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In Search of a Better Outcome: Opting Into the Live Donor Paired Kidney Exchange Program

Amanda J. Vinson[1], Bryce A. Kiberd[1], and Karthik K. Tennankore[1]

Abstract

Background: Live donor (LD) kidney transplantation is the best option for patients with end-stage kidney disease (ESKD). However, this may not be the best option if a patient's donor is older and considerably smaller in weight. Patient (A) with a less than ideal donor (Donor A) might enter into a live donor paired exchange (LDPE) program with the hopes of swapping for a better-quality organ. A second patient (B) who is in the LDPE may or may not benefit from this exchange with Donor A.
Methods: This medical decision analysis examines the conditions that favor Patient A entering into the LDPE compared to directly accepting a kidney from their intended donor, as well as the circumstances where Patient B also benefits by accepting a lower-quality organ.
Results: Under select circumstances, a paired exchange could benefit both Patients A and B. For example, a 30-year-old Patient A with a lower-quality donor might gain $_{1.20}1.52_{1.84}$ quality adjusted life years (QALYs) by entering into a LDPE for a better-quality kidney, whereas a 60-year-old Patient B might gain $_{0.93}1.03_{1.13}$ QALYs by accepting Donor A's kidney rather than waiting longer in the LDPE. The net benefit (or loss) of entering the LDPE differs by recipient age, donor organ quality, likelihood of Patient B being transplanted in LDPE, and likelihood of Patient A finding an ideal donor in the LDPE.
Conclusion: This study shows there are ways to increase live donor utilization and effectiveness that require further research and potentially changes to the LDPE process.

Abrégé

Contexte: La transplantation d'un rein provenant d'un donneur vivant (DV) est la meilleure option pour les patients atteints d'insuffisance rénale terminale (IRT). Il est toutefois possible que ce ne soit pas la meilleure option lorsque le donneur est plus âgé et de beaucoup plus faible poids que le patient. Un patient (A) jumelé à un donneur moins qu'idéal (donneur A) pourrait être inscrit à un programme de dons croisés avec donneurs vivants (DCDV) dans l'espoir d'obtenir un organe plus approprié. Un deuxième patient (B), déjà inscrit au programme de DCDV, pourrait quant à lui bénéficier ou non de cet échange avec le donneur A.
Méthodologie: Cette analyse des décisions médicales examine les conditions favorisant l'entrée du patient A dans le programme de DCDV comparativement à l'acceptation directe d'un rein du donneur prévu. On souhaitait également examiner les circonstances où un patient B bénéficie lui aussi de l'acceptation d'un organe de moindre qualité.
Résultats: Dans certaines circonstances, un don croisé pourrait bénéficier aux deux patients. Par exemple, un patient de 30 ans (A) jumelé à un donneur de moins bonne qualité pourrait gagner $_{1,20}1,52_{1,84}$ années de vie pondérée par la qualité (AVPQ) en entrant dans un programme de DCDV pour obtenir un rein de meilleure qualité, tandis qu'un patient de 60 ans (B) pourrait gagner $_{0,\ 93}1,03_{1,13}$ AVPQ en acceptant le rein du donneur A plutôt que d'attendre plus longtemps dans le programme. Le bénéfice net (perte) d'une participation à un programme de DCDV diffère selon l'âge du receveur, la qualité de l'organe du donneur, la probabilité que le patient B soit transplanté dans le programme et la probabilité que le patient A trouve un donneur idéal dans le programme.
Conclusion: Cette étude montre qu'il existe des moyens d'accroître l'utilisation et l'efficacité des donneurs vivants. Ces moyens nécessitent cependant des recherches plus poussées et de possibles changements dans le processus de dons croisés avec donneurs vivants.

Keywords

kidney transplantation, living kidney donation, kidney paired exchange, allocation, medical decision analysis

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Introduction

Kidney transplantation is the modality of choice for patients with end-stage kidney disease (ESKD). Transplantation lengthens recipient life, improves well-being, and is less costly compared to dialysis.[1,2] Maximizing the numbers of organs available for transplantation and finding new ways to lengthen kidney transplant allograft survival are important to patients and the health care system.

The introduction of live donor paired exchange (LDPE) programs around the world is an example of this innovation.[3] The LDPE has allowed greater use of live donors (LD) that were otherwise of good quality but unsuitable for their intended recipient due to human leukocyte antigen (HLA) antibodies or blood group incompatibility.

Unfortunately, there are many patients in LDPE networks that have a low probability of transplantation due to anti-HLA antibodies. Many may wait a number of years, and some may never be transplanted. On the other hand, there are some ESKD patients with a compatible LD that may have characteristics that are less than ideal to maximize patient and graft survival after transplantation in that particular recipient. Some potential recipients and their providers may be reluctant to consider lower quality LD kidneys (especially in the situation of younger recipients). Measures of organ quality have been developed and are an integral part of the current deceased donor Kidney Allocation System.[4] For deceased donors, a quality score can be calculated (KDPI, Kidney Donor Profile Index, or the related KDRI, Kidney Donor Risk Index) based on a number of characteristics.[5] Most advocate using kidneys from high KDPI (poorer quality) donors for recipients who are older or have limited life expectancy, and conversely using better quality organs in younger recipients to maximize net years of graft survival achieved at a societal level.[6] More recently, a calculator has been published for LD (LKDPI, Live Kidney Donor Profile Index).[7] This quality measure for live donor organs is currently not used in LDPE programs.

Although transplant with an organ from a LD is felt to provide superior outcomes to deceased donor transplantation, it is possible that there may be some scenarios where transplant with a patient's intended LD may not yield the best possible outcome. It seems intuitive for example, that there may be situations when a young, blood group A, male ESKD recipient has a blood group O donor that unfortunately may be a much older and smaller female. It is likely that this would be a kidney that would not last as long compared to a better-quality live donor organ or maybe even a high-quality deceased donor (DD) kidney transplant. There would certainly be potential recipients in the LDPE programs that are blood group O, do not have a blood group O donor (but may have a good quality blood group A donor), who will likely be waiting a long time for a suitable match. It might be better for those in a LDPE with a low probability of transplantation to accept a poorer quality organ sooner compared to waiting for an ideal LD in the LDPE, or conversely for a DD organ. Additionally, if the hard-to-match patient in a LDPE program eventually receives a deceased donor organ, a live donor organ has been permanently lost from the system.

This medical decision analysis intends to examine who (Patient A) would most benefit from entering a LDPE program despite having a suitable compatible LD (Donor A). In the same way, the analysis will examine what potential recipient (Patient B) already in a LDPE program might also benefit from such an exchange. Our hypothesis is that depending on the situation, some patients might do better to enter into the LDPE and others would do best to use their intended donor. We suspect that some of the influential variables would be organ quality, recipient life expectancy, the probability of transplantation within the LDPE and the probability of receiving a DD kidney.

Methods

We assume Patients' A and B are both eligible for immediate transplantation, both have eligible live donors (Donors A and B, respectively), both are able and willing to participate in a LDPE network and both are presently on dialysis.

Patient A has a compatible donor and surgery is available. Patients A's Donor (Donor A) has a high relative risk of graft loss based on the LKDPI criteria (as an example, Donor A could be an older female [mother] donor to a younger male recipient, relatively smaller body weight, 1 haplotype match).[7]

Patient B is available for immediate transplantation and is already in the LDPE. Donor B is ABO/HLA incompatible (does not want or not suitable for desensitization). Patient B has one or more donors. In the baseline case we assumed that Patient B would have a low probability of being transplanted within the first year in the LDPE program.

In this medical decision analysis, there are 3 options for Patient A. Option 1: Patient A is transplanted with their intended Donor A organ. Option 2: Patient A enters into LDPE and is matched to receive an ideal LD kidney. Option 3: Patient A does not accept their donor, does not enter into the LDPE, and is wait listed for a DD kidney.

[1]Department of Medicine, Dalhousie University, Halifax, NS, Canada

Corresponding Author:
Amanda J. Vinson, Department of Medicine, Dalhousie University, Room 5081, 5th Floor Dickson Building, Victoria General Hospital, 5820 University Ave, Halifax, NS, Canada B3H 1V8.
Email: Amanda.vinson@nshealth.ca

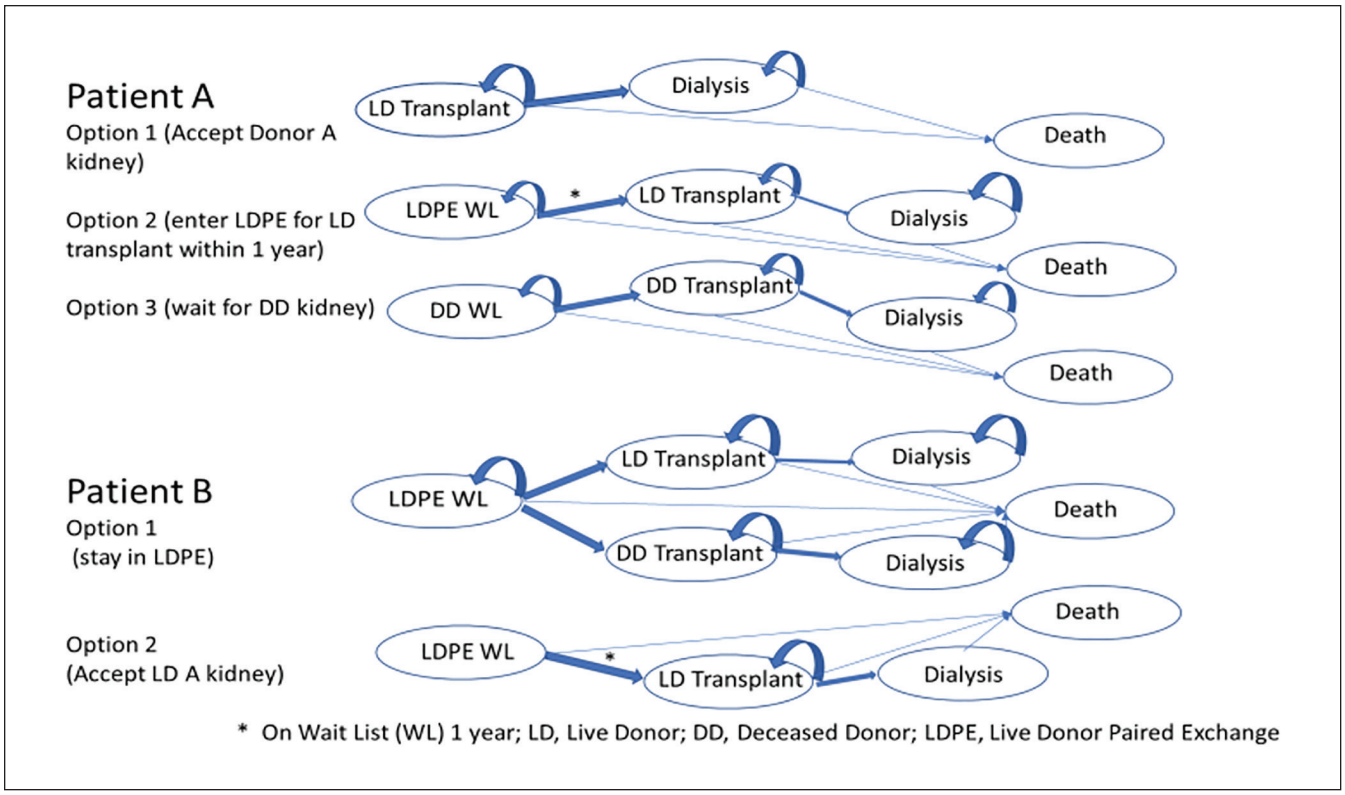

Figure 1. Decision tree.
Note. LD = live donor; LDPE = live donor paired exchange; WL = wait list.

For Patient B there are 2 options. Option 1: Patient B remains in the LDPE until a suitable LDPE kidney is found or eventually accepts a DD organ if available. Option 2: Patient B accepts Donor A's kidney (or similar kidney from a chain) of lower quality than desired, but is transplanted within the year.

For the primary analysis, the model projects the expected remaining quality adjusted life years (QALYs) for each option and for each patient. The difference between the options is then calculated. The option providing the most QALYs is the preferred option. The model also estimates the expected remaining life years (LYs) for each patient.

Assumptions for the base case: Patients examined were adults aged 20-70 years. The analysis horizon is projected to 40 years at a time when most kidneys would have failed. The utility health state scaling factors assigned were dialysis = 0.8, functioning transplant = 1.0, and death = 0, based on previous health outcome studies.[8] Age-related annual mortality rates per 1000 patient years for the health states of waitlist, functioning transplant, and return to dialysis were taken from the United States Renal Data System, Supplemental Table 1.[9] Annual rates of LD and DD graft loss (return to dialysis or receipt of another transplant) were derived from 5-year graft loss probabilities, Supplemental Table 2.[9] Wait list mortality rates took into account dialysis vintage.[9] The decision tree is shown in Figure 1.

Since the quality of Donor A's kidney will vary, we examined each of 4 categories of LKDPI (<0, 0-20, 20-40, >40) for this organ. We also examined different times to transplantation in the LDPE program for Patient B on the wait list. A baseline transplant rate in the LDPE for Patient B (Option 1) was 25 transplants per 100 patient-wait years with a range of 10-70 per 100 patient-wait years.[10] The deceased donor rate was set at 15 transplants per 100 patient-wait years (with a range of 10-40 patient-wait years to account for different Donor Service Areas).[10] In additional sensitivity analyses we examined the impact of sex (female/male) and diabetes mellitus status (DM) on outcomes.

TreeAge Pro Healthcare Version 2019 R2.1 (Tree Age Software, LLC, Williamstown, MA) was used for this medical decision analysis. Uncertainty in the model was examined using 1-, 2-, and 3-way sensitivity analyses for (age, LKDPI, KDPI and transplant rates [within LDPE and for a DD]). Since the quality of Donor A and Donor B's kidney will vary within each of the LKDPI categories and the quality of the DD kidney will vary for KDPI, a distribution of values for each of these parameters was assessed to be consistent with observed graft survival/failure rates.[7,11] Uncertainty in the net benefit was also examined by using a Monte Carlo simulation (probabilistic sampling of 100 trials) to calculate 95% confidence intervals for the differences between options. Confidence intervals are presented as

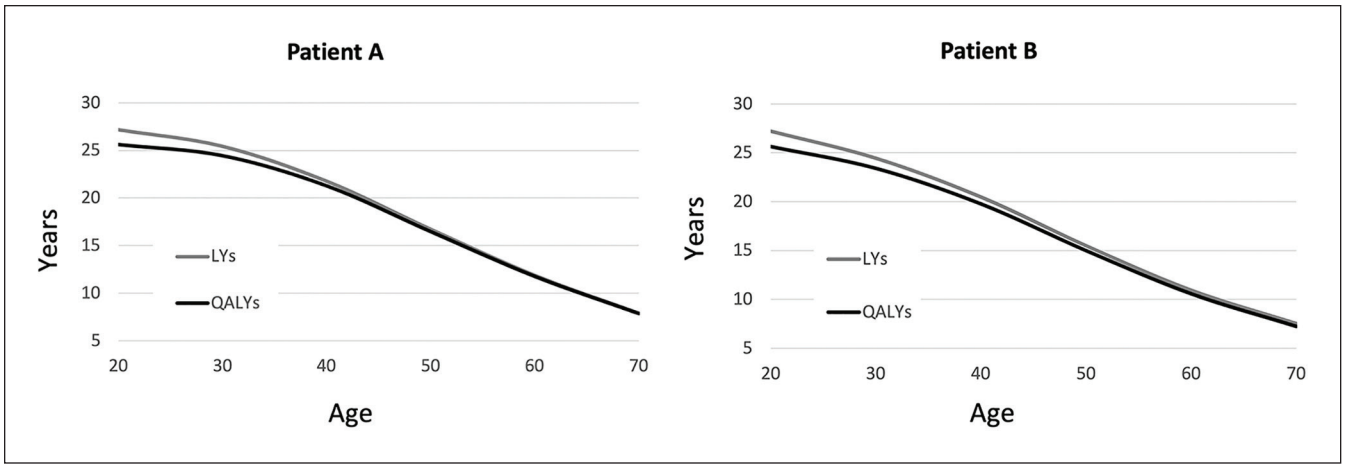

Figure 2. Projected outcomes (QALYs and LYs) for (A) Patient A and (B) Patient B, under Option 1.
Note. QALYs = quality adjusted life years; LYs = life years.

recommended by Lois and Zeger.[12] The study was submitted to our research ethics board, who felt a formal review was not required since the study relied exclusively on anonymous information.

Results

Patient A

Figure 2A shows the projected outcomes (QALYs and LYs) for Patient A under Option 1 (transplanted with intended Donor A), Supplemental Table 3. Assuming Patient A was to be transplanted with a LKDPI kidney 20-40, a 20-year-old recipient would derive $_{25.16}$ $25.62_{27.08}$ QALYs ($_{27.73}27.18$ $_{27.63}$ LYs) and a 60-year-old $_{11.85}12.25_{12.65}$ QALYs ($_{11.45}11.91_{12.37}$ LYs). The net benefit (QALYs) of Patient A entering into the LDPE and being transplanted with a LD (Option 2) compared with being transplanted with their intended LD (Option 1) is shown in Figure 3. The net benefit can be large for young recipients trading a lower-quality LD organ (Donor A, LKPDI 20-40 or >40) for a better-quality organ (LKPDI <0 or 0-20). For example, a 30-year-old Patient A with a lower-quality Donor A kidney (LKDPI 20-40) might gain $_{1.20}1.52_{1.84}$ QALYs by entering into a LDPE for a better-quality kidney (LKDPI <0). The benefits of entering into the LDPE become much smaller in patients over the age of 50. The shaded area in Figure 3 is approximately (given the uncertainties in the model) the 95% confidence interval for patient survival. If a patient enters into the LDPE and receives a similar or lower quality organ, then the net benefit is negative. Figure 4 shows the results of Option 3 for Patient A (wait for a DD kidney). For Patient A aged ≥40, there is no benefit to waiting for a better quality DD if a LD is available (data not shown). However, younger recipients (aged <30 years) might benefit from waiting for a DD transplant if their LD (Donor A) quality is particularly low (LKDPI >40), their likelihood of transplant is relatively high and

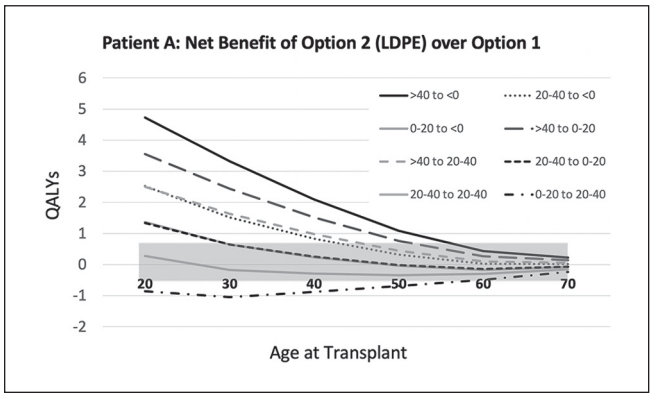

Figure 3. The net benefit to Patient A with Option 2 (transplanted with a living donor through the live donor paired exchange) versus Option 1 (transplanted with their intended living donor).
Note. Legend shows KDPI for Donor A versus Donor B. LDPE = Live Donor Paired Exchange; QALYs = quality adjusted life years; KDPI = Kidney Donor Profile Index.

especially if their DD organ quality is excellent (KDPI of <20% versus >35%).

In further sensitivity analyses, we examined sex and diabetes mellitus status in a theoretical Patient A receiving an ideal (LKDPI <0) transplant in the LDPE compared to accepting their live Donor A (KDPI 20-40), Supplemental Table 4. In the overall analysis, a 40-year-old would gain $_{0.59}0.84_{1.09}$ QALYs. A 40-year-old female Patient A was projected to gain slightly more ($_{0.65}0.90_{1.15}$) QALYs than a 40-year-old male ($_{0.51}0.76_{1.01}$ QALYs) or a patient with diabetes mellitus ($_{0.38}0.59_{0.80}$) QALYs.

Patient B

Figure 2B shows the projected outcomes (QALYs and LYs) for Patient B with Option 1 (wait in LDPE for an LD with the

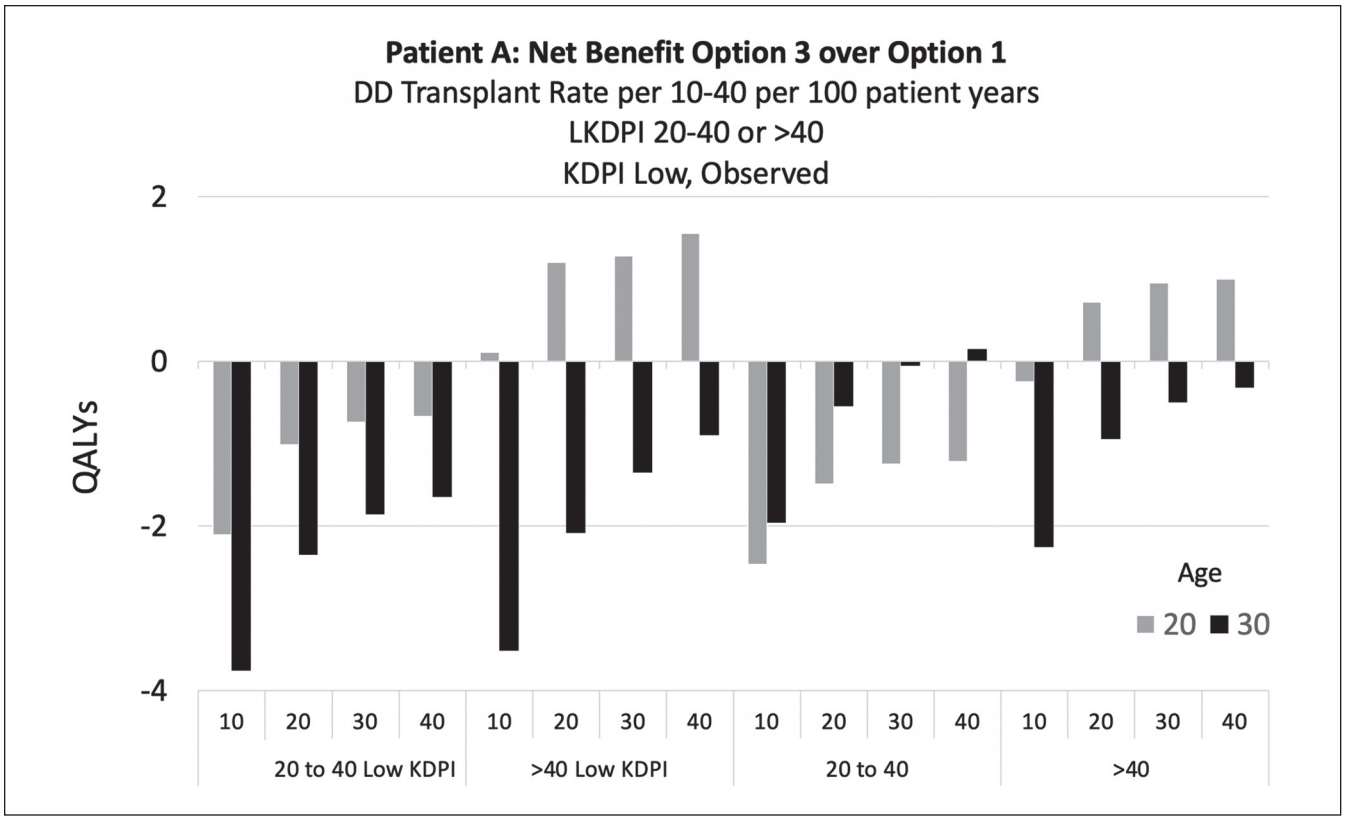

Figure 4. Projected outcomes (QALYs) for Patient A under Option 3 (wait for a DD kidney).
Note. Legend shows Patient A age (years). QALYs = quality adjusted life years; DD = deceased donor.

possibility of a DD). If Patient B stays in the LDPE with a LD transplant rate of 25 transplants per 100 patient-wait years and a DD rate of 15 transplants per 100 patient-wait years, the model predicts a 20-year-old recipient would derive $_{25.46}25.92_{26.32}$ QALYs ($_{27.33}27.73_{28.13}$ LYs) and a 60-year-old would derive $_{11.81}12.25_{12.69}$ QALYs ($_{10.51}11.02_{11.53}$ LYs). As with Patient A, Patient B outcomes will vary with the quality of organ received (data not shown but effectively Figure 3 with an inverted y-axis). However, there are other variables (likelihood of receiving a LD, possibility of a DD, and quality of the DD organ) that make predicting outcomes for Patient B more challenging. The more direct concern is who will benefit the most from a lower-quality LD option. Figures 5A-C show the net benefit of an older Patient B in the LDPE, receiving a lower-quality LD (A: LKDPI 20-40 as opposed to a LKDPI of 0-20, B: LKDPI >40 as opposed to a LKDPI of 20-40, C: LKDPI 20-40 as opposed to a LKDPI of <0), by age and LD transplant rate. The lower the likelihood of receiving a LD transplant, the better the prospects of receiving net benefit from a lower quality organ. The likelihood of benefit favors patients aged >60. A 60-year-old Patient B might gain $_{0.93}1.03_{1.13}$ QALYS for Donor A's kidney (LKDPI 20-40) rather than wait longer in the LDPE (LD transplant rate 10 transplants per 100 patient-wait years) (see Figure 5C) for an ideal kidney (LKDPI <0). This included the probability that Patient B could also be transplanted with a DD if the option presented itself. The baseline rate was 15 per 100 patient-wait years. If the DD transplant rate was higher at 30 per 100 patient-wait years, the net benefit for a Patient B >60 was only about 0.1 QALYs higher.

Discussion

As hypothesized, there are situations where a patient who has an eligible and compatible live donor (Patient A), appropriately forgoes this transplant option and enters into a LDPE program to receive a better-quality organ. Although there are many factors that impact this decision, the best candidates for this option are younger recipients (aged <40) that have donors with a projected risk of graft loss that is >1.6 fold higher (LKDPI >20) than ideal as calculated by the LKDPI. Others may benefit but that net benefit is likely to be a <0.5 QALY advantage, which is within the 95% confidence interval for survival across the age groups studied. This strategy has reportedly been used at selected centers, but is not currently widespread.[13]

There is another option for Patient A who has a less optimal LD, which is to forgo a LD option and take their chance on receiving a DD transplant. This works for younger patients, who have a particularly lower-quality LD organ and

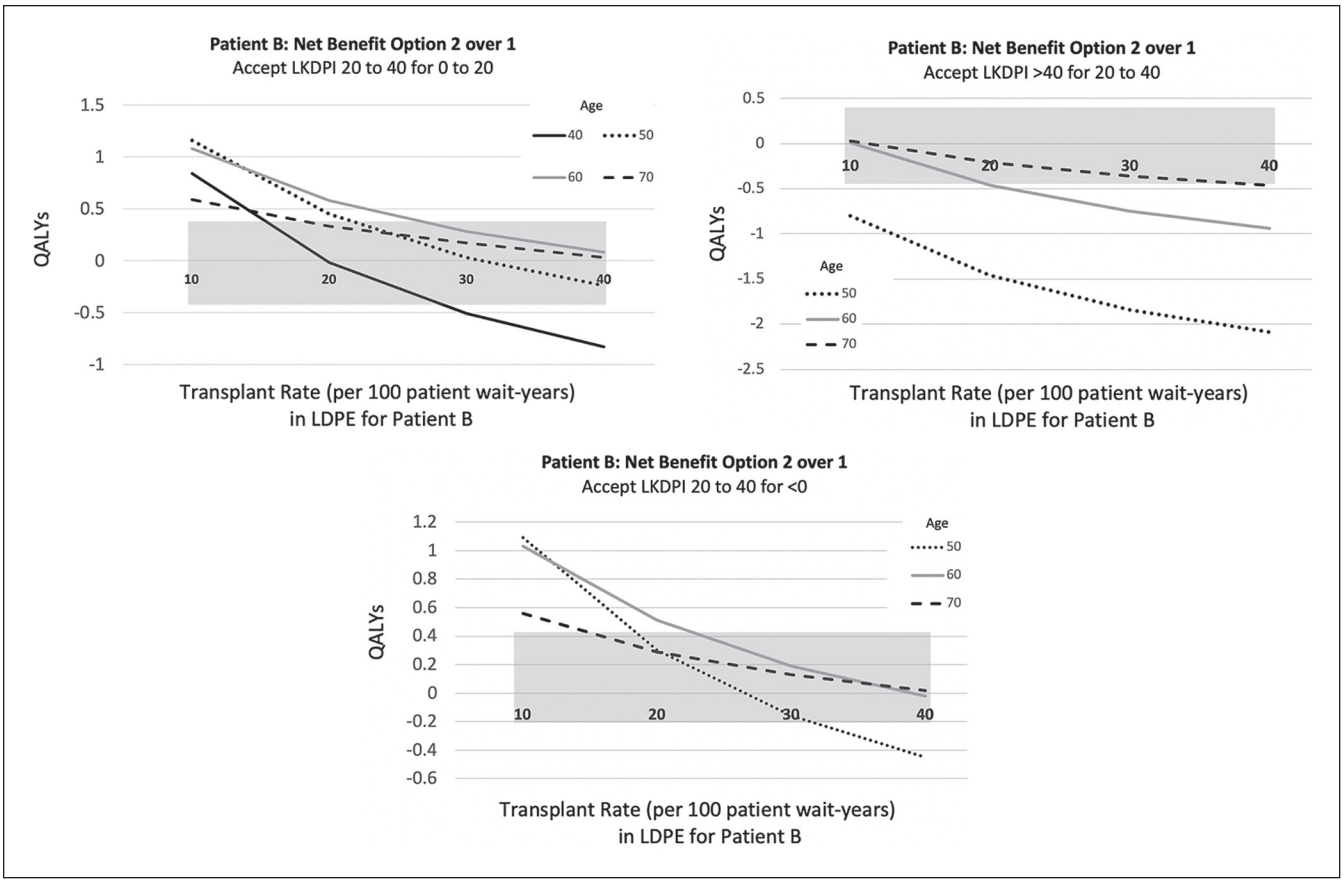

Figure 5. Net benefit of an older Patient B in the LDPE, receiving a lower-quality LD (A) LKDPI 20-40 as opposed to a LKDPI of 0-20, (B), LKDPI >40 as opposed to a LKDPI of 20-40, and (C), LKDPI 20-40 as opposed to a LKDPI of <0), by age and LD transplant rate.
Note. LDPE = Live Donor Paired Exchange; LD = live donor; QALYs = quality adjusted life years; LKDPI = Live Kidney Donor Profile Index.

can be transplanted within a reasonable time frame with a good quality DD kidney. However, this option results in a lost LD and utilizes a DD organ that could be used by someone who does not have a LD option, which is not optimal from a societal perspective.

This analysis also demonstrates the added benefit of helping someone (Patient B) in the LDPE registry who is not able to be guaranteed an ideal donor in exchange and is who might not otherwise be transplanted as quickly and is therefore is willing to accept a lower quality LD kidney. The study shows that this is a far more complicated estimate especially if Patient B is also open to receiving a DD kidney transplant (of uncertain quality). In general, the best LDPE candidates to accept a lower quality organ are Patient Bs that are aged >60 and have an otherwise low expected rate of transplantation within the LDPE program.

For the proposed strategy to work, LDPE programs might require several modifications to their governance/algorithms. Clinicians should be allowed to view the registry without compromising accepted privacy restrictions. Ideally the potential candidate (Patient A) should be able to input both their own and their donor's information into the LDPE registry to see if a suitable (ABO compatible, negative virtual cross match) donor-recipient pair is presently available before committing to the registry. Some registries may already allow healthcare providers the ability to see what donors are available before committing their potential recipient to the LDPE. However enough specific donor data would need to be available to make an informed decision. In the United States, there are several LDPE programs.[14] The likelihood of transplantation will differ by the number of pairs in the program, ABO status of recipient and donor, and PRA of the recipient.[10] Being able to access multiple registries simultaneously would be an advantage. Unlike the United States, however, most smaller countries including Canada have only one national registry.

The LDPE registries would need to utilize a robust validated measure of live donor kidney quality. This information would be vital to both Patient A and B. There is no benefit to Patient A if an otherwise suitable LDPE donor organ is the same or lower quality than their present option. Likewise, Patient B may not benefit from a poor-quality organ. The present LKDPI calculator uses donor age, body mass index, black race, smoking history, donor-recipient sex, and HLA mismatches.[5] The LKDPI calculator does not generate a relative risk of graft loss independent of death and this needs to

be done before this type of medical decision analysis is at the point to better inform clinicians.[5] For our use, we estimated the increase in relative risk of death censored graft loss from published data assuming death rates were proportionate across the range of all cause graft failure risks. Moreover, the concordance statistic for this index is relatively low at 0.59.[7] There are at least 2 other studies that have validated the LKDPI.[15,16] They demonstrate reductions in graft survival with higher LKDPI values in LD recipients, but with some overlap. Only one study examined death censored graft survival.[15] The sample sizes of these studies were also relatively small. They also found lower c-statistics (0.55). Continuously modifying the LKDPI to improve discrimination should be a research priority before it is accepted into routine practice.

The LDPE algorithms could incorporate measures of organ quality once a robust calculator has been developed. Currently, registries prefer that potential recipients have limited restrictions on organ acceptance in order to maximize transplant rates. This may not always be best for some members in the LDPE and particularly for the situations discussed in this analysis such as young recipients.

The LDPE programs might need to consider these potential entrants as non-directed donors that must be included in the next available iteration. Current LDPE allocation algorithms are already complex. Several iterations may be required and chains may unexpectantly break, delaying transplantation. It would be important to make the process efficient for this to benefit both parties. Given inherent friction and complexities, it still might be an additional 3-6 months before a transplant could take place. Avoiding unproductive delays will maximize benefits to those involved. Nonetheless this does not preclude Patient A's (Donor A's) participation in long chains. It is assumed that patients, recipients and donors, will be given adequate information to give informed consent for any and all decisions.

In addition to benefiting those in the LDPE directly, strategies to improve transplantability and live donor graft survival through the LDPE will also benefit society in general. There are economic benefits if Patient B is transplanted and comes off dialysis sooner, and the improved graft survival if Patient A receives a better quality organ will lead to less strain on the DD wait list when this first graft fails and Patient A returns to the wait list for re-transplant. Finally, forging interaction with the current DD kidney allocation system might provide additional benefit. For example, if a young recipient has a relatively low-quality LD donor prospect, there might be the option of donating to the DD wait list, with the proviso that this recipient would receive a reasonable quality organ from the DD pool within a specified time. A high LKDPI kidney could have the same projected benefit as a DD organ with an acceptable KDPI.[7] Currently, LD donating to the DD wait list is being used in the final step for non-directed donors but could be expanded for this proposed circumstance. Another concern for DD allocation is LDPE size. Relatively small registries will find fewer LD exchanges within the registry meaning that many may receive DD organs before a LDPE pair/chain is identified. Innovations that increase live donor registrations and transplantation will reduce dependency on DD organs.

This analysis has limitations in addition to those discussed above. Predicting with certainty who will survive the wait list, who will eventually be transplanted, how long a donor is willing to wait or travel, if they will agree to this option, and how long a graft will last is never certain. This type of analysis makes projections for large samples based on historic mortality and graft survival rates and cannot guarantee a certain expectation for any one individual. We did not include removal from the wait list other than death in this analysis. Therefore, we likely underestimated the benefit to older Patient Bs in the LDPE (Figure 5A and B), particularly if their wait for a DD or LD organ was projected to be long. In these cases, accepting an early transplant of lower quality would be better than no transplant at all. Others have demonstrated the value of transplanting DD kidneys with very high KDPIs in older patients. These studies use different statistical models and include wait list removal.[17,18] Our analysis examines the LD experience using a more conservative approach. The study also assumed that Patient B was not suitable or interested in desensitization. Although there has been progress in desensitization to overcome prohibitive antibodies, long term outcomes remain less than ideal.[19] Given the relatively short time lines, we did not take into account removal from the wait list in the LDPE due to illness. Including removal from illness in the model calculations is likely to have a larger impact on Patient B, who is likely to spend more time waiting. Including this would favor Patient B accepting a lower quality kidney from Patient A's donor rather than waiting for a better organ.

In conclusion, strategic entry of a patient with an eligible and compatible live donor of suboptimal quality into the LDPE may yield superior outcomes for that patient, while also facilitating transplantation of an otherwise difficult to transplant (ie, highly sensitized) patient already in the LDPE. It is not clear how frequently this strategy would take place on an annual basis in current LDPE programs. Some donors that are deemed to have kidneys of lower quality relative to their respective recipient may not be presently evaluated. The study does demonstrate the possibility of improving overall outcomes by bringing more patients into the LDPE programs and possibly the added exchange in the DD kidney pool. The study also identifies system processes that might need modification within current LDPE programs. In certain scenarios, this may lead to improved survival and quality of life at an individual level (for one or both recipients) as well as more live donor transplants/less strain on the deceased donor wait list from a societal perspective.

List of Abbreviations

DD, deceased donor; ESKD, end-stage kidney disease; LD, live donor; LDPE, live donor paired exchange; KDPI, Kidney Donor Profile Index; KDRI, Kidney Donor Risk Index; LKDPI, Live

Kidney Donor Profile Index; Lys, life years; QALYs, quality-adjusted life years.

Ethics Approval and Consent to Participate

The study was submitted to our research ethics board, who felt a formal review was not required since the study relied exclusively on anonymous information.

Consent for Publication

All authors consent to publication

Availability of Data and Materials

All probabilities and rates are published at the USRDS.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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ORCID iDs

Amanda J. Vinson https://orcid.org/0000-0002-9345-5252

Karthik K. Tennankore https://orcid.org/0000-0002-7919-6709

Supplemental Material

Supplemental material for this article is available online.

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