Evaluation of goodness of fit of semiparametric and parametric models in analysis of factors associated with length of stay in neonatal intensive care unit

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Background: Length of stay is a significant indicator of care effectiveness and hospital performance. Owing to the limited number of healthcare centers and facilities, it is important to optimize length of stay and associated factors.

Purpose: The present study aimed to investigate factors associated with neonatal length of stay in the neonatal intensive care unit (NICU) using parametric and semiparametric models and compare model fitness according to Akaike information criterion (AIC) between 2016 and 2018.

Methods: This retrospective cohort study reviewed 600 medical records of infants admitted to the NICU of Bandar Abbas Hospital. Samples were identified using census sampling. Factors associated with NICU length of stay were investigated based on semiparametric Cox model and 4 parametric models including Weibull, exponential, log-logistic, and log-normal to determine the best fitted model. The data analysis was conducted using R software. The significance level was set at 0.05.

Results: The study findings suggest that breastfeeding, phototherapy, acute renal failure, presence of mechanical ventilation, and availability of central venous catheter were commonly identified as factors associated with NICU length of stay in all 5 models ($P<0.05$). Parametric models showed better fitness than the Cox model in this study.

Conclusion: Breastfeeding and availability of central venous catheter had protective effects against length of stay, whereas phototherapy, acute renal failure, and mechanical ventilation increased length of stay in NICU. Therefore, the identification of factors associated with NICU length of stay can help establish effective interventions aimed at decreasing the length of stay among infants.

Key words: Semiparametric, Parametric models, Neonatal intensive care units, Length of stay, Iran

Key message

Question: Hospitalization in neonatal intensive care unit (NICU) is associated with life-threatening hazards. What factors associated with neonatal length of stay (LOS) in the NICU?

Finding: Breastfeeding, phototherapy, acute renal failure (ARF), mechanical ventilation, and central venous catheter (CVC) access were identified as factors associated with NICU length of stay.
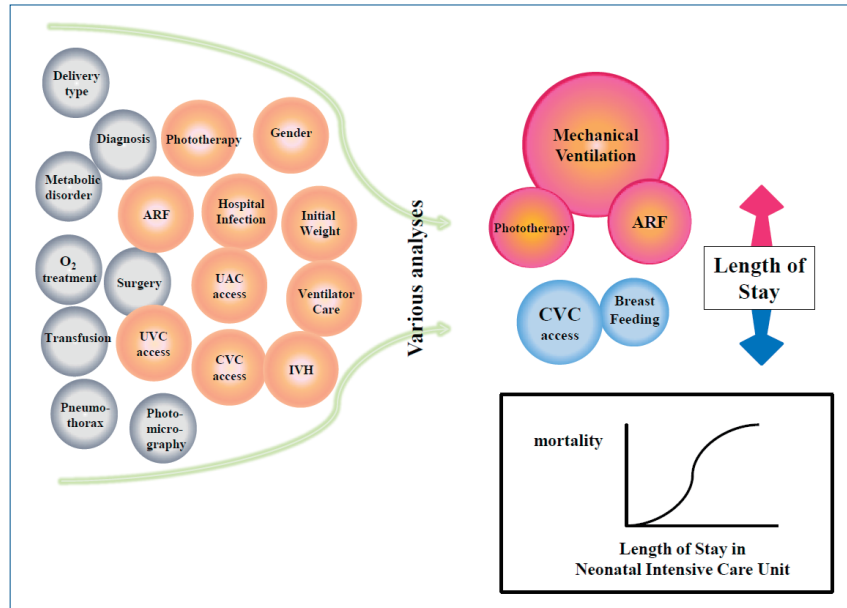
Meaning: Protective effects of breastfeeding and CVC access, whereas increase effects of phototherapy, ARF, and mechanical ventilation in LOS can be supporting evidence to establish effective interventions to reduce length of NICU stay.

Introduction

Identification of factors associated with neonatal length of stay (LOS) has become increasingly important, as elevated survival rate of premature infants is linked with prolonged hospitalization. Besides, it is necessary to estimate neonatal LOS to facilitate physician-parent communication regarding the predicted life-span of the infant.[1,2]

Hospitalization in neonatal intensive care unit (NICU) is associated with many life-threatening hazards and risks for the infant. A number of previous studies[3,4] have shown that 58% of infants with prolonged NICU stay were found dead or with severe disabilities after 1-year follow-up. Thus, identification of factors associated with NICU LOS may contribute to improve provided healthcare services and reduce neonatal LOS, as well as healthcare costs.[5,6]

Many studies have been carried out to determine causes of variability in survival distribution amongst different subgroups in heterogeneous populations. Comparison of parametric and semiparametric methods is a common technique to study predictors of survival distribution. There are 2 types of regres-

Graphical abstract. Factors associated with length of stay in neonatal intensive care unit. ARF, acute renal failure; UVC, umbilical venous catheter; UAC, umbilical arterial catheter; CVC, central venous catheter; IVH, intraventricular hemorrhage.

sion models for survival data: Cox proportional hazard model as a semiparametric method[7] and accelerated failure time models such as Weibull, exponential, log-logistic, log-normal as parametric methods. Cox proportional hazard model is the most common method for modeling factors associated with survival.[8,9] As an advantage, no particular form of probability distribution is assumed for the survival times in Cox model. However, there is an important and basic assumption in this model called proportional hazards, assumes that the hazard functions for 2 different levels of a covariate are proportional for all independent variables in the final model.[10-13] As such, the hazard ratio (HR) for a person, is a constant value for another person at a certain time.[14] If this assumption is met, interpretation of the obtained model will be easier than the parametric models, whereas if parametric model assumptions are met, the Cox model can be the best fitness and more efficiently estimated.[15]

Therefore, identification of risk factors for neonatal LOS in a clinical setting is very important, as it contributes to clinical diagnostic reasoning and supports clinical decisions. Furthermore, knowledge about risk factors associated with NICU LOS may help to develop strategies and interventions aimed at reducing mortality, neonatal LOS, and subsequently reducing related costs and complications. Therefore, the present study was carried out to evaluate factors associated with neonatal LOS in NICU using parametric and semiparametric models, and compare model fitness based on Akaike information criterion (AIC). The results of this study can be effectively used to reduce NICU LOS and consecutively reduce adverse effects and complications related to prolonged NICU stay.

Methods

This retrospective cohort study reviewed a total of 603 medical records of all NICU admitted newborns. First, a total of 600 infants admitted to NICU of Pediatric Department of Bandar Abbas Hospital with LOS longer than 24 hours were selected as target population. The required data on sex (male or female), type of delivery (normal or cesarean section), birth weight, type of feeding (breastfeeding, formula feeding), type of admission (emergency ward, other sections, other hospitals), nosocomial infection, antibiotic consumption during hospitalization, use of phototherapy, genetic disorders, metabolic disorders, acute renal failure, pneumothorax, use of mechanical ventilation, oxygen therapy, availability of umbilical arterial and venous catheters, availability of central venous catheter, intraventricular hemorrhage (IVH), blood product transfusion during the admission, and surgery during admission were collected by reviewing medical records of the patients.

The desired incident or failure in this study was death of infant admitted to NICU. Infants who were discharged by the physician's order or with the written consent of the parents at the end of the study were considered as censored cases.

Factor associated with LOS in NICU were evaluated using univariate ($P<0.20$), and multivariate ($P<0.05$) analyses based on semiparametric Cox model and 4 parametric models including Weibull, exponential, log-logistic and log-normal to determine the best fitted model. Data analysis was conducted using R ver. 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria), with significance level at 0.05.

This study was approved by the Ethics Committee (grant number: IR HUMS.REC.1397.07.02) of Bandar Abbas University of Medical Sciences.

1. Evaluation criterion

The AIC proposed by Akaike[16,17] was used to evaluate and compare candidate models in this study. AIC is a criterion for the fitness of statistical models and shows which model is more suitable for fitting data. The AIC is calculated by the following equation: $AIC = -2 \times \log(\text{likelihood}) + 2 \times (a+c)$. Where, a is the number of parameters in the model, and c is a constant coefficient which is applied depending on the type of model. as such, for exponential model, the c equals 1, while for Weibull, log-logistic and log-normal models, the value of c is equal to 2, and equal to zero in Cox model.[14,18] AIC is used to measure the degree of interaction between complexity of the model and model fit, and ultimately models with the lowest AIC will be selected as the best model.

Results

Demographic characteristics and extracted data on study variables from medical reports are shown in Table 1. Significant variables in univariate analysis by type of model are presented in Table 2. The significant variables are almost similar in all 5 models ($P<0.20$). Umbilical arterial catheter was exceptionally not significant in log-normal model. All study variables were eligible to be included in the multivariate regression model.

Log function of neonates survival is shown in Fig. 1, and results of multivariable analysis of Cox model and parametric models are presented in Table 3 ($P<0.05$). Fig. 2 shows curve of hazard function of neonates survival in Cox model. Although,

Table 1. Demographics and records of patients included in this study variable

Variable	No. (%)	Length of stay (day), median (IQR)
Age (day), median (IQR)	2 (1–7)	
Weight (g), median (IQR)	2,600 (1,750–3100)	
Sex		
Male	360 (59.7)	9 (4–16)
Female	243 (40.3)	11 (5–13)
Type of delivery		
Vaginal	298 (49.4)	9 (4–17)
Section	305 (50.6)	10 (5–17)
Type of feeding		
Breastfeeding	340 (56.4)	7 (6–18)
Formula	263 (43.6)	11 (3–15)
Cause of hospitalization		
Hospital infection		
Yes	327 (54.2)	12 (6–24)
No	276 (45.8)	8 (4–12)
Gastrointestinal disorders		
Yes	132 (21.9)	9 (5–17)
No	471 (78.1)	10 (5–21)
Respiratory disorders		
Yes	440 (73.0)	10 (5–17)
No	163 (27.0)	8 (6–24)

Table 1. Continued

Variable	No. (%)	Length of stay (day), median (IQR)
Heart disorders		
Yes	129 (21.4)	9 (4–12)
No	474 (78.6)	9 (5–21)
Genetic disorders		
Yes	61 (10.1)	11 (5–16)
No	542 (89.9)	9 (5–17)
Metabolic disorders		
Yes	51 (8.5)	12 (4–12)
No	552 (91.5)	9 (3–18)
Acute renal failure		
Yes	42 (7.0)	11.5 (4–15.2)
No	561 (93.0)	9 (4.5–22.5)
Pneumothorax		
Yes	53 (8.8)	10 (5–17)
No	550 (91.2)	9 (5–30)
Intraventricular hemorrhage		
Yes	76 (12.6)	12.5 (4–16)
No	527 (87.4)	9 (3–25.5)
Antibiotic therapy		
Yes	588 (97.5)	9.5 (5–16)
No	15 (2.5)	5 (3–19)
Umbilical venous catheterization		
Yes	54 (9.0)	5 (5–17)
No	549 (91.0)	10 (9–22.7)
Umbilical arterial catheterization		
Yes	6 (1.0)	5 (6–18)
No	597 (99.0)	10 (5–17)
Central venous catheterization		
Yes	38 (6.3)	3.5 (2–35.7)
No	565 (93.7)	10 (5–17)
Mechanical ventilation		
Yes	163 (27.0)	10 (2–13)
No	440 (73.0)	5 (6–18)
Oxygen therapy		
Yes	523 (86.7)	10 (5–17)
No	80 (13.3)	7 (4–12)
Surgery during hospitalization		
Yes	83 (13.8)	10 (6–18)
No	520 (86.2)	9 (4–17)
Blood transfusion		
Yes	269 (44.6)	14 (5–25)
No	334 (55.4)	7 (4–12)
Phototherapy		
Yes	257 (42.6)	10 (5–18)
No	346 (57.4)	9 (5–17)
Potomicrography		
Yes	526 (87.2)	10 (5–18)
No	77 (12.8)	8 (5–12)
Type of admission		
Emergency admission	163 (27.0)	9 (5–17)
Admission from other units	87 (14.4)	11 (6–15)
Referral from other hospitals	353 (58.5)	9 (4–18)

IQR, interquartile range.

Table 2. Final results of fitted Cox hazard proportional model and parametric models in univariate analysis for NICU length of stay (*P*<0.20)

Variable	Cox			Exponential			Weibull			Log-normal			Log-logistic		
	HR	*P* value	95% CI of HR	HR	*P* value	95% CI of HR	HR	*P* value	95% CI of HR	TR	*P* value	95% CI of TR	TR	*P* value	95% CI of TR
Sex	0.55	**0.004**	0.36–0.83	0.53	**0.002**	0.35–0.80	0.53	**0.003**	0.35–0.81	0.49	**0.004**	0.30–0.80	0.48	**0.004**	0.29–0.79
Type of delivery	1.04	0.843	0.66–1.40	1.05	0.250	0.72–1.52	1.05	0.815	0.72–1.52	1.07	0.783	0.67–1.69	1.05	0.828	0.67–1.66
Weight	1.00	**0.008**	0.99–1.00	0.99	0.076	0.99–1.00	1.00	**0.025**	0.99–1.00	0.99	**0.006**	0.99–1.00	0.99	**0.011**	0.99–1.00
Breastfeeding	0.12	**<0.001**	0.07–0.20	0.12	**<0.001**	0.07–0.20	0.12	**<0.001**	0.07–0.20	0.11	**<0.001**	0.07–0.19	0.10	**<0.001**	0.05–0.17
Type of admission	0.68	0.257	0.35–1.33	0.89	0.274	0.72–1.10	0.90	0.306	0.72–1.11	0.96	0.738	0.74–1.24	0.92	0.518	0.71–1.19
Hospital infection	2.11	**0.001**	1.38–3.23	1.70	**0.012**	1.12–2.57	1.90	**0.003**	1.25–2.91	2.06	**0.006**	1.23–3.45	2.22	**0.004**	1.29–3.83
Antibiotic therapy	0.30	**0.005**	0.13–0.69	0.25	**0.001**	0.11–0.57	0.27	**0.002**	0.12–0.63	0.24	**0.021**	0.07–0.24	0.22	**0.005**	0.07–0.64
Phototherapy	1.78	**0.003**	1.22–2.59	1.82	**<0.001**	1.24–2.64	1.77	**0.003**	1.22–2.58	2.00	**0.003**	1.27–3.16	1.97	**0.004**	1.25–3.11
Genetic disorder	1.80	**0.018**	1.11–2.93	1.69	**0.033**	1.04–2.75	1.74	**0.025**	1.07–2.83	2.02	**0.043**	1.02–3.99	1.96	**0.041**	1.03–3.75
Metabolic disorder	2.82	0.354	0.75–2.24	1.18	0.552	0.68–2.03	1.23	0.450	0.71–2.13	1.15	0.714	0.54–2.44	1.22	0.572	0.61–2.45
Kidney disorder	3.27	**<0.001**	2.08–5.15	2.93	**<0.001**	1.87–4.57	3.13	**<0.001**	2.00–4.90	4.97	**<0.001**	2.39–10.3	4.88	**<0.001**	2.48–9.62
Pneumothorax	5.29	**<0.001**	3.56–7.87	5.21	**<0.001**	3.52–7.72	5.29	**<0.001**	3.57–7.84	8.08	**<0.001**	4.16–15.7	8.01	**<0.001**	4.43–14.5
Mechanical ventilation	14.1	**<0.001**	8.85–22.2	14.6	**<0.001**	9.23–23.1	14.4	**<0.001**	9.09–22.8	15.1	**<0.001**	9.53–24.0	16.6	**<0.001**	10.1–27.4
Oxygen therapy	1.29	0.357	0.75–2.23	1.40	0.227	0.81–2.41	1.35	0.284	0.78–2.33	1.44	0.288	0.74–2.80	1.41	0.306	0.73–2.74
Umbilical venous catheterization	0.19	**<0.001**	0.13–0.28	0.19	**<0.001**	0.13–0.29	5.33	**<0.001**	3.58–7.94	0.11	**<0.001**	0.06–0.21	0.11	**<0.001**	0.06–0.19
Umbilical arterial catheterization	0.24	0.160	0.03–1.76	0.14	0.050	0.02–0.99	5.27	0.102	0.72–38.6	0.22	0.225	0.02–2.53	0.17	0.127	0.02–1.65
Central venous catheterization	0.47	**0.009**	0.27–0.83	0.56	**0.030**	0.32–0.94	0.50	**0.011**	0.29–0.85	0.25	**0.001**	0.11–0.56	0.28	**0.002**	0.12–0.63
Photomicrography	4.35	**0.012**	1.38–13.7	3.71	**0.025**	1.18–11.7	4.01	**0.018**	1.27–12.6	5.25	**0.004**	1.70–16.2	5.24	**0.013**	1.42–19.3
Intraventricular hemorrhage	1.72	**0.017**	1.10–2.68	1.59	**0.039**	1.02–2.47	1.64	**0.028**	1.05–2.55	1.61	0.134	0.87–3.00	1.68	0.079	0.94–3.00
Blood transfusion	0.27	**<0.001**	0.17–0.45	0.38	**<0.001**	0.24–0.61	0.32	**<0.001**	0.20–0.52	0.24	**<0.001**	0.14–0.44	0.23	**<0.001**	0.12–0.44
Surgery during hospitalization	1.21	0.497	0.70–2.09	1.28	0.374	0.74–2.21	1.24	0.442	0.72–2.14	1.48	0.254	0.75–2.91	1.33	0.390	0.69–2.58
Age NICU	1.04	**0.014**	1.01–1.08	1.04	**0.016**	1.01–1.07	1.04	**0.015**	1.01–1.08	1.04	**0.012**	1.01–1.08	1.05	**0.009**	1.01–1.09

NICU, neonatal intensive care unit; HR, hazard ratio; TR, time ratio; CI, confidence interval.
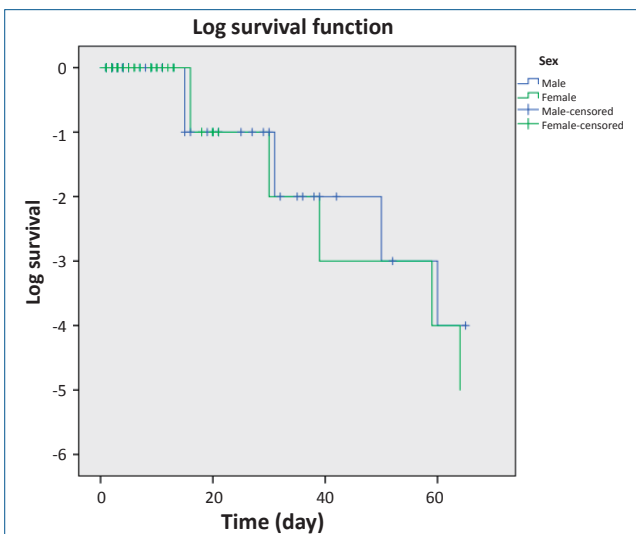Boldface indicates a statistically significant difference with *P*<0.05.

Fig. 1. Log survival function of neonatal care unit length of stay.

results of univariate analysis indicated similar goodness of fit of parametric and semiparametric models, according to AIC (Table 4), parametric model represented a better fitness compared to nonparametric Cox model. Also, among parametric models, exponential model was shown to be the best fitness.

Discussion

The purpose of this study was to examine factors associated with neonatal LOS in NICU using parametric and semiparametric models, and compare model fitness according to AIC. According to the results of this study, Breastfeeding, phototherapy, acute renal failure, use of mechanical ventilation, and availability of central venous catheter were commonly identified as factors associated with LOS in NICU in all 5 models (*P*<0.05). In addition, IVH and birth weight presented a proper fit in semiparametric Cox model, and availability of umbilical catheter showed a good fitness in parametric models. Also, gender in the Weibull model, hospital-acquired infection in log-normal and log-logistic models, and availability of umbilical arterial catheter with Weibull and logistic models were shown to be best fitted to the study data.

A population-based cohort study conducted in Australia (2017) revealed that IVH was the most leading cause of neonatal death in NICU (adjusted odds ratio [OR], 9.27; 95% confidence interval [CI], 6.30–13.64). Also, infant's gender (adjusted OR, 1.47; 95% CI, 1.10–1.96), and infant's weight (*P*<0.001) were proved to be associated with infants survival in NICU.[19]

Another cohort study done in Brazil (2017) proposed that infant's gender (*P*=0.038), intubation (*P*=0.028), length of NICU stay (*P*=0.012), and breastfeeding (*P*=0.030) were associated with survival of premature infants, with no significant

Table 3. Final multivariate analysis results of Cox and semiparametric models for neonatal intensive care unit length of stay (*P*<0.05)

Variable	Cox			Exponential			Weibull			Log-normal			Log-logistic		
	HR	*P* value	95% CI of HR	HR	*P* value	95% CI of HR	HR	*P* value	95% CI of HR	TR	*P* value	95% CI of TR	TR	*P* value	95% CI of TR
Sex	No significance			No significance			0.66	0.05	0.42–1.02	No significance			No significance		
Weight	1.00	**0.012**	0.99–1.00	No significance			No significance			No significance			No significance		
Breastfeeding	0.14	**<0.001**	0.08–0.25	0.15	**<0.001**	0.09–0.25	0.13	**<0.001**	0.07–0.22	0.23	**<0.001**	0.15–0.35	0.24	**<0.001**	0.15–0.38
Hospital infection	No significance			No significance			No significance			1.77	**0.006**	1.18–2.66	1.57	**0.035**	1.03–2.39
Phototherapy	1.89	**0.001**	1.28–2.78	2.11	**<0.001**	1.40–3.15	2.24	**<0.001**	1.48–3.37	1.64	**0.014**	1.11–2.44	1.85	**0.002**	1.26–2.73
Kidney disorder	2.22	**0.001**	1.41–3.51	2.07	**0.003**	1.28–3.35	2.10	**0.003**	1.29–3.40	2.04	**0.007**	1.22–3.41	2.14	**0.003**	1.29–3.56
Mechanical ventilation	14.9	**<0.001**	9.01–24.5	13.0	**<0.001**	7.71–21.8	15.1	**<0.001**	8.73–26.0	10.6	**<0.001**	6.61–16.9	10.5	**<0.001**	6.41–17.1
Umbilical venous catheterization	No significance			0.63	**0.047**	1.01–2.53	0.61	**0.035**	0.38–0.97	0.60	**0.030**	0.38–0.95	0.63	**0.037**	0.41–0.97
Umbilical arterial catheterization	No significance			No significance			0.10	**0.036**	0.01–0.86	No significance			0.17	**0.027**	0.03–0.81
Central venous catheterization	0.45	**0.008**	0.25–0.81	0.40	**0.002**	0.22–0.71	0.37	**0.001**	0.20–0.67	0.53	**0.028**	0.30–0.94	0.46	**0.004**	0.27–0.79
Intraventricular hemorrhage	1.75	**0.018**	1.10–2.78	No significance			No significance			No significance			No significance		

HR, hazard ratio; CI, confidence interval; TR, time ratio.
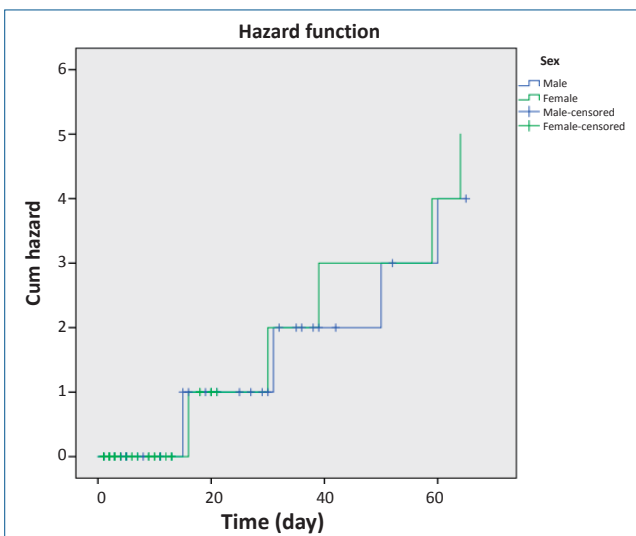Boldface indicates a statistically significant difference with *P*<0.05.

Fig. 2. Cumulative hazard function of neonatal intensive care unit length of stay.

Table 4. Comparison of fitness of models based on AIC

Model	Log likelihood	AIC
Exponential	-234.54	483.08
Weibull	-232.66	485.32
Log-normal	-234.45	486.90
Log-logistic	-232.17	484.34
Cox	-630.57	1279.14

AIC, Akaike information criterion.

relationship between infant's weight (*P*=0.094) and infant survival.[20] Besides, another cohort conducted in South Korean (2015) used Cox model and revealed that infant's gender (HR, 1.69; 95% CI, 1.10–2.60), length of ventilation (*P*<0.001), IVH (*P*<0.001), pneumothorax (*P*<0.001), and respiratory distress syndrome (*P*<0.001) were associated with LOS in NICU, with no significant association between metabolic disorders such as diabetes with infant survival.[21] According to results of a multicenter study conducted in China (2015), IVH was associated with infant survival (*P*=0.001), and ventilator associated pneumonia was shown to be the most common risk factor for nosocomial infection during NICU stay.[22] Cui et al.[23] reported that IVH and pulmonary hemorrhage were shown as major risk factors for infant survival in NICU. However, they found no significant relationship between infant survival with hospital-acquired infection (*P*=0.92) and respiratory distress syndrome (*P*=0.42).

Stroustrup and Trasande[4] and Assandri Dávila et al.[24] proposed that respiratory diseases are one of the most medical conditions in hospitalized infants, and a high percentage of these infants need mechanical ventilation and NICU admission. Stroustrup and Trasande[4] also proposed that newborn length of hospital stay significantly increased at birth. They concluded that less use of invasive mechanical ventilation may reduce newborn LOS. Marcin et al.[3] also indicated that essential use of mechanical ventilation and intracranial catheters were associated with prolonged NICU stay. Kotloff et al.[25] showed that NICU LOS was higher in infants treated with antibiotics during the hospitalization. The results of a cohort study by Freeman et al.[26] showed that the average LOS was 20 days more in infants with hospital-acquired infection than infants with no infection.

Many studies have been conducted to compare the efficacy of different regression models (parametric, semiparametric and nonparametric), especially for calculating survival rates of different types of cancers, cardiovascular diseases, AIDS, and so on. However, there are a limited number of studies on the survival of newborns in NICU. Unlike our study, Gohari et al.[27] (2012) selected the Cox model as the best fitness to estimate the average length of hospital stay, and showed that age and gender were associated with LOS. Kandi Kele et al.[28] also evaluated factors associated with NICU LOS using survival analysis based on Cox model as the best model, and reported that prematurity, admission and hospitalization of infants from other hospitals, admission due to gastrointestinal diseases and infections, treatment with mechanical ventilation, use of central venous catheter, and antibiotic treatment were associated with infant survival.

Ravangard et al.[29] showed in their study used Cox model to evaluate factors associated with LOS. They reported that gamma model is an appropriate model with good fit to analyze LOS data, which was consistent with the results of our study. In the present study, parametric models represented better fitness than Cox model.

One of the strength of this study was large sample size due to use of census sampling method. However, the relatively high amount of right censored data was one of the limitations of this study. For an acceptable good fitting of a parametric model, the amount of right censoring should not exceed 40%−50%.[30]

Despite the high tendency of researchers to use Cox model in the survival analysis, parametric models can provide better results and predictions in evaluations with minimal censoring compared to Cox model. In the present study, the parametric exponential model represented the best fitness to determine factors associated with neonatal LOS in NICU. Results of this study suggest that breastfeeding and availability of central venous catheter had protective effects against LOS, whereas phototherapy, acute renal failure, and mechanical ventilation increased LOS in NICU. Therefore, identification of factors associated with LOS in NICU can help to establish effective interventions to reduce length of NICU stay among infants. In addition, the findings of this study can help physicians and other healthcare providers to efficiently manage neonatal LOS in NICU. However, parametric models are not undoubtedly the best fitness in survival analysis. Hence, the goodness of fit of various models is variable, and effective analysis of data requires identification of models with the best fitness.

The required data were extracted from hospital information system, and some of the study variables may not be accurately documented. Besides, this study reviewed medical records of one single hospital and results cannot be generalized to other hospitals in Bandar Abbas city.

We suggest that future studies should use various comparative criteria among different models with longer follow-up periods to achieve higher incidence of LOS and reduce the percentage of right censored data.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

See the commentary "Survival model application for analysis of neonatal length of stay" via https://doi.org/10.3345/cep.2019.01508.

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