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RESEARCH ARTICLE

Resampled Cox Proportional Hazards Models for Infant Mortality at the Kigali University Teaching Hospital

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Abstract:

Introduction:

Resampling technique as a way of overcoming instability in Cox Proportional hazard model is used for measuring the risk and related standard error for the infant mortality, given socio-economic and clinical covariates for mother and children at the Kigali University Teaching Hospital in Rwanda.

Methods:

Bootstrap and jackknife Cox proportional hazards models was applied to N=2117 newborn data collected in 2016 at the Kigali University Teaching Hospital in Rwanda.

Results:

The unadjusted models revealed significance of the age of female parents, information on previous abortion, gender of a newborn, number of newborns at a time, APGAR, the weight of a newborn and the circumference of the head of a newborn.

Conclusion:

Statistical analysis supports two major findings: 1) parents under 20 years of age indicate a relatively higher risk of infant death, and 2) abnormality in the newborn's head and weight indicates a relatively higher risk of infant mortality. Recommendations include avoidance of pregnancy until after age 20 and clinically recommended nutrition for the mother during pregnancy to decrease the risk of infant mortality.

Keywords: Infant mortality, Survival analysis, Cox proportional hazards model, Bootstrap, Jackknife, Resampling, Covariate.

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1. INTRODUCTION

The resampling in Cox proportional hazards model consists of conducting the Cox Proportional Hazards Model (CPHM) on a given number of samples obtained after applying a relevant technique of resampling. The popular nonparametric techniques of resampling include *bootstrap method* which is based on random sampling with replacement [1], *jackknife method* which consists of making samples by leaving out one observation a time [1], and *jackknife after bootstrap* [2]. The interest in this study will be on Bootstrap Cox Proportional Hazards Model (BCPHM) and Jackknife Cox Proportional Hazards Model (JCPHM).

Hamada [3] points out the aim of using the resampling technique in CPHM. Firstly the resampling allows the assessment of the stability of the CPHM. The instability may be caused by the correlation of the covariates. Secondly, the resampling may be used when the sample size is relatively small. Model adequacy may be satisfied by selecting variable on which the model is stable rather than testing the proportionality of variables.

BCPHM and JCPHM have been extensively applied to different studies. In [4], bootstrap is applied for estimating the survival function and the hazard rate with respective standard errors. Belašková, Fišerová, and Krupicková [5] published a clinical study which used BCPHM with consideration of right censoring and delayed entries. The study of Belašková *et al.* adapted BCPHM due to the small sample size (N=61). Xu, Sen, and Ying [6] conducted the BCPHM with consideration of

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a change-point along the study time with right censored survival data. The study proved the consistency of the model by making a comparison with the model based on data simulation. The JCPHM was adopted by Xiao, Yao-Hua, and Dong-Sheng [7] together with a random weighting which consists of approximating the distribution of the maximum partial likelihood estimates in the CPHM [8 - 10]. Several other manuscripts also discussed the use of the resampled survival analysis including [11 - 17]. In this study, the BCPHM with 1000 bootstrap replicates and the JCPHM were used and compared to the CPHM in modeling the risk of infant death at the Kigali University teaching Hospital from 01-January-2016 to 31-December-2016. The study comprises five sections including the introduction presented in Section 1. Section 2 presents the methods of the study where mathematical formulation of bootstrap and jackknife are reviewed. Section 3 gives the main results. Section 4 discusses the results and Section 5 concludes the paper.

2. METHODOLOGY

2.1. Bootstrap Method

2.1.1. Bootstrap

Assume a sample

$$\mathbf{x} = x_1, x_2, \dots, x_n,$$

$x_{i,i \in [1,n]}$ are independent and identically distributed with distribution F_θ where θ is the statistical parameter of interest. Consider the distribution function F_{R_n} of a random variable $R_n(\mathbf{x}, F_\theta)$. The bootstrap method as described by Efron and Tibshirani [1], consists of generating

$$\mathbf{x}^* = \mathbf{x}^{*1}, \mathbf{x}^{*2}, \dots, \mathbf{x}^{*B},$$

where $\mathbf{x}_{i,i \in [1,B]}^{*i}$ are random samples of size n drawn with replacement from the sample \mathbf{x} . The variables $\mathbf{x}_{i,i \in [1,B]}^{*i}$ are independent and identically distributed with distribution $\hat{F}_{\theta,n}$ given \mathbf{x} ; $\hat{F}_{\theta,n}$ is an estimator of F_θ from \mathbf{x} ; B is a number of bootstrap samples (replications).

2.1.2. Bootstrap Standard Error

Assume B bootstrap samples $s \mathbf{x}^{*1}, \mathbf{x}^{*2}, \dots, \mathbf{x}^{*B}$. Efron and Tibshirani [1] propose the estimated standard error of the bootstrap statistic of interest $\hat{\theta}$ as:

$$\widehat{se}_B = \sqrt{\frac{1}{B-1} \sum_{b=1}^B \left[\hat{\theta}^*(b) - \frac{1}{B} \sum_{b=1}^B \hat{\theta}^*(b) \right]^2} \tag{1}$$

where $\hat{\theta}^*(b)$ is an estimate of the statistic of interest from the b^{th} bootstrap sample, $b=1,2, \dots, B$.

2.1.3. Bootstrap Cox Proportional Hazard Model (BCPHM)

Assume a CPHM, $h(t|\mathbf{x}_i)$ over the p fixed covariates with values $\mathbf{x}_i = (x_{i1}, x_{i2}, \dots, x_{ip})$ and the hazard function $h(t)$ when values of all covariates are zeros, that is

$$h(t|\mathbf{x}_i) = h_0(t) \exp(\boldsymbol{\beta}'\mathbf{x}_i) \tag{2}$$

[18], where $\boldsymbol{\beta} = (\beta_1, \beta_2, \dots, \beta_p)'$ is a p -dimensional vector of model parameters.

Consider three approaches of approximating the partial likelihood in the presence of tied events namely Breslow [19] approximation of the partial likelihood function given by:

$$L_B(\boldsymbol{\beta}) = \prod_{j=1}^r \frac{e^{\boldsymbol{\beta}'\mathbf{s}_j}}{\left[\sum_{l \in \mathfrak{R}(t_{(j)})} e^{\boldsymbol{\beta}'\mathbf{x}_l} \right]^{d_j}}; \tag{3}$$

Efron [20] approximation of the partial likelihood function is given by:

$$L_E(\boldsymbol{\beta}) = \prod_{j=1}^r \frac{e^{\boldsymbol{\beta}'\mathbf{s}_j}}{\prod_{k=1}^{d_j} \left[\sum_{l \in \mathfrak{R}(t_{(j)})} e^{\boldsymbol{\beta}'\mathbf{x}_l - \frac{k-l}{d_j} \sum_{l \in \mathfrak{R}(t_{(j)})} e^{\boldsymbol{\beta}'\mathbf{x}_l}} \right]}; \tag{4}$$

and Cox [21] approximation of the partial likelihood function is given by:

$$L_C(\boldsymbol{\beta}) = \prod_{j=1}^r \frac{e^{\boldsymbol{\beta}'\mathbf{s}_j}}{\sum_{l \in \mathfrak{R}(t_{(j)}, d_j)} e^{\boldsymbol{\beta}'\mathbf{s}_l}} \tag{5}$$

where $\mathfrak{R}(t_{(j)}, d_j)$ is the set of d_j individuals drawn from the risk set $\mathfrak{R}(t_{(j)})$ at time $t_{(j)}$. The inference of model (2) based on bootstrap consists of applying model (2) to each of the B bootstrap samples $\mathbf{x}^{*i}, \forall i \in [1, B]$ of covariates $\mathbf{x}_j, \forall j \in [1, p]$. Bootstrap model parameter estimation uses either Breslow, Efron or Cox approach. The bootstrap standard error is obtained by using Equation (1).

2.2. Jackknife Method

2.2.1. Jackknife

Assume a sample

$$\mathbf{x} = x_1, x_2, \dots, x_n,$$

where $x_{j,j \in [1,n]}$ are the values of the covariate \mathbf{x} . Let θ be a statistic of interest. The jackknife samples consist of leaving out one observation at a time, that is n samples

$\mathbf{x}^{*i} = (x_1, \dots, x_{i-1}, x_{i+1}, \dots, x_n) \forall i \in [1, n]$ [1]. The jackknife standard error estimate as proposed [1], is given as:

$$\widehat{se}_{jack} = \sqrt{\frac{n-1}{n} \sum_{i=1}^n \left[\hat{\theta}^*(i) - \frac{1}{n} \sum_{i=1}^n \hat{\theta}^*(i) \right]^2} \tag{6}$$

where $\hat{\theta}^*(i), i \in [1, n]$ is a statistic of interest for the i^{th} jackknife sample.

2.2.2. Jackknife Cox Proportional Hazard Model (JCPHM)

Model (2) based on jackknife is made by applying it to each of the n jackknife samples $\mathbf{x}^{*i} \forall i \in [1, n]$ of covariates $\mathbf{x}_j, \forall j \in [1, p]$. Either Breslow, Efron or Cox approach is used for estimating the jackknife model parameters, with the standard error given by Eq (6).

2.3. Dataset

Table 1 describes the variables of interest and Table 2 summarises the dataset. The full dataset can be obtained from the authors of this article.

Table 1. Description of variables in the dataset on newborns at Kigali University Teaching Hospital (KUTH) during the period 01-January-2016 to 31-December-2016.

Variable	Description	Codes/Values/Unit
Age	Age of parent	0=under 20, 1=20 years old to 34 years old, 2=35 years old and above
Residence	Indicator of the residential area of a parent	0=rural, 1=urban
Antecedents	Indicator on whether a new born is the first or not	0=Not the first newborn, 1 = first newborn,
Abortion	Indicator on whether a parent aborted previously	0=not aborted, 1=aborted once, 2= aborted more than once
Child birth	Type of child birth	0=born using ventouse, 1=born naturally, 2= born after surgery
Gender	Gender of a newborn	0=female, 1=male
Number	Indicator of the number of births at a time	0=singleton, 1=multiple
APGAR	Score of <i>appearance, pulse, grimaces, activity and respiration</i> of a newborn	0= APGAR less than 4/10, 1=APGAR from 4/10 to 6/10, 2=APGAR greater or equal to 7/10
Weight	Weight of a newborn	0 = under 2500 g, 1= 2500 g to 4500 g, 2= above 4500 g
Head	Head circumference of a newborn	0= below 32 cm, 1=32 cm to 36 cm, 2=above 36 cm
Height	Height of a newborn	0=below 46 cm, 1=46 cm to 54 cm, 2=above 54 cm
Time	Time from recruitment to study termination	Days
Event	Indicator describing if death occurred during the study time or not	0=censored, 1=dead
n_events	Indicator on the rank of records per subject	1=first record, 2=second record

The time to event primary dataset of 2117 newborns at the Kigali University Teaching Hospital (KUTH) was recorded from 1st January to 31st December 2016. A complete case analysis is considered where the event is the death of the infant.

Table 3. Breslow estimation.

Covariate (Reference)	Level	CPHM					BCPHM					JCPHM				
		HR	SE	z	P>z	95% CI	HR	SE	z	P>z	95% CI	HR	SE	z	P>z	95% CI
Age (Under 20 years old)	20 to 34 years old	0.172	0.086	-3.540	p < 0.001	[0.065; 0.456]	0.172	0.254	-1.190	0.234	[0.009; 3.124]	0.172	0.089	-3.400	0.001	[0.062; 0.475]
	35 years old and above	0.216	0.117	-2.840	0.005	[0.075; 0.623]	0.216	0.323	-1.020	0.306	[0.012; 4.058]	0.216	0.124	-2.660	0.008	[0.070; 0.667]
Residence (Rural)	Urban	1.014	0.240	0.060	0.954	[0.637; 1.614]	1.014	0.277	0.050	0.960	[0.594; 1.732]	1.014	0.285	0.050	0.961	[0.585; 1.758]

Eighty-two babies died during the study time, 69 stillborn babies were recorded and 1966 babies were censored. Eleven covariates of interest are demographic covariates that include the *age* and the place of *residence* for parents; clinical covariates for parents include obstetric *antecedents*, type of *childbirth* and previous *abortion*. Clinical covariates for children include *APGAR*; *gender*, *number* of births at a time, *weight*, circumference of the *head*, and *height*. The minimum sample size according to Peduzzi *et al.* [22] is $N = \frac{10k}{p}$ where k is the number of predictor variables and p is the number of events. This suggests the minimum sample size at KUTH as:

$$N = \frac{10 \times 11}{0.07132} \approx 1542.$$

Table 2. Summary of newborns under study.

Total Observations	2117
Deaths during the study time	82 (3.873%)
Stillborn babies	69 (3.259%)
Total events	151 (7.132 %)
Censored babies	1966 (92.867%)

3. RESULTS

STATA-15 displays the results in three tables: Table 3 presents estimates of unadjusted CPHM, BCPHM, JCPHM and corresponding adjusted models, by using Breslow estimation method. Both unadjusted and adjusted CPHM, BCPHM and JCPHM by Efron and Cox estimation are also presented in Tables 4 and 5. The results displayed by the jackknife model are relatively close to that of the Cox proportional hazards model (Table 3). The standard errors in JCPHM and CPHM are not critically different for all covariates except for the upper levels of covariates *weight*, *head* and *height* where the standard error in JCPHM is more than 40 times that of CPHM. The critical difference in standard error is also observed in BCPHM for the upper levels of covariates *weight*, *head* and *height*, for all levels of covariate *childbirth* and for the covariate *number* where the standard error is relatively higher in BCPHM. Also, BCPHM does not take *age* and *number* as significant covariates unlike the fact of JCPHM and CPHM where these covariates are included in significant covariates. Following suggestions in [23], the χ^2 test statistics suggest a higher performance of the JCPHM as compared to the CPHM and BCPHM since the value of the χ^2 is relatively everywhere lower for the JCPHM.

(Table 3) contd.....

		CPHM					BCPHM					JCPHM					
Covariate (Reference)	Level	HR	SE	z	P>z	95% CI	HR	SE	z	P>z	95% CI	HR	SE	z	P>z	95% CI	
Antecedents (Not 1st newborn)	1st newborn	0.778	0.221	-0.880	0.377	[0.446; 1.358]	0.778	0.223	-0.880	0.381	[0.444; 1.364]	0.778	0.218	-0.900	0.370	[0.449; 1.347]	
Abortion (Not aborted)	Aborted once	1.646	0.648	1.270	0.206	[0.761; 3.562]	1.646	0.695	1.180	0.238	[0.720; 3.763]	1.646	0.664	1.230	0.217	[0.746; 3.633]	
	Aborted more than once	1.111	0.503	0.230	0.817	[0.457; 2.700]	1.111	2.084	0.060	0.955	[0.028; 43.927]	1.111	0.556	0.210	0.834	[0.416; 2.966]	
Childbirth (Ventouse)	Natural	0.593	0.449	-0.690	0.490	[0.135; 2.612]	0.593	3.846	-0.080	0.936	[0.000; 1.963x 10 ⁵]	0.593	0.469	-0.660	0.509	[0.126; 2.797]	
	Surgery	0.777	0.580	-0.340	0.736	[0.180; 3.358]	0.777	5.021	-0.040	0.969	[0.000; 2.443x 10 ⁵]	0.777	0.611	-0.320	0.749	[0.166; 3.630]	
Gender (Female)	Male	1.964	0.472	2.810	0.005	[1.227; 3.146]	1.964	0.480	2.760	0.006	[1.217; 3.170]	1.964	0.504	2.630	0.009	[1.188; 3.248]	
Number (Singleton)	Multiple	0.306	0.136	-2.660	0.008	[0.128; 0.732]	0.306	0.730	-0.500	0.620	[0.003; 32.826]	0.306	0.136	-2.670	0.008	[0.128; 0.729]	
APGAR (Below 4/10)	4/10 to 6/10	0.335	0.133	-2.760	0.006	[0.154; 0.729]	0.335	0.160	-2.290	0.022	[0.131; 0.856]	0.335	0.157	-2.340	0.020	[0.134; 0.839]	
	7/10 and above	0.049	0.019	-7.860	p < 0.001	[0.023; 0.103]	0.049	0.020	-7.300	p < 0.001	[0.022; 0.110]	0.049	0.020	-7.380	p < 0.001	[0.022; 0.109]	
Weight (Under 2500 g)	2500 g to 4500 g	0.227	0.089	-3.790	p < 0.001	[0.105; 0.489]	0.227	0.102	-3.300	0.001	[0.094; 0.548]	0.227	0.105	-3.210	0.001	[0.091; 0.561]	
	Above 4500 g	0.392	0.421	-0.870	0.383	[0.048; 3.213]	0.392	8.103	-0.050	0.964	[0.000; 1.600x 10 ¹⁷]	0.392	17.310	-0.020	0.983	[0.000; 1.740x 10 ³⁷]	
Head (Below 32 cm)	32 cm to 36 cm	0.288	0.111	-3.230	0.001	[0.136; 0.613]	0.288	0.121	-2.960	0.003	[0.127; 0.658]	0.288	0.116	-3.090	0.002	[0.131; 0.635]	
	Above 36 cm	0.122	0.128	-2.010	0.045	[0.016; 0.951]	0.122	2.449	-0.100	0.917	[0.000; 1.670x 10 ¹⁶]	0.122	5.426	-0.050	0.962	[0.000; 1.220x 10 ³⁷]	
Height (Below 36 cm)	46 cm to 54 cm	0.567	0.235	-1.370	0.171	[0.251; 1.278]	0.567	0.240	-1.340	0.180	[0.247; 1.300]	0.567	0.247	-1.300	0.193	[0.241; 1.334]	
	Above 54 cm	1.020	1.100	0.020	0.986	[0.123; 8.444]	1.020	21.073	0.000	0.999	[0.000; 3.980x 10 ¹⁷]	1.020	44.687	0.000	1.000	[0.000; 2.150x 10 ³⁷]	
Adjusted CPHM						Adjusted BCPHM						Adjusted JCPHM					
Age (Under 20 years old)	20 to 34 years old	0.215	0.105	-3.150	0.002	[0.083; 0.559]	-	-	-	-	-	0.215	0.104	-3.190	0.001	[0.084; 0.554]	
	35 years old and above	0.308	0.159	-2.280	0.023	[0.112; 0.848]	-	-	-	-	-	0.308	0.160	-2.270	0.023	[0.111; 0.852]	
Gender (Female)	Male	1.942	0.459	2.810	0.005	[1.222; 3.085]	1.562	0.350	1.990	0.046	[1.007; 2.424]	1.942	0.476	2.700	0.007	[1.200; 3.142]	
Number (Singleton)	Multiple	0.264	0.115	-3.060	0.002	[0.112; 0.619]	-	-	-	-	-	0.264	0.117	-3.010	0.003	[0.111; 0.629]	
APGAR (Below 4/10)	4/10 to 6/10	0.411	0.154	-2.380	0.017	[0.198; 0.856]	0.695	0.288	-0.880	0.379	[0.308; 1.565]	0.411	0.185	-1.970	0.049	[0.170; 0.995]	
	7/10 and above	0.059	0.021	-7.850	p < 0.001	[0.029; 0.119]	0.100	0.039	-5.880	p < 0.001	[0.046; 0.215]	0.059	0.024	-6.810	p < 0.001	[0.026; 0.133]	
Weight (Under 2500 g)	2500 g to 4500 g	0.181	0.064	-4.860	p < 0.001	[0.091; 0.361]	0.200	0.084	-3.840	p < 0.001	[0.088; 0.455]	0.181	0.071	-4.390	p < 0.001	[0.084; 0.389]	
	Above 4500 g	0.372	0.384	-0.960	0.338	[0.049; 2.809]	0.438	8.985	-0.040	0.968	[0.000; 1.280x 10 ¹⁷]	0.372	16.296	-0.020	0.982	[0.000; 6.880x 10 ³⁶]	
Head (Below 32 cm)	32 cm to 36 cm	0.208	0.068	-4.830	p < 0.001	[0.110; 0.394]	0.216	0.088	-3.760	p < 0.001	[0.097; 0.480]	0.208	0.080	-4.060	p < 0.001	[0.098; 0.444]	

(Table 3) contd....

Covariate (Reference)	Level	CPHM					BCPHM					JCPHM				
		HR	SE	z	P>z	95% CI	HR	SE	z	P>z	95% CI	HR	SE	z	P>z	95% CI
	Above 36 cm	0.105	0.109	-2.180	0.029	[0.014; 0.797]	0.109	2.234	-0.110	0.914	[0.000; 2.600x 10 ¹⁶]	0.105	4.680	-0.050	0.960	[0.000; 9.160x 10 ³⁶]
$\chi^2 = 300.360, p < 0.001$						$\chi^2 = 296.290, p < 0.001$					$\chi^2 = 32.310, p < 0.001$					

Table 4. Efron estimation.

Covariate (Reference)	Level	CPHM					BCPHM					JCPHM				
		HR	SE	z	P>z	95% CI	HR	SE	z	P>z	95% CI	HR	SE	z	P>z	95% CI
Age (Under 20 years old)	20 to 34 years old	0.160	0.079	-3.680	p < 0.001	[0.060; 0.424]	0.160	0.323	-0.910	0.364	[0.003; 8.374]	0.160	0.087	-3.370	0.001	[0.055; 0.464]
	35 years old and above	0.199	0.107	-2.990	0.003	[0.069; 0.573]	0.199	0.406	-0.790	0.429	[0.004; 10.896]	0.199	0.120	-2.680	0.007	[0.061; 0.648]
Residence (Rural)	Urban	1.029	0.246	0.120	0.907	[0.643; 1.645]	1.029	0.307	0.090	0.925	[0.573; 1.847]	1.029	0.314	0.090	0.927	[0.565; 1.871]
Antecedents (Not 1st newborn)	1st newborn	0.723	0.212	-1.110	0.268	[0.407; 1.283]	0.723	0.227	-1.030	0.301	[0.391; 1.337]	0.723	0.233	-1.010	0.314	[0.384; 1.359]
Abortion (Not aborted)	Aborted once	1.588	0.628	1.170	0.242	[0.732; 3.448]	1.588	0.696	1.060	0.291	[0.673; 3.749]	1.588	0.659	1.110	0.265	[0.704; 3.585]
	Aborted more than once	1.147	0.519	0.300	0.762	[0.473; 2.782]	1.147	4.651	0.030	0.973	[0.000; 3.251x 10 ³]	1.147	0.587	0.270	0.789	[0.420; 3.127]
Childbirth (Ventouse)	Natural	0.532	0.400	-0.840	0.401	[0.122; 2.319]	0.532	3.646	-0.090	0.927	[0.000; 3.605x 10 ⁵]	0.532	0.448	-0.750	0.454	[0.102; 2.772]
	Surgery	0.695	0.515	-0.490	0.624	[0.163; 2.969]	0.695	4.766	-0.050	0.958	[0.000; 4.743x 10 ⁵]	0.695	0.579	-0.440	0.663	[0.136; 3.558]
Gender (Female)	Male	2.061	0.500	2.980	0.003	[1.282; 3.315]	2.061	0.556	2.680	0.007	[1.215; 3.496]	2.061	0.592	2.520	0.012	[1.173; 3.621]
Number (Singleton)	Multiple	0.243	0.113	-3.040	0.002	[0.098; 0.606]	0.243	0.135	-2.540	0.011	[0.082; 0.724]	0.243	0.141	-2.440	0.015	[0.078; 0.759]
APGAR (Below 4/10)	4/10 to 6/10	0.207	0.084	-3.880	p < 0.001	[0.094; 0.460]	0.207	0.116	-2.820	0.005	[0.070; 0.618]	0.207	0.120	-2.710	0.007	[0.066; 0.648]
	7/10 and above	0.030	0.012	-8.960	p < 0.001	[0.014; 0.065]	0.030	0.015	-7.070	p < 0.001	[0.011; 0.080]	0.030	0.016	-6.750	p < 0.001	[0.011; 0.083]
Weight (Under 2500 g)	2500 g to 4500 g	0.222	0.088	-3.800	p < 0.001	[0.102; 0.483]	0.222	0.105	-3.180	0.001	[0.088; 0.562]	0.222	0.107	-3.110	0.002	[0.086; 0.574]
	Above 4500 g	0.389	0.426	-0.860	0.389	[0.045; 3.338]	0.389	8.081	-0.050	0.964	[0.000; 1.950x 10 ¹⁷]	0.389	17.369	-0.020	0.983	[0.000; 4.530x 10 ³⁷]
Head (Below 32 cm)	32 cm to 36 cm	0.284	0.110	-3.250	0.001	[0.133; 0.607]	0.284	0.115	-3.100	0.002	[0.129; 0.629]	0.284	0.119	-3.000	0.003	[0.125; 0.647]
	Above 36 cm	0.110	0.117	-2.070	0.038	[0.014; 0.886]	0.110	2.350	-0.100	0.918	[0.000; 1.590x 10 ¹⁷]	0.110	3.679	-0.070	0.947	[0.000; 3.080x 10 ²⁷]
Height (Below 36 cm)	46 cm to 54 cm	0.569	0.238	-1.350	0.177	[0.251; 1.291]	0.569	0.252	-1.270	0.202	[0.239; 1.354]	0.569	0.273	-1.180	0.240	[0.222; 1.457]
	Above 54 cm	1.010	1.094	0.010	0.993	[0.121; 8.431]	1.010	21.269	0.000	1.000	[0.000; 18.460x 10 ¹⁷]	1.010	44.776	0.000	1.000	[0.000; 5.730x 10 ³⁷]
Adjusted CPHM		Adjusted BCPHM					Adjusted JCPHM									
Age (Under 20 years old)	20 to 34 years old	0.201	0.098	-3.280	0.001	[0.077; 0.524]	-	-	-	-	-	0.201	0.102	-3.170	0.002	[0.075; 0.543]

(Table 4) contd.....

Covariate (Reference)	Level	CPHM					BCPHM					JCPHM				
		HR	SE	z	P>z	95% CI	HR	SE	z	P>z	95% CI	HR	SE	z	P>z	95% CI
	35 years old and above	0.293	0.152	-2.360	0.018	[0.106; 0.811]	-	-	-	-	-	0.293	0.160	-2.250	0.025	[0.101; 0.856]
Gender (Female)	Male	2.071	0.495	3.050	0.002	[1.297; 3.308]	1.562	0.400	1.740	0.081	[0.946; 2.579]	2.071	0.587	2.570	0.010	[1.188; 3.611]
Number (Singleton)	Multiple	0.205	0.092	-3.520	p < 0.001	[0.085; 0.495]	-	-	-	-	-	0.205	0.118	-2.740	0.006	[0.066; 0.637]
APGAR (Below 4/10)	4/10 to 6/10	0.273	0.103	-3.430	0.001	[0.130; 0.573]	0.545	0.273	-1.210	0.226	[0.204; 1.457]	0.273	0.169	-2.100	0.036	[0.081; 0.919]
	7/10 and above	0.038	0.014	-8.980	p < 0.001	[0.019; 0.078]	0.077	0.036	-5.440	p < 0.001	[0.030; 0.193]	0.038	0.023	-5.530	p < 0.001	[0.012; 0.122]
Weight (Under 2500 g)	2500 g to 4500 g	0.179	0.063	-4.890	p < 0.001	[0.090; 0.356]	0.201	0.083	-3.880	0.000	[0.089; 0.452]	0.179	0.071	-4.360	p < 0.001	[0.082; 0.388]
	Above 4500 g	0.379	0.396	-0.930	0.353	[0.049; 2.938]	0.477	9.872	-0.040	0.971	[0.000; 2.040x 10 ¹⁷]	0.379	16.849	-0.020	0.983	[0.000; 2.970x 10 ³⁷]
Head (Below 32 cm)	32 cm to 36 cm	0.205	0.067	-4.860	p < 0.001	[0.108; 0.388]	0.215	0.090	-3.680	p < 0.001	[0.095; 0.487]	0.205	0.081	-4.030	p < 0.001	[0.095; 0.443]
	Above 36 cm	0.095	0.100	-2.250	0.025	[0.012; 0.740]	0.105	2.180	-0.110	0.914	[0.000; 5.960x 10 ¹⁶]	0.095	4.226	-0.050	0.958	[0.000; 5.340x 10 ³⁶]
$\chi^2 = 316.160, p < 0.001$						$\chi^2 = 297.200, p < 0.001$					$\chi^2 = 29.760, p < 0.001$					

Table 5. Cox estimation.

Covariate (Reference)	Level	CPHM					BCPHM					JCPHM				
		HR	SE	z	P>z	95% CI	HR	SE	z	P>z	95% CI	HR	SE	z	P>z	95% CI
Age (Under 20 years old)	20 to 34 years old	0.140	0.075	-3.690	p < 0.001	[0.050; 0.398]	0.140	0.257	-1.070	0.283	[0.004; 5.064]	0.140	0.084	-3.260	0.001	[0.043; 0.457]
	35 years old and above	0.171	0.098	-3.090	0.002	[0.056; 0.523]	0.171	0.313	-0.960	0.335	[0.005; 6.216]	0.171	0.111	-2.710	0.007	[0.048; 0.613]
Residence (Rural)	Urban	1.003	0.258	0.010	0.990	[0.606; 1.660]	1.003	0.347	0.010	0.993	[0.510; 1.974]	1.003	0.342	0.010	0.993	[0.514; 1.956]
Antecedents (Not 1st newborn)	1st newborn	0.726	0.231	-1.010	0.313	[0.389; 1.353]	0.726	0.280	-0.830	0.406	[0.341; 1.545]	0.726	0.268	-0.870	0.386	[0.351; 1.498]
Abortion (Not aborted)	Aborted once	1.671	0.686	1.250	0.211	[0.748; 3.735]	1.671	0.763	1.120	0.261	[0.683; 4.091]	1.671	0.722	1.190	0.234	[0.717; 3.897]
	Aborted more than once	1.388	0.697	0.650	0.514	[0.519; 3.712]	1.388	0.756	0.600	0.548	[0.477; 4.038]	1.388	0.849	0.540	0.593	[0.418; 4.609]
Childbirth (Ventouse)	Natural	0.533	0.422	-0.790	0.427	[0.113; 2.517]	0.533	3.473	-0.100	0.923	[0.000; 1.883x 10 ⁵]	0.533	0.449	-0.750	0.456	[0.102; 2.786]
	Surgery	0.759	0.590	-0.360	0.722	[0.166; 3.479]	0.759	4.946	-0.040	0.966	[0.000; 2.683x 10 ⁵]	0.759	0.628	-0.330	0.739	[0.150; 3.850]
Gender (Female)	Male	2.195	0.570	3.030	0.002	[1.319; 3.652]	2.195	0.672	2.570	0.010	[1.204; 3.999]	2.195	0.695	2.480	0.013	[1.179; 4.086]
Number (Singleton)	Multiple	0.203	0.110	-2.950	0.003	[0.071; 0.585]	0.203	0.693	-0.470	0.640	[0.000; 162.000]	0.203	0.196	-1.650	0.099	[0.031; 1.353]
APGAR (Below 4/10)	4/10 to 6/10	0.167	0.085	-3.500	p < 0.001	[0.061; 0.455]	0.167	0.602	-0.500	0.620	[0.000; 197.300]	0.167	0.180	-1.660	0.098	[0.020; 1.392]
	7/10 and above	0.022	0.010	-8.140	p < 0.001	[0.009; 0.055]	0.022	0.078	-1.070	0.284	[0.000; 24.091]	0.022	0.021	-3.880	p < 0.001	[0.003; 0.151]
Weight (Under 2500 g)	2500 g to 4500 g	0.221	0.088	-3.790	p < 0.001	[0.101; 0.482]	0.221	0.105	-3.180	0.001	[0.087; 0.560]	0.221	0.105	-3.170	0.002	[0.087; 0.562]

(Table 5) contd.....

Covariate (Reference)	Level	CPHM					BCPHM					JCPHM				
		HR	SE	z	P>z	95% CI	HR	SE	z	P>z	95% CI	HR	SE	z	P>z	95% CI
	Above 4500 g	0.324	0.362	-1.010	0.313	[0.036; 2.892]	0.324	6.266	-0.060	0.954	[0.000; 9.150x 10 ¹⁵]	0.324	10.526	-0.030	0.972	[0.000; 1.450x 10 ²⁷]
Head (Below 32 cm)	32 cm to 36 cm	0.285	0.110	-3.240	0.001	[0.133; 0.609]	0.285	0.119	-3.020	0.003	[0.126; 0.644]	0.285	0.117	-3.050	0.002	[0.127; 0.639]
	Above 36 cm	0.106	0.114	-2.090	0.036	[0.013; 0.866]	0.106	2.091	-0.110	0.909	[0.000; 5.660x 10 ¹⁵]	0.106	3.780	-0.060	0.950	[0.000; 1.910x 10 ²⁹]
Height (Below 36 cm)	46 cm to 54 cm	0.539	0.226	-1.480	0.140	[0.237; 1.225]	0.539	0.236	-1.410	0.158	[0.229; 1.270]	0.539	0.252	-1.320	0.186	[0.216; 1.346]
	Above 54 cm	1.037	1.120	0.030	0.973	[0.125; 8.613]	1.037	20.074	0.000	0.998	[0.000; 3.080x 10 ¹⁶]	1.037	41.221	0.000	0.999	[0.000; 7.290x 10 ³³]
Adjusted CPHM						Adjusted BCPHM					Adjusted JCPHM					
Age (Under 20 years old)	20 to 34 years old	0.173	0.092	-3.310	0.001	[0.061; 0.488]	-	-	-	-	-	0.181	0.096	-3.230	0.001	[0.064; 0.511]
	35 years old and above	0.250	0.139	-2.490	0.013	[0.084; 0.745]	-	-	-	-	-	0.248	0.139	-2.490	0.013	[0.083; 0.744]
Gender (Female)	Male	2.150	0.550	2.990	0.003	[1.302; 3.549]	2.031	0.473	3.050	0.002	[1.287; 3.205]	1.778	0.506	2.020	0.043	[1.018; 3.106]
Number (Singleton)	Multiple	0.176	0.091	-3.350	0.001	[0.064; 0.486]	-	-	-	-	-	-	-	-	-	-
APGAR (Below 4/10)	4/10 to 6/10	0.249	0.114	-3.030	0.002	[0.101; 0.612]	-	-	-	-	-	0.516	0.330	-1.030	0.301	[0.147; 1.809]
	7/10 and above	0.030	0.013	-8.220	p < 0.001	[0.013; 0.069]	-	-	-	-	-	0.060	0.035	-4.820	p < 0.001	[0.019; 0.188]
Weight (Under 2500 g)	2500 g to 4500 g	0.176	0.062	-4.910	p < 0.001	[0.088; 0.352]	0.149	0.053	-5.380	p < 0.001	[0.075; 0.299]	0.209	0.082	-3.990	p < 0.001	[0.097; 0.451]
	Above 4500 g	0.325	0.347	-1.050	0.293	[0.040; 2.636]	0.367	6.399	-0.060	0.954	[0.000; 2.450x 10 ¹⁴]	0.425	16.781	-0.020	0.983	[0.000; 1.840x 10 ³³]
Head (Below 32 cm)	32 cm to 36 cm	0.196	0.064	-5.020	p < 0.001	[0.103; 0.370]	0.120	0.038	-6.700	p < 0.001	[0.065; 0.224]	0.198	0.077	-4.180	p < 0.001	[0.093; 0.423]
	Above 36 cm	0.090	0.095	-2.290	0.022	[0.011; 0.706]	0.073	1.284	-0.150	0.882	[0.000; 7.170x 10 ¹³]	0.098	4.324	-0.050	0.958	[0.000; 3.360x 10 ³⁶]
$\chi^2 = 316.430, p < 0.001$						$\chi^2 = 210.070, p < 0.001$					$\chi^2 = 31.380, p < 0.001$					

4. DISCUSSION

The resampling methods adopted in the Cox Proportional Hazard Model (CPHM) include Bootstrap Cox Proportional Hazards Model (BCPHM) and Jackknife Cox Proportional Hazards Model (JCPHM) with three approaches of ties handling. The results by different approaches of ties handling are not critically different as expected. The analysis is then made on the STATA-15 default method [19]. The similarity observed between the results of JCPHM and those of CPHM is relatively stronger than that of BCPHM and CPHM. The similarity between CPHM and JCPHM suggests that the CPHM may be stable. The overall analysis confirms the significant difference of levels of covariates *age, gender, number, APGAR, weight* and *head*. The results show relatively higher risk of babies from under 20 years old parents as compared to the older parents, that is 4.651 times that of babies whose parents' ages range from 20 to 34 years, and 3.247 times that of babies whose parents are 35 years old and above. The risk of male babies is 1.942 times that of female babies. The

risk of multiple babies is 0.264 times that of singleton babies. Babies with APGAR below 4/10 are at a relatively higher risk, that is 2.433 times that babies with APGAR ranging from 4/10 to 6/10 and 16.949 times that of babies whose APGAR range from 7/10 to 10/10. The risk of babies whose weight is below 2500 g is 5.525 times that of babies whose weight range from 2500 g to 4500 g and 2.688 times that of babies with weight above 4500 g. The risk for babies born with a circumference of head below 32 cm is 4.808 times that of newborns whose circumference of head ranges from 32 cm to 36 cm, and 9.524 times that of newborns whose circumference of head is above 36 cm.

The results of BCPHM are also close to that of JCPHM and CPHM for all significant covariates but the model shows a relatively high standard error for non-significant levels of covariates. The critical discrepancy between standard errors after resampling for some covariates suggests instability of the CPHM at these specific covariates and this emphasizes their non-significance in the CPHM.

The dataset was recorded for one year. The stability of the adjusted CPHM is justified by the non-critical difference between the adjusted resampled models.

CONCLUSION

This paper reviewed different methods of resampling in Cox Proportional Hazards Model (CPHM) namely the Bootstrap Cox Proportional Hazards Model (BCPHM) and the Jackknife Cox Proportional Hazards Model (JCPHM). The results after resampling are compared to that of the CPHM for three different ties handling methods namely Breslow, Efron and Cox approximation. The test statistics show everywhere a higher performance of the JCPHM as compared to the CPHM and BCPHM.

The results displayed by the JCPHM and CPHM are very close and suggested the significance of the age of female parent, information on previous abortion, the gender of a newborn, the number of newborns at a time, APGAR, the weight of a newborn and the circumference of the head of a newborn. Male babies are at a relatively higher risk as compared to female babies. The risk is higher for babies whose parents are under 20 years old as compared to older parents. Babies born with APGAR less than 4/10 were found to have a higher risk as compared to newborns with APGAR greater than 4/10. Underweight babies were found to have a higher risk as compared to babies with normal weight and overweight. Babies with a normal circumference of the head were found to survive better than those with a relatively big head and relatively small head. Under-height babies were found to have a higher risk as compared to babies born with normal height and over-height newborns. The results of the BCPHM are not far from that of JCPHM and CPHM but the non-significant covariates displayed relatively higher standard error. The overall results for non-significant covariates showed a relatively higher standard error after resampling. Due to a relatively higher risk to death of an infant from under 20 years old parents, the pregnancy of parents belonging in such range of age should be avoided. Also as abnormality lead to a relatively higher risk to infant mortality, clinically recommended nutrition during pregnancy would decrease abnormality of the newborn; this would decrease the infant mortality.

Analysis was limited to one event which is the death of the infant. Resampling with multiple events could improve models where an alternative event is attracting a chronic disease or clinical complication for the infant during the study time.

LIST OF ABBREVIATIONS

APGAR = Appearance, Pulse, Grimace, Activity and Respiration
CPHM = Cox Proportional Hazards Model
BCPHM = Bootstrap Cox Proportional Hazards Model
JCPHM = Jackknife Cox Proportional Hazards Model
KUTH = Kigali University Teaching Hospital

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Kigali University Teaching Hospital where dataset was taken from the hospital database,

with consent that the names of both the parents and the children cannot be published.

HUMAN AND ANIMAL RIGHTS

No animals/ humans were used for the studies that are the basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of the article is available in the School of Mathematics, Statistics and Computer Science, University of KwaZulu Natal at <http://smscs.ukzn.ac.za/Homepage.aspxL>, reference number 00033 260 5610.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest, financial or otherwise.

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