Heading: The association of time to organ procurement on short- and long-term outcomes in kidney transplantation

Running head: The significance of procurement delay

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ABSTRACT

Background and objectives: Transplant centers in Europe aim to minimize the time from brain death to organ procurement (procurement delay), but evidence to justify this is scarce. In the US procurement times are significantly longer. Our objective was to analyze how procurement delay associates with kidney allograft outcomes.

Design, setting, participants and measurements: Kidney transplantations from brain dead donors were retrospectively analyzed from the Finnish Kidney Transplant Registry and Scientific Registry of Transplant Recipients (SRTR) in the US. Multivariable models were adjusted with donor and recipient characteristics, and the relationship between procurement delay and outcomes were modelled with cubic spline functions.

Results: 2,388 and 101,474 kidney transplantations in Finland and the US were included, respectively. The median procurement delay was 9.8 hours (IQR 7.8-12.4) in Finland and 34.8 hours (IQR 26.3-46.3) in the US. A nonlinear association was observed between procurement delay and the risk of delayed graft function (DGF), with highest risk seen in short and very long procurement delays. In multivariable models, the lowest risk of DGF was associated with procurement delay between 20 and 50 hours. In multivariable models, longer procurement delay was linearly associated with lower risk of graft loss (HR 0.90 per one hour longer, 95% CI 0.88-0.92, p<0.001). Acute rejection rates, for which data were only available from Finland, were not associated with procurement delay.

Conclusions: Longer procurement delay was associated with noninferior or even better kidney allograft outcomes.

INTRODUCTION

Vast majority of organ donations are carried out in brain dead donors (donation after brain death, DBD). Brain death causes excretion of cytokines (so called 'cytokine storm'), which leads to initial tachycardia and hypertension followed by a hypotensive phase. Cytokines increase oxygen consumption and inflammatory activation, and may lead to increase in oxygen free radicals, which may cause cell damage[1–4]. Furthermore, hypotensive phase may decrease oxygen supply to already compromised cells. This is further supported by data from animal experiments, in which prolongation of time after brain death has led to increased inflammation, coagulation and organ dysfunction in kidneys[1,5–7]. In addition, organ function is thought to deteriorate and eventually fail if procurement is excessively postponed. Because of these detrimental effects of brain death, it is generally considered that organs should be procured as soon as possible after brain death and European practises aim to minimize time from brain death to organ cold perfusion (procurement delay). However, usually the 'cytokine storm' settles within hours and brain dead organ donors are hemodynamically stable thereafter[8].

Contrary to these beliefs, some retrospective studies have demonstrated an advantageous correlation of longer time before organ retrieval in kidney transplant early function[9,10] and survival[9–11]. These studies may have attributed to the increasingly longer procurement times in the US, although retrospective and some having small cohort size[9,11] and lack of adjustment for confounders[9]. As such, procurement delays vary greatly between countries and optimal time is currently unknown. Knowing the ideal procurement delay has great implications in transplantation logistics, work shifts, resource allocation, and ultimately in patient and graft survival.

The aim of this study was to examine the association of procurement delay on kidney allograft early function and survival in two different transplant populations with different median times from brain death to organ procurement (Finland and the US).

MATERIALS AND METHODS

Donors and patients

Consecutive deceased donor kidney transplantations in Finland from June 2004 to December 2017 were included and followed until death, graft loss, or August 2018. The data were collected from the Finnish Kidney Transplant Registry and from donor medical documents. Only donors, in which the procurement was done within Finland were included, and kidneys that were received from other Scandiatransplant countries were excluded. Similarly, kidneys procured in Finland, but sent for transplantation to another country were excluded. All transplantations in Finland are performed in the Helsinki University Hospital, wherefrom a team of transplant surgeons is also responsible for the procurement surgery in the whole country. All donations were from donors after brain death (DBD). No donation after cardiac death (DCD) occurred in Finland during the study period and kidney transplantations from a living donor were not included.

Kidney transplantations recorded in Scientific Registry of Transplant Recipients (SRTR) database in the US between January 2008 to August 2018 were included. This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donor, wait-listed candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. Standard Analysis Files (Q3 2018 release) and DEATHS file were used. Data of recipients were linked with donor data using unique donor identification numbers. Only kidneys transplanted from DBD donors were included, and kidneys from DCD or living donors were excluded.

This study was approved by the Institutional Review Board of Helsinki University Hospital (HUS/459/2018) and SRTR. The clinical and research activities being reported are consistent

with the Principles of the Declaration of Istanbul as outlined in the 'Declaration of Istanbul on Organ Trafficking and Transplant Tourism'.

The following donor variables were collected for both Finnish and US cohort: donor gender and age, the time of declaration of brain death, the start time of cold perfusion in organ procurement surgery, cause of death, body mass index, race, use of kidney machine perfusion, resuscitation, laboratory results, donor history of hypertension, diabetes, smoking, alcohol and drug use, hepatitis C status, and number of organs transplanted from the same donor in addition to kidneys. Data on discarded organs was not available for the purpose of this study. Regarding the recipient and transplantation, the following data were collected: recipient sex and age, cause of kidney failure, body mass index, history of hypertension, time in dialysis, maximum panel-reactive antibody status, human leukocyte antigen mismatches, graft cold ischemia time, delayed graft function, rejection episodes and graft survival. Kidney Donor Profile Index (KDPI) was also calculated from these variables according to Organ Procurement and Transplantation Network/ United Network for Organ Sharing mapping table of 2017[12], for both Finnish and US donors. KDPI is calculated based on donor age, BMI, hypertension, diabetes, kidney function, cause of death, race, and status of hepatitis C virus. When KDPI was included in the models, the donor factors used to calculate KDPI were left out of the model due to possible multi-collinearity. Procurement delay was defined as the time from the declaration of brain death to the start of in situ cold perfusion.

Endpoints

Long-term dependent outcome measure was graft survival in which graft failure was defined as the need of retransplant, return to dialysis, or recipient death. Delayed graft function (DGF) was defined as the need for dialysis during the first week after transplantation. Data regarding acute rejection (AR), available only for the Finnish cohort, was defined as the need for rejection treatment in a biopsy-proven borderline or acute cellular or antibody-mediated rejection.

Statistical analysis

For presentation of the data, transplantations were divided into quartiles based on the length of procurement delay. We report frequencies and percentage for categorical data and median and interquartile range (IQR) for continuous data. Number of patients with missing values are stated in the table.

In the main analysis, we assessed the association between procurement delay (hours) and DGF, as well as procurement delay and kidney graft survival by fitting unadjusted and multivariable logistic regression models and Cox proportional hazards models, respectively. In multivariable analysis, we controlled for potential confounders, which we identified based on directed acyclic graphs (DAG)[13]. For both DGF and graft survival, we considered kidney donor profile index, recipient age (years), diabetes and dialysis vintage (months) as confounders (Supplemental Figure 1). Of these all except diabetes were used in analysis as continuous variables. All models were fitted on the complete-cases data formed by excluding observations with missing data on response variables or/and covariates. To account for clustering nature of the data due to relationship between kidneys from the same donor, we calculated cluster-robust standard errors of the estimates by using Huber-White method[14].

As the logistic regression and Cox models involve the assumption of linearity for the continuous data, we used restricted cubic spline function to account for potentially non-linear association between the outcome of interest and procurement delay, KDPI, recipient age and dialysis vintage. We tested for non-linearity and modelled the associations either as linear or non-linear. Linear associations between procurement delay and the outcome of interest were reported using the odds ratio (OR) or hazard ratio (HR) with 95% confidence interval (CI), as appropriate. The associations assessed with spline function were reported by plotting the predicted probability of DGF or the predicted relative hazard of graft survival as a function of procurement delay. As the Cox regression model is based on the assumption of proportional hazards, we tested for the potential non-proportionality. We accounted for the non-

proportionality by splitting the follow-up time into smaller intervals and by assessing time-varying coefficients or / and including interactions with follow-up time.

In addition, we performed several sensitivity analyses using the US data, which included enough observations for stratified analysis. We checked for consistency of the results with respect to implementation of kidney allocation system (KAS) in December 2014, number of organs transplanted from the same donor (organ yield), and cold ischemia time by dividing observations into strata and repeating the main analysis within each stratum. The number of strata varied between two for KAS (before and after KAS) to four for organ yield (only kidney(s), kidney(s) and one, two or more than two other organs) and cold ischemia time (<12, 12-18, 18-24, >=24 hours).

We set the significance level at 5%. All analyses were performed using either IBM SPSS version 25 for Windows (Armonk, NY), or R software, including survival and rms packages (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients

Between 1st June 2004 and 31st December 2017, 2,660 kidneys were procured in Finland, from which 74 were discarded and 198 were sent abroad, leaving 2,388 kidney transplantations from 1356 donors in the final analyses.

Between 1st January 2008 and 31st August 2018, 125,595 kidney transplantations from 72,290 deceased donors were recorded in SRTR database. Altogether 20,874 kidney transplantations, which were from DCD donors, were excluded. Furthermore, procurement delay could not be determined in 2,889 kidney transplant recipients because of missing date of brain death and thus these were excluded from the analysis. In addition, we excluded 349 transplantations with extreme (>120 h) procurement delay values. Final cohort from the US SRTR database included 101,474 kidney transplantations.

Basic donor and recipient characteristics among the cohorts from Finland and the US are depicted in Table 1. The median procurement delay was 9.8 hours (interquartile range (IQR) 7.8 - 12.4) in Finland and 34.9 hours (IQR 26.3 - 46.5) in the US (Figure 1).

Patients were divided into quartiles based on procurement delay. There were significant differences in basic donor and recipient characteristics between the delay quartiles (Table 2). Outcomes of patients, divided into quartiles, are presented in Table 3.

Short-term outcomes

Complete DGF response and confounder data were available on 2371 (99% of the initial cohort) and 89,337 (88%) transplantations in the Finnish and the US cohort, respectively. In the Finnish cohort, unadjusted analysis on the association between procurement delay and the probability of DGF demonstrated a linear relationship (crude OR=0.85, 95% CI 0.77-0.95, p=0.003; p=0.67 for non-linearity, Figure 2A), which, however, attenuated after adjustment (adjusted OR=0.99, 95% CI 0.89-1.11, p=0.88). In contrast, a strongly non-linear relationship was observed between procurement delay and the probability of DGF in the US cohort both in unadjusted (Figure 2B, $p<0.001$ for non-linear relationship) and multivariable analysis (Figure 2C, $p<0.001$). The lowest probability of DGF was associated with procurement delay between 20 and 50 hours, with higher probability in shorter or very long procurement delays.

Acute rejection

Acute rejection rates were not affected by procurement delay in Finnish cohort (Table 3, OR=0.92, 95% CI 0.81-1.05, p= 0.22 in unadjusted logistic regression). Data concerning acute rejections were not available for the US cohort.

Graft survival

Complete response and confounder data for graft survival analyses were available on 2371 (99% of the initial cohort) and 89,814 (89%) transplantations in the Finnish and the US cohort, respectively (Figure 3). Unadjusted graft survival rates in different quartiles of procurement delay are presented in Table 3 and Figure 3. In unadjusted analyses, we found

a non-linear association between procurement delay and kidney graft survival in the Finnish cohort (Figure 4, p=0.005 for non-linearity) but a linear association in the US cohort (Figure 4, p=0.24 for non-linearity), both showing lower hazard for graft loss associated with longer procurement delay. After adjustment for confounders, non-linearity persisted in the Finnish cohort (p=0.033) but was not present in the US cohort (p=0.67 for non-linearity). In the US cohort, modelling a linear association yielded the crude and adjusted HRs of 0.90 (95% CI 0.88-0.92, p<0.001) and 0.93 (95% CI 0.92-0.95, p<0.001) per one hour longer procurement delay, respectively. No significant interactions were found between procurement delay and recipient characteristics (p=0.054-0.73, p=0.41- 0.98), KDPI (p=0.96, p=0.50), or cold ischemia time (p= 0.14, p=0.41) for the Finnish and the US cohort, respectively.

In the unadjusted and multivariable Cox models fitted to the Finnish cohort, we found the assumption of proportional hazards to hold for all variables except dialysis vintage. In the unadjusted and multivariable Cox models fitted to the US cohort, we found non-proportionality for all variables including procurement delay. After accounting for non-proportionality by splitting the follow-up time and including interaction between dialysis vintage and follow-up time, a non-linear association between procurement delay and graft survival persisted (p=0.027 for non-linearity) in the Finnish cohort. In the US cohort, the association between procurement delay and hazard attenuated over time (Supplemental Table 1). After restricting the follow-up to 1.5 years, we found the assumption of proportional hazards to hold and the association to be non-linear in the unadjusted analysis (p=0.036) but linear in the multivariable analysis (HR=0.90, 95% CI 0.87-0.93).

In the US cohort, we performed sensitivity analysis in ten strata and found the results to be similar to that of the main analysis in all except two strata (Supplemental Figures 2-12). Before the implementation of the KAS in 2014, the median procurement delay was 31 hours (IQR 24–40), compared to 42h (IQR 32–55) after the implementation of KAS. However, in sensitivity analyses the association between procurement delay and graft outcomes remained similar in both groups (Supplemental Figures 2-3). When the number of organs

transplanted from the same donor was taken into account, no interaction was recorded between the organ yield and procurement delay (p=0.37-0.94) in either of the cohorts. In the sensitivity analysis within each stratum, the findings remained similar if maximum two other organs were transplanted in addition to kidneys from the same donor (Supplemental Figures 4-7). In the stratum including kidney transplants procured with more than two other transplanted organs, we found no statistically significant association between procurement delay and hazard (HR=0.96, 95% CI 0.91-1.00, p=0.08). When restricting cold ischemia time to 18-24 hours, we observed a non-linear relationship (p=0.04) between procurement delay and hazard in multivariable analysis (Supplemental Figure 11).

DISCUSSION

In this study of two countries, longer procurement delay was not associated with lower long-term kidney allograft survival. On the contrary, very short delay (<8 hours) was associated with worse graft survival, whereas increasing delay was associated with improved graft survival to a smaller extent, but without apparent upper limit. Of note, the median procurement delay in the longest delay quartile in Finland (15 hours) was shorter than the median delay in the shortest quartile in the US (21 hours). The probability of DGF was lowest between 20 and 50 hrs of procurement delay, whereas procurement delay was not associated with AR rates in Finnish transplants. These results together imply a sweet spot of approximately 24 – 48 hours after brain death for organ procurement.

In concordance with our results, three earlier studies reported association of increasing procurement delay with improved kidney graft survival[9–11], while one smaller study did not find an association[15]. Two of these studies found no association between procurement delay and the risk of DGF in multivariable models[10,11], whereas in our study the risk of DGF was higher with very long procurement delays. AR was not affected by procurement delay[10,11],

and none of the studies reported any benefits of shorter delay[9–11,15]. All studies conducted have been retrospective and therefore possibly limited by the same confounding factors. Although the findings in the current study are not novel, our study confirmed the findings of the previous studies in the largest cohort to date across two continents, with statistical methods taking account the nonlinear association between procurement delay and graft outcomes. We also demonstrate that the association between slightly better outcomes and longer procurement delay remains also in the current era, where times from brain death to organ procurement in the US are longer than in the earlier studies.

Median procurement delays vary markedly in the reported series. Shortest procurement delays were reported in Germany, median 8 hours[9], and longest in the US (median 24 hours)[10]. Interestingly, Nijboer et al[10] analyzed US data from 1994 to 2007, whereas our data included years 2008 – 2018, showing that the median delay increased from 24 hours to 35 hours between these two eras in the US. The reasons behind the different delays in different countries and the increase in median delay in the US over time seem logistics-driven, but no clear additional harm was observed from prolonging procurement over the years.

One of the concerns of longer procurement delay is the potential deterioration of the donor and potential loss of viable organs. However, evidence to justify this concern is scarce and possibly derives from hemodynamically unstable donors with insufficient donor management protocols in the past. A study from Brazil found over 30-hour procurement time to be a possible risk factor to losing a donor[16], whereas studies from the US found no difference in organ procurement rates up to over 60 hours after brain death[8,17].

In heart transplantation, prolonged donor management time, but not time after brain death, has been associated with poorer outcome[18]. However, newer studies found no significant survival difference in hearts[19], and a positive association of longer delay with better lung acute rejection- and bronchiolitis obliterans-free survival[20]. Interestingly no animal studies favoring longer procurement were found.

A limitation of this study is that causality cannot be established from this observational registry analysis. Also due to retrospective and non-randomized nature of the study, it is susceptible to residual confounding and distortion of the association due to non-random allocation. The latter cannot be controlled using standard statistical methods, such as model adjustment[21]. Moreover, the studied associations appear to be more complex than in the simplified DAG that was used to identify confounders. In fact, some covariates are likely to play both the role of confounder and mediator of the effect of interest. Only kidney transplantations were analyzed in this study, and further studies are needed to assess correlation of procurement delay on other organs. There are several strengths also. We tried to limit the bias by conducting multivariable analyses using multiple confounding variables, which should account for better quality organs distributing unevenly between procurement times. Another strength is the sample size, which is five times larger than in the biggest earlier report[10]. Analysis of two different cohorts from two continents with different organ procurement practices and large differences in times from brain death to organ procurement gives a broader perspective to this effect, although the relatively small sample size of the Finnish cohort limits our possibilities to adjust for confounding factors in this cohort in all analyses. The optimal delay seems to be over 8 hours, but procurement delays up to 50 hours do not seem harmful for kidney transplants. When considering the optimal timing of the organ procurement, multiple factors have to be taken into account. In the current data, longer procurement delays were associated with increasing number of organs transplanted from the same donor, which is indeed expected as the logistics of both the organ procurement and allocation takes more time. In addition to medical factors related to the outcome of the grafts, although beyond the scope of the current study, also economical costs of prolonging the procurement operation have to be considered.

The mechanisms, by which longer procurement delay is associated with better graft survival can only be speculated. Brain death (and its associated cytokine storm) and ischemia may be considered as ‘hits’ that affect kidney allografts negatively. In this two-hit theory, it could

be beneficial for the kidney to recover from the first hit (brain death) before it is exposed to the second hit (ischemia). Also protective mechanisms, such as heat-shock proteins and systemic mediators upregulated by ischemia could play a role in allograft preservation[22–24]. However, no serial data about the trend in urine output or kidney function in the donors were available, limiting our possibilities to further explore this hypothesis.

DISCLOSURES

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FIGURE LEGENDS

Figure 1. Distribution of time from declaration of brain death to cold perfusion in Finnish organ donors from June 2004 to December 2017 and SRTR organ donors from January 2008 to August 2018.

Figure 2. The estimated probability (black line) of delayed graft function as a function of procurement delay when assessed using unadjusted (A, B) and multivariable (C) logistic regression model with restricted cubic spline function. Grey area corresponds to 95% confidence band.

A) Finnish cohort: p=0.67 for non-linear association.

B) US cohort: p<0.001 for non-linear association.

C) US cohort: p<0.001 for non-linear association. Predicted values were calculated by setting confounder values to their median (KDPI=45, recipient age=53 years, dialysis vintage=45.57 months) or the most frequent category (no diabetes).

Figure 3. Graft survival of kidney transplants in Finland from June 2004 to December 2017 and the US from January 2008 to August 2018 by quartiles of time from brain death to cold perfusion (procurement delay in hours (h)). Outcome is defined as death, return to dialysis, or retransplantation.

Figure 4. The estimated relative hazard (black line) of graft failure or death as a function of procurement delay when assessed using unadjusted Cox regression model with restricted cubic spline function. Grey area corresponds to 95% confidence band, p=0.005 for non-linear association in Finnish cohort and p=0.11 for non-linear association in the US cohort.

TABLES

Table 1. Characteristics of donors and kidney transplantations in Finland from June 2004 to December 2017 and the US from January 2008 to August 2018.

Baseline characteristics	Finland 2,388 kidney transplantations 1,311 donors	US 101,474 kidney transplantations 58,792 donors	Missing Finland n (%)	Missing US n (%)
Donor time from brain death to organ perfusion, median (IQR), hours	9.8 (7.8-12.4)	34.8 (26.3-46.3)	0	0
Donor age, median (IQR), years	55 (45-63)	37 (23-50)	0	0
Donor BMI, median (IQR), kg/m^2	24.8 (23.1-27.7)	26.1 (22.6-30.5)	2 (0.2%)	0
Donor gender, male	674 (56%)	35,396 (60%)	0	0
Donor cardiac arrest prior to brain death	229 (18%)	4,427 (8%)	0	9 (0.0%)
Donor medical conditions,				
Hypertension	377 (29%)	15,481 (26%)	0	375 (0.6%)
Diabetes	57 (4%)	4,031 (7%)	0	0
Donor cause of death,			0	0
Cerebrovascular accident	896 (68%)	17,822 (30%)		
Trauma	340 (26%)	22,009 (37%)		
Anoxia	37 (3%)	17,447 (30%)		
Other	75 (6%)	1,514 (3%)		
Donor need of inotropic medication	1,210 (92%)	30,355 (52%)	0	123 (0.2%)
Donor creatinine, median (IQR), mg/dl	0.7 (0.5-0.8)	1.0 (0.7-1.3)	1 (0.1%)	0
KDPI[a], median (IQR)	60 (36-80)	44 (20-69)	4 (0.3%)	436 (0.7%)
Donor organ yield[b], median (IQR)	3 (2-3)	4 (3-4)	0	0
Cold ischemia time, median (IQR), hours	20.3 (17.2-23.4)	15.5 (10.4-21.9)	7 (0.3%)	1,985 (2%)
Recipient age, median (IQR), years	53 (42-62)	54 (42-63)	0	0
Recipient BMI, median (IQR), kg/m^2	25.0 (22.1-28.1)	27.4 (23.6-31.6)	527 (22%)	2,524 (3%)
Recipient gender, male	1,566 (66%)	60,867 (60%)	0	0
Retransplantation	249 (10%)	13,308 (13%)	0	0
Cause of kidney failure			0	0
Diabetic kidney disease	659 (28%)	25,722 (25%)		
Glomerulonephritis	623 (26%)	20,021 (20%)		
Polycystic kidney disease	427 (18%)	7,570 (8%)		
Other	679 (28%)	47,702 (47%)		
Unknown	0 (0.0%)	459 (0.5%)		
Recipient time in dialysis before transplantation, median (IQR), months	22 (13-38)	46 (23-73)	8 (0.3%)	10,962 (11%)

Pre-emptive transplantations	0 (0.0%)	12,343 (12%)	0	958 (1%)
Number of HLA A and B mismatches, median (IQR)	2 (1-2)	3 (2-4)	0	738 (0.7%)
Number of HLA DR mismatches, median (IQR)	1 (0-1)	1 (1-2)	0	739 (0.7%)
Number of HLA mismatches, median (IQR)	3 (2-3)	4 (3-5)	0	739 (0.7%)
Delayed graft function	849 (36%)	23,007 (23%)	0	596 (0.6%)
Acute rejection	430 (18%)	NA	0	NA
Graft survival at 1 year	95%	93%	1 (0.0%)	0
Graft survival at 3 years	90%	85%	1 (0.0%)	0
Graft survival at 5 years	82%	76%	1 (0.0%)	0
Graft survival at 10 years	61%	50%	1 (0.0%)	0

Median (IQR) and n (%) unless otherwise indicated. BMI= body mass index, HLA= human leukocyte antigen, KDPI= Kidney Donor Profile Index, NA= not available.
All variables were significantly different between the cohorts ($p < 0.001$ for every variable (recipient age $p < 0.003$).
[a] Percentiles 0 to 100, indicating higher risk of graft failure relative to other kidneys with increasing percentage.
[b] Organ yield from multiorgan donor, maximum of 7 (heart, lungs, liver, pancreas, intestine and two kidneys).
In graft survival outcome is defined as death, retransplantation or return to dialysis.

Table 2. Differences in characteristics of quartiles of kidney transplantations in Finland from June 2004 to December 2017 and the US from January 2008 to August 2008 by quartiles of time from brain death to organ perfusion (procurement delay).

Variable	Finland, quartiles of time from brain death to organ perfusion in organ donors				US, quartiles of time from brain death to organ perfusion in organ donors			
Quartile, n of donors, n of recipients	1st n: 321 n: 596	2nd n: 326 n: 598	3rd n: 330 n: 597	4th n: 334 n: 597	1st n: 14,689 n: 25,366	2nd n: 14,686 n: 25,371	3rd n: 14,711 n: 25,369	4th n: 14,706 n: 25,368
Time from brain death to organ perfusion, median (IQR), hours	6.5 (5.8-7.2)	8.7 (8.2-9.1)	10.8 (10.2-11.5)	15.1 (13.5-18.0)	20.5 (16.1-23.8)	30.6 (28.5-32.7)	39.6 (37.1-42.6)	57.1 (50.9-67.1)
KDPI, median (IQR), %	76 (55-89)	63 (43-81)	57 (34-79)	43 (23-62)	53 (25-77)	45 (20-69)	41 (19-66)	37 (17-62)
Donor age, median (IQR), years	61 (54-67)	56 (47-63)	53 (40-61)	48 (37-56)	43 (26-55)	37 (23-50)	35 (22-48)	34 (22-47)
Donor BMI, median, kg/m^2	25.7 (23.9-27.8)	25.0 (23.3-27.6)	24.7 (22.9-27.7)	24.5 (22.9-27.5)	26.4 (22.8-30.9)	26.0 (22.4-30.6)	26.0 (22.5-30.4)	25.9 (22.5-30.2)
Donor creatinine, median, mg/dl	0.68 (0.55-0.81)	0.67 (0.53-0.80)	0.63 (0.50-0.80)	0.64 (0.53-0.80)	1.00 (0.71-1.36)	1.00 (0.70-1.30)	1.00 (0.70-1.33)	0.99 (0.70-1.40)
Donor hypertension	125 (39%)	98 (30%)	82 (25%)	72 (22%)	4,741 (32%)	3,948 (27%)	3,589 (25%)	3,203 (22%)
Donor cause of death: cerebrovascular accident	236 (74%)	227 (70%)	221 (67%)	211 (63%)	5,367 (37%)	4,675 (32%)	4,189 (29%)	3,909 (27%)
Donor resuscitated	53 (17%)	60 (18%)	56 (17%)	60 (18%)	1,149 (8%)	1,142 (8%)	1,122 (8%)	1,014 (7%)
Donor diabetes	23 (7%)	15 (5%)	6 (2%)	13 (4%)	1,292 (9%)	1,028 (7%)	903 (6%)	808 (6%)
Donor organ yield[a], median	2 (2-2)	3 (2-3)	3 (2-3)	3 (2-4)	3 (2-4)	3 (3-4)	4 (3-5)	4 (3-5)
Cold ischemia time, median, hours	20.9 (18.1-23.6)	20.6 (18.0-23.8)	20.3 (16.9-23.3)	19.4 (14.5-22.9)	16.3 (10.8-23.0)	16.0 (11.1-21.1)	14.1 (9.7-21.2)	15.5 (10.2-21.5)
Recipient age, median, years	57 (48-65)	54 (42-62)	51 (40-60)	48 (37-58)	56 (45-64)	54 (42-63)	53 (41-62)	52 (40-62)
Recipient diabetes	147 (25%)	165 (28%)	162 (27%)	185 (31%)	9,232 (36%)	8,594 (34%)	8315 (33%)	8,167 (32%)
HLA MM total, median	3 (2-3)	3 (2-3)	3 (2-3)	3 (2-3)	4 (3-5)	4 (3-5)	4 (3-5)	4 (3-5)
Previous kidney transplant	65 (11%)	58 (10%)	64 (11%)	62 (10%)	2,960 (12%)	3,204 (13%)	3,481 (14%)	3,663 (14%)
Donor african-american	NA	NA	NA	NA	1,987 (14%)	2,405 (16%)	2,634 (18%)	2,655 (18%)
Recipient african-american	NA	NA	NA	NA	8,737 (34%)	8,499 (34%)	8,421 (33%)	7,545 (30%)
Recipient BMI, median, kg/m^2	25.5 (22.7-28.5)	25.2 (22.1-28.1)	24.8 (22.3-28.0)	24.3 (21.6-28.1)	27.6 (23.9-31.7)	27.5 (23.6-31.7)	27.3 (23.5-31.6)	27.1 (23.3-31.3)
Recipient time in dialysis, months, median (IQR)	23 (15-38)	23 (14-38)	22 (12-38)	19 (12-36)	43 (23-67)	43 (23-69)	46 (23-74)	51 (25-83)

BMI= body-mass index, HLA MM= human leukocyte antigen mismatches, KDPI= Kidney Donor Profile Index, NA= not available, Time from brain death to organ perfusion= time from declaration of brain death to in situ organ cold perfusion. KDPI is calculated from donor age, height, weight, history of diabetes and hypertension, cause of death, creatinine and race.

[a] Organ yield from multiorgan donor, maximum of 7 (heart, lungs, liver, pancreas, intestine and two kidneys)

Table 3. Outcomes of kidney transplantations in Finland from June 2004 to December 2017 and the US from January 2008 to August 2008 by quartiles of time from brain death to organ perfusion (procurement delay). Graft survival is defined as alive with a functioning graft.

Variable	Finland, quartiles of time from brain death to organ perfusion in organ donors				US, quartiles of time from brain death to organ perfusion in organ donors			
Quartile, n of transplantations	1st n: 596	2nd n: 598	3rd n: 597	4th n: 597	1st n: 14,635	2nd n: 14,828	3rd n: 14,838	4th n: 14,641
Delayed graft function	233 (39%)	222 (37%)	204 (34%)	190 (32%)	6059 (24%)	5614 (22%)	5458 (22%)	5944 (24%)
Acute rejection	115 (19%)	107 (18%)	106 (18%)	102 (17%)	NA	NA	NA	NA
1-year graft survival	93%	96%	94%	95%	92%	93%	94%	94%
5-year graft survival	75%	85%	84%	84%	74%	76%	77%	78%
10-year graft survival	54%	63%	62%	69%	47%	50%	53%	51%
Follow-up, median (IQR), years	4.1 (2.0-8.0)	5.2 (2.7-9.0)	5.3 (2.3-8.8)	4.1 (1.7-7.0)	4.2 (2.0-6.9)	3.8 (1.7-6.0)	2.9 (1.0-5.0)	1.9 (0.7-3.8)
Graft survival, median, years	10.9	13.0	>13.5[a]	13.5	9.7	10.0	10.3	10.1

NA = Not available for US cohort. [a] = Over 50% of grafts were still functioning at the end of follow-up. Median (>13,5 years) was thus not reached in follow-up. In graft survival outcome is defined as death, retransplantation or return to dialysis.

FIGURES

Figure 1. Distribution of time from declaration of brain death to cold perfusion in Finnish organ donors from June 2004 to December 2017 and SRTR organ donors from January 2008 to August 2018.

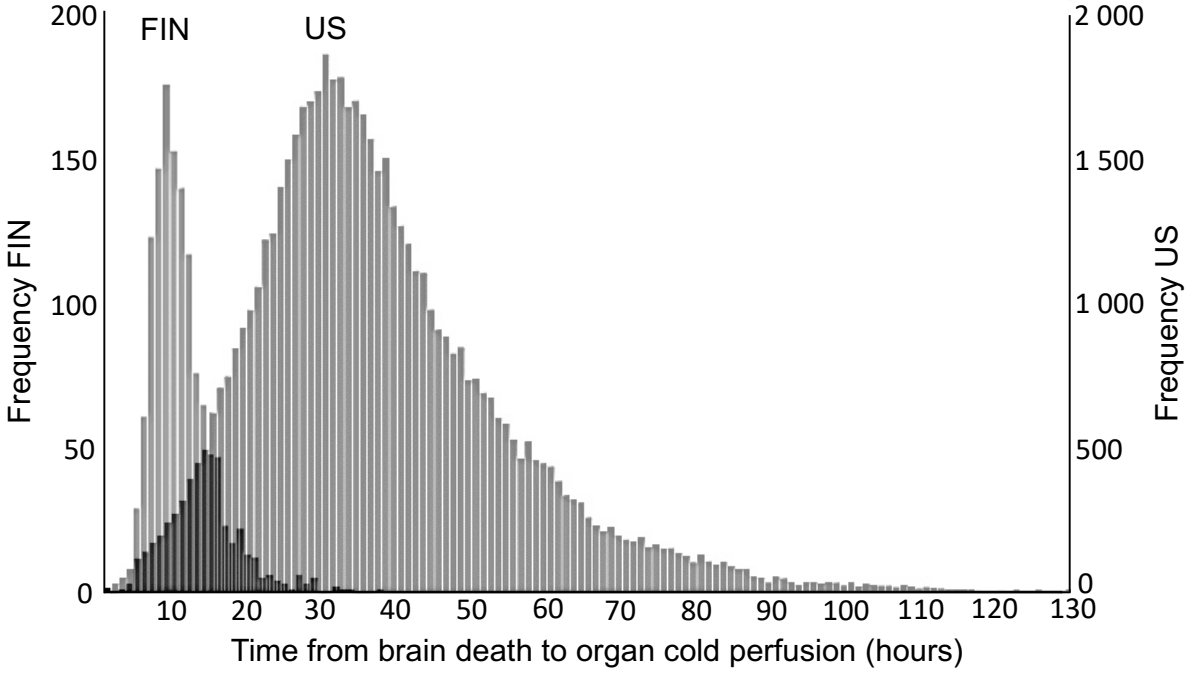


Figure 2. The estimated probability (black line) of delayed graft function as a function of procurement delay when assessed using unadjusted (A, B) and multivariable (C) logistic regression model with restricted cubic spline function. Gray area corresponds to 95% confidence band. A) Finnish cohort: p=0.67 for non-linear association. B) US cohort: p<0.001 for non-linear association. C) US cohort: p<0.001 for non-linear association. Predicted values were calculated by setting confounder values to their median (KDPI=45, recipient age=53 years, dialysis vintage=45.57 months) or the most frequent category (no diabetes).

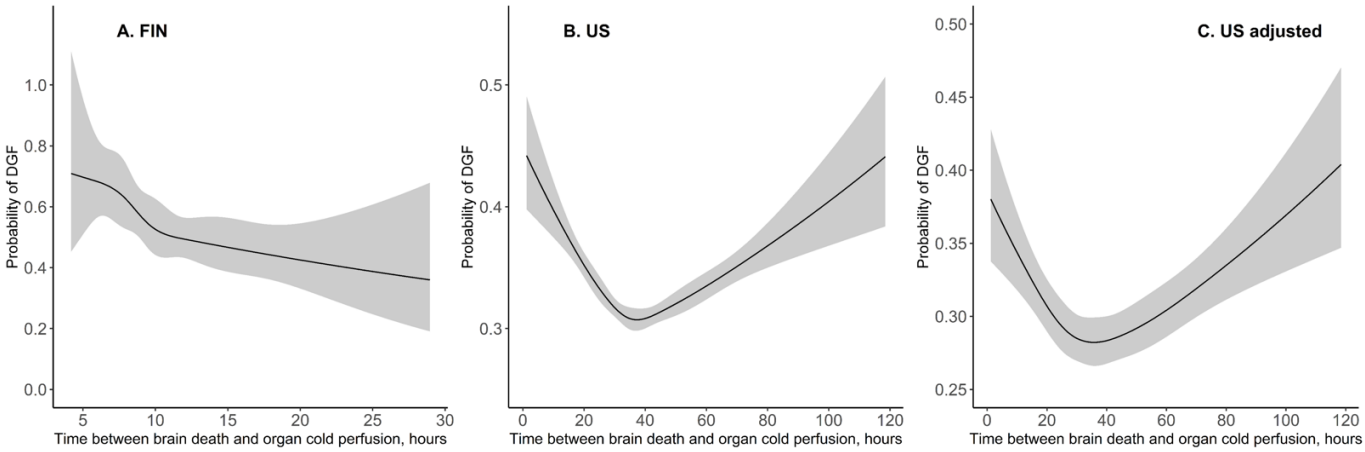


Figure 3. Graft survival of kidney transplants in Finland from June 2004 to December 2017 and the US from January 2008 to August 2018 by quartiles of time from brain death to cold perfusion (procurement delay in hours). Outcome is defined as death, return to dialysis, or retransplantation.

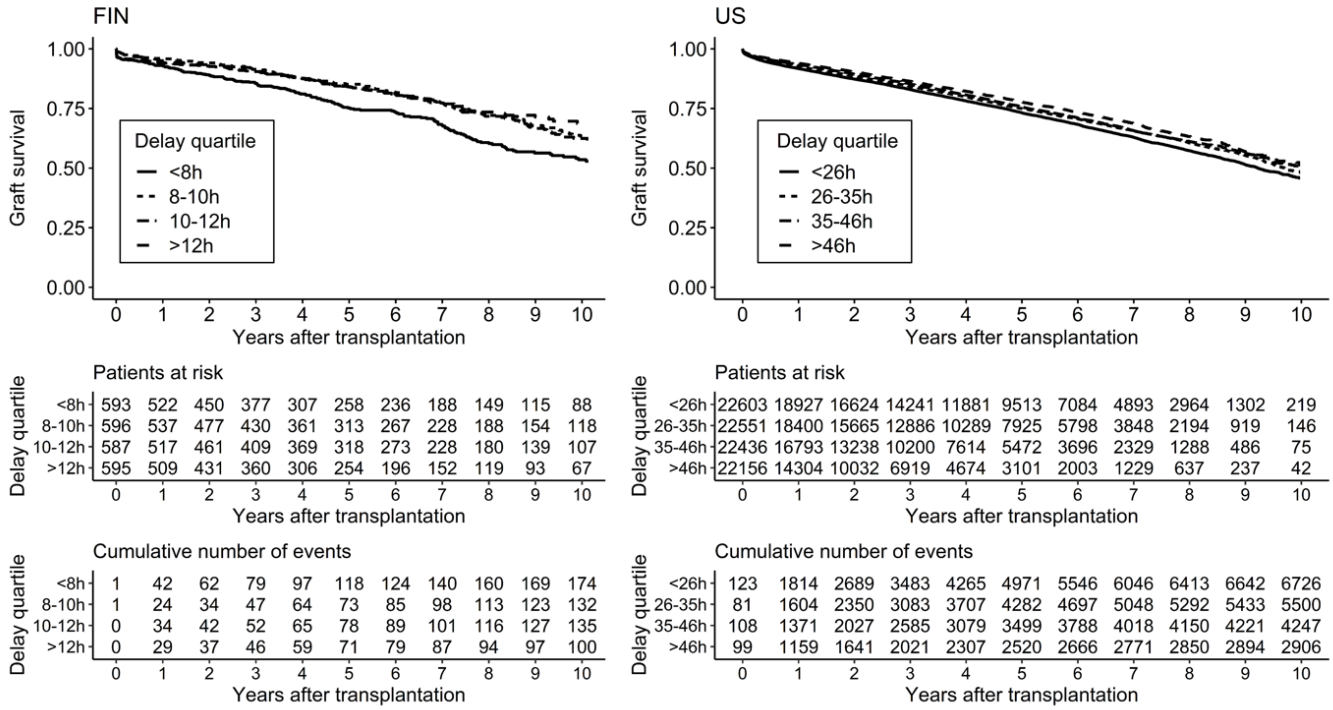
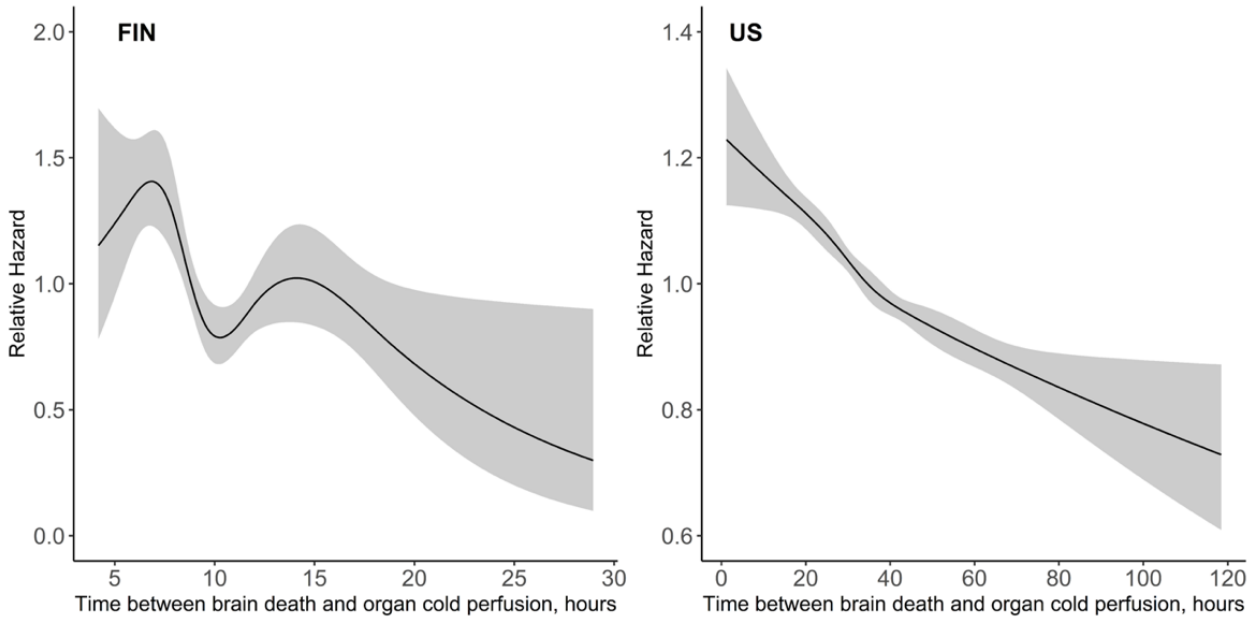


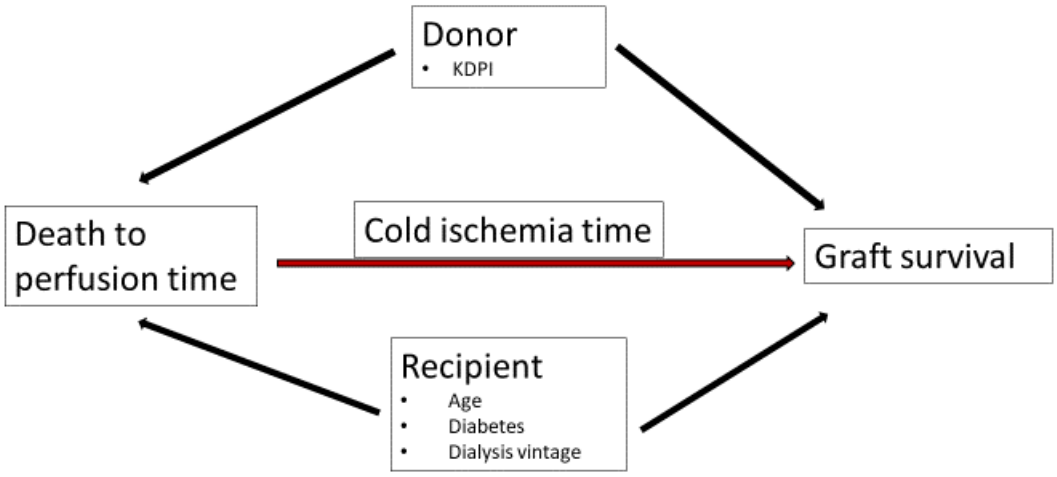
Figure 4. The estimated relative hazard (black line) of graft failure or death as a function of procurement delay when assessed using unadjusted Cox regression model with restricted cubic spline function. Grey area corresponds to 95% confidence band, p=0.005 for non-linear association in Finnish cohort and p=0.11 for non-linear association in the US cohort.



SUPPLEMENTAL MATERIAL

Directed acyclic graph (DAG)

Figure 1: Graphical presentation of confounding and mediators in our study



Sensitivity analyses

Table 1. US cohort, time dependent hazard ratio

In the US cohort, the association between procurement delay and hazard attenuated over time. We accounted for non-proportionality by splitting the follow-up time and assessing time-varying HRs of DTPT by three follow-up periods (0-1.5, 1.5-4, >4 years) without and with adjustment for confounders. Time-dependent variation of the confounder's regression coefficients was accounted for by introducing to the model interactions between confounders and follow-up time.

Univariate (FUT = follow-up time)

FUT	HR	95% CI	p-val
0-1.5y	0.9930	0.9914-0.9946.	<2e-16
1.5-4y	0.9968	0.9951-0.9986	0.000386
>4y	0.9973	0.9954-0.9993	0.008500

Multivariable

FUT	HR	95% CI	p-val
0-1.5y	0.9951	0.9936-0.9967	8.01e-10
1.5-4y	0.9982	0.9965-1.0000	0.04759
>4y	0.9993	0.9974-1.0013	0.50743

Cox regression model by KAS

Before KAS (55401 transplantations, 16686 events): p= 0.100 for non-linearity in the univariate model (Figure 1), adjusted HR= 0.948 (95% CI 0.931–0.965, p<0.0001)

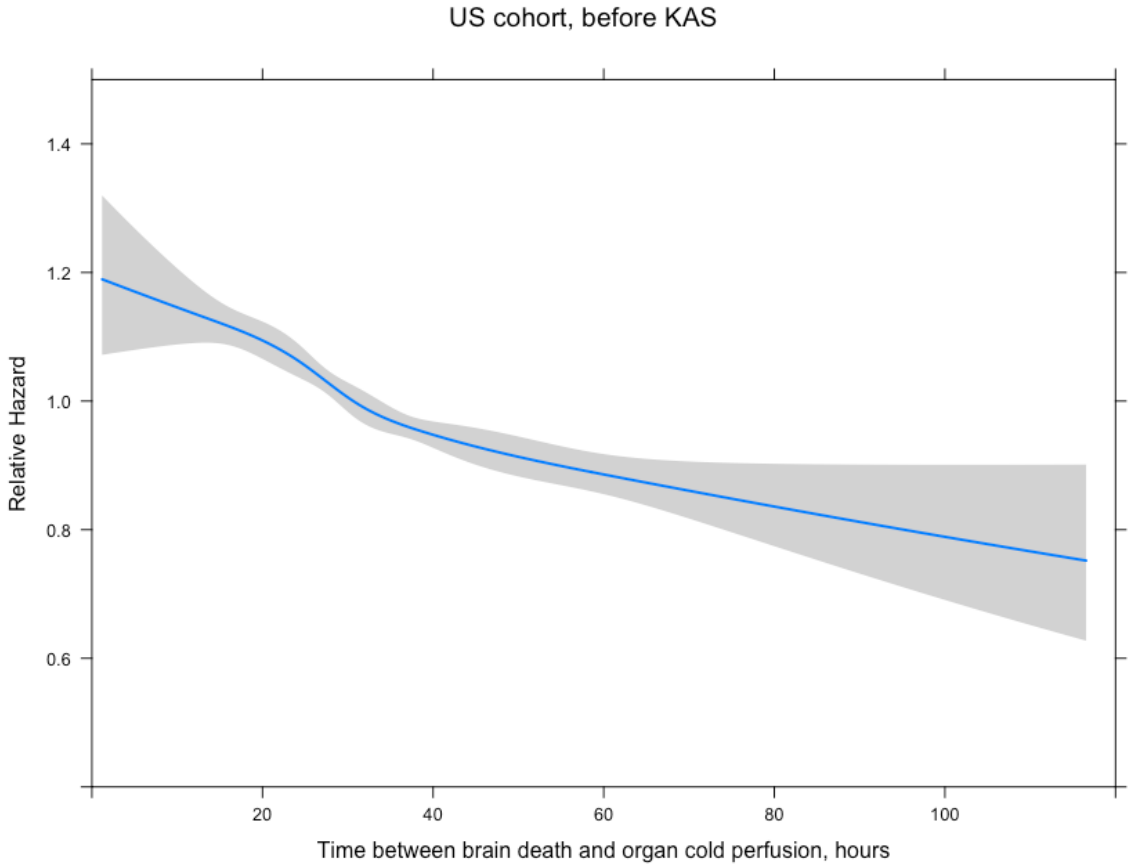


Figure 2. The relative hazard predicted from the univariate model with a restricted cubic spline. Sensitivity analysis before KAS, US cohort.

After KAS (34413 transplantations, 2737 events): p= 0.958 for non-linearity in the univariate model (Figure 2), adjusted HR= 0.949 (95% CI 0.904–0.997, p= 0.037)

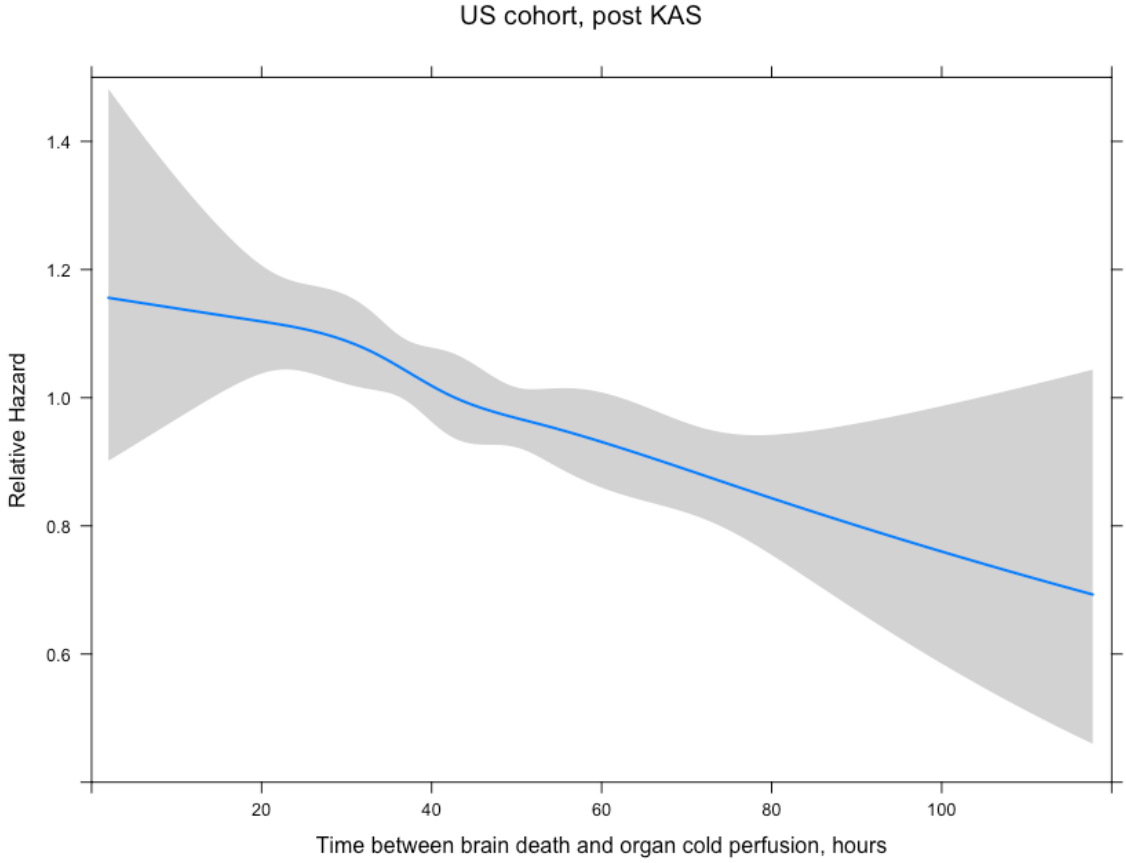


Figure 3. The relative hazard predicted from the univariate model with a restricted cubic spline. Sensitivity analysis after KAS, US cohort.

Cox regression model by organ yield

Procurement of kidney(s) only (9204 transplantations, 2410 events): p= 0.030 for non-linearity in the univariate model (Figure 3) and p= 0.429 in multivariable model; adjusted HR= 0.946 (95% CI 0.898–0.997, 0.040)

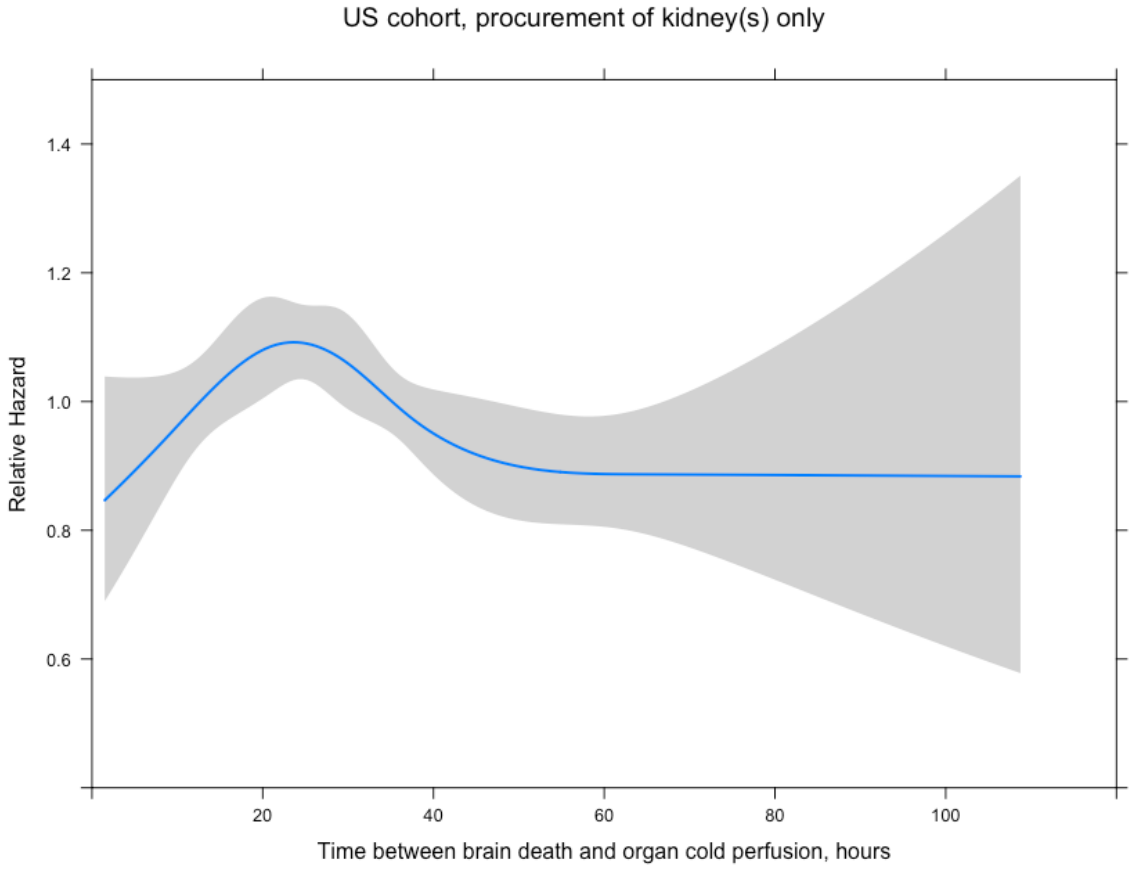


Figure 4. The relative hazard predicted from the univariate model with a restricted cubic spline. Sensitivity analysis of organ yield, kidneys only, US cohort.

Procurement of kidney(s) and one other organ (34996 transplantations, 8669 events): p= 0.576 for non-linearity in the univariate model (Figure 4) and p= 0.897 in multivariable model; adjusted HR= 0.933 (95% CI 0.907-0.960, p<0.0001)

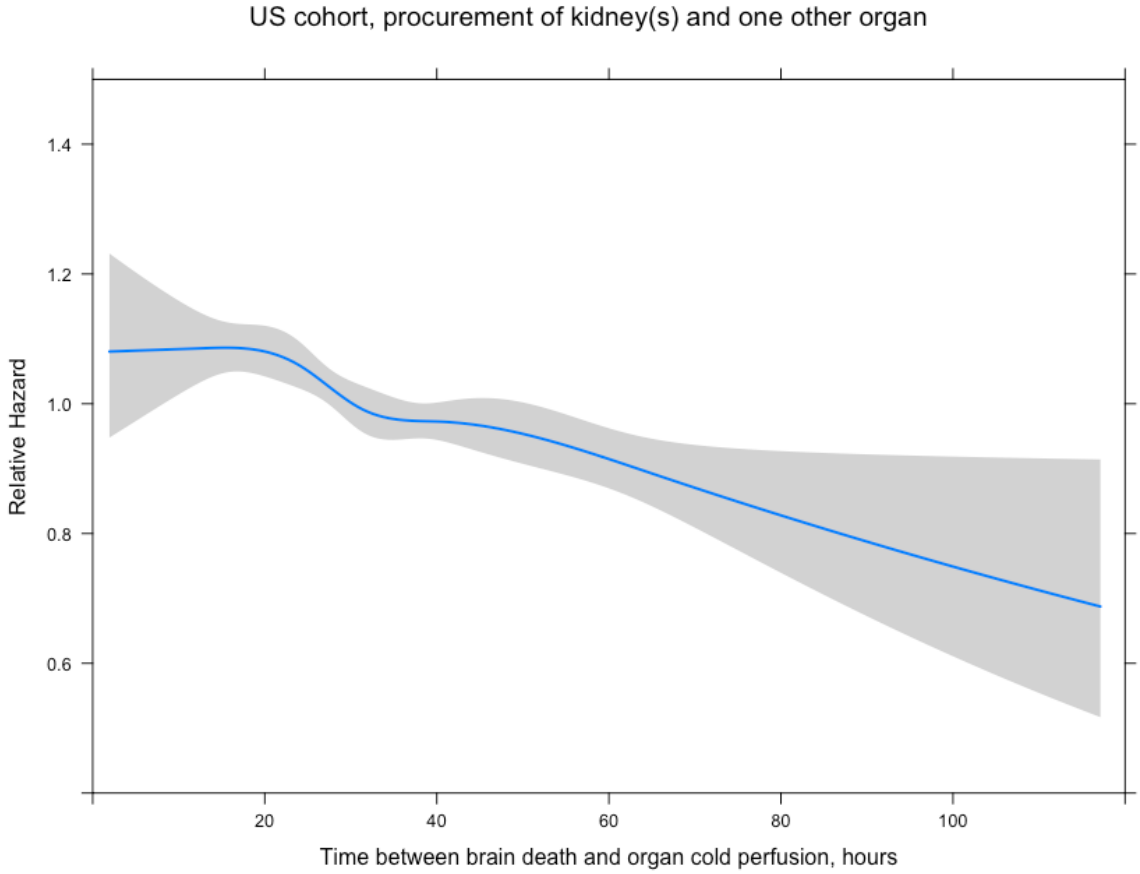


Figure 5. The relative hazard predicted from the univariate model with a restricted cubic spline. Sensitivity analysis of organ yield, kidneys and one other organ, US cohort.

Procurement of kidney(s) and two other organs (25892 transplantations, 4911 events): p= 0.083 for non-linearity in the univariate model (Figure 5) and p= p=0.109 in multivariable model; adjusted HR= 0.935 (95% CI 0.900-0.971, p=0.0005)

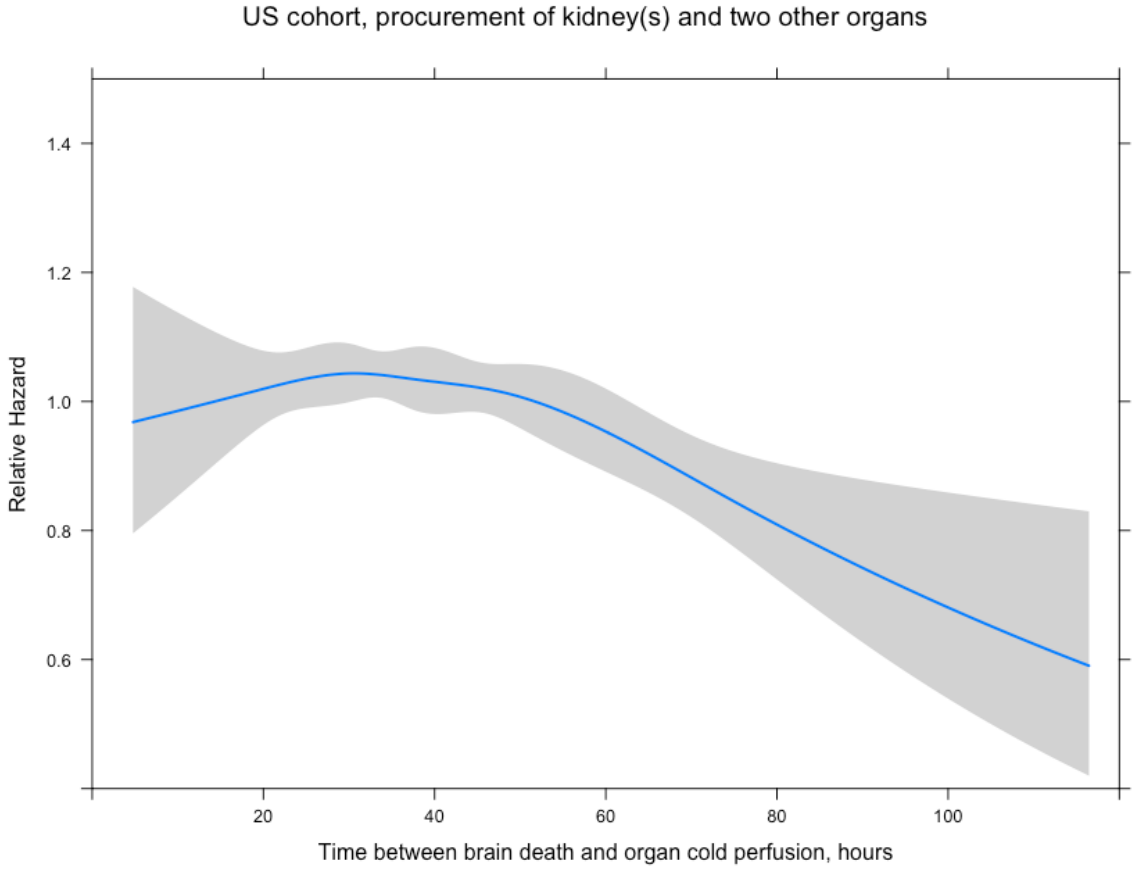


Figure 6. The relative hazard predicted from the univariate model with a restricted cubic spline. Sensitivity analysis of organ yield, kidneys and two other organs, US cohort.

Procurement of kidney(s) and more than two other organs (19722 transplantations, 3433 events): p= 0.576 for non-linearity in the univariate model (Figure 6) and p= 0.897 in multivariable model; adjusted HR=0.958 (95% CI 0.914-1.005, p=0.0770)

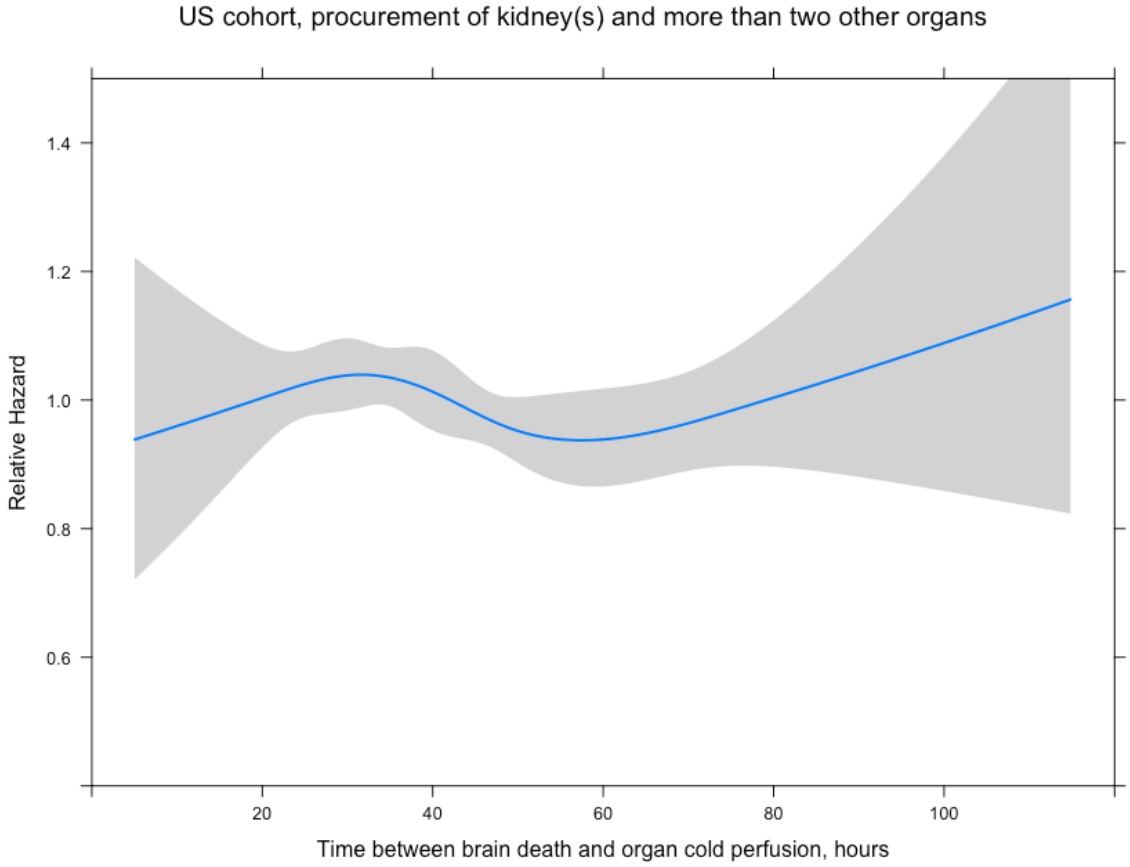


Figure 7. The relative hazard predicted from the univariate model with a restricted cubic spline. Sensitivity analysis of organ yield, kidneys and more than two other organs, US cohort.

Cox regression model by cold ischemia time (CIT)

CIT < 12h (29378 transplantations, 2410 events): p= 0.152 for non-linearity in the univariate model (Figure 7) and p= 0.035 in multivariable model (Figure 8); adjusted HR= 0.905 (95% CI 0.873-0.938, p<0.0001)

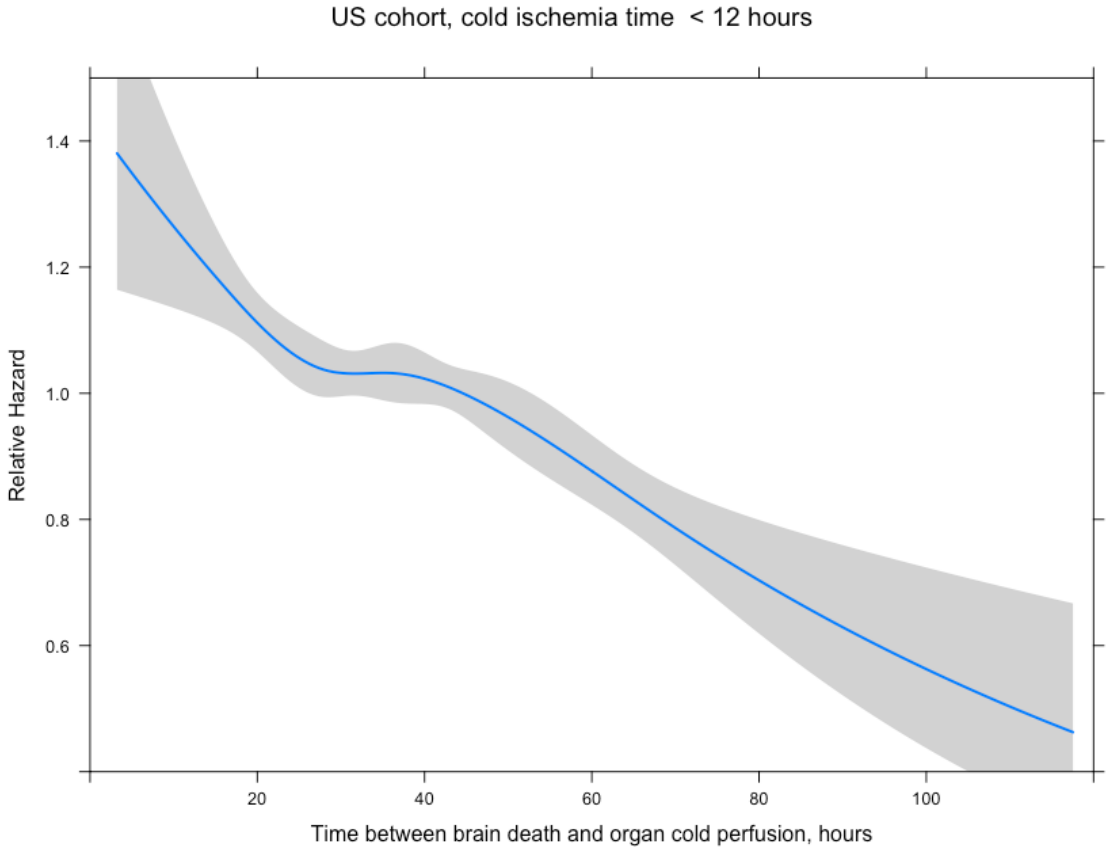


Figure 8. The relative hazard predicted from the univariate model with a restricted cubic spline. Sensitivity analysis of cold ischemia time <12h, US cohort.

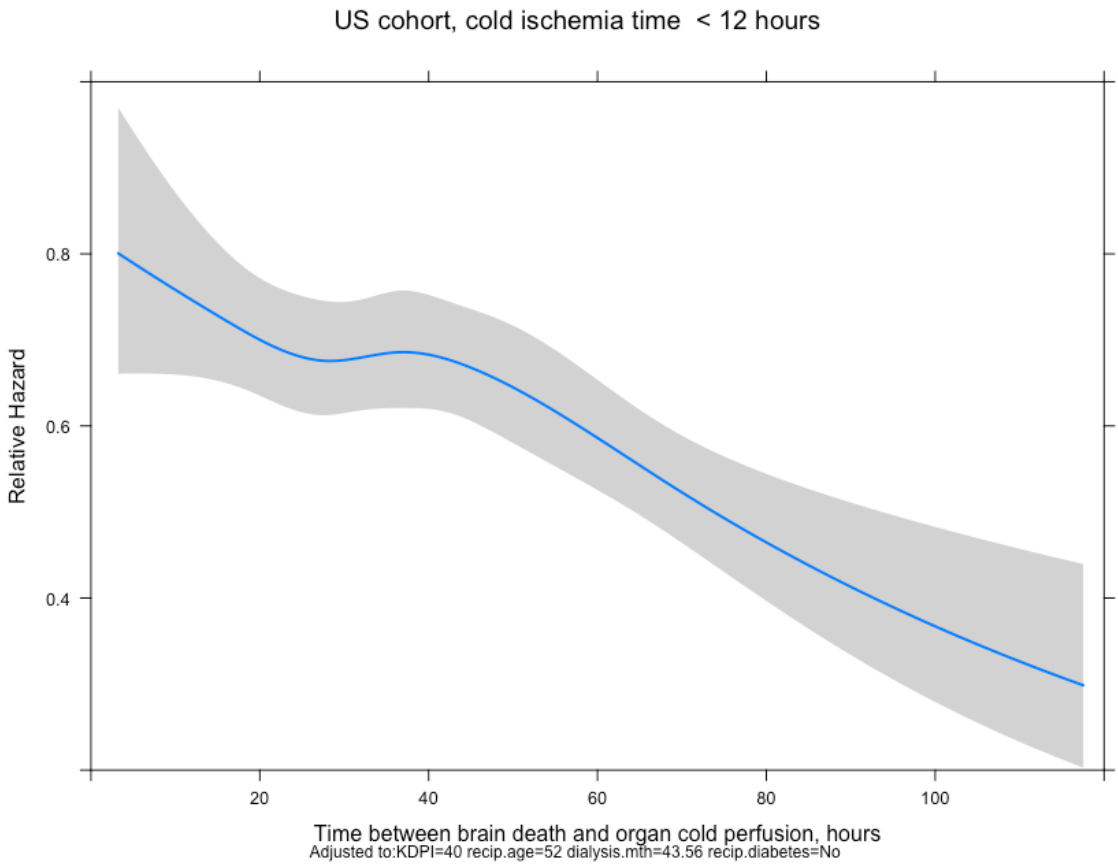


Figure 9. The relative hazard predicted from the multivariable model with a restricted cubic spline. Sensitivity analysis of cold ischemia time <12h, US cohort. The predicted hazard was calculated by setting confounder values to their median (continuous variables) or the most frequent category (categorical variables)

CIT 12-18 h (26799 transplantations, 5451 events): p= 0.123 for non-linearity in the univariate model (Figure 9) and p= 0.543 in multivariable model; adjusted HR= 0.963 (95% CI 0.931-0.996, p= 0.030)

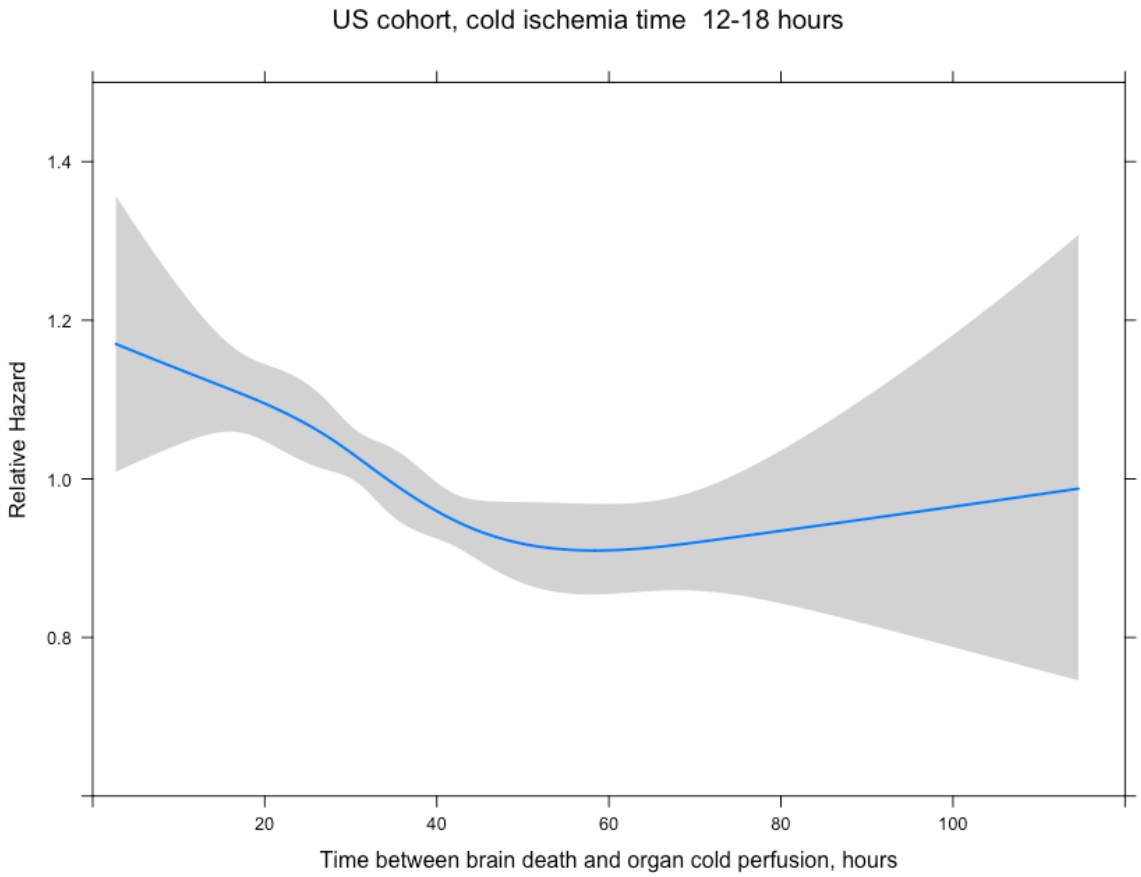


Figure 10. The relative hazard predicted from the univariate model with a restricted cubic spline. Sensitivity analysis of cold ischemia time 12 to 18 hours, US cohort.

CIT 18-24 h (29378 transplantations, 2410 events): p= 0.152 for non-linearity in the univariate model (Figure 10) and p= 0.035 in multivariable model; adjusted HR=0.927 (95% CI 0.891-0.965, p=0.0002)

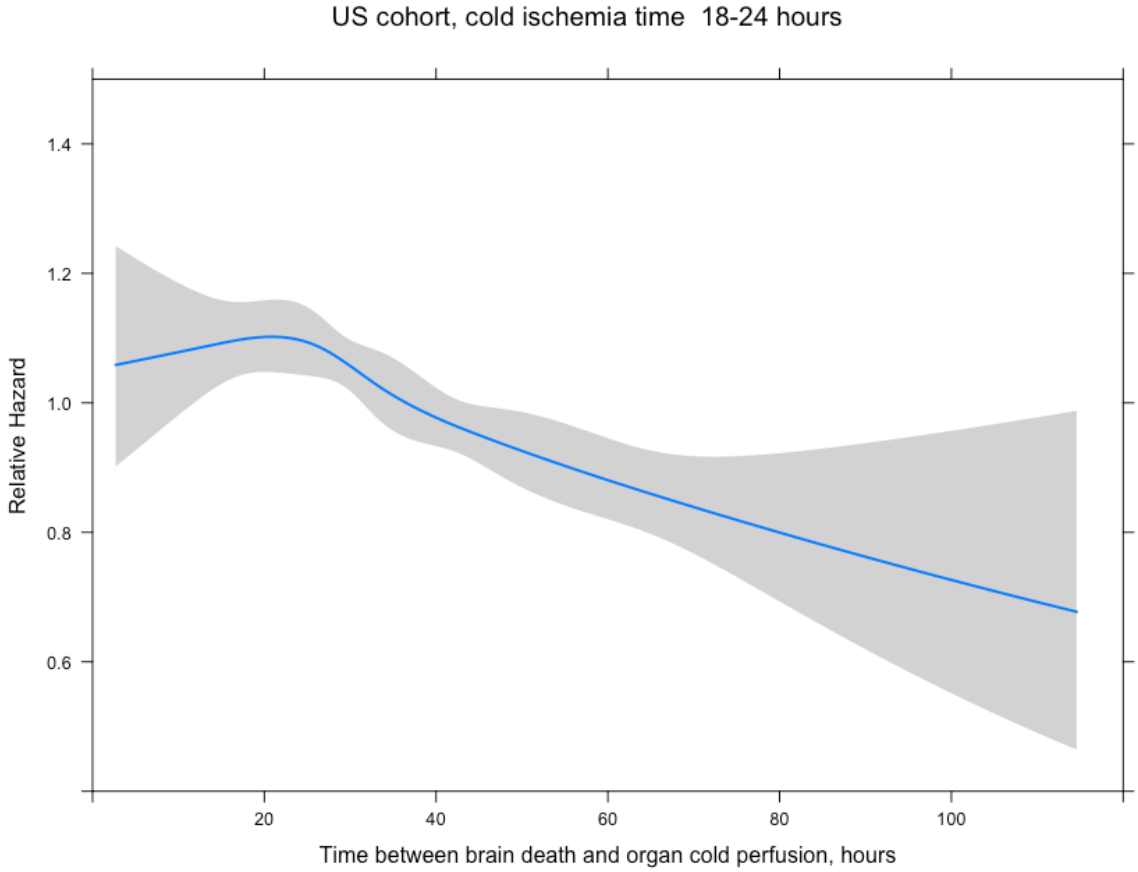


Figure 11. The relative hazard predicted from the univariate model with a restricted cubic spline. Sensitivity analysis of cold ischemia time 18 to 24 hours, US cohort.

CIT >=24 h (18537 transplantations, 3980 events): p= 0.016 for non-linearity in the univariate model (Figure 11) and p=0.489 in multivariable model; adjusted HR= 0.944, 95% CI 0.922-0.967, p<0.0001)

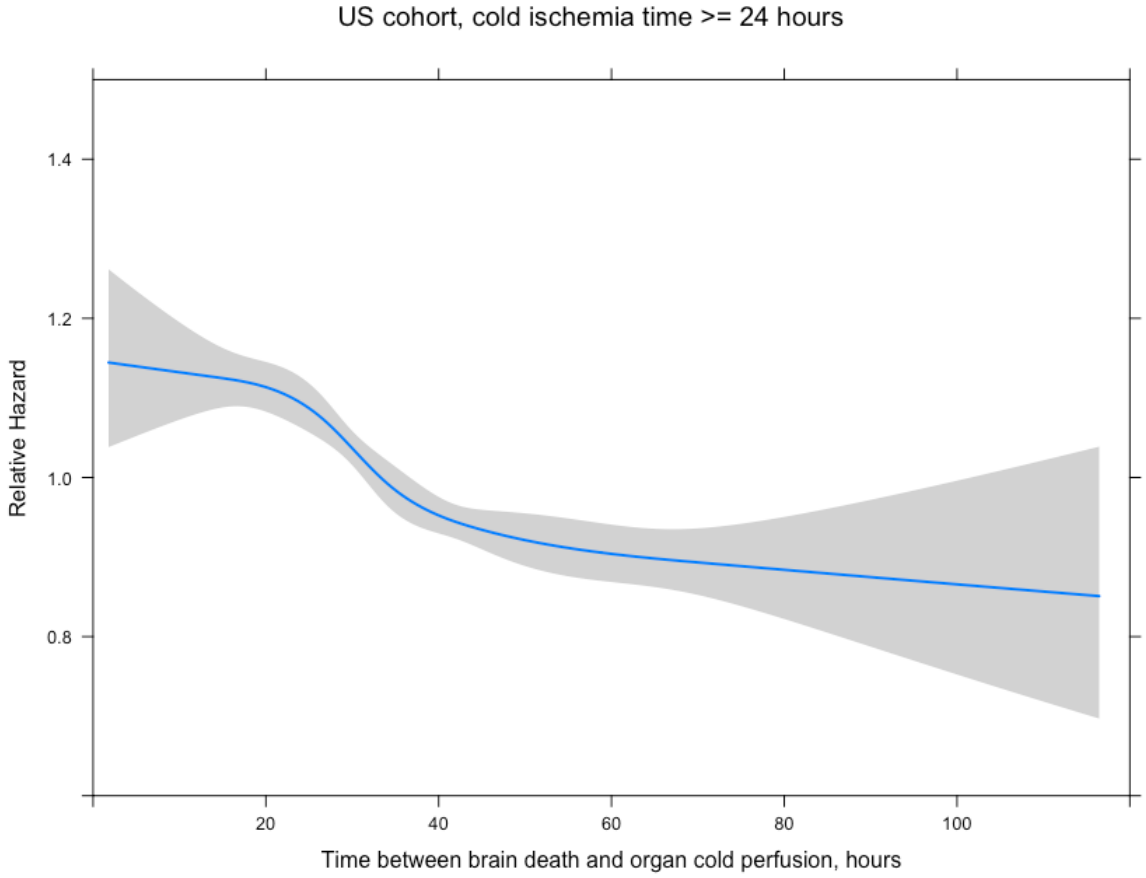


Figure 12. The relative hazard predicted from the univariate model with a restricted cubic spline. Sensitivity analysis of cold ischemia time >= 24 hours, US cohort.