

## Comparison of Nasal Intermittent Positive Pressure Ventilation and Nasal Continuous Positive Airway Pressure Treatments Using Parametric Survival Models

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### Abstract

**Objective:** The Cox model is the dominant tool in clinical trials to compare treatment options. This model does not specify any specific form to the hazard function. On the other hand, parametric models allow the researcher to consider an appropriate shape of hazard function for the event of interest. The aim of this article is to compare performance of Cox and parametric models.

**Methods:** We used data collected in a prospective clinical trial that aimed to compare performance of nasal intermittent positive pressure ventilation (NIPPV) and nasal continuous positive airway pressure (NCPAP) treatments in terms of survival of newborn infants who had respiratory distress syndrome (RDS). Performance of Cox, exponential, Weibull, and log-logistic models were compared in terms of goodness of fit.

**Findings:** Fitting the Cox model, we have seen that infants who received NCPAP were 4.23 (Hazard Ratio=4.23, 95% Confidence Interval: 1.87-9.59) times more likely to fail than those received NIPPV ( $P=0.001$ ). Adequacy of the exponential model was rejected. We have seen a decreasing hazard rate over time, in both treatment groups. This decrease was sharper in NCPAP group. Akaike information criterion corresponded to the log-logistic model and was lower than all other models followed by Weibull model.

**Conclusion:** Our results demonstrate the benefit of parametric survival models over traditional Cox regression model in terms of modeling of shape of hazard function. We saw a decreasing hazard that confirms the flexibility of parametric models in terms of the modeling of hazard rate.

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**Key Words:** Parametric Survival; Weibull; Infant Mortality; Respiratory Distress Syndrome

### Introduction

Survival data is a term used for data measuring the time to some event<sup>[1]</sup>. The Cox model is the most widely used in clinical studies to characterize disease progression on existing cases by revealing the importance of covariates. The model assumes that the underlying hazard rate (rather than

survival time) is a function of the independent variables multiplied to a baseline hazard function. No distributional assumption about the shape of hazard function is required<sup>[2]</sup>. Therefore Cox regression is known as a semi-parametric model. The basic assumption behind the Cox model is the Proportional Hazard (PH) assumption which indicates that the Hazard Ratio (HR) is a constant

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over time. This means that short benefit of a treatment would be translated into a long term benefit.

Cox regression model has been used frequently to address factors influence survival of infants. For example in a study in Nicaragua about infant mortality the Cox model was used<sup>[3]</sup>. Ronsmans implemented the Cox regression for modeling the Child Survival in Senegal<sup>[4]</sup>. In another study, the Cox proportional hazard models were used to adjust for potential confounding and to model potential effect modification for impact of supplementing newborn infants with vitamin A on early infant mortality in southern India<sup>[5]</sup>.

In the field of survival analysis, several parametric models are available. Parametric models require distributional assumption, and allow the researcher to consider an appropriate shape of hazard function for the event of interest<sup>[6]</sup>. Parametric models can be presented as Accelerated Failure Time (AFT) and/or PH models. AFT and PH forms are applications for comparison of survival times and hazards respectively. Statistics that would be used are Acceleration Factor (AF) and HR.

The PH models present the data in terms of HR, while AFT models concentrate on survival time<sup>[7]</sup>. For example suppose one wishes to compare risk of cancer recurrence of patients received treatment to those who got placebo. A HR of 0.22 indicates that patients with treatment are 78% less likely to experience the recurrence. On the other hand, AF of 4.6 indicates that survival of those received treatment is stretched out by a factor of 4.6. This means that HR <1 and AF >1 shows that the variable has a protective effect.

Field on survival analysis is dominated by Cox PH model. However, in many applications clinical knowledge can guide selection of appropriate shape for hazard function. For example, in the case of infant mortality, it is reasonable to assume that the hazard of death decreases over time. Therefore, there is room to apply parametric models and to extract more details from the data.

The most commonly used parametric models are exponential, Weibull, and log logistic. The exponential and Weibull regression models can be considered as both the AFT and PH models but log logistic model can be presented only in AFT form<sup>[8]</sup>. Therefore, when data does not satisfy the PH assumption, log logistic model can be

considered as an alternative for Cox PH model. The aim of this article is to address practice of commonly used parametric survival models. To do so, we used data from a clinical trial study in the field of infant mortality data.

## Subjects and Methods

### Patients:

We used data collected in a prospective clinical trial that was conducted in a level III neonatal unit. The aim of the study was to compare performance of two treatment options in terms of survival of newborn infants who had Respiratory Distress problems. Treatments compared were nasal continuous positive airway pressure (NCPAP) and nasal intermittent positive pressure ventilation (NIPPV).

We allocated 60 patients to each treatment arm. Only infants with gestational aged 28 to 36 week were approached.

Samples were taken from Afzalipour neonatal intensive care unit (affiliated to Kerman University of Medical Sciences). The infants in the NCPAP group received initially 5cm of water and flow 6-7 liters/min. The maximum allowable settings were CPAP 7 cmH<sub>2</sub>O and fraction of inspired oxygen (FiO<sub>2</sub>) 0/6. The infants in NIPPV (NCPAP+) group were initiated on peak inspiratory pressure (pc + PEEP) 11 cm of water, peak and expiratory pressure (PEEP) 5 cm of water, I:E 1:5.7 and flow 6-7 liters/min and rate of 15 per minute. The maximum permissible PEEP used was 7 cm of water and FiO<sub>2</sub> was 0/6. Targeted saturation was 88%-92%. Settings in both groups were adjusted based on arterial blood gases (ABG) and pulse oximetry.

Success was defined if the respiratory distress improved and the baby could be weaned off NCPAP or NIPPV. Event medical ventilator (Inspiration LS infant, Ireland) was used for both treatment groups via nasopharyngeal prongs.

Gestational age of the preterm infants admitted to Afzalipour neonatal intensive care was between 28 and 36 weeks and had respiratory distress. Also Silverman-Anderson retraction score of 6 and 7 of the infants were included.

Infants who had significant morbidity

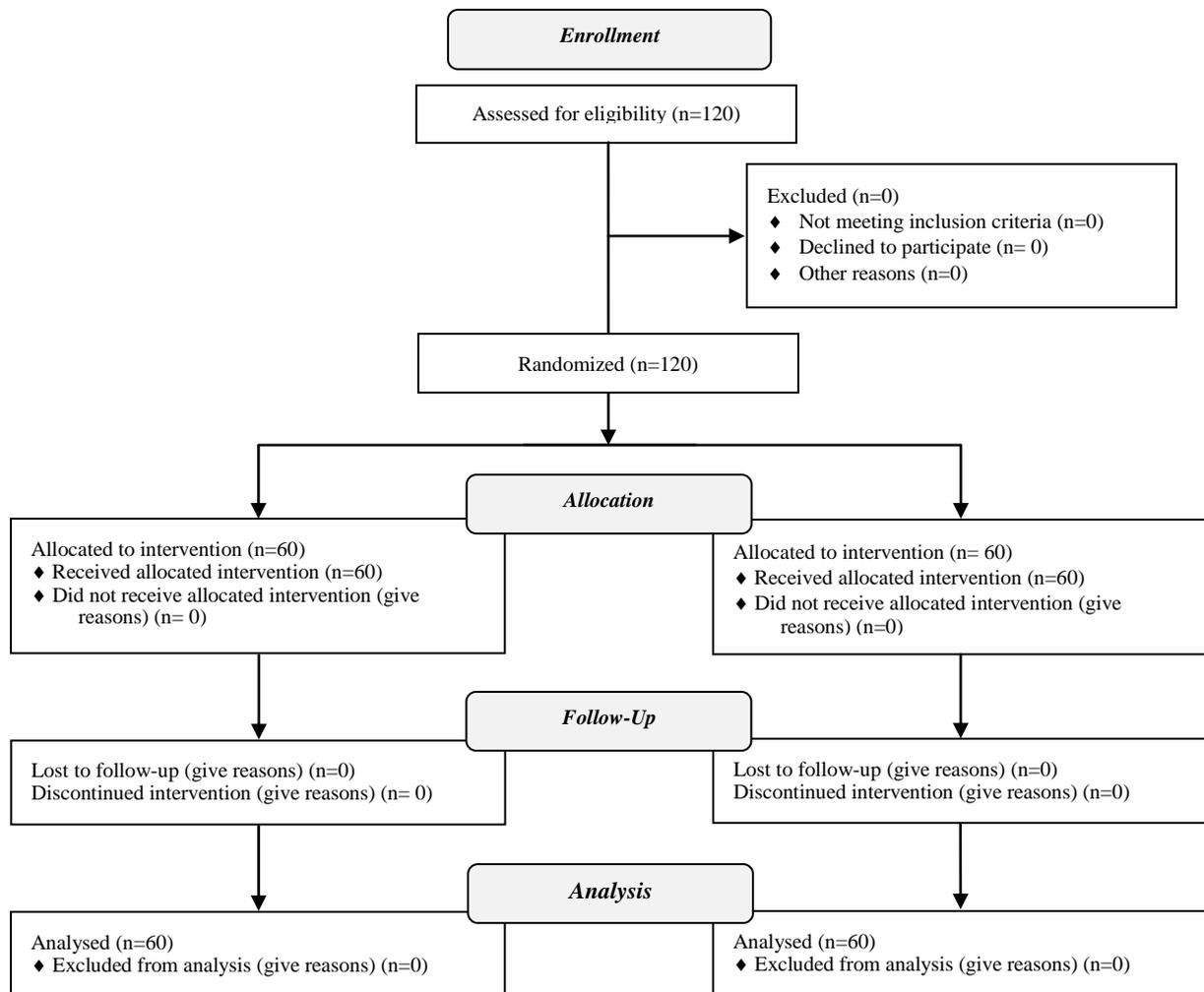


Fig. 1: CONSORT Flow Diagram

symptoms (i.e. those with cardiac disease - not including patent ductus arteriosus, congenital malformations including congenital diaphragmatic hernia, tracheoesophageal fistula and cleft lip/palate, cardiovascular or respiratory instability because of sepsis, anemia or severe intraventricular hemorrhage (IVH) on admission), were not included in the study.

#### Randomization method:

It is known that gender and birth weight have great impact on survival rate of infants in neonatal units. Therefore, for allocation of infants to treatment arms we implemented minimization of approach that balances the distribution of these two confounders in treatment groups.

#### Outcome and independent variables:

Survival was defined as duration between birth

time and treatment failure. The main independent variable was treatment (NCPAP vs NIPPV). Other variables that enrolled the multifactorial model, as potential confounders, were gestational age (week), type of delivery, steroid use, and surfactant use.

#### Statistical analysis:

We fitted the Cox PH as the basic model. To test whether PH assumption was hold, test of interaction term with time was performed [9]. A series of parametric models were then developed as follows. Exponential model was fitted in AFT and PH forms. This model assumes that the hazard rate is constant over time:  $h(t) = \lambda$

On the other hand the Weibull model allows more flexibility in modeling of hazard function. This model can be used to present monotonic hazard function (increasing or decreasing). The

**Table 1:** Comparison of background characteristics of patients in NIPPV and NCPAP groups

Variable	Treatment	NIPPV Frequency (%)	NCPAP Frequency (%)	P-value
Surfactant use	Yes	29 (48.3)	24 (40.0)	0.4
	No	31 (51.7)	36 (60.0)	
Steroid use	Yes	50 (83.3)	44 (73.3)	0.2
	No	10 (16.7)	16 (26.7)	
Type of delivery	Cesarean Section	49 (81.7)	42 (70.0)	0.2
	Normal Vaginal	11 (18.3)	18 (30.0)	
Gender	Boy	32 (53.3)	31 (51.7)	0.8
	Girl	28 (46.7)	29 (48.3)	
Gestational age	Mean (SD)	32.17 (2.1)	32.05 (2.9)	0.8

SD: Standard Deviation; NIPPV: Nasal Intermittent Positive Pressure Ventilation; NCPAP: Nasal Continuous Positive Airway Pressure

general form of hazard function is expressed as:

$$h(t) = \lambda pt^{p-1}$$

Here, parameter P is known as shape parameter. Values >1 indicate increasing hazard over time. Values <1 indicate decreasing hazard across time<sup>[10]</sup>. It has been shown that plot of logarithm of minus logarithm of survival function versus logarithm of time (ln (-ln(S (t))) vs ln (t)) provides a graphical test that the data follow the Weibull distribution. Parallel straight lines indicate that both PH and AFT assumptions are satisfied. In addition, exponential model is a special case of Weibull model if P=1. Therefore, test of P=1 was used to investigate the necessity of Weibull regression model. The log logistic model was fitted only in AFT form<sup>[11]</sup>. The general form of the hazard function is:

$$h(t) = \frac{\lambda pt^{p-1}}{1 + \lambda t^p}$$

The log-logistic model can be used to model both monotonic and non-monotonic shapes of hazard function. P is the shape of parameters where values <1 indicate decreasing hazard function. On the other hand, values >1 indicate that the hazard rate increases to a peak and then decreases over time<sup>[11]</sup>. Plot of logarithm of survival odds versus logarithm of time (ln (ln ((S (t)/1-S (t)) vs ln (t)) provides graphical assessment of AFT assumption<sup>[6]</sup>.

All regression models were fitted using ENTER method. Models were compared in terms of goodness of fit (Akiake Information Criterion (AIC)). The lower the AIC, the better the fit is. All analyses were performed using Stata software. The level of significance for all tests is 0.05. The study protocol was adopted by the university ethics committee of Kerman University of Medical Sciences. Informed consent of the parents, before

entering their infant in the study was obtained.

#### Ethical consideration:

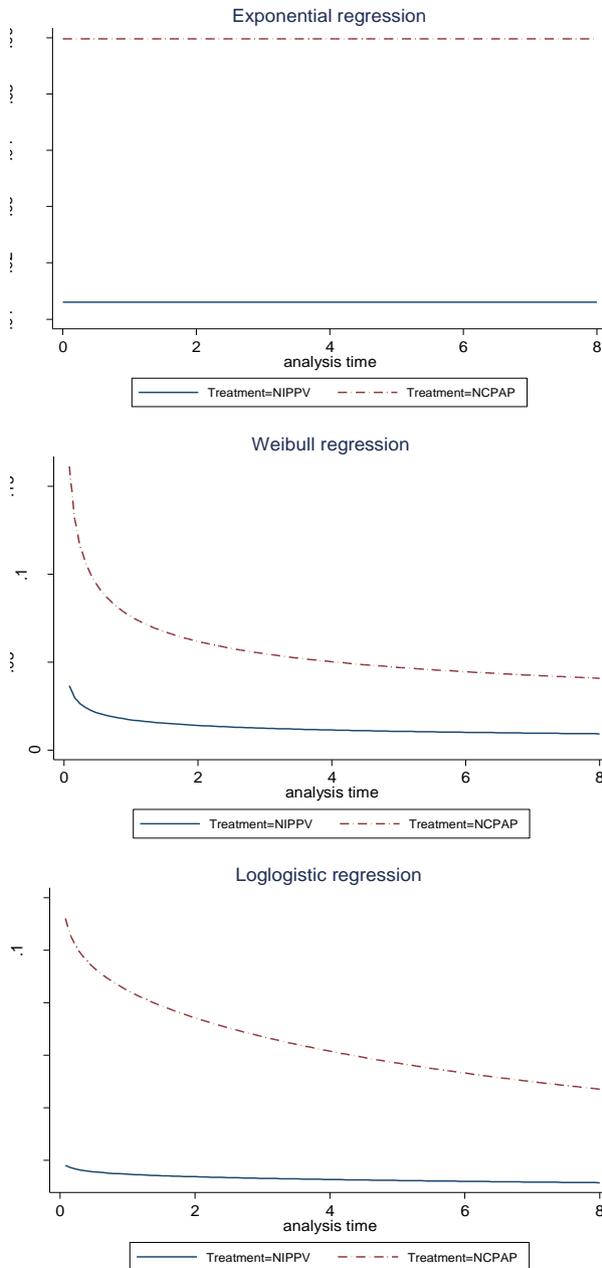
The study protocol was approved by local ethical committee of Kerman University of Medical Sciences. Registry code K/90/328 and Ethical Approval document is IRCT201202273250N6. All the parents signed informed consent before participating in the study. CONSORT flow Diagram for clinical trial papers is shown in Fig. 1.

#### Findings

Mean (standard deviation) gestational age in NIPPV and NCPAP groups was 32.17 (2.1) and 32.05 (2.9) respectively. Nearly 44% of patients were candidate for surfactant use (48% in NIPPV and 40% in NCPAP group). In addition, more than two thirds of patients had received steroid, and three-fourths of infants were born by cesarean section. No difference between groups was seen in terms of surfactant use, steroid use, type of delivery, gender, and gestational age (Table 1).

Applying the test of interaction with time tests, the PH assumption holds for all variables (data not shown). Fitting the Cox model, we have seen that infants who received NCPAP were 4.23 (95% C.I: 1.87-9.59) times more likely to fail than those that received NIPPV (P=0.001). This model provided the highest AIC value at 294.9 (Table 2).

Fitting the PH exponential model, the estimated hazard rate of failure for infants received NCPAP and NIPPV were estimated at 0.06 and 0.013 respectively (Fig. 2, top panel). These rates were



**Fig. 2:** Plot for hazard ratio applying Exponential (top panel), Weibull (middle panel), and log-logistic (bottom panel) distributions

constant over time and gave HR at 4.60 (95% C.I: 2.00-10.58) with  $P < 0.001$ . Fitting the AFT form, the AF was estimated at 0.22 which indicates that survival time of infants that received NCPAP was 0.22 (95% C.I: 0.09-0.50) times that of those who got NIPPV (Table 2).

In the next step, Weibull regression model was fitted. Equality of P with one was highly rejected with  $P < 0.001$ . This suggested that the exponential model was not an appropriate choice. Fig. 3 suggests that AFT assumption was hold by the data. Fig. 2 middle panel clearly suggested a decreasing hazard rate over time, in both groups. This decrease was sharper in NCPAP group, as the hazard rate in this group at the start was around 4 times higher. HR and AF corresponding to Weibull models were 4.43 (95% C.I: 1.94-10.12) and 0.12 (95% C.I: 0.03-0.44) respectively, which were highly significant. The AIC for this model was lower than Cox and exponential models.

Fitting log-logistic AFT model, we estimated AF at 0.14 (95% C.I: 0.05-0.41) which was highly significant. This indicates that survival time of infants that received NCPAP was 0.14 times that of those who got NIPPV. Fig. 2 middle panel shows decreasing risk in NCPAP group. Hazard rate in NIPPV group was much lower than in NCPAP group, from the first hour. AIC corresponding the log-logistic model was lower than all other models.

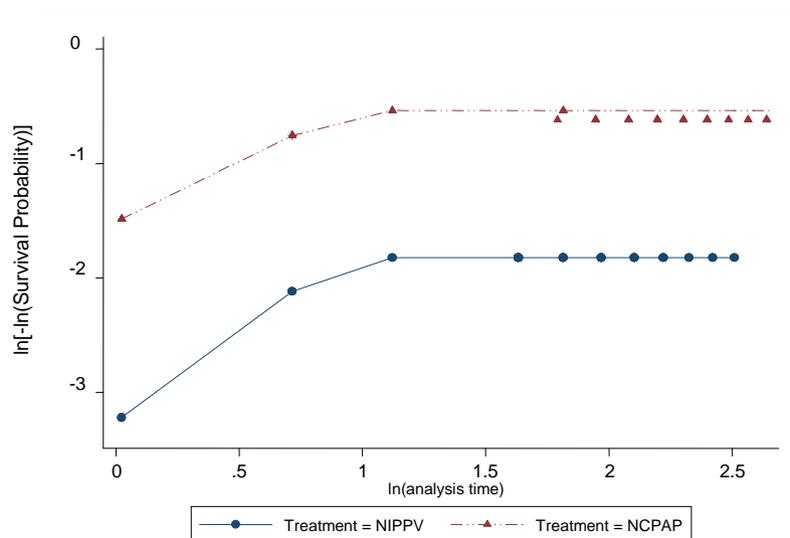
### Discussion

Our results demonstrate the benefit of parametric survival models, over traditional Cox regression model, in terms of modeling of shape of hazard function. Several studies applied the traditional

**Table 2:** Estimation of Hazard Ratio for treatment at each model

	Exponential (PH)	Exponential (AFT)	Weibull model (PH)	Weibull model (AFT)	Log logistic model (AFT)	Cox (PH)
HR	4.6 (2, 10.58)	-	4.43 (1.94-10.12)	-	-	4.23 (1.84-9.59)
AF	-	0.22 (0.09, 0.50)	-	0.12 (0.03-0.44)	0.14 (0.05-0.41)	-
P. Value	<0.001	<0.001	<0.001	0.002	<0.001	0.001
AIC		229.36		225.17	217.97	294.9

PH: Proportional Hazard, AFT: Acceleration Factor Time, HR: Hazard Ratio, AF: Acceleration Factor



**Fig. 3:** Plot of the log negative log Kaplan-Meier survival estimates against the log of time

Cox proportional hazard model for infant mortality<sup>[3,12-13]</sup>. However, plotting hazard rate functions, we clearly saw decreasing hazard of treatment failure. In many situations the use of the parametric models is more effective than the Cox model<sup>[14]</sup>, as such models allow flexibility in modeling of hazard rate. In addition, they provided AF which compares survival times across treatment arms<sup>[15]</sup>.

In our study, the performance of the log logistic model was superior to all other semiparametric and parametric models in terms of AIC. After that, performance of the Weibull model was better than other approaches.

Application of parametric survival models in the analysis of infant and child morbidity has been addressed by other authors. In a study in Kenya the Weibull model was used to explore the factors that govern the child mortality. It has been shown that the biodemographical factors, relative to socioeconomic and sociocultural factors, were much important in explaining infant mortality<sup>[16]</sup>. In another study in Nigeria relationship of low birth weight and other factors on infant mortality were estimated using Weibull hazard function. A strong inverse association between low birth weight and infant survival has been seen<sup>[17]</sup>.

Another aspect of our work was to compare two treatment options in management of newborn infants. We have seen that NIPPV was more successful than NCPAP in terms of reduction of rate of endotracheal ventilation. In the Weibull and log logistic models the difference was more

obvious. Especially at the initial time in the NCPPV group the risk of failing is high. This suggests that the appropriate management of infants in the first hours is crucial.

## Conclusion

Our experience suggests that the parametric survival models are not popular among researchers. However, such models might provide better fit and extract more details about benefits of treatment options. We do recommend application of parametric models as well as standard Cox model, to make the most use of the data.

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## Authors' Contribution

Concept and design: M.R. Baneshi, B. Bahmanbijari  
 Acquisition of the data: B. Bahmanbijari, R. Mahdian  
 Data analysis and interpretation: M.R. Baneshi, R. Nikbakht, S. Haji-Maghsoudi  
 Manuscript preparation: All authors  
 Critical revision of the manuscript: M.R. Baneshi, B. Bahmanbijari  
 All authors approved final version of the manuscript

**Conflict of Interest:** None

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