

Original Article

Prediction of time to reflux using accelerated failure time model of Weibull distribution in children with antenatal hydronephrosisMaryam Nazemipour¹, Abdol-Mohammad Kajbafzadeh², Kazem Mohammad³, Mahmood Mahmoudi^{3*}¹ Department of Epidemiology and Biostatistics, School of Public Health, International Campus, Tehran University of Medical Sciences, Tehran, Iran² Pediatric Urology Research Center, Department of Pediatric Urology, Children's Hospital Medical Center, Tehran University of Medical Sciences, Tehran, Iran³ Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

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ABSTRACT

Background & Aim: Prediction of time to reflux can aid healthcare providers and preparation programs. We constructed a risk prediction instrument for occurrence reflux in children with antenatal hydronephrosis.**Methods & Materials:** Demographic and clinical information was collected retrospectively in children with the antenatal hydronephrosis and mostly with reflux, followed at least 5 years.**Results:** Accelerated failure time model of data from 333 children was developed to assess the risk of time to reflux. Likelihood ratio tests of statistical significance were used to identify best fitting predictive function. Variables "gender", "Sr", and "severity of ANH (in severe level)" were highly significant ($p < 0.05$) in multivariate model, adjusting for some traditional risk factors.**Conclusion:** This proposed risk probability model allows prediction of time to reflux for children with antenatal hydronephrosis to better inform parents from possible time of occurrence reflux and treatment strategies.**Introduction**

Antenatal hydronephrosis, diagnosed by ultrasonography, is known to be associated with vesicouretral reflux (VUR) (1). The incident of VUR in children antenatally diagnosed hydronephrosis, ranges from 7-38% (1-3). VUR in infants and children can lead to renal damage, causing infection and end stage renal disease (4, 5). Clinicians attempt to predict time to occurrence vesicouretral reflux in children borned with antenatal hydronephrosis. This prediction is important due to many reasons. First of all to inform the patient about the outcome of her/his disease. Second, is used as a guideline for the clinician for an appropriate therapy. Third, to test the differential therapeutic

benefits and finally is a guide for researcher in diagnosing, clinical trials, or effect of a single factor on prognosis in an observational study (6).

Survival analysis technique has been applied in medical research widely to explore the duration of time from a certain time until occurrence of the event or events (7) and it is common to have incomplete event time (8). There are two types of regression models in survival analysis, Cox proportional hazard (PH) model (9) and accelerated failure time (AFT) model (10). Proportional hazard model directly refers to the effect of some covariates on the hazard function while the accelerated failure time model describes the failure time affected by the covariates and explains how they accelerate or decelerate the life course of the disease. Cox models have been widely used in medical researches although AFT models are applied just in prediction of time to a certain event accelerated by different factors (11). Theme of this paper is, application of an AFT parametric

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model to predict time to reflux for children with antenatal hydronephrosis.

Methods

A total of 333 children with ANH, admitted to the Pediatric Urology Research Center of Children’s Hospital Medical Center affiliated to Tehran University of Medical Sciences between 2003 and 2005 and nearly most of whom had VUR, were enrolled in this study. They were followed up for at least 5 years for measuring and evaluating time of occurrence their reflux. Information on their demographic and clinical as well as the time were extracted from their medical records and by phoning their family. Data analysis was done using R software version 2.14.1 and $p < 0.05$ was considered statistically significant. This information can prepare a guide for helping a pregnant woman on the postnatal effect of ANH.

We applied an accelerated failure time survival model to analysis the number of days from diagnosis of ANH until the reflux event. Time to reflux was in agreement with the Weibull distribution. The stepwise AFT regression models show five factors are in association with the outcome. The variables included in the stepwise models analysis were “Sr”, “gender”, “consanguinity marriage”, “severity of ANH” and “Direction of ANH”.

Ethics Committee Approval: All the data were collected after Tehran University of Medical Sciences Institutional Review Board (TUMS IRB) approval

Weibull distribution model: The probability distribution of the Weibull distribution is defined by $f(t) = \lambda p t^{p-1} \exp(-\lambda t^p)$

Where $p > 0$ and $\lambda > 0$. In this formula p is a shape parameter. The survival and hazard function of Weibull are $S(t) = \exp(-\lambda t^p)$ and $(t) = \lambda p t^{p-1}$ respectively, so that when $p > 1$, hazard increases, when $p < 1$, hazard decreases and if $p = 1$, the hazard will be constant over time (exponential model). For the PH model we reparametrize $\lambda = \exp(\beta_0 + \beta X)$ and for the AFT form is assumed $\frac{1}{\lambda^p} = \exp(\alpha_0 + \alpha X)$.

Therefore, survival function can be written as follows:

$$S(t) = \exp\{-[t * \exp\{-(\alpha_0 + \alpha X)\}]^p\}$$

and finally the risk of an event (here reflux is the event) by time t is computed with $1 - S(t)$.

In another analysis using the Cox

proportional hazard model we found that the parameter estimates (hazard ratio) were almost similar between the two methods (analysis available on request). The method of AFT model was used to be consistent with the work of Anderson et al (1991) (12) to estimate the predictive impact of variables from a single observation. Values from the first time of diagnosis ANH were used and the values of predictor variables were not changed during the follow up study.

To assess relative goodness of fit and the discriminatory ability of the models, log-likelihood statistic also C-Statistic (13, 14) was applied. All the HRs, calculated from the variable coefficients in the AFT model, have been presented as the effect of individual predictor variables.

Results

Clinical and demographical characteristics of 333 children identified with ANH are listed in Table 1. Mean diagnosis of ANH was 29.86

Table 1. Characteristics of 333 children with ANH

Variables	Status	No.	Proportion (%)
Gender	Boy	278	83.5
Consanguinity marriage	YES	80	24
Kidney disease background in parent	YES	19	5.7
UI	YES	159	47.7
Constipation	YES	145	43.5
UC	YES	130	39
UA	YES	130	39
HUN	YES	255	76.6
HN	YES	328	98.5
BWT	Abnormal	90	27
PVR	Abnormal	5	1.5
APD_Right	Abnormal	67	20.1
APD_Left	Abnormal	82	24.6
CA19_9baby	Abnormal	227	68.2
Sr	Abnormal	22	6.6
Cr	Abnormal	4	1.2
Urethra	Abnormal	254	76.3
Bladder	Abnormal	289	86.8
Direction of ANH	Bilateral	180	54.1
Baseline (Right)	Unilateral (Left)	90	27
Grade of ANH	Moderate	43	12.9
Baseline (Mild)	Severe	68	20.4
Week of diagnosis ANH*		29.86	6.006

*Mean (SD), UI or UTI: Urinary tract infection, UC: Urine culture, UA: Urine analysis, HUN: Hydroureteronephrosis, HN: Hydronephrosis, BWT: Bladder wall thickness, PVR: Post-void residual, APD: Anterior-posterior diameter, CA19_9baby: Carbohydrate antigen19-9, Sr: Sacral ratio, Cr: Urine creatinine, ANH: Antenatal hydronephrosis

Table 2. Result of accelerated failure time for Weibull regression

Variables	Status	Weibull		
		Coef	Std.Err	HR (CI.95%)
Week of diagnosis ANH		0.016	0.011	0.985 (0.966 , 1.006)
Gender*	Girl	0	-	1
	Boy	-0.446	0.190	1.501 (1.070 , 2.107)
UI	No	0	-	1
	Yes	-0.123	0.136	1.119 (0.878 , 1.426)
Constipation	No	0	-	1
	Yes	0.120	0.145	0.897 (0.693 , 1.161)
UC	No	0	-	1
	Yes	0.067	0.150	0.941 (0.719 , 1.230)
UA	No	0	-	1
	Yes	-0.214	0.148	1.215 (0.932 , 1.584)
HUN	No	0	-	1
	Yes	-0.042	0.164	1.040 (0.775 , 1.392)
BWT	Normal	0	-	1
	Abnormal	-0.068	0.153	1.064 (0.810 , 1.398)
APD_Right	Normal	0	-	1
	Abnormal	0.216	0.244	0.821 (0.531 , 1.270)
APD_Left	Normal	0	-	1
	Abnormal	0.245	0.222	0.800 (0.539 , 1.188)
Direction of ANH	Unilateral (Right)	0	-	1
	Bilateral	-0.178	0.189	1.176 (0.840 , 1.647)
	Unilateral (Left)	0.153	0.233	0.870 (0.575 , 1.318)
Severity of ANH*	Mild	0	-	1
	moderate	-0.414	0.254	1.457 (0.926 , 2.294)
	Severe*	-0.683	0.235	1.862 (1.223 , 2.837)
CA19-9-baby	Normal	0	-	1
	Abnormal	-0.179	0.153	1.177 (0.896 , 1.546)
Sr*	Normal	0	-	1
	Abnormal	-1.132	0.253	2.803 (1.767 , 4.447)
Urethra	Normal	0	-	1
	Abnormal	-0.106	0.167	1.101 (0.818 , 1.484)
Bladder	Normal	0	-	1
	Abnormal	-0.105	0.204	1.101 (0.764 , 1.585)
Kidney disease background in parent	No	0	-	1
	Yes	-0.060	0.287	1.056 (0.633 , 1.763)
Consanguinity marriage	No	0	-	1
	Yes	-0.256	0.159	1.262 (0.951 , 1.676)
Cons		8.280	0.586	
Ancillary parameters				P=0.911

*Significant variable

weeks with the standard deviation of 6.006. Of these patients 83.5% were boy and 24% had consanguinity marriage. 20.4% of all had ANH in severe level also 54.1% were bilateral. The highest abnormality was for bladder with 86.8% and the lowest was in PVR and Cr. Table 2 presents result of weibull accelerated failure time model.

The highest HR is seen for the “Sr” with 2.803 and the lowest for the “APD_Left” with 0.8 so one of them is very risky and the other one is protective. Table 3 presents result of the stepwise accelerated failure time models. Variety of AFT models for the outcome were used. Variables “Sr”, “gender”, “consanguinity marriage”, “severity of ANH” and “Direction of ANH” come to stepwise models step by step

from model A through E in Table 3 along with the HR for the all five predictor variables of reflux. The effect estimates for all these variables vary little across the models. The magnitude of the log-likelihood statistic similar to the C-statistics was the greatest one (the smallest one without considering the negative) in the full multivariate analysis (model E), although adding variable to model always increase the log-likelihood. The values of C-statistics for the five reflux models vary little from 3.727 to 4.885 and its p-value from 0.444 to 0.299. The p-value of 0.80 is usually regarded as boundary between acceptable and excellent discrimination (14). The discriminatory power of fit as measured by the log-likelihood and C-statistics are virtually equivalent for these models.

Table 3. Result from AFT models for the time of reflux

Predictor	Status	HR (CI .95)				
		A	B	C	D	E
Sr	Normal	1	1	1	1	1
	Abnormal	2.526 (1.624,3.928)	2.560 (1.646,3.983)	2.639 (1.694, 4.112)	2.651 (1.701,4.131)	2.676 (1.716,4.171)
gender	Girl	-	1	1	1	1
	Boy	-	1.542 (1.115,2.135)	1.563 (1.129,2.164)	1.546 (1.117,2.141)	1.486 (1.070,2.063)
Consanguinity marriage	No	-	-	1	1	1
	Yes	-	-	1.398 (1.067,1.832)	1.381 (1.054,1.810)	1.350 (1.029,1.770)
Severity of ANH (Severe level)	No	-	-	-	1	1
	Yes	-	-	-	1.380 (1.038,1.833)	1.347 (1.013,1.792)
Direction of ANH (Bilateral)*	No	-	-	-	-	1
	Yes	-	-	-	-	1.249 (0.983,1.587)
log likelihood		-556.813	-553.045	-550.248	-547.934	-546.268
C-statistic		3.727	4.784	4.996	4.885	4.885
P-value		0.444	0.310	0.288	0.299	0.299

*This variable was in the borderline ($0.05 < p < 0.1$) and important. So it was included in the model

Finally it should be mention that the data was fitted with an AFT survival model based on the weibull distribution. This model yeilds a linear function of the predictor variables X and coefficients α with an intercept α_0 as follows

$$L(X) = \alpha_0 + \alpha_1 X_1 + \dots + \alpha_5 X_5$$

(the model for the time to reflux event has five predictor variable)

Along with the shape parameter p , for a person with the particular predictor variables, the predicted survival at time t is given by

$$S(t) = \exp(-(t * \exp(-L(X)))^p)$$

So the risk of the event by time t is obtained as follows

$$1 - S(t)$$

Discussion

From five predictor variables in the Table 3, all of them were negatively related to the long-term incidence of reflux. All the five predictor variables were statistically significant and the difference between the value of the log-likelihood statistics among the models were modest. The variables, Sr, gender of child, consanguinity marriage, severity of ANH and Direction of ANH were hazardous. This study has some limitation in which has been reported only the experience of one hospital. Obtaining the result in other geographic areas, for managing the risk factors, require considering race, ethnicity of population as well as calender year of the experience.

Conclusion

Being interested to analyzing children detected with ANH and avaluating factors affecting on the time to occurrence VUR, this study analysed children diagnosed with ANH most of whom have VUR. It showed gender of child, severity of ANH and Sr in addition to some other clinical factors were related to the risk of occurence reflux. These information can prepare a guideline for helping the pregnant women on the postnatal effect of ANH.

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Conflicts of interests

The authors declare that there is no conflict of interest regarding the publication of this article.

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