailty random variable, the time to dental implant failure would follow a Cox proportional hazards model. Multiple dental implants from each individual share a common frailty random variable, which accounts for the within-individual correlation. Under this model, we described procedures for predicting the conditional and joint survival probabilities for dental implants with given covariate information. In particular, the non-parametric maximum likelihood estimator for the unknown parameters in the model (Parner, 1998) was used to construct plug-in estimators for the survival probabilities. The bootstrap method (Efron and Tibshirani, 1993) was used to obtain the interval estimates. The set of covariates selected to be used in this study—*i.e.*, current tobacco use, timing of implant placement, and implant staging—was previously identified by means of the Cox frailty

regression model, adjusted for clustered observations (Chuang *et al.*, 2005). Databases were stored in SAS-PC Version 8.2 (SAS Institute, Inc., 1999) files. The statistical program for clustered survival predictions was written by the co-author (Cai) in the S-plus environment (Version 6.0, 2000). [We have made the S-plus computer codes available on the Internet at the following addresses: http://biosun1.harvard.edu/~tcai/FUN_CoxFrailtyPred.q and http://biosun1.harvard.edu/~tcai/CoxFrailtyPred.q.]

Statistical Notation

Let T_{ik} denote the failure time of the kth implant for the ith individual, $k = 1,2,3,\ldots,K_i$; $i = 1,2,3,\ldots,n$, where n is the sample size. Let Z_{ik} be the corresponding covariate vector for T_{ik} and C_{ik} be the censoring time. For T_{ik}, one can observe only $X_{ik} = \min(T_{ik}, C_{ik})$ and $\delta_{ik} = 1(T_{ik} = X_{ik})$. Conditional on the covariate vector $Z_i = (Z_{i1},\ldots,Z_{iKi})'$, the censoring vector, $C_i = (C_{i1}, \ldots,C_{iKi})'$, is assumed to be independent of the failure time vector, $T_i = (T_{i1},\ldots,T_{iKi})'$. We assume that, conditional on Z_i and an unobserved frailty w_i, T_{ik} follows a Cox proportional hazards model:

$$\lambda_{ik}(t)=\lambda_0(t)w_i\exp(\beta' Z_{ik}),t>0 \quad (1)$$

where $\lambda_{ik}(t)$ is the hazard function for T_{ik}, $\lambda_0(t)$ is an unspecified baseline hazard function, and β is the true regression coefficient vector. The frailty w_i accounts for the within-individual correlation, due to some unobserved common covariate information. The unobserved W_i*'s* are assumed to be independent and identically distributed, with unit mean and some unknown variance σ^2. Different individuals could have different values of frailty, and the variability in the W_i*'s* reflects the heterogeneity of risks between individuals. For computational convenience, the frailty distribution is often taken to be a Gamma, *i.e.*, $w_i \sim \sigma^2\text{gamma}(\sigma^{-2})$, and thus we assume a gamma-frailty throughout.

Various inference procedures have been proposed for the covariate effect β, the baseline cumulative hazard function, $\Lambda_0(t)=\int_0^t \lambda_0(u)du$, and the variance component σ^2 (Klein, 1992; Nielsen *et al.*, 1992; Parner, 1998). One popular estimator is the non-parametric maximum likelihood estimator (NPMLE) studied by Parner (1998). The NPMLE can be implemented through an EM-algorithm (Therneau and Grambsch, 2000), which alternates between two steps: (1) the M-step, in which β and Λ_0 are updated as in normal Cox regression by treating the current estimates of $\{w_1, \ldots, w_n\}$ as fixed values and offsets; and (2) the E-step, in which $\{w_1,\ldots, w_n\}$ are computed as the expected value, given the current values of β and Λ_0 and the data. These estimates depend on σ^2 and are denoted by $\hat{\beta}(\sigma^2)$ and $\hat{\Lambda}_0(\cdot|\sigma^2)$. σ^2 can then be estimated by maximizing the profile log-likelihood (Parner, 1998). [See Hougaard (2000) and Therneau and Grambsch (2000) for more details on the estimation procedures for β, Λ_0, and the variance component σ^2.]

To predict the survival probabilities for the implants based on the Cox gamma frailty model, we noted that the survival probability for an implant with covariate $\mathbf{Z}$ can be expressed as:

$$S(t|\mathbf{Z})=P(T \geq t|\mathbf{Z})=E\{P(T \geq t|\mathbf{Z},w)|\mathbf{Z}\}=\left\{1+\sigma^2\Lambda_0(t)e^{\beta'\mathbf{Z}}\right\}^{-\sigma^{-2}} \quad (2)$$

Note that $S(t|\mathbf{Z})$ here is the population average survival probability, averaged across all implants with covariate Z and all possible frailty levels w. A plug-in estimator for $S(t|\mathbf{Z})$ may be obtained as $\hat{S}(t|\mathbf{Z}) = \{1 + \hat{\sigma}^2\hat{\Lambda}_0(t)e^{\hat{\beta}'\mathbf{Z}}\}^{-\hat{\sigma}^2}$, where $\hat{\sigma}^2$, $\hat{\beta}$, and $\Lambda\,\hat{}_0$ are the respective estimators for σ^2, β, and Λ_0. The main strength of the frailty model is in its ability to make simultaneous joint inference about the survival probabilities of multiple implants from the same individual. For example, for K implants of an individual with covariate levels $(\mathbf{Z}_{11},\ldots,\mathbf{Z}_{1K})$, the joint survival probability, $S(t_1,\ldots,t_K) = P(T_{11} \geq t_1,\ldots, T_{1K} \geq t_K \mid \mathbf{Z}_{11},\ldots, \mathbf{Z}_{1K})$, can be estimated by

$$\widehat{S}(t_1,\ldots,t_K)=\left\{1+\widehat{\sigma}^2\sum_{k=1}^{K}\widehat{\Lambda}_0(t_K)e^{\widehat{\beta}'\mathbf{Z}_{ik}}\right\}^{-\widehat{\sigma}^{-2}} \quad (3)$$

This also allowed us to predict the conditional survival probability for a future implant, given the information on the survival of existing implants and their covariate levels. This can be achieved based on the definition of the conditional probability:

$$P(T_{1K}\geq t|T_{11}\geq t_1,\ldots,T_{1K-1}\geq t_{K-1},\mathbf{Z}_{11},\ldots,\mathbf{Z}_{1K})=\frac{P(T_{11}\geq t_1,\ldots,T_{1K-1}\geq t_{K-1},T_{1K}\geq t|\mathbf{Z}_{11},\ldots,\mathbf{Z}_{1K})}{P(T_{11}\geq t_1,\ldots,T_{1K-1}\geq t_{K-1}|\mathbf{Z}_{11},\ldots,\mathbf{Z}_{1K-1})} \quad (4)$$

To construct confidence intervals for these predicted survival probabilities, we needed to account for the variabilities in all the estimated parameters, and thus required the estimation of the covariance of $\hat{\theta}=\hat{\sigma}^2,\hat{\beta},\hat{\Lambda}_0(t_1),\ldots,\hat{\Lambda}_0(t_K))'$. Due to the difficulty in obtaining an analytical variance-covariance estimator for $\hat{\theta}$, we approximated the limiting distribution of $\hat{\theta}$ by the bootstrap method (Efron and Tibshirani, 1993; Monaco *et al.*, 2005), which is widely used in practice when analytical variance of an estimator is difficult to obtain. To account for within-individual correlations, we treated multiple observations from the same individual as a unit, and thus the original dataset was treated as n datapoints. We obtained each bootstrap sample by sampling a size of n datapoints with replacement from the original data; we used a total of 1000 bootstrap samples. For the *m*th bootstrap sample, we obtained a bootstrap estimator for 3, denoted by $\hat{\theta}_{(m)}$. Plugging $\hat{\theta}_{(m)}$ into Eq. (3), we obtained a corresponding bootstrap estimator for the survival probability $\hat{S}_{(m)}(t_1,\ldots t_K)$. Then the distribution of $\hat{\theta}$, $\hat{S}(t_1,\ldots t_K)$, and the estimated conditional probabilities could be approximated by the empirical distribution of their respective bootstrap replicates. For example, the variance of $\hat{S}(t_1,\ldots t_K)$ can be estimated by

$$\frac{1}{1000}\sum_{m=1}^{1000}\left\{\widehat{S}_{(m)}(t_1,\ldots t_K)-\widehat{S}(t_1,\ldots t_K)\right\}^2.$$

A 95% confidence interval for $S(t_1,\ldots,t_K)$ can be obtained based on the 2.5% and 97.5% quantiles of $\{\hat{S}_{(1)}(t_1,\ldots t_K),\ \ldots,\hat{S}_{(1000)}(t_1,\ldots t_K)\}$.

RESULTS

The study group had 677 participants, who had 2349 dental implants placed. On average, 3.5 implants (range, 1–22) were placed *per* person. There were 137 implants that failed. There were 57 smokers (10.3%, N = 554). Out of 2349 implants, 339 (14.4%) were placed in one stage, and 243 (10.3%) were placed immediately after tooth extraction. The details of the descriptive statistics have been described (Chuang *et al.*, 2002a).

We previously identified 3 key variables associated with implant survival: current tobacco use (yes or no), timing of implant placement (delayed *vs*. immediate), and implant staging (one- or two-stage) (Chuang *et al.*, 2002a). Based on a clustered marginal approach (Chuang *et al.*, 2002b), we found that, among those who had a delayed procedure, did not smoke, and underwent a two-stage implant procedure (best-case scenario), the predicted one- and five-year survival rates were 97.2% and 93.4%, respectively. For those who had an immediate implant placed, smoked, and underwent a one-stage procedure (worst-case scenario), the predicted survival rates at 1 and 5 yrs were 58.5% and 27.6%, respectively. We compared the predicted survival probabilities based on the marginal approach (Chuang *et al.*, 2002b) and the current frailty prediction method for non-smokers with immediate implant placement in one stage (Table 1). The predicted 12-month (1 yr) survival was 83.7%, based on the marginal method, and 85.8% with the frailty method. Estimates from these 2 methods were not drastically different, suggesting that both models may fit the data well.

In this study, we were particularly interested in making joint inference about multiple implants in the same individual. First, we considered the subgroup of non-smoking persons having 2 immediate implants placed in 1 stage. The predicted survival probability (95% confidence interval) was 75.1% (62.1%, 84.7%) for both implants surviving 12 mos (1 yr), and was 55.4% (36.2%, 71.6%) for both implants surviving 60 mos (5 yrs) (Table 2). In an individual with an existing implant, one may be interested in predicting the survival for a future implant, given the survival status of the current implant. For example, for a non-smoker with an existing immediate one-stage implant that has survived 1 yr, the predicted probability for a future implant with the same covariate surviving one year is 87.5%, with a 95% confidence interval (80.3%, 92.4%) (Table 3). We next considered those who were non-smokers having the first implant placed in a delayed fashion in 1 stage, and having the second implant placed in an immediate fashion in 1 stage. The predicted one- and five- survival rates for such 2 implants were 79.6% (70.3%, 86.5%) and 61.6% (44.0%, 74.4%), respectively (Table 4). The results of the above analyses were specific and unique only to the frailty approach prediction method. This cannot be performed with the marginal approach method.

DISCUSSION

Multivariate failure times with clustered or dependent data observations are commonly encountered in dental research. To make valid and efficient statistical inference in such settings, one needs to account for within-cluster correlations. Useful tools for analyzing clustered survival data include the marginal and frailty survival models. The marginal approach leaves the correlation structure unspecified, and adjusts for the correlation by using a sandwich-type variance estimator (Lee *et al.*, 1992). The frailty approach specifies the correlation structure through the distribution of the unobserved shared frailty random variable w. One main advantage of the frailty model is in its ability to make joint prediction of the survival of multiple implants from the same individual. It also allows us to predict the survival of a future implant based on the survival status of current implants and covariate information. The purposes of this study were two-fold: to produce joint predictions of the survival of multiple implants, based on valid and efficient survival methods, accounting for within-cluster correlation; and to compare and contrast how the marginal approach and the frailty approach differ in survival predictions, given important exposure information. The estimators used in this paper for the unknown parameters in the frailty model were based on the non-parametric maximum likelihood method (Parner, 1998), and the implementation of this method has been discussed in detail (Therneau and Grambsch, 2000).

To illustrate the strength of the frailty model, we investigated within-cluster implant prediction using the ‘other implant(s) information’ from the same individual. Our first model (marginal method) consisted of results from our previous study (Chuang *et al.*, 2002b) (Table 1). In our second model, we utilized the frailty approach using implants from the same individual for survival predictions (frailty method). When comparing the two valid analytic strategies, we found that the one- and five-year survival point estimates did not differ drastically, but the variance estimates did differ. The 95% confidence intervals for the marginal method were wider than those of the frailty method. This can be partly attributed to the fact that the frailty method assumes a stronger model by specifying the correlation structure. In the setting of clustered observations, we believe that both methods are valid and efficient, as long as the assumed models fit the data well. The ultimate choice of method depends on the research question and the goals for the particular study.

In summary, clustered survival observations are frequently encountered in many different areas of person-oriented dental research. In particular, we are interested in making joint predictions for the survival of multiple dental implants in the same individual, given various clinical parameters. The Cox frailty model used in this study produced valid and efficient estimates,

with the strength of allowing for joint prediction. Using available information about clinical parameters, along with the survival status of existing implants, we were able to make more precise predictions about the survival of future implants. Such predictions can assist in surgical treatment-planning and thus lead to better clinical decision-making and patient care.

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Table 1

Predicted S(t), the Survival Probability of T ≥ t (mos), for an Immediate Implant Placed in One Stage in a Non-smoker, along with 95% Confidence Intervals, Based on Both the Marginal Method and the Frailty Method

t	Marginal Method			Frailty Method		
	Predicted $\hat{S}(t)$	95%CI Lower Bound	95%CI Upper Bound	Predicted $\hat{S}(t)$	95%CI Lower Bound	95%CI Upper Bound
12	83.7	73.3	94.2	85.8	77.0	91.7
24	77.2	62.2	92.3	80.7	68.9	88.8
36	73.6	55.9	91.3	77.9	64.4	87.1
48	67.9	46.4	89.3	73.5	57.7	84.5
60	65.2	42.2	88.2	71.5	54.5	83.6

Table 2

Predicted $S(t_1,t_2)$, the Joint Survival Probability of $T_1 \geq t_1$ (mos) and $T_2 \geq t_2$ (mos) for Two Immediate Implants Placed in One Stage in a Non-smoker

t_1	t_2	Predicted $S(t_1,t_2)$	95%CI Lower Bound	95%CI Upper Bound
12	12	75.1	62.1	84.7
12	24	71.1	56.3	82.1
12	36	68.9	53.5	80.6
12	48	65.4	48.2	78.0
12	60	63.8	46.2	77.4
24	24	67.6	51.3	79.9
24	36	65.5	49.1	78.3
24	48	62.3	44.3	75.9
24	60	60.9	42.5	75.1
36	36	63.6	46.0	77.0
36	48	60.6	42.4	74.6
36	60	59.2	40.6	73.8
48	48	57.8	38.6	73.1
48	60	56.6	37.2	72.3
60	60	55.4	36.2	71.6

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Table 3

Predicted Conditional Probability of $T_2 \geq t_2$ (mos) Given $T_1 \geq t_1$ (mos) for Two Immediate Implants Placed in Stage One in a Non-smoker

t_1	t_2	Predicted Conditional Probability, $\hat{S}(t)$	95%CI Lower Bound	95%CI Upper Bound
12	12	87.5	80.3	92.4
12	24	82.9	72.8	89.6
12	36	80.3	68.0	87.9
12	48	76.2	61.7	85.7
12	60	74.3	58.9	84.9
24	12	88.1	81.4	92.7
24	24	83.7	74.2	89.9
24	36	81.2	69.6	88.3
24	48	77.2	63.8	86.0
24	60	75.4	61.3	85.3
36	12	88.5	81.9	93.0
36	24	84.1	74.9	90.1
36	36	81.7	70.8	88.4
36	48	77.8	64.9	86.3
36	60	76.1	62.6	85.5
48	12	89.0	82.6	93.3
48	24	84.9	76.0	90.5
48	36	82.5	72.0	88.8
48	48	78.8	66.5	86.6
48	60	77.1	64.3	85.8
60	12	89.3	82.8	93.4
60	24	85.2	76.4	90.6
60	36	82.9	72.6	89.0
60	48	79.2	66.9	86.7
60	60	77.5	64.9	86.0

Table 4

Predicted Joint Probabilities of T_1 and T_2 Both Exceeding t (mos) Given the Different Exposures for the Two Implants

$t = t_1 = t_2$	Smoke	First Implant Immediate	Staging	Smoke	Second Implant Immediate	Staging	Predicted Survival Probability, $\hat{S}(t)$	95% CI Lower Bound	95% CI Upper Bound
12	No	No	1	No	Yes	1	79.6	70.3	86.5
12	No	No	1	No	No	2	89.5	85.0	92.7
12	No	Yes	1	No	Yes	2	82.4	72.9	88.9
12	Yes	No	1	Yes	Yes	1	52.6	33.4	71.3
12	Yes	No	1	Yes	No	2	71.0	57.6	83.9
12	Yes	Yes	1	Yes	Yes	2	57.3	37.2	75.0
60	No	No	1	No	Yes	1	61.6	44.0	74.4
60	No	No	1	No	No	2	77.9	67.4	84.6
60	No	Yes	1	No	Yes	2	66.0	48.8	77.9
60	Yes	No	1	Yes	Yes	1	31.2	12.2	53.7
60	Yes	No	1	Yes	No	2	50.1	30.5	71.2
60	Yes	Yes	1	Yes	Yes	2	35.4	15.2	57.2