www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2020;9(1):e090101
doi: 10.7363/090101
Received: 2018 Dec 16; revised: 2019 May 10; accepted: 2019 Jun 06; published online: 2019 Dec 17

Original article

Predictive model for the cure rate of NICU admitted preterm neonates: the mixture cure model

Mohammad Aghaali[1,2], Parvaneh Sadeghi-Moghaddam[3], Soheila Khodakarim[4]

[1]Department of Epidemiology, School of Public Health, Qom University of Medical Sciences, Qom, Iran
[2]Department of Epidemiology, School of Public Health and Safety, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Department of Neonatal-Perinatal Medicine, School of Medicine, Qom University of Medical Sciences, Qom, Iran
[4]Department of Epidemiology, School of Allied Medical Sciences, School of Public Health and Safety, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Abstract

Background: Predicting the survival of preterm neonates admitted to Neonatal Intensive Care Unit (NICU) care is important for counseling parents, informing care, and planning services. This study was conducted to establish a predictive model for evaluating the survival of NICU admitted preterm neonates by the cure model.

Materials and methods: 1,200 preterm neonates admitted to the NICU of a tertiary referral hospital in Qom, Iran, were enrolled to build a model and to train relevant parameters for prediction. The time to discharge from hospital and potential predictive factors were collected for analysis. A mixture cure model with the Stata version 14.2 was applied to predict the cure rate. Established factors and significant variables in the simple models were included in the multiple model.

Results: The cure rate of all patients by birth weight were: > 2,500 g, 87.31%; 1,500-2,500 g, 84.68%; 1,000-1,499 g, 75.31%; and < 1,000 g, 46.39%. The significant predictors in the final model include congenital abnormality, resuscitation, Apgar score, invasive procedure, pneumothorax, ventilation and birth weight. The result of the area under the curves for the final model on the validation data was 0.89 (95% CI, 0.823-0.951). It showed that predictive validity was satisfactory.

Conclusion: By using the cure model survival analysis, we identified significant predictors of the cure rate of NICU admitted preterm neonates. The model showed a satisfactory predictive validity, which prompted one to make an individual prediction.

Keywords

Survival analysis, infant, premature, intensive care units, neonatal, mixture cure model, Apgar score, pneumothorax.

Corresponding author

Dr Soheila Khodakarim, Shahid Beheshti University of Medical Sciences, Arabi Ave, Daneshjoo Blvd, Velenjak, Tehran, Iran; phone number: +98-21-22432040; email: lkhodakarim@gmail.com.

How to cite

Aghaali M, Sadeghi-Moghaddam P, Khodakarim S. Predictive model for the cure rate of NICU admitted preterm neonates: the mixture cure model. J Pediatr Neonat Individual Med. 2020;9(1):e090101. doi: 10.7363/090101.

Introduction

Preterm birth is defined as birth before 37 weeks of pregnancy. The global neonatal mortality rate has declined in the past decade [1]. However, the absolute number and rates of preterm birth have increased [2], and now preterm birth and its complications are the second leading cause of death in children under five years old and lead about 35% of neonatal deaths worldwide [3]. In Iran, like other developing countries, with improvement in intensive care, the mortality of preterm neonates is declining. However, preterm birth is still one of the main causes of neonatal mortality [4, 5].

Predicting the survival of preterm neonates admitted to the Neonatal Intensive Care Unit (NICU) is important for counseling parents, informing care, and planning services. There are many situations when a physician, researcher or parent may wish to predict the outcome of a neonate. This may be to try to explain the wide variations in mortality between different NICUs. In addition, it may be the estimated probability of mortality or cure in a particular infant that is of interest, the need to identify high-risk infants suitable for inclusion in a clinical trial, or comparing study groups for similarity of risk or determining trends in results over time [6].

One of the approaches to determining the factors affecting the survival of neonates is the use of regressions, such as logistics regression. This approach has the disadvantage of discarding any information that could be drawn from censored neonates (neonates who drop out of observation during the follow-up interval, or neonates who have not yet completed the entire follow-up interval of interest). It has noted that discarding the information from censored neonates results in loss of statistical precision [7]. Another approach is to use survival models. There are a large number of prediction models that have been proposed to estimate survival for preterm or low birth weight deliveries [6, 8]. Nevertheless, all of them used Cox proportional hazards models or another parametric survival model. For the neonatal survival, the relative survival curve often appears to plateau after a number of days. This plateau effect occurs when the mortality rate of preterm or low birth weight deliveries is the same as the mortality rate in the normal neonates. At the point from which the preterm neonates no longer experience excess mortality, we refer to the group as being “cured” (or “statistically cured”). It is important to note that this definition of cure is from a population perspective and it does not provide information on individuals [9]. For data with survival trends appears to plateau after a number of days, cure models can be a useful alternative to the standard Cox proportional hazards models, because the assumption of proportional hazards can fail when survival curves have plateaus at their tails and survival plots with long plateaus may indicate heterogeneity within a population that can be useful to describe explicitly. In these cases, cure models allow us to investigate what covariates are associated with either short-term or long-term effects [10].

Cure models are a popular topic within statistical literature but are not as widely known in the clinical literature [10]. This study was conducted to establish a predictive model for evaluating the survival of NICU admitted preterm neonates by cure model survival analysis.

Methods

This study analyzed prospectively collected data from the NICU of a tertiary referral hospital in Qom, Iran. Institute Ethics Committees of Qom University of Medical Sciences approved the study protocol.

All preterm neonates admitted to the NICU of Izadi hospital in Qom were enrolled in this study. This hospital had a high standard of obstetric care and neonatal resuscitation facilities, ensuring about 8,500 deliveries per year.

Data was collected prospectively using standard definitions. Preterm birth was defined as a birth before 37 weeks of pregnancy (calculated from the first day of the last menstrual period) [11]. Mortality was defined as deaths occurring before discharge from the participating hospital.

A liveborn neonate was eligible for inclusion in the study if it was born between March 21, 2013 (the beginning of the Iranian New Year) and March 20, 2017. Enrolled neonates were followed until the final disposition from the hospital.

The time to discharge from hospital and potential predictive factors were collected for analysis. Predictive value included congenital abnormality, gender, C-reactive protein (CRP), white blood cell (WBC) count, multiple gestation, patent ductus arteriosus (PDA), respiratory distress syndrome (RDS), type of delivery, pneumothorax, resuscitation, Apgar score, invasive procedure, ventilation, birth weight and gestational age.

The laboratory tests were completed at the time of admission and the need for resuscitation was considered positive if neonate resuscitated at birth. For ventilation, more than 24 hours were considered positive. The invasive procedure included intubation, umbilical catheter insertion, chest tube insertion, lumbar puncture and placement of a central catheter.

A Weibull mixture cure model with a logit link was applied to predict the cure rate. Stata version 14.2 was used for data analysis [12].

Cross-validation was performed to evaluate the accuracy of the model. The data were randomly assigned to a training set and a validating set. Established factors and significant variables in the simple models were included in the multiple model to select the final model. Statistical significance was defined at a p-value of less than 0.05.

Predicted improvement probabilities and observed results for each individual were used to plot the receiver operating characteristic (ROC) curves. The area under the ROC curves was calculated to evaluate the prediction validity.

Result

A total of 1,200 neonates were included in the study. Among enrolled neonates, 141 (11.75%) neonates died before discharge from the hospital. Baseline characteristics of the study population are detailed in **Tab. 1**. Survivor functions adjusted for congenital abnormality, Apgar score and pneumothorax based on birth weight are shown in **Fig. 1**.

The cure fraction of all patients by birth weight were: > 2,500 g, 87.31%; 1,500-2,500 g, 84.68%; 1,000-1,499 g, 75.31%; and < 1,000 g, 46.39% (**Tab. 2**).

Fig. 2 shows the predicted relative survival functions for the whole and for the uncured group. The relative survival curve for the whole group shows the asymptote at the cure fraction.

The significant predictors in the final model include congenital abnormality, resuscitation, Apgar score, invasive procedure, pneumothorax,

Table 1. Baseline characteristics of the study population used for cure fraction estimation.

Variable		All patients (n = 1,200)
Birth weight (g)	> 2,500	402 (33.5%)
	1,500-2,500	469 (39.08%)
	1,000-1,500	221 (18.42%)
	< 1,000	108 (9%)
Multiple gestation		225 (18.75%)
Male sex		660 (55%)
Gestational age	Extremely preterm	147 (12.25%)
	Very preterm	303 (25.25%)
	Moderate to late preterm	750 (62.5%)
Death		141 (11.75%)
Ventilation		359 (29.92%)
Pneumothorax		116 (9.67%)
Invasive procedure		704 (58.67%)
Resuscitation		217 (18.08%)
Cesarean section		868 (72.33%)
Congenital abnormality		171 (14.25%)
Respiratory distress syndrome		683 (56.92%)
Patent ductus arteriosus		204 (17%)

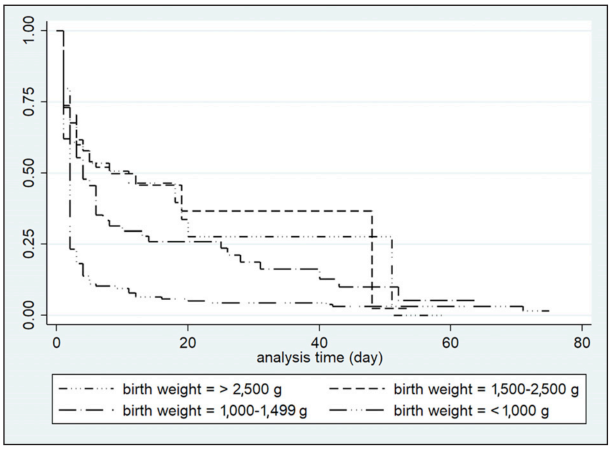

Figure 1. Survivor functions adjusted for congenital abnormality, Apgar score and pneumothorax based on birth weight.

Table 2. Cure rate of NICU admitted preterm neonates based on birth weight.

Birth weight	Derivation data (866)		Validation data (334)		Total (1,200)	
	Cure fraction	95% CI	Cure fraction	95% CI	Cure fraction	95% CI
> 2,500	91.67	85.18-98.16	69.49	40.88-98.1	87.31	76.96-97.66
1,500-2,500	84.91	62.06-100	81.35	52.91-100	84.68	57.90-100
1,000-1,500	70.54	45.39-95.69	85.62	74.62-96.63	75.31	60.04-90.57
< 1,000	43.47	31.66-55.27	54.41	35.62-72.65	46.39	36.38-56.4
Total	77.86	70.36-85.35	84.56	78.42-90.7	79.9	74.63-85.22

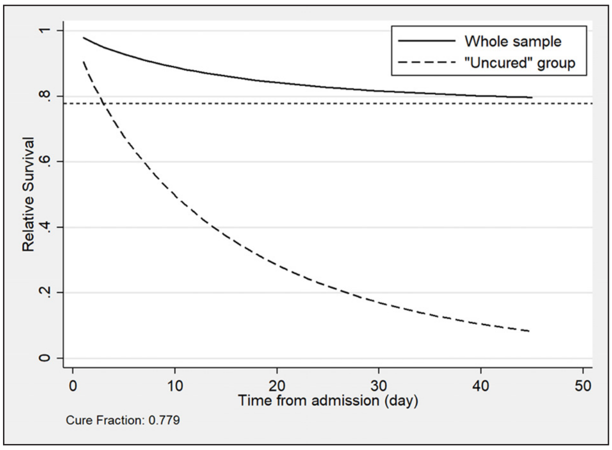

Figure 2. The predicted relative survival functions for the whole and for the uncured group. The relative survival curve for the whole group shows the asymptote at the cure fraction.

ventilation and birth weight. **Tab. 3** shows the odds ratios (OR) and confidence intervals for the cured group (long-term survivors). The OR for neonates with congenital abnormality was 0.3, meaning that a smaller proportion of neonates are cured in neonates with congenital abnormality than neonates without it. In addition, a larger proportion of neonates with higher Apgar score and higher birth weight are cured.

The result of the area under the curves for the final model on the validation data was 0.89 (95% CI, 0.823-0.951). It showed that predictive validity was satisfactory (**Fig. 3**).

Discussion

This study was conducted to establish a predictive model for evaluating the survival of NICU admitted preterm neonates by cure model survival analysis. For preterm neonates or low birth weight neonates in which some patients may be long-term survivors, cure models can be an interesting way to characterize and study survival.

Some studies have been carried to determine which variables are associated with preterm or low birth weight neonates' survival [8, 13-15]. These studies have used traditional survival models (like the Cox proportional hazard model) for the analysis of their data. The Cox model is an appropriate and popular analysis for survival. However, when some patients may be long-term survivors, the use of mixture cure models are better than usual analyses such as the Cox model, because it captures residual heterogeneity that cannot be explained by traditional survival analyses [10]. The mixture cure model divides people into two groups: long-term (cured group) and short-term (uncured) survivors.

The predictive model under the context of a cure model survival analysis provided a good prediction of the probability of long-term survival. This model allows estimating the predicted long-term survival (cure); this ability is very helpful in clinical consultation for predicting the long-term survival of preterm neonates. There was no other study in the literature review, which has used the mixture cure model in preterm neonatal survival for further discussion.

The results of this study showed that congenital abnormality, resuscitation, Apgar score, invasive procedure, pneumothorax, ventilation and birth weight had a significant association with odds of cure. Nevertheless, there is no evidence that the cure rate is different based on gender, CRP, WBC, multiple gestation, PDA, RDS, type of delivery.

In line with previous studies, this study showed that congenital abnormality, Apgar score and birth weight are predictors of neonatal survival [2, 16].

This study and some other studies showed that cesarean delivery does not improve the outcomes of preterm neonates as compared with normal vaginal delivery [17-19]. Nevertheless, Zou et al. have shown that neonates delivered by cesarean had significantly lower mortality [20]. Zou

Table 3. Predictive model for survival of NICU admitted preterm neonates.

Full model containing all predictors				
Variable	**Odds ratio**	**P > lzl**	**[95% Conf. Interval]**	
Congenital abnormality (yes)	0.33	0.020	0.13	0.84
Gender (male)	1.62	0.183	0.80	3.29
CRP	0.53	0.246	0.18	1.56
WBC	1.00	0.327	1.00	1.00
Twin (yes)	1.24	0.650	0.49	3.17
PDA (yes)	0.91	0.820	0.42	2.01
RDS (yes)	1.06	0.905	0.41	2.78
Type of delivery (cesarean section)	1.30	0.513	0.60	2.81
Pneumothorax (yes)	0.12	0.000	0.04	0.33
Resuscitation (yes)	0.09	0.000	0.04	0.20
Apgar score	1.49	0.000	1.21	1.84
Invasive procedure (yes)	0.18	0.000	0.07	0.45
Ventilation (yes)	0.31	0.003	0.14	0.68
Birth weight (for 100 g)	1.12	0.005	1.03	1.20
Gestational age (week)	0.75	0.237	0.47	1.21
Final model with remaining variables having a p-value of less than 0.05				
Variable	**Odds ratio**	**P > lzl**	**[95% Conf. Interval]**	
Congenital abnormality (yes)	0.30	0.005	0.13	0.70
Resuscitation (yes)	0.09	0.000	0.05	0.19
Apgar score	1.42	0.000	1.18	1.71
Invasive procedure (yes)	0.16	0.000	0.07	0.37
Pneumothorax (yes)	0.14	0.000	0.05	0.36
Ventilation (yes)	0.30	0.001	0.15	0.61
Birth weight (for 100 g)	1.08	0.001	1.03	1.12

CRP: C-reactive protein; WBC: white blood cell; PDA: patent ductus arteriosus; RDS: respiratory distress syndrome.

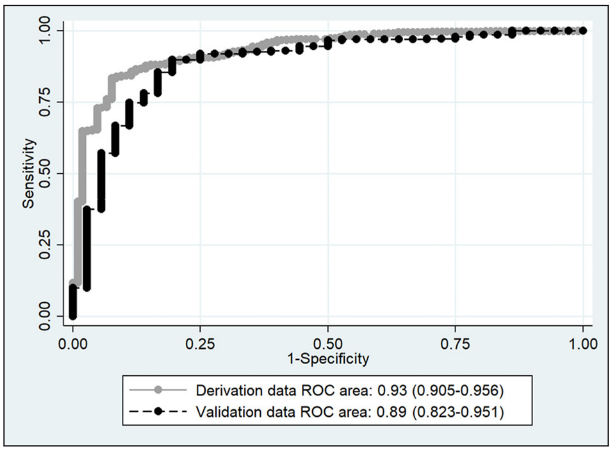

Figure 3. The result of the area under the curves for the final model on the validation data was 0.89 (95% CI, 0.823-0.951). It showed that predictive validity was satisfactory.

believes that it is possible that parents who have requests for cesarean section take an active role in their care, which could lead to their neonates receiving better care.

The use of models for predicting individual outcomes is controversial, because of variation in the approach to clinical care adopted by different units as well as important ethical and legal concerns [6]. In addition, no mathematical formula can completely capture the complex clinical processes in a neonate. However, predicting individual outcomes was used commonly (for example, a birth weight of under 500 g is often used as a reason for not starting intensive care) and predicting an individual's prognosis, regardless of the influence of the care received, was needed for counseling or for stratifying infants into a study.

Stevens et al. showed that clinicians are good at identifying high-risk infants but tend to overestimate the risk of death. It is possible that combining clinicians' assessments with models could improve the accuracy of risk assessment, although using clinicians' views for research purposes would introduce an unacceptable level of subjectivity and potential bias [21].

Conclusion

By using the cure model survival analysis, we identified significant predictors of the cure rate of NICU admitted preterm neonates. The model showed a satisfactory predictive validity, which prompted one to make an individual prediction.

Further studies, recommended for testing new factors, are to confirm that our current model is optimal.

Declaration of interest

The Authors declare that there is no conflict of interest.

References

1. Liu L, Johnson HL, Cousens S, Perin J, Scott S, Lawn JE, Rudan I, Campbell H, Cibulskis R, Li M, Mathers C, Black RE. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet. 2012;379(9832):2151-61.
2. Shah R, Mullany LC, Darmstadt GL, Talukder RR, Rahman SM, Mannan I, Arifeen SE, Baqui AH. Neonatal mortality risks among preterm births in a rural Bangladeshi cohort. Paediatr Perinat Epidemiol. 2014;28(6):510-20.
3. Howson CP, Kinney MV, McDougall L, Lawn JE. Born too soon: preterm birth matters. Reprod Health. 2013;10(Suppl 1):S1.
4. Murki S, Kumar N, Chawla D, Bansal A, Mehta A, Shah M, Bhat S, Rao S, Bajaj N, Chowdhary G, Singal A, Kadam S, Jain N, Baswaraj T, Thakre R. Variability in survival of very low birth weight neonates in hospitals of India. Indian J Pediatr. 2015;82(6):565-7.
5. Sadeghi-Moghaddam P, Arjmandnia M, Shokrollahi M, Aghaali M. Does training improve compliance with hand hygiene and decrease infections in the neonatal intensive care unit? A prospective study. J Neonatal Perinatal Med. 2015;8(3):221-5.
6. Dorling JS, Field DJ, Manktelow B. Neonatal disease severity scoring systems. Arch Dis Child Fetal Neonatal Ed. 2005;90(1):F11-6.
7. Brenner H, Gefeller O. Deriving more up-to-date estimates of long-term patient survival. J Clin Epidemiol. 1997;50(2):211-6.
8. Manktelow BN, Seaton SE, Field DJ, Draper ES. Population-based estimates of in-unit survival for very preterm infants. Pediatrics. 2013;131(2):e425-32.
9. Lambert PC, Thompson JR, Weston CL, Dickman PW. Estimating and modeling the cure fraction in population-based cancer survival analysis. Biostatistics. 2007;8(3):576-94.
10. Othus M, Barlogie B, Leblanc ML, Crowley JJ. Cure models as a useful statistical tool for analyzing survival. Clin Cancer Res. 2012;18(14):3731-6.
11. [No authors listed]. The prevention of perinatal mortality and morbidity. Report of a WHO Expert Committee. World Health Organ Tech Rep Ser. 1970;457:1-60.
12. Lambert PC. Modeling of the cure fraction in survival studies. Stata J. 2007;7(3):351-75.
13. Simic M, Amer-Wahlin I, Lagercrantz H, Marsal K, Kallen K. Survival and neonatal morbidity among extremely preterm born infants in relation to gestational age based on the last menstrual period or ultrasonographic examination. J Perinat Med. 2014;42(2):247-53.
14. Wennerstrom EC, Simonsen J, Melbye M. Long-Term Survival of Individuals Born Small and Large for Gestational Age. PLoS One. 2015;10(9):e0138594.
15. Mengesha HG, Wuneh AD, Lerebo WT, Tekle TH. Survival of neonates and predictors of their mortality in Tigray region, Northern Ethiopia: prospective cohort study. BMC Pregnancy Childbirth. 2016;16(1):202.
16. Chen A, Feresu SA, Barsoom MJ. Heterogeneity of preterm birth subtypes in relation to neonatal death. Obstet Gynecol. 2009;114(3):516-22.
17. Reddy UM, Zhang J, Sun L, Chen Z, Raju TN, Laughon SK. Neonatal mortality by attempted route of delivery in early preterm birth. Am J Obstet Gynecol. 2012;207(2):117.e1-8.
18. Werner EF, Savitz DA, Janevic TM, Ehsanipoor RM, Thung SF, Funai EF, Lipkind HS. Mode of delivery and neonatal outcomes in preterm, small-for-gestational-age newborns. Obstet Gynecol. 2012;120(3):560-4.
19. Malloy MH. Impact of cesarean section on intermediate and late preterm births: United States, 2000-2003. Birth. 2009;36(1):26-33.
20. Zou L, Wang X, Ruan Y, Li G, Chen Y, Zhang W. Preterm birth and neonatal mortality in China in 2011. Int J Gynaecol Obstet. 2014;127(3):243-7.
21. Stevens SM, Richardson DK, Gray JE, Goldmann DA, McCormick MC. Estimating neonatal mortality risk: an analysis of clinicians' judgments. Pediatrics. 1994;93(6 Pt 1):945-50.