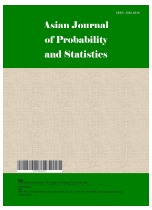

Asian Journal of Probability and Statistics

11(3): 1-10, 2021; Article no.AJPAS.65948
ISSN: 2582-0230

Frailty Models for Predicting Eruption Time and Sequence of Permanent Dentition in Sri Lankan Children

Chamilanka Wanigasekara[1], Lakshika S. Nawarathna[2*] and V. S. N. Vithanaarachchi[2]

[1]Department of Statistics and Computer Science, Faculty of Science, University of Peradeniya, Peradeniya, Sri Lanka.
[2]Division of Orthodontics, Faculty of Dental Sciences, University of Peradeniya, Peradeniya, Sri Lanka.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJPAS/2021/v11i330266
Editor(s):
(1) Dr. Manuel Alberto M. Ferreira, Lisbon University, Portugal.
Reviewers:
(1) Nivedita Palia, Guru Gobind Singh Indraprastha University, India.
(2) Cardei Petru, The National Institute of Research – Development for Machines and Installations, Romania.
Complete Peer review History: http://www.sdiarticle4.com/review-history/65948

Original Research Article

Received: 05 January 2021
Accepted: 10 March 2021
Published: 23 March 2021

Abstract

The main goal of this study is to create a suitable model to predict the tooth eruption pattern of Sri Lankan children. Also, we identify the relationship between variables associated with eruption sequence, compare the eruption sequence between sexes, compare the eruption sequences between upper and lower jaws, identifying common polymorphisms of tooth eruption sequences of children and determine the frequencies of occurrence of emergence polymorphisms for different tooth pairs. This analysis was performed using the data of the extent of tooth eruption of all 28 teeth at 10 different time points in each year. Welch two-sample t-test was used to identify the relationship between variables associated with eruption sequence. Frailty models and Cox-Proportional Hazard models developed for each tooth type separately and the model selection procedures Akaike information criterion (AIC), Bayesian information criterion (BIC) and Root Mean Square Error (RMSE) values are measured for each model. Since Gamma Frailty models have the smallest AIC and BIC for seven types of tooth which divide according to the eruption stage of the each tooth, we choose Gamma Frailty models as the best predictor for the tooth eruption. There is a significant difference between the eruption pattern of gender and jaw associated with time. However, no significant difference between sides associated with the eruption sequence was observed.

**Corresponding author: E-mail: lakshikas@pdn.ac.lk;*

Keywords: Cox-proportional hazard model; frailty model; primary dentition; tooth eruption.

1 INTRODUCTION

Tooth eruption is a process in tooth development in which the teeth enter the mouth and become visible. Most people have two sets of teeth during their lifetime; a set of primary or baby teeth and the permanent or adult teeth. Besides helping to pronounce words and to chew, primary teeth hold a place in the jaws for the permanent teeth, which begin to push through the gums as the primary teeth are shed. These primary teeth are eventually replaced by 32 permanent teeth, 16 in each jaw. Fig. 1a shows the primary dentition of a child, the eruption of the first set of teeth in the human mouth. There are 20 primary teeth; 10 in each of the upper and lower jaws. Primary teeth consist of 4 incisors, 2 canines, and 4 molars in each jaw. In most children, the first tooth erupts through the gum about 6 months after birth [1]. Thereafter one or more teeth erupt about every month until all 20 have appeared. The primary teeth are usually shed between the ages of 6 and 13 years, although the timing varies greatly from child to child [1]. Fig. 1b shows permanent dentition which is comprised of 32 teeth. There are 16 teeth in the maxilla and 16 in the mandible. In each, there are 2 central incisors, 2 lateral incisors, 4 premolars, and 6 molars there are 16 teeth in the maxilla and 16 in the mandible. In each arch there are two central incisors, two lateral incisors, two canines, four premolars, and six molars. The permanent central incisors, lateral incisors, first and second premolars replace the primary dentition. The primary molars are replaced with the permanent molars that erupt posterior to those [2].

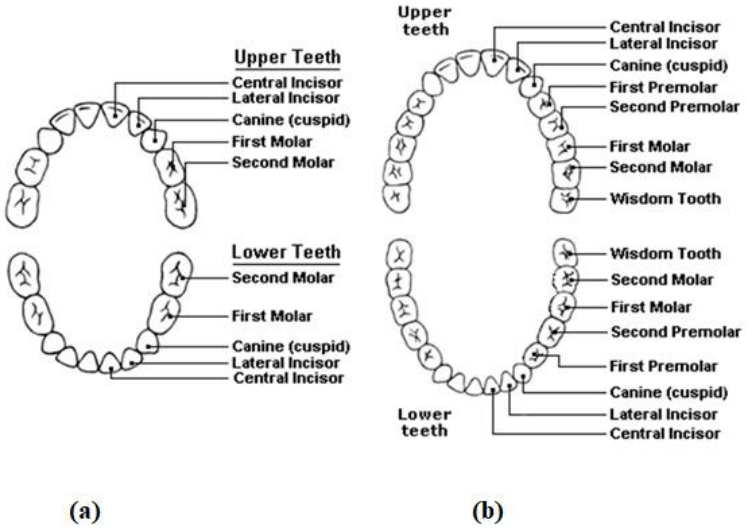

Fig. 1. (a) Primary Dentition of a child and (b) permanent dentition of an adult

The main goal of this study is to create a suitable statistical model for tooth eruption time of Sri Lankan children. Most commonly survival data are handled utilizing the proportional hazards regression model. The frailty model, an extension of the proportional hazard model is used for this study [3] . Therefore we used three types of frailty models and proportional odds model for this analysis. Using this best model we identify common polymorphisms of tooth eruption sequences of children and determine the frequencies of occurrence of the emergence of polymorphisms of different tooth pairs. Also, we identify the relationship between variables associated with eruption sequence, comparing the eruption sequence between genders, comparing the eruption sequences between Maxilla (upper jaw) and Mandibular (lower jaw).

A large number of studies regarding tooth eruption and sequence of permanent dentition have been conducted around the world [4,5] [2,3] but there is only one study done regarding tooth eruption time and

sequence in Sri Lanka. It has been conducted nearly twenty-five years ago. It is only based on the Kandy district and has conducted a preliminary analysis of the data [6].

We identify genetic tooth patterns and tooth eruption times throughout this study. Tooth patterns and tooth eruption times which were identified from this analysis can be also used to figure out any abnormalities in tooth eruption of children before the emergence gets worse. In comparison with other countries [7], Sri Lankans have different genetic patterns, living styles, socio-economic status, climate, weather, etc. Due to these reasons, tooth eruption time and sequence of Sri Lankan children differ from children in other countries. Therefore, this study is important to predict the eruption time and this study can be used to compare the tooth eruptions of Sri Lankans with others.

This article is organized as follows. In Section 2, we describe the nature of the data set utilized for the analysis. Section 3 outlines the survival regression analysis used for analysis with specific reference to the Cox proportional-hazards (CoxPH) model and the Gamma Frailty model along with its applicability for the current interest of the study. Section 4 expands on the statistical analysis conducted with the aid of *R* statistical software and the key results derived. To sum up, in Section 5, the conclusion states the main findings with direct comparisons against the only previous study conducted in Sri Lanka and also against literature published worldwide and further discusses the limitations of the finding(s) for the reader's reference.

2 MATERIALS AND METHODS

This study contains tooth emergence data of 1073 students were in the age range 5 to 15 years from 18 schools from 10 districts in 6 provinces. Data were collected twice during a year from the sample. Since we have to make multiple observations on the same subject over the development of the child we collected tooth emergence data for around 10 years of these students and Table 1 illustrates the description of the variables considered in this study.

Table 1. Description of variables considered in this study

Variable	Description
Gender	Male, Female
Jaw	Upper, Lower
Side	Right, Left
District	Colombo,Kaluthara,Gampaha,Kurunagala,Puththalam,Anuradhapura,Kegalle, Rathnapura, Galle, Badulla
Tooth	Upper right permanent : (UR1,UR2,UR3,UR4,UR5,UR6,UR7) Upper left permanent : (UL1, UL2, UL3, UL4, UL5, UL6, UL7) Lower right permanent : (LR1, LR2, LR3, LR4, LR5, LR6, LR7) Lower left permanent : (LL1, LL2, LL3, LL4, LL5, LL6, LL7)
Type	I1 : Central Incisor, I2 : Lateral Incisor, C : Canine, PM1 : First premolar, PM2 : Second premolar, M1 : First molar, M2 : Second molar

Welch two-sample t-test was used to identify the relationship between variables (gender, jaw, side) associated with the eruption sequence [8]. Also, we developed a Cox proportional Hazard model and the Frailty model to predict tooth eruption time of children.

2.1 Cox Proportional Hazard Model

The Cox model is a mathematical process that will be used for survival time (time-to-event) results for one or more predictors. The variance of the response is a risk function $\lambda(t)$, which assesses the likelihood that an event of interest (in this case, death) occurred before t. Types of equation this risk is the function of the

descriptive exporter (λ_0) where all the covariates are absent and β is the coefficient vector and X is the covariate vector [9].

$$\lambda(t) = \lambda_0(t) \exp(\beta_1 X_1 + \cdots + \beta_k X_k)$$

The Cox-equivalent risk model makes two assumptions: (1) The survival curves of the various strands must have dangerous activities equal to the t. Examples of covariates can be in categories such as race or treatment groups, or continue as a biomarker focus [9].

2.2 Frailty Model

Most commonly, survival data are treated with a risk reduction model developed by Cox (1972). However, the relevant index supports those models that require independent and uniform samples [10,11]. Nonetheless, subjects could also be exposed to deferent risk levels, even after controlling known risk factors. This is usually because some of the appropriate covariates are available to the researcher or may not be known. Also, the number of people surveyed can be divided and grouped so that subjects from the same group behave more cohesively than subject t s from different groups. The frailty model is defined in terms of the conditional hazard [12,13].

$$h\left(\frac{t}{u_i}\right) = h_0(t) \exp({x_{ij}}^T \beta)$$

where, $h_0(t)$: Baseline hazard function, u: Frailty term of all subjects in group i, x_{ij} : vector of covariates for subject j in group i and β: Vector of regression coefficients with $i \in I = \{1, \ldots, G\}$ and $j \in J_i = \{1, \ldots, n_{ij}\}$, If the amount of subjects n_i is 1 for all groups, then the univariate frailty model is obtained, otherwise the model is called the shared frailty model because all subjects within the same cluster share an equivalent frailty value u_i.[13].

The frailty u_i is an unobservable realization of a variate U with probability density function $(\cdot)$—the frailty distribution [4]. Since u_i multiplies the hazard function, U has got to be positive. Another obstacle is needed for diagnostic reasons, almost as a zero-zero barrier of random effect on a standard mixed line model.[13]. More specifically, the mean U is usually restricted to unity when possible (i.e., when $E(U)$ exists) to separate the underlying risk from the general level of random frailties.

Several frailty distributions are identified [14,15], during this study, we shall specialize in the gamma, frailty distribution. In all frailty distributions, one heterogeneity parameter (denoted either θ or υ) indexes the degree of dependence [13]. In the following,ξ is employed as a generic notation to denote either θ or υ.

The parametric Frailty model is additionally called the Shared frailty model [16]. It is a mix model. Because the mixture terms, the frailty and the notation $\boldsymbol{Y}$ will be used. The model is shared because the values of Y are constant over time and mutual to the individuals within the group. The foremost important thing is that the model assumes that each one observation is independent. In other words, shared frailty is a conditional independence model. In the case of independent data, the event counts corresponding to an ordinary Poisson process. This suggests that future events are independent of previous ones.

The frailty variation is not a gaggle variation but a variation between individuals and the variation described by the hazard function is not an individual variation, but a variation within individuals, which for recurrent events alternatively could be called the Poisson variation. For recurrent events data, the risk set is constant over the observation period. The frailty approach indicates variation within the number of events, even though the observation time is equal for all individuals [17].

In a shared frailty model, frailty is defined as a measure of the relative risks which individuals in a group share [13]. Thus, the frailty variable is related to groups of individuals instead of individuals. The hazard model for each equivalent to the standard univariate frailty model.

$$(t, Z) = Z\,\lambda_0\,(t)$$

A shared frailty model in survival analysis is defined as follows. Suppose there are n clusters and which the i^{th} cluster has n_i individuals and associates with an unobserved frailty $Z_i, (1 \leq i \leq n)$. A vector X_{ij} $(1 \leq i \leq n, 1 \leq j \leq ni)$ is related to the ij -th complete survival time T_{ij} of the j-th individual within the i-th cluster. Conditional on frailties Z_i, the survival times are assumed to be independent and their hazard functions to be of the form;

$$\lambda(t) = Z_i\,\lambda_{0j}(t)\exp\,(\beta^T X_{ij})$$

Where $\lambda_{0j}(t)$ are the baseline hazard functions and β is a vector of fixed effect parameters to be estimated. The frailties Z_i are assumed to be identically and independently distributed random variables with a standard density function $f(z, \theta)$ where θ the parameter of the frailty distribution is. A semi-parametric shared frailty model is a frailty model with a nonparametric baseline hazard function $\lambda_{0j}(t)$.

For shared frailty models, the scale parameter of the frailty distribution might be treated variously [18]. For recurrent events, it is often convenient to restrict some other parameters instead. In this study, we have discussed the Gamma Frailty distribution.

2.3 Gamma Frailty Distribution

The Gamma Frailty distribution has been used for many years to produce blends in exponential and Poisson models. From a calculation point of view, they are very much in line with the survival model, because it is easy to find formulas for any number of events.. In this case, we use the parameterization of the gamma distribution, gamma (δ, θ)

A gamma frailty term is a random variable $U \sim Gam*(\theta)$ with probability density function

$$f(u) = \frac{\theta^{-\frac{1}{\theta}}\,u^{(\frac{1}{\theta}-1)}\,\exp(-\frac{u}{\theta})}{\Gamma\left(\frac{1}{\theta}\right)} \qquad \theta > 0$$

where $\Gamma(\cdot)$ is the gamma function. It equals a gamma distribution (μ, θ) with μfixed to 1 for identifiability. Its variance is then θ. The associated Laplace transform is written by Munda et al. [13].

$$L(S) = (1 + \theta s)^{-\frac{1}{\theta}} \qquad s \geq 0$$

and it is easy to show that, for $q \geq 1$,

$$L^{(q)}(s) = (-1)^q\,(1 + \theta s)^{-q}\left[\prod_{l=0}^{q-1}(1 + l\theta)\right] L(s)$$

The gamma distribution, Kendall's tau, which measures the interaction between any two event times from a single set in a multivariate case, can be calculated as,

$$\tau = \frac{\theta}{\theta + 2} \in (0,1)$$

2.4 Model Selection and Model Accuracy

We used the Akaike information criterion (AIC) and Bayesian information criterion (BIC) and Root Mean Square Error (RMSE) was used to select the best model. The smallest AIC, BIC, and RMSE values suggest that the model is a better fit for the data than other models.

3 RESULTS AND DISCUSSION

We used Welch two-sample t-test to identify the relationship between gender, jaw and side of the tooth with eruption time shown in Table 2, and performed separate statistical analysis for the eruption of each tooth type.

Table 2. Summary results of Welch two-sample t-test

Variables	T value	DF	P value	95% Confidence Interval	
				Lower	Upper
Gender	11.57	25217	2.2e-16	0.2552387	0.3593532
Jaw	9.4461	29992	2.2e-16	0.1946349	0.2965558
Side	0.063169	30042	0.9496	-0.04939125	0.05268087

As shown in Table 2 both gender and jaw have P value less than 0.05. Therefore we can claim that there is a significant difference between male and female, and a difference between upper and lower jaws.

Table 3. Comparison of mean eruption times of permanent dentition in two Sri Lankan studies

Jaw	Tooth	Sinhalese of Kandy [5]		Current Study	
		Males	Females	Males	Females
Upper	I1	7.55	7.28	7.61	7.32
	I2	8.41	8.15	8.96	8.30
	C	11.41	10.88	11.25	10.62
	PM1	9.95	9.72	10.71	10.51
	PM2	10.87	10.72	11.28	11.12
	M1	6.35	6.24	6.66	6.58
	M2	12.30	11.73	11.69	11.50
Lower	I1	6.8	6.60	6.96	6.82
	I2	7.89	7.20	8.17	7.73
	C	10.97	10.08	10.824	10.26
	PM1	10.42	10.07	10.95	10.58
	PM2	11.20	10.79	11.36	11.09
	M1	6.28	6.17	6.54	6.47
	M2	11.66	11.17	11.55	11.34

Table 3 shows the comparison of mean eruption times of permanent dentition of Sri Lankan male and female students between 1993 and 2018 [6].

Fig. 2 illustrate the comparison of descriptive statistics between past study and the current study for males and females. According to the figure there is a considerable difference between the eruption time of tooth type PM1 in upper jaw and type C in lower jaw of male students in current study and the past study. When we consider the comparison of female students there is a difference between the mean eruption time of tooth type PM1 in both upper and lower jaws and also type I2 in lower jaw in present and past study.

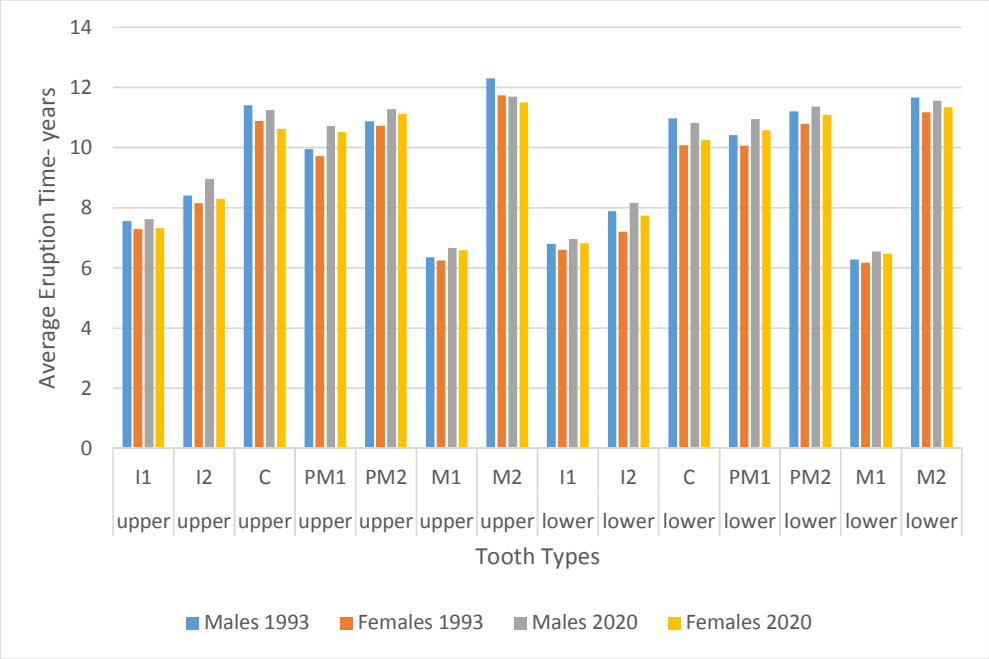

Fig. 2. Mean eruption time (years) of male and female students

To achieve the required computations the statistical software R studio is used. First of all the data set is divided into seven subsets according to the tooth type (I1, I2, C, PM1, PM2, M1 and M2). Table 4 shows the AIC and BIC values computed for seven Cox PH models and seven Gamma Frailty models separately.

Table 4. AIC and BIC values of Cox PH and gamma frailty statistical models

Tooth type	Cox PH model		Gamma Frailty model	
	AIC	BIC	AIC	BIC
I1	58218.28	58262.37	23943.41	24006.44
I2	56657.69	56701.6	24674.37	24737.40
C	45336.62	45379.05	22920.55	22983.58
PM1	46997.14	47039.75	23333.52	23396.55
PM2	39930.06	39971.60	21145.81	21208.84
M1	58880.98	58925.10	23272.12	23335.15
M2	34868.74	34909.40	19382.21	19445.24

The AIC and BIC values are computed for the Cox PH model and Gamma Frailty model with exponential baseline hazard function for each tooth type. One can see from the table, that the Gamma Frailty model with exponential baseline hazard function is better than the Cox PH model for all seven types of teeth.

Table 5. Summary results of gamma frailty models

Type	Gender	Type	Side	Jaw	Districts	Province	Race	SS
I1	0.321	0.949	0.938	0.013	0.473	0.509	0.867	0.548
I2	0.025	0.776	0.985	0.001	0.032	0.030	0.641	0.574
C	<0.001	0.004	0.808	0.003	<0.001	<0.001	0.134	0.372
PM1	0.020	0.082	0.851	0.346	0.524	0.518	0.472	0.192
PM2	0.001	0.732	0.926	0.538	0.330	0.239	0.241	0.064
M1	0.751	0.034	0.984	0.607	0.909	0.821	0.828	0.734
M2	0.002	0.816	0.533	0.001	0.929	0.839	0.409	0.912

Table 5 illustrates the summary of seven frailty models which have been developed for each tooth type separately. According to the first model, only the jaw has a significant impact on the hazard of infection while it is not affected by gender, type, or side. When we consider the second model which has been developed for type I2 only gender, jaw, district and province have a significant impact on the hazard of infection while it is not affected by type, side, race, or socioeconomic status. The hazard of tooth eruption for a female at any time t is estimated to be $exp\ (0.073) = 1.0757$ times that of a male. According to the summary of the frailty model which is developed for type C gender, type, jaw, district and province has a significant impact on the hazard of infection while it is not affected by side, race, or socioeconomic status. The hazard of tooth eruption for a female at any time t is estimated to be $exp\ (0.169) = 1.1841$ times that of a male. And the fourth model shows that only gender has a significant impact on the hazard of tooth eruption while it is not affected by any other variable. The hazard for a female at any time t is estimated to be $exp\ (0.083) = 1.0865$ times that of a male.

According to the frailty model which has been developed for type PM1 only gender has a significant impact on the hazard of tooth eruption while it is not affected by any other variable. The hazard for a female at any time t is estimated to be $exp\ (0.120) = 1.1275$ times that of a male. When we consider model 06 it is not affected by any variables. According to model 07, gender and jaw have a significant impact on the hazard of tooth eruption while it is not affected by other variables. The hazard for a female at any time t is estimated to be $exp\ (0.169) = 1.1841$ times that of a male.

We used Root Mean Square values (RMSE) to find the accuracy of Gamma Frailty models. As shown in the Table 6 all seven Gamma Frailty models have high accuracies between 89% and 95%.

Table 6. RMSE values and accuracy of gamma frailty models

Type	RMSE value	Accuracy
I1	6.259459	93.740541
I2	7.443426	92.556574
C	9.898495	90.101505
PM1	9.800061	90.199390
PM2	10.323890	89.676110
M1	5.614530	94.385470
M2	10.628160	89.371840

4 CONCLUSION

This current study focuses on survival analysis to develop a novel model to predict tooth eruption time and sequence pattern on Sri Lankan children and is the second study representative of total population [19]. From the statistical analysis we figured that, Gamma Frailty models have the smallest AIC and BIC for all seven tooth types, we choose Gamma Frailty models as the best predictor for the tooth eruption. There is a significant difference between the eruption pattern of males and females and between upper and lower jaws associated with time. However, no significant difference between sides (right and left) associated with the eruption sequence was observed.

There is an agreement of this study with the previous descriptive study [6] on the significant difference between the eruption time of male students and female students. All teeth in the female students erupted earlier than male students. Moreover, the eruption time of the upper jaw is significantly different from the eruption time of the lower jaw. But there is no significant difference between the left side and right side of the mouth with eruption time. The mean eruption time of male students and female students concerning tooth type is approximately equal to the past study done in Sri Lanka [6].

There is a major limitation of this study, in both studies which considered the total population [19], considered the tooth to have erupted if at least part of the teeth was visible. However, for a better establishment we suggest collecting data until completion of tooth eruption.

CONSENT

As per international standard or university standard guideline participant consent has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

[1] Manconi B, Cabras T, Pisano E. Modifications of the acidic soluble salivary proteome in human children from birth to the age of 48 months investigated by a top-down HPLC–ESI–MS platform. Journal of Proteomics. 2013;91:536-543.

[2] Tooth eruption,The peremanent teeth. American Dental Association. 2006;127. Available:https://www.ada.org/~/media/ADA/Publications/Files/patient_58.ashx

[3] Vaupel J, Manton K, Stallard E. The impact of heterogeneity in individual frailty on the dynamics of mortality. Demography. 1979;16(3):439-454.

[4] Almonaitiene R, Balciuniene I, Tutkuviene J. Factors influencing permanent teeth eruption. Part one–general factors. Baltic Dental and Maxillofacial Journa. 2008;12:67-72.

[5] Almonaitiene R, Balciuniene I, Tutkuviene J. Standards for permanent teeth emergence time and sequence in Lithuanian children, residents of Vilnius city. Stomatologija, Baltic Dental and Maxillofacial Journal. 2012;14:93-100.

[6] Nanayakkara C, Chandrasekera M, Wikramanayake E. Norms for the eruption of the permanent dentition in the Sinhalese of Kandy district. The Ceylon Journal of Medical Science. 1993;36:23-27.

[7] Smith BH, Garn SM. Polymorphisms in eruption sequence of permanent teeth in American Children. American Journal of Physical Anthropology. 1987;74:289-303.

[8] Kardaun, Otto J. Classical Methods of Statistics (1 ed.). Verlag Berlin Heidelberg: Springer; 2005.

[9] Hashim D, Weiderepass E. Cancer survival and survivorship. (P. Boffetta, & P. Hainaut, Eds.) Academic Press; 2019.

[10] Gorfine M, De-Picciotto R, Hsu L. Conditional and marginal estimates in case-control family data - extensions and sensitivity analyses. HHS Public Access. 2012;82:1449–1470.

[11] Hanagal, David D. Modeling survival data using frailty models (2 ed.). Singapore: Springer; 2019.

[12] Duchateau L, Janssen P. The frailty model. Springer-Verlag; 2008

[13] Munda M, Rotolo F, Legrand C. Parfm: parametric frailty model in R. Journal of Statistical Software. 2017;1:4.

[14] Mallick M, Ravishankar N. Additive positive stable frailty models. Methodol Comput Appl Probab. 2006;8:541-558.

[15] Mallick M, Ravishankar N, Kannan N. Bivariate positive stable frailty models. Statistics and Probability Letters. 2008;78:2371-2377.

[16] Tessema B, Ayalew S, Mohammed K. Modeling the determinants of time-to-age at first marriage in ethiopian women: A comparison of various parametric shared frailty models. Science Journal with Public Health. 2015;3(5):707-718.

[17] Scheike TH, Peterson JH, Martinussen T. Retrospective ascertainment of recurrent events: An application to time to pregnency. Journal of the American Statistical Association. 1999;94:713-725.

[18] Qiou Z, Ravishanker N, Dey D. Multivariate survival analysis with positive stable frailties. Biometrics. 1999;55:637-644.

[19] Jayathilake A, Nawarathna LS, Ravishanker N, Wijekoon P, Nawarathna RD, Vithanaarachchi VS, et al. New standards for eruption time and sequence of permanent dentition in Sri Lankan children. Communications in Statistics: Case Studies, Data Analysis and Applications. 2019;5:2:92-100.

Peer-review history:
The peer review history for this paper can be accessed here (Please copy paste the total link in your browser address bar)
http://www.sdiarticle4.com/review-history/65948