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Research Article
A Study on Childhood Mortality Using Shared Frailty Modeling Approach

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Abstract
The aim of the study was to develop shared frailty models accountable for individual and community level heterogeneity. With an objective that proper steps can be taken both at individual family and community levels in any society prior to any planning for child survival programmes. Analysis includes 51,555 live births that occurred 5 year preceding the National Family Health Family Health Survey-3, India. Multivariable fractional polynomial approach was used to shortlist potential variables based on modified Mosley and Chen framework. After verifying proportional hazard assumptions the traditional Cox and extended Cox model were applied it was observed that for correlated/hierarchical data the estimates of Cox-PH model can be misleading so proper care should be taken for consideration of frailty while assessing childhood mortality in any clustered population.

Key words: Shared frailty, cox PH, under-five mortality, traditional cox, extended cox model

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

In the social, medical and biological sciences multilevel or hierarchically structure data are the norm (Rondeau and Gonzalez, 2005). One can't assess childhood mortality truly while ignoring such structures. The present study aim's at exploring such random effect via modelling. An individual is said to be frail if he or she is much more susceptible (exposed or infected) to adverse events than others. Vaupel *et al.* (1979) introduced the term frailty to indicate that different individuals are at risks even though on the surface they may appear to be quite similar with respect to measurable attributes such as age, gender (Rondeau, 2010). They used the term frailty to represent an unobservable random effect shared by subjects with similar (unmeasured) risks in the analysis of mortality rates. A random effect describes excess risk or frailty for distinct categories, such as individuals or families, over and above any measured covariates. Frailty models are extensions of the Cox proportional hazards model (Fox, 2008) which is the most popular model in survival analysis (Kleinbaum and Klein, 2005; Hougaard, 2000; Wienke, 2010). In many clinical applications, the study population needs to be considered as a heterogeneous sample or as a cluster of homogeneous groups of individuals such as families or geographical areas. Sometimes, due to lack of knowledge or for economic reasons, some covariates related to the event of interest are not measured. The frailty approach is a statistical modelling method which aims to account for the heterogeneity caused by unmeasured covariates (Rondeau *et al.*, 2012). It does so by adding random effect which acts multiplicatively on the hazard function. For the present study shared frailty modelling approach at individual and community level is used. In India, 2.1 million children die before their fifth birthday. Half of these children die even before they are 28 days old, accounting for one-fourth global infant deaths (IIPS and Macro International, 2007). Of the 9.7 million child deaths worldwide annually, one-third occur in India (UNICEF., 2007). The statistics are equally shocking among neonates-children new born to a maximum age of 28 days old. While around 4 million children die within the first 28 days of life across the planet every year, India records around one million of these cases (Sharma, 2008).

India has realized impressive gains in child survival over the last two decades. However, at the current pace, the country is unlikely to achieve the Millennium Development Goal (MDG) 4-which aims to reduce Under-Five Mortality (U5MR) by two thirds between 1990 and 2015 unless the related socio-economic, maternal and demographic and environmental determinants are urgently addressed (UNDP., 2015). There is a small or no decline in Early Neonatal Mortality Rate (ENMR), which hovers at around 30/1000 live births. The ENMR is an indicator of quality of perinatal care.

The famous Mosley and Chen analytical framework (Mosley and Chen, 1984) of child survival have identified the proximate determinants of under-five mortality namely under five categories (maternal factor, environmental contamination, nutrient deficiency, injury, personal illness and control) however only handful of studies are done considering the entire proximate determinants framework moreover the presence of unidentified heterogeneity is unanimously ignored.

MATERIALS AND METHODS

Data sources: The present study uses National Family Health Survey (NFHS-3) data of India. National Family Health Survey-3 collected information from a nationally representative sample of 109,041 households, 124,385 women age 15-49 and 74,369 men age 15-54. The NFHS-3 sample covers 99% of India's population living in all the 29 states (IIPS and Macro International, 2007). The NFHS-3 provides information on fertility, mortality, family planning, HIV-related knowledge and important aspects of nutrition, health and health care however for the present study fertility, mortality and vital variables related to family planning aspects were studied.

Study variables: The primary outcome, childhood mortality, was defined as time to death of a live born baby before his/her fifth birthday. Available potential predictors of child survival as summarized in the conceptual Mosley and Chen framework was considered for the present study.

Selection of potential determinants using Multivariable Fractional Polynomials (MFP): One of the most tedious job in model development is selection of potential variables, problem of under fitting or over fitting is often seen while dealing with regression models. In fitting regression models data analysts are often faced with many predictor variables which may influence the outcome. Several strategies for selection of variables to identify a subset of 'important' predictors are available for many years. A further issue to model building is how to deal with non-linearity in the relationship between outcome and a continuous predictor. Traditionally, for such predictors either a linear functional relationship or a step function after grouping is assumed. However, the assumption of linearity may be incorrect, leading to a misspecified final model. For multivariable model building a systematic approach to investigate possible non-linear functional relationships based on fractional polynomials and the combination with backward elimination was applied in the present study.

Analytical models

Cox proportional hazards model: Mathematically, it is written as:

$$h(t) = h_o(t)e^{\beta Z_k},\ t > 0$$

where, $h_o(t)$ is an unspecified baseline hazard function and β denotes the regression coefficients for associated with covariates Z_k (k = 1, 2...p). The Cox developed a modification of the likelihood function called partial likelihood to estimate the coefficients β not taking into account the time dependent term of the hazard function:

$$\log[L(\beta)] = \sum_{i=1}^{n} \beta x_i - \log\left[\sum_{j} t(j) \geq t(i)e^{\beta x_j}\right]$$

To estimate the β parameters of the model (the coefficients of the linear function), we try to maximize the partial likelihood function.

Cox model shared frailty: The term frailty is used in survival analysis to describe regression models with random effects. A frailty is a latent random effect that enters multiplicatively on the hazard function for a cox model, the data are organized as i = 1, 2...n groups with j = 1,2,3...n_i subjects in group i for the jth subject in the ith group, then, the hazard is:

$$h_{ij}(t) = h_o(t)\alpha_i e^{(x_{ij}\beta)}$$

where, α_i is the group-level frailty. The frailties are the unobserved positive quantities and are assumed to have mean 1 and variance θ, to be estimated from data, for $v_i = \log \alpha_i$, the hazard can be expressed as:

$$h_{ij}(t) = h_o(t)\exp(X_{ij}\beta + v_i)$$

and thus the log frailties, v_i, are analogous to random effects in standard linear models. The cox model with shared frailty is simply a random-effects cox model. Shared frailty models are used to model within group correlation, observation within group are correlated because they shared the same frailty's and the extent of the correlation is measured by θ. For example, we could have survival data on individuals within family and we would expect (or at least willing to allow) those subjects within each family to be correlated because some families would inherently be more frail than others. When θ = 0, then the cox shared frailty model simply reduces to standard cox model for the present study shared frailty at individual level i.e., family component is considered and at community level Primary Sampling Unit (PSU) is considered (NFHS-3 considered a cluster of thirty households as primary sampling unit).

Model fitting: The model performance was assessed using Akaike's Information Criterion (AIC), log-likelihood, R-square Cox-Snell residual plots along with Harrell's C Index with Somer's D and the model-based concordance probability. To assess the ability of a prognostic model, two dimensions are usually used: discrimination and calibration. We focus here on discrimination. Discrimination is the ability of a model to separate patients with good outcome from those with poor outcome. Concordance is one measure of this ability and is widely used when assessing new prognostic models. Concordance is defined as the probability that, between two patients randomly chosen, the one who has the shorter predicted survival time will be the one with the shorter observed survival time i.e. (Mauguen *et al*., 2013):

$$\text{Concordance} = \Pr\{\beta' x_2 < \beta' x_1 | T_2 > T_1\}$$

Statistical analysis: The complete data of NFHS-3 was downloaded from Demographic Health Survey data distribution system via website: http://www.measuredhs.com the available potential determinants affecting under-five mortality were identified using Multivariable Fractional Polynomials (MFP) approach three models: the traditional Cox proportional hazard model, Cox shared frailty model at individual level and Cox shared frailty model at community level were developed. The results were reported as hazard ratio with 95% CI and β-Coefficients. For all statistical computation and model fitting the R-software (version 3.2.1, 2015, the R foundation for Statistical Computing) was used.

RESULTS

The prominent covariates associated with childhood mortality were represented in Table 1. The major findings of the study suggest that infant mortality among women married before legitimate age of marriage was thrice (neonatal = 72%, post-neonatal = 75% and child mortality = 76%) compared to females married after 17 years of age. Promotion of early initiation of breast feeding has the potential to make a major

Table 1: Percentage distribution of neonatal, post neonatal and child mortality with respect to potential covariates

Potential determinants	Neonatal (%)	Post-neonatal (%)	Child (%)
Sex of baby			
Male	789 (57.2)	164 (48.3)	545 (47.0)
Female	589 (42.8)	175 (51.7)	614 (53.0)
Mother's age at marriage			
≤18 years	382 (27.7)	85 (25.0)	284 (24.5)
>18 years	995 (72.3)	254 (75.0)	875 (75.5)
Weight at birth			
≤2.5 kg	157 (55.6)	36 (47.3)	166 (68.8)
>2.5 kg	125 (44.4)	40 (52.7)	75 (31.2)
Months of breastfed			
≤6 months	*	*	264 (25.0)
>6 months	478 (100.0)	261 (100.0)	770 (75.0)
Caste			
General	366 (27.4)	77 (23.7)	237 (21.1)
Others	970 (72.6)	248 (73.6)	891 (78.9)
Religion			
Hindu	1027 (74.0)	248 (73.1)	788 (68.1)
Others	351 (26.0)	91 (26.9)	369 (31.9)
Wealth index			
Rich/average	731 (53.0)	169 (49.8)	505 (43.6)
Poor	647 (47.0)	170 (50.2)	654 (56.4)
Desire for more child			
No	647 (47.0)	182 (53.6)	634 (54.7)
Yes	731 (53.0)	157 (46.4)	525 (45.3)
Parity			
≥2	1260 (87.7)	245 (87.5)	1023 (88.3)
<2	177 (12.3)	35 (12.5)	136 (11.7)
Birth order			
≥2	860 (62.4)	185 (54.5)	534 (46.1)
<2	518 (37.6)	154 (45.5)	625 (53.9)

*No observation

contribution in the achievement of the child survival millennium development goal. Table 1 reflects that there was no mortality in neonatal phase among women's who adopted exclusive breast feeding strategy and majority (75%) of child death (excluding neonatal phase) were observed among children who were not on exclusive breast feeding during early phase of life. The likelihood of under-five mortality was highest (<85%) among nulliparous/early parity females compared to older mothers. The mortality burden, across the life course in India, falls disproportionately on economically disadvantaged and lower-caste groups there was almost 75% mortality among socially backward groups compared to general population moreover the figures were high (70%) among Hindu's compared to non-Hindu population.

The distribution of childhood mortality across potential determinants using traditional Cox (model I), Cox shared frailty model at individual level (model 2) and Cox shared frailty model at community level (model 3) were presented in Table 2. All the 3 models suggest that the hazard of under-five mortality is less (H.R = 0.57) among females compared to that of males. Low birth weight continuous to be a risk factor contributing in childhood mortality and as we move from model-I to model 3 almost a 10% increase (1.79-1.99) in the hazard level was seen. The models suggest that non Hindu population were at lower risk (H.R~0.63) of early mortality however, a hazard rate of 1.5 was obtained for backward caste compared to general population similar findings were observed for family wealth index covariate also. The most prominent hazard contributing in under-five mortality rate was presence/absence of exclusive breast feeding all the three models suggest that infants who were not exclusive breastfed were 50 times more at risk than to infants who were on exclusively breast feeding. Desire for male child was another prime factor accelerating childhood mortality risk to almost 5 times. Similar estimates were obtained for Model-I, Model-2 and Model-3 only standard errors were corrected for shared frailty models resulting an adjustment both at individual and community level variance. At individual level frailty variance (θ) was 1.52 were as for community level θ = 1.83. Model fitting increases as we move from tradition Cox model to shared frailty models (Model-2 and Model-3) (Table 3). Log-likelihood, R^2 and the AIC (Alkaline Information Criterion) score was raised which was well supported by Cox-Snell

Table 2: Distribution of childhood mortality across potential determinants using traditional Cox (model I), Cox shared frailty model at individual level (model 2) and Cox shared frailty model at community level (model 3)

	Model I			Model 2			Model 3		
Potential determinants	β-coefficient	Hazard ratio	p-value	β-coefficient	Hazard ratio	p-value	β-coefficient	Hazard ratio	p-value
Sex of baby									
Male (ref)	-	1	-	-	1	-	-	1	-
Female	-0.56	0.57 (0.45, 0.73)	***	-0.56	0.56 (0.44, 0.72)	***	-0.56	0.57 (0.44, 0.74)	***
Mother's age									
at marriage									
≤18 years (ref)	-	1	***	-	1	-	-	1	-
>18 years	0.66	1.92 (1.55, 2.50)		0.54	1.72 (1.33, 2.24)	***	0.67	1.96 (1.47, 2.61)	***
Weight at birth									
≤2.5 kg (ref)	-	1	-	-	1	-	-	1	-
>2.5 kg	0.58	1.79 (1.39, 2.29)	**	0.58	1.78 (1.39, 2.29)	**	0.69	1.99 (1.51, 2.62)	***
Months of breastfed									
≤6 months (ref)	-	1	-	-	1	-	-	1	-
>6 months	3.86	46.32 (30.16, 71.13)	***	3.68	39.87 (25.91, 61.34)	***	4.02	55.86 (35.94, 86.81)	***
Caste									
General (ref)	-	1	-	-	1	-	-	1	-
Others	0.45	1.57 (1.22, 2.03)	***	0.46	1.50 (1.15, 1.94)	***	0.55	1.73 (1.29, 2.31)	***
Religion									
Hindu (ref)	-	1	-	-	1	-	-	1	-
Others	-0.42	0.65 (0.49, 0.86)	**	-0.49	0.61 (0.46, 0.81)	***	-0.44	0.64 (0.47, 0.89)	***
Wealth index									
Rich/average (ref)	-	1	-	-	1	-	-	1	-
Poor	0.57	1.77 (1.32, 2.38)	***	0.46	1.58 (1.17, 2.12)	***	0.62	1.86 (1.31, 2.62)	***
Desire for more child									
No (ref)	-	1	-	-	1	-	-	1	-
Yes	1.54	4.67 (3.58, 6.08)	***	1.61	5.01 (3.85, 6.54)	***	1.73	5.61 (4.17, 7.54)	***
Parity									
≥2 (ref)	-	1	-	-	1	-	-	1	-
<2	0.39	1.48 (1.07, 2.05)	0	0.10	1.01 (0.67, 1.44)	0.94	0.37	1.46 (0.99, 2.14)	0.52
Birth order									
≥2 (ref)	-	1	-	-	1	-	-	1	-
<2	0.21	1.22 (1.11, 1.35)	***	0.27	1.31 (1.19, 1.44)	***	0.25	1.28 (1.13, 1.43)	***
Variance of frailty (θ)	-	-	-	1.52		***	1.83		***

*p<0.05, **p<0.001, ***p<0.0001, -: No observation

Table 3: Model fitting

Parameters	Model-I	Model-2	Model-3
R^2	6.60%	7.40%	8.10%
Log-likelihood	-1916.34	-1892.58	-1745.76
AIC	3842.00	3815.17	3511.52
Harrell's C-Index	0.54	0.66	0.74
Somers D	0.08	0.32	0.44

residual plots (Fig. 1). A measure of concordance was by Harell's C Index and Somer's D rank correlation. Harrell's C index was estimated to be 0.66 (Model-2) and 0.74 for Model-3 indicating that by incorporating individual level or community level frailty the predictive accuracy of the survival models were enhanced. Somers' D rank correlation is closely related with Harrell's index (D = 2(C-0.5)) and can be interpreted in terms of correlation.

DISCUSSION

In most parts of the world Infant mortality is higher in boys than girls China and India are the only countries where both infant mortality and overall under-five mortality were estimated to be higher for girls than for boys (Sawyer, 2012). This has been explained by sex differences in genetic and biological makeup, with boys being biologically weaker and more susceptible to diseases and premature death the present study also reports a lower hazard rate for female population. which is in concordance with many similar studies (Drevenstedt *et al*., 2008; Jehan *et al*., 2009; DESA., 2011). Maternal factors such as mothers age at marriage, duration of breast feeding, parity, birth order and desire of male child

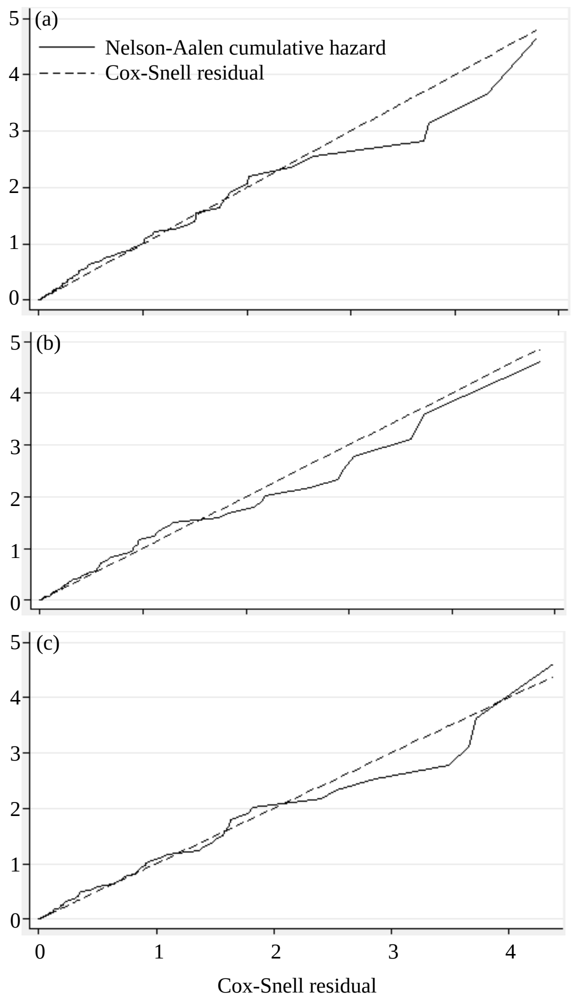

Fig. 1(a-c): Cox-Snell residual for the developed 3 models, (a) Model 1, (b) Model 2 and (c) Model 3

continuous to be the prominent risk factors for childhood mortality the present models also suggest the same however, parity is the only variable which was not found significant for Model 2 and Model 3 similar findings were reported by Sharma *et al*. (2008), Anthony *et al*. (2009) and Yadav and Yadav (2015) in independent different studies however, few studies do present difference of opinion to that of present findings. Presence of heterogeneity was observed both at individual and community level components similar frailty models have been developed for the analysis of bivariate survival data and a variance of greater than zero was reported similar to our findings (Yashin *et al*., 1995; Mani *et al*., 2012).

CONCLUSION

The present study focuses on semi-parametric Cox proportional hazard model and its extension. Traditional Cox model is widely used in literature however, for correlated/hierarchical data the estimates of Cox-PH model can be misleading. The aim of the study was to develop shared frailty models accountable for individual and community level heterogeneity. So that proper steps can be taken both at individual family and community levels in any society prior to any planning for child survival programmes.

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REFERENCES

Anthony, S., G.W. Jacobusse, K.M. Van Der Pal-de Bruin, S. Buitendijk and J. Zeitlin, 2009. Do differences in maternal age, parity and multiple births explain variations in fetal and neonatal mortality rates in Europe?-Results from the EURO-PERISTAT project. Paediatr. Perinatal Epidemiol., 23: 292-300.

DESA., 2011. Sex differentials in childhood mortality. ST/ESA/SER.A/314, United Nations Department of Economic and Social Affairs/Population Division, New York, USA., pp: 1-228.

Drevenstedt, G.L., E.M. Crimmins, S. Vasunilashorn and C.E. Finch, 2008. The rise and fall of excess male infant mortality. Proc. Natl. Acad. Sci. USA., 105: 5016-5021.

Fox, J., 2008. Cox proportional-hazards regression for survival data. https://socserv.socsci.mcmaster.ca/jfox/Books/Companion-1E/appendix-cox-regression.pdf.

Hougaard, P., 2000. Analysis of Multivariate Survival Data. Springer-Verlag, New York, USA., ISBN: 978-1-4612-7087-4, Pages: 542.

IIPS and Macro International, 2007. National Family Health Survey (NFHS-3), 2005-06: India. Vol. 1, International Institute for Population Sciences (IIPS), Mumbai, India, Pages: 540.

Jehan, I., H. Harris, S. Salat, A. Zeb and N. Mobeen *et al*., 2009. Neonatal mortality, risk factors and causes: A prospective population-based cohort study in urban Pakistan. Bull. World Health Organ., 87: 130-138.

Kleinbaum, D.G. and M. Klein, 2005. Survival Analysis: A Self-Learning Text. In: Statistics for Biology and Health, Gail, M., K. Krickeberg, J. Samet, A. Tsiatis and W. Wong (Eds.). 2nd Edn., Springer, New York, USA., ISBN-13: 9780387239187.

Mani, K., S.N. Dwivedi and R.M. Pandey, 2012. Determinants of under-five mortality in rural empowered action group states in India: An application of cox frailty model. Int. J. MCH AIDS, 1: 60-72.

Mauguen, A., S. Collette, J.P. Pignon and V. Rondeau, 2013. Concordance measures in shared frailty models: Application to clustered data in cancer prognosis. Stat. Med., 32: 4803-4820.

Mosley, W.H. and L.C. Chen, 1984. An analytical framework for the study of child survival in developing countries. Popult. Dev. Rev., 10: 25-45.

Rondeau, V. and J.R. Gonzalez, 2005. *frailtypack*: A computer program for the analysis of correlated failure time data using penalized likelihood estimation. Comput. Methods Program Biomed., 80: 154-164.

Rondeau, V., 2010. Statistical models for recurrent events and death: Application to cancer events. Math. Comput. Modell., 52: 949-955.

Rondeau, V., Y. Mazroui and J.R. Gonzalez, 2012. *frailtypack*: An R package for the analysis of correlated survival data with frailty models using penalized likelihood estimation or parametrical estimation. J. Stat. Software, 47: 1-28.

Sawyer, C.C., 2012. Child mortality estimation: Estimating sex differences in childhood mortality since the 1970s. PLoS Med., Vol. 9. 10.1371/journal.pmed.1001287

Sharma, S., 2008. Childhood mortality and health in India. Working Paper Series No. E/292/2008, Institute of Economic Growth University of Delhi Enclave North Campus, New Delhi, India, pp: 1-32. http://www.iegindia. org/workpap/wp292.pdf.

Sharma, V., J. Katz, L.C. Mullany, S.K. Khatry and S.C. LeClerq *et al*., 2008. Young maternal age and the risk of neonatal mortality in rural Nepal. Arch. Pediatr. Adolesc. Med., 162: 828-835.

UNDP., 2015. The millennium development goals report-2015. United Nations, New York, USA., pp: 1-72. http://www.undp.org/content/dam/undp/library/MDG/english/UNDP_MDG_Report_2015.pdf.

UNICEF., 2007. The State of the World's Children 2008: Child Survival. United Nations Children's Fund (UNICEF), New York, USA., ISBN-13: 9789280641912, Pages: 154.

Vaupel, J.W., K.G. Manton and E. Stallard, 1979. The impact of heterogeneity in individual frailty on the dynamics of mortality. Demography, 16: 439-454.

Wienke, A., 2010. Frailty Models in Survival Analysis. CRC Press, Boca Raton, FL., USA., ISBN-13: 9781420073881, Pages: 312.

Yadav, A.K. and R.J. Yadav, 2015. A study on determinants of fertility and its association with child mortality in India. Asian J. Applied Sci., 3: 799-805.

Yashin, A.I., J.W. Vaupel and I.A. Iachine, 1995. Correlated individual frailty: an advantageous approach to survival analysis of bivariate data. Math. Popul. Stud., 5: 145-159.