Scholars Journal of Physics, Mathematics and Statistics

OPEN ACCESS

Abbreviated Key Title: Sch J Phys Math Stat
ISSN 2393-8056 (Print) | ISSN 2393-8064 (Online)
Journal homepage: https://saspublishers.com

Viability of Transplanted Organs Based on Donor's Age

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DOI: 10.36347/sjpms.2023.v10i04.001 | **Received:** 15.04.2023 | **Accepted:** 22.05.2023 | **Published:** 26.05.2023

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Abstract | **Original Research Article**

Organ transplantation is becoming a major public health issue in many countries due to its attributable death rate and the excessive cost. There is a growing gap between organ supply and demand for organ transplantation in the US, which is causing major public health crisis. Twenty people on average die each day while waiting for a transplant because the supply of available organs from deceased donors does not meet the demand. National organ donation has increased in the past two decades; however, the number of individuals who need transplants has risen much faster as new patient is added to the national transplant waiting list every ten minutes. To address this disparity, not only the number of donors must be increased, but also the discard rate of available organs must be reduced. The kidney discard rate has increased by almost four times from the late 1980s to 2009, from approximately five percent to nearly 20 percent. So, it is important to investigate factors that may decrease the chance of an organ to be discarded as well as increase the survival time of transplanted organs. In this paper, we perform statistical survival analysis to study the impact of donor's age on organ survival. Transplanted kidneys, livers, and intestines between 1987 and 2010 are investigated in this study. The results show that donor's age is an important factor for transplanted kidneys and livers donated by younger donors and survive for longer times while donor's age does not seem to be correlated with the survival time of transplanted intestines.

Keywords: Survival time, Parametric and Non-parametric models, Risk ration, Organ transplanted.

INTRODUCTION

Often, the preferred treatment for chronic organ failure is organ transplantation. Organ transplantation involves replacing the organs that have failed their functions. The lives of many patients have been prolonged by successful organ transplantation. Organ transplantation has become a major public health issue in the United States due to growing disparity between organ supply and the transplantation demand. The number of organs which are offered for transplantation is limited. Hence, there is a waiting list for receiving the donated organs. For example, during the last decade in the United States, the available kidneys for transplantation were 11,000 per year while the waiting list for kidney transplantation has exceeded 100,000 candidates [1]. The increasing gap is associated with increasing death rate of people who are waiting for organ transplantation. On average 140 patients die each week while waiting for a transplant because the supply of available organs from deceased donors does not meet the demand [2]. The number of individuals who need transplants is rising much faster than national organ donation as six new patients are added to the national transplant waiting list every hour [2].

In spite of the improvement in organ procurement, the number of available organ transplants continues to lag far behind the need, and waiting lists are still growing. As a result of this waiting period, many patients may wait more than 5 years for an organ and many never receive the transplant that they need [3]. Moreover, when an organ becomes available, there may be several choices to be made regarding the acceptance of the transplant or a continuation of waiting for the next available organ [4]. Three factors that might be addressed to reduce the waiting list. First, increasing the number of donors by encouraging people to be become a registered donor. Second, reducing the organ discard rate of available organs. For example, the kidney discard rate has increased by almost four times from the late 1980s to 2009, from approximately five percent to nearly 20 percent [5]. Third, improving the survival time of transplanted organs to reduce the

chance of transplanted organ failure and so reduce the demand for repeated transplantation for the same patients.

We have addressed the second factor in our previous work [6-8]. In this paper, we address the third factor by investigating factors that may increase the survival time of transplanted organs. There are several factors that have an effect on survival of a transplanted organ and the graft failure time (GFT) such as donor's age, location, gender, cause of death, history of cancer, history of smoking, and ethnicity [1, 3]. Multiple studies have determined that the donor's age is a major reason for organ discard [3, 9]. Other studies have connected the donor's gender with the risk factor of death and rejection \cite{ [10], while donor's race has been determined by some clinical studies to be one of the factors that have corresponded with graft survival time for transplanted organs [9]. One of the major factors that may have a significant impact on prolonging the transplanted organ survival is the donor's age and have been used to analyze its impact on graft failure time [3, 9]. To study this factor, we have applied statistical survival analysis on 128,992 kidney transplants, 72,794 liver transplants, and 1,588 intestines. To analyze the influence of donor's age on graft failure time, we designed a nonparametric method (Kaplan-Meier) and a parametric method (Cox proportional hazard model) where the donor's age is considered as an independent factor. The relative risk RR was used to demonstrate the impact of the donor's age on graft survival time.

METHODOLOGY

Survival data is regularly analyzed in terms of time to an event or time to death. Survival Analysis Models (SAM) are the underlying distribution of the event time variable t [11]. The distribution of nonnegative time t which refers to survival time can be specified in different ways [12]. For the survival applications, the three important distributions are the survival function of t, the probability density function of t, and the hazard function of t [13]. Different methods have been developed to deal with survival data such as Kaplan Meir and Cox proportional hazard model. Statistical analysis methods including Kaplan Meir and Cox proportional hazard as well as ANOVA, pairwise t-test, and Tukey are applied to study the effect of donor's age on graft survival time.

Non-parametric Method

The Kaplan Meier (KM) is a popular non-parametric survival analysis method that estimates the probability of survival to a given time. The Kaplan Meier estimate is also known as *product limit formula*. To determine the Kaplan Meier, estimate of the survivor function $\lambda(t)$ from a sample of censored survival data, we used

$$\hat{\lambda}(t) = \prod_{i=1}^{k} \frac{n_i - d_i}{n_i} = \prod_{i=1}^{k} 1 - \frac{n_i}{d_i} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots (1)$$

For $t_k < t < t_{k+1}, k = 1,2,..,\lambda(t) = 1$ when $t < t_1$, and n_i denoted to the number of individual organs at risk at time $t_{(i)}, d_i$ is the number of failure organs at time $t_{(i)}$[14]

Semi-parametric Method

The Cox proportional hazard model (PH) is the most common technique that is used to model and analyze the survival data. The Cox regression model differs significantly from other models because it is built on the proportional hazards assumption and uses partial likelihood for parameter estimation [15]. Even though the Cox model includes parameters, the model is described as a semi-parametric model because the distribution of residuals outcome is unknown [12, 14]

$$\Lambda(t/x) = \lambda_0(t) e^{\beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_k x_k} \quad \ldots\ldots\ldots\ldots\ldots (2)$$

Where $\lambda_0(t)$ is called the baseline hazard function; this is an arbitrary function of t, x is the explanatory variable [16]. The function $e^{\beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_k x_k}$ is called risk ratio or relative risk (RR) [12]. We use the RR for comparing between two independent covariates x_1 and x_2 on the survival time or to compare between two groups when the independent variable is dichotomous [17].

$$RR = \frac{\Lambda(t/x_1)}{\Lambda(t/x_2)} = \frac{\lambda_0(t) e^{\beta_1 x_1}}{\lambda_0(t) e^{\beta_2 x_2}} = e^{(\beta_1 x_1 - \beta_2 x_2)} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots (3)$$

In this work, we applied Cox proportional hazard model and Kaplan-Meier on survival data to demonstrate the effects of the donor's age on the organ survival time [18]. Using the Cox proportional hazard model, we try to evaluate whether the different donor's ages have significant effects on the graft survival time or whether the relative risk will increase or decrease when the donor old [19, 20].

Data Section

In spite of the increased number of transplants by 9.2% for the fourth consecutive years (2012 to 2016) [2], thousands of eligible recipients with end-organ failure are waiting for transplantation in the United States. Because there is organ supply is much lower than organ demand, many patients may not receive organ transplants in time [1, 21]. The U.S Congress passed the National Organ Transplant Act in 1985 The act set up the Organ Procurement and Transplantation Network (OPTN) to maintain a national registry for

organ coordination. By 1987, the Department of Health & Human Services (HHS) and OPTN set up a framework to collect, store, analyze, and publish data pertaining to the patient waiting list, organ matching, and transplants. Under the federal act, the UNOS turned into the principal non-profit association for gathering clinical information about organ donors, transplant candidates, and transplant recipients [6].

In this study, we use a dataset of 203,374 organs provided by United Network for Organ Sharing (UNOS). The dataset was collected from deceased donors from 1987 to 2010. The dataset provides the graft failure time and some other factors that are associated with donors of the three organs including kidney, liver, and intestine. To explore the donor age effect on graft survival time, we applied a non-parametric model (Kaplan-Meier) and a semi-parametric model (Cox proportional hazard) for exploring the effect.

RESULTS AND DISCUSSION

More than 203,374 transplanted organs in the data set including $n_1 = 128{,}992$ kidneys, $n_2 = 72{,}794$ livers, and $n_3 = 1{,}588$ intestines that were transplanted in the USA between 1987 and 2010. To study the impact of donor's age on the graft survival time, we classified the data based on age factor. We divided the data to five groups including below 20, 20 to 40, 40 to 60, 60 to 80, and over 80 years old. We analyzed the survival data for each individual organ separately. By evaluating the graft survival time using the Kaplan-Meier model, we noticed that there are salient differences between the Kaplan-Meier curves for different donor age groups. Graft survival time for different organs is depicted in following figures, we will discuss it later in each section.

Pairwise t-test shows a significant difference between the kidneys mean survival times based on donor age. The kidney means survival times based on donor's age is 4.77, 4.32, 3.78, 3.25, and 2.36 years with the p-value $P < 0.0001$ where the average age of donors are 13.26, 28.83, 49.11, 64.73, and 81.88 years. We can say, with advancing donor's age the graft survival time will decrease or that longer graft survival time is always associated with younger donor's age. The change in mean graft survival time based on donor's age groups is summarized in

Table ***1***. We established a t-test to test whether the mean graft survival time of groups 20-40 years, 40-60 years, 60-80 years and > 80 years are significantly different from the mean graft survival time of the control group <20. As we can see in Tab.2, there is a significant difference between the kidneys mean survival time based on donor age groups comparing with the kidneys mean survival time of the reference group. According to the t-test outcome, we can say that the kidneys survival time for which the donor age is lower than 20 years is higher than the mean survival time of kidneys for which the donor age is greater than 20 years old.

The majority of kidney transplants (38.69%) came from donors with ages between 40-60 years with a mean survival time of 3.78 years. The mean survival time for this group is about one year behind the mean survival time of the control group. Furthermore, it was about four months shorter than the mean graft survival time regardless of the donor's age.

Table ***1*** shows Cox regression model estimates using the graft survival time for different organs assuming donor's age as an independent factor. The P-values showed that the donor's age factor was highly The significant. The estimated coefficients of the model show that $\hat{\beta}_1$'s are significantly different from zero (P-values; 0.00, 0.00, and 0.028) which means the donor's age has a significant impact on the organ survival time.

Table 1: Cox Regression Parameters Estimation

Organs	Variables	Parameters	z	P-value
Kidney	Age	0.0133	47.4	0.000
Liver		0.0110	32.2	0.000
Intestine		0.0062	2.20	0.028

The Cox proportional hazard model was established to explain how the risk function changes when the donor's age was changed. To evaluate the donor's age impact on kidney survival time using PH model, we computed the relative risk (RR) at each individual donor's age group comparing to the reference (<20) group. For kidney, RR for four different donor age groups were (1.03, 1.41, 2.06, and 3.75). The corresponding P-values of RR were (0.024,0.00, 0.00, and 0.00) respectively. As we can observe, RR for the transplanted kidneys doubled after the donor was older than 60yrs old.

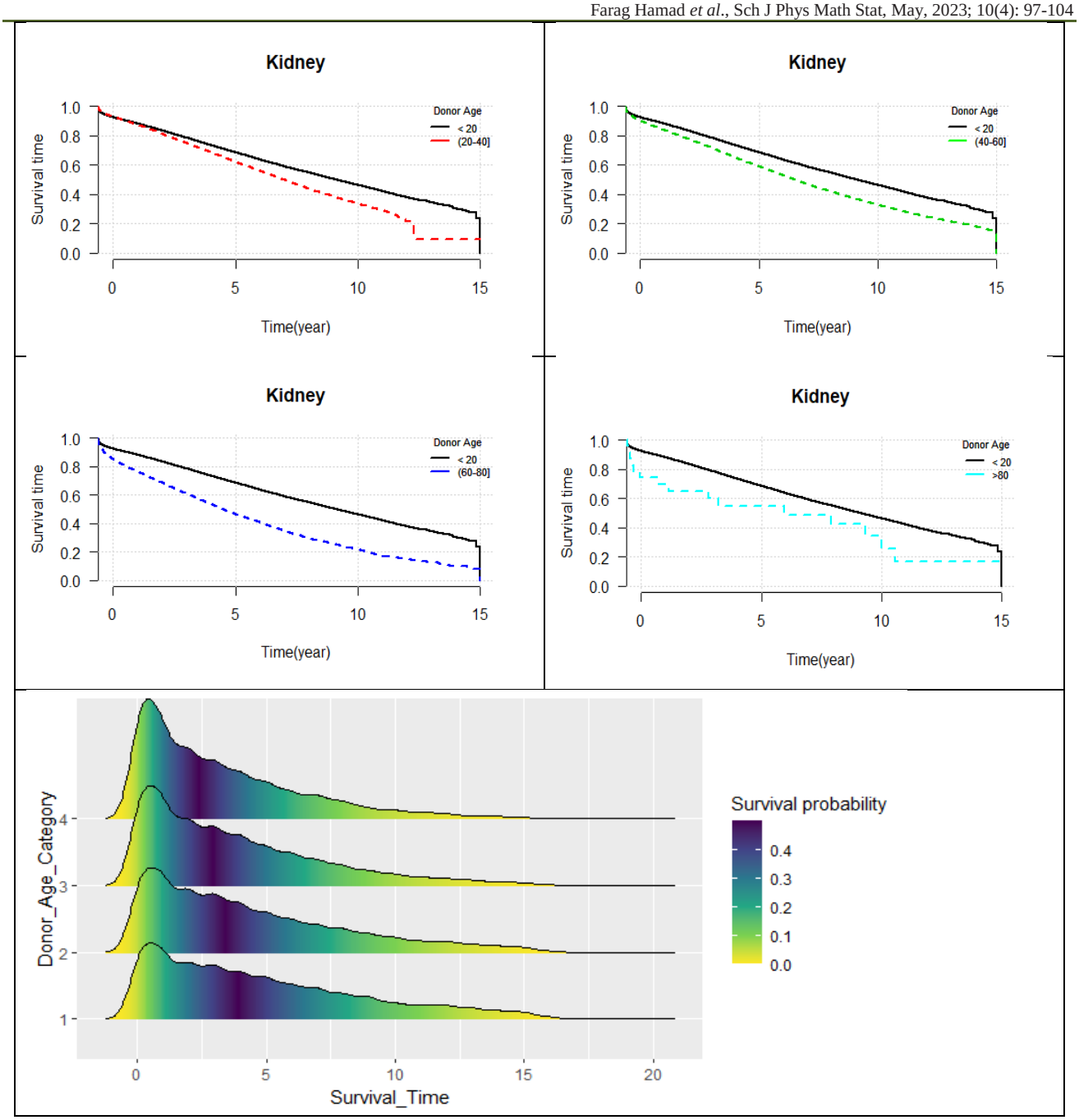


Figure 1: Survival probability for transplanted kidneys based in donor's age categories

Overall, the mean survival time for kidney transplants was 4.11 years. There is significant difference between the mean survival times based on donor's age groups (P <0.0001). The kidneys mean survival time began to decrease slightly after the second decade of the donor's age. However, the relative risk began to increase slightly after the second decade of the donor's age. As we can see in

Table 2, the mean kidney survival time decreased from 4.77 years to 4.32 years for the donor's age group 20-40 year that is about 9.5% decrease. Also, the donor's age RR for 20-40 years donor's age versus the base group is 1.03 with 95% corresponding confidence interval (1.00, 1.06) and the p-value of P=0.024. So, we can say with 95% confidence that RR is increased by 6% when the donor's age is in 20-40 years in comparison with the reference group < 20 years old. Figure 1 (Top right) shows Kaplan-Meier curves for 20-40 years in comparison with reference group. Most of the kidneys were donated by donors whose age are between 40-60 years old (39.78%). The kidneys mean survival time of this group was 3.78 years with 20.7% decrease compared to the kidneys mean survival time of the control group. In general, we can observe in Figure 2, there is slight difference between Kaplan-Meier survival time of this group in comparison with the reference group.

Table 2: Kidney transplantation outcomes performed

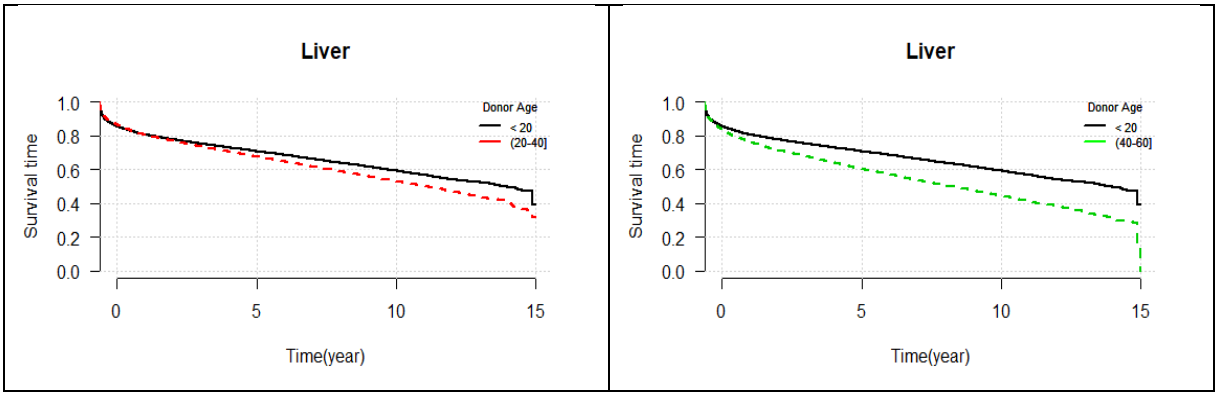
Organ	Age (Category)	n	%	Mean (Sd)	RR	95% CI	P-value
Kidney	< 20	26192	20.31%	4.77(3.75)	1.00	Ref	-
	[20-40)	41663	32.30%	4.32(3.73)	1.03	(1.00,1.06)	0.024
	[40-60)	49911	38.69%	3.78(3.42)	1.41	(1.38,1.45)	0.000
	[60-80)	11202	8.68%	3.25(3.13)	2.06	(1.99,2.13)	0.000
	> 80*	24	0.02%	2.36(2.33)	3.75	(2.26,6.23)	0.000
Liver	< 20	16061	22.06%	4.98(4.44)	1.00	Ref	-
	[20-40)	22746	31.25%	4.30(4.05)	1.14	(1.09,1.18)	0.000
	[40-60)	24575	33.76%	3.76(3.72)	1.43	(1.39,1.49)	0.000
	[60-80)	9073	12.46%	3.28(3.40)	1.80	(1.73,1.88)	0.000
	> 80*	339	0.47%	2.59(2.55)	2.18	(1.86,2.56)	0.000
Intestine	< 20	1232	77.58%	2.78(3.06)	1.00	Ref	-
	[20-40)	279	17.57%	2.73(2.88)	1.01	(0.83,1.22)	0.923
	> 40*	77	4.85%	2.09(2.58)	1.61	(1.19,2.16)	0.002

Likewise, we studied the donor's age impact for transplanted kidneys donated by donors who are between 60-80 years and transplanted kidneys donated by donors who are over 80 years old. The kidneys mean survival time are 3.25 years and 2.36 years respectively with 31.86% & 50.50% decreases in comparison with the mean survival time of control group. As we observe in

Table 2, the RR associated with donors between 60-80 years comparing to the control group is increased by 2.06 with 95% CI (1.99, 2.13) and P<0.001. The Kaplan-Meir curve of kidneys survival time based on donor's age 60-80 years and >80 years are shown in Figure 1 (Middle left) and Figure 1 (Middle right) respectively. Moreover, the distribution of survival time of transplanted kidneys based on the donor's age groups are demonstrated in the Figure 1 (Bottom).

Table 2 shows the analysis of the liver mean survival time based on donor's age. For donor's age below 20 years old, the liver mean survival time is 4.98 years (reference group). When the donor's age is between 20-40 years, the liver mean survival time is 4.30 years with 13.6% decreases comparing to the reference group. At the same time the RR associated with the same donor's age group increased to 1.14 (95% CI; 1.09,1.18; P< 0.001).

Regarding liver transplants for patients, the mean survival time of liver is 4.13 years regardless of the donor's age factor. By ANOVA test P<0.0001, we can say, that there are significant differences between the mean survival time of liver considering donor's age factor.



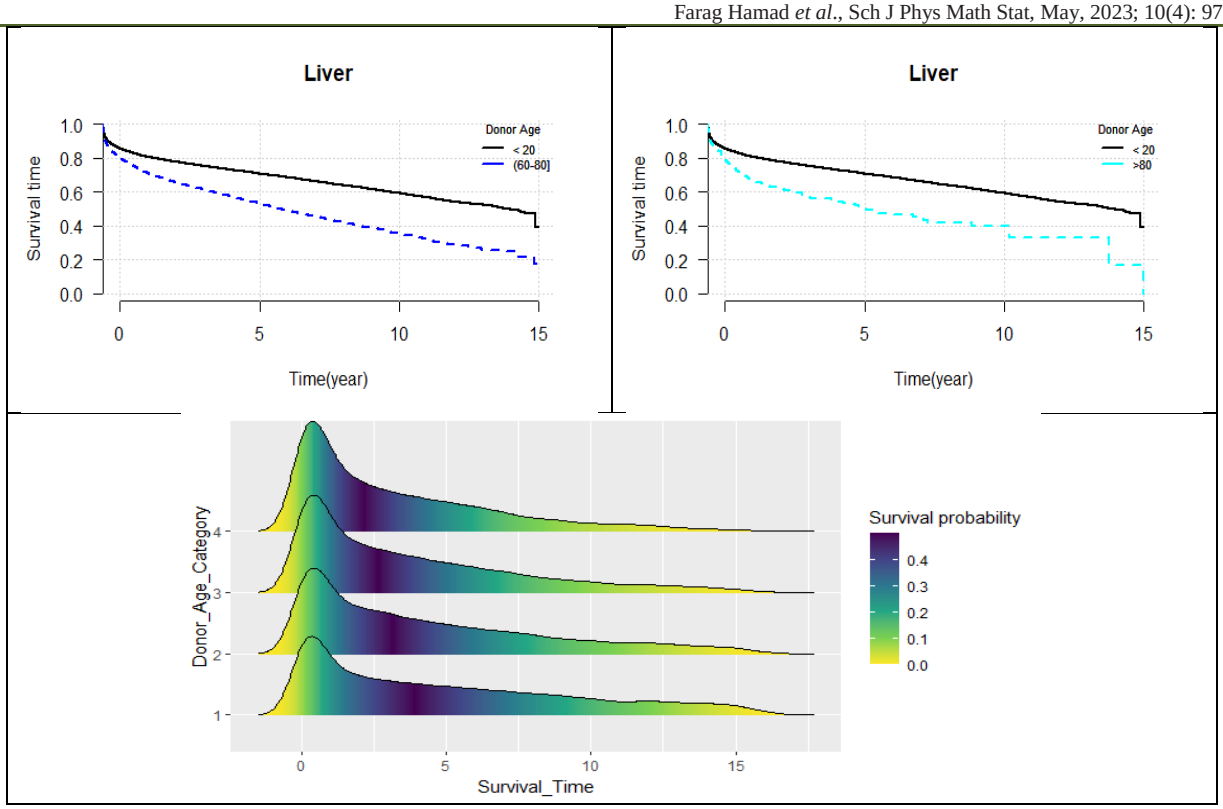


Figure 2: Survival probability for transplanted livers based in donor's age categories

Kaplan-Meir curve depicted in Figure 2 (Top left) shows the liver survival time for the donor's age 20-40 yeas in comparison with reference group. Similar to kidney, the most livers were donated with donors age between 40-60 years old (33.76%). The mean liver

Table 2, the RR associated with this group is 1.43 with 95% confidence interval of 1.39 and 1.49

Table 2, 3.28 years and 2.59 years are mean liver survival time for donor's age 60-80 years and over 80 years old respectively. As we can observe, the mean survival time is decreased by about 34% and 50% comparing to the mean survival time of the reference group. The pairwise t-test and ANOVA showed significant difference between those groups means and the reference group mean. Also, the associated relative risk RR with these groups are 1.80 (95% CI; 1.73, 1.88; survival time for this group is 3.76 years which is decreased by 24.5% comparing to mean survival time of the reference group. The test of significant (t-test) shows that there is significant difference between group means with P<0.000. As shown in
with P<0.000. Kaplan-Meier curves depicted in Figure 2 (Top right) shows liver survival time for donors age 40-60 years in comparison with the reference group. As shown in
P<0.000) and 2.18(95% CI; 1.86,2.56; P<0.000) respectively. Figure 2 (Middle left) and Figure 2 (Middle right) show the Kaplan-Meir survival time for donors age 60-80 yeas and over 80 years. Therefore, we can see a visible difference between the survival time of transplanted livers based on the donor's age groups in comparison with the reference group. Moreover, the distribution of survival time of transplanted livers based on the donor's age groups are demonstrated in the Figure 2 (Bottom).

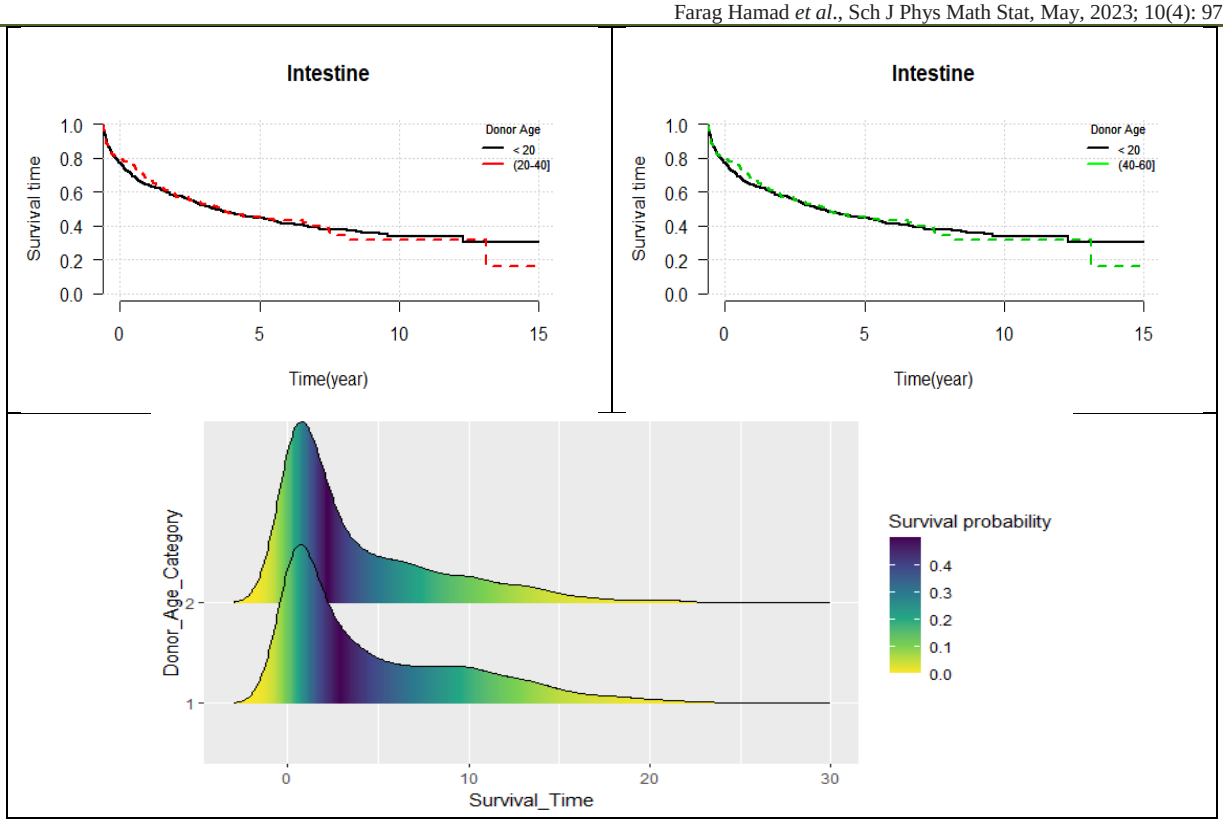


Figure 3: Survival probability for transplanted intestines based in donor's age categories

The majority of the intestines were donated by donors below 20 years old (77.58%). The mean survival time for the reference group is 2.78 years which is closed from the grand mean. Regardless of the donor's age, the mean intestine survival time is 2.73 years. By applying t-test, Tukey, and ANOVA (P=0.151) we did not observe significant difference between the intestine mean survival time based on donors age. The intestine mean survival time for donors age 20-40 is 2.73 years. Likewise, the corresponding RR is 1.01 with 95% CI of 0.83 and 1.22 with P=0.923. As shown in

Table 2 the intestine mean survival time for donors age over 40 years old is 2.09 years. The corresponding relative risk is 1.61 (95% CI; 1.19,2.16; P=0.002). We can see there is no considerable difference in Kaplan-Meir survival curves in Figure 3 (Top left) and Figure 3 (Top left) for 20-40 and over 40 years respectively. Moreover, the distribution of survival time of transplanted intestines based on the donor's age groups are demonstrated in the Figure 3 (Bottom).

CONCLUSION

There is a significant gap in the number of available organs and the number of patients in the waiting list for organ transplantation. We are facing a serious public health issue as this gap between the supply and demand is widening. This problem is three-fold, and in this study, we addressed the survival time of transplanted organs based on donor's factors. The main factor that was investigated here was donor's age. We observed that there is significant difference between graft time failures of transplanted organs for different donors' ages for Kidney and Liver. Donated organs received from deceased donors who are below 20 years old survive for longer times for Kidney and Liver. However, in our analysis, we did not observe association between the survival time of transplanted intestines and donor's age. In summary, the survival time began to decrease slightly after the second decade of the donor's age whereas; the relative risk began to increase slightly after the second decade of the donor's age. The increase in the donor's age is associated with shorter survival times for the transplanted Kidneys and Livers, but not for Intestines. In our future work, we would like to investigate the match and mismatch between the donor's age and recipient's age factors in order to collectively and identify the improvement of the survival time of the transplanted organs.

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