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Original Article

Methods of competing risks analysis of time to occurrence of reflux among children with antenatal hydronephrosis

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ABSTRACT

Background & Aim: We aimed to describe a standard survival analysis, so that we can analyze some factors related to the time of occurrence of different types of reflux (unilateral-left, unilateral-right, and bilateral) in children with antenatal hydronephrosis (ANH) and to provide an approach taking competing risks into account.
Methods & Materials: We used data of 193 children that was collected from Pediatric Urology Research Center of Children's Hospital Medical Center, affiliated to Tehran University of Medical Sciences, Iran. The cause-specific and subdistribution hazard were computed. $P < 0.05$ was considered as statistically significant. R packages were used for analyzing the data.
Results: Among these infants (36 girls, 157 boys), 117 (68%) cases had bilateral reflux as the event of interest. The variables "Sex" and "Direction of ANH (in bilateral level)" were significantly different ($P<0.05$), while "Severity of ANH (in moderate level)" and "Number of other kidney diseases beside ANH and vesicoureteral reflux (VUR)" were borderline. The cumulative incidence derived from the competing risks approach was at a lower level of estimate in comparison with the Kaplan-Meier method. The cumulative incidence curve depicted for the bilateral reflux in subgroups of the sex variable, confirmed the effect of sex.
Conclusion: In the competing risks framework, it is inappropriate to use the Cox and Kaplan-Meier methods, which do not take competing risks into account. Multivariate regression model like the subdistribution hazard model besides the cumulative incidence curve are recommended.

Introduction

Survival analysis is a statistical tool, which has been applied in medical research widely to explore the duration of time from a certain time until occurrence of an event or events (1, 2). It is common to have incomplete event times. In this framework, there are some situations in which it is not appropriate to apply the usual survival methods. One of those is when we face with more than one event or competing risks.

The situation involving the competing risks has been expressed by different authors and in several different ways. Since many of these authors have taken different aspects into consideration when doing it, a few of them are presented here to give the best picture possible.

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The competing risks model has been designed for multiple events. In these situations, some authors consider the event of interest as failure and every other event as censored, also they assume independency between the time to failure and censoring mechanism (3, 4) although this assumption cannot be verified.

The concept of the competing risks is defined as the circumstances where more than one type of event compete with each other to be observed so that, one type of event precludes the occurrence of other events under investigation (5, 6).

The aim of this study was applying the method of the competing risks for analyzing the factors related to the time of occurrence of vesicoureteral reflux (VUR), which is defined as the return of urine from bladder to the ureters (7) that provides a mechanism by which bacteria in the bladder can reach the kidney and produce pyelonephritis and reflux nephropathy (8).

Another important issue in this research was to investigate the postnatal effects of antenatal hydronephrosis (ANH) on unilateral (left or right sided) or bilateral reflux, which was considered as three competing risks in this study. The 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 one of the most important reasons for the prevalence of VUR, which is the most common congenital anomaly detected in postnatal evaluation. So, this information can help pregnant women on the postnatal impact of ANH.

The VUR in Caucasian has an estimated prevalence about 1% and this is one the most common anomalies in congenital detection (9-11). This backflow of the urine from bladder to the kidneys and severity of that is considered to be correlated with the risk of developing permanent renal scarring that may lead to serious sequelae later in life such as hypertension, proteinuria, and end-stage renal disease (12, 13). Many children are recognized after having urinary tract infections (UTI), also with renal damages. So, detecting the VUR as early as possible can minimize the renal damages (14).

Methods

A total of 193 children with ANH were enrolled in this study, who nearly most of them had VUR and had been admitted to Pediatric Urology Research Center of Children's Hospital Medical Center affiliated to Tehran University of Medical Sciences, Iran, between 2002 and 2003. They were followed up for at least five years for measuring the type, unilateral (right or left sided) or bilateral, and time of occurrence of their reflux as three competing events. Information on their demographic, clinical and family characteristics as well as the type and time of occurrence of first event after ANH were extracted from their medical records and by phoning their family. The direct parametric method was applied to estimate the cumulative incidence function (CIF) of competing risks while we adjusted for the effects of some covariates. Data analysis was done using R software version 2.14.1 and P-value < 0.05 was considered statistically significant.

In this study, we evaluated children detected with ANH and mostly with VUR. This information can prepare a guide for helping pregnant women on the postnatal impact of ANH. Our findings were compared with the results obtained from analyzing data in which competing risks had not been considered.

Statistical methods

a. Survival with single event time

Suppose T is a random variable, representing time until occurrence of an event of interest or survival time. Survival function at time t is shown with $S(t)$. It denotes the probability that the survival time be beyond the t, and it is given by $S(t) = p(T > t)$. Hazard function or hazard rate, which is defined by:

$h(t) = \lim_{\Delta t \to 0} \left\{ \frac{p(t \le T < t+\Delta t | T \ge t)}{\Delta t} \right\}$, specifies the instantaneous death rate or cause-specific failure rate at time t, given that the individual survives until the time t or the event of interest has not occurred prior to the time t. The hazard function for the Cox proportional hazard model associated with the covariate vector X, with t as

the time to event, has the following form: $h(t;X) = h_0(t)\exp(\beta' X)$, in which $h_0(t)$ is called baseline hazard function (BHF) and it does not have to be specified. The cumulative hazard function given X, is defined by $H(t;X) = H_0(t)\exp(\beta' X)$ where $H_0(t)$ is called cumulative baseline hazard and it means $H_0(t) = \int_0^t h_0(v)dv$. By these definitions the association between the cumulative hazard function and survival function can be written as follows: $S(t) = \exp(-H(t))$.

b. Competing risks

The methods based on the cumulative incidence function are the best method for analyzing the competing risks, which are often of interest for medical researchers and it is used as a good way of showing the results over time (15, 16). Hereof, Fine and Gray introduced a regression model for the cumulative incidence function and proprietary implementation for analyzing the competing risks situations, so that with applying this model we can find the effect of covariate on it (6, 17).

The cumulative incidence function of kth event (CIF_k) is known as the subdistribution function of the event k, and is defined as the probability of failing from a specific cause k in the presence of other competing events (6, 16, 18).

If $h_k(t;X)$ is considered as the hazard of subdistribution for the event k, then under the assumption of proportionality for the hazard (19-21), we can define:

$h_k(t;X) = h_{0k}(t)\exp(\gamma' X)$

The CIF_k as the subdistribution of the event k is as follows:

$$F_k(t;X) = 1 - \exp(-\int_0^t h_k(u;X)du)$$

And the hazard of subdistribution for the event type k is defined as (18):

$h_k(t;X) = \lim_{\Delta t\to 0}\left\{\frac{p(t\le T<t+\Delta t, c=k \mid T>t \text{ or } (T\le t \text{ and } c\neq k))}{\Delta t}\right\} = \frac{-d\ln(1-F_k(t;X))}{dt}$,

where the variable c indicates the event type in this formula.

The relationship between the hazard of subdistribution, subdensity and subdistribution function, which demonstrates covariates directly affect the CIF (19, 21), is expressed as follows:

$$h_k(t;X) = \frac{f_k(t;X)}{1 - F_k(t;X)}$$

Besides, Gray's test is used for comparing the CIF for various patient groups (18).

In this paper the estimate of CIF for the all specific events, also covariate's coefficients, have been calculated by the partial likelihood approach in the form of standard Cox model.

c. Cause-specific hazard model

With the assumption of non-informative censoring, the cause-specific hazard model is usually applied for analyzing the competing risks data (17, 22). In this classical method, for analyzing each specific event, that event is considered as failure and occurrence of other events are considered as censored. Under this assumption, the censored patient would have the same probability of experiencing the event of interest like other patients at risk, who have remained under the study yet, if she/he did not fail. This assumption, however, cannot be verified (22). In other words, with this assumption, the probability of a specific event is estimated in an ideal world where the other events have been omitted (6, 23).

In case of being interested to only one failure type, the analysis must be just restricted to estimate the hazard ratio for that type of event. So, the cause-specific hazard function for the event type k as the event of interest is defined as follows:

$$h_k(t) = \lim_{\Delta t\to 0}\left\{\frac{p(t \le T < t+\Delta t \mid T \ge t)}{\Delta t}\right\}$$

T in this formula is the time to failure from the event k, $k = (1,2,3)$ (#event type). In addition, the Cox proportional hazard model or cause-specific hazard model for the event type k, with the predictors X, has the following form:

$$h_k(t;X) = h_{0k}(t)\exp[\sum_{i=1}^{p}\beta_{ik}x_i] \quad k = (1,2,3)$$

In this model β_{ik} allows the effect of x_i to be different for each event type.

The application of the Cox regression models for the cause-specific hazard has some advantages. They are so easy to fit and they provide single rate ratio interpretations.

However, this model does not provide a simple relationship between the covariates and interpretation of CIF (20, 21, 24).

Results

Characteristics of 193 infants identified with ANH are listed in table 1. Of these patients 157 cases (81.3%) were male and 15.7% had reflux in the right kidney, 16.3% in the left kidney and 68% had bilateral reflux. Mean and standard deviation for the time of diagnosis of unilateral (right, left) or bilateral reflux was 145 ± 147, 269 ± 395 and 242 ± 401 days, respectively.

Table 1. Characteristics of the children with antenatal hydronephrosis and their family

Variables	Status	Number (%)
Sex	Girl	36 (18.7)
	Boy	157 (81.3)
Severity of ANH	Mild	134 (69.4)
	Moderate	26 (13.5)
	Severe	33 (17.1)
Direction of ANH	Unilateral (Right)	31 (16.1)
	Unilateral (Left)	52 (26.9)
	Bilateral	110 (57.0)
Severity of VUR*	Mild	41 (23.8)
	Moderate	39 (22.7)
	Severe	92 (53.5)
Consanguineous marriage	No	145 (75.1)
	Yes	48 (24.9)
Kidney disease background in parents	No	182 (94.3)
	Yes	11 (5.7)
History of abortion before the child	No	139 (72.0)
	Yes	54 (28.0)
Treatment	Medicine	72 (37.3)
	Surgery	121 (62.7)
Outcome (types of VUR)*	Unilateral (Right)	27 (15.7)
	Unilateral (Left)	28 (16.3)
	Bilateral	117 (68.0)
		Mean (SD)
Time of outcome (Days)	Right	145 (147)
	Left	269 (395)
	Both	242 (401)
Number of other kidney diseases beside ANH and VUR		0.82 (0.80)
Mother's age of delivery (Years)		29.30 (5.36)
Birth spacing (Years)		5.28 (3.34)

* Has been computed from 172 cases because 21 cases were censored.
ANH: Antenatal hydronephrosis, VUR: Vesicoureteral reflux

Mother's mean age of delivery at the time of their birth along with the standard deviation of that age was 29.3 ± 5.36 years old. Mean and standard deviation for the variable "birth spacing", which is the birth interval between the child and his/her previous sibling, was 5.28 ± 3.34 years and 116 (60.1%) of them had some other kidney diseases beside the ANH and VUR. At the end of the follow up period, 21 (10.9%) of patients who did not have reflux were considered as censored.

An association was found between the severity and type of reflux ($P < 0.001$). It has been shown in table 2 that with increasing the severity of reflux the number of children with bilateral reflux increases. In other words, in the high levels of severity, the probability that VUR be bilateral is more than the lower levels.

Table 2. The association between the severity and the type of reflux

Severity / Type	Mild	Moderate	Severe	Total
Unilateral VUR (Right)	13 (7.6)*	6 (3.5)	8 (4.6)	27 (15.7)
Unilateral VUR (Left)	10 (5.8)	7 (4.1)	11 (6.4)	28 (16.3)
Bilateral VUR	18 (10.5)	26 (15.1)	73 (42.4)	117 (68)
Total	41 (23.8)	39 (22.7)	92 (53.5)	172 (100)

* Proportion from 172 cases.
VUR: vesicoureteral reflux

The estimate of CIF for the all possible outcomes, which have been considered as three competing risks, can be seen in figure 1.

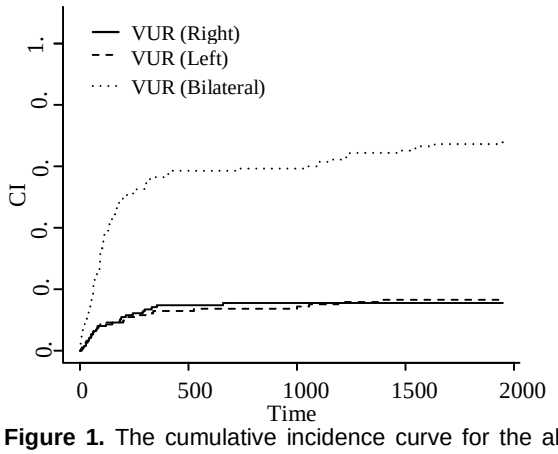

Figure 1. The cumulative incidence curve for the all possible outcomes, taking competing risks approach
VUR: Vesicoureteral reflux; CIF: Cumulative incidence function

The complement of the Kaplan-Meier (KM) curve and the estimate of CIF for the time to occurrence of bilateral reflux, which have been obtained by the two methods of estimate (KM method and competing risks method), are shown in figure 2. The cumulative incidence in the competing risks approach was at a lower level of estimate compared to the KM method. In addition, the difference between them incremented by increasing in the time of follow-up. In other word, the probability of occurrence of bilateral reflux using the KM approach was wrongly over estimated and this difference becomes more significant when the period of follow up is getting larger.

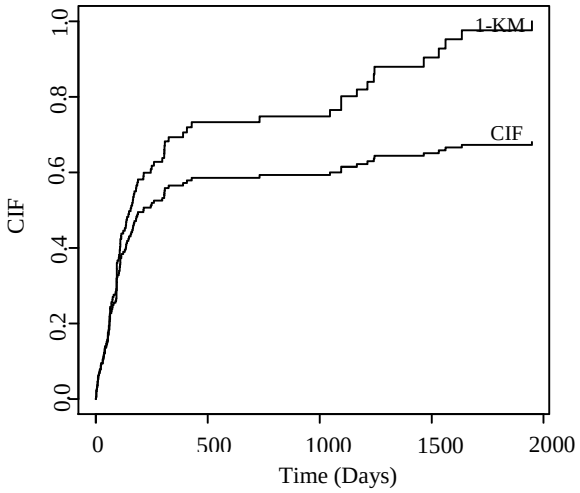

Figure 2. The complement of the Kaplan-Meier estimate and the cumulative incidence curve for the bilateral reflux
CIF: Cumulative incidence function

Cause-specific and cumulative incidence by regression model:

The results of modeling the hazard of subdistribution (Fine-Gray model) and cause-specific hazard for unadjusted (univariate) and adjusted (multivariate) effect of covariates for all the possible events (right, left and bilateral reflux) are shown in table 3 and table 4. The CIF derived from the Fine-Gray model has been depicted in figure 3, only for the bilateral reflux as the event of interest and just in each group of sex. It can be seen that males presented a higher risk of bilateral reflux in comparison with females.

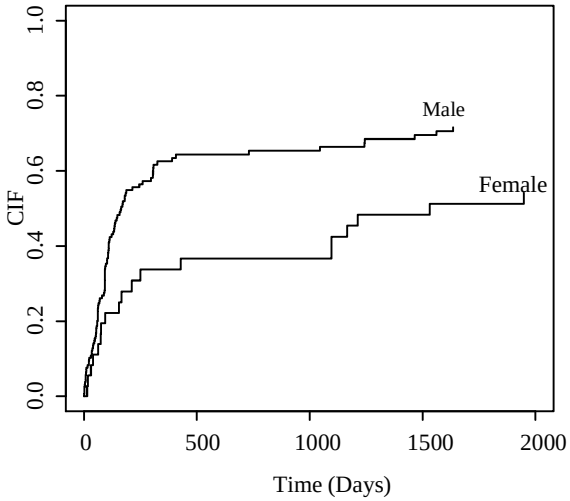

Figure 3. The cumulative incidence curve for the bilateral outcome in each group of sex (Gray's test: P = 0.015)
CIF: Cumulative incidence function

Considering the subdistribution multivariate model for the bilateral reflux, variables "sex" and "direction of ANH (bilateral level)" were statistically significant ($P < 0.05$), also variables "severity of ANH (moderate level)" and "number of other kidney diseases beside ANH and VUR" were borderline.

According to the unadjusted models (cause-specific hazard and subdistribution hazard) for the bilateral reflux, it can be seen that variables "sex" and "direction of ANH (bilateral level)" were significant. In addition, the effects of those variables for the both models were quite close. However, in the cause-specific hazard model "birth spacing" also "severity of ANH (moderate level)" were significant and "number of other kidney diseases beside ANH and VUR" was borderline unlike the subdistribution hazard model that just "severity of ANH" in both level were in borderline.

In the cause-specific multivariate model alike the subdistribution model, risk of having the bilateral reflux was more for the males comparing to females [P = 0.003; hazard ratio (HR): 2.23; 95%CI: 1.31, 3.81]. Moreover, variables "severity of ANH (moderate level)" and "number of other kidney diseases beside ANH and VUR" were significant, but "direction of ANH (bilateral level)" and "birth spacing" were borderline (P = 0.090 and P = 0.056, respectively).

Table 3. The Fine-Gray model for the right, left and the bilateral reflux

Type	Variables	Status	Univariate (Unadjusted)			Multivariate (Adjusted)		
			HR	CI 95%	P value	HR	CI 95%	P value
Right VUR	Sex	Girl	1.00	-	-	1.00	-	-
		Boy	1.13	(0.44, 2.87)	0.800	1.86	(0.69, 5.01)	0.220
	Severity of ANH	No	1.00	-	-	1.00	-	-
	(Moderate level)	Yes	1.67	(0.69, 4.03)	0.250	2.10	(0.66, 6.62)	0.210
	Severity of ANH	No	1.00	-	-	1.00	-	-
	(Severe level)	Yes	0.43	(0.10, 1.86)	0.260	0.67	(0.14, 3.08)	0.600
	Direction of ANH	No	1.00	-	-	1.00	-	-
	(Left)	Yes	0.19	(0.07, 0.51)	0.001	0.17	(0.06, 0.49)	0.001
	Direction of ANH	No	1.00	-	-	1.00	-	-
	(Bilateral)	Yes	0.14	(0.06, 0.32)	< 0.001	0.12	(0.05, 0.32)	< 0.001
	Consanguineous	No	1.00	-	-	1.00	-	-
	marriage	Yes	0.65	(0.24, 1.72)	0.380	1.14	(0.36, 3.59)	0.820
	Kidney disease	No	1.00	-	-	1.00	-	-
	background in parent	Yes	1.25	(0.30, 5.17)	0.760	0.84	(0.15, 4.81)	0.850
	History of abortion	No	1.00	-	-	1.00	-	-
	before the child	Yes	1.07	(0.48, 2.42)	0.870	0.84	(0.33, 2.10)	0.700
	Number of other kidney diseases beside ANH and VUR		0.56	(0.32, 0.95)	0.032	0.54	(0.30, 0.96)	0.036
	Mother's age of delivery (Years)		0.99	(0.93, 1.05)	0.670	1.01	(0.93, 1.10)	0.790
	Birth spacing (Years)		1.01	(0.92, 1.10)	0.830	1.02	(0.89, 1.16)	0.820
Left VUR		Girl	1.00	-	-	1.00	-	-
		Boy	0.35	(0.17, 0.74)	0.006	0.35	(0.17, 0.71)	0.004
		No	1.00	-	-	1.00	-	-
		Yes	0.65	(0.21, 2.05)	0.460	0.35	(0.12, 1.03)	0.057
		No	1.00	-	-	1.00	-	-
		Yes	0.35	(0.08, 1.53)	0.160	0.38	(0.05, 2.75)	0.340
		No	1.00	-	-	1.00	-	-
		Yes	7.52	(1.70, 33.36)	0.008	10.27	(1.82, 57.9)	0.008
		No	1.00	-	-	1.00	-	-
		Yes	0.88	(0.17, 4.46)	0.880	1.30	(0.21, 8.17)	0.780
		No	1.00	-	-	1.00	-	-
		Yes	0.97	(0.41, 2.26)	0.940	0.75	(0.33, 1.71)	0.500
		No	1.00	-	-	1.00	-	-
		Yes	1.99	(0.60, 6.53)	0.260	1.35	(0.33, 5.46)	0.680
		No	1.00	-	-	1.00	-	-
		Yes	0.69	(0.28, 1.72)	0.430	0.78	(0.35, 1.75)	0.560
	Number of other kidney diseases beside ANH and VUR		1.21	(0.82, 1.78)	0.330	1.18	(0.76, 1.84)	0.470
	Mother's age of delivery (Years)		1.00	(0.93, 1.07)	0.970	1.04	(0.97, 1.10)	0.290
	Birth spacing (Years)		0.96	(0.84, 1.09)	0.480	0.93	(0.82, 1.06)	0.290
Bilateral VUR		Girl	1.00	-	-	1.00	-	-
		Boy	1.68	(1.06, 2.67)	0.028	1.66	(1.01, 2.72)	0.046
		No	1.00	-	-	1.00	-	-
		Yes	0.58	(0.32, 1.05)	0.072	0.56	(0.29, 1.05)	0.070
		No	1.00	-	-	1.00	-	-
		Yes	1.53	(0.99, 2.36)	0.057	1.09	(0.64, 1.85)	0.760
		No	1.00	-	-	1.00	-	-
		Yes	0.84	(0.42, 1.66)	0.620	0.83	(0.40, 1.70)	0.610
		No	1.00	-	-	1.00	-	-
		Yes	2.66	(1.48, 4.80)	0.001	2.44	(1.27, 4.61)	0.006
		No	1.00	-	-	1.00	-	-
		Yes	1.11	(0.75, 1.65)	0.590	1.08	(0.71, 1.63)	0.730
		No	1.00	-	-	1.00	-	-
		Yes	0.69	(0.32, 1.47)	0.330	0.70	(0.34, 1.42)	0.320
		No	1.00	-	-	1.00	-	-
		Yes	1.21	(0.81, 1.79)	0.350	1.13	(0.70, 1.83)	0.620
	Number of other kidney diseases beside ANH and VUR		1.22	(0.94, 1.59)	0.140	1.28	(0.96, 1.71)	0.095
	Mother's age of delivery (Years)		1.01	(0.97, 1.04)	0.710	1.00	(0.96, 1.04)	0.860
	Birth spacing (Years)		1.03	(0.98, 1.08)	0.180	1.03	(0.97, 1.09)	0.350

HR: Hazard ratio; ANH: Antenatal hydronephrosis, VUR: Vesicoureteral reflux

Table 4. The Cox proportional hazard regression (cause-specific hazard) model for the right, left and the bilateral reflux

Type	Variables	Status	Univariate (Unadjusted)			Multivariate (Adjusted)		
			HR	CI 95%	P value	HR	CI 95%	P value
Right VUR	Sex	Girl	1.00	-	-	1.00	-	-
		Boy	1.59	(0.60, 4.25)	0.351	2.49	(0.87, 7.15)	0.090
	Severity of ANH	No	1.00	-	-	1.00	-	-
	(Moderate level)	Yes	1.06	(0.42, 2.68)	0.894	1.31	(0.47, 3.61)	0.603
	Severity of ANH	No	1.00	-	-	1.00	-	-
	(Severe level)	Yes	0.43	(0.10, 1.86)	0.261	0.80	(0.16, 3.91)	0.783
	Direction of ANH	No	1.00	-	-	1.00	-	-
	(Left)	Yes	0.18	(0.06, 0.49)	0.001	0.16	(0.05, 0.48)	0.001
	Direction of ANH	No	1.00	-	-	1.00	-	-
	(Bilateral)	Yes	0.17	(0.07, 0.40)	< 0.001	0.14	(0.05, 0.38)	< 0.001
	Consanguineous	No	1.00	-	-	1.00	-	-
	marriage	Yes	0.65	(0.24, 1.71)	0.379	1.00	(0.34, 2.94)	0.998
	Kidney disease	No	1.00	-	-	1.00	-	-
	background in parent	Yes	1.03	(0.24, 4.36)	0.971	1.09	(0.25, 4.77)	0.909
	History of abortion	No	1.00	-	-	1.00	-	-
	before the child	Yes	1.24	(0.54, 2.83)	0.613	0.79	(0.32, 1.92)	0.599
	Number of other kidney diseases beside ANH and VUR		0.63	(0.35, 1.13)	0.123	0.69	(0.37, 1.29)	0.249
	Mother's age of delivery (Years)		0.99	(0.92, 1.06)	0.788	1.02	(0.94, 1.11)	0.630
	Birth spacing (Years)		1.05	(0.94, 1.16)	0.423	1.06	(0.93, 1.21)	0.377
Left VUR		Girl	1.00	-	-	1.00	-	-
		Boy	0.60	(0.28, 1.32)	0.205	0.63	(0.27, 1.47)	0.290
		No	1.00	-	-	1.00	-	-
		Yes	0.45	(0.14, 1.52)	0.201	0.35	(0.10, 1.20)	0.094
		No	1.00	-	-	1.00	-	-
		Yes	0.30	(0.07, 1.30)	0.107	0.41	(0.08, 2.02)	0.274
		No	1.00	-	-	1.00	-	-
		Yes	4.76	(1.11, 20.41)	0.036	5.73	(1.28, 25.5)	0.022
		No	1.00	-	-	1.00	-	-
		Yes	0.90	(0.18, 4.48)	0.900	1.22	(0.24, 6.34)	0.812
		No	1.00	-	-	1.00	-	-
		Yes	0.91	(0.39, 2.14)	0.826	0.74	(0.29, 1.88)	0.528
		No	1.00	-	-	1.00	-	-
		Yes	1.86	(0.55, 6.25)	0.318	1.63	(0.43, 6.21)	0.475
		No	1.00	-	-	1.00	-	-
		Yes	0.87	(0.35, 2.15)	0.758	1.07	(0.39, 2.97)	0.895
	Number of other kidney diseases beside ANH and VUR		1.43	(0.86, 2.39)	0.166	1.38	(0.78, 2.44)	0.268
	Mother's age of delivery (Years)		1.00	(0.94, 1.07)	0.943	1.01	(0.93, 1.09)	0.832
	Birth spacing (Years)		1.01	(0.90, 1.13)	0.840	0.97	(0.86, 1.09)	0.576
Bilateral VUR		Girl	1.00	-	-	1.00	-	-
		Boy	2.09	(1.26, 3.48)	0.004	2.23	(1.31, 3.81)	0.003
		No	1.00	-	-	1.00	-	-
		Yes	0.45	(0.24, 0.86)	0.014	0.41	(0.21, 0.79)	0.008
		No	1.00	-	-	1.00	-	-
		Yes	1.09	(0.68, 1.75)	0.710	0.90	(0.54, 1.52)	0.704
		No	1.00	-	-	1.00	-	-
		Yes	0.58	(0.29, 1.18)	0.134	0.57	(0.27, 1.17)	0.125
		No	1.00	-	-	1.00	-	-
		Yes	1.83	(1.03, 3.23)	0.038	1.68	(0.92, 3.07)	0.090
		No	1.00	-	-	1.00	-	-
		Yes	1.06	(0.71, 1.60)	0.763	0.89	(0.57, 1.38)	0.601
		No	1.00	-	-	1.00	-	-
		Yes	0.81	(0.35, 1.84)	0.608	0.75	(0.32, 1.78)	0.520
		No	1.00	-	-	1.00	-	-
		Yes	1.33	(0.89, 1.99)	0.161	1.14	(0.73, 1.78)	0.562
	Number of other kidney diseases beside ANH and VUR		1.24	(0.97, 1.60)	0.088	1.41	(1.08, 1.83)	0.011
	Mother's age of delivery (Years)		1.00	(0.97, 1.04)	0.933	0.97	(0.93, 1.01)	0.145
	Birth spacing (Years)		1.06	(1.00, 1.11)	0.034	1.06	(1.00, 1.13)	0.056

HR: Hazard ratio; ANH: Antenatal hydronephrosis, VUR: Vesicoureteral reflux

In general, since the results were affected by the way of competing risks have been distributed; we will not be able to interpret the results without examining and with ignoring the effect of these covariates on the competing risks.

Discussion

The use of the competing risks method especially with the estimation of cumulative incident function among children with ANH can be rarely found in literature. To our knowledge, a few authors like, Kim (16), Lim et al. (20) and Teixeira et al. (21) have applied the competing risks approach in some particular research areas, such as cancer, end-stage renal disease and mortality among people with diabetes, and nephrology. Moreover, among these studies, most statistical approaches were nonparametric and semiparametric.

In this study, the CIF for different types of reflux, which was 68% bilateral and 32% unilateral, was estimated using the Fine-Gray method after following them up for at least five years from the time of ANH diagnosis. Results showed that the risk factors associated with the bilateral reflux derived from the multivariate Fine-Gray method were sex and direction of ANH in bilateral level. On the other hand, by the cause-specific method, the risk factors were sex, severity of ANH in moderate level and the number of other disease beside ANH and VUR. In addition, according to the unadjusted model (cause-specific hazard and subdistribution hazard) for the bilateral reflux, both method were quite close.

Our results agreed with the Fine-Gray method in comparison with the observed CIF. Particularly for the bilateral reflux, direct approach gave estimates much closer to the observed values relative to the estimates derived from the cause-specific hazard approach. Therefore, it seems that results and estimates using the Fine-Gray method are more precise than the cause-specific method. Moreover, since some covariates may have effect on the CIF of competing events, by considering these covariates in the regression models, we can reach to more precise estimates.

The analysis of competing risks data yields some interesting results which are usually summarized either by assessing the hazard function or through directly estimating the probability of competing risks. Likewise, regression study of the competing risks data falls within two broad categories, modeling the hazard function and direct modeling of the CIF.

For interpreting the results in competing risks framework, we should always consider all causes. Ignoring other competing risks and considering them as censored (1 minus Kaplan-Meier estimate) for interpreting one cause, will wrongly overestimate the risk of the event of interest which will badly influence on our interpretation. So, in the presence of competing risks, it is inappropriate to use the Kaplan-Meier methods and Cox proportional hazard model, which do not take competing risks into account. Those analyses will be valid and useful for the event of interest under the identifiability assumption and when the assumption of independent risks is true, which is very hard to confirm. Thus, using these methods does not address any correlations among the risks. Many authors have also pointed out that for a particular failure type, the effects of covariates on the CIF may be very different from those in the related cause-specific hazard function. Thus, modeling CIF becomes essential in studying the competing risks data.

To sum up, it is appropriate to put forward both the cumulative incidence curve and result of modelling the hazard of subdistribution for the event of interest. In comparison with the hazard functions, it is easier to interpret if we are interested in survival probabilities or how many subjects fail of any particular failure type at some points of time. Furthermore, visualizing a CIF is more straightforward while a hazard function needs smoothing techniques to accomplish better visualization. Having these in mind, CIFs should be combined with the hazard function so as to enhance the analysis and investigation of the competing risks data.

In general, researchers should pay more attention to set the model correctly in order to answer some specific questions on the theme of research. Furthermore, graphical approaches of

showing the CIF beside the model will give a simpler understanding of the result. The statistical test like Grey's test and log-rank test with a graphical approach could be complementary measures of the risk interpretation for competing risks studies.

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