

DR. KEROLLOS WANIS (Orcid ID : 0000-0003-1934-3380)

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Estimating the effect of increasing utilization of living donor liver transplantation using observational data

Kerollo N Nashat Wanis^{a,b,*}, Aaron Sarvet^a, Luis I. Ruffolo^c, Mark A Levstik^d, Koji Tomiyama^c, Bandar M Al-Judaibi^d, Mats J Stensrud^a, Roberto Hernandez-Alejandro^c

^a*Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA,
USA*

^b*Department of Surgery, Western University, Ontario, Canada*

^c*Division of Transplantation/Hepatobiliary Surgery, Department of Surgery, University of Rochester, New York, USA*

^d*Division of Transplant Hepatology, University of Rochester, New York, USA*

*Contact information for corresponding author:

Kerollo N. Wanis, Department of Surgery, Western University. London Health Sciences Centre, Rm. C8-114, London, Ontario, Canada, N6A 5A5. knwanis@g.harvard.edu

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Abbreviations: LDLT, living donor liver transplantation; SRTR, Scientific Registry of Transplant Recipients; OPTN, Organ Procurement and Transplantation Network; MELD, model for end-stage liver disease

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Authorship

KNW, AS, MJS, and RHA participated in research design. All authors participated in writing and revising the final manuscript. KNW performed the data analysis. KNW, AS, and MJS contributed to the development of the methodological tools utilized.

Key words: transplantation; organ utilization; causal inference; health policy; epidemiology

Abstract

Background: There has been a recent increase in enthusiasm for expansion of living donor liver transplantation (LDLT) programs.

Methods: Using all adults initially placed on the waiting list in the US, we estimated the risk of overall mortality under national strategies which differed in their utilization of LDLT. We used a generalization of inverse probability weighting which can estimate the effect of interventions in the setting of finite resources.

Results: From 2005 to 2015, 93,812 eligible individuals were added to the waitlist – 51,322 received deceased donor grafts while 1,970 underwent LDLT. Individuals who underwent LDLT had more favourable prognostic factors, including lower mean MELD score at transplant (14.6 vs 20.5). The 1-year, 5-year, and 10-year cumulative incidence of death under the current level of LDLT utilization were 18.0% (95% CI: 17.8, 18.3%), 41.2% (95% CI: 40.8, 41.5%), and 57.4% (95% CI: 56.9, 57.9%) compared to 17.9% (95% CI: 17.7, 18.2%), 40.6% (95% CI: 40.2, 40.9%), and 56.4% (95% CI: 55.8, 56.9%) under a strategy which doubles LDLT utilization.

Conclusion: Expansion of LDLT utilization would have a measurable, modest effect on the risk of mortality for the entire cohort of individuals who begin on the transplant waiting list.

Introduction

In Western countries, liver donation from living donors has been used in settings where the number of deceased donors is inadequate to provide transplants for all eligible individuals on the waiting list. Surprisingly, even though death on the waiting list is common in the United States, living donor liver utilization has not grown considerably over the past decade [1].

The slow adoption of living donor liver transplantation (LDLT) in the United States is in part driven by concerns regarding donor morbidity [2, 3], donor mortality [4], the ethical concerns of harming one individual to benefit another [5, 6, 7], and the potential negative media attention following high-profile donor complications due to living donation. Recent evidence suggests that LDLT is a safe and effective alternative to deceased donor liver transplantation [8, 9, 10]. Further, donor morbidity, mortality and long-term quality of life have been shown to be acceptable when LDLT is performed in experienced centers [11-13]. Perhaps most importantly, wait-listed candidates evaluated for transplant with a living donor organ have reduced mortality if transplanted instead of continuing to wait on the waiting list [14]. Not surprisingly, there is renewed enthusiasm for expanding living donor liver transplantation in the United States where liver allograft shortages have created a significant unmet need.

Although it seems intuitive that expanding living donor transplantation will positively affect other wait-listed individuals through reduced wait-times, it is unclear to what extent overall mortality for individuals entering the waiting list would improve. Since living donor liver transplant is usually reserved for less critically ill patients on the waiting list, increasing utilization of living donor organs may not address the areas of greatest demand.

A recently introduced generalization of inverse probability weighting [15] can be used to estimate the effects of treatment strategies which vary in their utilization of limited resources. These methods account for the impact that one individual's treatment utilization has on the entire population of individuals under study. This is necessary since, in the setting of limited resources, the timing and type of treatment received by one individual may affect the timing and type of treatment received by all other individuals. Transplantation is an ideal example of such a setting.

In this paper we analyze national data from the United States in which we estimate the effect of increasing utilization of living donor liver transplantation on mortality for all individuals entering the waiting list (i.e. all potential recipients).

Methods

Data source

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The study was reviewed by the institutional review board of the Harvard T.H. Chan School of Public Health and was determined to be not human subjects research. The SRTR data system includes information on all donors, 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, U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. The SRTR collects data on waitlist candidate mortality directly from transplant centers and via linkage to the Social Security Death Master File [1].

Eligibility criteria

Our analysis included individuals aged 18 or older in the United States with complete baseline covariate information, and with no prior history of liver transplantation, who were eligible for liver transplantation and were added to the OPTN waiting list to receive a liver graft between 2005 to 2015.

Utilization strategies

We compared scenarios which varied in the utilization of living donor livers. Starting with the observed live donation rate over the study period ('the current strategy'), we estimated what would have happened over the same time period if there had been increased utilization of living donor organs in 10% increments, up to a 150% increase, without changing deceased donor donation patterns. For example, if 2,000 living donor livers and 50,000 deceased donor livers were used over the study period (i.e. under the current strategy), a strategy in which utilization of liver donor livers is

increased by 110% would result in 4,200 living donor livers and 50,000 deceased donor livers being used.

Outcomes

We computed cumulative incidence curves for all-cause mortality under each strategy, and the difference in cumulative incidence at 10-years comparing each strategy in which living donor organ utilization is increased to the current strategy.

Follow-up

For each eligible individual, follow-up started when they were first added to the transplant waiting list and ended at the time of death, loss to follow-up as reported by individual transplant programs, or May 31st, 2016, whichever came first. Note that individuals continue to be followed regardless of whether they receive a transplant or not. As such, mortality is estimated for the entire cohort of individuals who *began* on the waiting list. This is necessary in order to capture the overall effect of increasing living donor liver utilization: by affecting those on the waiting list, and by affecting those who receive an organ (by potentially changing the type of organ they receive or the time at which they receive it).

Statistical analysis

Estimating the survival under utilization strategies like those described above poses challenges. Specifically, since individuals in the real world are only exposed to a single living donor utilization strategy (the current one), estimating the potential outcomes of other strategies requires us to specify how the hypothetical strategies would impact the distribution of transplantation (i.e. the timing of transplant and type of graft received), if one is received at all, after being placed on the waiting list. Further, any analysis must account for the effect that each person's treatment will have on the timing and type of transplant received by all other individuals on the waiting list.

In this analysis, we use an approach to estimating potential outcomes under treatment utilization strategies which explicitly accounts for the previously mentioned factors [15]. The approach is a

generalization of inverse probability of treatment weighting [16, 17] to settings in which treatment resources are limited. We provide a technical summary and the exact form of the weights in the supplementary materials.

Intuitively, the utilization of living and deceased donor livers in the weighted population constructed using these IP weights is equal to the utilization that would have been observed in the study cohort had the same number of deceased donor organs been used over the study period while the number of living donor organs used was increased by a multiplicative factor [15]. Because, in the real-world, the type of graft that an individual receives, and the time that they receive it, might depend on their prognostic factors (e.g. their MELD score), to validly estimate the effect of policies which change the timing of transplantation and type of graft received, the weights must adjust for differences in patient characteristics [18, 19, 20].

The components of the weights were computed using pooled (over time) logistic models which adjust for the following baseline patient characteristics: year of listing to the waiting list, waiting list priority (i.e. model for end-stage liver disease [MELD] score, MELD score exception, urgent-need status), gender, race, age, height, weight, willingness to accept a less optimal organ (i.e. a liver segment, a organ from an incompatible blood type donor, or a donor with hepatitis B or C), need for life support, functional status, primary diagnosis leading to liver failure, history of complications or procedures related to liver failure (i.e. spontaneous bacterial peritonitis, portal vein thrombosis, transjugular intrahepatic portosystemic shunt); and time-varying characteristics: most recent MELD score and MELD exception. All continuous variables were modelled flexibly using restricted cubic splines with four knots (at the 5th, 35th, 65th, and 95th percentiles), and interactions with time (in 30-day intervals) since baseline were added for time-varying characteristics.

For an illustration, see Figure 1 in which the number of living donor grafts received under the current observed living donor utilization strategy is compared to the number of living donor grafts received in the weighted population (with weights described above) used to estimate the effect of a strategy which increases living donor liver utilization by 50%.

We then use the weighted dataset to compute the patient survival under the assigned living donor liver utilization strategy by estimating the (discrete-time) hazard of death using a weighted pooled logistic model [21]. Confidence intervals were obtained using a percentile bootstrap. All analyses were performed using R version 3.5.2 and code is available to reproduce the results and to estimate survival under other user-specified levels of living donor graft utilization.

Results

From 2005 to 2015, 93,812 eligible individuals were added to the liver transplantation waiting list. Over the 11-year study period, 51,322 of these individuals received deceased donor organs while 1,970 received living donor organs. The proportion of LDLT performed in the US increased from 3.9% in 2005 to 4.4% in 2015. The baseline characteristics for individuals who received a transplant over the study period is displayed in Table 1. In general, individuals who received living donor grafts had more favourable prognostic factors, including lower mean MELD score at transplant (14.6 vs 20.5). The proportion of living donor transplants performed per year for the cohort is displayed in Figure 2. Over the study period, 0.15% (95% CI: 0.00, 0.36%) of living donors died within 6 months of the donor surgery. Since the 1,970 LDLT were performed over the study period, a strategy which doubles LDLT utilization would have result in an estimated 3 (95% CI: 0, 7) additional donor deaths.

The 1-year, 3-year, and 5-year cumulative incidence of death under the current level of living donor liver utilization were 18.0% (95% CI: 17.8, 18.3%), 31.8% (95% CI: 31.5, 32.0%), and 41.2% (95% CI: 40.8, 41.5%), respectively. The estimated 1-year, 3-year, and 5-year cumulative incidence of death under a strategy which doubles living donor liver utilization was 17.9% (95% CI: 17.7, 18.2%), 31.4% (95% CI: 31.1, 31.7%), and 40.6% (95% CI: 40.2, 40.9%), respectively. Such a doubling of LDLT utilization would mean that the proportion of LDLT, out of all liver transplants, in the US would be 7.2%. 5-year cumulative incidence of death estimates for each 30% increase in living donor liver utilization are displayed in Table 2.

As shown in Table 2, the estimated 10-year cumulative incidence of death under the current level of living donor liver utilization was 57.4% (95% CI: 56.9, 57.9%). The estimated 10-year cumulative incidence of death under a strategy which increases living donor liver utilization by 10% was 57.3%

(95% CI: 56.7, 57.8%). The estimates for each 30% increase in living donor liver utilization are displayed in Table 2. Estimated 10-year cumulative incidence of death was further reduced by approximately 0.1% for each 10% increase in living donor liver utilization. This trend continued at more extreme values of utilization increase with estimated 10-year cumulative incidence of death being 53.3% under a strategy which increases utilization to 5 times the current utilization and 48.7% under a strategy which increases utilization to 10 times current utilization. Utilization would need to be increased to 6 times current utilization to reduce estimated 10-year mortality by 5%. The estimated cumulative incidence of death curves under the current strategy and strategies which increase utilization by 50%, 100%, and 150% are displayed in Figure 3.

Discussion

For individuals initially placed on the liver transplant waiting list in the United States, we estimated that increasing utilization of living donor livers would have an overall impact on the 10-year cumulative incidence of death. For example, a doubling of LDLT would result in 1% improvement in 10-year survival for the average patient on the waitlist. Although this may be less dramatic than predicted prior to conducting this study, such an improvement would represent a significant number of mortalities avoided when applied to an entire population of transplant candidates.

There has been a recent increase in enthusiasm for expanding living donor liver transplantation to address the persistently high waiting list demand, and waiting list mortality, in the United States [19, 20]. This enthusiasm may stem from recent studies which found that individuals who received living donor livers had better survival than those who received deceased donor livers [10, 24, 25]. But individuals who received living donor livers differed from those who received deceased donor livers across several prognostic factors, so the previous finding is biased for the effect of the treatments ‘receive a living donor liver’ versus ‘receive a deceased donor liver’ (assuming both are simultaneously available). In studies where prognostic factors have been adjusted for to reduce this bias, receiving a living donor liver has been found to be comparable to receiving a deceased donor liver, among those who receive a transplant [25, 24, 23, 8, 9].

However, since a living donor and deceased donor organ are unlikely to be simultaneously available for a waiting list candidate, the comparison of the strategies ‘receive a living donor liver’ versus ‘receive a deceased donor liver’ may not be clinically relevant. Rather, a more relevant comparison is ‘receive a living donor liver’ versus ‘do not receive a living donor liver (and continue waiting on the waitlist for a deceased donor organ)’ among individuals who are assessed for living donor transplant. The difference in the effectiveness of these strategies incorporates the possible biological differences between the two types of organs as well as the prolonged time on the waiting list due to not receiving the living donor organ. A study comparing these strategies found that receipt of a living donor graft results in lower mortality, likely due to reduction in time spent on the waiting list [14].

While relevant to individuals who are assessed for transplantation with a living donor organ, the previous result does not help policy makers decide whether to expand living donor organ utilization on a system-wide scale. Rather, policy makers would be interested in learning the effects of strategies such as ‘increase utilization of living donor organs by 50%’ versus ‘maintain current utilization of living donor organs’. This effect further incorporates the consequences of an individual accepting a living donor organ on the experience of other individuals on the waiting list; in particular, when more living donor organs are available, the average waiting time to receive a transplant will be reduced for a given patient, which may contribute to a reduction in mortality. Recent literature has emphasized the importance of estimating such population intervention effects as they are felt to be more relevant for public health policy [27, 28].

Until recently, methodology to tractably estimate the effects of system-wide policy strategies when treatment resources are finite, like the ones mentioned previously, was not available and the potential benefits of expanding living donor organ utilization could not be quantified [15]. While it had been hypothesized that expanding living donor transplantation would have a sizeable impact on mortality [22], the extent of improved survival had not been known. Of course, expanding living donor transplant programs should be weighed against the risks incurred by living donors [29, 30, 31]. As such, any significant increase in living donor liver transplantation should be taken with caution, expecting that transplant programs have regulations in place to protect living donors. In this study,

donor mortality was 0.15% and unless donor mortality improves as LDLT is expanded, one would expect that this rate of mortality would extend to the settings in which LDLT utilization has increased.

In this study we remained agnostic about which specific policies decision-makers could implement to increase live donation. The strategies considered in our study could be achieved by a number of hypothetical policies including ones that increase funding and support for existing living donor programs, establish new living donor transplantation programs, provide financial and social support to donors, and increase recipient and potential donor awareness of living donation as an alternative to deceased donation.

Our study has several limitations. As with all observational studies, the validity of our estimates relies on adequate adjustment for all confounders but utilization of registry data limits the number of variables available for confounding adjustment, particularly time-varying variables. Further, other assumptions required for our estimates to have a causal interpretation may be incorrect. Specifically, expansion of living donor transplantation might lead to different results than we estimated if the outcomes of those who receive living donor grafts are different after expansion compared to the current utilization strategy. For example, this might be the case if most of the expansion occurs at low-volume programs which might lead to worse outcomes as those programs acquire experience. The utilization scenarios considered in this study may not reflect realistic utilization policies since utilization of deceased donor livers may increase or decrease alongside increased LDLT utilization. Methods used in this study can readily be applied to estimate the effects of utilization strategies which increase the use of deceased donor organs (e.g. extended criteria organs). Lastly, as discussed in more detail elsewhere [15], we have considered settings in which a change in the utilization of a treatment resource will result in the same multiplicative change in the probability of receiving the treatment for each individual. If this assumption is not approximately correct (e.g. if expansion of living donor organ programs in the real world would substantially change which *types* of patients are more likely to receive living donor livers) then our estimates may not accurately predict the outcomes under real world living donor utilization strategies. Currently, work is underway to extend methods used in this paper to settings in which treatment utilization strategies impact which *types* of patients

receive resources. This would allow investigators to estimate effects of living donor liver utilization strategies which focus on specific higher or lower risk recipient categories.

Ultimately, the utilization of living donor livers is not a simple policy issue. The choice to undergo LDLT depends on the patient and the potential donor, with many complex social and ethical issues at play. Policy makers contemplating whether strategies to expand utilization of living donor livers are justified must consider the effect on mortality for transplant-eligible patients as well as the impact on donor risk, among other factors. Our study provides evidence for the former, while other work [11-13] has suggested that living donation has little impact on donor quality of life.

In summary, we estimated the effect of living donor liver utilization strategies which vary the utilization of living donor organs. Besides the expected result that LDLT benefits those particular recipients who receive living donor grafts by shortening their waiting time, we quantified the extent to which expansion of LDLT benefits all individuals on the waiting list – even those *not recipient* of the living donor liver. Expansion of living donor liver transplantation in the US, though typically targeted to lower risk patients, would have a measurable, modest effect on 10-year survival for the population of individuals who begin on the transplant waiting list.

Figure legends

Figure 1: Living donor transplants under the current strategy and under a strategy which increases living donor liver utilization

by 50%

Figure 2: Living donor transplants, as a proportion of total liver transplants, performed per year

Figure 3: Cumulative incidence of death curves comparing living donor organ utilization strategies

SRTR disclaimer

The data reported here have been supplied by the Hennepin Healthcare Research Institute (HHRI) as the contractor for the Scientific Registry of Transplant Recipients (SRTR). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the SRTR or the U.S. Government.

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Table 1: Baseline characteristics for 53,292 individuals who received a transplant over the study period, stratified by type of liver received

	Received deceased donor graft N=51322	Received living donor graft N=1970
Year of listing		
2005	4181 (8.1)	198 (10.1)
2006	4693 (9.1)	187 (9.5)
2007	4685 (9.1)	174 (8.8)
2008	4632 (9.0)	163 (8.3)
2009	4758 (9.3)	159 (8.1)
2010	4977 (9.7)	189 (9.6)
2011	4927 (9.6)	169 (8.6)
2012	4788 (9.3)	181 (9.2)
2013	4943 (9.6)	171 (8.7)
2014	4772 (9.3)	207 (10.5)
2015	3966 (7.7)	172 (8.7)
Race		
Asian	2333 (4.5)	59 (3.0)
Black	5142 (10.0)	67 (3.4)
Hispanic	7020 (13.7)	185 (9.4)
Multi-Racial	236 (0.5)	6 (0.3)
Native American	310 (0.6)	9 (0.5)
Pacific Islander	83 (0.2)	5 (0.3)
White	36198 (70.5)	1639 (83.2)
Functional Status		
Requires no assistance	29963 (58.4)	1439 (73.0)
Requires some assistance	15575 (30.3)	491 (24.9)
Requires total assistance	5784 (11.3)	40 (2.0)
Primary diagnosis		
Cholestatic	3564 (6.9)	486 (24.7)
Fulminant hepatic failure	2217 (4.3)	44 (2.2)

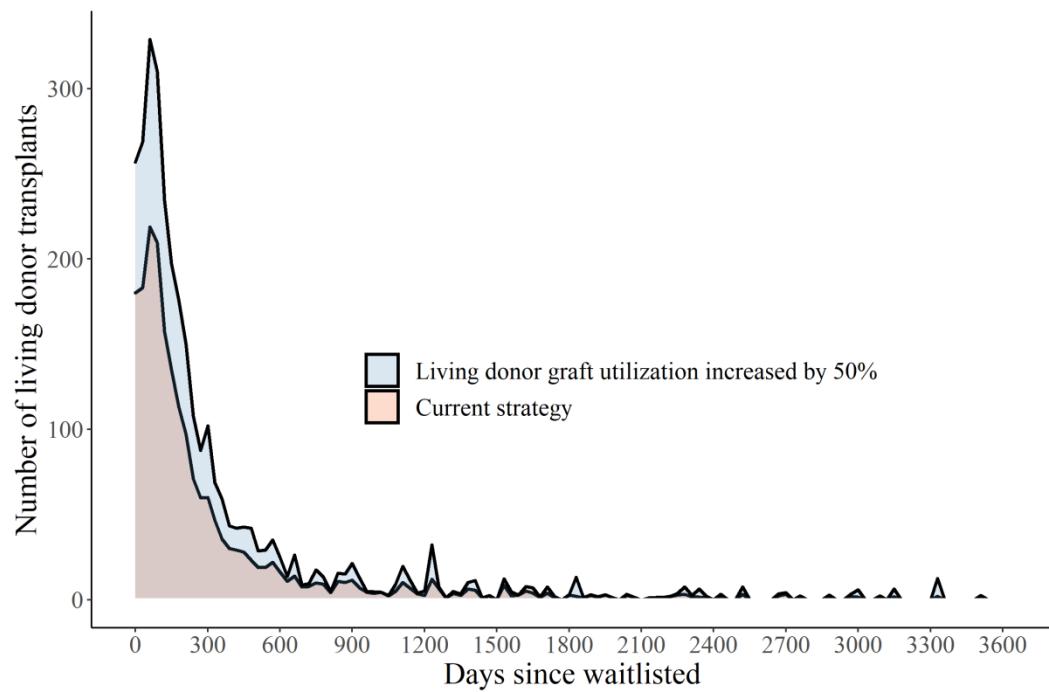
Malignant neoplasm	6211 (12.1)	197 (10.0)
Metabolic	1103 (2.1)	46 (2.3)
Non-cholestatic	35969 (70.1)	1100 (55.8)
Other	2258 (4.4)	97 (4.9)
MELD exception	6683 (13.0)	97 (4.9)
Status 1	1623 (3.2)	10 (0.5)
Male gender	34681 (67.6)	1125 (57.1)
Willing to accept incompatible blood type donor	553 (1.1)	2 (0.1)
Willing to accept extra corporeal liver support	1025 (2.0)	43 (2.2)
Willing to accept liver segment	43844 (85.4)	1895 (96.2)
Willing to accept HBV positive donor	32905 (64.1)	1449 (73.6)
Willing to accept HCV positive donor	20010 (39.0)	702 (35.6)
On life support	1741 (3.4)	8 (0.4)
History of spontaneous bacterial peritonitis	3381 (6.6)	106 (5.4)
History of portal vein thrombosis	2138 (4.2)	69 (3.5)
History of TIPSS	3218 (6.3)	116 (5.9)
MELD at listing	16.0 [12.0, 24.0]	13.0 [10.0, 17.0]
Age (years)	56.0 [49.8, 61.4]	54.8 [46.2, 60.8]
Height (cm)	172.7 [165.1, 180.3]	170.2 [162.6, 177.8]
Weight (kg)	83.9 [72.1, 98.0]	77.1 [66.2, 88.9]

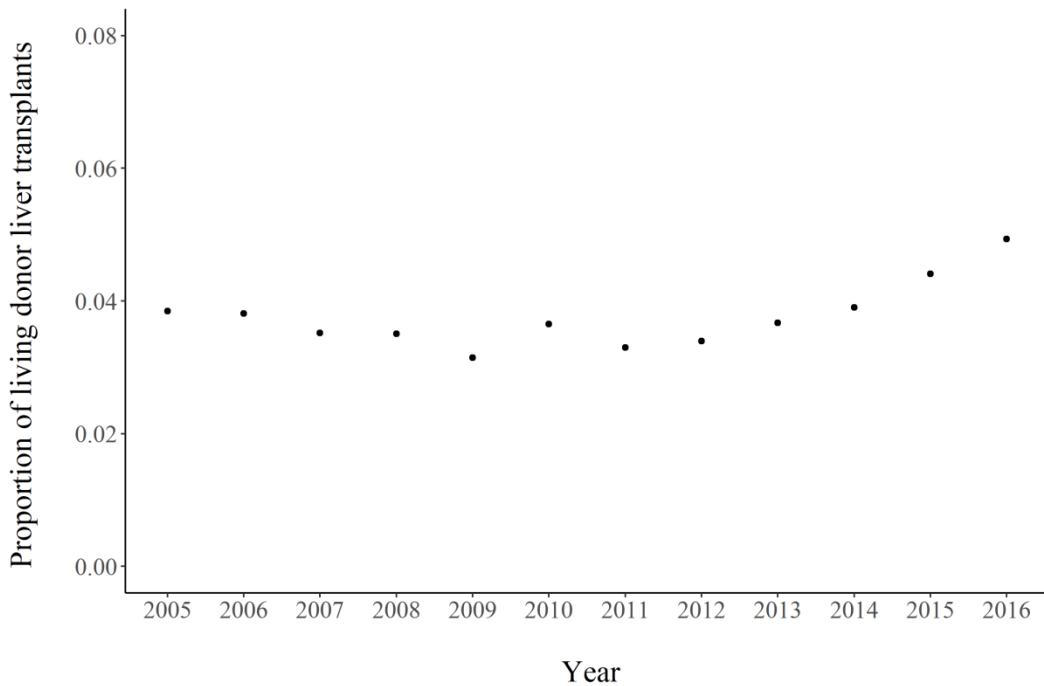
Categorical variables presented as number (%) and continuous variables presented as median [interquartile range]

Table 2: Cumulative incidence of death under strategies which vary utilization of living donor livers

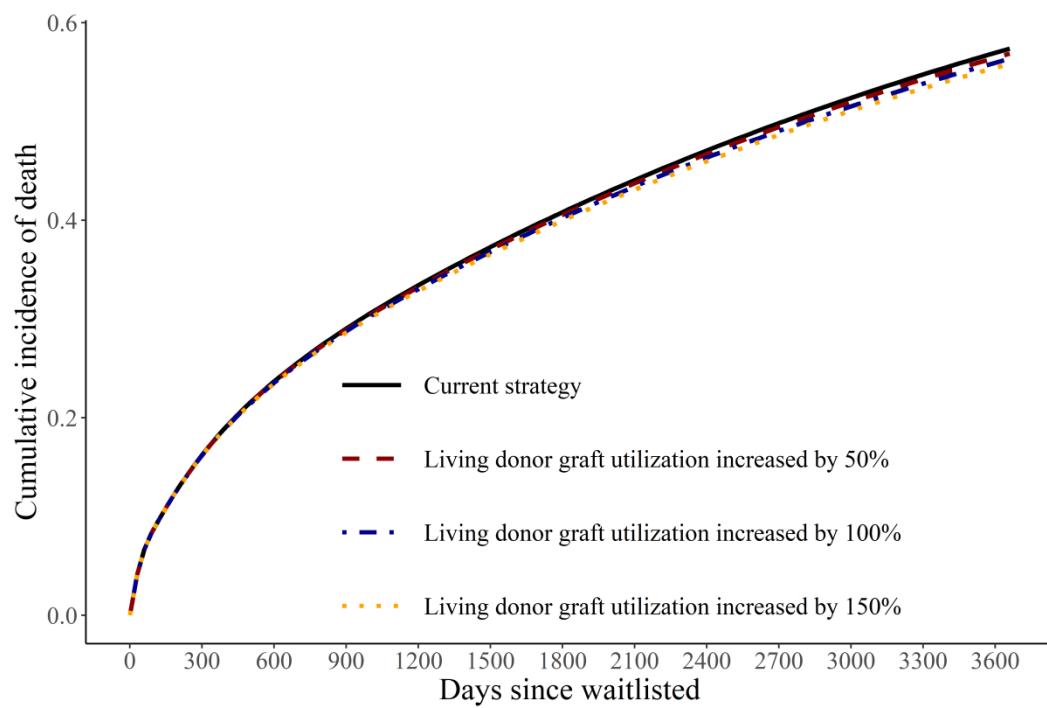
Strategy	5-year risk of death	5-year Risk difference compared to current utilization	10-year risk of death	10-year Risk
				difference compared to current utilization
Current utilization	41.2 (40.8, 41.5)	NA	57.4 (56.9, 57.9)	NA
Utilization increased by 30%	41.0 (40.6, 41.3)	-0.2 (-0.2, -0.1)	57.1 (56.5, 57.6)	-0.3 (-0.4, -0.2)
Utilization increased by 60%	40.8 (40.4, 41.2)	-0.4 (-0.4, -0.3)	56.8 (56.2, 57.3)	-0.6 (-0.7, -0.5)
Utilization increased by 90%	40.6 (40.3, 41.0)	-0.6 (-0.6, -0.4)	56.5 (55.9, 57.0)	-0.9 (-1.1, -0.7)
Utilization increased by 120%	40.5 (40.1, 40.8)	-0.7 (-0.8, -0.6)	56.1 (55.5, 56.7)	-1.2 (-1.5, -0.9)
Utilization increased by 150%	40.3 (39.9, 40.7)	-0.9 (-1.0, -0.7)	55.8 (55.2, 56.4)	-1.5 (-1.8, -1.1)

Risk (i.e. cumulative incidence) estimates are given as percentages (95% confidence interval), and risk differences are given as absolute percentage point differences (95% confidence interval)





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