NONPARAMETRIC ESTIMATION OF THE ASSOCIATION BETWEEN LIVER TRANSPLANTATION WAITING TIME AND POSTTRANSPLANT GRAFT FAILURE

by

Chunyan Wang

B.S., University of Science and Technology Beijing, China, 1983

M.S., University of Science and Technology Beijing, China, 1989

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

2016

UNIVERSITY OF PITTSBURGH

Graduate School of Public Health

This thesis was presented

by

Chunyan Wang

It was defended on

April 18, 2016

and approved by

Committee Member:
Yu Cheng, PhD
Associate Professor
Departments of Statistics and Psychiatry
Dietrich School of Arts and Science, and School of Medicine
University of Pittsburgh

Committee Member:
Ada Youk, PhD
Associate Professor
Departments of Biostatistics and Epidemiology
Graduate School of Public Health
University of Pittsburgh

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

Chung-Chou H. Chang, PhD

NONPARAMETRIC ESTIMATION OF THE ASSOCIATION BETWEEN LIVER TRANSPLANTATION WAITING TIME AND POSTTRANSPLANT GRAFT FAILURE

Chunyan Wang, MS

University of Pittsburgh, 2016

ABSTRACT

Liver transplantation is the most effective treatment for patients with end-stage liver disease. While many factors are associated with posttransplant graft failure, it has been suspected that liver transplant waiting time is negatively associated with posttransplant survival. Due to the suspicion, efforts have been made to reduce wait time for patients. There were some studies investigating this relationship recently. However, these studies were performed either with restricted samples or using data from a single center, and the results were inconclusive. For example, a study showed that after the Model for End-Stage Liver Disease (MELD) era, a longer waiting time predicts longer posttransplant survival for adult patients with hepatocellular carcinoma, whereas another study found no significant relationship between waiting time and posttransplant survival.

In this study, we quantified the time-varying association (time-varying odds ratio) between liver transplant waiting time and posttransplant mortality in the presence of retransplantation as a competing risk. We also applied two different methods to estimate the cumulative incidence of posttransplant mortality. In the first method, the univariate cumulative incidence function method, we assume independence between the liver transplant waiting time and posttransplant survival. The second method, the bivariate cumulative incidence function

method, takes into account the association between transplant waiting time and posttransplant survival. Our analytic dataset was extracted from the United Network for Organ Sharing (UNOS) Standard Transplant Analysis and Research (STAR) database. The subjects in our study included 1,265 transplant candidates who were first on the liver transplant waiting list from 2002 to 2012 and were 1-11 years old. Our analysis showed that liver transplant waiting time is positively associated with posttransplant survival. Further investigation is needed to understand whether this finding was because of survivor bias; that is, those who were able to wait longer were healthier. Our analysis also indicated that retransplantation has a weak association with liver transplant waiting time.

PUBLIC HEALTH SIGNIFICANCE: We applied two different methods to pediatric liver transplant data in estimating cumulative incidence of posttransplant mortality. The findings will be the first step to help the liver transplant community understand the impact of liver transplant waiting time on posttransplant survival, and will help researchers further identify indicators of liver transplantation for reducing posttransplant mortality thus have a significant impact on future public health research.

TABLE OF CONTENTS

PREFACE X

1.0 INTRODUCTION 1

2.0 METHODS 4

2.1 DATASET 4

2.2 UNIVARATE CUMULATIVE INCIDENCE FUNCTION MODEL 5

2.3 BIVARIATE CUMULATIVE INCIDENCE FUNCTION MODEL 6

3.0 RESULTS 11

3.1 WAITING TIME AMONG LIVER TRANSPLANT CANDIDATES 11

3.2 WAITING TIME AMONG LIVER TRANSPLANT RECIPIENTS 14

3.3 ESTIMATED CUMULATIVE INCIDENCE OF POSTTRANSPLANT MORTALITY USING THE UNIVARIATE MODEL 17

3.4 ESTIMATED CUMULATIVE INCIDENCE OF POSTTRANSPLANT MORTALITY USING THE BIVARIATE MODEL 21

4.0 DISCUSSION 35

APPENDIX: R CODE FOR BOOTSTRAP RESAMPLES 37

BIBLIOGRAPHY 41

LIST OF TABLES

Table 1. PELD score at the time of listing among liver transplant candidates 11

Table 2. PELD score at the time of listing and waiting time among liver transplant recipients .. 14

Table 3. Cumulative incidences of posttransplant mortality and retransplantation among 911 liver transplant recipients 18

Table 4. Cumulative incidences of posttransplant mortality and retransplantation by listing PELD score among 911 liver transplant recipients..... 18

Table 5. Cumulative incidences of posttransplant mortality and retransplantation accounted for waiting time (standard errors are in the parentheses) 23

Table 6. Cumulative incidences of posttransplant 5-year mortality and retransplantation accounted for waiting time by listing PELD score (standard errors are in the parentheses) 23

Table 7. PELD score at the time of listing by liver transplant waiting time..... 32

LIST OF FIGURES

Figure 1. Kaplan-Meier curve of liver transplant rate with 95% confidence interval 12

Figure 2. Kaplan-Meier curve of liver transplant rate by listing PELD score among candidates waiting 0 to 3000 days 13

Figure 3. Kaplan-Meier curve of liver transplant rate by listing PELD score among candidates waiting 0 to 500 days 13

Figure 4. Kaplan-Meier curve of posttransplant survival rate with 95% confidence interval 15

Figure 5. Kaplan-Meier curve of posttransplant survival rate by listing PELD score among recipients surviving 0 to 4000 days posttransplantation 16

Figure 6. Kaplan-Meier curve of posttransplant survival rate by listing PELD score among recipients surviving 0 to 500 days posttransplantation 16

Figure 7. Cumulative incidences of posttransplant mortality and retransplantation (the left panel is for failure time 0 to 4000 days and the right panel is for failure time 0 to 200 days)..... 19

Figure 8. Cumulative incidences of posttransplant mortality and retransplantation by listing PELD (the left panel is for failure time 0 to 4000 days and the right panel is for failure time 0 to 200 days) 20

Figure 9. Cumulative incidences of posttransplant mortality and retransplantation accounted for liver transplant waiting time (the top panel is for the recipients who received LT earlier or later

than 3 days and the bottom panel is for the recipients who received LT earlier or later than 30 days 27
Figure 10. Cumulative incidences of posttransplant mortality and retransplantation accounted for liver transplant waiting time (the top panel is for the recipients who received LT earlier or later than 60 days and the bottom panel is for the recipients who received LT earlier or later than 90 days) 28
Figure 11. Odds ratios of posttransplant death between the recipients who received LT earlier than 3, 30, 60, and 90 days and the recipients who received LT later than 3, 30, 60, and 90 days along with 95% confidence intervals 30
Figure 12. Odds ratios of posttransplant death between the recipients who received LT earlier than 3, 30, 60, and 90 days and the recipients who received LT later than 3, 30, 60, and 90 days along with 95% confidence intervals (odds ratios are up to 10) 31
Figure 13. Odds ratios of posttransplant death between the recipients who received LT earlier than 3, 30, 60, and 90 days and the recipients who received LT later than 3, 30, 60, and 90 days by listing PELD 34

PREFACE

I would first and foremost like to thank my advisor Dr. Chung-Chou H. Chang for all the help and guidance she has provided during the work on this thesis. I could not have finished my thesis without her tremendous patience and continuous encouragement. Second, I would like to thank my thesis committee members Dr. Yu Cheng and Dr. Ada Youk for the time and effort that they have dedicated to this project. Thanks to Dr. Yu Cheng for her help and guidance to statistical methodology. Thanks to Dr. Ada Youk for her advice and help during my graduate study. I would also like to extend my sincere gratitude to Dr. Andriy Bandos for his valuable advice and suggestions during my graduate study. Finally, I would like to thank my family for all their love and support throughout my education.

1.0 INTRODUCTION

Liver transplantation (LT) is the most effective treatment for patients with end-stage liver disease. Currently, the 5-year survival rate for pediatric liver transplant recipients is greater than 80% in the United States [1]. However, the number of patients on the LT waiting list exceeds the number of available grafts. For the period from 2012 to 2014, among 1,589 pediatric recipients, 36.1% of recipients waited less than 31 days and 14.7% waited 31 to 60 days [1]. Patients who qualify for liver transplantation are stratified according to the severity of their illness in order to identify more urgent need of liver transplantation. For example, the severity of chronic liver disease for patients younger than 12 years of age is measured according to the Pediatric End-Stage Liver Disease (PELD) scoring system. A higher PELD score indicates a more critical medical condition. Under the “sickest children first” allocation policy, pediatric patients younger than 12 years of age receive priority according to their PELD scores to reduces pretransplantation mortality without reducing posttransplantation survival [2].

The recovery following liver transplantation is a complex process during which patients might experience a series of complications, including rejection and possible infection. As a result of these complications, some patients require a second or even third LT. From 2012 to 2014, 8.8% of pediatric recipients required retransplantation [1]. Furthermore, the timing of liver transplantation is critical to minimizing the risk of patients dying on the waiting list in order to ensure that the children are in optimal condition to survive transplantation [3]. Efforts have been

made to reduce the time on the waiting list [4]. There is limited research on the association between the time on the LT waiting list and LT survival. A single-center study for adult patients with hepatocellular carcinoma (HCC) has shown that waiting time has no relation with posttransplant survival [5]. In contrast, another study for adult patients with HCC in a national transplant registry has demonstrated that a longer waiting time for HCC patients predicts longer posttransplant survival, while a longer waiting time for non-HCC patients predicts shorter posttransplant survival [6]. The association between the LT waiting time and posttransplant survival remains inconclusive.

To study the association between the LT waiting time and the posttransplant survival, retransplantation has to be taken into account because retransplantation prevents or delays the occurrence of posttransplant mortality; this is referred to as a competing risk in survival analysis. In addition, because that liver transplantation and posttransplant graft failure are two successive events, the posttransplant graft failure time is observable only when the LT waiting time is first observed; this is referred to as dependent censoring in survival analysis. These two issues must be accounted for when we evaluate the association between the LT waiting time and posttransplant graft failure. Our study aims to address these two issues of estimating the cumulative probabilities of posttransplant graft failure and examining the time-varying association between the liver transplant waiting time and posttransplant mortality in the presence of retransplantation competing risk.

One way to estimate the cumulative probabilities of the cause-specific failure is to use the univariate cumulative incidence function (CIF) model [7]. The drawbacks of using this model are that it ignores the impact of LT waiting time on the posttransplant mortality and that the estimation is restricted to LT recipients.

A number of studies were done on the time-to-event data for successive events with censoring by the first event, and a number of estimators were proposed [8-13]. In addition, bivariate time-to-event data with competing risks censoring were studied and several estimators were proposed [14-16]. However, none of these methods is appropriate for the LT data being analyzed in this study. Recently, a bivariate cumulative incidence function model was proposed for data with two successive event times to estimate the cumulative probabilities of the cause-specific failure in the subsequent event, in which there exists dependent censoring between the two events and the second event time is subject to competing risks [17]. This model also provided estimation of the cause-specific odds ratio that can be used to describe the association between the two event times. We adopted the method of the bivariate CIF model to investigate the association between the LT waiting time and the posttransplant graft failure time.

To explore the impact of the LT waiting time on posttransplant graft failure, the following assumptions were made: 1) Patient death or retransplantation, whichever comes first, is defined as a posttransplant graft failure. Each LT recipient could fail from only one of these two causes. 2) The LT waiting time had right independent censoring only, and no other competing event could occur. 3) The posttransplant graft failure time was subject to censoring related to the LT waiting time and it was also subject to independent right censoring.

The rest of the thesis is organized as follows. In Section 2, we describe the structure of the data used in the study, the univariate CIF model, and the bivariate CIF model. We also detail the nonparametric estimation of the bivariate CIF, the conditional CIF, and the cause-specific odds ratio. In Section 3, we present the results of applying the univariate CIF model and the bivariate CIF model to the LT data. We conclude the study with a discussion in Section 4.

2.0 METHODS

2.1 DATASET

The data used in this study is adopted from the United Network for Organ Sharing (UNOS) Standard Transplant Analysis and Research (STAR) data file for patients on the liver transplant waiting list. The analytic dataset consists of 1,289 pediatric liver transplant candidates whose age at the time of listing was between 1 and 11 years old and whose primary diagnoses were not cancers or acute liver disease. For the purpose of our study, we further removed 24 transplant recipients because they did not have any posttransplant information. The final dataset includes 1,265 liver transplant candidates. Variables of interest include PELD score at the time of listing, days from listing to transplant, transplant status (transplant or censored), days from transplant to graft failure, and posttransplant status (posttransplant death, retransplantation, or censored).

Two types of time-to-event variables are considered in this study. The first time-to-event variable is the LT waiting time and the second one is the posttransplant graft failure time. The first time-to-event variable is censored if a transplant candidate had not received a transplant by the study cutoff date or was removed from the waiting list for reasons other than transplant (e.g., no longer eligible to be a candidate because the patient is too sick or too healthy). The second time-to-event variable includes two types of failure: posttransplant patient mortality and retransplantation. The posttransplant patient mortality is treated as the event of interest and

retransplantation is considered as a competing risk. Transplant recipients are censored if they were alive and not retransplanted at the cutoff date for this study.

2.2 UNIVARATE CUMULATIVE INCIDENCE FUNCTION MODEL

We assume that each subject may experience two consecutive events. Those who do not experience the first event will not have a chance to experience the second event. Those who experience the first event may fail from one of the two causes for the second event. The univariate CIF model [17] has been developed to estimate cumulative incidence of the second event in presence of competing causes and is subject to the assumption of the independence of the two successive events. We ignore the first time-to-event and apply the model to data including only subjects who had experienced the first event.

Suppose there are n subjects at the beginning of the study. Among them, m ($\leq n$) subjects experience the first event, and each of the m subjects is subject to two failure types (l = 1, 2) in the subsequent event. Let T denote the potential gap time between these two successive events and C denote the time of the independent right censoring (i.e., T is independently censored by C). We observe (Y, η) for each subject, where Y = min (T, C), η = l·I($Y \leq C$). The data consist of m independent and identically distributed copies of (Y, η), denoted as $\{(Y_i, \eta_i), i = 1, \ldots, m.\}$

The univariate CIF is defined by

$$F_l(t) = P(T \leq t, \in= l\,) = \int_0^t \lambda_l(u) S(u -) du\,,$$

where ε is a cause indicator and l = 1, 2 is corresponding to the two competing causes in the subsequent event; $S(t) = P(T > t)$ is the all-cause survival distribution of T; and $\lambda_l(t)$ is the cause-specific hazard function. Note that $\lambda_l(t)$ is defined by

$$\lambda_l(t) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} P(t \leq T < t + \Delta t, \epsilon = l \mid T \geq t).$$

The univariate CIF $F_l(t)$ can be estimated by using the m observed pairs (Y_i, η_i) with the empirical form [18]

$$\hat{F}_l(t) = \sum_{u \leq t} \hat{S}(u-) \frac{\sum_{i=1}^{m} I(Y_i = u, \eta_i = l)}{\sum_{i=1}^{m} I(Y_i \geq u)}, \qquad (2.2.1)$$

where l = 1, 2 is corresponding to the two competing causes; $\hat{S}(u-)$ is the Kaplan-Meier estimator of the all-cause survival distribution of T evaluated at time just before u; $\hat{S}(t)$ is calculated from $\{(Y_i, \eta_i), i = 1, \ldots, m\}$ by treating any one of the two competing causes as the event of interests,

$$\hat{S}(t) = \prod_{u \leq t} \left(1 - \frac{\sum_{i=1}^{m} I(Y_i = u, \eta_i = 1) + \sum_{i=1}^{m} I(Y_i = u, \eta_i = 2)}{\sum_{i=1}^{m} I(Y_i \geq u)}\right).$$

2.3 BIVARIATE CUMULATIVE INCIDENCE FUNCTION MODEL

The univariate CIF model is useful only when the assumption of independence of the two successive time-to-event data holds. If the two events are indeed correlated, ignoring the dependence between these two consecutive times may lead to a biased estimation of the cumulative incidence of the cause specific failure in the subsequent event. The bivariate CIF

model [17] has been developed to address this issue with no assumptions about the independence of two successive time-to-events. The model provides a nonparametric analysis about association between the two successive times based on the bivariate cumulative incidences and the conditional cumulative incidences, accounting for the dependence of the two successive times.

We consider that n subjects may experience two successive events and each of them is subject to two failure types (l = 1, 2) in the subsequent event. Let X denote the potential first gap time and T denote the potential second gap time. Let C denote the time of the independent right censoring. Event times X and T are independently censored by C. Note that T is censored by (C - X)I($X < C$) because T is observable only when X is observed. We observe (Y_1, Y_2, η_1, η_2) for each subject, where $Y_1 = \min(X, C)$, $Y_2 = \min\{(X + T), C\}$, $\eta_1 = I(X \leq C)$, and $\eta_2 = l \cdot I(X + T \leq C)$. The data consist of n independent and identically distributed copies of (Y_1, Y_2, η_1, η_2), denoted as $\{(Y_{1i}, Y_{2i}, \eta_{1i}, \eta_{2i}), i = 1, \ldots, n\}$. The pair ($Y_{1i}$, η_{1i}) is the time to the first event and event status, and the pair (Y_{2i}, η_{2i}) is the time to the subsequent event and its status.

The bivariate CIF is defined by

$$F_l(x,t) = P(X \leq x, T \leq t, \in = l) = \int_0^x \int_0^t \lambda_l(u,v) S(u-, v-) du dv,$$

where ε a is cause indicator and l = 1, 2 is corresponding to the two competing causes in the subsequent event, $S(x, t) = P(X > x, T > t)$ is the bivariate all causes survival distribution of X and T, and $\lambda_l(x, t)$ is the bivariate cause-specific hazard function. $\lambda_l(x, t)$ is defined by

$$\lambda_l(x,t) = \lim_{\Delta x \to 0, \Delta t \to 0} \frac{1}{\Delta x \Delta t} P(x \leq X < x + \Delta x, t \leq T < t + \Delta t, \in = l \,|X \geq x, T \geq t).$$

$F_l(x, t)$ is estimated directly by using the observed times and its status $\{(Y_{1i}, Y_{2i}, \eta_{1i}, \eta_{2i}), i = 1, \ldots, n\}$.

$$\hat{F}_l(x,t) = \frac{1}{n}\sum_{i=1}^{n} \frac{I(Y_{1i} \le x, \eta_{1i}=1, Y_{2i}-Y_{1i} \le t, \eta_{2i}=l)}{\hat{G}(Y_{2i}-)} \quad , \tag{2.3.1}$$

where l = 1, 2 is corresponding to the two competing causes, $\hat{G}(Y_{2i}-)$ is the Kaplan-Meier estimator of the survival distribution $G(c) = P(C > c)$ of the independent censoring time C evaluated at just before time Y_{2i}, and $\hat{G}(c)$ is calculated from $\{(Y_{2i}, \eta_{2i}), i = 1, \ldots, n\}$ by treating censoring as an event and any one of two competing causes as censoring,

$$\hat{G}(c) = \prod_{u \le c}\left(1 - \frac{\sum_{i=1}^{n} I(Y_{2i}=u, \eta_{2i}=0)}{\sum_{i=1}^{n} I(Y_{2i} \ge u)}\right) .$$

Another approach to estimate $F_l(x, t)$, which is the equivalent to the estimator defined in Equation (2.3.1), is by means of the estimation of bivariate cumulative cause-specific hazard function and the bivariate all-cause survival distribution of time X and T. For details, refer to Chen's PhD dissertation [17].

To study the distribution of T while accounting for the dependence of X and T, the conditional CIF is defined by

$$F_l(t|x) = P(T \le t, \in = l | X \le x) = \frac{F_l(x,t)}{F_X(x)} ,$$

where ε is a cause indicator and l = 1, 2 is corresponding to the two competing causes, $F_X(x) = P(X \le x)$ is the marginal distribution of X, $F_X(x) = 1 - S_X(x)$ and $S_X(x)$ is the survival distribution of X. $F_l(t|x)$ is estimated by

$$\hat{F}_l(t|x) = \frac{\hat{F}_l(x,t)}{\hat{F}_X(x)} , \tag{2.3.2}$$

where l = 1, 2 is corresponding to the two competing causes, $\hat{F}_X(x)$ is calculated from {(Y_{1i}, η_{1i}), i = 1, …, n} by means of the Kaplan-Meier estimator $\hat{S}_X(x)$ of the survival distribution of X,

$$\hat{F}_X(x) = 1 - \hat{S}_X(x) = 1 - \prod_{u \le x} \left(1 - \frac{\sum_{i=1}^{n} I(Y_{1i}=u, \eta_{1i}=1)}{\sum_{i=1}^{n} I(Y_{1i} \ge u)}\right). \qquad (2.3.3)$$

$\hat{F}_l(t|x)$ quantifies the cumulative risk of the occurrence for a specific type of event, given the occurrence of the previous event by a certain time [17]. When X and T are independent of each other, the conditional CIF estimator $\hat{F}_l(t|x)$ defined in Equation (2.3.2) agrees with the univariate CIF estimator $\hat{F}_l(t)$ defined in Equation (2.2.1)

To study cause-specific association between X and T based on the conditional CIF $F_l(t|x)$, the cause-specific odds ratio, which is a time-dependent association measure, is defined as follows.

$$\emptyset_l(x, t|M) = \frac{P(T \le t,\ \in=l|\ X \le x)/\{1-P(T \le t,\ \in=l|\ X \le x)\}}{P(T \le t,\ \in=l|\ x < X \le M)\ /\{1-\ P(T \le t,\ \in=l|\ x < X \le M)\}},$$

where ε is a cause indicator and l =1, 2 is corresponding to the two competing causes in the subsequent event, and M is a fixed constant that can be chosen as appropriate.

$\Phi_l(x, t\,|M)$ is the ratio of the odds for having a cause l successive event by time t between those who have early occurrence of the first event and those who develop the first event later [17]. $\Phi_l(x, t\,|M) = 1$ indicates that for cause l , T is independent with X. $\Phi_l(x, t\,|M) > 1$

indicates that for cause l , T is positively associated with X. $\Phi_l(x, t|M) < 1$ indicates that for cause l , T is negatively associated with X.

$\Phi_l(x, t|M)$ is estimated by

$$\widehat{\emptyset}_l(x,t|M) = \frac{\hat{F}_l(t|x)/(1-\hat{F}_l(t|x))}{\hat{P}(T\le t,\in=l|x<X\le M)/(1-\hat{P}(T\le t,\in=l|x<X\le M))}\ , \tag{2.3.4}$$

$$\hat{P}(T \le t, \in= l|x < X \le M) = \frac{\hat{F}_l(M,t)-\hat{F}_l(x,t)}{\hat{F}_X(M)-\hat{F}_X(x)}\ , \tag{2.3.5}$$

where l =1, 2 is corresponding to the two competing causes, $\hat{F}_l(M,t)$ and $\hat{F}_l(x,t)$ are from Equation (2.3.1), $\hat{F}_l(t|x)$ is from Equation (2.3.2), $\hat{F}_X(M)$ and $\hat{F}_X(x)$ are from Equation (2.3.3).

3.0 RESULTS

3.1 WAITING TIME AMONG LIVER TRANSPLANT CANDIDATES

Table 1 summarizes the PELD score at the time of listing among the LT candidates. A total of 1,265 LT candidates were included in the study, in which 911 (72%) were LT recipients. Of the 1,265 candidates, 453 (35.81%) candidates had listing PELD scores less than 0, 408 (32.25%) had listing PELD scores between 0 and 10, 228 (18.02%) had listing PELD scores between 11 and 20, 113 (8.83%) had listing PELD scores between 21 and 30, and the rest of the candidates, 63 (4.98%), had listing PELD scores greater than 30. For the subsequent analyses, we divided the candidates into 4 groups according to their listing PELD score (<0, 0-10, 11-20, and >20). We collapsed the candidates whose listing PELD scores were greater than 20 into one group to increase the sample size.

Table 1. PELD score at the time of listing among liver transplant candidates

	All (n=1,265)	Alive and waiting LT^ (n=354)	LT^ Recipient (n=911)
PELD* n (%)			
< 0	453 (35.81)	145 (40.96)	308 (33.81)
0 - 10	408 (32.25)	97 (27.40)	311 (34.14)
11 - 20	228 (18.02)	64 (18.08)	164 (18.00)
21 - 30	113 (8.93)	32 (9.04)	81 (8.89)
> 30	63 (4.98)	16 (4.52)	47 (5.16)

* Pediatric end-stage liver disease model
^ Liver transplantation

The LT waiting time and posttransplant graft failure time are two consecutive event times in the study. We examined the distribution of the LT waiting time and the results are summarized as follows. Figure 1 illustrates the Kaplan-Meier estimate (with 95% CI) of rate of LT. Figures 2 and 3 depict the rates by the category of the listing PELD scores. The median waiting time to LT was 113 days (95% CI: 100-136 days). The results showed that candidates with listing PELD score greater than 20 (the sickest patients) had the shortest median waiting time of 11 days (95% CI: 8-18 days) while candidates with listing PELD scores less than 0 (the healthiest patients) had the longest median waiting time of 176 days (95% CI: 147-222 days). The median waiting time among candidates with listing PELD scores 0-10 was 128 days (95% CI: 106-166 days), and the median waiting time among candidates with listing PELD scores 11-20 was 90 days (95% CI: 69 to 133).

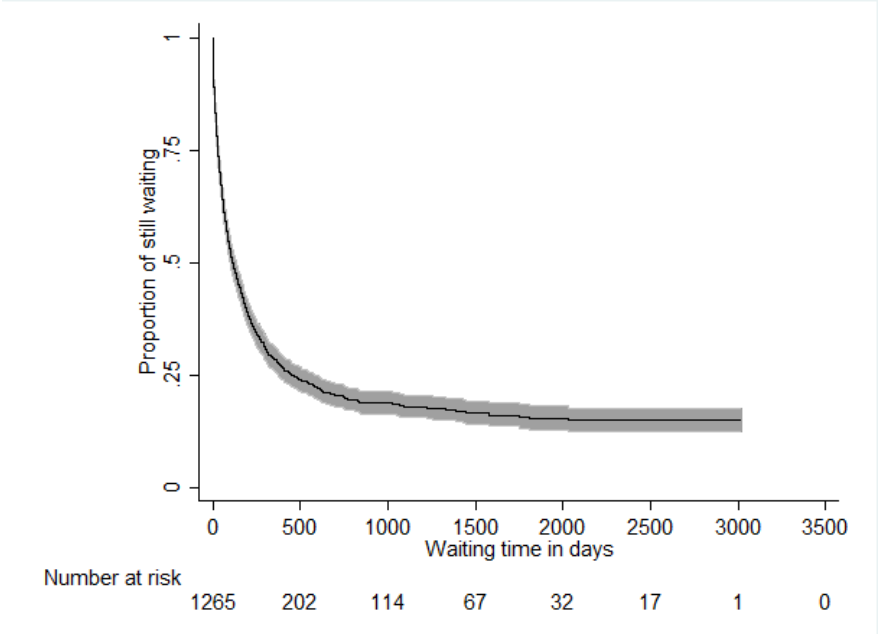

Figure 1. Kaplan-Meier curve of liver transplant rate with 95% confidence interval

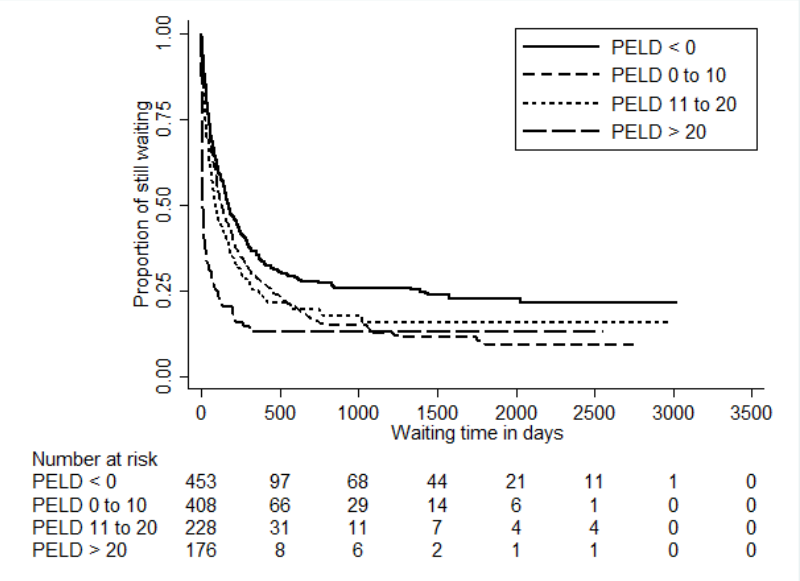

Figure 2. Kaplan-Meier curve of liver transplant rate by listing PELD score among candidates waiting 0 to 3000 days

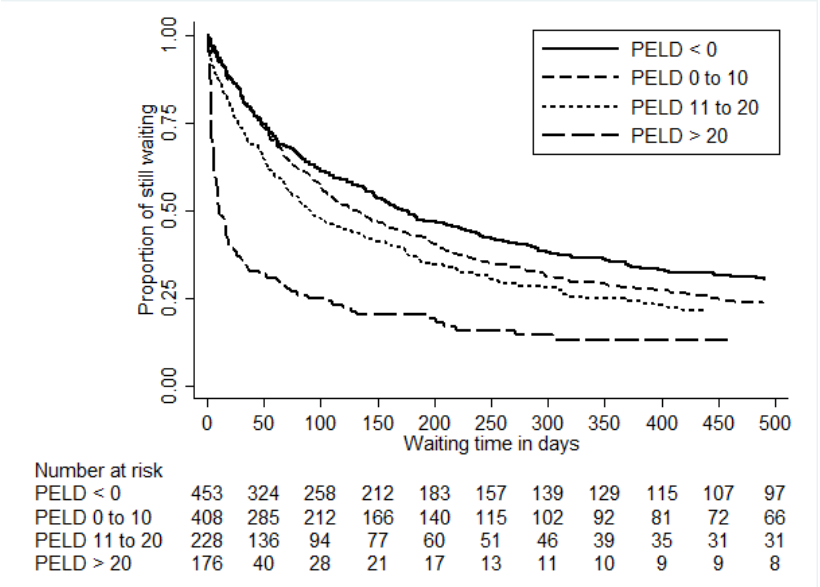

Figure 3. Kaplan-Meier curve of liver transplant rate by listing PELD score among candidates waiting 0 to 500 days

3.2 WAITING TIME AMONG LIVER TRANSPLANT RECIPIENTS

Table 2 summarizes the waiting time of all LT recipients in accordance with their PELD scores at the time of listing. Of the 911 LT recipients, 81 (8.9%) received retransplantation and 69 (7.6%) died without retransplantation. Among 911 LT recipients, 308 (33.8%) had listing PELD scores less than 0, 311 (34.1%) had listing PELD scores between 0 and 10, 164 (18.0%) had listing PELD scores between 11 and 20, 81 (8.9%) had listing PELD scores between 21 and 30, and 47 (5.2%) had listing PELD scores greater than 30. The median waiting time among all recipients was 62 days.

Table 2. PELD score at the time of listing and waiting time among liver transplant recipients

	All (n=911)	Alive (n=761)	Retransplantation (n=81)	Death (n=69)
PELD* n (%)				
< 0	308 (33.81)	268 (35.22)	27 (33.33)	13 (18.84)
0 - 10	311 (34.14)	253 (33.25)	28 (34.57)	30 (43.38)
11 - 20	164 (18.00)	137 (18.00)	15 (18.52)	12 (17.39)
21 - 30	81 (8.89)	69 (9.07)	7 (8.64)	5 (7.25)
> 30	47 (5.16)	34 (4.47)	4 (4.94)	9 (13.04)
Waiting time (days)				
Median (IQR)	62 (18 - 175)	66 (19 - 183)	49 (17 - 165)	42 (8 - 107)
Mean ± SD	144 ± 230	148 ± 228	147 ± 285	98 ± 165
Range	1 - 2029	1 - 1085	1 - 2029	1 - 1068

*PELD = Pediatric end-stage liver disease model

Figure 4 illustrates the Kaplan-Meier estimates of posttransplant survival rate among LT recipients. The overall 5-year posttransplant survival rate of LT recipients was 84.05% (95% CI: 81.97% to 86.38%).

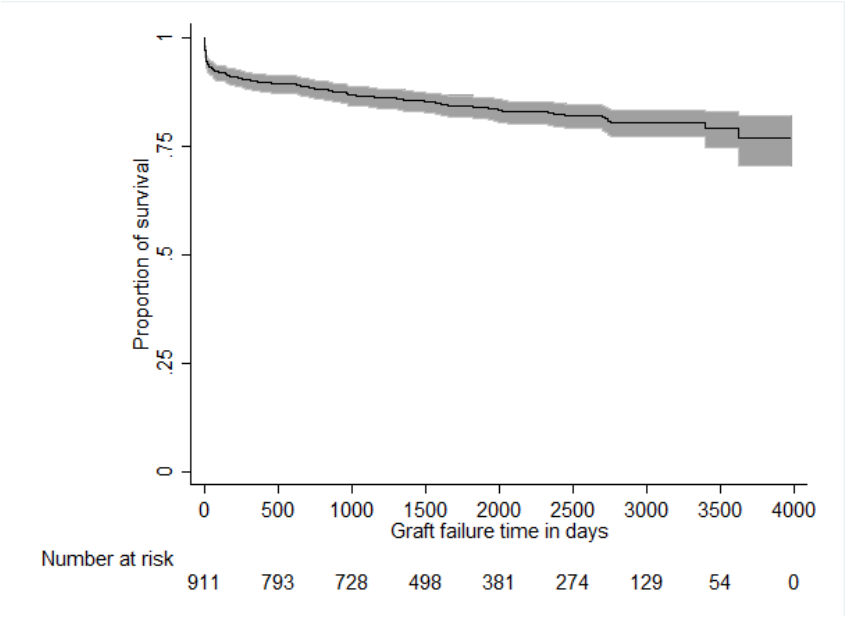

Figure 4. Kaplan-Meier curve of posttransplant survival rate with 95% confidence interval

Figure 5 and 6 illustrate the Kaplan-Meier estimates of posttransplant survival rate among LT recipients stratified by their listing PELD scores. The survival rates within 1 month after LT were similar across the four PELD groups. The recipients who had listing PELD scores less than 0 and those who had listing PELD scores 11-20 had similar 1-year survival rates. The 5-year survival rates for the recipients who had listing PELD scores less than 0, 0-10, 11-20, and greater than 20 were 87.5% (95% CI: 83.1%-90.8%), 82.7% (95% CI: 77.7%-86.7%), 83.2% (95% CI: 75.9%-88.4%), and 80.0% (95% CI: 71.8%-86.3%), respectively.

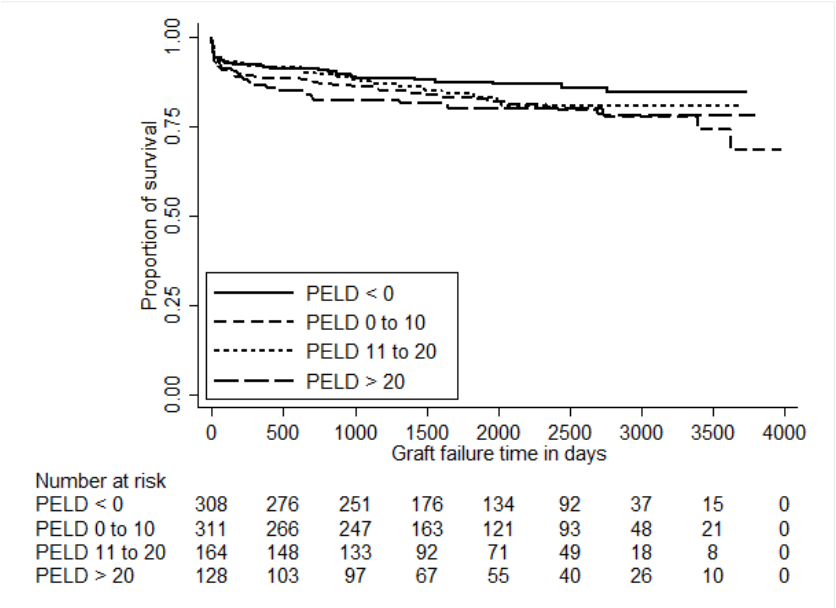

Figure 5. Kaplan-Meier curve of posttransplant survival rate by listing PELD score among recipients surviving 0 to 4000 days posttransplantation

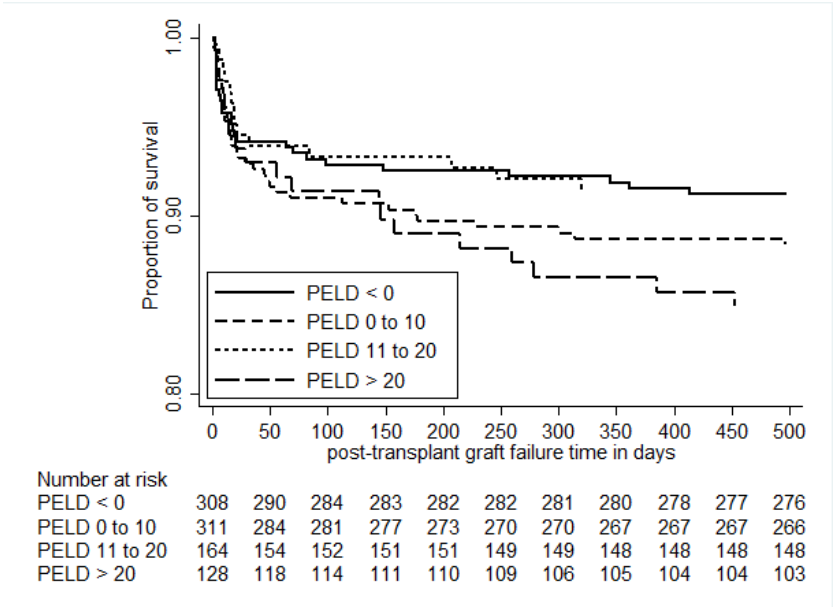

Figure 6. Kaplan-Meier curve of posttransplant survival rate by listing PELD score among recipients surviving 0 to 500 days posttransplantation

3.3 ESTIMATED CUMULATIVE INCIDENCE OF POSTTRANSPLANT MORTALITY USING THE UNIVARIATE MODEL

While ignoring the dependency between the transplant waiting time and posttransplant survival we used Equation (2.2.1) to estimate the cumulative incidences of posttransplant mortality. Let l indicate the type of graft failure, where $l = 1$ indicates posttransplant mortality and $l = 2$ indicates retransplantation. Let random variable T denote the graft failure time and m be the total number of LT recipients. In our study, $m = 911$. We used the R function cuminc from the library cmprsk to estimate the cumulative incidence functions.

Table 3 summarizes the estimated cumulative incidences of posttransplant mortality and retransplantation. We selected 0.5, 1.0, 1.5, 2.0, 2.5, 3, and 5 years after LT for demonstration. The results showed that posttransplant mortality rates were lower than the retransplantation rates at all selected time points. We further estimated these rates stratified by the listing PELD scores. Table 4 shows that recipients with listing PELD score less than 0 had the lowest mortality rate, while recipients with listing PELD score greater than 20 had the highest mortality rate. Mortality rates for the recipients with listing PELD scores 0-10 were higher than those with listing PELD score 10-20. Retransplantation rates among the 4 PELD groups were similar.

Table 3. Cumulative incidences of posttransplant mortality and retransplantation among 911 liver transplant recipients

	Graft failure time (years)						
Event	0.5	1.0	1.5	2.0	2.5	3	5
Posttransplant death	0.0407	0.0486	0.0508	0.0554	0.0589	0.0636	0.0724
Retransplantation	0.0473	0.0529	0.0552	0.0608	0.0655	0.0702	0.0871

Table 4. Cumulative incidences of posttransplant mortality and retransplantation by listing PELD score among 911 liver transplant recipients

	Posttransplant death time (years)						
PELD*	0.5	1.0	1.5	2.0	2.5	3	5
< 0	0.0195	0.0228	0.0228	0.0228	0.0297	0.0332	0.0332
0 to 10	0.0581	0.0614	0.0614	0.0647	0.0618	0.0749	0.0749
11 to 20	0.0305	0.0428	0.0428	0.0553	0.0553	0.0619	0.0619
> 20	0.0532	0.0875	0.1040	0.1123	0.1123	0.1123	0.1123
	Retransplantation time (years)						
PELD*	0.5	1.0	1.5	2.0	2.5	3	5
< 0	0.0552	0.0618	0.0651	0.0651	0.0685	0.0720	0.0825
0 to 10	0.0452	0.0518	0.0551	0.0618	0.0651	0.0651	0.0651
11 to 20	0.0366	0.0428	0.0428	0.0491	0.0491	0.0556	0.0621
> 20	0.0471	0.0471	0.0471	0.0638	0.0638	0.0638	0.0638

*PELD = Pediatric end-stage liver disease model

Figure 7 and 8 summarize these estimated cumulative incidences graphically. The cumulative probabilities of posttransplant death were lower than the probabilities of retransplantation within 10 years. When the recipients survived beyond 10 years, the cumulative probabilities of death became higher than those of retransplantation. Recipients with listing PELD scores less than 0 had the lowest mortality rates over time. Recipients with listing PELD scores greater than 20 had the highest mortality rates within 10 years of LT. Mortality rates among recipients with listing PELD scores 0-10 became the highest after posttransplant 10 years. Recipients with listing PELD scores 0-10 had higher mortality rates overtime compared with those with listing PELD scores 11-20. The retransplantation rates across the 4 PELD groups were similar.

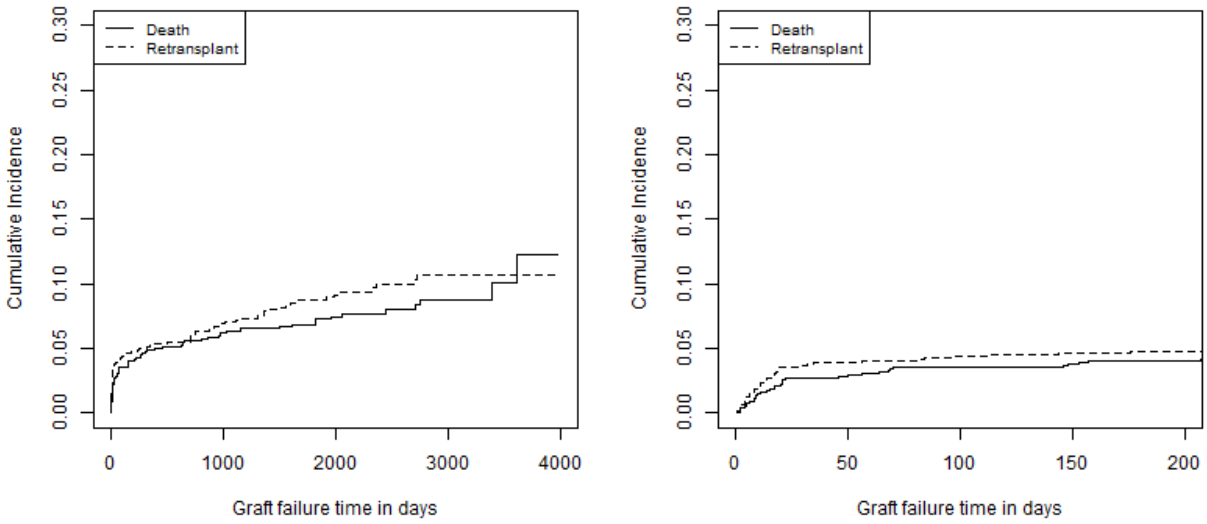

Figure 7. Cumulative incidences of posttransplant mortality and retransplantation (the left panel is for failure time 0 to 4000 days and the right panel is for failure time 0 to 200 days)

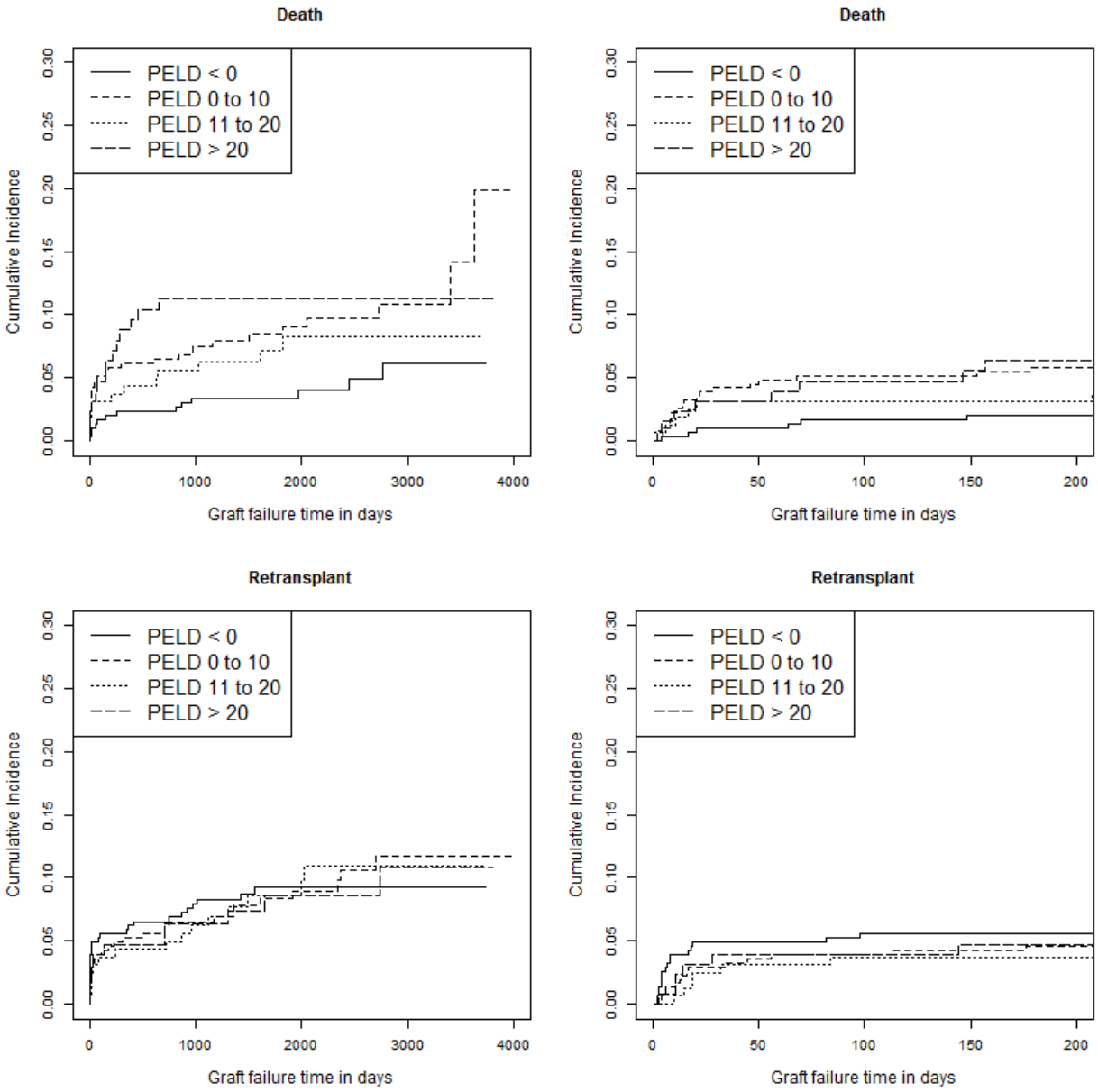

Figure 8. Cumulative incidences of posttransplant mortality and retransplantation by listing PELD (the left panel is for failure time 0 to 4000 days and the right panel is for failure time 0 to 200 days)

3.4 ESTIMATED CUMULATIVE INCIDENCE OF POSTTRANSPLANT MORTALITY USING THE BIVARIATE MODEL

To account for the dependency between the waiting time and posttransplant mortality, we used Equations (2.3.1), (2.3.2), (2.3.3), (2.3.4), and (2.3.5) to estimate the cumulative incidence of posttransplant mortality and the odds of posttransplant death for recipients who had different LT waiting time. Let random variable X indicate LT waiting time and n be the number of LT candidates. In our study, n = 1,265 and M was set to be 305 days to include the longest graft failure time in the dataset. The bivariate cumulative incidence of transplant waiting time and posttransplant mortality, and the conditional cumulative incidence of posttransplant mortality for given transplant waiting time were both estimated using the R function Estimator_LinCFKcondi [17] (personal contact).

Table 5 summarizes the estimated cumulative incidences of posttransplant mortality and retransplantation conditional the LT waiting time, evaluated at the waiting time of 3, 30, 60, and 90 days and posttransplant death time of 0.5, 1.0, 1.5, 2.0, 2.5, 3 and 5 years. The standard errors were estimated based on 1,000 bootstrap samples. The R code for bootstrap resamples is provided in the Appendix. For the LT waiting times of 3 and 30 days and any fixed graft failure time, the cumulative probabilities of posttransplant death were higher than the cumulative probabilities of retransplantation. For the LT waiting time of 60 and 90 days and most of graft failure times, the cumulative probabilities of death were also higher than the probabilities of retransplantation. The estimated conditional cumulative incidence of posttransplant mortality using the bivariate CIF model did not agree with that using the univariate CIF model. It is worth noting that we employed two different approaches [17] to estimate the CIFs and both approaches gave similar results.

Table 6 summarizes the estimated cumulative incidences stratified by the PELD scores at the time of listing, evaluated at the LT waiting times of 3, 30, 60, and 90 days and posttransplant death time of 5 years. For any fixed waiting time, the LT recipients with listing PELD scores less than 0 had the lowest cumulative probabilities of posttransplant death, while the probabilities of posttransplant death for the recipients with listing PELD scores 11-20 and that for the recipients with listing PELD score greater than 20 were similar.

Table 5. Cumulative incidences of posttransplant mortality and retransplantation accounted for waiting time (standard errors are in the parentheses)

	Posttransplant death (years)						
	0.5	1.0	1.5	2.0	2.5	3	5
LT^ waiting time (days)							
3	0.0851 (0.0320)	0.1129 (0.0394)	0.1153 (0.0377)	0.1278 (0.0414)	0.1332 (0.0404)	0.1519 (0.0446)	0.1872 (0.0506)
30	0.0587 (0.0142)	0.0704 (0.0149)	0.0715 (0.0149)	0.0743 (0.0145)	0.0900 (0.0170)	0.1050 (0.0184)	0.1118 (0.0184)
60	0.0487 (0.0039)	0.0582 (0.0123)	0.0650 (0.0125)	0.0681 (0.0131)	0.0726 (0.0136)	0.0824 (0.0144)	0.0902 (0.0153)
90	0.0439 (0.0097)	0.0557 (0.0115)	0.0574 (0.0114)	0.0687 (0.0143)	0.0732 (0.0135)	0.0797 (0.0134)	0.0868 (0.0135)
	Retransplantation (years)						
	0.5	1.0	1.5	2.0	2.5	3	5
LT^ waiting time (days)							
3	0.0453 (0.0215)	0.0543 (0.0263)	0.0552 (0.0271)	0.0565 (0.0278)	0.0583 (0.0280)	0.0571 (0.0280)	0.0800 (0.0347)
30	0.0431 (0.0121)	0.0332 (0.0501)	0.0507 (0.0129)	0.0520 (0.0125)	0.0653 (0.0149)	0.0797 (0.0170)	0.0934 (0.0179)
60	0.0483 (0.0116)	0.0568 (0.0125)	0.0590 (0.0124)	0.0634 (0.0133)	0.0708 (0.0132)	0.0853 (0.0157)	0.1000 (0.0177)
90	0.0481 (0.0107)	0.0532 (0.0107)	0.0537 (0.0112)	0.0586 (0.0115)	0.0685 (0.0130)	0.0804 (0.0142)	0.0949 (0.0152)

*PELD = Pediatric end-stage liver disease model
^ Liver transplantation

Table 6. Cumulative incidences of posttransplant 5-year mortality and retransplantation accounted for waiting time by listing PELD score (standard errors are in the parentheses)

	Posttransplant death by PELD			
	< 0	0 to 10	11 to 20	> 20
LT^ waiting time (days)				
3	0.1060 (0.1011)	0.1219 (0.1255)	0.1551 (0.0621)	0.1538 (0.0625)
30	0.0739 (0.3160)	0.0990 (0.0288)	0.1519 (0.0481)	0.1519 (0.0481)
60	0.0435 (0.0188)	0.0916 (0.0357)	0.0946 (0.0267)	0.0946 (0.0267)
90	0.0488 (0.0168)	0.0912 (0.0244)	0.0794 (0.0274)	0.0794 (0.0274)
	Retransplantation by PELD			
	< 0	0 to 10	11 to 20	> 20
LT^ waiting time (days)				
3	0.0000 (0.0000)	0.0985 (0.0952)	0.0942 (0.0957)	0.0925 (0.0947)
30	0.0992 (0.0514)	0.0952 (0.0937)	0.0898 (0.0388)	0.0993 (0.0434)
60	0.0992 (0.0284)	0.0960 (0.0305)	0.0800 (0.0265)	0.0800 (0.0265)
90	0.0873 (0.0255)	0.0847 (0.0246)	0.0843 (0.0292)	0.0843 (0.0292)

*PELD = Pediatric end-stage liver disease model
^ Liver transplantation

Figure 9 illustrates the estimated cumulative incidences of posttransplant mortality and retransplantation for the LT recipients who received LT within 3 and 30 days on the waiting list, respectively, and for those who received LT between 4 and 305 days and between 31 and 305 days on the waiting list, respectively. The estimated univariate cumulative incidences regardless of the LT waiting time were also presented in Figure 9. The curve of the univariate cumulative incidences of posttransplant death fell in between the two curves of the conditional cumulative incidences of death for the recipients who received early LT and late LT, suggesting that posttransplant mortality is dependent on the liver transplant wait time. LT recipients who received early LT had a higher posttransplant mortality rate compared with those who receive LT late. The curves of the conditional cumulative incidences of retransplantation for the recipients who received early LT and late LT agreed with the curve of the univariate cumulative incidences of retransplantation, suggesting that the retransplantation time has a weak association with LT waiting time.

Figure 10 illustrates the cumulative incidences of posttransplant mortality and retransplantation for the LT recipients who received LT within 60 and 90 days of listing, respectively, and for those who received LT between 61 and 305 days of listing and between 91 and 305 days of listing, respectively. The cumulative incidences of posttranplant mortality were similar to those having the LT waiting time of 3 days and that of 30 days, which suggests that posttransplant mortality is associated with the LT waiting time and that the retransplantation time has a weak association with the LT waiting time.

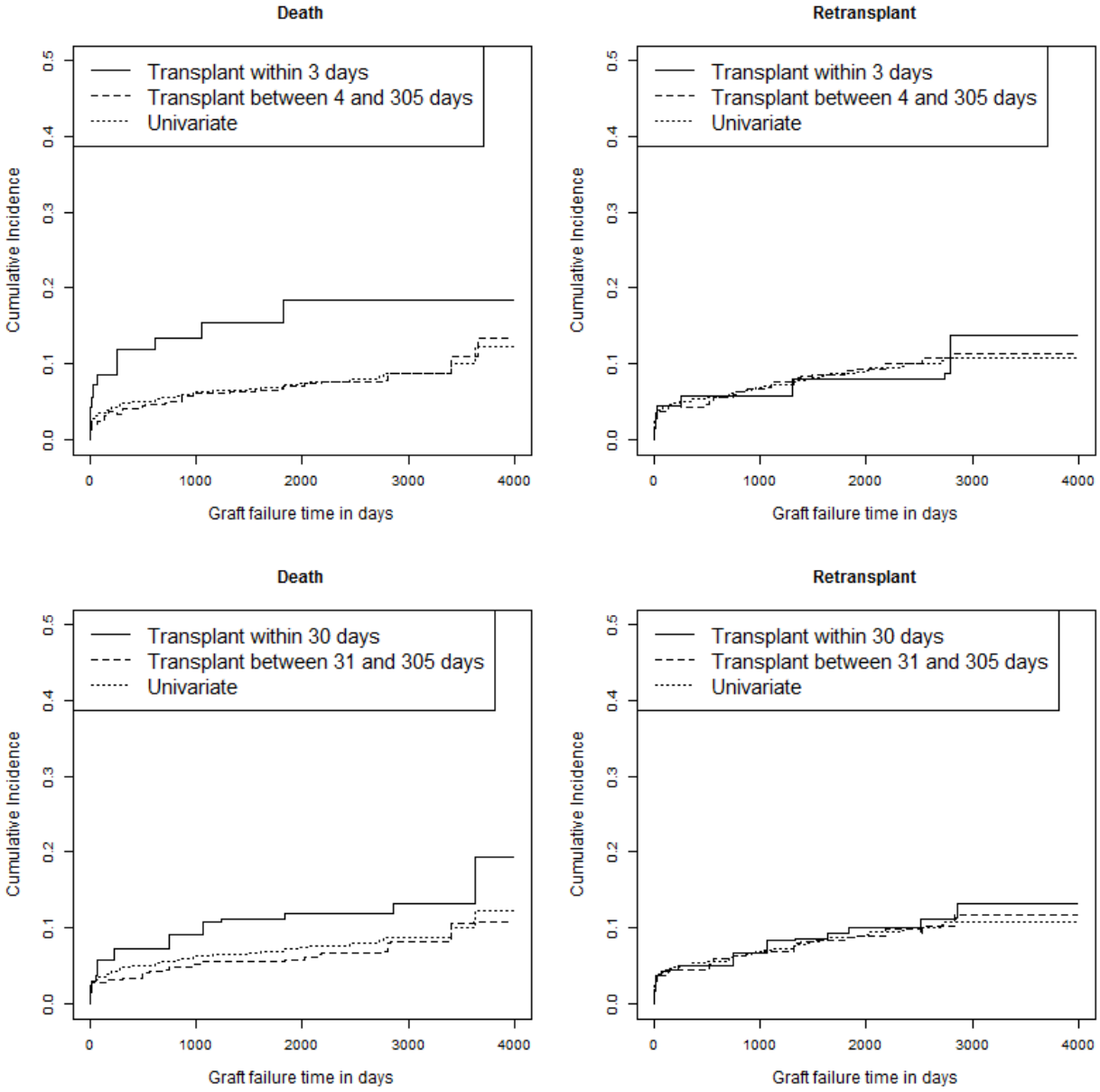

Figure 9. Cumulative incidences of posttransplant mortality and retransplantation accounted for liver transplant waiting time (the top panel is for the recipients who received LT earlier or later than 3 days and the bottom panel is for the recipients who received LT earlier or later than 30 days

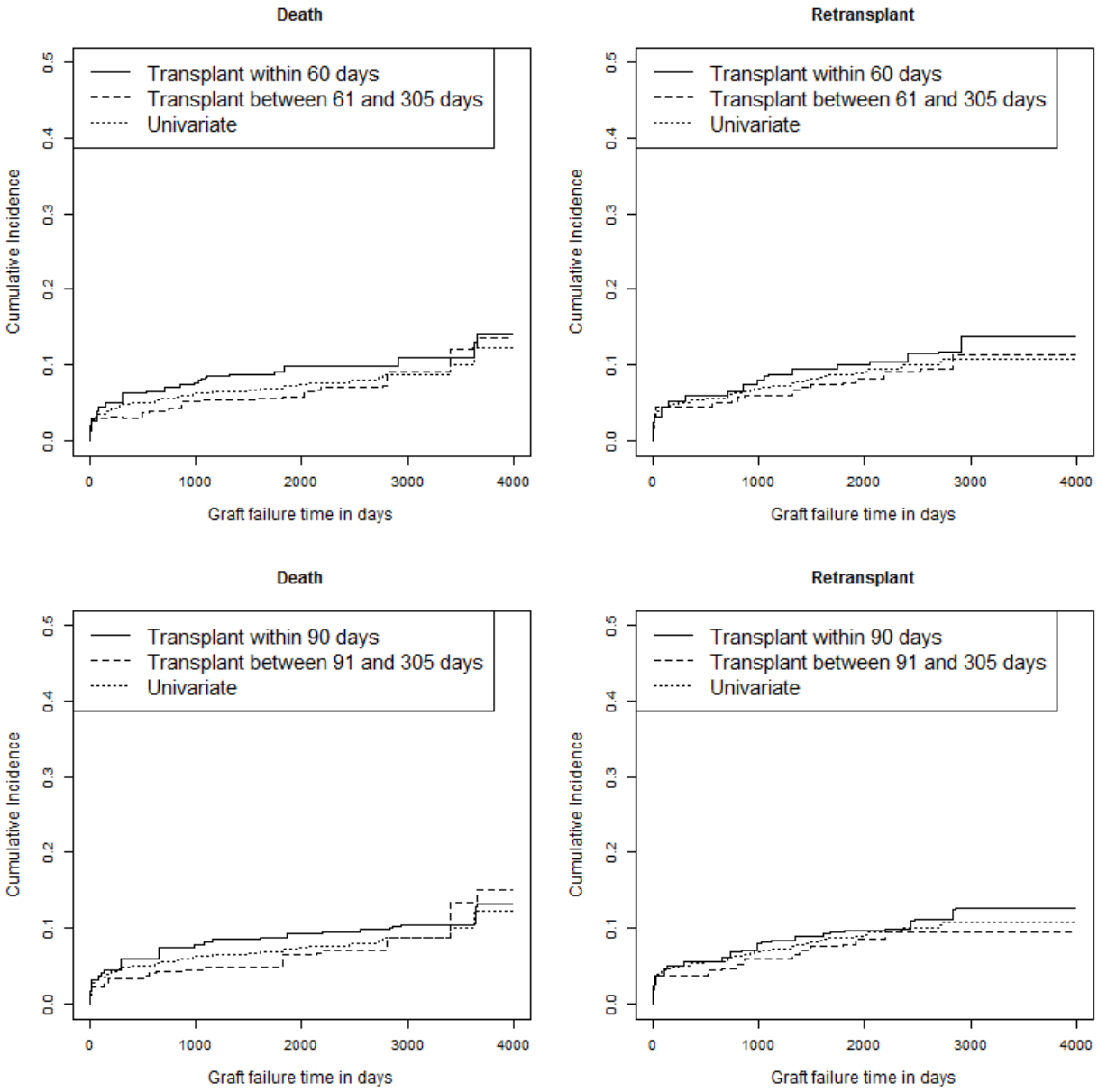

Figure 10. Cumulative incidences of posttransplant mortality and retransplantation accounted for liver transplant waiting time (the top panel is for the recipients who received LT earlier or later than 60 days and the bottom panel is for the recipients who received LT earlier or later than 90 days)

The time-varying association between the LT waiting time and the posttransplant death time was estimated through Equation (2.3.4). The odds of posttransplant death were compared between the LT recipients who received LT earlier and those who received LT later by various cutoff times.

Figure 11 illustrates the point estimates of the odds ratios of posttransplant death with 95% confidence intervals for the LT recipients who received LT earlier vs. later using cutoff time points of 3, 30, 60, and 90 days. The 95% confidence intervals were obtained based on 1,000 bootstrap samples. Figure 12 is a zoom-in of Figure 11, truncating odds ratios up to 10. The estimated time-varying odds ratios of posttransplant mortality for the recipients who received LT within 3 days versus the recipients who received LT greater than 3 days on the waiting list were around the value of 2 and the corresponding 95% confidence intervals included 1. Note that because of a few number of death and retransplantation cases, estimation of odds ratio may not be reliable 10 years after LT. In other scenarios presented in Figure 12, the estimated time-varying odds ratios of posttransplant death were around the values between 1 and 2 with the 95% confidence intervals including 1. These results suggest that the posttransplant survival time is positively associated with the LT waiting time, that is, a longer LT waiting time is associated with a lower probability of posttransplant mortality.

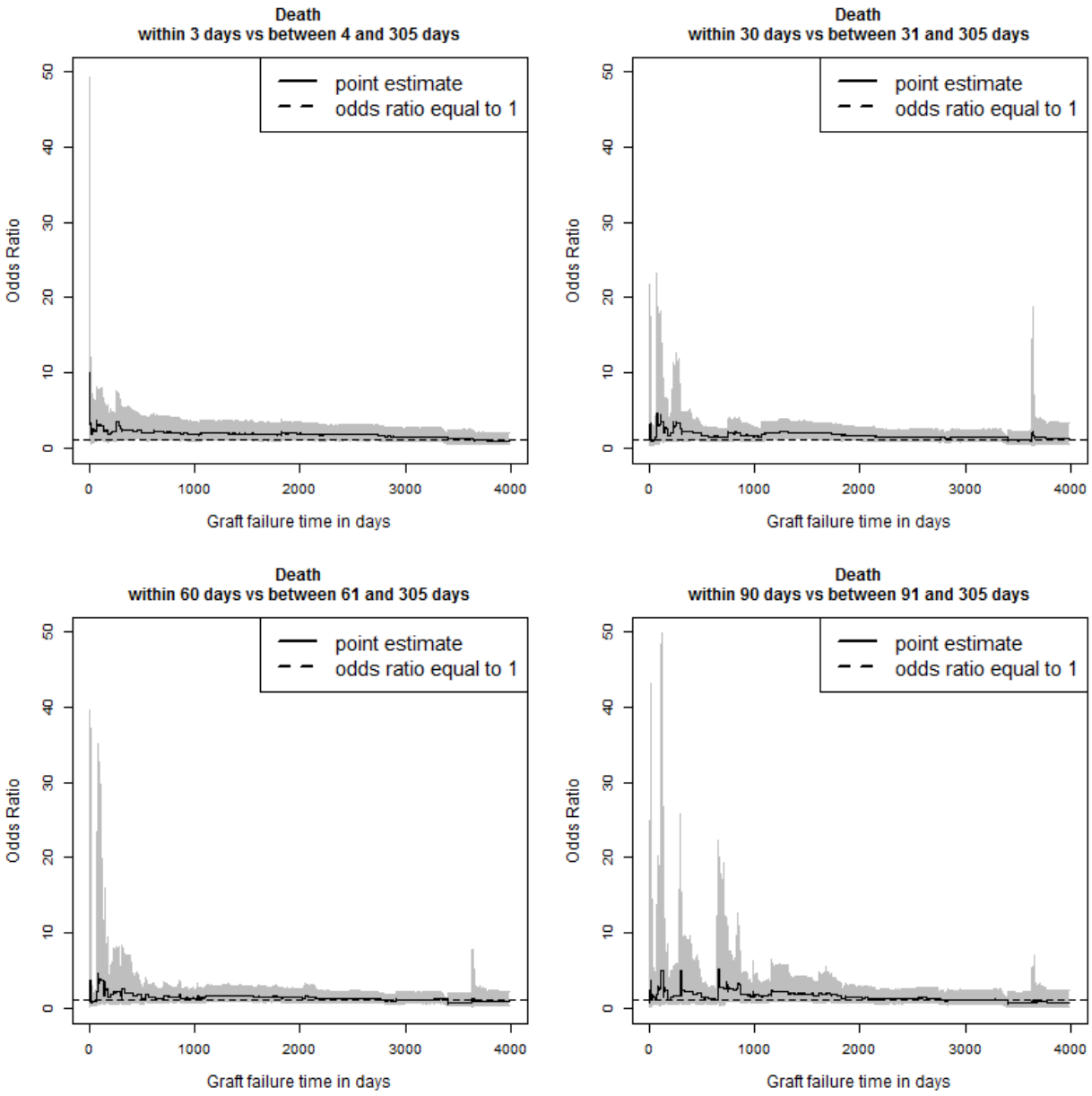

Figure 11. Odds ratios of posttransplant death between the recipients who received LT earlier than 3, 30, 60, and 90 days and the recipients who received LT later than 3, 30, 60, and 90 days along with 95% confidence intervals

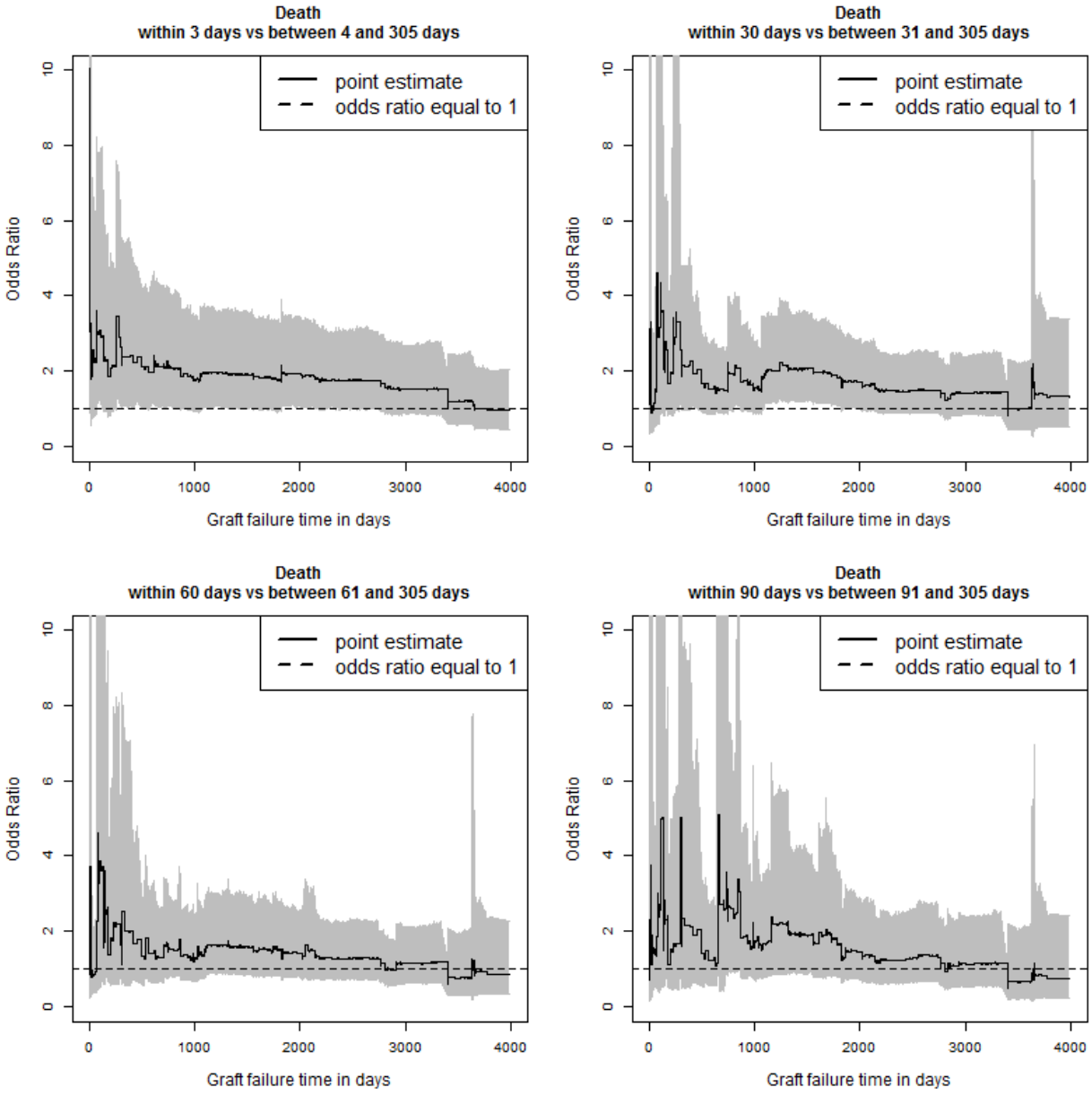

Figure 12. Odds ratios of posttransplant death between the recipients who received LT earlier than 3, 30, 60, and 90 days and the recipients who received LT later than 3, 30, 60, and 90 days along with 95% confidence intervals (odds ratios are up to 10)

Table 7 summarizes the PELD score at the time of listing by various LT waiting times among the LT recipients. Comparing the deceased LT recipients who received LT within 3 days with those who received LT after 3 days of listing, we found that over 45% of the recipients who received LT within 3 days of listing had PELD score greater than 20 whereas only 15% of the recipients who received LT after 3 days of listing had PELD score greater than 20. Among the recipients receiving early LT (within 30 days or within 60 days compared to greater than 30 days and greater than 60 days, respectively), over 30% of the recipients had PELD score greater than 20; among the recipients receiving late LT, only 3% of the recipients had PELD score greater than 20. The odds ratios of posttransplant death between the recipients who received early LT and late LT were greater than 1; a possible explanation is that those recipients who received early LT were much sicker than those who received late LT.

Table 7. PELD score at the time of listing by liver transplant waiting time

	LT^ waiting time among the deceased recipients (days)							
	≤ 3 (n=11)	> 3 (n=58)	≤ 30 (n=34)	> 30 (n=35)	≤ 60 (n=42)	> 60 (n=27)	≤ 90 (n=48)	> 90 (n=21)
PELD* n (%)								
< 0	2 (18.18)	11 (18.97)	4 (11.76)	9 (25.71)	5 (11.90)	8 (29.63)	7 (14.58)	6 (28.57)
0 - 10	3 (9.09)	29 (50.00)	11 (32.35)	19 (14.29)	15 (35.71)	15 (55.56)	17 (35.42)	13 (61.90)
11 - 20	6 (27.27)	9 (15.52)	6 (17.65)	6 (17.14)	9 (21.43)	3 (11.11)	10 (20.83)	2 (9.52)
> 20	11 (45.45)	9 (15.52)	13 (38.24)	1 (2.86)	13 (30.95)	1 (3.70)	14 (29.17)	0 (0.00)
	LT^ waiting time among all recipients (days)							
	≤ 3 (n=72)	> 3 (n=839)	≤ 30 (n=206)	> 30 (n=605)	≤ 60 (n=451)	> 60 (n=460)	≤ 90 (n=542)	> 90 (n=369)
PELD* n (%)								
< 0	11 (15.28)	297 (35.40)	77 (25.16)	231 (38.18)	130 (28.82)	178 (38.70)	161 (29.70)	147 (39.84)
0 - 10	10 (13.89)	301 (35.88)	67 (21.90)	244 (40.33)	123 (27.27)	188 (40.87)	156 (28.78)	155 (42.01)
11 - 20	12 (16.67)	152 (18.12)	59 (19.28)	105 (17.36)	88 (19.51)	76 (16.52)	108 (19.93)	56 (15.18)
> 20	39 (54.17)	89 (10.61)	103 (33.66)	25 (4.13)	110 (24.39)	18 (3.91)	117 (21.59)	11 (2.98)

*PELD = Pediatric end-stage liver disease model
^ Liver transplantation

We also estimated the odds ratios of posttransplant death for the LT recipients who received LT earlier vs. later stratified by their PELD scores at the time of listing. Figure 13 illustrates the point estimates of these odds ratios. The results indicated that the positive association between LT waiting time and posttransplant survival was more pronounced among sicker patients (higher PELD scores at the time of listing). Note that because of small sample sizes, odds ratios were not estimable for all time points.

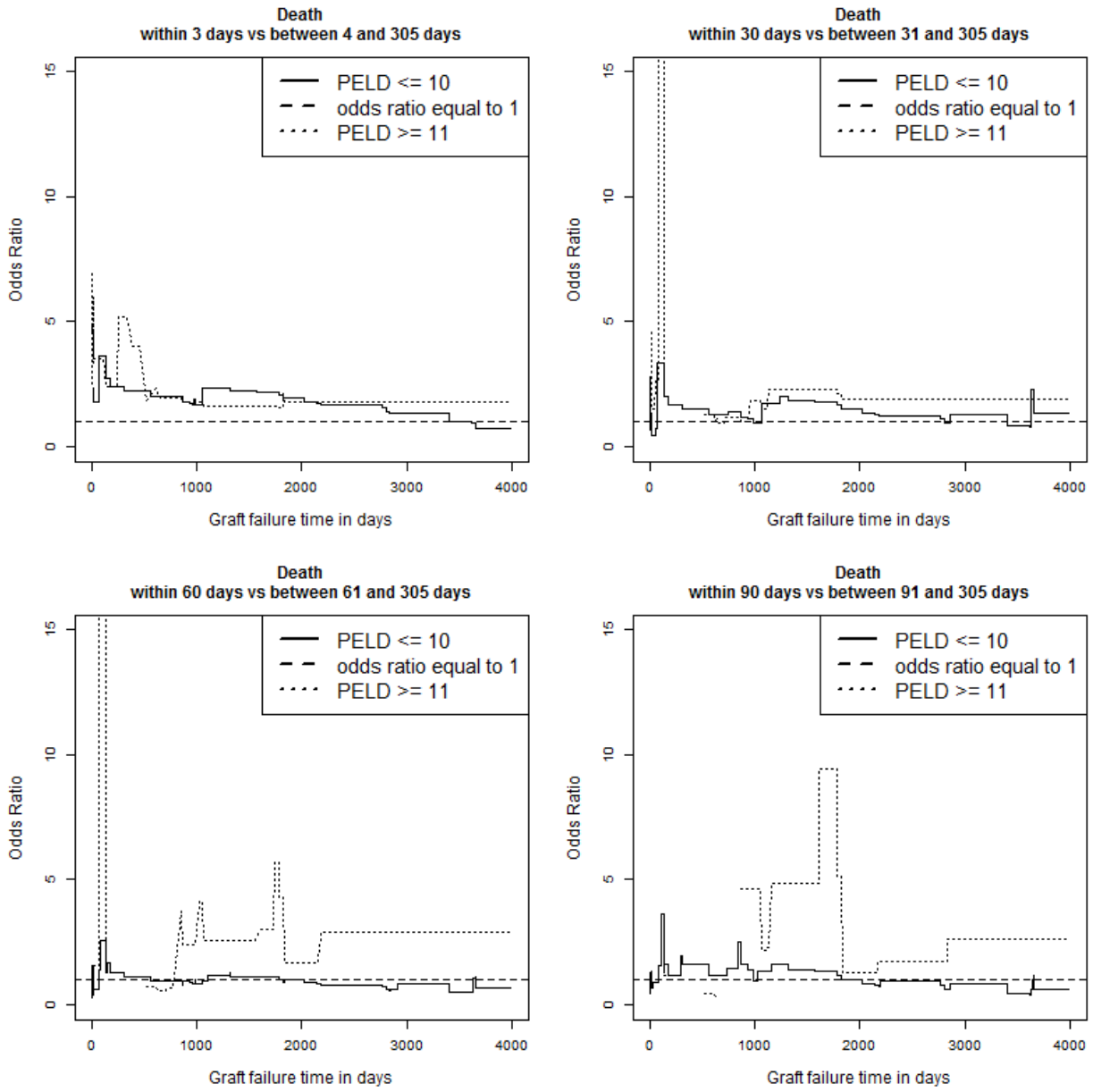

Figure 13. Odds ratios of posttransplant death between the recipients who received LT earlier than 3, 30, 60, and 90 days and the recipients who received LT later than 3, 30, 60, and 90 days by listing PELD

4.0 DISCUSSION

In this study, we analyzed 1,265 pediatric LT candidates with chronic liver disease who were younger than 12 years old when being placed on the waiting list. Methods of the univariate and the bivariate cumulative incidence function were used to estimate the cumulative probabilities of posttransplant mortality and the odds ratios of posttransplant mortality between early LT recipients and late LT recipients. We found that posttransplant death time is dependent on the LT waiting time and that retransplantation has a weak association with LT waiting time. Our analysis also showed that LT waiting time is positively associated with posttransplant death time, meaning that LT recipients with shorter wait time had higher risk of posttransplant mortality.

There are several limitations in estimating the association between the LT waiting time and the posttransplant survival in our study. First, among 911 LT recipients, 761 (83.5%) were not retransplanted and were alive at the study cutoff date therefore were censored in the analysis. This high censoring rate significantly reduced the effective sample size and therefore reduced the estimation power. Second, we suspected that our results of shorter waiting time being associated with higher risk of posttransplant mortality may be due to survivor bias. We will need to further investigate this by extending our study period so that more LT recipients will experience the outcomes of interest (posttransplant death or retransplantation). Third, our analysis did not take into account the fact that PELD scores may vary over time. A sensitivity analysis may be needed

to investigate the impact of using the PELD score at the time of liver transplantation vs. using the PELD score at the time of being put on the waiting list.

In conclusion, the bivariate cumulative incidence function model is suitable for studying the association between liver transplant waiting time and posttransplant survival having retransplantation as a competing risk. Although our study found that liver transplant waiting time is positively associated with posttransplant survival and that retransplantation has a weak association with LT waiting time, more work should be done to further investigate the causes behind these findings.

APPENDIX: R CODE FOR BOOTSTRAP RESAMPLES

```
#############################################################################################################
##Create Resample ID for Bootstrap Resample n=1000
##output csv file:  sampleXX: xxth sample
##patient ID:  recode to 1 to 1265
#############################################################################################################
##resample index;
rs.data=c(1:1265)
Tx.Size=1000

##resample for bootstrap;
set.seed(123)
Tx.Resamples=lapply(1:Tx.Size, function(i) sample(rs.data,replace=TRUE))

##convert to dataframe;
Tx.Resamples.df = do.call("cbind", lapply(Tx.Resamples, as.data.frame))
Tx.Resamples.name=unlist(lapply(1:Tx.Size, function(i) paste("sample", i, sep = "")))
colnames(Tx.Resamples.df) = Tx.Resamples.name

##save as CSV file;
write.csv(Tx.Resamples.df, file = "LiverTxResample.csv", row.names=FALSE)
```

```
#############################################################################################################
##Calculate CIF table for each sample of Bootstrap Resample
#############################################################################################################
##load LinCFK;
source("Estimator_LinCFKcondi.R")

##load LiverTx dataset;
LiverTx.Data = read.csv("LiverTxRecode.csv",header=TRUE, na.string = "NA", fill = TRUE, sep=",")
LiverTx.Data.dm=data.matrix(subset(LiverTx.Data,
select=c("ptid","y1","y2","x","t","eta1","eta2")))

##load Resample patientID dataset;
LiverTx.ReSample= read.csv("LiverTxReSample.csv",header=TRUE, na.string = "NA", fill = TRUE,
sep=",")

##CIFs for each sample;
for (i in 1:1000) {
    ##get resample column name
    TxPID = paste("sample", i, sep = "")
    Tx.pt.dm = data.matrix(subset(LiverTx.ReSample,select=c(TxPID)))
    colnames(Tx.pt.dm)= "ptid"
    #str(Tx.pt.dm)
```

```
    ##retrive data by ptid index;
    Tx.Data.dm=LiverTx.Data.dm[c(Tx.pt.dm),]
    LiverTx.df=data.frame(Tx.Data.dm, row.names=NULL)

    ##rearrange data to call estimator of  LinCFK
    Tx.Data =subset(LiverTx.df,select=c("y1","y2","eta1","eta2"))
    Tx_X    = LiverTx.df[,c("x")]
    Tx_T    = LiverTx.df[,"t"]
    Tx_ptid = LiverTx.df[,c("ptid")]
    numpt   = length(Tx_ptid)

    ##estimate CIF by using LinCFK;
    TxOut = Est.LinCFKcondi(Tx.Data,Tx_X,Tx_T)
    Tx.CIF = TxOut$out.CIF
    Tx.Sx  = TxOut$out.Sx

    ##get CIF Estimation of X and Y,  KM Estimation of X by patientID;
    LinFxy1   =Tx.CIF[,1:numpt]
    LinFxy2   =Tx.CIF[,(numpt+1):(2*numpt)]
    LinCFxy1  =Tx.CIF[,(2*numpt+1):(3*numpt)]
    LinCFxy2  =Tx.CIF[,(3*numpt+1):(4*numpt)]
    IPCWFxy1  =Tx.CIF[,(4*numpt+1):(5*numpt)]
    IPCWFxy2  =Tx.CIF[,(5*numpt+1):(6*numpt)]
    IPCWCFxy1 =Tx.CIF[,(6*numpt+1):(7*numpt)]
    IPCWCFxy2 =Tx.CIF[,(7*numpt+1):(8*numpt)]
    Sx        = Tx.Sx[,1:numpt]
    ptid.CIF.df =
cbind(Tx_ptid,Tx.Data,Tx_X,Tx_T,LinFxy1,LinFxy2,LinCFxy1,LinCFxy2,IPCWFxy1,IPCWFxy2,IPCWCFxy1,
IPCWCFxy2, Sx)

    ##Save as CSV file;
    write.csv(ptid.CIF.df, file = CIFpt.File.C, row.names = FALSE)

    ##CIF tablesof X and Y for each cause sort by X and Y;
    ##KM table of X;

ptid.Fxy=data.matrix(ptid.CIF.df[,c("Tx_X","Tx_T","LinFxy1","LinCFxy1","IPCWFxy1","IPCWCFxy1","Li
nFxy2", "LinCFxy2", "IPCWFxy2", "IPCWCFxy2", "Sx")])
    ptid.Sx=data.matrix(ptid.CIF.df[,c("Tx_X","Sx")])
    LiverTx.Fxy=unique(ptid.Fxy[order(ptid.Fxy[,"Tx_X"],ptid.Fxy[,"Tx_T"]),])
    LiverTx.Sx=unique(ptid.Sx[order(ptid.Sx[,"Tx_X"]),])

    ####--Save as CSV file;
    Fxy.File.C = paste("./LiverTxBootStrap/LiverTxCIF_S", i, ".csv", sep = "")
    Sx.File.C  = paste("./LiverTxBootStrap/LiverTxSx_S", i, ".csv", sep = "")
    write.csv(LiverTx.Fxy, file =Fxy.File.C, row.names = FALSE)
    write.csv(LiverTx.Sx, file =Sx.File.C, row.names = FALSE)

}




##############################################################################################
##Calculate OR and 95% CI
##############################################################################################
##load Fxy dataset;
LiverTx.CIF= read.csv("./LiverTxBootStrap/LiverTxCIFBS.csv",header=TRUE, na.string = "NA", fill =
TRUE, sep=",")

for (k in c(1:1000)) {
```

```
    RSIDN = paste("RS", k, sep = "")
    LiverTx.CIF.df = subset(LiverTx.CIF, LiverTx.CIF$RSID==RSIDN,
select=c("Tx_X","Tx_T","LinFxy1","IPCWFxy1","LinCFxy1","IPCWCFxy1","Sx","RSID"))


    ##find Fxy for fixed timepoint of x and t;
    for (x in c(3,30,60,90,305)) {

        T.list=subset(LiverTx.CIF.df, LiverTx.CIF.df$Tx_X <= x, select=c("Tx_T"))
        Tx_T=unique(sort(T.list[,1]))
        T.num=length(Tx_T)
        Tx_X=c(rep(x,T.num))
        m.TX=cbind(Tx_X,Tx_T)

        Tx.X = subset(LiverTx.CIF.df, LiverTx.CIF.df$Tx_X==x, select=c("Tx_X","Tx_T","IPCWCFxy1",
"IPCWFxy1","Sx"))
        Sx.L=min(Tx.X[,"Sx"])

        CIF.TX=merge(Tx.X, m.TX, by = "Tx_T", all = TRUE, sort = TRUE, suffixes = c(".X",".L"))

        for(i in 1:T.num ) {
           if (is.na(CIF.TX[i,"IPCWFxy1"])) {
               CIF.TX[i,"Sx"]=Sx.L
                x.L=CIF.TX[i,"Tx_X.L"]
                t.L=CIF.TX[i,"Tx_T"]
                CIF.TX.L.df= subset(LiverTx.CIF.df, LiverTx.CIF.df$Tx_X <= x.L &
LiverTx.CIF.df$Tx_T <= t.L, select=c("Tx_X","Tx_T","IPCWFxy1"))
                Fxy1.L=max(CIF.TX.L.df$IPCWFxy1, na.rm = TRUE)
                CIF.TX[i,"IPCWFxy1"]=Fxy1.L
            }
        }
       Yu.CIF.TX= paste("./LiverTxCIFORBootS/LiverTxCIFYuBS/LiverTxCIF_Death_x", x, "_S",
k,".csv", sep = "")
       write.csv(CIF.TX, file=Yu.CIF.TX, row.names = FALSE)
    }

    ##merge dataset and calculate Fxy when no timepoint matched;
    tm=305
    TMFile=paste("./LiverTxCIFORBootS/LiverTxCIFYuBS/LiverTxCIF_Death_x305","_S", k,".csv", sep =
"")
    LiverTx.CIF.TM= read.csv(TMFile,header=TRUE, na.string = "NA", fill = TRUE, sep=",")
    Tx.M = subset(LiverTx.CIF.TM, select=c("Tx_X.L","Tx_T","IPCWFxy1","Sx"))


    for (tx in c(3,30,60,90)){

        tx.File= paste("./LiverTxCIFORBootS/LiverTxCIFYuBS/LiverTxCIF_Death_x", tx,
"_S",k,".csv", sep = "")
        LiverTx.CIF.TX= read.csv(tx.File,header=TRUE, na.string = "NA", fill = TRUE, sep=",")
        Tx.X = subset(LiverTx.CIF.TX, select=c("Tx_X.L","Tx_T","IPCWFxy1","Sx"))

        CIF.Fix=merge(Tx.X, Tx.M, by = "Tx_T", all = TRUE, sort = TRUE, suffixes = c(".X",".M"))

        numrow = length(CIF.Fix$Tx_T)
        km = min(which(CIF.Fix$IPCWFxy1.M >0))
        km.IPCW.CIF = CIF.Fix[km,"IPCWFxy1.M"]
        km.Sx.M = CIF.Fix[km,"Sx.M"]
        km.M  = CIF.Fix[km,"Tx_X.M"]
        kx = min(which(CIF.Fix$IPCWFxy1.X >0))
        kx.IPCW.CIF = CIF.Fix[kx,"IPCWFxy1.X"]
        kx.X  = CIF.Fix[kx,"Tx_X.X"]
```

```
        kx.Sx.X = CIF.Fix[kx,"Sx.X"]

        ##set CIF for each time point;
        for ( j in 1:numrow){
            if ( (j < km) & is.na(CIF.Fix[j,"IPCWFxy1.M"])) {
                 CIF.Fix[j,"IPCWFxy1.M"]=0
             }
             if (j > km) {
                jm.IPCW.CIF=CIF.Fix[j,"IPCWFxy1.M"]

                if (is.na(jm.IPCW.CIF)) {
                    CIF.Fix[j,"IPCWFxy1.M"]=km.IPCW.CIF
                }
                else {
                    km.IPCW.CIF=jm.IPCW.CIF
                }
             }

             CIF.Fix[j,"Sx.M"]=km.Sx.M

            if ( (j < kx) & is.na(CIF.Fix[j,"IPCWFxy1.X"])) {
                CIF.Fix[j,"IPCWFxy1.X"]=0
             }
            if (j > kx)  {
                jx.IPCW.CIF=CIF.Fix[j,"IPCWFxy1.X"]

                if (is.na(jx.IPCW.CIF)) {
                   CIF.Fix[j,"IPCWFxy1.X"]=kx.IPCW.CIF
                }
                else {
                   kx.IPCW.CIF=jx.IPCW.CIF
                }
             }
             CIF.Fix[j,"Sx.X"]=kx.Sx.X
        }

        ##joint CIF;
        CIF.OR = CIF.Fix[!(is.na(CIF.Fix$Tx_T)),]
        row.names(CIF.OR)=c(1:length(CIF.OR[["Tx_T"]]))
        F.MX = CIF.OR$Sx.X[1] - CIF.OR$Sx.M[1]

        ##Conditional CIF for <=x
        CIF.OR$IPCWCFxy1.X=CIF.OR$IPCWFxy1.X/(1-CIF.OR$Sx.X)

        ##Conditional CIF for between x and M
        CIF.OR$IPCWCFxy1.XM=ifelse((CIF.OR$Sx.X - CIF.OR$Sx.M) > 0,(CIF.OR$IPCWFxy1.M -
CIF.OR$IPCWFxy1.X)/F.MX, NA)
        CIF.OR$IPCWCFxy1.XM[CIF.OR$IPCWCFxy1.XM < 0 ] = 0

        ##Odds Ratio
        CIF.OR$IPCW_OR = round(CIF.OR$IPCWCFxy1.X * (1-CIF.OR$IPCWCFxy1.XM )/
CIF.OR$IPCWCFxy1.XM*(1- CIF.OR$IPCWCFxy1.X),4)
        CIF.OR$IPCW_OR[!(is.finite(CIF.OR$IPCW_OR)) | CIF.OR$IPCW_OR <= 0] = NA


       Tx.OR.File.C = paste("./LiverTxCIFORBootS/BSYu_LiverTxOR_M", tm, "_x", tx, "_S",k,".csv",
sep = "")
       write.csv(CIF.OR, file = Tx.OR.File.C, row.names = FALSE)

   }
}
```

BIBLIOGRAPHY

1. Kim W.R., J.R. Lake, et al. (2016). OPTN/SRTR annual data report 2014. *American Journal of Transplantation. 16* (S2) 4-215.

2. Bourdeaux C, T.T. Tri, et al. (2005). PELD score and posttransplant outcome in pediatric liver transplantation: retrospective study of 100 recipients. *Transplantation 79* (9), 1273-1276.

3. Vilca-Melendez, H., N.D. Heaton (2004). Pediatric liver transplantation: the surgical view. *Postgrad Med J 80*, 571-576.

4. Tector, A.J., R.S., Mangus, et al. (2006). Use of extended criteria livers decreases wait time for liver transplantation without adversely impacting posttransplant survival. *Ann Surg 244*, 439 – 450

5. Salvalaggio P. R., G. Felga (2015). List and liver transplant survival according to waiting time in patients with Hepatocellular Carcinoma. *American Journal of Transplantation 15,* 668–677.

6. Schlansky B., Y. Chen (2014). Waiting time predicts survival after liver transplantation for Hepatocellular Carcinoma: a cohort study using the united network for organ sharing registry. *Liver Transplantation 20* 1045–1056.

7. Kalbeisch, J. D., R. L. Prentice (2002). *The statistical analysis of failure time data*. New York: Wiley.

8. Lin, D. Y., W. Sun, and Z. Ying (1999). Nonparametric estimation of the gap time distributions for serial events with censored data. *Biometrika 86*, 59-70.

9. Schaubel, D. E., J. Cai (2004). Non-parametric estimation of gap time survival functions for ordered multivariate failure time data. *Statistics in Medicine 23* (12), 1885-1900.

10. Pena, E. A., R. L. Strawderman and M. Hollander (2001). Nonparametric estimation with recurrent Event Data. *Journal of the American Statistical Association 96,* 1299-1315.

11. Wang, M. C., and S. H. Chang (1999). Nonparametric estimation of a recurrent survival function. *Journal of the American Statistical Association 94*, 146-153.

12. Lin, D. Y. and Z. Ying (2001). Nonparametric tests for the gap time distributions of serial events based on censored data. *Biometrics 57* (2), 369-375.

13. Huan, C.Y. and M.C. Wang (2005). Nonparametric estimation of the bivariate recurrence time distribution. *Biometrics 61* (2), 392-402.

14. Bandeen-Roche, K. and J. Ning (2008). Nonparametric estimation of bivariate failure time associations in the presence of a competing risk. *Biometrika 95*, 221-232.

15. Cheng, Y. and J. P. Fine (2008). Nonparametric estimation of cause-specific cross hazard ratio with bivariate competing risks data. *Biometrika 95*, 233-240.

16. Cheng, Y., J. P. Fine, and M. R. Kosorok (2007). Nonparametric analysis of bivariate competing risks data. *Journal of the American Statistical Association 102*, 1407-1416.

17. Chen, X. (2015). *Association analysis of successive event and diagnostic accuracy analysis for competing risk data* (Unpublished PhD dissertation). University of Pittsburgh, Pittsburgh, PA.

18. Klein, J. P., M. L. Moeschberger (2003). *Survival analysis: techniques for censored and truncated data*. New York: Springer.