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## ABSTRACT

Because dental implant failure patterns tend to cluster within subjects, we hypothesized that the risk of implant failure varies among subjects. To address this hypothesis in the setting of clustered, correlated observations, we considered a retrospective cohort study where we identified a cohort having at least one implant placed. The cohort was composed of 677 patients who had 2349 implants placed. To test the hypothesis, we applied an innovative analytic method, *i.e.*, the Cox proportional hazards model with frailty, to account for correlation within subjects and the heterogeneity of risk, *i.e.*, frailty, among subjects for implant failure. Consistent with our hypothesis, risk for implant failure among subjects varied to a statistically significant degree ( $p = 0.041$ ). In addition, the risk for implant failure is significantly associated with several factors, including tobacco use, implant length, immediate implant placement, staging, well size, and proximity of adjacent implants or teeth.

**KEY WORDS:** survival analysis, dental implants, risk factors, follow-up study, Cox regression analysis, clustered survival data, frailty approach, gamma distribution.

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# Frailty Approach for the Analysis of Clustered Failure Time Observations in Dental Research

## INTRODUCTION

Most current survival analyses used in patient-oriented dental research assume that the underlying risk of outcomes is the same among different subjects (homogenous risk). Common sense dictates that the underlying risk of outcomes would depend on subject characteristics and may vary among subjects. In the setting of dental implants, failures tend to cluster within subjects, suggesting heterogeneous risk among subjects. As such, newer survival methodologies need to be developed and applied to adjust survival estimates for both within-subject clustering of observations and heterogeneous risk among subjects.

Using a marginal approach with the proportional hazards model, our group has published previous work estimating implant survival and identifying risk factors for failure in the presence of clustered observations (Chuang *et al.*, 2001, 2002). This analytic approach, while representing a significant advancement in the analyses of clustered observations, does not address the issue of heterogeneity of risk among subjects. In addition, the marginal regression approach, while having the benefit of not requiring specification of the correlation structure within subjects, cannot predict the risk of future implant by the use of failure times and covariate information from other members (implants) in the same cluster (patient).

In this paper, we consider the frailty model as an alternative approach to the analysis of correlated implant failure time data. A frailty model is a mixed-effects model, where the frailty, an unobserved cluster-specific univariate component, has a multiplicative effect on its hazard function. In contrast to the marginal approach, the frailty approach provides means to examine the heterogeneity among subjects and to estimate the distribution of a future failure time with the use of failure times and covariate information from other members in the cluster. For these reasons, frailty models have been widely used for the analysis of clustered failure time data (Clayton, 1978; Hougaard, 1986; Oakes, 1992). Among frailty models, Cox's proportional hazards model, with a gamma frailty, is the most popular (Klein, 1992; Nielsen *et al.*, 1992; Murphy, 1994, 1995; Pamer, 1998). This model assumes that, conditional on the value of the unobserved frailty, the failure times follow the usual proportional hazards model. Excellent discussions on this model can be found in Hougaard (1995, 2000) and Therneau and Grambsch (2000). Application of this method in patient-oriented dental research to date has been sparse (Kalwizki *et al.*, 2002).

The study's specific aims were to determine whether the risk of implant failure varies among subjects and to identify factors associated with the risk of implant failure. Based on the observation that implant failures cluster within subjects, we hypothesized that the risk for implant failure among subjects is heterogeneous, *i.e.*, some subjects are more likely to have implants fail than others, as evidenced by a frailty term with non-zero variance. The null hypothesis was that the variance of the frailty term is

zero. By applying the Cox proportional hazards frailty model, we tested the hypothesis by determining whether the variance of the frailty term was statistically different from zero. We believe that this is one of the very few reports of theoretical clustered frailty survival methodologies with integrated clinical applications in dental research (Therneau and Grambsch, 2000).

## MATERIALS & METHODS

### Study Design/Source Population

To address our specific aims, we re-analyzed data from a retrospective cohort study on dental implant failure. The study cohort had different exposures and was derived from the source population of patients who had at least one dental implant (Bicon®, Inc., Boston, MA, USA) inserted at the Implant Dentistry Center at Faulkner Hospital (IDC-FH, Boston, MA, USA), between May 20, 1992, and July 6, 2000 (Rothman and Greenland, 1998). This study was approved by the institutional human studies review committee.

Criteria for study inclusion were that all surgical treatment was completed at the IDC-FH, and all patients—regardless of medical health status, age, gender, race, or abilities—were also included. Exclusion criteria included inadequate or unavailable patient charts.

The details of the study and outcome variables have been described by Chuang *et al.* (2002). In brief, patient charts were reviewed for abstract variables grouped into the following categories: demographics, health status, anatomic, implant- and abutment-specific, anticipated restoration, peri-operative chemotherapy, reconstructive, and operator. The major outcome variable of interest was implant failure, defined as the removal of the implant (explantation) for any reason (Dental Implant Clinical Research Group, 1997). Survival time was estimated by computation of the difference in time (mos) between implant placement and explantation, or the date of the last follow-up visit for patients whose implants had not been removed.

### Statistical Issues

Two fundamental approaches to the modeling of clustered or dependent data have gained popularity over the last few years. In the first approach, the marginal approach, the dependence structure between failure times is not specified. One estimates the regression parameters by ignoring within-subject correlations. But the variance-covariance matrix of the estimators is estimated, accounting for the possible correlation by the use of a robust sandwich estimator. These models, which we will call 'variance-corrected' models, can be estimated in S-plus (2000) and in SAS (2001) (proc phreg with the 'covsandwich [aggregate]' option, or 'covs[aggregate]' option). In clinical dental applications, investigators have illustrated the principal ideas and procedures for estimating these models using the marginal Cox proportional hazards model (Chuang *et al.*, 2002). This approach, however, fails to address whether the underlying risk varies among subjects.

The second approach is to apply the frailty model, in which the association between failure times is explicitly modeled with a random-effect term, commonly called the 'frailty'. Frailties are unobserved random factors shared by all members (implants) of the same cluster (patient). These unmeasured effects are assumed to follow a given statistical distribution, often the gamma distribution, with mean equal to 1 and unknown variance. This paper considers application of the Cox proportional hazards frailty model to the setting of implant failure.

### Statistical Notations

Let  $T_{ik}$  denote the failure time of the  $k$ th implant in the  $i$ th individual,  $k = 1, 2, 3, \dots, K_i$ ;  $i = 1, 2, 3, \dots, n$ . We assume that  $K_i$  is relatively small with respect to  $n$ , the total number of patients in the study. Let  $Z_{ik}$  be a  $p \times 1$  vector of bounded covariates and  $C_{ik}$  be the censoring variable. For  $T_{ik}$ , one can observe only a bivariate vector  $(X_{ik}, \delta_{ik})$ , where  $X_{ik} = \min(T_{ik}, C_{ik})$  and  $\delta_{ik} = 1$ , if  $T_{ik} = X_{ik}$  is observed, 0 otherwise. Conditional on the covariate vector  $Z'_i = (Z_{i1}, \dots, Z_{iK_i})'$ , the censoring vector,  $C'_i = (C_{i1}, \dots, C_{iK_i})'$ , is assumed to be independent of the failure time variables  $T'_i = (T_{i1}, \dots, T_{iK_i})'$ . We supposed that, conditional on the frailty,  $b_i$ , the hazard function  $\lambda_{ik}(t)$  for  $T_{ik}$  follows the usual proportional hazards form:

$$\lambda_{ik}(t) = \lambda_0(t) \exp(\beta' Z_{ik} + b_i), t > 0 \quad (*),$$

where  $\lambda_0(t)$  is an unspecified baseline hazard function and  $\beta'$  denoted the vector of the true regression coefficients. The random effect (frailty)  $b_i$  accounts for the within-subject correlation due to some unobserved common covariate information. The unobserved  $b_i$ s are assumed to be independent and identically distributed with unit mean and some unknown variance  $\sigma^2$ . Each subject could have different values of random effects, and the variability in the  $b_i$ s reflects the heterogeneity of risks between subjects. For computational convenience and convergence, the frailty distribution is often taken to be a gamma. This leads to the random effect in model (\*) with  $\exp(b_i) \sim \sigma^2 \text{gamma}(\sigma^{-2})$ .

For inference about the regression parameters  $\beta$  and the variance component  $\sigma^2$ , non-parametric maximum likelihood estimators (NPMLE) have been studied. The NPMLEs are consistent and asymptotically normal (Nielsen *et al.*, 1992; Murphy, 1994, 1995). The NPMLEs are often obtained numerically by an EM algorithm proposed by Klein (1992). The variance-covariance matrix of the NPMLEs is estimated by the inverse of a discrete observed information matrix (Parner, 1998).

### Data Management and Analysis

We created a database with appropriate checks to identify errors. Descriptive statistics were generated. We used univariate analyses to identify covariates associated with survival. Covariates with  $p$ -values  $\leq 0.15$ , based on univariate analyses and biologically relevant variables, were entered into a multivariate Cox proportional hazards frailty regression model. Estimates of the regression coefficients and their standard errors were provided. To examine our main hypothesis about heterogeneity of risks between subjects, we used a likelihood ratio test for testing the null hypothesis that the frailty term has zero variance—that is,  $\sigma^2 = 0$ . It is important to note that because zero is on the boundary of the parameter space, the null distribution of the likelihood ratio test is no longer a chi-square distribution, but rather a 50:50 mixture of a chi-square with 0 degree of freedom and a chi-square with 1 degree of freedom (Self and Liang, 1987; Nguti *et al.*, 2003). Fitting a Cox proportional hazards model with a gamma frailty is not difficult to implement with the use of the statistical software S-plus (2000). We utilized this user-friendly software (coxph command with function frailty) for implementing the estimation and hypothesis testing procedures.

## RESULTS

The study cohort was composed of 677 subjects who had a total of 2349 dental implants inserted. The cohort's mean

age was  $53.1 \pm 13.8$  yrs, and 50.4% were female. The descriptive statistics for all of the study variables have been published previously (Chuang *et al.*, (2002). Briefly, most subjects ( $\approx 99\%$ ) were healthy or had mild systemic disease (ASA scores  $\leq 2$ ), and 10.3% reported tobacco use at the time the implant was placed. The mean duration of follow-

up was 23.8 mos (ranges, 0.3 to 90.9 mos). During the study interval, 137 ( $\sim 6\%$ ) implants failed.

The univariate relationships between the study variables and implant failure have been summarized (Table 1). Based on the univariate analyses, we identified the following variables to be at least marginally associated with implant failure at the

significance level of  $p \leq 0.15$ : current tobacco use, history of tobacco use, anatomic location, implant length, coating, well size, prosthetic type, abutment diameter, proximity of the implant to other teeth or implants, immediate placement of implants, and implant stage.

Parsimonious multivariate Cox frailty regression models were developed for further assessment of the covariate effects on implant failure, accounting for the clustering effect of implants within the same subject. Variables included in the multivariate model were selected because of either biologic importance (such as age and gender) or statistical significance, with  $p$ -value  $\leq 0.15$  in the univariate analyses (Table 2). In the parsimonious multivariate Cox model, *i.e.*, a model based on a reduced set of predictors, current tobacco use, implant length, well size, immediate implant, and implant staging remained statistically associated with implant failure ( $p \leq 0.05$ ). The variance of the frailty term was statistically significantly different from zero ( $p = 0.041$ ), suggesting that the risk of implant failure was heterogeneous among subjects (Table 3).

## DISCUSSION

Applications of theoretical survival methods for estimating and predicting risk have been a major challenge in dental research for decades (Kalwizki *et al.*, 2002). Datasets from patient-oriented dental

**Table 1.** Univariate Analysis for Factors (Exposures) Associated with Implant Failure (n = 677 patients; k = 2349 dental implants)

	Hazard Ratio	95% CI	Frailty Robust P-value
<b>Demographic Variables</b>			
Age at time of first implant	1.00	(0.99, 1.02)	0.70
Gender (female)	0.83	(0.54, 1.27)	0.38
<b>Health Status Variables</b>			
ASA status	1.24	(0.81, 1.89)	0.32
Medical compromise	0.81	(0.38, 1.73)	0.59
Current tobacco use	3.48	(2.00, 6.06)	< 0.01
History of tobacco use	3.22	(1.85, 5.61)	< 0.01
<b>Anatomic Variables</b>			
Anatomic position of the implant (post. maxilla)	2.65	(1.10, 6.41)	0.03
Anatomic position of the implant (ant. maxilla)	1.95	(0.78, 4.90)	0.16
Anatomic position of the implant (post. mandible)	1.58	(0.64, 3.90)	0.33
Anatomic position of the implant (ant. mandible)	1.00		
Proximity of implant (1 tooth and 1 implant)	0.41	(0.23, 0.76)	< 0.01
Proximity of implant (2 adjacent implants)	0.17	(0.08, 0.39)	< 0.01
Proximity of implant (1 adjacent implant)	0.43	(0.23, 0.80)	< 0.01
Proximity of implant (2 natural teeth)	0.42	(0.22, 0.81)	< 0.01
Proximity of implant (1 adjacent tooth)	0.40	(0.17, 0.97)	0.042
Proximity of implant (no adjacent tooth or implant)	1.00		
Quality of bone	0.90	(0.70, 1.14)	0.37
<b>Implant-specific Variables</b>			
Implant diameter	1.13	(0.85, 1.51)	0.40
Implant length	0.80	(0.71, 0.89)	< 0.01
Coating of implant, HA	0.88	(0.52, 1.50)	0.65
Coating of implant, TPS	2.02	(1.17, 3.46)	0.011
Uncoated implant	1.00		
Well size	1.62	(0.85, 3.09)	0.14
Staging of implant	0.28	(0.17, 0.44)	< 0.01
Immediate implant	1.85	(1.11, 3.08)	0.018
<b>Abutment-specific Variables</b>			
Abutment diameter	1.38	(0.89, 2.14)	0.15
Abutment angle	0.83	(0.46, 1.50)	0.54
<b>Prosthesis Variables</b>			
Removable denture	2.25	(1.23, 4.12)	< 0.01
Fixed bridge/denture	0.65	(0.39, 1.08)	0.098
Crown	1.00		
<b>Peri-operative Variables</b>			
Antibiotics usage	0.67	(0.41, 1.09)	0.11
<b>Reconstructive Variables</b>			
Bone graft augmentation	1.36	(0.93, 2.00)	0.11
Barrier membrane usage	0.58	(0.17, 2.00)	0.39

research are frequently composed of clustered observations, e.g., caries studies with multiple surfaces *per tooth per subject*, or periodontal research with multiple sites *per tooth per subject*. Additionally, the risk for outcome of interest is frequently assumed to be homogenous among subjects. The recent introduction of the frailty model and its integration with clustered analyses is an important advancement for datasets commonly encountered in patient-oriented dental research, *i.e.*, multiple clustered observations within subjects and heterogeneous risk among subjects.

This study's primary specific aim was to apply the clustered frailty multivariate model to evaluate heterogeneity for implant failure among subjects. Consistent with previous reports, the results of our analyses suggest that the risk for implant failure does vary between subjects (adjusted frailty term with  $p = 0.041$ ) (Aalen, 1988). The study's secondary specific aim was to identify factors associated with the risk of implant failure. The clinical findings associated with an increased risk for implant failure, and confirmed from this study—current tobacco use, implant length, immediate implant placement, staging, well size, and proximity of adjacent implants or teeth—were findings gleaned from the similar dataset published previously (Chuang *et al.*, 2002).

The frailty model is a powerful analytic tool and should be considered in the setting of clustered survival analyses. The inference procedures utilized here are relatively convenient for use with the methodological methods for Cox's gamma frailty model (Klein, 1992; Nielsen *et al.*, 1992; McGilchrist, 1993; Parner, 1998; Therneau and Grambsch, 2000). In this paper, we chose to apply the semi-parametric Cox frailty model, because it simultaneously adjusts parameter estimates for clustered observations and for a heterogeneous individual risk for the outcome of interest. We believe this paper to be among the very few applications of these rigorous survival methods in patient-oriented dental research. The Cox gamma frailty model should be considered as a special case of the linear transformation model, discussed previously, with the log(-log) link function and a log-gamma random effect (Cai *et al.*, 2002). When the Cox frailty model does not fit the data well, previously developed methods provide a useful alternative (Cai *et al.*, 2002).

In a previous study, we applied the marginal Cox approach to model clustered implant data (Chuang *et al.*, 2002). If we were interested in making inferences only regarding the covariate effects on each of the dental implant failure times, we could use

**Table 2.** Multivariate Frailty Cox Regression Model (Adjusted) (n = 677 patients; k = 2349 dental implants)

	Hazard Ratio	95% CI	Frailty Robust P-value
Age at time of first implant	0.99	(0.97, 1.01)	0.28
Gender	1.01	(0.65, 1.59)	0.95
Current tobacco use	3.06	(1.73, 5.40)	< 0.01
Peri-operative antibiotics	0.93	(0.49, 1.78)	0.83
Anatomic position of the implant (post. maxilla)	1.59	(0.52, 4.92)	0.42
Anatomic position of the implant (ant. maxilla)	1.75	(0.55, 5.54)	0.34
Anatomic position of the implant (post. mandible)	1.14	(0.37, 3.57)	0.82
Anatomic position of the implant (ant. mandible)	1.00		
Proximity of implant (1 tooth and 1 implant)	0.54	(0.22, 1.36)	0.19
Proximity of implant (2 adjacent implants)	0.19	(0.06, 0.60)	< 0.01
Proximity of implant (1 adjacent implant)	0.47	(0.19, 1.16)	0.10
Proximity of implant (2 natural teeth)	0.45	(0.17, 1.20)	0.11
Proximity of implant (1 adjacent tooth)	0.42	(0.12, 1.40)	0.16
Proximity of implant (no adjacent tooth or implant)	1.00		
Implant length	0.70	(0.59, 0.83)	< 0.01
Coating of implant, HA	0.74	(0.39, 1.43)	0.37
Coating of implant, TPS	1.22	(0.62, 2.41)	0.56
Uncoated implant	1.00		
Bone graft augmentation	1.36	(0.93, 2.00)	0.16
Well size	0.33	(0.15, 0.76)	< 0.01
Staging of implant (2 stages)	0.26	(0.14, 0.47)	< 0.01
Immediate implant	1.79	(0.95, 3.39)	< 0.01
Prosthetics: removable denture	0.89	(0.36, 2.22)	0.80
Prosthetics: fixed bridge/denture	0.86	(0.43, 1.72)	0.67
Prosthetics: crown	1.00		
Frailty term (b <sub>i</sub> )			0.048

the marginal procedures proposed by others (Lee *et al.*, 1992; Lin, 1994). [Please refer to Chuang *et al.* (2002) for details on how these procedures can be applied to clinical dental research, particularly to analyze clustered implant failure times data.] However, because the within-subject correlation structure is not specified, this approach cannot assess the heterogeneity of risk among subjects, which is of primary interest in our research. On the contrary, the frailty approach provides a straightforward answer to this question. Another disadvantage of the marginal compared with the frailty approach is that it cannot handle an important prediction problem: estimating the distribution of a future dental implant failure time using failure times and covariate information from other implants in the same subject.

It should be noted, however, that the regression parameters

**Table 3.** Parsimonious Multivariate Frailty Cox Regression Model (adjusted for age at first implant surgery, gender, proximity of the implant) (n = 677 patients; k = 2349 dental implants)

Exposure	Hazard Ratio	95% CI	Frailty Robust P-value
Current tobacco use	3.40	(1.97, 5.88)	< 0.01
Implant length	0.73	(0.64, 0.84)	< 0.01
Immediate implant	2.03	(1.16, 3.52)	0.013
Staging of implant	0.24	(0.14, 0.40)	< 0.01
Well size	0.35	(0.16, 0.76)	< 0.01
Frailty term (b <sub>i</sub> )			0.041

$\beta$  under the marginal proportional hazards model and the proportional hazards frailty model have different interpretations.  $\beta$  is the population-level relative risk in the marginal model and the subject-level relative risk in the frailty model. That is, the hazard ratio refers to the within-subject hazard ratio as opposed to the population-averaged hazard ratio in the marginal model. The marginal model estimates the population-average relative risk (hazard ratio) due to treatment, and the frailty model estimates the relative risk within the clusters. As such, the treatment coefficients, *e.g.*, main covariates, are not expected to be the same in the marginal and frailty models, since they estimate different quantities unless the within-cluster correlation is zero.

In summary, this paper confirms the hypothesis that the risk of implant failure between subjects is heterogeneous and identifies multiple risk factors associated with implant failure. Several of these risk factors may be modified pre-operatively to enhance implant survival. In the setting of correlated survival observations, we recommend adjusting for the correlation of the observations by either the marginal or the frailty approach, depending on the particular research issue, to provide statistically valid estimates of the parameters.

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