JBE Journal of Biostatistics and Epidemiology
J Biostat Epidemiol. 2025;11(3): 282-289

ORIGINAL ARTICLE
DOI: *https://doi.org/10.18502/jbe.v11i3.21369/*
*Received **April** 14, 2025; Accepted **May** 14, 2025;*
*Published online **September** 15, 2025.*

Survival Analysis of Childbirth Using a Mixture Cure Frailty Model

Azadeh **Naderi**[1], Abbas **Rahimi Foroushani**[1], Ali **Moghadas Jafari**[2], Mohammed **I M Gubari**[3], Mehdi **Yaseri**[1]*, Mostafa **Hosseini**[1]*

[1]Department of Biostatistics and Epidemiology, Tehran University of Medical Sciences, Tehran, Iran.
[2]Farhikhtegan Hospital, Azad University of Medical Sciences, Tehran, Iran.
[3]Community Medicine, College of Medicine, University of Sulaimani, Sulaimani, Iraq.

ABSTRACT

Introduction: Childbirth plays a crucial role in population growth and maternal health. In recent decades, many nations, including Iran, have experienced declining birth rates. Since childbirth is a recurrent event in a parent's life, it is useful to analyze it through the lens of recurrent event analysis. This methodological framework, commonly employed in biomedicine, allows for a nuanced examination of the relationship between multiple childbirth experiences and the potential for cured subjects. This study explores childbirth rates in Hamadan province.

Methods: A total of 633 mothers who gave birth to their first child in 2012 at Fatemiyeh Hospital in Hamadan participated in this retrospective cohort study. Both mixture cure frailty models and simple frailty models were fitted. The analyses were conducted using the RSTAN package in RStudio version 26.2.4.

Results: In this study, we analyzed the childbearing patterns of couples and found that the majority (60.6%) had two children. Additionally, we discovered that 49% of mothers and 55.9% of fathers had education levels below a diploma. The Kaplan-Meier (KM) curves indicated a cure pattern for families with three or more children, revealing that only 10.6% of individuals had three children, and a mere 0.8% had four. Furthermore, results from a mixture cure frailty model demonstrated that maternal education plays a crucial role in influencing childbirth probabilities.

Conclusion: Based on the findings of this study, we recommend utilizing mixture cure frailty models rather than simple frailty models when the dataset contains individuals who are cured.

Key words: Birth; Mixture cure; Frailty model

*Corresponding Authors:
m.yaseri@gmail.com
Mhossein110@yahoo.com

INTRODUCTION

The number of childbirths is closely linked to both population growth and maternal health. The delay in having children has led to extremely low birth rates in certain nations. A comparable pattern of deferred parenthood, along with extended gaps between births, has been observed in Iran, where the overall fertility rate has persistently stayed beneath replacement levels for the last decades.[1] The decreasing number of children and parents' preference for smaller families have contributed to the decline in the fertility rate in Iran.[2] The proportion of families having more than three children is relatively low in Iran.[3] Several factors have influenced the childbirth rate, including the age at marriage, women's education levels, menstrual health, contraceptive usage, ideal family size, and socioeconomic status.[4-6]

Childbirth is an event that parents can experience multiple times, making it a recurrent event. The lack of childbearing (resulting from the death or divorce of parents and etc) is considered right-censoring. Therefore, we can apply methods from recurrent events data analysis. Recurrent event data analysis is quite prevalent in bio-medicine, with many statistical models specifically designed for this type of data.[7] The recurrent events data consists of same failure times that exhibit characteristics such as within-subject correlation, frailty, and the potential for cure. Due to the advancement of treatments, it is possible that some people may be cured or insusceptible for main event.[8, 9] In the context of cure modeling, it is crucial to first evaluate the presence of a cure. A long right tail plateau in the KM curve suggests the existence of a cure pattern within the data.[10] Once this has been established, appropriate models can then be applied to analyze the data effectively.[11] In these situations, it is advisable to utilize a mixture cure frailty model in order to determine the probability of event recurrence (or, alternatively, the probability of being cured). This model then assesses the rate of event recurrence among those who remain uncured by applying a simple frailty model.[12, 13]

The present study aimed to investigate the survival analysis of probability of cure and birth rate to different numbers of children.

METHODS

This retrospective cohort study included all mothers who delivered their first child at Fatemiyeh Hospital in Hamadan, Iran, in 2012. The data was updated in 2022 through phone interviews. Mothers who reported that their first child had died during childbirth or shortly before or after were excluded from the study. Additionally, some individuals declined to participate, while others provided incorrect phone numbers, leading to their exclusion as well. Ultimately, 633 mothers were included in the analysis, with a study period spanning ten years. The birth of second or subsequent children were considered as the recurrence of event. three gap times for births were examined. which indicate the times between the births of successive children. The study provides data on parents' level of education (upper diploma/diploma/under diploma). Descriptive statistics were summarized.

In our study, we observed a cure pattern for each recurrence in the KM curves. For the survival

analysis, we utilized a mixture cure model comprised of two parts.

$$S(t_{ij}) = 1-\pi_j(z) + \pi_j(z)\, S_u(t_{ij};z)$$

The first part (incidence) estimated the probabilities of each recurrence (or cure) of events using inverse logistic regression model.

$$n_j(z) = \frac{exp(\psi_{ij})}{1+exp(\psi_{ij})} \qquad \psi_{ij} = \omega_i^T \alpha + \tau_i \qquad \omega_i = (1 \quad z^T)^T$$

To capture all recurrent events of an individual, a frailty term (τ) has been incorporated into this model to address the dependency between events. It's important to note that this part of the mixture cure model estimates the probability of cure not as an overall proportion, but rather after each recurrence and for all individuals under study.

The recurrence rate of events can be modeled using both semi-parametric and parametric hazard functions.[14, 15] In the second part (latency) of the model, we assessed the event rate by employing a Weibull hazard function (shape parameter: μ) derived from a simple frailty model. To account for the heterogeneity of individuals in the hazard of events, frailty has also been incorporated into this part of the model. $h(t_{ij}) = h_0(t_{ij})\ exp(\beta X_{ij} + u_i)$

In order to evaluate the necessity of incorporating the cure fraction into our analysis, we compared this model to a simple frailty model that analyzes recurrent events without accounting for cure subjects. The models were assessed based on the variance of frailties, with smaller values indicating a preferable fit. The calculations were performed using the Variational Bayes (VB) technique with the RSTAN package in RStudio version 26.2.4.

RESULTS

The number of children ranged from one to four, with the majority of couples (60.6%) having two children. Only 177 mothers remained with one child, while the rest gave birth to a greater number of children. Additionally, 310 mothers (49%) had under diploma level of education. It was found that 354 fathers (55.9%) also had under diploma education (see the frequency distribution based on childbirth data in table 1).

In figure 1, in the first gap times of KM curves, the survival probability is almost the same for all education categories. In the second and third gap time, the right tail of the curves is plateau, which indicates cure pattern in third and fourth children. Table 1 further supports this claim, as only 10.6% of individuals have three children, and merely 0.8% have had a fourth child.

Based on the results from the latency component of the mixture cure frailty model, mothers with a diploma or lower take a considerable amount of time to have another child. Furthermore, the incidence

Table 1. Frequency distribution based on the childbirth data

Variables	Number(percent)
birth	
1	177 (%28)
2	384 (%60.6)
3	67 (%10.6)
4	5 (%0.8)
Mothers' education	
Under diploma	310 (49%)
Diploma	216 (34.1%)
Upper diploma	107 (16.9%)
Fathers' education	
Under diploma	354 (55.9%)
Diploma	175 (27.7%)
Upper diploma	104 (16.4%)

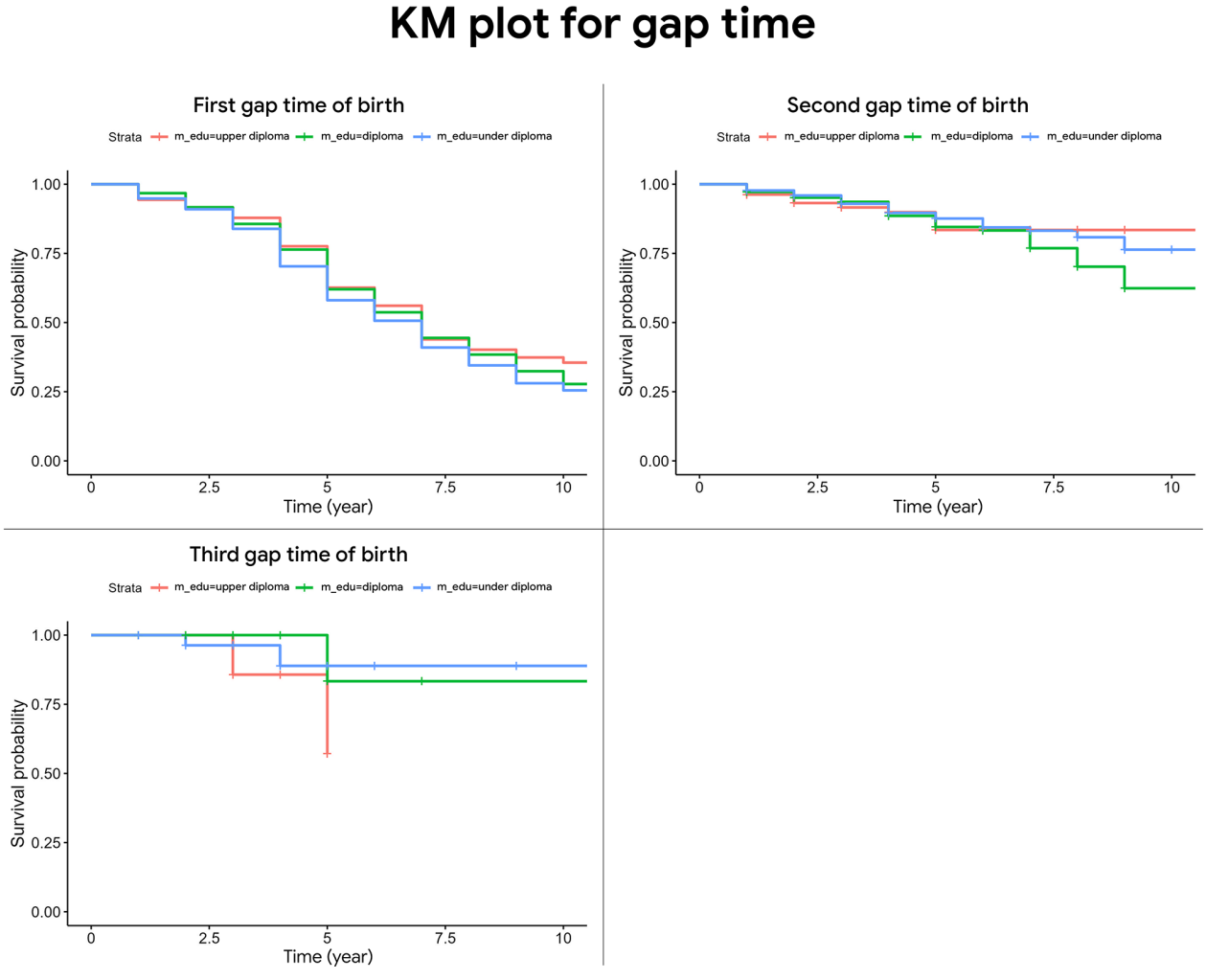

Figure 1. The KM curves for each recurrence of birth, based on mothers' education

component reveals that a higher level of maternal education significantly decreases the probability of recurrence compared to mothers with under diploma level of education. This suggests that an increase in maternal educational attainment has a meaningful effect on the probability of being cured. In the simple frailty model, the influence of parents' education levels on child birth rates contrast with the effects seen in the mixture cure frailty model. The assessment of frailties and their corresponding standard errors suggests that incorporating a cure fraction improves the model's performance. The value of the shape parameter of the Weibull distribution ($\mu>1$), indicates that the variation of rate of occurrence of births has increased over time. (see the estimates of mixture cure frailty model and frailty model based on the childbirth data in table 2).

Table 2. Estimates of mixture cure frailty model and frailty model based on the childbirth data

Part of model	Parameters	Categories	Mixture cure frailty model			Frailty model		
			Estimate	SE	P-Value	Estimate	SE	P-Value
Incidence	Mother's education (Ref= Upper Diploma)	Diploma	-4.069	1.291	0.001			
		Under Diploma	-0.908	0.199	<0.001			
	Father's education (Ref= Upper Diploma)	Diploma	0.256	0.292	0.810			
		Under Diploma	-0.351	0.172	0.021			
	frailty		0.499	0.038				
Latency	Mother's education (Ref= Upper Diploma)	Diploma	-0.396	0.035	<0.001	0.063	0.039	0.945
		Under Diploma	-0.217	0.019	<0.001	0.028	0.029	0.831
	Father's education (Ref= Upper Diploma)	Diploma	0.045	0.056	0.787	-0.019	0.049	0.348
		Under Diploma	-0.030	0.041	0.234	0.023	0.025	0.516
	frailty		0.221	0.004		0.239	0.007	
	μ		1.933	0.054		1.805	0.047	

Significant at 0.05
Ref=Reference group

DISCUSSION

One research study focused on analyzing trends and patterns in fertility rates and found a significant decline, with the number of births per woman decreasing to an average of two children.[16] This result is consistent with the findings of our study. The findings from Najafi et al. indicate a downward trend in population growth in Iran, especially in Hamedan, attributed to longer intervals between births. Our research corroborates this trend, with the majority of families surveyed having two children at most. Moreover, their study found that the likelihood of conceiving after having a third child has diminished, aligning with our own findings.[3] In the present study, we found that maternal education significantly impacts birth rates. Previous research has indicated that factors such as the mother's education level, age, and father's occupation also influence birth rates.[5, 17, 18]

In a study analyzing recurrent event data, a cure frailty model was employed in two ways. The first model defined cured individuals as those who had not experienced the event of interest over an extended period, while the second model assessed the probability of cure after each recurrence of the event. Additionally, the frailty model was utilized to estimate the latency component. A comparison of the fit between the two models indicated that incorporating the cure improved the analysis of recurrent events.[19] Our research aligns with the second approach, focusing on the assessment of cure following each recurrence. At the end, it is suggested for further studies to take into consideration more covariates of parents and using mixture cure joint frailty models to incorporating more aspects of recurrent event analysis.

CONCLUSION

Since the occurrence of the birth event and the time it happens are of interest, survival models were selected for analysis. Based on the findings of this study, we recommend using mixture cure frailty models when there are individuals in the data who are cured.

Conflict of Interests

It clearly communicates that the authors have stated there are no conflicts of interest related to the writing, authorship order, or publication of the article.

Ethical consideration

This study has been approved by the TUMS research ethics committee, Tehran university of medical sciences (Ethics ID: IR.TUMS.SPH.REC.1397.212).

Abbreviations

KM, Kaplan-Meier;
VB, Variational Bayes;

REFERENCES

1. Erfani A, Nojomi M, Hosseini H. PROLONGED BIRTH INTERVALS IN HAMEDAN, IRAN: VARIATIONS AND DETERMINANTS. Journal of Biosocial Science. 2017;50:1-15.

2. Jafari H, Pourreza A, Kabiri N, Khodyari-Zarnaq R. Main actors in the new population policy with a growing trend in Iran: a stakeholder analysis. Journal of health, population, and nutrition. 2022;41(1):57.

3. Najafi-Vosough R, Soltanian AR, Fayyazi N. Influence Factors on Birth Spacing and Childbearing Rates using Survival Recurrent Events Model and Parity Progression Ratios: J Res Health Sci. 2017 Jul 7;17(3):384. eCollection 2017 Summer.

4. Shayan Z, Ayatollahi SM, Zare N, Moradi F. Prognostic factors of first birth interval using the parametric survival models. Iranian journal of reproductive medicine. 2014;12(2):125-30.

5. Fallahzadeh H, Farajpour Z, Emam Z. Duration and determinants of birth interval in Yazd, Iran: a population study. Iranian journal of reproductive medicine. 2013;11(5):379-84.

6. Ekawati R, Rahayuwati L, Nurhidayah I, S Agustina H, Rahayu E. DETERMINANT FACTORS OF FERTILITY IN REPRODUCTIVE AGE WOMEN IN WEST JAVA PROVINCE INDONESIA. Jurnal Keperawatan Padjadjaran. 2019;7.

7. Sagara I, Giorgi R, Doumbo O, Piarroux R, Gaudart J. Modelling recurrent events: Comparison of statistical models with continuous and discontinuous risk intervals on recurrent malaria episodes data. Malaria journal. 2014;13:293.

8. Conlon AS, Taylor JM, Sargent DJ. Multi-state models for colon cancer recurrence and death with a cured fraction. Statistics in medicine. 2014;33(10):1750-66.

9. Ahmad Reza B, zahra Arab B, Elaheh Talebi G, Ali Akbar Khadem m, Anahita S, Ali A. Joint frailty model of recurrent and terminal events in the presence of cure fraction using a Bayesian approach. Journal of Biostatistics and Epidemiology. 2023;8(3).

10. Tsodikov A.D, Ibrahim J.G, Yakovlev A.Y. Estimating Cure Rates from Survival Data: An Alternative to Two-Component Mixture Models. Journal of the American Statistical Association. 2003;98(464):1063-78.

11. Sevda R, Mahboobe R, Jamileh A, Moein Y, Azita A, Asieh A. Contribution Factors on Long- term and Short- term Survival of Thalassemia Major Patients. Journal of Biostatistics and Epidemiology. 2021;7(4).

12. Amanpour F, Akbari S, Azizmohammad Looha M, Abdehagh M, Pourhoseingholi MA. Mixture cure model for estimating short-term and long-term colorectal cancer survival. Gastroenterology and hepatology from bed to bench. 2019;12(Suppl1):S37-s43.

13. Kim Y-J. Joint model for recurrent event data with a cured fraction and a terminal event. Biometrical Journal. 2020;62(1):24-33.

14. Xu Y, Cheung Y. Frailty Models and Frailty-Mixture Models for Recurrent Event Times. Stata Journal. 2015;15:135-54.

15. Tawiah R, McLachlan GJ, Ng SK. A bivariate joint frailty model with mixture framework for survival analysis of recurrent events with dependent censoring and cure fraction. Biometrics. 2020;76(3):753-66.

16. Hosseini-Chavoshi M, Abbasi-Shavazi M, McDonald P. Fertility, Marriage, and Family Planning in Iran: Implications for Future Policy. Population Horizons. 2017;13.

17. Kashem SR, Arokiasamy JT, Khanam ST, Anthonisamy AN, Bhatt P, Islam M. Sociodemographic factors associated with birth interval: a study among rural women in Chandina, Comilla, Bangladesh. Journal of Public Health. 2020;28:11-5.

18. Zare N, Soltani M, Sayadi M, Rajaeefard A. Factors affecting inter-birth in rural areas of Zarrindasht (Fars province). Iranian South Medical Journal. 2015;17(6):1143-52.

19. Rondeau V, Schaffner E, Corbière F, Gonzalez JR, Mathoulin-Pélissier S. Cure frailty models for survival data: Application to recurrences for breast cancer and to hospital readmissions for colorectal cancer. Statistical methods in medical research. 2013;22(3):243-60.