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Cost-effectiveness of Deceased-donor Renal Transplant Versus Dialysis to Treat End-stage Renal Disease: A Systematic Review

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Abstract: Deceased-donor renal transplant (DDRT) is an expensive and potentially risky health intervention with the prospect of improved life and lower long-term costs compared with dialysis. Due to the increasing shortage of kidneys and the associated rise of transplantation costs, certain patient groups may not benefit from transplantation in a cost-effective manner compared with dialysis. The objective of this systematic review was to provide a comprehensive synthesis of evidence on the cost-effectiveness of DDRT relative to dialysis to treat adults with end-stage renal disease and patient-, donor-, and system-level factors that may modify the conclusion. A systematic search of articles was conducted on major databases including MEDLINE, Embase, Scopus, EconLit, and the Health Economic Evaluations Database. Eligible articles were restricted to those published in 2001 or thereafter. Two reviewers independently assessed the suitability of studies and excluded studies that focused on recipients with age <18 years old and those of a living-donor or multiorgan transplant. We show that while DDRT is generally a cost-effective treatment relative to dialysis at conventional willingness-to-pay thresholds, a range of drivers including older patient age, comorbidity, and long wait times significantly reduce the benefit of DDRT while escalating healthcare costs. These findings suggest that the performance of DDRT on older patients with comorbidities should be carefully evaluated to avoid adverse results as evidence suggests that it is not cost-effective. Delayed transplantation may reduce the economic benefits of transplant which necessitates targeted policies that aim to shorten wait times. More recent findings have demonstrated that transplantation using high-risk donors may be a cost-effective and promising alternative to dialysis in the face of a lack of organ availability and fiscal constraints. This review highlights key concepts of health economic evaluations and the relevance of cost-effectiveness to inform care and decision-making in renal programs.

(*Transplantation Direct* 2020;6: e522; doi: 10.1097/TXD.0000000000000974. Published online 13 January, 2020.)

Health economic evaluations aim to inform care planning and ensure value-for-resources expended on care recipients by simultaneously assessing the costs and effects of different interventions.[1] In the field of nephrology, ranking the cost-effectiveness of different treatments for end-stage renal disease (ESRD) has been a long-standing research interest. In fact, cost-effectiveness analysis was first applied in the health area to compare renal transplantation and dialysis in 1968,[2] which was followed by a series of studies published in the 1990s,[3-6] all suggesting transplantation offered superior patient outcomes and cost-savings relative to dialysis.

Although there is minimal controversy over living-donor renal transplant,[7] the cost-effectiveness of deceased-donor renal transplant (DDRT) over dialysis has not been fully established.[7,8] This gap in knowledge is accentuated in the contemporary era due to worldwide paradigm shifts in renal care delivery. Notably, an increased number of Expanded Criteria Donor kidneys are now accepted for use in transplantation by transplant programs in North America,[9-11] South America,[12] Europe,[13] Australia,[14] and Asia.[15] While transplanting these kidneys may still benefit patients,[9] the high upfront cost may not be defrayed until more than a decade after transplant, resulting in a potential reduction

in the overall costs saved by transplantation.[8] Furthermore, alternatives to in-center hemodialysis (HD), including at-home HD[16] and peritoneal dialysis,[17] are shown to improve outcomes at a reduced cost, which has opened up new discussions on the cost-effectiveness of DDRT over dialysis.

Previous reviews on the cost-effectiveness of DDRT compared with dialysis did not present specific cost-effectiveness measures[18] or drivers,[19] were based on only 2 studies[20] or examined renal transplantation in general without specifying the type of donor.[7,17] We addressed this knowledge gap in this systematic review by examining a 2-fold objective, including (1) to provide a comprehensive evidence synthesis of the incremental cost-effectiveness ratios (ICERs) of DDRT compared with dialysis and (2) to identify drivers of the resulting ICERs at 3 levels: patient, donor, and system.

MATERIALS AND METHODS

In this section, we describe the structure of our literature review, highlight the primary and secondary outcomes assessed, specify the study inclusion and exclusion criteria used, describe the data items collected, report on the assessment of study quality, and end with an outline of data synthesis.

Literature Search and Eligibility Criteria

This review included studies that assessed the cost-effectiveness of DDRT compared with dialysis to treat adults with ESRD. The review followed the **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (SDC,** http://links.lww.com/TXD/A238) guidelines.[21] Studies were limited to English-language, peer-reviewed articles that were published on January 1, 2001, and thereafter. This time period was chosen to reflect major policy reforms for DDRT, including the implementation of the Expanded Criteria Donor algorithm in the United States (in 2001[10]) and Canada (by 2006[9]). A comprehensive literature search was performed on major databases including MEDLINE, Embase, Scopus, EconLit, and the Health Economic Evaluations Database. We also checked the reference list of the included studies. Tables S1–S5 (SDC, http://links.lww.com/TXD/A238) detailed the search strategy used in the 5 databases and the search results. To qualify for inclusion, studies must have either reported an ICER that directly compares DDRT and dialysis or have reported both the cost and the effect associated with both treatments so that an ICER could be calculated (see below). Studies that included patients with age <18 years old at transplantation were excluded to prevent bias of including pediatric patients who are prioritized on the waitlist.[22] Studies that did not report separate results for DDRT by examining different types of transplants, including living-donor and multiorgan transplants, were also excluded due to different patient cohorts and allocation routines.[23]

Outcomes

Primary Outcome

In this review, we focused on the ICER of DDRT over dialysis, a standard measure used in economic evaluation to compare healthcare interventions.[1] Here, an ICER is calculated as a ratio of the incremental cost (ΔC) to the incremental effect (ΔE) of DDRT compared with dialysis:

$$\text{ICER} = \frac{\Delta C}{\Delta E} = \frac{C_{DDRT} - C_{Dialysis}}{E_{DDRT} - E_{Dialysis}}$$

where C_{DDRT} and $C_{Dialysis}$ are the costs associated with DDRT and dialysis, respectively, while E_{DDRT} and $E_{Dialysis}$ are the effects of DDRT and dialysis, respectively. Because the ICER represents the additional cost needed for DDRT to gain 1 extra unit of effect over dialysis, 4 cost-effectiveness outcomes are established that correspond to the 4 quadrants on the cost-effectiveness plane (left side of Figure 1), including (1) the Southeast quadrant: DDRT dominates dialysis since it is both more effective and reduce costs (ICER <0 where ΔC <0 and ΔE >0); (2) the Northeast quadrant: DDRT is more effective but also more costly than dialysis (ICER >0 where ΔC >0 and ΔE >0); (3) the Northwest quadrant: DDRT is dominated by dialysis since it is less effective at higher costs (ICER <0 where ΔC >0 and ΔE <0); and (4) the Southwest quadrant: DDRT is less effective but saves costs compared with dialysis (ICER >0 where ΔC <0 and ΔE <0).

For ICERs that are found in (2) and (4), the cost-effectiveness of DDRT relative to dialysis is unclear unless a willingness-to-pay (WTP) threshold is specified, that is, the maximum expense the payer is willing to pay for 1 more unit of effect gained by DDRT over dialysis. Hence, 2 zones were defined in the Northeast and Southwest quadrants, respectively, including (2a): DDRT was sufficiently more effective despite being more costly than dialysis so that DDRT was cost-effective (0 < ICER < WTP where ΔC >0 and ΔE >0); (2b): DDRT was more effective but the required costs exceeded the maximum threshold (ICER > WTP, ΔE >0); (4a): DDRT was sufficiently cheaper than dialysis despite resulting in a reduction in effectiveness so that DDRT was still cost-effective (ICER > WTP where ΔC <0 and ΔE <0); and (4b): DDRT was less effective but the costs were not sufficiently lower than dialysis to make DDRT cost-effective (0 < ICER < WTP, ΔE <0) (right side of Figure 1). Consistent with previous reviews,[19,24,25] we used $100K (USD in 2018 values) as the maximum WTP (or threshold) for an ΔE. It is worth mentioning that while ICERs in zones (1), (4a), and (4b) all indicate DDRT is cheaper than dialysis, only those in zones (1) and (4a) suggest DDRT is cost-effective in addition to being cheaper.

In this review, studies were allowed to assess the cost of DDRT and dialysis from any perspective, including that of the patient, hospital, payer, and society. We set no limitation on the length of the time horizon or the measurement of effectiveness, accepting all of life years (LYs), quality-adjusted LYs (QALYs), and disability-adjusted LYs (DALYs). LYs are a crude measure of the remaining life expectancy, which could be a relevant outcome in an evaluation of interventions that improve all-cause survival, such as transplantation. QALYs are an alternative outcome measure that are calculated by multiplying LYs (ie, the length of life) with a utility score from 0 to 1 with 1 meaning perfect health and 0 meaning death (ie, the quality of life). One QALY can be thought to as 1 year of life in perfect health.[26] DALYs represent the sum of the Years of Life Lost due to premature mortality and the Years Lost due to Disability. One DALY can be thought to as 1 lost year of disability-free life.[27]

Secondary Outcome

We assessed whether the included studies explicitly identified cost-effectiveness drivers, that is, factors that modified the ICER. This information was either embedded in the study objective (eg, studies that examined the effect of patient age on the cost-effectiveness of DDRT and dialysis) or in the study cohort (eg, exclusively elderly patients), or was discussed in sensitivity analyses where the uncertainty of ICER was tested by varying different parameters.
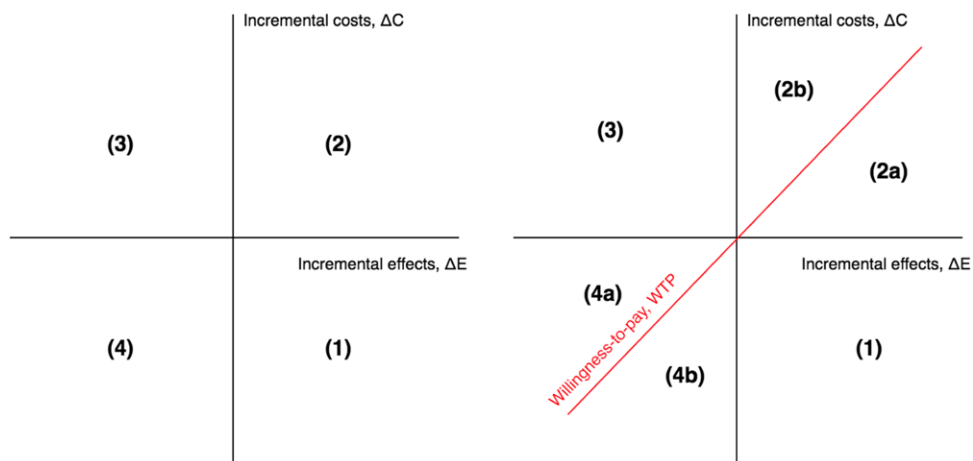
FIGURE 1. Cost-effectiveness plane. The cost-effectiveness plane is defined by the incremental effect (ΔE) on the *x*-axis and the incremental cost (ΔC) on the *y*-axis. WTP, willingness-to-pay.

Study Selection

Citations from the initial search of the 5 databases were imported into EndNote (version X 9.2) to check for duplications. Two reviewers (R.F. and N.S.) independently assessed the suitability of studies by screening the titles and the abstracts. Full texts of potentially relevant studies were then examined in detail by the same 2 reviewers to ensure alignment with the inclusion and exclusion criteria. A third reviewer (P.C.C.) reviewed the final selection of studies. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram (Figure 2) was used to document the screening and selection process of eligible studies.

Data Collection and Data Items

Two Microsoft Excel forms were created to store relevant data items (see below) extracted from the included studies. The first form (**Table S6, SDC,** http://links.lww.com/TXD/A238) contains the following items that correspond to the primary outcome of the review, including: (1) publication information: author(s) and year of publication; (2) description of patient cohort: the type (real-world versus simulated) and size of patient cohort, and the type of treatment examined; (3) evaluation methods: time horizon, measure(s) of effectiveness, techniques (ie, trial-based versus model-based), perspective, and country; (4) cost components for dialysis and DDRT; and (5) ICER results: ICER derived from the primary analysis in original currency and year. The second form (**Table S7, SDC,** http://links.lww.com/TXD/A238) extracts the secondary outcomes, including (1) sensitivity analyses results: parameters that modified the primary ICER finding; (2) other ICER drivers assessed in the study; and (3) the discount rate. Two reviewers (R.F. and N.S.) independently extracted data from the included studies, and a third reviewer (P.C.C.) resolved any disagreements in terms of the obtained data.

Quality Assessment

Methodologic quality of the included studies was independently assessed by 2 reviewers (R.F. and N.S.) using the 10-item checklist by Drummond et al,[1] a standard appraisal tool for economic literature (**Table S8, SDC,** http://links.lww.com/TXD/A238). A total score from 0 to 10 was calculated for each study. Consistent with a previous review[28] that used this checklist, for the 3 items that included both a cost and a consequence component (item 5–7), we assigned 0.5 points to each component. We calculated an average score for each study by dividing its total score by 10.[29] We then classified studies to have low risks if their average scores were between 0.9 and 1.0 (inclusive), medium risks if the scores were between 0.7 and 0.9 (exclusive), and high risks if they scored at or below 0.7.[29]

Data Synthesis and Summary Measures

ICERs reported from the included studies were converted to US dollars in 2018 constant values using the Medical Care Consumer Price Index calculator.[30] All ICERs were plotted in a cost-effectiveness plane by the choice of effectiveness measures and risk of bias (low, medium, or high risk). A narrative synthesis method was used to summarize ICER drivers at 3 levels: patient; donor; and system.

RESULTS

Study Selection

An initial search revealed 1755 articles, of which 1146 were unique (Figure 2). An additional 4 articles were identified through handsearching. Screening of titles and abstracts identified 57 studies eligible for full-text assessment. Exclusion was performed on the following studies: editorials or reviews; cost analyses; studies that did not report separate results for DDRT or dialysis; and studies that compared types of transplant, listing strategies, or compositions of renal program (eg, a program with an increased proportion of DDRT versus current program). This resulted in a total of 11 studies included in the final review.

Study Characteristics

Table 1 summarizes the characteristics of each included study. More than half of these studies were conducted in North America,[11,31-35] while the remainder were set in Asia[36-38] and Europe.[39,40] The majority (n = 9) of them[11,31-36,40,41] used a simulated cohort of ESRD patients, while 2 (18%)[37,38] relied entirely on real-world patient cohort data. QALYs[11,31-36,40,41] were the most prevalent measure of effectiveness (n = 9, 82%), followed by DALYs (n = 2, 18%).[37,38] All QALY-based studies were rated to have low risks (n = 5, 45%) or medium risks (n = 4, 36%); the 2 DALY-based studies were rated to have
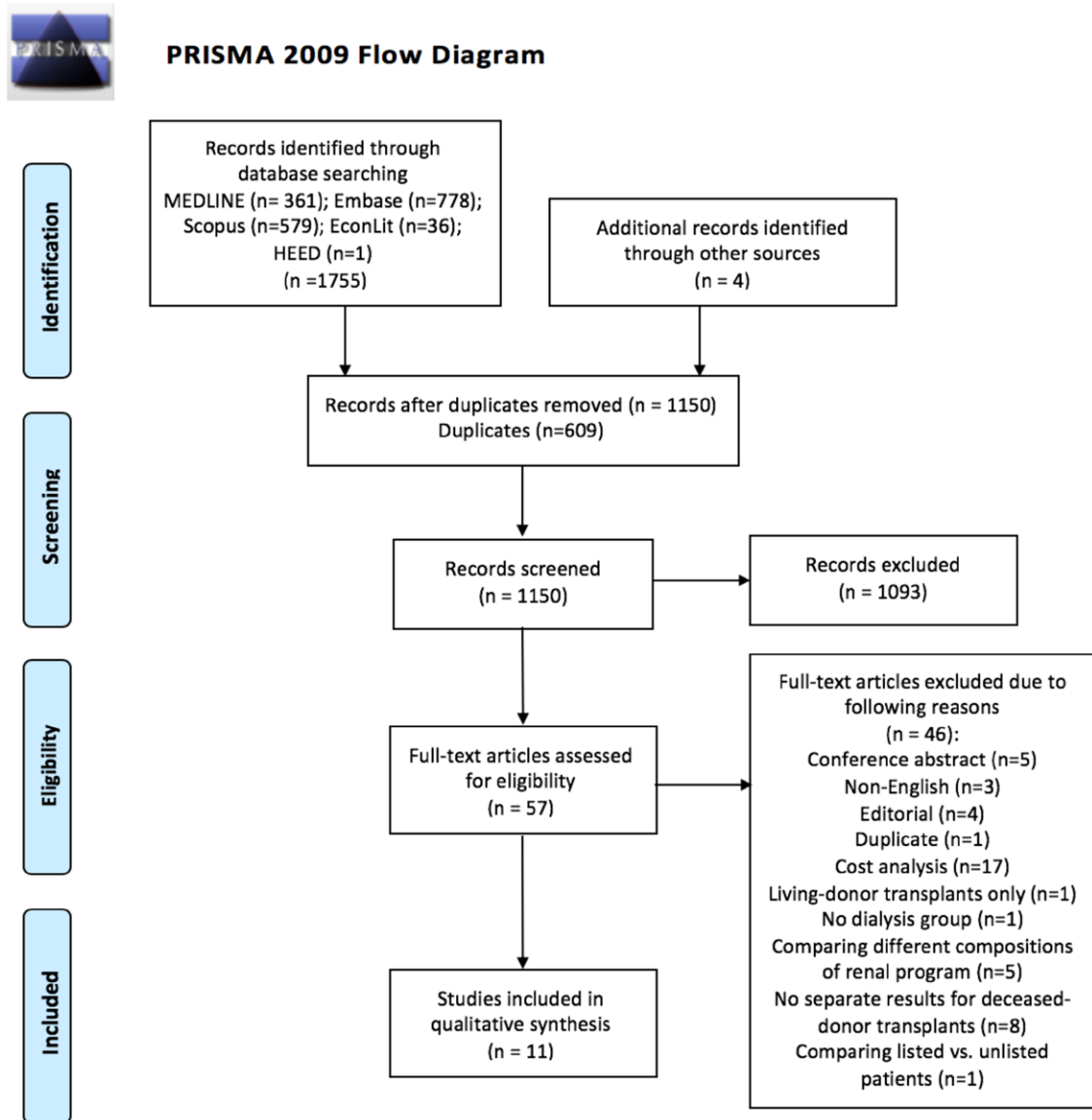
FIGURE 2. PRISMA flow diagram showing the inclusion and exclusion of eligible studies. Literature search was performed on June 12, 2019, on MEDLINE, Embase, Scopus, EconLit, and the Health Economic Evaluations Database (HEED).

high risks. Time horizon varied from 5 years to lifetime. One study[37] was undertaken with a patient perspective, while the remainder adopted a payer's perspective.

Synthesis of Results

Primary Outcome: ICERs for DDRT Versus Dialysis

We reported the main cost-effectiveness conclusion of each study in Table 1. Half[34,35,38,40,41] of studies reported DDRT to always dominate dialysis, meaning that it offered both longer life expectancy or promoted better life quality at a lower cost relative to dialysis. Among the other studies, 2[32,33] suggested that DDRT dominated dialysis for certain patient groups and was always cost-effective, 3[11,31,36] concluded that DDRT always improved health outcomes at an increased cost; and 1[37] reported that DDRT reduced outcomes in exchange for a lower cost.

We presented the 51 ICERs yielded by all studies in Table 2 and plotted them in Figure 3 in a cost-effectiveness plane,

where ICERs were grouped by their measures of effectiveness and risk of bias. QALYs and DALYs were used in the calculation of 46 and 5 ICERs, respectively. Using a WTP threshold of $100K, DDRT dominated dialysis in 23 cases (zone 1; 45%), was more effective and cost-effective in 10 cases (zone 2a; 20%), not cost-effective because its extra costs were too high relative to its associated gain in effectiveness in 16 cases (zone 2b; 32%), and not cost-effective because the cost saved were insufficient to overcome the substantial reduction in effects in 2 cases (zone 4b; 4%).

Secondary Outcome: Factors Influencing ICERs
Patient-level Factors
Age

The cost-effectiveness of DDRT varies by patient age.[31,34,38] In Canada,[31] the economic advantage of DDRT over in-center HD generally diminishes for patients ≥60 years old. Specifically, despite moderate gains in QALYs through DDRT compared with in-center HD, the extra cost increases dramatically

TABLE 1.

Characteristics of the 11 included studies in the review

References	Country	Design	Perspective	Discounting, %	Time horizon	Comparator	Effects	Main conclusion	ICER zones	Risk of bias
Axelrod et al[11]	United States	Model	Payer	3	10 y	Dialysis	QALY	CE but not dominant	2a	Medium
Domínguez et al[41]	Chile	Model	Payer	8	20 y	Dialysis	QALY	Dominant	1	Medium
Jassal et al[31]	Canada	Model	Payer	3	Lifetime	In-center HD	QALY	CE for some patients; not CE for others	2a and 2b	Low
Kaminota[38]	Japan	Population	Payer	3	Lifetime	Dialysis	DALY	Dominant	1	High
Mendeloff et al[32]	United States	Model	Payer	3	Unstated	Dialysis	QALY	CE or dominant	1 and 2a	Low
Mutinga et al[33]	United States	Model	Payer	5	20 y	Dialysis	QALY	CE or dominant	1 and 2a	Low
Ong et al[36]	Singapore	Model	Payer	3	5 y	HD	QALY	CE but not dominant	2a	Low
Quinn et al[34]	Canada	Model	Payer	5	25 y	Dialysis	QALY	Dominant	1	Medium
Roels et al[40] 2007	Germany	Model	Payer	5	20 y	Dialysis	QALY	Dominant	1	Medium
Whiting et al[35] 2003	Canada	Model	Payer	5	20 y	Dialysis	QALY	Dominant	1	Low
YaghoubiFard et al[37]	Iran	Population	Payer and patient	3	Lifetime	In-center HD	DALY	Not CE	4b	High

CE, cost-effective; DALY, disability-adjusted life year; HD, hemodialysis; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

from $116 530/QALY for a 60-year-old, to $131 120/QALY for a 65-year-old, to $192 587/QALY for a 75-year-old, and eventually exceeds $440K/QALY for an 85-year-old with no comorbidities and a 2-year wait time.[31] The authors further noted an exception was when a 65-year-old is transplanted preemptively. In that case, DDRT may be cost-effective compared with in-center HD if this patient is not suffering from both diabetes and cardiovascular disease (CVD).

For patients younger than 60 years old, DDRT remains a preferable strategy relative to dialysis as no age effect was detected in either a Japanese study[38] or a Canadian study.[28] Kaminota[38] reported DDRT to dominate dialysis for adults <50 years old as it was customary at that time not to perform transplants on older patients in Japan. Quinn et al[34] showed DDRT to dominate dialysis for patients in all 4 age groups (<20, 20–39, 40–59, and 60+). However, Quinn et al[34] did not include the costs associated with acute rejection, posttransplant complications, and fees for reinitiating dialysis after graft failure in their analysis, which we argue are essential components that drive up total transplant costs for older patients. Hence, the current evidence points to patients ≥60 years old to be a subpopulation of ESRD for whom DDRT is not cost-effective.

Comorbidities

Multiple comorbidities may reduce the economic attractiveness of DDRT for older patients in the long run, but the effect is sensitive to wait time and the type of comorbidity. In Singapore,[36] DDRT was found to be cost-effective compared with HD to treat diabetic adults at an expense of $48 246/QALY. However, this result only extends to 5 years. A lifetime evaluation has been conducted in Canada,[31] where a 65-year-old with diabetes or CVD was shown to incur 2-fold higher costs with DDRT than with in-center HD while gaining as little as 0.7 additional QALYs in a lifetime, assuming a 2-year wait time.[31] This resulted in an ΔC of $268 240/QALY for a diabetic patient, $213 430/QALY for a patient with CVD, or $384 213/QALY for a patient with both conditions, all far exceeded the $100K/QALY threshold. However, this high cost due to comorbidities may not persist with an abundant kidney supply and no wait time, as a 65-year-old with diabetes or CVD required only $85 177 or $92 986 to gain 1 QALY by DDRT, rendering DDRT a potentially preferred mode of treatment.

Ethnicity

Mutinga et al[33] suggested that while DDRT was superior to dialysis for Caucasian, African American, and Asian patients, it required an additional $4K/QALY than dialysis for patients belonging to other minority groups over a 20-year time horizon. Compared with Caucasians, these patients have comparable health outcomes, but their health system costs incurred during the first year leading to transplantation, year 1 after transplant, and year 2 after transplant are 13.7%, 9.8%, and 19.6% higher on average. However, since $4K/QALY is significantly smaller than $100K/QALY, DDRT is generally cost-effective regardless of patient ethnicity based on this study.

Patient-borne costs

An Iranian study[37] considered a patient perspective and included payments made by patients, including the costs of travel, accommodation, and salary losses due to work absence from DDRT or dialysis. In their analysis, DDRT saved an average of

TABLE 2.

Detailed cost-effectiveness results of each study that compares transplantation to dialysis

References	Cost-effectiveness drivers	Categories	Incremental cost (USD, 2018)	Incremental effect	ICER (USD, 2018)
Axelrod et al[11]	Donor risk	Standard donor	$177	2.04 QALYs	$87
		High-KDPI donor	$40204	1.17 QALYs	$34362
		PHS increased-risk donor	$15612	1.88 QALYs	$8304
Domínguez et al[41]	—	—	−$36132	2.98 QALYs	−$12125
Jassal et al[31]	Patient age, comorbidities (diabetes and CVD), and wait time	60-y-old, 2-y wait, healthy	$136339	1.17 QALYs	$116529
		60-y-old, 4-y wait, healthy	$169374	0.5 QALYs	$338748
		65-y-old, no wait, healthy	$57688	2.0 QALYs	$28844
		65-y-old, no wait, CVD	$161836	1.9 QALYs	$85177
		65-y-old, no wait, diabetic	$148778	1.6 QALYs	$92986
		65-y-old, no wait, CVD and diabetic	$221159	1.5 QALYs	$147439
		65-y-old, 2-y wait, healthy	$144232	1.1 QALYs	$131120
		65-y-old, 2-y wait, CVD	$149401	0.7 QALYs	$213430
		65-y-old, 2-y wait, diabetic	$187768	0.7 QALYs	$268240
		65-y-old, 2-y wait, CVD and diabetic	$76843	0.2 QALYs	$384213
		65-y-old, 4-y wait, healthy	$187263	0.5 QALYs	$374525
		70-y-old, 2-y wait, healthy	$165805	1.08 QALYs	$153523
		70-y-old, 4-y wait, healthy	$184794	0.42 QALYs	$439985
		75-y-old, 2-y wait, healthy	$177180	0.92 QALYs	$192587
		75-y-old, 4-y wait, healthy	$194720	0.33 QALYs	$590061
		80-y-old, 2-y wait, healthy	$200221	0.75 QALYs	$266961
		80-y-old, 4-y wait, healthy	$267255	0.25 QALYs	$1069018
		85-y-old, 2-y wait, healthy	$223590	0.5 QALYs	$447179
		85-y-old, 4-y wait, healthy	—	0 QALYs	$28215794
Kaminota[38]	Patient age	Ages 20–29	−$2731659	8.8 DALYs	−$310416
		Ages 30–39	−$2110009	4.6 DALYs	−$458698
		Ages 40–49	−$1506776	2.3 DALYs	−$655120
Mendeloff et al[32]	—	Best case	−$206003	6.93 QALYs	−$29726
		Central case	−$3086	4.4 QALYs	−$701
		Worst case	$198014	2.53 QALYs	$78266
Mutinga et al[32]	Patient race and matching algorithm (HLA-B)	Caucasians, with HLA-B matching	−$45550	3.9 QALYs	−$11679
		African Americans, with HLA-B matching	−$141284	2.8 QALYs	−$50458
		Asians, with HLA-B matching	−$310608	3.6 QALYs	−$86280
		Other races, with HLA-B matching	$20004	4.5 QALYs	$4445
		Caucasians, without HLA-B matching	−$44562	4.4 QALYs	−$10128
		African Americans, without HLA-B matching	−$138884	2.7 QALYs	−$51439
		Asians, without HLA-B matching	−$308974	3.6 QALYs	−$85826
		Other races, without HLA-B matching	$20294	3.4 QALYs	$5969
Ong et al[36]	Patient comorbidities (diabetes)	Adults with type-I diabetes	$69474	1.44 QALYs	$48246
Quinn et al[34]	Patient age and access to transplant	Ages <20, equal access	−$339663	1.9 QALYs	−$178770
		Ages 20–39, equal access	−$299892	1.4 QALYs	−$214208
		Ages 40–59, equal access	−$208327	1.0 QALYs	−$208327
		Ages 60+, equal access	−$160578	0.6 QALYs	−$267629
		Overall, equal access	−$233542	1.1 QALYs	−$212311
		Ages <20, no access for 60+ patients	−$387126	2.2 QALYs	−$175966
		Ages 20–39, no access for 60+ patients	−$342205	1.6 QALYs	−$213878
		Ages 40–59, no access for 60+ patients	−$238387	1.1 QALYs	−$216715
		Overall, no access for 60+ patients	−$239617	1.1 QALYs	−$217833
Roels et al[40]	Donor action	—	−$245250	2.42 QALYs	−$101343
Whiting et al[35]	Donor action	—	−$175604	1.99 QALYs	−$88243
YaghoubiFard et al[37]	Patient-borne cost	Payer's perspective (hospital)	−$111769	−1.4 DALYs	$79835
		Patient's perspective	−$106763	−1.4 DALYs	$76259

CVD, cardiovascular disease; DALY, disability-adjusted life year; ICER, incremental cost-effectiveness ratio; KDPI, Kidney Donor Profile Index; PHS, Public Health Service; QALY, quality-adjusted life year; USD, United States dollar.

$106763 for a patient at the expense of 1.4 DALYs over a lifetime. This translates into $76259 per DALY forgone for patients, rendering DDRT a less preferred mode of treatment relative to dialysis. However, we argue that findings from this single-center study are limited by their small sample (29 DDRT recipients and 32 HD recipients) and other flaws in methodology, including using lump sum estimates for DDRT and dialysis costs (detailed in **Discussion, SDC,** http://links.lww.com/TXD/A238).
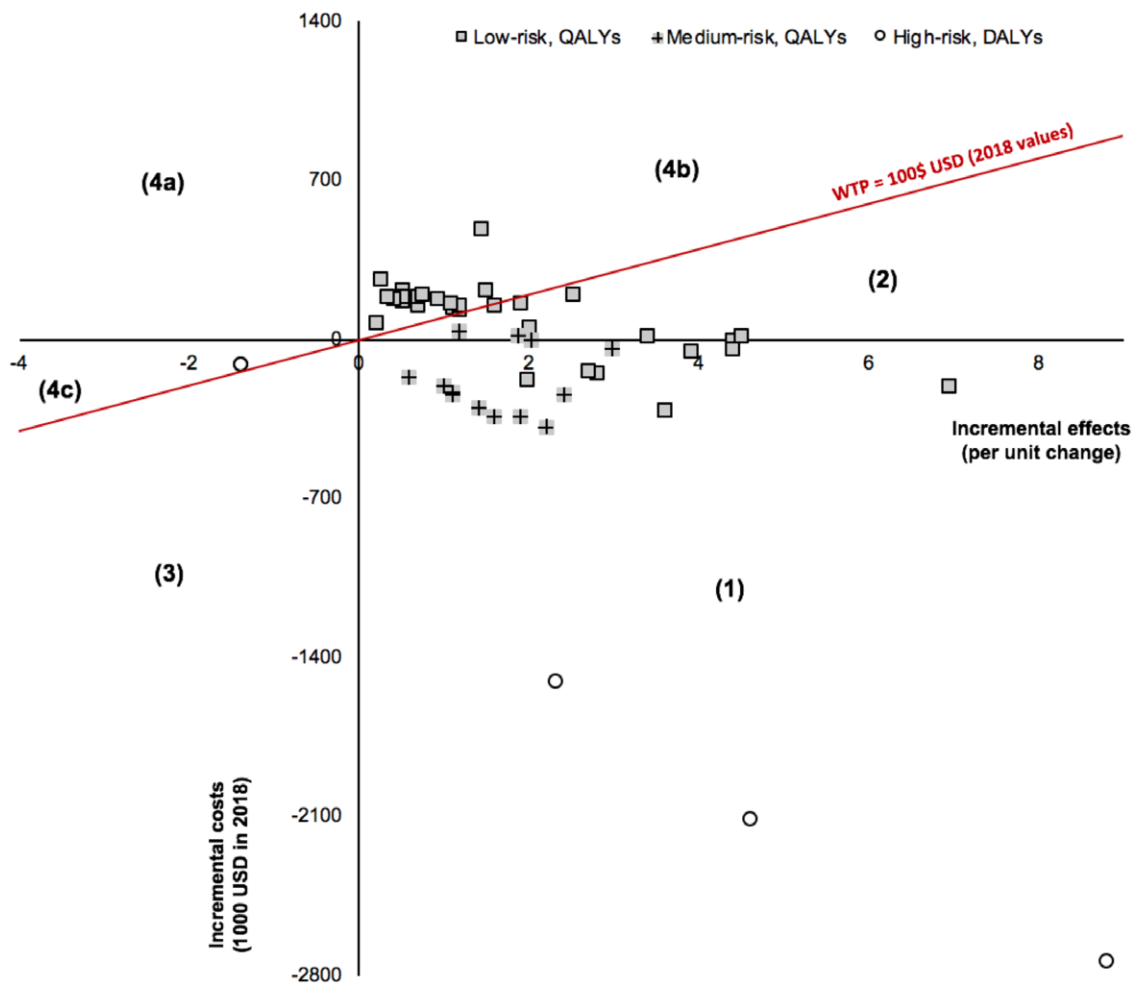
FIGURE 3. Summary of all incremental cost-effectiveness ratios (ICERs) in the cost-effectiveness plane. Squares and circles are used to denote studies that used quality-adjusted life years (QALYs) and disability-adjusted life years (DALYs) as the measure of effectiveness, respectively. Low-risk studies were represented by filled symbols, medium-risk studies by symbols with a cross inside, and high risk with hollow (white) symbols. We did not include the point estimate of ICER reported by Jassal et al[31] for healthy patients with age 85 years old and a 4-year wait time in the plot due to its substantial large value (ICER = $28 215 794/QALY or $28 216K/QALY). WTP, willingness-to-pay.

Donor-level Factors
Risk Factors

A recent study[11] suggested that DDRT, using 2 types of high-risk kidneys, led to cost-effective results compared with dialysis. The first type was determined by the US Public Health Services to carry significant risks of virally transmitted diseases such as hepatitis C. There is a small chance that recipients of these transplants will get infected and, consequently, require lifelong medication. The second type was characterized by a Kidney Donor Profile Index score >85%. These high-Kidney Donor Profile Index kidneys were deemed generally unsuitable for transplant, due to high chances of graft failure. The study findings suggested that DDRT using both types of high-risk kidneys was slightly more expensive than dialysis over 10 years but that DDRT was still cost-effective ($87/QALY and $34 362/QALY, respectively).

System-level Factors
Access to Transplant

Quinn et al[34] illustrated in their analysis that a kidney allocation strategy that banned all elderly patients, with ages >60 years old, from transplantation would not generate additional gains for younger people, or the system. In fact, restricting

transplant access only brought a marginal reduction in cost ($5818 per person) and minimal improvements in outcomes (0.1 LYs or 0.2 QALYs) over 25 years for prioritized patients with ages below 60 years old. Meanwhile, elderly patients who were disqualified from DDRT suffered loss of potential LYs and experienced escalation of healthcare costs, which cancelled out the slight benefits achieved by their younger counterparts.

Wait Time

Long wait times before DDRT, a common phenomenon among elderly patients, is a strong factor that reduces the cost-effectiveness of DDRT, according to one study.[31] In Canada, doubling the wait time from 2 to 4 years would triple the ΔC needed to gain 1 QALY for a 60-year-old (from $116 529/QALY to $338 748/QALY), quadruple ΔCs for an 80-year-old (from $266 961/QALY to $1 069 018/QALY), and sextuple ΔCs for an 85-year-old (from $447 179/QALY to $28 215 794/QALY).[31]

Matching Algorithm

Minority transplant candidates reported delayed access to DDRT, due to priorities granted to Caucasian patients who

are more likely to have HLA-B matching with Caucasian donors.[33] While eliminating HLA-B matching did not alter the superior cost-effectiveness of DDRT over dialysis for individual patients of all races, as a society, this saved $6.5 million at the expense of 649 QALYs of Caucasian patients (−$10034/ QALY), indicating the elimination of HLA-B matching to be not cost-effective.

Implementation of Donor Initiative Programs

Donor initiative programs were discussed in 2 studies,[35,40] both focused on Donor Action (DA), an international program that promotes collaboration between hospitals and critical care units to increase awareness of organ donation and effectiveness of organ retrieval. Investing in DA has the potential to amplify the economic gains of DDRT by increasing the number of DDRT performed. While DA requires a large lump sum for its initial establishment and consistent investments for sustainable results, the combination of DA and DDRT still dominates dialysis, as seen in Germany.[40] In Canada, investing up to $15 million in DA for yielding one more donor per million population would still be cost-saving to the healthcare system.[35]

DISCUSSION

We identified a very strong body of evidence from the literature that suggests that DDRT generally produces better health outcomes at a reduced cost compared with dialysis. Additionally, we showed that the complexity of transplant-enhancing interventions (eg, elimination of HLA-B matching to improve the access to transplant) was largely underestimated.

Three important observations were derived from the review that pointed to ESRD subpopulations that may not benefit from DDRT in a cost-effective way. First, older patient age is a strong factor that diminished the economic advantage of DDRT, where 60 years old appeared to be a meaningful benchmark. Second, the detrimental effect of older patient age may be accentuated by prolonged wait times exceeding 2 years. Third, comorbidity escalates the healthcare costs of patients >65 years old over their remaining lifetime but may not have any immediate impact on younger patients. These observations are congruent with early reviews[19,20,24] and have potentially important implications in countries with rapidly ageing ESRD population. There is an urgent need to plan alternative cost-effective modes of treatment to these high-risk patients to optimize their quality of life with a limited healthcare budget. Studies have shown that peritoneal dialysis may lead to comparative outcomes[42,43] with at-center HD to treat patients with advanced age and high comorbidity burden while generating cost-savings[44]; however, its long-term cost-effectiveness relative to DDRT for these patients remains unclear.

Findings of our review highlight the challenges faced by the nephrologist community and policy makers in developing new transplant practices and policies that strengthen the benefits of DDRT. While some efforts have proven successful, including the use of suboptimal kidneys and investments into donor initiative programs, others are demonstrated to be inefficient, which may seem to be counterintuitive at first glance. For example, a complete ban on DDRT for patients over 60 years old would not bring significant cost-savings to the health system nor additional benefits for younger people. Furthermore,

attempts to increase transplantation among minority patients by eliminating HLA-B matching may reduce the cost-effectiveness associated with transplantation to the society due to the increased life loss among Caucasian patients. These results underscore the need for cooperative efforts among stakeholders including kidney professionals, policy makers, and patient representatives to develop effective transplant-enhancing interventions within the highly intricate kidney allocation and transplantation system.

Our review also identified a few gaps in the current economic literature about DDRT and dialysis. First, some studies lacked a clear definition of the targeted population, which in our case, consisted of ESRD patients who are eligible for both dialysis and DDRT. Since the general, unlisted dialysis recipients are usually sicker and incur higher healthcare costs compared with those awaiting transplantation,[32] studies that did not make this distinction by using the general dialysis patients as a comparator to transplant recipients were at risk of producing results favoring transplantation. Second, a societal or patient's perspective is rarely taken by investigators, who thereby exclude consideration of indirect costs and the productivity losses. Third, average cost-effectiveness ratios for each type of treatment are still used by many studies as the sole endpoint without the computation of incremental ratios. As observed by health economists,[45] this can lead to erroneous conclusions that defeat the very purpose of conducting a cost-effectiveness analysis. To ensure the validity of this review, we manually calculated an ICER (or ICERs) for studies that did not report any. Forth, the standard practice of discounting both future costs and effects[45] was poorly implemented. A wide range of annual discount rates (3%–8%) was used by studies. Omission of discounting can lead to potential bias in the cost-effectiveness result especially since transplantation has immediate, high cost and is thus more sensitive to discounting.[46] Finally, several studies did not perform sufficient sensitivity analyses, including both 1-way (or multivariate) and probabilistic sensitivity analysis, to verify the robustness of their main results (see **Discussion, SDC,** http://links.lww.com/TXD/ A238), which poses serious threats to the validity of their conclusions.[1]

This review has several limitations. First, we focused on the point estimate for each ICER included in the reviewed studies and did not examine directly the uncertainty of these estimates. However, we did summarize parameters that were identified by the authors in their sensitivity analysis to influence the primary ICER findings in Table S7 (SDC, http:// links.lww.com/TXD/A238). Second, we did not conduct any subgroup analysis to compare studies that used the same measure of effectiveness. However, among the 6 studies that found DDRT did not dominate dialysis, only 1 used DALYs.[37] Hence, the small number of studies that did not use QALYs has limited our ability to perform any subgroup analysis. We did, however, present the 5 DALY-based ICERs in Figure 3 and distinguish them from other QALYs-based ICERs. Third, we did not perform any statistical analysis to investigate the impact of the heterogenous nature of the included studies, as one would do in a meta-analysis. For example, the included studies differed in their countries which may had different kidney allocation routines and dialysis initiation policies. However, we argue that our use of a universal WTP threshold of 100K USD is plausible after we have carefully inflated

and converted the original ICERs. This method has been used in previous reviews that examined a similar objective.[19] Furthermore, the included studies did not generally report estimates of internal variability of their results that would have allowed such analysis.

We demonstrated some key strengths in this review. First, similar systematic reviews of economic literature seldom go beyond summarizing ICERs to examine factors that influence the cost-effectiveness of interventions. We achieved this objective by extracting information outside the main body of the included studies (eg, sensitivity analysis). Second, we used a well-established appraisal metric[1] to examine the quality of the included studies, which revealed gaps in methodologies and reporting in the current literature.

In summary, this systematic review found evidence that renal transplantation from a deceased donor is a cost-effective treatment when compared with dialysis for adults with ESRD. The health and economic benefits associated with transplantation are less prominent for patients with older age, comorbidities, and long wait times, which warrants investigations into alternative treatment plans for these patients to meet their needs with a limited healthcare budget. More research is needed to guide the development of interventions that enhance transplant outcomes and optimize renal care.

REFERENCES

1. Drummond M, Sculpher M, Torrance G, et al. *Methods for the Economic Evaluation of Health Care Programmes*. 3rd ed. New York, NY: Oxford University Press; 2005.
2. Klarman HE, Francis JO, Rosenthal GD. Cost effectiveness analysis applied to the treatment of chronic renal disease. *Med Care*. 1968;6:48–54. Available at https://www.jstor.org/stable/3762651. Accessed January 14, 2019.
3. de Wit GA, Ramsteijn PG, de Charro FT. Economic evaluation of end stage renal disease treatment. *Health Policy*. 1998;44:215–232.
4. Karlberg I, Nyberg G. Cost-effectiveness studies of renal transplantation. *Int J Technol Assess Health Care*. 1995;11:611–622.
5. Laupacis A, Keown P, Pus N, et al. A study of the quality of life and cost-utility of renal transplantation. *Kidney Int*. 1996;50:235–242.
6. Douzdjian V, Ferrara D, Silvestri G. Treatment strategies for insulin-dependent diabetics with ESRD: a cost-effectiveness decision analysis model. *Am J Kidney Dis*. 1998;31:794–802.
7. Jarl J, Gerdtham U-G. Economic evaluations of organ transplantations - a systematic literature review. *Nord J Health Econ*. 2012;1:61–82. Available at https://www.journals.uio.no/index.php/NJHE/article/view/168. Accessed July 2, 2019.
8. Whiting JF, Woodward RS, Zavala EY, et al. Economic cost of expanded criteria donors in cadaveric renal transplantation: analysis of Medicare payments. *Transplantation*. 2000;70:755–760.
9. Young A, Dixon SN, Knoll GA, et al. The Canadian experience using the expanded criteria donor classification for allocating deceased donor kidneys for transplantation. *Can J Kidney Health Dis*. 2016;3:15.
10. Ojo AO. Expanded criteria donors: process and outcomes. *Semin Dial*. 2005;18:463–468.
11. Axelrod DA, Schnitzler MA, Xiao H, et al. An economic assessment of contemporary kidney transplant practice. *Am J Transplant*. 2018;18:1168–1176.
12. González-Martínez F, Curi L, Orihuela S, et al. Cardiovascular disease and/or elderly donors in renal transplantation: the outcome of grafts and patients. *Transplant Proc*. 2004;36:1687–1688.
13. Aubert O, Kamar N, Vernerey D, et al. Long term outcomes of transplantation using kidneys from expanded criteria donors: prospective, population based cohort study. *BMJ*. 2015;351:h3557.
14. Verran DJ, deLeon C, Chui AK, et al. Factors in older cadaveric organ donors impacting on renal allograft outcome. *Clin Transplant*. 2001;15:1–5.
15. Kute VB, Suresh GK, Patel HV, et al. Expanding the donor pool for kidney transplantation in India. *Indian J Transplant*. 2017; 11:111–116.

16. Howard K, Salkeld G, White S, et al. The cost-effectiveness of increasing kidney transplantation and home-based dialysis. *Nephrology (Carlton)*. 2009;14:123–132.
17. Haller M, Gutjahr G, Kramar R, et al. Cost-effectiveness analysis of renal replacement therapy in Austria. *Nephrol Dial Transplant*. 2011;26:2988–2995.
18. Vanholder R, Annemans L, Brown E, et al. Reducing the costs of chronic kidney disease while delivering quality health care: a call to action. *Nat Rev Nephrol*. 2017;13:393–409.
19. Menzin J, Lines LM, Weiner DE, et al. A review of the costs and cost effectiveness of interventions in chronic kidney disease: implications for policy. *Pharmacoeconomics*. 2011;29:839–861.
20. Knoll GA. Is kidney transplantation for everyone? The example of the older dialysis patient. *J Am Soc Nephrol*. 2009;4:2040–2044.
21. Moher D, Liberati A, Tetzlaff J, et al; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Plos Med*. 2009;6:e1000097.
22. Canadian Institute for Health Information. Treatment of End-Stage Organ Failure in Canada, Canadian Organ Replacement Register, 2009 to 2018: End-Stage Kidney Disease and Kidney Transplants – Data Tables. 2019. Available at: https://www.cihi.ca/en/organ-replacement-in-canada-corr-annual-statistics-2019. Accessed October 20, 2019.
23. Zaltzman J. The new kidney allocation in Ontario. In: *Paper Presented at: St. Michael's Hospital*. Ontario, Canada; 2014. Available at http://www.stmichaelshospital.com/pdf/programs/renal-transplant/kidney-allocation-system-in-Ontario.pdf. Accessed May 30, 2019.
24. Machnicki G, Serrai L, Schnitzler MA. Economics of transplantation: a review of the literature. *Transplant Rev*. 2006;20:61–75.
25. Cameron D, Ubels J, Norström F. On what basis are medical cost-effectiveness thresholds set? Clashing opinions and an absence of data: a systematic review. *Glob Health Action*. 2018;11:1447828.
26. Prieto L, Sacristán JA. Problems and solutions in calculating quality-adjusted life years (QALYs). *Health Qual Life Outcomes*. 2003;1:80.
27. Anand S, Hanson K. Disability-adjusted life years: a critical review. *J Health Econ*. 1997;16:685–702.
28. Chao TE, Sharma K, Mandigo M, et al. Cost-effectiveness of surgery and its policy implications for global health: a systematic review and analysis. *Lancet Glob Health*. 2014;2:e334–e345.
29. Chung R, Howard K, Craig JC, et al. Economic evaluations in kidney transplantation: frequency, characteristics, and quality-a systematic review. *Transplantation*. 2014;97:1027–1033.
30. Webster I. Official Data Foundation: Inflation Calculator. Alioth LLC Website. 2019. Available at http://www.in2013dollars.com. Accessed January 22, 2019.
31. Jassal SV, Krahn MD, Naglie G, et al. Kidney transplantation in the elderly: a decision analysis. *J Am Soc Nephrol*. 2003;14:187–196.
32. Mendeloff J, Ko K, Roberts MS, et al. Procuring organ donors as a health investment: how much should we be willing to spend? *Transplantation*. 2004;78:1704–1710.
33. Mutinga N, Brennan DC, Schnitzler MA. Consequences of eliminating HLA-B in deceased donor kidney allocation to increase minority transplantation. *Am J Transplant*. 2005;5:1090–1098.
34. Quinn RR, Manns BJ, McLaughlin KM. Restricting cadaveric kidney transplantation based on age: the impact on efficiency and equity. *Transplant Proc*. 2007;39:1362–1367.
35. Whiting JF, Kiberd B, Kalo Z, et al. Cost-effectiveness of organ donation: evaluating investment into donor action and other donor initiatives. *Am J Transplant*. 2004;4:569–573.
36. Ong SC, Lee VTW, Lim JFY, et al. Is simultaneous pancreas kidney transplant the most cost-effective strategy for type 1 diabetes patients with renal failure? *Proc Singap Healthc*. 2016;25:127–134.
37. YaghoubiFard S, Goudarzi R, Etminan A, et al. Cost-effectiveness analysis of dialysis and kidney transplant in patients with renal impairment using disability adjusted life years in Iran. *Med J Islam Repub Iran*. 2016;30:390.
38. Kaminota M. Cost-effectiveness analysis of dialysis and kidney transplants in Japan. *Keio J Med*. 2001;50:100–108.
39. Kaló Z, Járay J, Nagy J. Economic evaluation of kidney transplantation versus hemodialysis in patients with end-stage renal disease in Hungary. *Prog Transplant*. 2001;11:188–193.
40. Roels L, Kalo Z, Boesebeck D, et al. Cost-benefit approach in evaluating investment into donor action: the German case. *Transpl Int*. 2003;16:321–326.
41. Domínguez J, Harrison R, Atal R. Cost-benefit estimation of cadaveric kidney transplantation: the case of a developing country. *Transplant Proc*. 2011;43:2300–2304.

42. Lai S, Amabile MI, Bargagli MB, et al; Study Group on Geriatric Nephrology of the Italian Society of Nephrology (SIN). Peritoneal dialysis in older adults: evaluation of clinical, nutritional, metabolic outcomes, and quality of life. *Medicine (Baltimore)*. 2018;97:e11953.

43. Kim H, An JN, Kim DK, et al. Elderly peritoneal dialysis compared with elderly hemodialysis patients and younger peritoneal dialysis patients: competing risk analysis of a Korean prospective cohort study. *PLoS One*. 2015;10:e0131393.

44. Chang YT, Hwang JS, Hung SY, et al. Cost-effectiveness of hemodialysis and peritoneal dialysis: a national cohort study with 14 years follow-up and matched for comorbidities and propensity score. *Sci Rep.* 2016;6:30266.

45. Cohen DJ, Reynolds MR. Interpreting the results of cost-effectiveness studies. *J Am Coll Cardiol*. 2008;52:2119–2126.

46. Katz DA, Welch HG. Discounting in cost-effectiveness analysis of healthcare programmes. *Pharmacoeconomics*. 1993;3:276–285.