STATISTICS IN TRANSITION new series, June 2023
Vol. 24, No. 3, pp. 201–211, https://doi.org/10.59170/stattrans-2023-044
Received – 03.05.2022; accepted – 16.01.2023

Bayesian modelling for semi-competing risks data in the presence of censoring

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Abstract

In biomedical research, challenges to working with multiple events are often observed while dealing with time-to-event data. Studies on prolonged survival duration are prone to having numerous possibilities. In studies on prolonged survival, patients might die of other causes. Sometimes in the survival studies, patients experienced some events (e.g. cancer relapse) before dying within the study period. In this context, the semi-competing risks framework was found useful. Similarly, the prolonged duration of follow-up studies is also affected by censored observation, especially interval censoring, and right censoring. Some conventional approaches work with time-to-event data, like the Cox-proportional hazard model. However, the accelerated failure time (AFT) model is more effective than the Cox model because it overcomes the proportionality hazard assumption. We also observed covariates impacting the time-to-event data measured as the categorical format. No established method currently exists for fitting an AFT model that incorporates categorical covariates, multiple events, and censored observations simultaneously. This work is dedicated to overcoming the existing challenges by the applications of R programming and data illustration. We arrived at a conclusion that the developed methods are suitable to run and easy to implement in R software. The selection of covariates in the AFT model can be evaluated using model selection criteria such as the Deviance Information Criteria (DIC) and Log-pseudo marginal likelihood (LPML). Various extensions of the AFT model, such as AFT-DPM and AFT-LN, have been demonstrated. The final model was selected based on minimum DIC values and larger LPML values.

Key words: censoring, illness-death models, accelerated failure time model, Bayesian Survival Analysis, semi-competing risks.

1. Background

Survival analysis is one of the important fields of mathematical statistics and expands to deal with time-to-event data when interest is intended on time and before passing the time an event has occurred, then this kind of data arises. Besides, including statistical methods, it is used for analyzing the time until an event of interest has occurred, where the event is death, the occurrence of any reasonable disease, or other experience of interest. However, we cannot expect each participant to experience the event of interest (like death, cancer) within the study period and get the real data. The prolonged duration of the study period is also affected by censored observation, especially interval censoring, and right censoring.

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We expect subjects to experience only one type of event over follow-up like death from cancer. But in real life, there are so many types of possibilities that subjects can experience more than one type of event in the study period. If death is our interest, then from our observation, we can see that some patients can die from cancer or any traffic accident or in a sudden heart attack. When this kind of event occurs, we refer to these events as "competing events" and the probability of these events as "competing risks." To better understand competing risk scenarios, we can think of a patient who may die from cancer or a heart attack, but he cannot die from both. Sometimes the non-terminal event (like cancer relapse, or readmission) is our research interest. Still, the terminal event (e.g. death) averts the case of the non-terminal event, and it is remarked as semi-competing risk data (Haneuse et al. 2016). Innately we can think of participants of these settings as transitioning through a series of states. For example, we can take cancer relapsing as the non-terminal event and death as the terminal event. Semi-competing risks are inclusive in studies of aging. Here we will give an example for a better understanding of a semi-competing event scenario: a patient who may experience cancer relapse. After some time, he dies of cancer. We can represent the semi-competing risks data in one or more of three transitions: 1) Transition 1: initial condition to the non-terminal event. 2) Transition 2: initial condition to a terminal event. 3) Transition 3: non-terminal events to the terminal event. Semi-competing risks visit the setting where our interest lies to infer a non-terminal event (e.g., disease recurrence, cancer relapse) and a terminal event (e.g., death) and, if possible, for both cases. Let T_{i1} and T_{i2} denote time to the non-terminal event and also the terminal event for the i^{th} study participant respectively. A sturdy association exists between the event's time, so we cannot apply the univariate survival model because it will take the terminal event as an independent event and supply us with overestimated biased results. The semi-competing risks analysis framework appropriately treats the terminal event as a competing event. It considers the dependence between non-terminal and terminal events as a component of the model specification.

The Cox proportional hazard model (Prentice et al. 1992) is used to relate the survival time of a subject to the covariate. We want to find out for which covariate the survival time gets affected. Besides the Cox model, accelerated failure time (AFT) is the essential regression model for censored data (Buckley et al. 1979). The AFT model helps us consider the effect of covariates on survival time. It can offer new insight into risk factors associated with the non-terminal event (cancer relapse) when we conduct such a study among older people, and age is a very relevant factor. In this type of situation, data may have been left truncation. If it is not handled appropriately, each of these situations can give us a biased result of our analysis (Odell et al. 1992). While a statistician or a researcher has so many options for handling these types of situations, there are some works that we have considered. Most of these are on the Cox model for hazard function. About AFT models for semi-competing risk data, there are some recent works, (Dam Ding et al. 2009; Ghosh et al. 2012; Ghosh et al. 2006; Armero et al. 2016; Jiang et al. 2017), but each of them has some limits as they do not consider left-truncation or interval-censoring.

So, this work is dedicated to overcoming the challenges in semi-competing risk data when left-truncation and interval censoring are present. So, we adopt the flexible, study Bayesian framework (Lee et al. 2017) for our analysis of the simulated data as both censorings are adopted in their model. One of the advantages of this framework is we can

take parametric and semi-parametric forms for our baseline survival distribution. We obtained that the developed methods using the functions named **BayesID_AFT** and **initiate.startValues_AFT**, which are suitable to run with the help of **SemiCompRisks** (Lee et al. 2015) packages in R.

2. Model Framework: Illness death Model

Semi-competing risk data are presented by the participants ready to encounter the two kinds of events and possibly both. We modelled the association between covariates and the two types of event time within the AFT model specification. T_{i1} and T_{i2} represent the time of the non-terminal event and also the terminal event for the i^{th} study participant. Here we adopt the following AFT model specifications (model the times of the events directly) under the illness death modelling framework:

$$log(T_{i1}) = \boldsymbol{x}_{i1}^T \boldsymbol{\beta}_1 + \kappa_i + \varepsilon_{i1},\ T_{i1} > 0 \tag{1}$$

$$log(T_{i2}) = \boldsymbol{x}_{i2}^T \boldsymbol{\beta}_2 + \kappa_i + \varepsilon_{i2},\ T_{i2} > 0 \tag{2}$$

$$log(T_{i2} - T_{i1}) = \boldsymbol{x}_{i3}^T \boldsymbol{\beta}_3 + \kappa_i + \varepsilon_{i3},\ T_{i2} > T_{i1} \tag{3}$$

where $\boldsymbol{x}_{ig}$ denotes the vector of transition-specific covariates ,$i = 1,\ldots,n$ and $g \in \{1,2,3\}$. $\boldsymbol{\beta}_g$ represents the vector of transition specific regression parameters, and ε_{ig} denotes the transition-specific random variable whose distribution determines that of corresponding transition time, $g \in \{1,2,3\}$. Finally, κ_i denotes the random effect of a specific subject in each of (1)-(3) equations that instigates a positive sign of dependency between the two event times.

Let us briefly consider the interpretation of the regression parameter in an AFT model.

From our model given by equation (1), we can write the survivor distribution for the i^{th} individuals:

$$S_1(t;x_{i1}) = S_{01}\{t \times \exp(-\boldsymbol{x}_{i1}^T \boldsymbol{\beta_1})\} \tag{4}$$

where S_{01} represents the baseline survivor function between the individuals with $\boldsymbol{x}_{i1} = 0$. We can interpret this as a special case when the covariate is dichotomous. Let x_{i1} be simply a dichotomous covariate with $x_{i1} = 1$ denoting individuals who have received treatment and $x_{i1} = 0$ indicates those who did not take treatment. Equation (4) implies that the median time ratio to reason 1 among treatment receiver and non-receiver is $\exp(\beta_1)$. For example, if x_{i1} was a treatment indicator and β_1 = 0.4, we could say that individuals who received the treatment survived 50% longer (as $\exp(0.4) \approx 1.50$) than those individuals who did not receive the treatment, and if $\beta_1 = -0.4$ then we get $\exp(-0.4) \approx 0.67$ which indicates 33% shorter survival. If values of $\exp\{\beta_g\}$ are less than 1.0 for the AFT model, then it indicates an increased risk due to the specific factor. From these results, we can say that a negative value of β suggests increased risk because the event occurs sooner in time.

3. Semi-parametric approach in AFT Illness-Death model

There are several works carried on the AFT model through frequency and Bayesian extension (e.g. Christensen et al. 1988; Kuo, L et al. 1997). In this work, we preferred to work with Dirichlet Process Mixture (DPM) prior along with normal distribution for each ε_{ig} (Ferguson et al 1973). It helped us to draw ε_{ig} independently from a mixture of M_g with mean and variances from the normal distribution as $(\mu_{gr}, \sigma^2_{gr})$, for $r \in 1, ..., M_g$. Perhaps, it is difficult to identify the distributional form of the $(\mu_{gr}, \sigma^2_{gr})$, so we take each component from normal distribution as being specific to some class and since which class it belongs to is not known to us we prefer to draw from G_{g0} as a choice of centring distribution. If the 'true' class of membership is not known to us, then p_{gr} defines the probability to belongs as r^{th} class for transition g and $\boldsymbol{p}_g = (p_{g1}, ..., p_{gM_g})$ by the probabilistic representation. It is safe to consider the conjugate symmetric. Dirichlet $(\tau_g/M_G, ..., \tau_g/M_G)$ as a choice of prior distribution while the class of memberships for the n individuals belongs to the M_g classes, and τ_g is presented for the precision parameter. Therefore the mixture distribution is presented as

$$\begin{aligned} \varepsilon_{ig}|r_i &\sim Normal(\mu_{r_i}, \sigma^2_{r_i}), \\ (\mu_{gr}, \sigma^2_{gr}) &\sim G_{g0}, \text{for } r = 1, \ldots, M_g, \\ r_i|\boldsymbol{p}_g &\sim Discrete(r_i|p_{g1}, \ldots, p_{gM_g}), \\ \boldsymbol{p}_g &\sim Dirichlet(\tau_g/M_G, ..., \tau_g/M_G). \end{aligned} \tag{5}$$

Now $M_g \to \infty$ is presented as DPM along with the normal distribution. This work is presented as Gamma(a_{τ_g}, b_{τ_g}), and hyper-prior for τ_g. Now we can take the non-informative flat priors through the real line aligned with the regression line. We can consider κ_i draws from the Normal distribution with $(0, \theta)$ and finally presented as $\kappa = \{\kappa_1, \ldots, \kappa_n\}$. Sometimes, we can consider the prior knowledge on the variance component θ and adopt the conjugate of the inverse-Gamma hyperprior as IG (a_θ, b_θ). It is useful to proceed with G_{g0} as a normal distribution with mean and variance μ_{g0}, σ^2_{g0}.

4. Parametric approach in AFT Illness-Death Model

Sometimes in a small-sample setting parametric-specific model looks more logical as it is easy to handle. For the parametric AFT model, some distributions including Weibull, log-logistic, and log-normal have been proposed for univariate time-to-event data. We consider the log-normal formulation for Bayesian parametric analysis and ε_{ig} are taken from an independent normal distribution with mean μ_g and variance σ^2_g for $g \in \{1, 2, 3\}$. We consider flat priors for location parameters (μ_1, μ_2, μ_3) on the real line. Independent inverse gamma distributions are considered for (σ^2_g) and denoted as IG $(a_{\sigma_g}, b_{\sigma_g})$. We take the same priors for $\boldsymbol{\beta}_g$, κ, and θ, which we took for the DPM model.

5. Model comparison criteria

Most of the time, researchers and analysts balanced the compatibility of the specified model with the limitation of the data. In this regard, it is critical to compare the models concerning goodness-of-fit. We used two criteria for this: the deviance information criterion (DIC; Spiegelhalter et al. 2002) and the log-pseudo marginal likelihood statistic (LPML; Geisser et al. 1979). For DIC, we note that work (Celeux et al. 2006) gives a couple of different DIC measures and discusses them in the context of mixture-based random-effects models. In this context, we take their DIC_3 measure based on their guides for our AFT illness-death model given by (1)–(3) and propose the following measure:

$$\begin{aligned} DIC_{ID} &= -4E_{\Theta}[\log L(t_{1i}, t_{2i}, \mathscr{D}_i|\Theta)|t_{1i}, t_{2i}, \mathscr{D}_i] \\ &\quad + 2\log \prod_{i=1}^{n} E_{\Theta}[L(t_{1i}, t_{2i}, \mathscr{D}_i|\Theta)|\boldsymbol{t}_1, \boldsymbol{t}_2, \{\mathscr{D}_i\}_{i=n}^{n}] \end{aligned} \tag{6}$$

In equation (6) all model parameters are denoted by Θ, either $\{\Theta_{SP}, \kappa\}$ or $\{\Theta_P, \kappa\}$. In the equation (6) the first term is associated with a deviance that evaluates a goodness-of-fit and the second term computes the measure of complexity. For the purpose of our analysis, we estimate the DIC_{ID} with the help of Monte Carlo approximation:

$$\begin{aligned} \hat{DIC}_{ID} &= -\frac{4}{Q}\sum_{q=1}^{Q} \log\left\{\prod_{i=1}^{n} L(t_{1i}^{(q)}, t_{2i}^{(q)}, \mathscr{D}|\Theta^{(q)})\right\} \\ &\quad + 2\log\left\{\prod_{i=1}^{n} \frac{1}{Q}\sum_{q=1}^{Q} L(t_{1i}^{(q)}, t_{2i}^{(q)}, \mathscr{D}|\Theta^{(q)})\right\} \end{aligned} \tag{7}$$

At the q^{th} MCMC iteration, $\Theta^{(q)}$ denotes the values of Θ, $q = 1, 2, 3, \ldots, Q$. A model having a smaller DIC value suggests a better fit to the data.

The LPML (2nd comparison criteria) measure is basically the sum of the logarithms subject-specific conditional predictive ordinates and given as $\sum_{i=1}^{n} \log CPO_i$,

$$\begin{aligned} CPO_i &= L(t_{i1}, t_{i2}, \mathscr{D}_i|\{t_{1k}, t_{2k}, \mathscr{D}_k\}_{k\neq i}) \\ &\approx \left\{\frac{1}{Q}\sum_{q=1}^{Q} L(t_{1i}^{(q)}, t_{2i}^{(q)}, \mathscr{D}_i|\Theta^{q})^{-1}\right\}^{-1} \end{aligned} \tag{8}$$

The approximation part in equation (8) pursues from the Monte Carlo estimator (Chen et al. 2012). Note, a model having larger values of LPML suggests a better fit for the data. In this context, one can use the pseudo-Bayes factor (PBF) for the two models by taking the exponent of difference in their LPML values.

6. Data

For illustration purposes, we perform some analyses using our simulated data with the primary goal of comparing the two models (parametric & semi-parametric). We simulate

the data consisting of n=5000 on the frame of semi-competing risk data where the interest lies in a non-terminal event that is subject to a terminal event which is a competing risk for the non-terminal event but not vice versa. We have developed this kind of semi-competing risk data frame with five dichotomous covariates and fit the model. Table 1 represents the baseline characteristic (sex, race, etc.) of 5000 participants. We adopted interval censoring and left truncation also. It also provides a 60-months summary of outcomes, overall and within levels of the factors reported. From the first row of Table 1, we can see that 25.58% participants are censored for both events and 25.24% experienced both events. We also see that a total of 1239 individuals experienced the non-terminal event and were censored for the terminal event, and 1220 participants have experienced the terminal event without having the non-terminal event.

Beyond the overall rates, Table 1 reveals substantial variation in the distribution of the four outcome types across levels of certain factors. We see, for example, that the rates at which individuals have experienced both events within 60 months is 26.02% among the individuals having $I_{(1)} = 1$ to 24.03% among individuals having $I_{(1)} = 0$.

Table 1: Overall information about covariates based on 5000 individuals experienced on non-terminal and/or terminal events.

	Total n(%)	censored n(%)	Non-terminal event only n(%)	Terminal event only n(%)	Both events n(%)
Total	5000 (100)	1279 (25.58)	1239 (24.76)	1220 (24.4)	1262 (25.24)
Covariate 1					
$I_{(1)} = 1$	3032 (60.64)	740 (24.41)	757 (24.97)	746 (24.60)	789 (26.02)
$I_{(1)} = 0$	1968 (39.36)	539 (27.39)	482 (24.49)	474 (24.09)	473 (24.03)
Covariate 2					
$I_{(2)} = 1$	4532 (90.64)	1156 (25.51)	1123 (24.78)	1109 (24.47)	1144 (25.24)
$I_{(2)} = 0$	468 (9.36)	123 (26.28)	116 (24.79)	111 (23.72)	118 (25.21)
Covariate 3					
$I_{(3)} = 1$	3896 (77.92)	991 (25.44)	983(25.23)	968 (24.84)	954 (24.49)
$I_{(3)} = 0$	1104 (22.08)	228 (20.65)	256 (23.19)	252 (22.83)	288 (26.09)
Covariate 4					
$I_{(4)} = 1$	2550 (51)	649 (25.45)	637 (24.98)	648 (25.41)	616 (24.16)
$I_{(4)} = 0$	2450 (49)	630 (25.71)	602 (24.57)	572 (23.35)	646 (26.37)
Covariate 5					
$I_{(5)} = 1$	2789 (55.78)	701 (25.13)	690 (24.74)	692 (24.81)	706 (25.31)
$I_{(5)} = 0$	2211 (44.22)	578 (26.14)	549 (24.83)	528 (23.88)	556 (25.15)

7. Results

7.1. Overall model fit

Table 2 provides the calculated values obtained on AFT-LN and AFT-DPM by corresponding DIC and LPML values. The models, i.e., AFT-LN and AFT-DPM, considered the κ_i (random effect) and resulted in DIC values as 34810 and 30975. So, AFT-DPM is relevant in this data analysis context compared to the AFT-LN model. Similarly, the second measure (LPML) obtained on AFT-LN and AFT-DPM is -16156 and -15719. It also confirms that AFT-DPM is more relevant than AFT-LN.

Table 2: DIC and LPML for two proposed models fit to simulated data.

	DIC	LPML
AFT-LN	34810	-16156
AFT-DPM	30975	-15719

7.2. Analysis: Covariate effect

As mentioned earlier in Section 3, if values of $\exp\beta_g$ are less than 1.0 for the AFT model, then it indicates an increased risk due to the specific factor. Table 3 presents the posterior median (PM) and 95% credible interval for the regression parameter from our analysis having a patient-specific random effect.

From the first column of Table 3, we have found proof that individuals with 0 indicators for 1st covariate $I_{(1)}$ significantly increased for reason 1 for the AFT-DPM analyses. The median time to reason 1 is estimated to be 6.5% shorter for these individuals than those with one indicator for $I_{(1)}$.

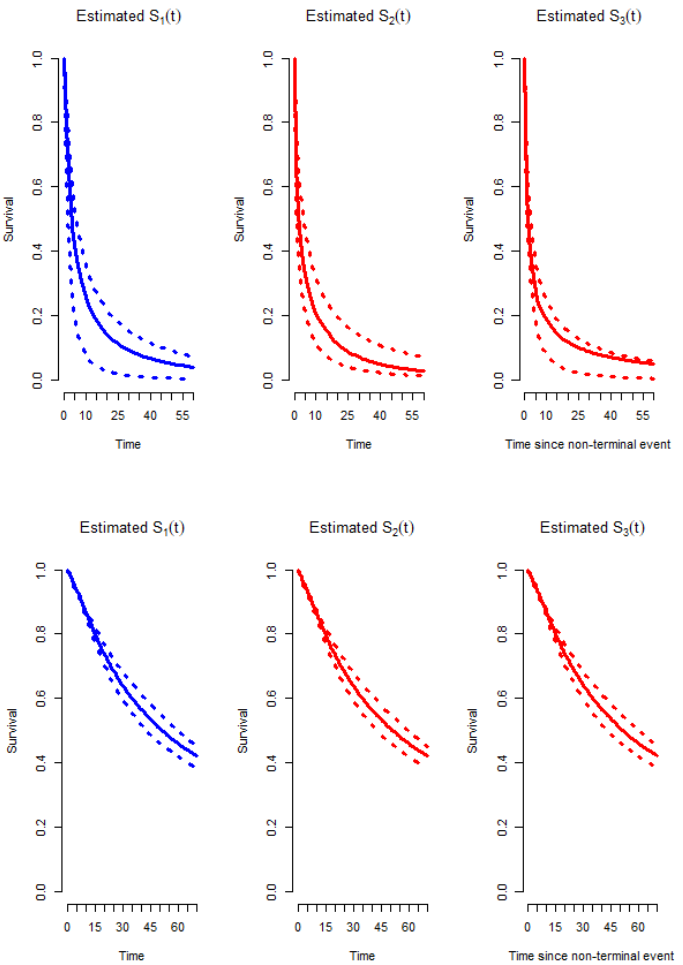
We also find that individuals with 0 indicators for 2nd covariate $I_{(2)}$ have a lower risk of reason 3. Their median time to reason 3 (non-terminal to terminal event) is estimated to be 64.7% and 7.6% longer than individuals who have the one indicator under the AFT-LN and AFT-DPM model, respectively.

Table 3: Estimated posterior medians along with 95% credible intervals (CI) for transition $g = 1,2,3$ based on two type of AFT-illness death model including the patient-specific random effect.

	Transition 1 (95% CI)	Transition 2(95% CI)	Transition 3 (95% CI)
Covariate 1			
AFT-LN	1.432(1.235,2.280)	2.719(2.072,3.758)	1.578(1.468,2.351)
AFT-DPM	0.935 (0.893,0.966)	1.079(1.008,1.151)	1.082(1.053,1.108)
Covariate 2			
AFT-LN	3.070(2.626,3.429)	2.080(1.828,2.659)	1.647(1.262,2.493)
AFT-DPM	1.127(1.099,1.155)	1.296(1.110,1.369)	1.076(0.984,1.087)
Covariate 3			
AFT-LN	1.991(1.709,2.262)	2.385(2.129,4.117)	2.464(1.928,2.853)
AFT-DPM	1.045(1.031,1.105)	1.009(0.925,1.038)	1.079(1.056,1.149)
Covariate 4			
AFT-LN	1.725(1.402,2.384)	1.758(1.602,2.351)	2.275(1.786,4.046)
AFT-DPM	1.058(1.058,1.058)	0.975(0.890,0.997)	1.208(1.042,1.851)
Covariate 5			
AFT-LN	1.604(1.389,1.721)	2.697(1.596,3.605)	2.028(1.471,2.339)
AFT-DPM	1.073 (1.070,1.075)	1.181(0.895,1.417)	1.191(1.145,1.237)

8. Discussion

In this work, we discuss the semi-competing risks framework as a way of investigating variation in risk for a non-terminal event where the occurrence of the event is subject to a



Estimated survival function for the three transitions specific survival distribution based on the AFT-LN & AFT-DPM model respectively.

terminal event. In this context, we have analyzed the semi-competing risk data using the proposed AFT illness death model (Lee et al. 2017), which serves as a helpful complement of the traditional hazard-based model of say (Xu et al. 2010) and (Lee et al. 2015).

Crucially the two modelling frameworks characterize associations through fundamentally different contrasts (see Section 2.2) and, in this sense, jointly provide an expanded scope for scientific inquiry. As such, reckoning on the scientific background and goals, analysts may value more highly to consider one or the other or possibly both.

In this text, our main objective is to find which model is a better fit for our frame and to estimate the effects of the covariates on the risk of the non-terminal event (e.g. cancer relapse). At the same time, we assume that death plays a vital role in the analysis. We have handled the data carefully as left truncation and interval censoring are present. If we do not consider these things, we will get a biased result.

In this article, we build the framework through the Bayesian model, which will help the researchers to take the advantage of well-known benefits including the ability to naturally incorporate prior information and the automated quantification of prediction and uncertainty.

Finally, we note that there are a number of ways in which one could build the proposed framework. First, while the focus of this article has been on semi-competing risk data, we have developed and implemented analogous parametric and semi-parametric univariate AFT models in settings where left truncation and interval censoring are present. Such a model might, for example, be useful if interest lies in whether there are differences in mortality between patients with and without a diagnosis of Alzheimer's and dementia. Some specific areas where the model can be used include pregnancy, where delivery is the terminal event and Preeclampsia will be the non-terminal event and palliative care where death is the terminal event and readmission will be the non-terminal event.

Ethical statement

Authors consciously assure that the following is fulfilled for the manuscript:
1) This material is the authors' own original work, which has not been previously published elsewhere.
2) The paper is not currently being considered for publication elsewhere.
3) The paper reflects the authors' own research and analysis in a truthful and complete manner.
4) The paper properly credits the meaningful contributions of co-authors and co-researchers.
5) The results are appropriately placed in the context of prior and existing research.
6) All sources used are properly disclosed (correct citation). Literally copying of text must be indicated as such by using quotation marks and giving proper reference.
7) All authors have been personally and actively involved in substantial work leading to the paper, and will take public responsibility for its content.

Conflict of interest

The authors declared there is no conflict of interest.

Acknowledgement

The author would like to acknowledge the support and resources provided by the Section of Biostatistics, Centre for Cancer Epidemiology, Tata Memorial Centre's staff, administrators, and teachers who work tirelessly to ensure their students receive the highest quality education.

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