ORIGINAL ARTICLE

Predicting Time to Reflux of Children With Antenatal Hydronephrosis: A Competing Risks Approach

Maryam Nazemipour[1], Abdol-Mohammad Kajbafzadeh[2], Kazem Mohammad[3], Abbas Rahimi Foroushani[3], and Mahmood Mahmoudi[3]

[1] *Department of Epidemiology and Biostatistics, School of Public Health, International Campus, Tehran University of Medical Sciences, Tehran, Iran*
[2] *Department of Pediatric Urology, Pediatric Urology Research Center, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran*
[3] *Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran*

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Abstract- The aim of this study was describing methodological aspects and applying a trivariate Weibull survival model using the competing risks concept to predict time to occurrence different types of reflux (unilateral (left, right) or bilateral) in children with antenatal hydronephrosis. Data from 333 children in Pediatric Urology Research Center of Children's Hospital Medical Center, affiliated with Tehran University of Medical Sciences was used. The effect of some demographic and clinical factors on child's reflux was studied. The assumption of independent between times of different types of reflux was evaluated. Of infants 80.5% were boy. The percentage of children experienced right, left and bilateral reflux or have been censored are 15.3%, 14.1%, 60.4% and 10.2% respectively. For the time of left reflux, variables, Week of diagnosis ANH, UC, UA, HUN, HN, APD_Right, Direction of ANH, CA19-9 baby, Urethra were significant. For the time of right reflux, variables, constipation, UC, UA, HUN, APD_Right, Direction and Severity of ANH, Bladder, and finally for the time of bilateral reflux, variables, Week of diagnosis ANH, Gender, UA, HUN, HN, APD_Left, Urethra, and Bladder were significant *P*<0.05. In the presence of competing risks, it is inappropriate to use the Kaplan-Meier method and standard Cox model which do not take competing risks into account. Trivariate Weibull survival model using competing risks not only is able to calculate the hazard rate of variables with different type of events but also it will be able to compare the hazard rate within the same type of event with different covariates.

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Introduction

The backflow of the urine from the bladder to the kidneys which provides a mechanism by that bacteria in the bladder can reach the kidney and produce pyelonephritis and reflux nephropathy, is termed vesicoureteral reflux, and it is one of the most anomalies in congenital detection. The prevalence of that in children is approximately about 1% (1-5).

VUR and the severity of that are thought to be correlated with the risk of developing urinary tract infection and permanent renal scarring that may lead to serious sequel later in life, such as hypertension, proteinuria, and end stage renal disease. With this description, detect of VUR as early as possible can minimize renal damage (6-9).

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. It is common to have incomplete event times (10,11).

Understanding almost all the inferential statistical analysis is related to the concepts of the probability distribution. The mathematical explanation that be an exclusive expression for individual probabilities so that a random variable will take each set of the specified values is known as probability density function.

In life data analysis, clinicians attempt to predict and investigate in a population, effects of some covariates and the association between some etiologies in patient's

Corresponding Author: M. Mahmoudi
Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 21 88950185, Fax: +98 21 88989127, E-mail address: mahmoodim@tums.ac.ir

life, by fitting a statistical distribution for a sample of life data. The parameters of the distribution for that set of data can be used to evaluate factors related to the interested etiological agent, with using a survival method for the specific times of failure which are related to the mean of life.

There is a wide range of literature about parametric distribution (Exponential, Weibull, Lognormal, and Log-logistic) for analyzing time to occurrence or diagnosis data in medical researches (12-15). For instance applying Weibull and Exponential regression for modeling survival data of CABG patients (16). There are also lots of researchers who have obtained some parametric regressions for analyzing time to occurrence data (12,13,17-22).

In some situations, it is not appropriate to apply the usual survival methods. One of this situation is when we involving competing risks which have been expressed by different authors in several different ways. The competing risk model is designed for multiple events (statistical events). Some authors consider the event of interest as the failure and the other events as censored (23,24). We define the concept of competing risk as the situation where we face with more than one type of event that competes with each other to be observed so that one type of event preclude the occurrence of other events under investigation (25,26).

The aim of this study was, applying the method of competing for risk for analyzing factors related to the time of occurrence different types of reflux (unilateral (left, right) or bilateral). Another important issue in this research was to investigate the postnatal etiological effect of antenatal hydronephrosis (ANH) on being unilateral (left or right) or bilateral reflux which has been considered as three competing risks in this study. ANH refers to distension and dilation of the renal pelvis and calyces. It is one of the most common abnormality detected prenatally in ultrasound imaging, and it is one of the most important etiology of vesicoureteral reflux (VUR) in the postnatal evaluation. To study time to occurrence any specific event, we consider the time to each type of reflux be a random variable which follows the Weibull distribution. Thus a trivariate Weibull survival model is proposed.

Materials and Methods

In this study, 333 children with ANH who had been admitted to Pediatric Urology Research Center of Children's Hospital Medical Center, affiliated with Tehran University of Medical Sciences between 2002 and 2003 were enrolled. They were followed up for 8 years for measuring time to occurrence and type of their reflux. Information on their demographic and clinical as well as the type and time of diagnosis VUR (occurrence first statistical event) after ANH was extracted from their medical records.

Time to event is the random variable in survival analysis. Therefore the first step is defining the event so that we are able to measure time to the event. In this study, the event has been considered different types of reflux.

To evaluate the association between times of occurrence different types of reflux, we define R_r, R_l and R_b denoting right, left and bilateral reflux respectively. Also we consider T_1 as the time to occurrence R_r, T_2 as the time to occurrence R_l and T_3 as the time to occurrence R_b. In other word R_r, R_l and R_b are three events that compete with each other for occurring in each child after experiencing ANH. With these definitions it is said that failure has happened for a child due to occurrence each type of the event (R_i $,(i = r, l, b)$) and he/she is considered as a censored when none of them occur before the end of the study period.

With the assumption of independence between the three types of reflux, we depicted the cumulative hazard curves base on Kaplan-Meier estimates for each type of event in figure 1.

Constant slopes of the hazard curve for unilateral reflux (Right and Left) suggest that T_1 and T_2 almost have constant hazard rate while T_3 has decreasing hazard rate. Based on these findings we choose Weibull distribution as the marginal survival function for T_1, T_2 and T_3 and that is why we use trivariate Weibull survival function.

We know the survival function of the Weibull is $\exp(-\left(\frac{t}{\lambda}\right)^p)$ with the hazard function $\frac{p}{\lambda^p}t^{p-1}$. P in this model is called the shape parameter because it determines the shape of the hazard curve so that if this is greater than 1, the hazard rate increases, if P is less than 1, the hazard rate decreases, and if it is equal 1, the hazard rate remains constant (Exponential).

Analyzing data with trivariate weibull survival function:

The multivariate Weibull model for the competing risk survival function of T_1 , T_2 and T_3 in general is as follows (27).

$$S_{T_1,T_2,T_3}(t_1, t_2, t_3) = exp\left\{-\left[(\frac{t_1}{\lambda_1})^{\frac{p_1}{\alpha}} + (\frac{t_2}{\lambda_2})^{\frac{p_2}{\alpha}} + (\frac{t_3}{\lambda_3})^{\frac{p_3}{\alpha}}\right]^{\alpha}\right\}$$

Where α , $(0 < \alpha \leq 1)$ is the association parameter among the three random variable T_1 , T_2 and T_3. So in a situation like our study that there is no association between the three types of reflux, α will be equal 1, and the model will be as follows

$$S_{T_1,T_2,T_3}(t_1, t_2, t_3) = exp\left\{-\left[(\frac{t_1}{\lambda_1})^{p_1} + (\frac{t_2}{\lambda_2})^{p_2} + (\frac{t_3}{\lambda_3})^{p_3}\right]\right\}$$

In this formula, the estimates of the parameters will be obtained by maximizing the log-likelihood function which has been derived from the trivariate Weibull function.

The likelihood function is

$$L(\theta) = \prod_{i=1}^{N}\left[-\frac{\delta}{\delta T_1}S_{T_1,T_2,T_3}\left(t_{1_i}, t_{2_i}, t_{3_i}\right)\right]^{f_{1_i}} \times \left[-\frac{\delta}{\delta T_2}S_{T_1,T_2,T_3}\left(t_{1_i}, t_{2_i}, t_{3_i}\right)\right]^{f_{2_i}} \times \left[-\frac{\delta}{\delta T_3}S_{T_1,T_2,T_3}\left(t_{1_i}, t_{2_i}, t_{3_i}\right)\right]^{f_{3_i}} \times \left[S_{T_1,T_2,T_3}(t_c, t_c, t_c)\right]^{1-f_{1_i}-f_{2_i}-f_{3_i}}$$

Where $t_{1_i}, t_{2_i}, t_{3_i}$ are the observed times of R_r, R_l and R_b respectively for the ith child. t_c is the observed censored time for the children that have not had reflux before the end of the study period, and $f_{1_i}, f_{2_i}, f_{3_i}$ are case indices in connection with the event types.

For those whose $f_1 = 1$, all other the case indices are 0 and the likelihood function equals to the first component so that it accounts for the children who have experienced only R_r. Similarly, if $f_2 = 1$, then all other the case indices are 0 and, the likelihood function equals to the second component and, it accounts for children who have experienced only R_l. In the same way if $f_3 = 1$ then all other the case indices are 0 and the likelihood function equals to the third component and it, accounts for children who have experienced R_b. Being all the f_j, $j = 1, 2, 3$ equal to zero, causes the likelihood function equals to the fourth component so that it is accounted for the children who have experienced none of the reflux types by the end of the study or are censored. Thus the times in that condition will be equal to the t_c.

If there is an association between two events, it can be derived by extending the bivariate case of Lawless (13).

In this study the number and percentage of the children who have experienced R_r, R_l, R_b or they have been censored are 51(15.3%), 47(14.1%), 201(60.4%) and 34(10.2%) respectively.

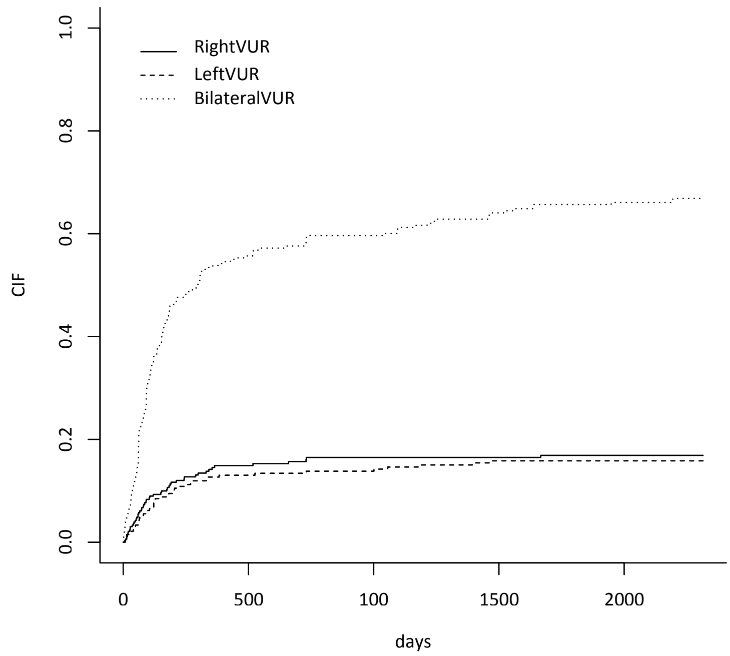

Figure 1. Kaplan-Meier cumulative hazard of T_1 , T_2 and T_3(right, left and bilateral)

Table 1. The characteristics of 333 children with ANH

Variables	Status	No.	Proportion (%)
Gender	Boy	268	80.5
Consanguinity marriage	YES	77	23.1
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	38	11.4
Cr	Abnormal	4	1.2
Urethra	Abnormal	254	76.3
Bladder form	Abnormal	289	86.8
Direction of ANH	Bilateral	180	54.1
	Unilateral(Left)	90	27
Grade of ANH	Moderate	43	12.9
	Severe	62	18.6
Week of diagnosis ANH*	--	29.86	6.006

*mean(SD)
UI: 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

Results

After showing the characteristic of the children in table 1, we fitted the model with no covariate which the results have been demonstrated in table 2. All parameter is significantly different from zero, and it can be seen that all estimates of the parameter P ,for each type of reflux, are less than 1 which indicate T_1 , T_2 and T_3 have decreasing hazard rate. From the parameters estimates in table 2 we were able to calculate the hazard rates of T_1, T_2 and T_3 against t which can be seen in figure 2.

Table 2. The parametric estimation of trivariate weibull distribution with Std. error

Parameters	Estimate	Std. error	CI.95%	$h(t_j)$
p_1	0.921	0.094	(0.736 , 1.105)	$h(t_1) = \frac{p_1}{\lambda_1^{p_1}} t_1^{p_1-1}$
λ_1	294.628	44.814	(206.795 , 382.461)	
p_2	0.900	0.094	(0.715 ,1.085)	$h(t_2) = \frac{p_2}{\lambda_2^{p_2}} t_2^{p_2-1}$
λ_2	372.022	60.319	(253.799 ,490.245)	
p_3	0.760	0.039	(0.684 ,0.836)	$h(t_3) = \frac{p_3}{\lambda_3^{p_3}} t_3^{p_3-1}$
λ_3	257.768	24.618	(209.518 ,306.018)	

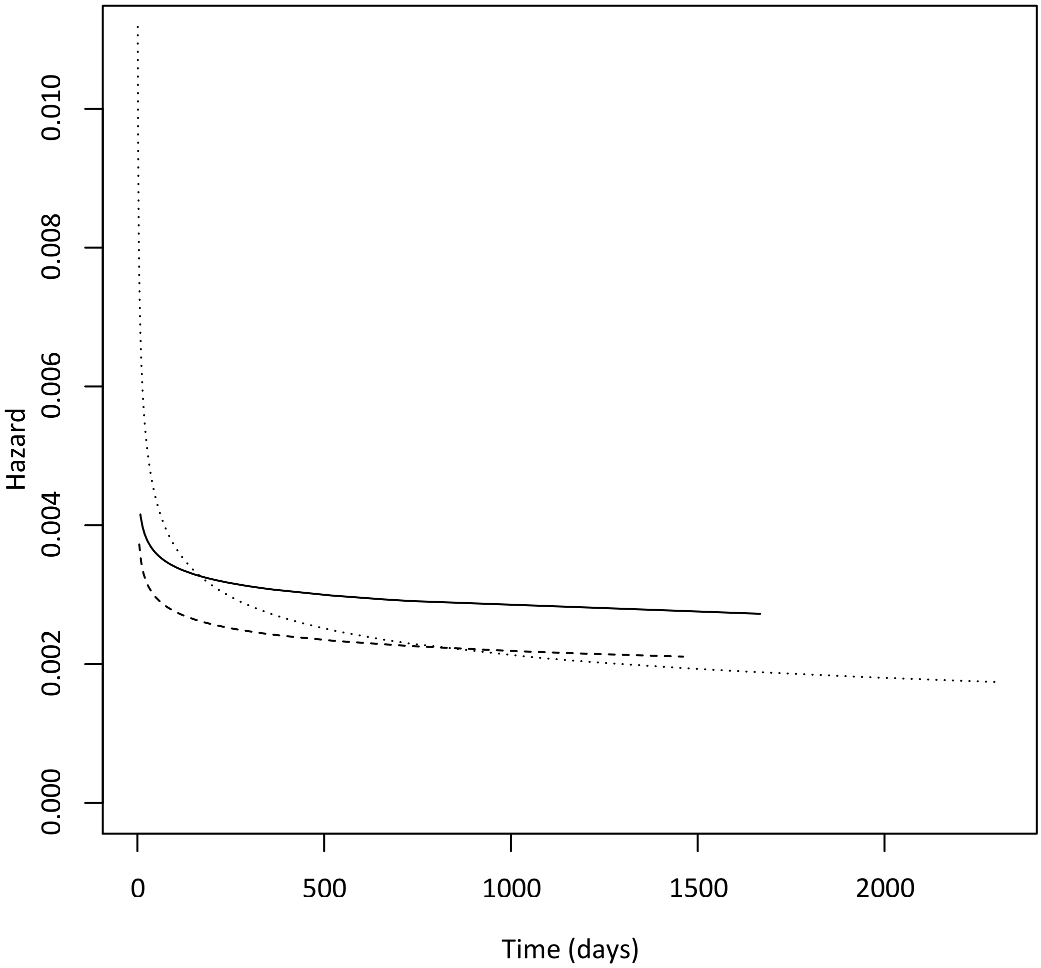

Figure 2. Trivariate Weibull hazard of T_1 , T_2 and T_3 that has depicted by solid, dashed and dotted lines respectively

Contributing the predictor variables (X) in the model, we reparametrized each scale parameter $\lambda_j, (j = 1, 2, 3)$ toward the exponential function of the covariates so that $\frac{1}{\lambda_j{}^p} = \exp(\beta_{0j} + \beta_{1j}x_{1j} + \cdots + \beta_{nj}x_{nj})$. So the model was fitted with the most defined covariates in table1.

The parameters estimate have been shown in table $3a$, $3b$ and $3c$ for the right, left and bilateral reflux respectively. Being eligible for some comparisons, we use Carrol (2003) formula to calculate hazard ratio or relative hazard for the Weibull distribution. It also gave a formula for calculating the variance of the hazard ratio (28).

As we can see in the table$3a$ the results show that, having abnormality for constipation, UC and APD_Right, decrease the hazard rate or delay the occurrence of the right reflux P<0.05. But having more severe and getting involved both kidney with ANH also having HUN and abnormality in UA and in the form of bladder, increase the hazard rate or decrease (accelerate) the time of occurrence right reflux P<0.05.

In the table 3b having abnormality for APD_Right, urethra, and Sr also in UA decrease the hazard rate or delay the occurrence of the left reflux P<0.05. But delay in diagnosing ANH, getting involved both kidney or the left one with ANH towards just the right one also having HN, HUN also abnormality in UC and CA19-9, increase the hazard rate or reduce (accelerate) the time of occurrence left reflux P<0.05.

Finally, in table$3c$ we can see that being girl, occurring ANH sooner, having HUN and HN also abnormality in UA, being abnormal in APD_right, CA19-9, urethra and form of bladder, increase the hazard rate or accelerate occurrence of bilateral reflux P<0.05

Table 3a. Parametric estimates of trivariate weibull model for right reflux with hazard ratio (HR) and their confidence interval

Variables	Status	Coef	s.e(β)	HR	CI.95%for HR
Constant	--	-3.807	--	--	--
Week of diagnosis ANH	--	0.009	0.005	0.992	0.983 1.001
Gender	Girl	0	--	1	--
	Boy	0.124	0.078	0.892	0.766 1.039
UI	No	0	--	1	--
	Yes	0.037	0.236	0.967	0.609 1.534
Constipation*	No	0	--	1	--
	Yes	0.473	0.209	0.648	0.430 0.975
UC*	No	0	--	1	--
	Yes	0.811	0.218	0.475	0.310 0.728
UA*	No	0	--	1	--
	Yes	-0.796	0.258	2.077	1.252 3.444
HUN*	No	0	--	1	--
	Yes	-0.556	0.169	1.666	1.196 2.321
HN	No	0	--	1	--
	Yes	-0.063	0.143	1.060	0.801 1.402
BWT	Normal	0	--	1	--
	Abnormal	-0.305	0.277	1.324	0.769 2.280
APD_Right*	Normal	0	--	1	--
	Abnormal	0.820	0.277	0.471	0.274 0.811
APD_Left	Normal	0	--	1	--
	Abnormal	0.341	0.333	0.731	0.380 1.405
Direction of ANH*	Bilateral	-0.913	0.258	2.312	1.394 3.835
	Unilateral(Left)	-0.158	0.333	1.156	0.601 2.221
	Unilateral (Right)	0	--	1	--
Severity of ANH*	Mild	0	--	1	--
	Severe	-1.429	0.354	3.712	1.856 7.422
	Moderate	-1.215	0.333	3.051	1.588 5.864
CA19_9baby	Normal	0	--	1	--
	Abnormal	-0.043	0.162	1.040	0.757 1.430
Sr	Normal	0	--	1	--
	Abnormal	-0.363	0.500	1.396	0.524 3.718
Urethra	Normal	0	--	1	--
	Abnormal	-0.216	0.151	1.219	0.907 1.638
Bladder*	Normal	0	--	1	--
	Abnormal	-0.771	0.154	2.030	1.500 2.747
Kidney disease background in parent	No	0	--	1	--
	Yes	0.251	0.707	0.794	0.199 3.176
Consanguinity marriage	No	0	--	1	--
	Yes	-0.227	0.354	1.232	0.616 2.463
P		0.918	--	--	--

Table 3b. Parametric estimates of trivariate Weibull model for left reflux with hazard ratio (HR) and their confidence interval

Variables	Status	Coef	s.e(β)	HR	CI.95% for HR
Constant		-1.386	-	-	-
Week of diagnosis ANH*		-0.043	0.005	1.041	1.031 1.051
Gender	Girl	0	-	1	-
	Boy	0.108	0.084	0.903	0.767 1.064
UI	No	0	-	1	-
	Yes	0.233	0.218	0.802	0.523 1.231
Constipation	No	0	-	1	-
	Yes	0.266	0.218	0.778	0.507 1.194
UC*	No	0	-	1	-
	Yes	-0.895	0.229	2.328	1.485 3.650
UA*	No	0	-	1	-
	Yes	0.477	0.213	0.638	0.420 0.969
HUN*	No	0	-	1	-
	Yes	-0.716	0.169	1.965	1.411 2.737
HN*	No	0	-	1	-
	Yes	-1.386	0.146	3.699	2.779 4.923
BWT	Normal	0	-	1	-
	Abnormal	-0.097	0.289	1.096	0.622 1.930
APD_Right*	Normal	0	-	1	-
	Abnormal	0.981	0.408	0.396	0.178 0.882
APD_Left	Normal	0	-	1	-
	Abnormal	-0.206	0.289	1.214	0.690 2.138
Direction of ANH*	Bilateral	-1.799	0.333	5.464	2.843 10.500
	Unilateral(Left)	-0.493	0.167	1.592	1.148 2.207
	Unilateral (Right)	0	-	1	-
Severity of ANH	Mild	0	-	1	-
	Severe	-0.542	0.500	1.668	0.626 4.444
	Moderate	-0.829	0.408	2.187	0.983 4.868
CA19_9baby*	Normal	0	-	1	-
	Abnormal	-0.540	0.180	1.666	1.171 2.368
Sr*	Normal	0	-	1	-
	Abnormal	1.237	0.500	0.311	0.117 0.829
Urethra*	Normal	0	-	1	-
	Abnormal	0.453	0.164	0.652	0.473 0.900
Bladder	Normal	0	-	1	-
	Abnormal	-0.117	0.151	1.117	0.831 1.501
Kidney disease background in parent	No	0	-	1	-
	Yes	-0.407	0.447	1.468	0.611 3.528
Consanguinity marriage	No	0	-	1	-
	Yes	-0.510	0.333	1.618	0.842 3.110
P		0.944		-	-

*most of the individuals in this group (left reflux) have the same HN

Table 3c. Parametric estimates of trivariate Weibull model for bilateral reflux with hazard ratio (HR) and their confidence interval

Variables	Status	Coef	s.e(β)	HR	CI.95%for HR
Constant		-3.177	--	--	--
Week of diagnosis ANH*		0.007	0.002	0.995	0.990 1.000
Gender*	Girl	0	--	1	--
	Boy	0.556	0.038	0.652	0.605 0.702
UI	No	0	--	1	--
	Yes	-0.131	0.098	1.106	0.913 1.341
Constipation	No	0	--	1	--
	Yes	-0.019	0.107	1.015	0.822 1.252
UC	No	0	--	1	--
	Yes	0.219	0.113	0.845	0.678 1.053
UA*	No	0	--	1	--
	Yes	-0.453	0.113	1.417	1.137 1.767
HUN*	No	0	--	1	--
	Yes	-0.262	0.080	1.224	1.047 1.431
HN*	No	0	--	1	--
	Yes	-1.251	0.071	2.621	2.280 3.013
BWT	Normal	0	--	1	--
	Abnormal	0.198	0.129	0.859	0.667 1.106
APD_Right	Normal	0	--	1	--
	Abnormal	0.362	0.158	0.757	0.555 1.032
APD_Left*	Normal	0	--	1	--
	Abnormal	-0.444	0.144	1.407	1.061 1.868
Direction of ANH	Bilateral	0.196	0.086	0.860	0.726 1.018
	Unilateral(Left)	0.170	0.169	0.877	0.630 1.222
	Unilateral (Right)	0	--	1	--
Severity of ANH	Mild	0	--	1	--
	Severe	-0.153	0.156	1.125	0.828 1.527
	Moderate	-0.339	0.229	1.298	0.828 2.035
CA19_9baby	Normal	0	--	1	--
	Abnormal	-0.220	0.086	1.185	1.000 1.404
Sr	Normal	0	--	1	--
	Abnormal	-0.229	0.189	1.193	0.824 1.728
Urethra*	Normal	0	--	1	--
	Abnormal	-0.252	0.082	1.214	1.033 1.427
Bladder*	Normal	0	--	1	--
	Abnormal	-0.371	0.076	1.331	1.146 1.545
Kidney disease background in parent	No	0	--	1	--
	Yes	-0.447	0.301	1.411	0.781 2.547
Consanguinity marriage	No	0	--	1	--
	Yes	-0.102	0.140	1.082	0.822 1.423
P	--	0.770	--	--	--

Discussion

In this paper we focus on methodological aspects and applying a trivariate Weibull survival model using the competing risks concept to predict time to occurrence different types of reflux [unilateral (left, right) or bilateral] in children with antenatal hydronephrosis. The assumption of independence time to occurrence of different types of reflux were assumed. In the presence of competing risks, it is inappropriate to use the Kaplan-Meier and standard Cox model which does not take competing risk into account. Trivariate Weibull survival model using the competing risks not only is able to calculate the hazard rate of variables with different types of events but also it will be able to compare the hazard rate within the same type of event with different covariates. The model was fitted with no covariate, and the results are in table 1. All the parameters estimate are almost significantly different from zero. The shape parameters also were shown that is less than 1 which indicates the hazard rate of the events has been decreasing. From the parameters estimated in table 2, we can calculate the hazard rate of T_1, T_2 and T_3 at t. As we can see in the table 3a, 3b and 3c there are several significant variables in common for the three type of reflux like UA, HUN, APD_Right or Left, Bladder. However, from table 3a and 3b more common variables affecting on the left and right reflux with the same direction.

We used a trivariate Weibull model to study time of different direction of reflux by assuming independence between times. By using the trivariate Weibull model not only we were able to calculate the hazard rate for a random variable which diagnosis time of individuals was facing at any given reflux type, but also we were able to compare the hazard rates in the same type of reflux with different covariates. The trivariate Weibull model can be extended to a multivariate model with higher dimension or in other words, is defined with more type of events.

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