Cost-effectiveness Analysis of Renal Replacement Therapy with Living-donor Kidney Transplantation in Older Patients in Japan

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Abstract

Background: Older patients have less opportunity of receiving kidney transplantation although kidney transplantation improves patient mortality and quality of life more than dialysis regardless of age. One solution to the less opportunity is to consider living-donor kidney transplantation (LDKT). More evidence about LDKT in older patients is useful for determination of the direction of renal replacement therapy (RRT). The economic assessment of LDKT in older patients is still limited worldwide. ***Objective:*** In this study we evaluated the cost-effectiveness of RRT with the option of LDKT compared with RRT without this option in older patients in Japan. ***Method:*** We estimated the incremental cost-effectiveness ratio of the two clinical scenarios of RRT using the Markov model. We determined the variables used in the Markov model based on a review from the medical literature. ***Result:*** By adopting the option of LDKT, the total cost was reduced by 95,195 JPY, and the total quality-adjusted life year was increased by 0.0251 for 10 years on average per patient. RRT with the option of LDKT was dominant. One-way sensitivity analyses suggested the robustness of the better cost-effectiveness of RRT with the option of LDKT. ***Conclusion:*** The present study showed that RRT with the option of LDKT was more cost-effective than RRT without this option in older patients in Japan.

Keywords: Living-donor kidney transplantation, older population, Markov model, cost-effectiveness analysis

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Introduction

Patients with end-stage kidney disease (ESKD) eventually require renal replacement therapy (RRT). There are 3 types of RRT available worldwide, namely, hemodialysis (HD), peritoneal dialysis (PD), and kidney transplantation. Patients receive one of the 3 RRTs throughout their lives while switching between them when appropriate. Although patient mortality and quality of life (QoL) are improved in recipients of kidney transplantation in comparison with those staying on HD or PD (Cameron et al., 2000), patients need to wait for organ donation on a waiting list due to the huge disparity between organ demand and supply (Wu et al., 2017). In Japan, the number of deceased-donor kidney transplantation per year was around 200 at most and it has not increased over the past 10 years. More than 12,000 ESKD patients are listed on the waiting list for kidney donation as of 2020 and the average waiting time has reached 14 to 15 years (Japan Organ Transplant Network).

Another aspect of RRT is the high number of older people who require RRT in association with the increased life expectancy. In Japan, the incidence of ESKD patients requiring RRT is approximately 40,000 patients per year and the proportion of patients aged 60 years or older is almost 80% (Nitta et al., 2019). Unfortunately, older patients have less opportunity of receiving living-donor kidney transplantation (LDKT), and those without the option of LDKT are more likely to be delisted or die while waiting on the waiting list than non-older patients (Laging et al., 2019; Segall et al., 2016). Older patients are also less frequently referred to the waiting list (Tong et al., 2014; Selter et al., 2014), although practice guidelines from medical societies do not limit kidney transplantation based on the recipient’s age alone

(Knoll, 2009). It is true that older patients have more age-related comorbidities that are contraindications for kidney transplantation (Laging et al., 2016). However, older patients are often not listed despite having no formal contraindications.

One approach to the less opportunity of kidney transplantation among older patients is further considering LDKT (Laging et al., 2019; Segall et al., 2016). The approach might be more feasible in countries like Japan where LDKT accounts for the majority of cases, while there is another solution of increasing deceased donors by accepting expanded criteria for deceased donors (Concepcion et al., 2016). A superior outcome is generally reported with LDKT than deceased-donor kidney transplantation (Israni et al., 2014). In contrast, clinical evidence such as the risk index of clinical outcomes of LDKT, especially in older recipients, is still limited compared with that of deceased-donor kidney transplantation. We should also consider the cost-effectiveness of kidney transplantation as well as its health outcomes from the perspective of the sustainable healthcare system because kidney transplantation is not the only life-saving therapy, unlike heart or liver transplantation. Some earlier studies have reported that kidney transplantation was more cost-effective than dialysis (Elgaard Jensen et al., 2014; Haller et al., 2011; Sánchez-Escuredo et al., 2015). However, data on cost-effectiveness analysis of LDKT in older patients is still limited worldwide (Heldal et al., 2019).

In this study we evaluated the cost-effectiveness of the clinical course of RRT with the option of LDKT compared with RRT without this option in older patients (60 to 74 years) in Japan. We estimated the cost and the utility of having the option of LDKT under the current situation of RRT in Japan. Japan is one of the aging societies in the world and the average age of dialysis initiation has reached almost 70 years (Nitta et al., 2019). Japan is also characterized by the fact that the proportion of deceased-donor kidney transplantation is quite low and approximately 90% of kidney transplantation is performed from living donors (Japan Society for Clinical Renal Transplantation and Japan Society for Transplantation, Annual report 2019). It is thus worthwhile to evaluate the cost-effectiveness of LDKT in the older population in Japan to serve as a reference for the future direction of policy and relevant guidelines for RRT in the older population.

Materials and Methods

We evaluated the cost-effectiveness of RRT with the option of LDKT compared with RRT without this option in older ESKD patients in Japan. The age range was set from 60 to 74 years, assuming that LDKT is generally applicable in Japan. We estimated the cost per quality-adjusted life-year (QALY) gained with these two clinical scenarios. The incremental cost-effectiveness ratio (ICER) was also calculated. We used 5.0 million Japanese yen (JPY) per QALY as the threshold of ICER to be cost-effective (Shiroiwa et al., 2010). Only direct costs were considered for the cost calculation from the healthcare payer perspective. We excluded the option of deceased-donor kidney transplantation because our study focused on the influence of LDKT on the cost-effectiveness of RRT. Note that LDKT covers the majority of kidney transplantation in Japan and the proportion of deceased-donor kidney transplantation was only 9.8% in 2018 (Japan Society for Clinical Renal Transplantation and Japan Society for Transplantation, Annual report 2019).

Markov model

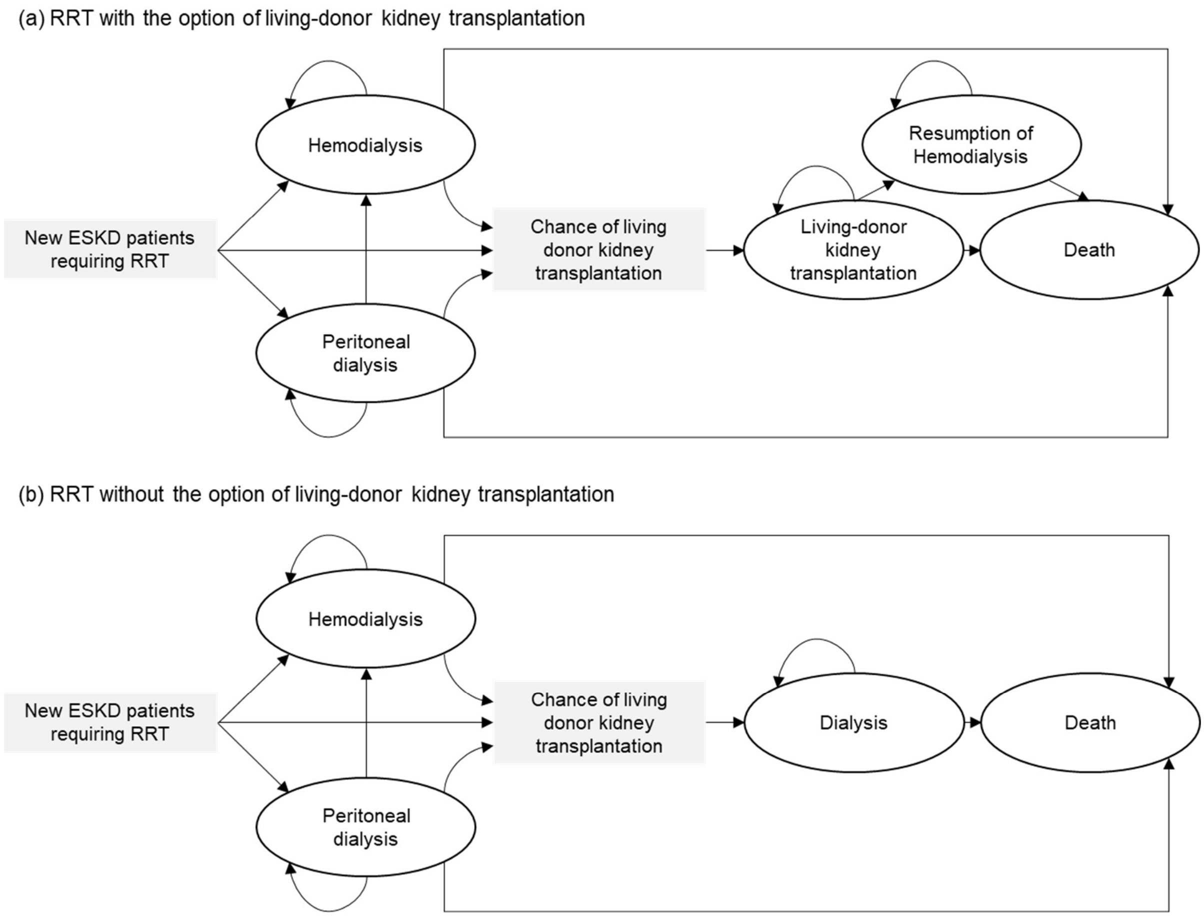
We developed a Markov model and evaluated the cost-effectiveness using TreeAge software (version 2020). The Markov model is frequently used to estimate costs and benefits of a group of patients of interest. The Markov model defines health states, and these theoretical patients move between the predefined health states with distinct transition probabilities. Specific cost and benefit, which is QALY in our study, are assigned to each health state. The Markov model simulates the health trajectory and computes cost and benefit of these theoretical patients until the predefined time frame.

In the clinical course of RRT with the option of LDKT (Figure 1-a), new ESKD patients requiring RRT could undergo LDKT without any experience of dialysis, which is namely pre-emptive kidney transplantation, or initiate HD or PD in the first year. In subsequent years, those who initiated dialysis (HD or PD) might stay on dialysis, have LDKT, or die. Those who had LDKT might continue graft survival (i.e., stay on the LDKT health state), experience graft loss (i.e., move to the health state of the resumption of HD), or die. The option of PD after graft loss was excluded in our model. In contrast, in the clinical course of RRT without the option of LDKT (Figure 1-b), we created another health state of dialysis (HD or PD) named “Dialysis” for the purpose of the analysis. New ESKD patients initiate HD, PD, or “Dialysis” in the first year. Those who initiated HD or PD might stay in the current health state or move to “Dialysis” in subsequent years. In the clinical course of RRT without the option of LDKT, patients move to the “Dialysis” state instead of the LDKT state at the same probability as that of moving to the LDKT state in the model of Figure 1-a.

In our Markov model, we adopted several simplifications for the health trajectory of RRT. First, we ruled out the combination therapy of HD and PD because the proportion was as low as 0.4% in 2017 (Nitta et al., 2019). Secondly, patients who initiated HD do not switch to PD during the entire course of RRT. Those on HD could stay on HD, have LDKT (Figure 1-a), move to the “Dialysis” state (Figure 1-b), or die. In contrast, patients who initiated PD could switch to HD in the course of RRT.

Figure 1

Markov Model for RRT with and without Option of LDKT



Model assumption

We made several assumptions in our Markov model. New ESKD patients receive dialysis (HD or PD) or LDKT (i.e., pre-emptive kidney transplantation). Patients continue RRT until the end of life. The Markov model was set to run for 10 years (10 cycles in TreeAge) with a duration of one year due to limited long-term data. All costs and benefits (utilities) after the initial year were discounted by 3.0%.

Data sources

Transition probabilities, costs, and utilities were determined based on review of the medical literature. We referred to the medical literature reported in Japan only. We added some clinical and analytical assumptions when determining the variables.

Probabilities

In principle, our study referred to the annual national registry reports of the Japan Society for Dialysis Therapy (JSDT) (Nitta et al., 2019), Japan Society for Clinical Renal Transplantation (JCRT), and Japan Society for Transplantation (JST). Note that the interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the JSDT, JCRT, and JST. We referred to the transition probability to death in the health states of HD, PD, Dialysis, and Resumption of HD in the JSDT data, because the average age of the patients on dialysis was over 60 years. We did not treat the mortality rate of HD and PD separately. For calculation of the transition probabilities from PD to other health states, they were estimated using prevalence of PD patients by the PD period, assuming the transition probabilities were the same between all patients and patients aged 60 to 74 years. Concerning LDKT in older patients, Yagisawa et al. (2019) reported the patient and graft survival rates of LDKT by the recipient age based on the national registry data.

Costs

Medical costs of HD, PD, and LDKT specific to older patients aged 60 to 74 years were not obtained from review of the medical literature. For the medical cost of HD, we referred to the survey on medical expenses for dialysis in 2016 by JSDT (Ota et al., 2017). The survey included health insurance claims of 11,086 outpatients in 164 facilities in Japan. The average age of HD patients was 65.4 years. The medical cost of PD was obtained from a multicenter study in which a total of 179 PD patients were investigated between 2010 and 2014 (Takura et al., 2019). The average age of PD patients was 64.6 years. There is a gap between the medical cost of kidney transplantation in the first and subsequent years as the surgery-related cost is included in the first year. In our study, the medical cost of LDKT in the first year was estimated from a report using the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB) from 2009 to 2010 (Kitazawa et al., 2017). The study reported the average cost of LDKT one month before transplantation and for the following 2 months. The cost 2 months after transplantation was extrapolated to those in the remaining months of the first year. In subsequent years, by adding some analytical assumptions, we estimated the cost from a study in which 45 patients in one institution were investigated between 2002 and 2007 (Nakatani et al., 2009). No information about the age of the recipients was reported in these two studies of LDKT.

Utilities

The effect of RRT was measured in QALY, which is calculated by integrating utility values over each patient's lifetime. The utility values represent QoL, which usually ranges from 0 (utility of death) to 1 (utility of perfect health). The preference-based measure is recommended to evaluate utility values. EuroQoL 5 dimension (EQ-5D) is one of the preference-based measures and is frequently used for the utility value assessment. We hence referred to studies where EQ-5D was evaluated in Japanese patients for the utility values of HD, PD and LDKT. Note that we did not obtain utility values specific to older patients aged 60 to 74 years. The utility values of HD and PD were obtained from a multicenter study (Takura et al., 2019). The average ages of HD and PD were 62.8 and 64.6 years, respectively. Hiragi et al. (2019) reported that recipients gained 0.07 in the utility value after the transplant surgery. We estimated the utility value of LDKT +0.07 compared to that of HD.

Table 1

Transition Probabilities of Markov Model

Markov State	**Transition probability (%)**		
End-stage kidney disease patients requring RRT			
Hemodialysis			94.2
Peritoneal dialysis			5.1
Chance of Living donor kidney transplantation			0.6
Hemodialysis			
Hemodialysis			90.0
Chance of Living donor kidney transplantation			0.2
Death			9.8
Peritoneal dialysis	1-year	2~5-year	6~10-year
Peritoneal dialysis	80.2	74.2	71.9
Hemodialysis	8.9	14.9	17.3
Chance of Living donor kidney transplantation	1.0	1.0	1.0
Death	9.8	9.8	9.8
Dialysis			
Dialysis			90.2
Death			9.8
Living donor kidney transplantation	1-year	2~5-year	6~10-year
Living donor kidney transplantation	95.9	98.1	96.5
Resumption Hemodialysis	0.8	0.3	0.4
Death	3.3	1.7	3.0
Resumption Hemodialysis			
Resumption Hemodialysis			90.2
Death			9.8

Table 2

Costs of Health States in the Markov Model

Markov State		Cost (JPY)
Hemodialysis		4,773,540
Peritoneal dialysis		4,394,394
Living donor kidney transplantation	1-year	7,330,584
	subsequent years	1,909,900
Dialysis		4,773,540
Resumption of Hemodialysis		4,773,540

Table 3

Utilities of Health States in Markov Model

Markov State	Utility
Hemodialysis	0.785
Peritoneal dialysis	0.825
Living donor kidney transplantation	0.855
Dialysis	0.785
Resumption of Hemodialysis	0.785

Sensitivity Analysis

We performed one-way sensitivity analyses for the mortality rates, the rate of graft loss, the costs, and the utilities to assess the impact of the uncertainties of the variables. The mortality rates and the rate of graft loss varied by ±50% from the base values (Table 4). The costs varied by ±25% from the base values (Table 5). The 95% confidence interval (CI) was used for sensitivity analysis of the utilities (Table 6).

Table 4

Ranges of Sensitivity Analysis for Mortality Rate and Rate of Graft Loss

Transition probability	Low	High	Range
Mortality Rate of Dialysis			
Hemodialysis	4.9	14.7	± 50%
Peritoneal Dialysis			
Dialysis			
Resumption of Hemodialysis			
Rate of Graft Loss	1-year		
	0.40	1.20	± 50%
	2~5-year		
	0.13	0.38	± 50%
	6~10-year		
	0.21	0.63	± 50%
Mortality Rate of Living-donor Kidney Transplantation	1-year		
	1.65	4.95	± 50%
	2~5-year		
	0.83	2.48	± 50%
	6~10-year		
	1.52	4.56	± 50%

Table 5

Ranges of Sensitivity Analysis for Costs

Cost	Low	High	Range
Hemodialysis	3,580,155	5,966,925	± 25%
Dialysis	3,580,155	5,966,925	± 25%
Resumption of Hemodialysis	3,580,155	5,966,925	± 25%
Peritoneal Dialysis	3,295,796	5,492,993	± 25%
Living-donor Kidney Transplantation	1-year		
	5,497,938	9,163,230	± 25%
	Subsequent years		
	1,432,425	2,387,375	± 25%

Table 6

Ranges of Sensitivity Analysis for Utilities

Utility (QALY)	Low	High	Range
Hemodialysis	0.714	0.856	95%CI
Dialysis	0.714	0.856	95%CI
Resumption of Hemodialysis	0.714	0.856	95%CI
Peritoneal Dialysis	0.799	0.851	95%CI
Living-donor Kidney Transplantation	0.785*	0.933	95%CI

* The lowest value was the same utility value as Hemodialysis

Change in Composition of LDKT in Older Patients

Older patients have less opportunity for LDKT than non-older patients in Japan. Table 7 shows the rates of LDKT by the age range in Japan. We estimated impact on the cost-effectiveness compared to the base-case when the rate of LDKT in the older patients aged 60 to 74 years increases to the same rate as non-older patients. We estimated the impact on the 3 scenarios in Table 8. We used net monetary benefit (NMB) for comparison with the threshold of willing-to-pay as 5.0 million JPY per QALY in the analysis.

Table 7

Rates of Living-Donor Kidney Transplantation by Age Range

Age range	Pre-emptive LDKT per 1,000 ESKD patients	LDKT per 1,000 HD patients	LDKT per 1,000 PD patients
45~59	20.7	6.2	26.3
60~74	6.3	1.7	10.4

Table 8

Scenarios of Increasing LDKT in Older Patients

Scenario	
Scenario 1	Pre-emptive LDKT increased **3.29 times** (Increase at the same rate between ages 45 and 59 years)
Scenario 2	LDKT from Hemodialysis increased **3.76 times** (Increase at the same rate between ages 45 and 59 years)
Scenario 3	LDKT from Peritoneal Dialysis increased **2.52 times** (Increase at the same rate between ages 45 and 59 years)

Ethical Statement

The study was conducted based on literature review. Ethics committee approval was not applicable.

Results

Base-case Analysis

The results of the cost-effectiveness analysis are shown in Table 9. The average total cost of RRT without the option of LDKT after 10 years was 28,151,962 JPY and the average total QALY was 4.649. In contrast, the average total cost and QALY of RRT with the option of LDKT after 10 years were 28,056,767 JPY and 4.674 QALY, respectively. By adopting the option of LDKT, the total cost was reduced by 95,195 JPY, and the total QALY was increased by 0.0251 over 10 years on average per patient. The RRT with the option of LDKT was dominant in patients aged 60 to 74 years.

Table 9

Cost-effectiveness Analysis of RRT in Older Patients

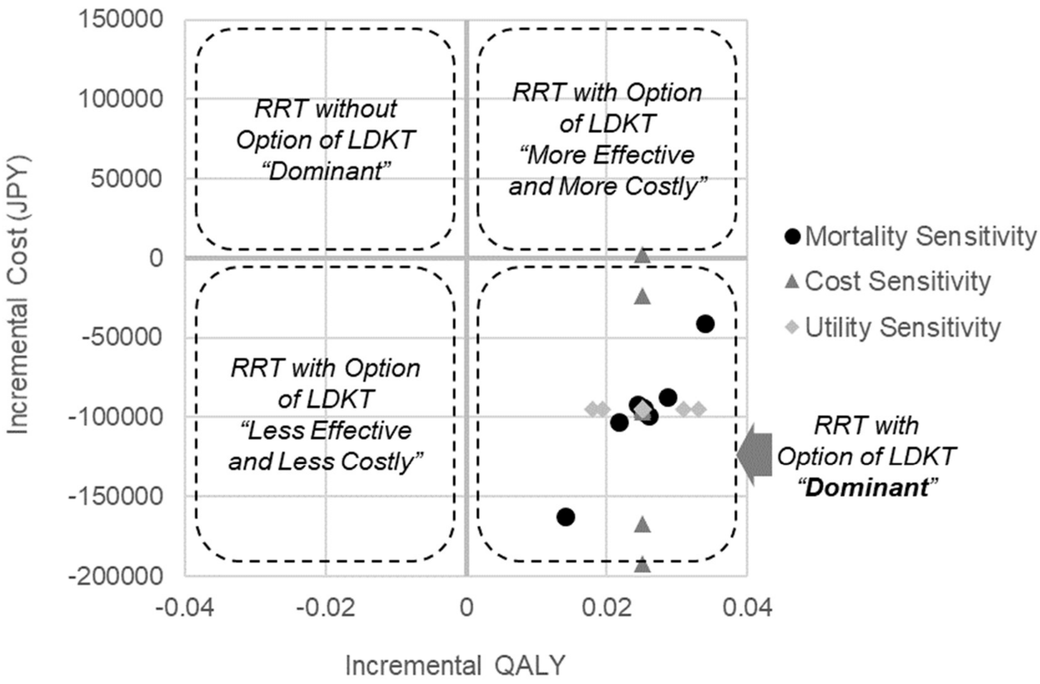
RRT for ESKD patients	Cost (JPY)	Difference in Cost (JPY)	QALY	Difference in QALY	ICER (JPY/QALY)
RRT **without** Option of LDKT	28,151,962	-	4.649	-	-
RRT **with** Option of LDKT	28,056,767	-95,195	4.674	0.0251	Dominant

Sensitivity Analyses

Figure 2 shows plots of the incremental cost and QALY of RRT with the option of LDKT in comparison with RRT without this option. The circles, squares, and triangles in Figure 2 represent the results of sensitivity analyses for mortality rates including the rate of graft loss, the costs, and the utilities, respectively. RRT with the option of LDKT was still dominant (i.e., the total cost reduced and the total QALY increased) in all cases of the sensitivity analyses except for one case when the cost for “Dialysis” was reduced by 25%. The one-way sensitivity analyses showed the robustness of better cost-effectiveness of RRT with the option of LDKT.

Figure 2

Incremental Cost-effectiveness Plots of Sensitivity Analyses



Change in Composition of LDKT in Older Patients

Table 10 shows the results of the cost-effectiveness analysis of the 3 scenarios. Figure 3 shows the incremental cost and QALY of the 3 scenarios versus the current composition of RRT with the option of LDKT. The most cost-effective scenario was scenario 1 where the rate of pre-emptive LDKT increased while the difference in NMB was small with scenario 2. The increase in NMB compared to the current composition of RRT in scenario 1 and 2 was 259,100 JPY and 230,908 JPY, respectively.

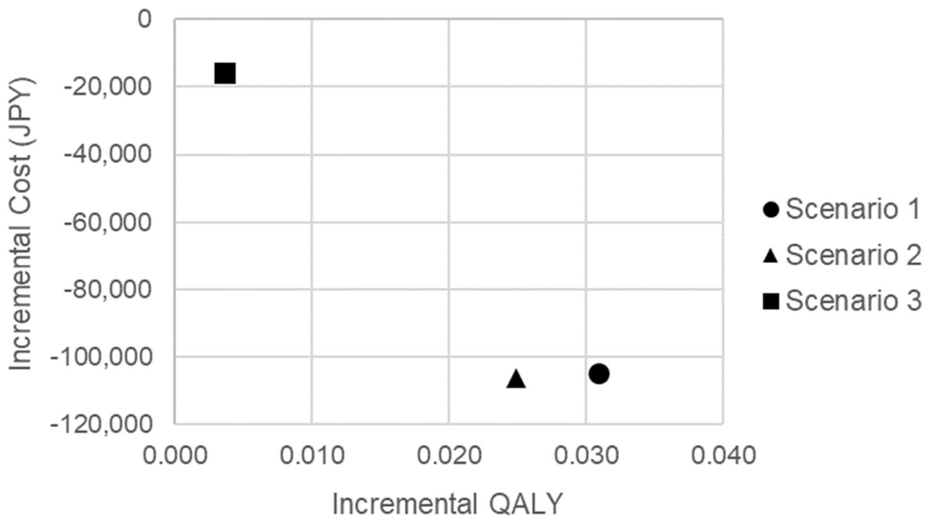
Table 10

Cost-effectiveness Analysis of RRT in 3 Scenarios

Scenario		Cost (JPY)	Utility (QALY)	Difference in NMB (JPY)
Base	Current Composition of RRT	28,056,767	4.674	-
Scenario 1	Pre-emptive LDKT **3.29 times**	27,952,135	4.705	259,100
Scenario 2	LDKT from HD **3.76 times**	27,950,557	4.699	230,908
Scenario 3	LDKT from PD **2.52 times**	28,041,045	4.677	34,197

Figure 3

Incremental Cost-effectiveness Plots of 3 Scenarios



Discussion

In our study, RRT with the option of LDKT was dominant compared to RRT without this option in ESKD patients aged 60 to 74 years in Japan. There is increasing evidence suggesting that kidney transplantation regardless of donor types is the most cost-effective therapy among the available RRTs (Bavanandan et al., 2015; Fu et al., 2020; Sánchez-Escuredo et al., 2015). Since the medical cost of kidney transplantation is higher than dialysis in the first year, Whiting et al. (2000) reported that the breakeven cost with hemodialysis occurred at some point between 3 and 14 years after surgery depending on the organ quality. In older patients, Heldal et al. (2019) reported that the cost per QALY of kidney transplantation at 1 year was higher than that of dialysis in Sweden. The authors also mentioned the preliminary analysis suggested a better economic effect with kidney transplantation than dialysis in the long term. We compared the cost per QALY between LDKT and dialysis in ESKD patients aged 60 to 74 years in Japan (the results are not shown). In comparison with dialysis, LDKT reduced the total cost by 7,228,170 JPY and increased the total QALY by 2.15 after 10 years in average per patient. However, in clinical practice, not all new ESKD patients could receive pre-emptive kidney transplantation. In 2018, approximately 70% of patients had an experience of dialysis prior to kidney transplantation in Japan (Japan Society for Clinical Renal Transplantation and Japan Society for Transplantation, Annual report 2019). We thus evaluated the economic impact of having the option of LDKT for RRT. In our model, ESKD patients could experience dialysis before receiving LDKT. Patients also do not necessarily receive LDKT for 10 years of RRT, even in the Markov model with the option of LDKT. The degree of cost reduction (95,195 JPY) and the QALY gained (0.0251 QALY) was much smaller in our study than the results of the direct comparison (7,228,169 JPY and 2.15 QALY) because the proportion of LDKT is quite low in the current composition of RRT in Japan.

The cost per QALY for RRT with the option of LDKT was 6,003,156 (JPY/QALY) in our study, which was lower than that reported by Shimizu et al. (2012) in Japanese patients. The authors reported that the cost per QALY was 84,008 US dollar/QALY (7,372,626 JPY/QALY) after the cost and QALY were discounted by 3.0% per year. This difference might be explained by the gap in QALY especially for HD and PD in addition to the differences in the target population and the time frame. While Shimizu et al. (2012) referred to the result based on a survey conducted by one center in the United Kingdom (Lee et al., 2005), our study adopted the results of a prospective and multicenter study in Japan (Takura et al., 2019). The QALY for HD and PD in the study by Takura et al. was higher than that in the study by Lee et al. The better clinical outcomes of dialysis in Japan might affect the higher QALY in Japan (Matsuda, 2017).

Our study showed a cost reduction of 95,195 JPY and a gain in QALY of 0.0251 on average per patient with the option of LDKT in ESKD patients aged 60 to 74 years. Considering that the prevalence of ESKD patients on RRT between 60 and 74 years was approximately 145,000 at the end of 2017 in Japan (Nitta et al., 2019), the option of LDKT contributes to a cost reduction of 13.8 billion JPY and gained QALY of 3,642 over 10 years. We showed that the rate of LDKT decreases as the recipient age increases in Japan. We evaluated several scenarios in which the LDKT rates in older patients increased. With the prevalence of ESKD patients between 60 and 74 years, the additional cost reduction and QALY gained over 10 years are estimated to be 15.2 billion JPY and 4,480 QALY respectively when the proportion of pre-emptive LDKT increased from 0.63% (the proportion aged 60 to 74 years) to 2.07% (the proportion aged 45-59 years). The option of LDKT could be recommended from the perspective not only of the clinical outcome but also the healthcare payer in Japan.

We consider that more evidence encourages discussion about including the option of LDKT also for older ESKD patients. First, it is key to provide risk factors of post-transplant graft function and graft loss. The Kidney Donor Profile Index (KDPI) is used for deceased-donor allocation in the US as the risk index (KDPI Guide for Clinicians). The KDPI is calculated with the Kidney Donor Risk Index (KDRI), which is an estimate of the relative risk of graft loss using donor characteristics. In comparison with deceased-donor kidney transplantation, there is less information about the risk index for LDKT. In Japan, academic transplant societies develop the guidelines for recipients and living donors. However, there is still limited evidence of the association between recipient/donor characteristics of and the clinical outcomes in LDKT. Matsukuma et al. (2019) reported that donor age, donor-estimated glomerular filtration rate, donor hypertension, and donor/recipient body weight ratio were predictive factors of low graft function at 1 year after LDKT. It is expected that evidence for the predictive factors of short-term and long-term outcomes will increase. Such evidence encourages physicians to discuss the option of LDKT.

Second, we should take care of living donors with LDKT. Ibrahim HN et al. (2009) reported that there is no difference in the survival rate and the risk of ESKD between living donors and the general population. In contrast, living donors have a higher risk of ESKD compared with the matched healthy population (Muzaale et al., 2014). The estimated risk of ESKD at 15 years after the donation was 30.8 and 3.9 per 10,000 for living donors and the matched healthy population, respectively. Moreover, the QoL of living donors may also deteriorate by donation (Hiragi et al., 2019). Therefore, it is vital to accumulate evidence concerning the risk of ESKD and QoL deterioration among living donors for the optimal selection of RRT.

The study has several limitations. We namely added some clinical and analytical assumptions when determining variables. All transition probabilities and the mortality rates were determined based on the national registries and there is potential bias in the registries. We did not treat the mortality rate of HD and PD separately due to the limited available information. We also did not have available data on costs and utilities specific to patients aged 60 to 74 years. It is reasonable to use the data of the overall population for HD and PD since the average age for HD and PD is older than 60 years. Due to the uncertainties, we conducted one-way sensitivity analyses for mortality rate, rate of graft loss, costs, and utilities. Finally, the Markov models were set to run for 10 years, mainly due to a lack of long-term data.

The present study showed that RRT with the option of LDKT was more cost-effective than RRT without this option in older patients in Japan. Further studies of the cost-effectiveness including deceased-donor kidney transplantation and living donors give us some additional insights for the future direction of RRT in older patients in Japan.

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