POST-TRANSPLANT SURVIVAL IN PEDIATRIC LIVER TRANSPLANT PATIENTS WITH BILIARY ATRESIA: A COMPARISON OF COMPETING RISK MODELS

by

Lu Wang

B.Med. in Public Health, Shandong University, China, 2011

Submitted to the Graduate Faculty of

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Master of Science

University of Pittsburgh

2013

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

This thesis was presented

by

Lu Wang

It was defended on

June 12, 2013

and approved by

Ruosha Li, Ph.D, Assistant Professor, Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh

Yu Cheng, Ph.D, Associate Professor, Departments of Statistics and Psychiatry, Dietrich School of Arts and Sciences, University of Pittsburgh

Thesis Advisor: Chung-Chou H. Chang, Ph.D, Associate Professor, Departments of Medicine and Biostatistics, School of Medicine and Graduate School of Public Health, University of Pittsburgh

Chung-Chou H. Chang, Ph.D

POST-TRANSPLANT SURVIVAL IN PEDIATRIC LIVER TRANSPLANT PATIENTS WITH BILIARY ATRESIA: A COMPARISON OF COMPETING RISK MODELS

Lu Wang, M.S.

University of Pittsburgh, 2013

ABSTRACT

Liver transplantation is the ultimate treatment for patients with end-stage liver diseases. Among the primary diagnosis of pediatric liver transplant candidates, biliary atresia is the most common cause of liver failure. In this study, we aimed to identify factors associated with marginal posttransplant survival among pediatric liver transplant recipients with primary diagnosis of biliary atresia. The main event of interest was time from transplant to death. Retransplantation was the competing event and alive at the study cutoff was indepenent censoring. We analyzed data using five different competing risks regression models and compared the results. These models include Cox proportional hazards (PH) model treating competing events as censoring, Cox PH model treating competing events as the main event, Fine and Gray proportional subdistribution hazards model, random signs censoring regression model, and the joint model of time to the main event and time to the competing event. The assumptions of each method are described in this thesis. Joint model was used as the gold standard in our analysis and the results obtained from other methods were compared to the gold standard. Our analysis showed that Cox PH model treating competing event as censoring gave similar results as those obtained from the joint model. On ventilator or not, allocation type, split or nonsplit organ,

presence of ascites, and presence of portal vein thrombosis at treatment were the risk factors for marginal posttransplant survival among pediatric patients with biliary atresia.

Public health significance: Risk factors of marginal posttransplant survival can be identified only if a regression model with appropriate assumption of the dependence structure between the event of interest and the competing events is used. We compare the results from three commonly used and two newly developed survival regression models for data with competing risks. The underlying assumptions of the dependence of the events and the pros and cons of these models are described and discussed. Our findings will help a researcher to appropriately choose a regression model to identify risk factors when competing risks are present in the data.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PREFACE

I would like to thank my advisor Professor Chung-Chou H. Chang for introducing me to this fascinating field. I also wish to thank Professor Cheng Yu and Professor Li Ruosha for being on my thesis committee. In the end, I cannot come this far without my parents' and friends' love and support.

1.0 INTRODUCTION

Liver transplantation (LT) is the ultimate treatment for patients with end-stage liver diseases. Among the primary diagnosis of pediatric liver transplant candidates, biliary atresia (BA) is the most common cause of liver failure.

BA is a progressive cholangiopathy disorder of infants, characterized by biliary obstruction of unknown pathogenesis. This panbiliary disease affects both the intrahepatic and extrahepatic biliary trees and can lead to early development of secondary biliary cirrhosis. Incidence of BA varies from one in 8,000 to 18,000 live births. The prognosis for untreated BA remains extremely poor, with a patient's median survival ranging from 8 to 16 months. [1-3] Although there exists some treatment methods to improve survival of the native liver, LT remains the only effective treatment for patients with end-stage BA. After LT, patients still have to overcome challenges in fighting with infection, rejection, and a series of complications. Unfortunately, 9% to 29% of pediatric LT recipients require retransplantation which offers the only chance for survival when a transplanted liver fails. [4]

To study the survival of pediatric liver transplantation, retransplantation is an important issue which prevents the occurrence of the main event, death. This issue refers to competing risk in the survival analysis, characterized that individuals experience either the main event (death, T1) or the competing event (retransplantation, T2). Method selection in analyzing data with competing risks depends on different purpose and assumptions. In this thesis, we will focus on

analyzing covariate effects on marginal survival, that is, probability of death in the absence of competing risks. Under this situation, dependence structure between the failure times (main event and competing events) is needed. When the competing event is independent of the main event, e.g. death from the disease of interest and death from traffic accident, the competing event can be treated as random censoring, as in Cox Proportional Hazards (PH) model, which is the most common used method in competing risk analysis. [5] In another situation, when the competing event and main event are related. For example, patients on the wait list of retransplantation are in high risk of dying. In this case, it is also reasonable to treat competing event as the main event by Cox PH model; the relationship between competing event and main event is perfectly positive. Another common used method is Fine and Gray model based on the cumulative incidence function (CIF). [6] Although this model is applicable to analyzing crude probability, the probability of the occurrence of the main event in the presence of competing risks, it can also be viewed as a model of marginal survival probabilities in which the main event is considered never happen when the competing event occurs. For example, death is a competing event for relapse of breast cancer. The effort to reduce death may adversely affect the risk of relapse. Moreover, patients who die from breast cancer cannot be at further risk of relapse; therefore in this case the competing event can be treated as perfectly negatively related to the main event. In another scenario, when the competing event is a protective approach to avoid the observation of the main event, e.g. retransplantation and death, a newly developed method, random signs censoring (RSC), is applicable in this situation. [7] Since the competing event and main event may not be independent, we constructed a joint model to investigate the association of the competing event and main event. [8]

To date, only a few published works that address the competing risks approach in analyzing posttransplant survival for pediatric liver transplantation. Chardot et al. reviewed 588 BA patients performed LT between the years 1986 and 2009 in France. Although the retransplantation rate was 15.3%, indicating that 90 among 588 recipients underwent more than one LT, the study did not consider retransplantation as a competing event in the Cox PH model. [9] Utterson et al. studied 755 children with BA listed for their first LT from May 1995 to June 2003. A competing-risk analysis was used to assess the likelihood of death while waiting, death after LT, and death after retransplantation. In their analysis of posttransplant survival, retransplantation was treated as a covariate, rather than a competing outcome, in the cause-specific Cox proportional hazards model. [10]

In this study, we aim to identify factors associated with marginal posttransplant survival among pediatric LT recipients with primary diagnosis of biliary atresia, and to compare the results from competing risks models which were constructed under different association assumption of main event of interest and competing events.

2.0 METHODS

2.1 DATA

The data used in this study was extracted from the Standard Transplant Analysis and Research (STAR) of the United Network of Organ Sharing (UNOS), which includes all liver transplant recipients in United States who were on the transplant waiting list between February 28, 2002 and June 20, 2010. We removed transplant recipients who were 18 years or older at the time of listing, and further excluded patients who eventually received multi-organ transplantation or who received LT before listing (n=3,471). Based on the cause of liver failure, we selected patients whose primary diagnosis were biliary atresia (n=1,489). During the data checking and cleaning phase, one transplant recipient was excluded due to large number of missing values. Finally, a cohort of 1,488 pediatric liver transplant recipients with primary diagnosis of biliary atresia was included in the analysis.

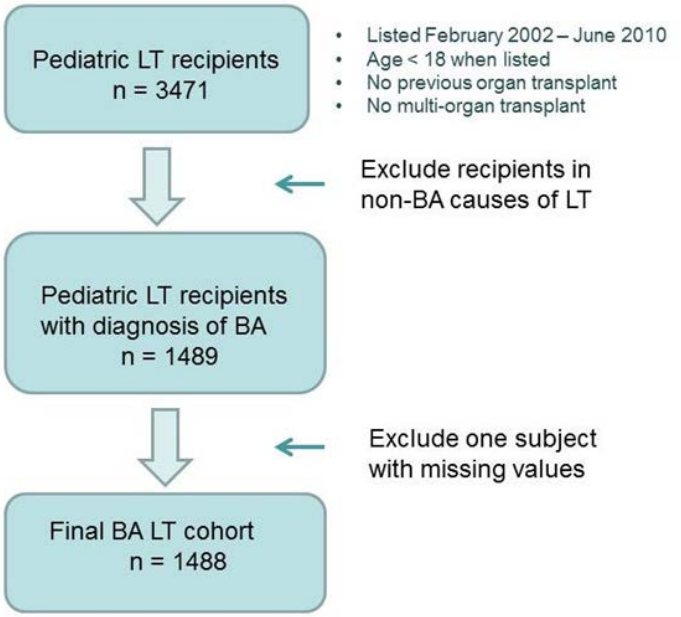

Figure 1. Flowchart of data selection

2.2 COVARIATES

Among hundreds of variables in the raw data, we selected 26 relevant variables as our potential covariates, which can be divided into the following three different types:

Recipient characteristics: demographics (age at the time of transplant, gender, and race); blood type; presence of portal hypertensive bleeding before transplant; laboratory tests at the time of transplantation (serum albumin, total bilirubin, International Normalized Ratio [INR], and creatinine), split or nonsplit organ, on ventilator or not, presence of encephalopathy, presence of ascites, presence of portal vein thrombosis, presence of spontaneous bacterial peritonitis, positive cytomegalovirus (CMV) test, growth failure or not, and region of transplant center.

Donor characteristics: demographics (age, gender, and race), blood type, donor type (cadaveric or living), distance from donor hospital to transplant center, and allocation type (local, regional, or others).

Recipient-donor match variables: blood type compatibility.

2.3 MODELS

In this section, we introduce the models that will be used in analyzing marginal postransplant survival. Suppose there are n independent patients included in the study, and k competing events ($k = 1$ indicating the main event and $k = 2$ indicating competing events). Let T_i, $i = 1,...,n$ be the failure time with respect to subject i. The observed values for individual i include $\{X_i, \delta_i, Z_i\}$, where X_i is the observed failure time; $\delta_i = 0,1,2$ is the event indicator for censoring, main event, and competing event, respectively; and Z_i is a p-dimensional vector of covariates.

Cox Proportional Hazards Model

Cox PH model is a widely used semiparametric survival regression model based on the PH assumption. Let $\lambda_k(t \mid Z)$ be the *k*th cause-specific hazard rate at time *t* with risk vector *Z* for an individual. The Cox PH model has the following form:

$$\lambda_k(t \mid Z) = \lambda_{k,0}(t) \exp(\beta^T Z), \tag{2.3.1}$$

where $\lambda_{k,0}(t)$ is an unknown baseline hazards rate for cause *k*; and $\beta = \left(\beta_1, \ldots, \beta_p\right)'$ is a vector of unknown regression parameters. The hazard ratio (HR) of two individuals with covariate values

Z and Z^* can be derived as HR = $\frac{\lambda(t \mid Z)}{\lambda(t \mid Z^*)} = \exp[\sum_{k=1}^{p} \beta_k (Z_k - Z^*_k)]$. The unknown regression coefficients β are estimated by the score equation

$$U^*(\beta) = \sum_{i=1}^{n} \int_0^{\tau} \{Z_i - \overline{Z}^*(\beta, t)\} dN^*_{1i}(t), \tag{2.3.2}$$

where $$\overline{Z}^*(\beta, t) = \frac{S^{*(1)}(\beta, t)}{S^{*(0)}(\beta, t)},$$

$$S^{*(k)}(\beta, t) = n^{-1} \sum_{j=1}^{n} Y^*_j(t) \exp(\beta^T Z_j) Z_j^{\otimes k},$$

$N^*_{1i}(t)$ is the indicator function of whether main event occurs for individual i ($N^*_{1i}(t) = I(T_{1i} \le t)$), $Y^*_{1i}(t)$ is the indicator function of whether individual i is at risk ($Y^*_{1i}(t) = I(T_{1i} \ge t)$), and τ is any time point greater than the maximum observed main event time.

In this study, we built two Cox PH models: treating competing risk (retransplantation) as an event, and treating competing risk as censoring. The former model assumes that competing event is perfectly positively correlated with the event of interest (death), while the later one treats retransplantation as independent censoring.

Fine and Gray Model

Fine and Gray model is a semiparametric proportional subdistribution hazards model. Subdistribution is defined as the cumulative incidence function (CIF) for the corresponding cause of failure, i.e., the probability of experiencing a particular cause of failure up to time *t*, in the presence of all the other possible causes. The CIF at time *t* for cause *j* can be written as the form:

$$F_k(t) = P(X \le t, \delta = j) = \int_0^t h_k(u)S(u-)du\,. \tag{2.3.3}$$

The hazard of subdistribution is a function of the cumulative incidence and can be represented as:

$$\lambda_k(t) = -\frac{d\log(1-F_k(t))}{dt}\,. \tag{2.3.4}$$

Given a vector of risk factors *Z*, the Fine and Gray model of the subdistribution hazards for cause *k* has the form

$$\lambda_k(t \mid Z) = \lambda_{k,0}(t)\exp(\beta_k^T Z)\,, \tag{2.3.5}$$

where $\lambda_{k,0}(t)$ is the baseline subdistribution hazards function; and β_k is a vector of unknown regression parameters. As the cumulative incidence defined and treating it as a marginal probability, the event of interest and the competing events can be viewed as perfectly negatively associated because the event of interest would never occur if one of the *k* competing events happened.

Random Signs Censoring Model

Random signs censoring (RSC) posits that the potential failure time of the event of interest is independent of the sign: competing event happens before the main event. There exists a signal prior to failure, for example, failure of the transplanted organ, leading to some actions to prevent the occurrence of the main event, e.g. death. The RSC assumption requires that the normalized subdistribution function of the main event is stochastically lower than that of the competing event. It can be checked from the survival curves, showing that the curve of main event is above that of competing event ($\tilde{S}_1(t) > \tilde{S}_2(t)$). Let T1 be the failure time of the main

event and T2 be the failure time of the competing event. Suppose T1 follows a Cox PH model. Then, the hazard $\lambda_1^*(t \mid Z)$ of T1 has the form $\lambda_1^*(t \mid Z) = \lambda_{10}^*(t)\exp(\beta' Z)$. If data does not contain independent right censoring, unknown regression parameters β can be estimated by the partial likelihood estimating equation (2.3.2) by removing individuals with competing events from the dataset. When data contains independent right censoring, the estimating equation of the RSC regression model incorporates inverse probability of censoring weights (IPCW):

$$U(\beta) = \sum_{i=1}^{n} \int_0^{\tau} \{Z_i - \bar{Z}(\beta, t)\} \frac{\delta_i}{G(X_i)} dN_i(t), \tag{2.3.6}$$

where $\delta = I(T \le C)$, C is the random variable of censoring time which assumed to be independent of T1 and T2; $G(t) = \Pr(C > t)$ is the underlying survival distribution of *C*;

$$\bar{Z}(\beta, t) = \frac{S^{(1)}(\beta, t)}{S^{(0)}(\beta, t)};$$

$$S^{(k)}(\beta, t) = n^{-1} \sum_{j=1}^{n} \frac{\delta_j}{G(X_j)} \varepsilon_{1j} Y_j(t) \exp(\beta' Z_j) Z_j^{\otimes k};$$

$\varepsilon_1 = I(\text{T1} \le \text{T2})$; and $X = \min(C, T)$. In practice, $G(t)$ has to be replaced by a consistent estimator (e.g., Kaplan-Meier estimator of censoring).

Joint Modeling

Joint modeling method was used to account for informative dropouts. Basically, it jointly models the process of the time to the main event of interest, and the process of the dropouts due to competing risks. The dependence between the main event and competing risks is captured via random effects terms. The likelihood function of the joint model with shared random effects has the following form:

$$L_i(T_{ki};\beta_k,\lambda_{k0},\theta,Z_i,\upsilon_i)=\prod_{i=1}^{n}\int_{\upsilon_i}\prod_{k=1}^{2}l_k(T_{ki};\Omega,Z_{ki}\mid\upsilon_i)\,f(\upsilon_i)d\upsilon_i\,, \tag{2.3.7}$$

where $f(\upsilon_i)$ is the probability density function of the random terms υ_i; $\Omega=\{\beta_k,\lambda_{k0},\theta\}$; θ is a vector of parameters in the density function of the random terms, and $\theta=\sigma^2$ when assuming the random terms υ_i follows a normally distribution with mean zero and standard deviation σ^2; l_k denotes the marginal likelihood function of event *k* with the following form

$$l_k(t\mid\upsilon_i)=\{\lambda_{ki}(t\mid\upsilon_i)\}^{\delta_{ki}}\exp\{-\int_0^t(\lambda_{ki}(t\mid\upsilon_i)dt\}\,. \tag{2.3.8}$$

The hazards function specified here is assumed to follow a proportional hazards two-parameter Weibull distribution with baseline hazards function of the form:

$$\lambda_{ki}(t)=\lambda\alpha t^{\alpha-1}\exp\{\beta_k^T Z_{ki}+\phi^{I(k=2)}\upsilon_i\}\,, \tag{2.3.9}$$

where $I(k=2)$ is an indicator function of competing event (*k* = 2); the λ and α are the scale and shape parameters, respectively; and ϕ is the coefficient of the shared random effect term, which reflecting the direction of the association between the main event and competing event. The main challenge of parameter estimation is the multidimensional integration towards the random terms. The Gaussian quadrature method can be used to solve the estimating equations.

In modeling marginal survival for data with competing risks, it is important to make assumptions about the dependence structure between the potential failure times. Peterson (1976) states that there exist lower and upper bounds for the marginal survival function $S_i(t)$, when the risks are dependent. [11] When the competing event is equivalent to the main event, the marginal survival function $S_i(t)$ becomes the total survival function $S_T(t)$. On the other hand, when the risks are perfectly negatively related, the marginal survival function $S_i(t)$ becomes one minus the

cumulative incidence function, $1-F_i(t)$. These lower and upper bounds can be achieved if we analyze data using a Cox PH model treating competing events as the main event and using a Fine and Gray model, respectively.

2.4 STATISTICAL ANALYSIS

We first checked each variable for missing values, and removed variables from the candidate list if they had great amount of missing. Recipients age was divided into three groups, less than one, one to two, and greater than two years old; while Donors age was categorized into less than one and greater than or equal to one years old. Dummy variables were created for categorical variables, e.g. recipients' race of white or other, CMV test positive or negative, on ventilator or not at the time of transplant, etc.

Variables retained were included in the univariable analysis which consists of five models. The results of univariable analysis were used to select variables into the final multivariable model if a variable was significant at the level of 0.15 in at least one model among the five. To compare the differences of the models, we fit the five models using the same set of selected variables. As the sensitivity test, we repeated the univariable and multivariable analysis steps restricted only to patients received cadaveric liver transplants. All data management and analysis were implemented in SAS 9.3 and R version 2.14.1.

3.0 RESULTS

3.1 DESCRIPTIVE ANALYSIS

Table 1 shows the descriptive statistics for the covariates considered in the univariable analysis. Among 1,488 LT recipients, 93 (6.25%) died, 127 (8.53%) received retransplantation, and the rest 1,268 (85.23%) were alive at the study cutoff date. The median follow-up time was 764 days (approximately 2.09 years).

In the initially selected variables (see Section 2.2), three of them were excluded due to large percentage of missing values: presence of portal hypertensive bleeding before transplant (missing=998, 67.1%), presence of spontaneous bacterial peritonitis at transplant (missing=703, 47.2%), and growth failure or not (missing=139, 9.3%). Moreover, encephalopathy was removed because of collinearity with positive CMV test.

Table 1. Characteristics of the covariates considered in the univariable models

Characteristics	All Recipients (N = 1488)	Patient Outcome		
		Alive (N = 1268)	Retransplant (N = 127)	Died (N = 93)
Recipient Characteristics				
Time follow-up, median, mean ± SD(days)	764, 981 ± 822	1069, 1107 ± 805	15, 243 ± 451	27, 275 ± 487
Demographics				
Age, median, mean ± SD (years)	0, 1.88 ± 3.66	0, 1.97 ± 3.75	0, 1.51 ± 3.37	0, 1.09 ± 2.50
Gender, No. (%)				
Female	852 (57.26)	720 (56.78)	76 (59.84)	56 (60.22)
Male	636 (42.74)	548 (43.22)	51 (40.16)	37 (39.78)
Race / ethnicity, No. (%)				

Table 1. Continued

White	721 (48.45)	606 (47.79)	70 (55.12)	45 (48.39)
Other	767 (51.55)	662 (52.21)	57 (44.88)	48 (51.61)
Medical/Clinical Covariates				
Blood type, No. (%)				
A	510 (34.27)	432 (34.07)	49 (38.58)	29 (31.18)
AB	70 (4.70)	63 (4.97)	5 (3.94)	2 (2.15)
B	190 (12.77)	166 (13.09)	9 (9.68)	9 (9.68)
O	718 (48.25)	607 (47.87)	58 (45.67)	53 (56.99)
On ventilator, No. (%)				
Yes	64 (4.30)	56 (3.63)	6 (4.72)	12 (12.90)
No	1424 (95.70)	1222 (96.37)	121 (95.28)	81 (87.10)
Laboratory values, Median , Mean ± SD				
Albumin (g/dl)	3.0, 3.03 ± 0.77	3.0, 3.03 ± 0.78	3.0, 3.01 ± 0.66	3.0, 3.01 ± 0.72
Bilirubin (mg/dl)	10.9, 12.75 ± 10.63	10.8, 12.71 ± 10.67	8.1, 11.30 ± 9.49	13.5, 15.38 ± 11.20
Serum creatinine (mg/dl)*	0.3, 0.33 ± 0.26	0.3, 0.33 ± 0.27	0.3, 0.31 ± 0.23	0.3, 0.30 ± 0.20
INR	1.4, 1.74 ± 2.61	1.4, 1.75 ± 2.80	1.4, 1.67 ± 1.08	1.5, 1.74 ± 0.96
Positive cytomegalovirus (CMV) test, No. (%)				
Yes	482 (32.39)	415 (32.73)	38 (29.92)	29 (31.18)
No	1006 (67.61)	853 (67.27)	89 (70.08)	64 (68.82)
Presence of ascites, No. (%)				
Yes	730 (49.06)	603 (47.56)	71 (55.91)	56 (60.22)
No	390 (26.21)	351 (27.68)	23 (18.11)	16 (17.20)
Unknown	368 (24.73)	314 (24.76)	33 (25.98)	21 (22.58)
Presence of portal vein thrombosis, No. (%) **				
Yes	53 (3.62)	41 (3.29)	5 (3.97)	7 (7.53)
No	1362 (93.10)	1166 (93.65)	116 (92.06)	80 (86.02)
Unknown	48 (3.28)	38 (3.05)	5 (3.97)	6 (6.45)
Previous abdominal surgery, No. (%) **				
Yes	1077 (73.62)	921 (73.98)	87 (69.05)	69 (74.19)
No	336 (22.97)	281 (22.57)	34 (26.98)	21 (22.58)
Unknown	50 (3.42)	43 (3.45)	5 (3.97)	3 (3.23)
Other Characteristics				
Donor type, No. (%)				
Deceased	1250 (84.01)	1053 (83.04)	114 (89.76)	83 (89.25)
Living	238 (15.99)	215 (16.96)	13 (10.24)	10 (10.75)
Donor age, median, mean ± SD (years)	8, 12.19 ± 12.71	9, 12.43 ± 12.63	2, 9.25 ± 12.70	9, 12.83 ± 13.36
Donor gender, No. (%)				
Female	707 (47.51)	603 (47.56)	56 (44.09)	48 (51.61)
Male	781 (52.49)	665 (52.44)	71 (55.91)	45 (48.39)
Donor race / ethnicity, No. (%)				
White	863 (58.00)	736 (58.04)	76 (59.84)	51 (54.84)
Other	625 (42.00)	532 (41.96)	51 (40.16)	42 (45.16)
Donor blood type, No. (%)				
A	499 (33.53)	427 (33.68)	47 (37.01)	25 (26.88)
AB	26 (1.75)	24 (1.89)	1 (0.79)	1 (1.08)

Table 1. Continued

B	160 (10.75)	135 (10.65)	16 (12.60)	9 (9.68)
O	803 (53.97)	682 (53.79)	63 (49.61)	58 (62.37)
ABO compatible, No. (%)				
Yes	1448 (97.31)	1232 (97.16)	124 (97.64)	92 (98.92)
No	40 (2.69)	36 (2.84)	3 (2.36)	1 (1.08)
Transplantation Related Characteristics				
Center location (region), No. (%)				
1: CT, ME, MA, NH, RI	42 (2.82)	41 (3.23)	0 (0.00)	1 (1.08)
2: DC, DE, MD, NJ, PA, WV	150 (10.08)	128 (10.09)	17 (13.39)	5 (5.38)
3: AL, AR, FL, GA, LA, MS, PR	188 (12.63)	154 (12.15)	19 (14.96)	15 (16.13)
4: OK, TX	156 (10.48)	125 (9.86)	17 (13.39)	14 (15.05)
5: AZ, CA, NV, NM, UT	324 (21.77)	287 (22.63)	23 (18.11)	14 (15.05)
6: AK, HI, ID, MT, OR, WA	32 (2.15)	29 (2.29)	2 (1.57)	1 (1.08)
7: IL, MN, ND, SD, WI	126 (8.47)	104 (8.20)	13 (10.24)	9 (9.68)
8: CO, IA, KS, MO, NE, WY	149 (10.01)	128 (10.09)	13 (10.24)	8 (8.60)
9: NY, VT	94 (6.32)	79 (6.23)	10 (7.87)	5 (5.38)
10: IN, MI, OH	136 (9.14)	116 (9.15)	7 (5.51)	13 (13.98)
11: KY, NC, SC, TN, VA	91 (6.12)	77 (6.07)	6 (4.72)	8 (8.60)
Allocation type, No. (%)				
Local	700 (47.58)	608 (47.95)	60 (47.24)	40 (43.01)
Regional	556 (37.37)	476 (37.54)	38 (29.92)	42 (45.16)
Other	224 (15.05)	184 (14.51)	29 (22.83)	11 (11.83)
Procurement distance, Median, Mean ± SD (miles)	128, 270 ± 400	124, 268 ± 401	158, 316 ± 448	141, 239 ± 301
Partial or split donor organ, No. (%)				
Partial or split	699 (46.98)	601 (47.40)	46 (36.22)	52 (55.91)
Whole	789 (53.02)	667 (52.60)	81 (63.78)	41 (44.09)

Abbreviation: SD (Standard Deviation).
* Serum creatinine values were missing for 72 children: 61 alive, 6 retransplanted and 5 dead.
** Both portal vein thrombosis and previous abdominal surgery have missing values in 25 subjects: 23 alive, 1 retransplanted, and 1 dead.

3.2 UNIVARIABLE ANALYSIS

Table 2 shows the univariable analysis results from the five models. Age of recipients, on ventilator, presence of ascites, and presence of portal vein thrombosis were significant in all five models at the level of 0.15. For donor age and serum total bilirubin, the Cox PH models with retransplant as event had the opposite results with other models. Donor's age was only significant in the former, while bilirubin was significant in the latter ones rather than the former. It may be caused by the inflating of sample size of event (death) in the Cox model where competing event (retransplant) was also considered as the main event.

Figure 2 shows the survival curves of main event and competing event without censoring, indicating that the RSC assumption is satisfied. However, the RSC univariable models had quite different results from other models. Beside of the variables mentioned above, some factors were significant with p-value less than 0.15, including recipient race, procurement distance, serum creatinine, CMV test positive, and allocation type. Moreover, hazard ratios (HRs) were also inconsistent with other models in 7 variables among the 21 factors in total. For example, the HR of serum creatinine was no greater than 0.8 in the Cox, Fine and Gray and joint model, while it was 5.57 in the RSC model. The joint modeling result showed not only HR, but ϕ estimates, which indicates the relationship between main event and competing event. All the ϕ estimates were greater than zero and p-values were larger than 0.05, indicating a non-significant positive association of death and retransplantation in this data.

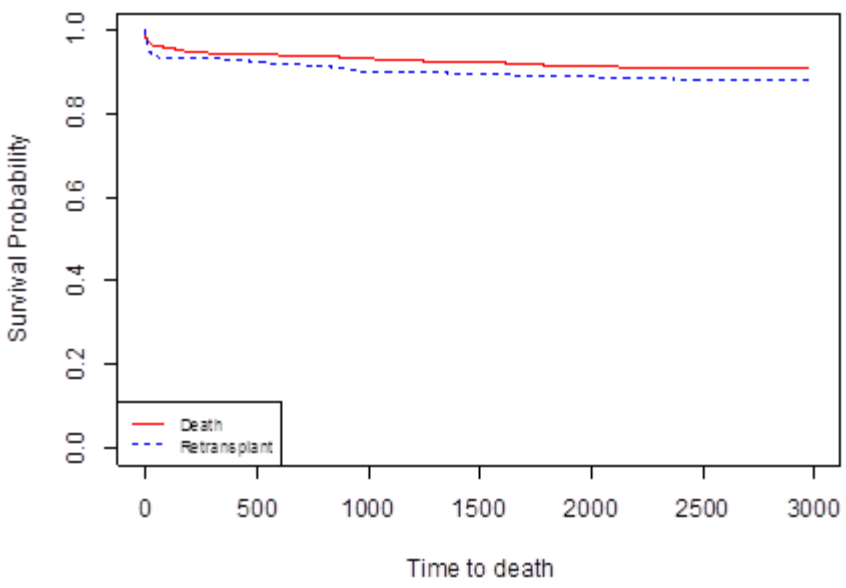

Figure 2. Check the RSC assumption: Survival curves for death and retransplant

Table 2. Univariable analysis

		Cox - Retransplant as event				Cox - Retransplant as censor				Fine & Gray model				RSC				Joint Modeling							
		HR	95% CI		p-value	HR	95% CI		p-value	HR	95% CI		p-value	HR	95% CI		p-value	HR	95% CI		p-value	phi		sigma	
			LL	UL			LL	UL			LL	UL			LL	UL			LL	UL		EST	p-value	EST	p-value
Recipient age	1--2	0.92	0.66	1.26	0.589	0.87	0.53	1.43	0.577	0.87	0.53	1.43	0.590	1.72	1.08	2.74	0.021‖	0.83	0.47	1.45	0.504	1.17	0.198	1.75	0.050
	> 2	0.61	0.42	0.89	0.010‖	0.57	0.32	1.02	0.059‖	0.58	0.33	1.05	0.070‖	1.62	0.94	2.78	0.081‖	0.53	0.27	1.02	0.056‖				
Donor age		0.46	0.34	0.62	<0.001‖	0.75	0.44	1.28	0.292	0.82	0.48	1.40	0.460	0.88	0.55	1.42	0.607	0.78	0.42	1.45	0.435	1.11	0.435	1.80	0.222
Recipient gender		1.12	0.85	1.47	0.412	1.13	0.74	1.71	0.573	1.12	0.74	1.69	0.590	0.80	0.54	1.17	0.243								
Donor gender		0.98	0.75	1.28	0.903	1.17	0.78	1.76	0.453	1.18	0.79	1.78	0.410	0.91	0.64	1.31	0.624	1.23	0.63	2.40	0.553	0.82	0.846	2.15	0.708
Recipient race (White/Other)		1.17	0.90	1.53	0.243	1.00	0.67	1.50	0.995	0.99	0.66	1.48	0.950	1.38	0.95	2.02	0.094‖								
Donor race (White/Other)		0.99	0.75	1.29	0.914	0.88	0.58	1.32	0.528	0.88	0.58	1.32	0.520	1.14	0.79	1.64	0.492								
ABO compatible		1.41	0.52	3.79	0.498	2.40	0.33	17.19	0.385	2.39	0.33	17.30	0.390	0.40	0.06	2.78	0.352	2.28	0.25	20.52	0.461	0.93	0.570	2.01	0.315
Recipient blood type	A	0.99	0.74	1.32	0.927	0.77	0.49	1.20	0.249	0.76	0.48	1.19	0.230	1.01	0.68	1.51	0.960	0.73	0.43	1.26	0.261	1.06	0.421	1.85	0.191
	B	0.82	0.53	1.27	0.372	0.64	0.32	1.30	0.219	0.64	0.32	1.30	0.220	1.00	0.55	1.84	0.991	0.62	0.28	1.40	0.253				
	AB	0.64	0.30	1.36	0.244	0.38	0.09	1.55	0.177	0.38	0.09	1.53	0.170	1.20	0.32	4.48	0.787	0.37	0.08	1.74	0.209				
Donor blood type	A	0.98	0.73	1.31	0.872	0.70	0.44	1.13	0.144	0.70	0.44	1.11	0.130	0.90	0.60	1.36	0.623	0.69	0.40	1.20	0.191	1.08	0.499	1.83	0.277
	B	1.05	0.69	1.62	0.808	0.79	0.39	1.59	0.507	0.78	0.39	1.56	0.480	0.96	0.52	1.75	0.888	0.77	0.34	1.73	0.527				
	AB	0.49	0.12	1.98	0.317	0.51	0.07	3.69	0.505	0.52	0.07	3.69	0.510	1.24	0.19	8.05	0.823	0.59	0.07	4.96	0.630				
On ventilator		2.23	1.38	3.62	0.001‖	3.73	2.03	6.84	<0.001‖	3.67	1.98	6.79	<0.001‖	2.61	1.42	4.79	0.002‖	6.18	1.42	26.83	0.015‖	0.91	0.361	2.03	0.108
Procurement distance		1.00	1.00	1.00	0.411	1.00	1.00	1.00	0.575	1.00	1.00	1.00	0.430	1.00	1.00	1.00	0.048‖								
Albumin		0.96	0.81	1.15	0.659	0.96	0.73	1.26	0.771	0.96	0.74	1.25	0.770	1.00	0.74	1.34	0.984	0.94	0.66	1.34	0.728	0.83	0.678	2.14	0.424
Bilirubin		1.00	0.99	1.01	0.693	1.02	1.00	1.04	0.016‖	1.02	1.01	1.04	0.007‖	1.00	0.99	1.02	0.654	1.02	1.00	1.04	0.047‖	1.42	0.375	1.51	0.213
INR		0.99	0.93	1.06	0.867	1.00	0.93	1.08	0.966	1.00	0.97	1.04	0.920	1.02	0.85	1.22	0.819	1.00	0.89	1.13	0.559	0.75	0.661	2.26	0.368
Serum creatinine *		0.72	0.39	1.33	0.291	0.76	0.30	1.91	0.553	0.78	0.35	1.75	0.550	5.57	1.87	16.66	0.002‖	0.69	0.24	2.00	0.489	1.02	0.252	1.92	0.060
CMV positive		0.89	0.66	1.18	0.408	0.92	0.59	1.42	0.700	0.93	0.60	1.43	0.730	0.57	0.37	0.86	0.008‖								
Allocation type (Local/Other)		0.85	0.65	1.10	0.219	0.76	0.51	1.15	0.197	0.78	0.52	1.17	0.230	0.45	0.30	0.67	<0.001‖	0.67	0.40	1.12	0.130‖	0.97	0.270	1.97	0.059
Ascites		1.32	1.01	1.72	0.043‖	1.46	0.96	2.22	0.074‖	1.46	0.96	2.21	0.077‖	1.68	1.12	2.50	0.011‖	1.53	0.91	2.58	0.110‖	0.96	0.284	1.98	0.065
Split donor organ		0.87	0.67	1.14	0.320	1.38	0.92	2.08	0.124	1.42	0.95	2.14	0.091‖	0.58	0.40	0.86	0.007‖	1.33	0.69	2.57	0.397	2.75	0.904	0.91	0.885
Portal vein thrombosis **		1.58	0.88	2.82	0.125‖	2.23	1.03	4.83	0.041‖	2.21	1.00	4.87	0.050‖	3.49	1.60	7.62	0.002‖	3.27	0.69	11.10	0.057‖	0.88	0.299	2.08	0.057
Previous abdominal surgery **		0.92	0.69	1.24	0.602	1.10	0.68	1.76	0.699	1.10	0.69	1.77	0.680	0.74	0.48	1.15	0.188								

Abbreviation: CI (Confidence Interval), LL(Lower Limit), UL(Upper Limit), HR(Hazard Ratio), EST(Estimate).

* Serum creatinine values were missing for 72 children: 61 alive, 6 retransplanted and 5 dead.

** Both portal vein thrombosis and previous abdominal surgery have missing values in 25 subjects: 23 alive, 1 retransplanted, and 1 dead.

‖Statistically significant at the level of 0.15.

3.3 MULTIVARIABLE ANALYSIS

Table 3 shows the multivariable analysis results. On ventilation was significant in all models, while donor age and presence of ascites were only significant in the Cox model with retransplant as the event of interest (Model 1). Fine and Gray (Model 3) shared the same list of significant covariates with the Cox model which treated competing event as censoring (Model 2), as well as the joint model (Model 5), including on ventilator, allocation type, and the presence of portal vein thrombosis. RSC (Model 4) had the greatest number of significant covariates than others.

Most of the HRs in Model 1, 2, 3, and 5 were close to each other, except two covariates, on ventilator and the presence of portal vein thrombosis, whose HRs were greater in Model 2, 3 and 5 than in Model 1. HRs in Model 4 were far apart from those in other models, especially the HR of serum creatinine which changed from 0.6 to 0.8 in Model 1 - 3, and to 9.3 in Model 4.

The estimated ϕ from Model 5 was 1.02 with a p-value of 0.054, reflecting a non-significant positive relationship between retransplant and death.

Allocation type in Model 1 and presence of portal vein thrombosis in Model 2 violate the PH assumption, which indicates that HR of the variable varies over time. The HR obtained from a proportional hazards regression model gave a weighted average of the time-varying HR. We can fit a Gray time-varying coefficients model to check how HR changes over time. [12]

Table 3. Multivariable analysis

	Cox - Retransplant as event				Cox - Retransplant as censor				Fine & Gray model				RSC - W1				Joint Modeling							
	HR	95% CI		p-value	HR	95% CI		p-value	HR	95% CI		p-value	HR	95% CI		p-value	HR	95% CI		p-value	phi		sigma	
		LL	UL			LL	UL			LL	UL			LL	UL			LL	UL		est	p-value	est	p-value
Recipient age 1 -- 2	0.89	0.62	1.26	0.502	0.91	0.53	1.56	0.732	0.92	0.52	1.63	0.780	1.52	0.85	2.72	0.161	0.89	0.48	1.66	0.719				
Recipient age > 2	0.80	0.52	1.22	0.297	0.86	0.44	1.67	0.658	0.88	0.45	1.70	0.700	1.38	0.64	2.99	0.411	0.79	0.37	1.70	0.554				
Donor age	0.48	0.32	0.71	<0.001‖	0.71	0.36	1.43	0.343	0.75	0.37	1.52	0.430	1.36	0.64	2.87	0.425	0.81	0.37	1.78	0.601				
Recipient race (White/Other)	1.22	0.92	1.60	0.168	1.03	0.67	1.58	0.895	1.01	0.65	1.57	0.970	1.02	0.60	1.74	0.944	0.96	0.58	1.57	0.859				
Bilirubin	0.99	0.98	1.00	0.141	1.01	0.99	1.03	0.271	1.01	0.99	1.03	0.230	0.97	0.94	0.99	0.015‖	1.01	0.98	1.03	0.527				
Serum creatinine *	0.84	0.45	1.56	0.575	0.69	0.25	1.85	0.456	0.69	0.29	1.63	0.400	9.31	2.43	35.61	0.001‖	0.61	0.19	1.94	0.399				
Procurement distance	1.00	1.00	1.00	0.904	1.00	1.00	1.00	0.180	1.00	1.00	1.00	0.110	1.00	1.00	1.00	0.312	1.00	1.00	1.00	0.107	1.02	0.054	1.93	0.002
On ventilator	2.41	1.44	4.03	0.001‖	3.16	1.62	6.18	<0.001‖	3.12	1.57	6.20	<0.001‖	4.40	2.09	9.23	<0.001‖	5.64	1.86	17.11	0.002‖				
CMV positive	0.97	0.72	1.30	0.832	1.03	0.65	1.62	0.903	1.03	0.65	1.64	0.890	0.76	0.47	1.21	0.241	0.99	0.57	1.72	0.982				
Allocation type (Local/Other)	0.87	0.62	1.22	0.433	0.53	0.32	0.90	0.019‖	0.53	0.32	0.88	0.015‖	0.39	0.20	0.76	<0.001‖	0.42	0.21	0.82	0.011‖				
Ascites	1.36	1.02	1.81	0.033‖	1.38	0.88	2.15	0.156	1.38	0.87	2.18	0.170	1.64	1.00	2.71	0.052	1.53	0.89	2.66	0.127				
Split donor organ	1.12	0.79	1.60	0.524	1.56	0.90	2.71	0.110	1.60	0.93	2.76	0.090	1.45	0.76	2.77	0.256	1.48	0.78	2.80	0.226				
Portal vein thrombosis **	1.42	0.79	2.55	0.247	2.50	1.14	5.48	0.022‖	2.54	1.11	5.79	0.027‖	5.76	2.32	14.30	<0.001‖	3.88	1.25	12.09	0.019‖				

Abbreviation: CI (Confidence Interval), LL(Lower Limit), UL(Upper Limit), HR(Hazard Ratio), EST(Estimate).

* Serum creatinine values were missing for 72 children: 61 alive, 6 retransplanted and 5 dead.

** Portal vein thrombosis has missing values in 25 subjects: 23 alive, 1 retransplanted, and 1 dead.

‖Statistically significant at the level of 0.05.

3.4 SENSITIVITY ANALYSIS

Data of recipients who had cadaveric donor was included in this sensitivity analysis. Among 1250 recipients, there were 83 (6.64%) died, 114 (9.12%) retransplanted, and 1,053 (84.24%) were alive at the study cutoff date. Table 4 shows the univariable results. Covariate selection was the same as that in models using the entire data, although some covariates were significant in sensitivity test and not in the entire data study. These covariates included presence of portal vein thrombosis in the Cox model with retransplant as event, and split or nonsplit organ in the Cox model with retransplant as censoring and in the joint model. In addition, all the univariable models in the joint model were converged in the sensitivity analysis.

Table 5 shows the multivariable results which appeared to have more significant covariates than that in the model using entire data. The difference came from two covariates, presence of ascites and split organ, which were significant in models with recipients of cadaveric organs, but not in the models with all recipients. From the joint model, estimated ϕ was positive and its p-value was less than 0.05, indicating that retransplant and death were significantly positively related.

Table 4. Sensitivity analysis - univariable analysis

		Cox - Retransplant as event				Cox - Retransplant as censor				Fine & Gray model				Random Signs Censoring				Joint Modeling							
		HR	95% CI		p-value	HR	95% CI		p-value	HR	95% CI		p-value	HR	95% CI		p-value	HR	95% CI		p-value	phi		sigma	
			LL	UL			LL	UL			LL	UL			LL	UL			LL	UL		est	p-value	est	p-value
Recipient age	1 -- 2	0.86	0.62	1.21	0.395	0.69	0.40	1.20	0.190	0.70	0.40	1.20	0.190	1.79	1.09	2.95	0.022‖	0.63	0.35	1.15	0.134‖	1.36	0.153	1.54	0.048
	> 2	0.54	0.37	0.80	0.002‖	0.49	0.27	0.91	0.023‖	0.51	0.28	0.93	0.029‖	1.93	1.09	3.42	0.025‖	0.45	0.23	0.88	0.019‖				
Donor age		0.49	0.36	0.67	<0.001‖	0.81	0.47	1.39	0.440	0.88	0.51	1.51	0.640	0.83	0.51	1.34	0.443	1.19	0.67	2.12	0.548	1.01	0.237	1.88	0.052
Recipient gender		1.04	0.78	1.38	0.807	1.06	0.69	1.64	0.789	1.06	0.68	1.64	0.800	0.74	0.49	1.10	0.139	1.04	0.64	1.69	0.889	1.10	0.241	1.78	0.069
Donor gender		1.01	0.76	1.34	0.951	1.11	0.72	1.71	0.640	1.12	0.73	1.72	0.610	0.85	0.58	1.25	0.409	1.14	0.70	1.86	0.603	1.07	0.251	1.81	0.070
Recipient race (White/Other)		1.21	0.92	1.60	0.178	0.99	0.64	1.52	0.958	0.97	0.63	1.49	0.880	1.47	0.98	2.18	0.061‖	0.97	0.60	1.57	0.889	1.10	0.238	1.79	0.066
Donor race (White/Other)		0.99	0.75	1.31	0.943	0.85	0.55	1.30	0.445	0.84	0.55	1.30	0.430	1.18	0.80	1.73	0.407	0.83	0.51	1.34	0.442	1.12	0.213	1.76	0.057
ABO compatible		1.44	0.53	3.87	0.472	2.42	0.34	17.40	0.379	2.41	0.33	17.45	0.380	0.36	0.05	2.56	0.309	2.39	0.30	19.20	0.412	1.13	0.231	1.75	0.067
Recipient blood type	A	1.01	0.74	1.37	0.956	0.73	0.46	1.18	0.201	0.72	0.45	1.16	0.180	0.99	0.65	1.49	0.947	0.71	0.42	1.20	0.198	1.65	0.424	1.32	0.296
	B	0.77	0.48	1.24	0.280	0.52	0.24	1.15	0.107	0.52	0.24	1.15	0.110	1.11	0.56	2.20	0.764	0.52	0.22	1.19	0.123				
	AB	0.46	0.19	1.14	0.095	0.19	0.03	1.36	0.097	0.19	0.03	1.34	0.096	1.29	0.20	8.42	0.787	0.20	0.03	1.46	0.112				
Donor blood type	A	0.93	0.69	1.26	0.645	0.62	0.37	1.01	0.056	0.61	0.37	1.00	0.048	0.87	0.57	1.34	0.533	0.59	0.34	1.03	0.065	1.41	0.313	1.49	0.166
	B	0.90	0.56	1.43	0.651	0.60	0.27	1.33	0.211	0.60	0.27	1.32	0.200	1.07	0.54	2.10	0.853	0.60	0.26	1.40	0.237				
	AB	0.44	0.11	1.78	0.250	0.44	0.06	3.20	0.420	0.45	0.06	3.22	0.430	1.25	0.19	8.09	0.818	0.50	0.06	3.91	0.505				
On ventilator		2.00	1.18	3.38	0.010‖	2.96	1.48	5.92	<0.001‖	2.90	1.45	5.87	<0.001‖	2.60	1.31	5.19	<0.001‖	4.38	1.39	13.78	0.012‖	0.99	0.184	1.90	0.029
Procurement distance		1.00	1.00	1.00	0.944	1.00	1.00	1.00	0.306	1.00	1.00	1.00	0.210	1.00	1.00	1.00	0.017‖	1.00	1.00	1.00	0.313	1.02	0.218	1.88	0.044
Albumin		0.94	0.78	1.13	0.485	0.94	0.71	1.25	0.682	0.94	0.71	1.26	0.690	1.01	0.74	1.37	0.957	0.91	0.64	1.29	0.610	1.09	0.241	1.79	0.067
Bilirubin		1.00	0.99	1.01	0.763	1.02	1.00	1.04	0.055‖	1.02	1.00	1.03	0.026‖	1.00	0.98	1.02	0.896	1.02	1.00	1.04	0.126	1.41	0.300	1.49	0.154
INR		0.99	0.93	1.06	0.869	1.00	0.91	1.09	0.931	1.00	0.95	1.04	0.840	1.02	0.85	1.24	0.809	0.99	0.88	1.13	0.936	1.10	0.240	1.78	0.068
Serum creatinine*		0.63	0.32	1.23	0.174	0.62	0.22	1.75	0.367	0.66	0.26	1.66	0.370	6.23	1.91	20.30	0.002‖	0.54	0.17	1.72	0.297	1.21	0.157	1.69	0.039
CMV positive		0.79	0.58	1.08	0.139	0.79	0.49	1.27	0.331	0.80	0.50	1.29	0.360	0.51	0.32	0.81	0.004‖	0.72	0.40	1.29	0.269	1.02	0.223	1.88	0.047
Allocation type (Local/Other)		0.99	0.74	1.31	0.918	0.86	0.55	1.35	0.517	0.88	0.56	1.36	0.560	0.36	0.23	0.56	<0.001‖	0.81	0.48	1.37	0.425	1.12	0.218	1.77	0.057
Ascites		1.43	1.07	1.90	0.014‖	1.75	1.12	2.74	0.014‖	1.74	1.11	2.73	0.015‖	1.87	1.20	2.90	0.005‖	1.85	1.09	3.14	0.024‖	1.23	0.186	1.66	0.055
Split donor organ		1.03	0.77	1.37	0.847	1.71	1.11	2.64	0.014‖	1.76	1.14	2.70	0.010‖	0.51	0.34	0.77	0.002‖	1.69	1.08	2.66	0.023‖	2.41	0.551	0.97	0.474
Portal vein thrombosis**		1.65	0.92	2.95	0.094‖	2.34	1.08	5.07	0.032‖	2.31	1.04	5.12	0.040‖	3.63	1.65	7.98	0.001‖	3.35	1.07	10.56	0.039‖	1.01	0.168	1.89	0.024
Previous abdominal surgery**		0.88	0.64	1.20	0.410	1.05	0.64	1.72	0.849	1.06	0.65	1.73	0.820	0.71	0.45	1.12	0.139	1.19	0.67	2.12	0.548	1.01	0.237	1.88	0.052

Abbreviation: CI (Confidence Interval), LL(Lower Limit), UL(Upper Limit), HR(Hazard Ratio), EST(Estimate).

* Serum creatinine values were missing for 72 children: 61 alive, 6 retransplanted and 5 dead.

** Both portal vein thrombosis and previous abdominal surgery have missing values in 25 subjects: 23 alive, 1 retransplanted, and 1 dead.

‖Statistically significant at the level of 0.15.

Table 5. Sensitivity analysis - multivariable analysis

		Cox - Retransplant as event				Cox - Retransplant as censor				Fine & Gray model				RSC - W1				Joint Modeling							
		HR	95% CI		p-value	HR	95% CI		p-value	HR	95% CI		p-value	HR	95% CI		p-value	HR	95% CI		p-value	phi		sigma	
			LL	UL			LL	UL			LL	UL			LL	UL			LL	UL		est	p-value	est	p-value
Recipient age	1 -- 2	0.84	0.58	1.22	0.373	0.72	0.40	1.31	0.281	0.73	0.39	1.37	0.320	1.48	0.77	2.81	0.236	0.68	0.35	1.33	0.260				
	> 2	0.74	0.47	1.16	0.191	0.77	0.39	1.56	0.474	0.79	0.39	1.59	0.510	1.37	0.59	3.21	0.466	0.70	0.31	1.56	0.382				
Donor age		0.48	0.32	0.72	<0.001‖	0.71	0.35	1.42	0.332	0.75	0.37	1.53	0.430	1.27	0.58	2.78	0.542	0.81	0.37	1.78	0.603				
Recipient race (White/Other)		1.24	0.92	1.66	0.152	0.99	0.63	1.57	0.975	0.97	0.61	1.53	0.880	0.95	0.52	1.72	0.857	0.93	0.55	1.58	0.787				
Bilirubin		0.99	0.97	1.00	0.126	1.01	0.99	1.03	0.524	1.01	0.99	1.03	0.470	0.97	0.94	0.99	0.020‖	1.00	0.98	1.03	0.836				
Serum creatinine *		0.81	0.42	1.59	0.542	0.66	0.22	1.96	0.454	0.68	0.26	1.74	0.420	11.22	2.51	50.10	0.002‖	0.57	0.16	2.02	0.383				
Procurement distance		1.00	1.00	1.00	0.895	1.00	1.00	1.00	0.167	1.00	1.00	1.00	0.100	1.00	1.00	1.00	0.393	1.00	1.00	1.00	0.104	1.06	0.036	1.87	0.001
On ventilator		2.18	1.24	3.82	0.007‖	2.52	1.18	5.39	0.017‖	2.47	1.10	5.52	0.028‖	4.26	1.87	9.69	0.001‖	4.20	1.36	12.94	0.013‖				
CMV positive		0.87	0.64	1.20	0.410	0.87	0.54	1.42	0.585	0.88	0.54	1.44	0.610	0.68	0.41	1.14	0.147	0.81	0.45	1.46	0.481				
Allocation type (Local/Other)		0.99	0.70	1.40	0.959	0.61	0.36	1.06	0.079	0.61	0.35	1.04	0.067	0.34	0.16	0.71	0.004‖	0.50	0.25	0.99	0.046‖				
Ascites		1.48	1.09	2.01	0.012‖	1.69	1.04	2.74	0.034‖	1.68	1.02	2.77	0.042‖	1.70	0.97	2.99	0.065	1.99	1.09	3.63	0.026‖				
Split donor organ		1.26	0.87	1.80	0.220	1.72	0.99	3.00	0.053	1.76	1.01	3.05	0.044‖	1.47	0.76	2.84	0.253	1.69	0.89	3.23	0.110				
Portal vein thrombosis **		1.47	0.81	2.66	0.201	2.62	1.19	5.79	0.017‖	2.69	1.16	6.22	0.021‖	6.29	2.43	16.25	<0.001‖	4.24	1.34	13.37	0.014‖				

Abbreviation: CI (Confidence Interval), LL(Lower Limit), UL(Upper Limit), HR(Hazard Ratio), EST(Estimate).

* Serum creatinine values were missing for 72 children: 61 alive, 6 retransplanted and 5 dead.

** Portal vein thrombosis has missing values in 25 subjects: 23 alive, 1 retransplanted, and 1 dead.

‖Statistically significant at the level of 0.05.

4.0 DISCUSSION

We studied five different models in analyzing marginal posttransplant survival when some patients received retransplantats. One of the commonly used approaches is Fine and Gray model, which assumes that the main event would never occurs if the competing event is observed. Obviously this assumption is not applicable for analyzing posttransplantation survival, where recipients may die even after retransplantation. On the other hand, patients on the wait list of retransplantation could die due to graft failure or other complications. Since the competing events could overtake the occurrence of the main event, the RSC method can be applied in this situation. Opposite to the Fine and Gray method, the main event and competing event is positively associated in a RSC model. Although in our study of posttransplantation survival, the RSC model is more suitable than the Fine and Gray model according to the scientific explanation, the results of the RSC model were inconsistent with other methods. It could be the performance of the IPCW estimators used in the RSC method is only acceptable under low or moderate censoring percentage (<35%). Unfortunately, the censoring rate in our data was as high as 85.23%. We then devised the joint modeling approach, which was used as the gold standard to test the relationship of the main and the competing events. The estimated value of ϕ was positive but not significant, which indicates that there is no evidence to reject the independence claim of the two events. It is worth noting that working with joint

modeling could be challenging if one cannot make it convergence, and the model fitting is time consuming. Based on the assumption that death and retransplant are independent, the Cox PH model treating competing event as censoring was the best choice.

In conclusion, Fine and Gray model will perform the best if the competing event is perfectly negatively associated to the main event. If the events are positively associated, the RSC method could the model of choice but only when the censoring percentage is below 35%. Meanwhile, the joint modeling approach could be used as a standard to verify the relationship between the main and competing events, although it may have convergence issue. If unfortunately neither of these models fit well, one may choose to fit a Cox PH model treating competing event as censoring.

BIBLIOGRAPHY

1. Bates MD, Bucuvalas JC, Alonso MH, Ryckman FC. Biliary atresia: pathogenesis and treatment. Semin Liver Dis 1998; 3: 281–293.

2. Goss JA, Shackleton CR, Swenson K, Satou NL, Nuesse BJ, Imagawa DK, Kinkhabwala MM, Seu P, Markowitz JS, Rudich SM, McDiarmid SV, Busuttil RW. Orthotopic liver transplantation for congenital biliary atresia: a 11-year, single center experience. Ann Surg 1996; 224:276–287.

3. Fouquet V, Alves A, Branchereau S, Grabar S, Debray D, Jacquemin E, Devictor D, Durand P, Baujard C, Fabre M, Pariente D, Chardot C, Dousset B, Massault PP, Bernard D, Houssin D, Bernard O, Gauthier F, Soubrane O. Long-term outcome of pediatric liver transplantation for biliary atresia: a 10-year follow-up in a single center. Liver Transpl 2005; 11(2):152–160.

4. Davis A, Rosenthal P, Glidden D. Pediatric liver retransplantation: outcomes and a prognostic scoring tool. Liver Transpl 2009; 15(2):199–207.

5. Cox DR. Regression models and life tables (with discussion). Journal of the Royal Statistical Society – Series B 1972; 34:187–220.

6. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. Journal of the American Statistical Association, 1999; 94:496–509.

7. Yabes JG. Semiparametric Estimators in Competing Risks Regression Models (Unpublished PhD dissertation). University of Pittsburgh, Pittsburgh, PA.

8. Fu B. Joint Modeling of Time-to-Event Data with Competing Risks (Unpublished PhD dissertation). University of Pittsburgh, Pittsburgh, PA.

9. Chardot C, Buet C, Serinet MO, Golmard JL, Lachaux A, Roquelaure B, Gottrand F, Broué P, Dabadie A, Gauthier F, Jacquemin E. Improving outcomes of biliary atresia: French national series 1986-2009. J Hepatol 2013; 58(6):1209–1217.

10. Utterson EC, Shepherd RW, Sokol RJ, Bucuvalas J, Magee JC, McDiarmid SV, Anand R; Split Research Group. Biliary atresia: clinical profiles, risk factors, and

outcomes of 755 patients listed for liver transplantation. J Pediatr 2005; 147(2):180–185.

11. Peterson AV. Bounds for a joint distribution function with fixed sub-distribution functions: Application to competing risks. Proc Natl Acad Sci USA 1976; 73(1):11–13.

12. Gray RJ. Flexible methods for analyzing survival data using splines, with applications to breast cancer prognosis. Journal of the American Statistical Association 1992; 87(420): 942–951.