Barriers to the Donation of Living Kidneys for Kidney Transplantation

Kyungok Min
Seoul National University Hospital
Tai Yeon Koo
Seongnam Citizens Medical Center
Young Hui Hwang
University of Ulsan
Jaeseok Yang (jcyjs@snu.ac.kr)
Seoul National University Hospital

Research Article

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Abstract

Since the waiting time for deceased donor kidney transplantation continues to increase, living donor kidney transplantation is an important treatment for end stage kidney disease patients. Barriers to living kidney donation have been rarely investigated despite a growing interest in the utilization of living donor transplantation and the satisfaction of donor safety. Here, we retrospectively analyzed 1,658 potential donors and 1,273 potential recipients who visited the Seoul National University Hospital for living kidney transplantation between 2010 and 2017 to study the causes of donation failure. Among 1,658 potential donors, 902 (54.4%) failed to donate kidneys. The average number of potential donors that received work-up was 1.30 ± 0.66 per recipient. Among living donor kidney transplant patients, 75.1% received kidneys after work-up of the first donor and 24.9% needed work-up of two or more donors. Donor-related factors (49.2%) were the most common causes of donation failure, followed by immunologic or size mismatches between donors and recipients (25.4%) and recipient-related factors (16.2%). Interestingly, withdrawal of donation will along with refusal by recipients or family were the commonest causes, suggesting the importance of non-biomedical aspects. The elucidation of the barriers to living kidney donation could ensure more efficient and safer living kidney donation.

Introduction

Kidney transplantation is the best renal replacement therapy that can improve the survival and quality of life of patients with end-stage kidney disease (ESKD). However, the number of deceased kidney donation is limited as compared to the number of ESKD patients; therefore, the waiting time for deceased donor kidney transplantation (DDKT) is prolonged, especially in Asian countries where the donation rate of deceased donor kidneys is much lower than that in Western countries. Living donor kidney transplantation (LDKT) is an important alternative to ESKD patients due to severe organ shortage.

Kidney donation does not significantly affect quality of life, kidney function, or survival of living donors[1]. Although kidney donation is based on spontaneity, the physical risks from procurement of healthy kidneys and the uncertainty of future health conditions must be endured[2]. Since living donation is dependent on voluntary, free will of healthy people, safety of living donors is the most important concern. Therefore, potential donors should receive objective information with respect to the biomedical as well as the non-biomedical aspect.

However, the criteria for living kidney donors are variable among different transplantation centers and periodic follow-up of kidney donors after donation is poor[3]. Furthermore, an aggravating discrepancy between the need and supply has made the criteria for living kidney donors more flexible over time[4,5].

The Live Donor Practice of Community within the American Society of Transplantation hosted a Consensus Conference on Live Kidney Donation Best Practices to educate recipients and donors, evaluate efficiency of living kidney donation, and identify knowledge gaps that could affect LDKT with focus on the systematic barriers to LDKT[6]. There are several steps in the LDKT process, including a

medical evaluation of the living donors, which could delay kidney transplantation beyond the appropriate timing[7]. The screening procedures for living donors should be as simple as possible, and standard protocols of medical evaluations required to discover important and ancillary information as a donor, and plan surgical procedures for organ procurement must be established[7]. There are limited studies exploring the causes of donation failure from living kidney donors despite a growing interest in this topic[8]. There have been few studies on living kidney donors in Asian countries where LDKT is dominant over DDKT[3].

The number of living kidney transplants in Korea has been continuously increasing from 796 cases in 2010 to 1,432 cases in 2020[9]. According to the World Health Organization Global Database On Donation And Transplantation statistics in 2019, Korea ranked 3rd in the world for the highest number of living donor kidney transplantations[10], indicating that living donor evaluation is essential in Korea. For safe and efficient living donation, it is vital to understand the current barriers to successful living donation and make an effort to overcome them. In this study, we analyzed the factors that affect donor access to verify appropriateness of donor selection, identified the causes of donation failure from living kidney donors, provide objective statistics to potential donors to ensure informed decision-making, and improve the process of donor preparation for kidney transplantation.

Methods

Medical records of 1,273 potential recipients and potential 1,658 donors who visited Seoul National University Hospital between 2010 and 2017 for living donor kidney transplantation were retrospectively analyzed to investigate the causes of donation failure during the donor work up process.

The donor evaluation consists of three steps. The first step is to check the contraindications for living kidney donation through history taking and physical examination by physicians and basic laboratory tests including blood test, urine test, simple chest radiography, electrocardiogram, ABO/Rh blood typing and cross-match test with the recipient at an out-patient clinic. After fulfilling the first step, the second step of donor evaluation in either out-patient clinic or on an in-patient basis, includes viral marker study, human leukocyte antigen (HLA) typing, endoscopy, mammography, simple imaging of kidney, ureter, and bladder (KUB), paranasal sinus (PNS) series, computed tomography (CT) angiography, cardiac evaluation according to risk profiles, and several consultations. Potential donors with hypertension receive fundoscopic examination and echocardiography to exclude target organ damage of hypertension. Donors with a family history of DM or those with notably high blood sugar levels during the first step should receive oral glucose tolerance test (OGTT). In case of borderline eGFR, direct GFR measurement using ^{51}Cr-ethylenediamine tetraacetic acid (EDTA) or renal scan is performed. Dental and otorhinolaryngological evaluations to check malignancy and active infection are performed by consultation. A psychiatric consultation is essential to check the presence of anxiety, stress, and major psychotic disorders and spontaneity of donation will. Interviews with a transplant coordinator and a medical social welfare team are also conducted to evaluate spontaneity of donation will and psychosocial problems. In the third step, a joint meeting of the transplantation team including physicians,

surgeons, and coordinators finally determine suitability of potential donors as living kidney donors and the side from which the kidney will be procured from donors (Fig. 1).

This study was approved by the Institutional Review Board of the Seoul National University Hospital (H-2002-162-1106) and all methods were performed in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was waived by the Institutional Review Board of the Seoul National University Hospital.

Results

Clinical characteristics of potential living donors and recipients

A total of 1,658 potential living kidney donors received cross-match tests with corresponding 1,273 potential kidney transplant recipients and received a stepwise donor evaluation (Fig. 1). The mean age of the potential donors was 44.9 ± 11.4 years and 50.8% were females (n=838). Related donors and unrelated donors were 1,076 (64.9%) and 578 (34.9%), respectively. Spouse donors were most common (n=467, 28.2%). A donor exchange program provided 4 donors (0.2%). The time from the initial work-up to living donor kidney transplantation operation was 194.0 ± 173.0 days. Other clinical characteristics of potential donors are summarized in Table 1.

The mean age of the potential recipients was 43.8 ± 16.2 years and 42.9% were females (n=711). Glomerulonephritis (19.6%) was the most common cause of ESKD, followed by diabetes mellitus (DM) (12.0%). Two hundred fifty-one patients (11.0%) planned to proceed to pre-emptive transplantation and 788 (34.5%) patients were under hemodialysis. Other clinical characteristics of potential recipients are summarized in Table 2.

Proceed to kidney transplantation after work-up of potential living donors

The average number of potential donors that received donor work-up was 1.30 ± 0.66 per recipient. The number of potential donors that received donor work-up in recipients with positive cross-match results or donor specific antigen (DSA) (2.10 ± 1.50) was higher than that in recipients without positive cross-match results and DSA (1.56 ± 0.86, $P < 0.001$), and that in recipients with ABO-incompatible donors (1.65 ± 0.89, $P < 0.001$).

After work-up, 756 donors among the 1,658 potential living donors succeeded in donating their kidneys (45.6%) and 756 living donor kidney transplantations were successfully performed for 1,273 recipients (59.4%). Of the patients who received living donor kidney transplantation, 75.1% received kidneys after work-up of the first potential donor and 24.9% needed work-up of two or more potential donors (Fig. 2). ABO blood group-incompatible living donor transplantation was performed in 103 cases (13.6%). After failure to receive living donor kidneys, 59 patients (4.6%) received deceased donor kidney transplantation and 347 patients were still on the waitlist for deceased donor kidney transplantation (27.3%). Two or more potential donors were assessed but failed to donate kidneys in 82 patients (20.2%) among a total of

406 DDKT and wait-list patients. Fourteen patients died (1.1%) and 97 patients (7.6%) were lost to follow-up.

Causes of donation failure of potential living donors

Among 1,658 potential living kidney donors, 902 (54.4%) failed to donate kidneys. Causes of donation failure are summarized in Table 3. Donor-related factors (n=444, 49.2%) were the most common causes. Recipient-related factors and mismatches between donors and recipients led to donation failure in 146 (16.2%) and 229 (25.4%) cases, respectively. According to the stepwise donor evaluation process, 687 (76.2%) potential donors did not fulfil the criteria of living kidney donors at the first step and donation failure occurred in 98 (10.9%) and 117 (13.0%) patients in the second and third step, respectively.

Among donor-related factors, various medical disorders such as DM, hypertension with target organ damage and malignancy were the most common barriers to donation. However, withdrawal of donation was the most common cause among donor-related causes (n=113). The third most common cause among donor-related causes was the presence of better donors among multiple potential donors (n=61). The Korean Network for Organ Sharing (KONOS) did not approve living donation in 48 unrelated donors since their documents could not sufficiently prove their altruistic and voluntary donation without illegal incentives including financial incentives. Glomerulonephritis and genetic diseases that potential recipients shared, were barriers to donation in 25 and 7 donors, respectively. The number of donation failures due to a low estimated glomerular filtration rate (eGFR) (n=17) and other anatomical causes (n=5) as a cause of donation failure was relatively small.

Among recipient-related factors, refusal by recipients was the most common cause (n=53). Among medical complications of recipients, presence of cardiovascular diseases (n=22) and malignancy (n=28) were most common causes of donation failure.

There were immunologic mismatches (n=222) and size mismatches (n=7) in mismatch-related causes. Among immunologic factors, positive cross-match test results (n=192) or presence of DSA with negative cross-match test results (n=6) were the most common causes of donation failure among mismatch-related causes. ABO-incompatibility itself or very high titer of anti-ABO antibodies (> 1:1024) were causes of donation failure in 14 cases.

There were also other factors (n=83, 9.2%) that caused donation failure. The donor's primary guardian, for example, parents or spouse of potential donors, did not consent in 39 cases. Transfer to other hospitals or follow-up loss in the middle of work-up occurred in 38 cases.

Discussion

In this study, we followed up with potential living donors after donor evaluation and analyzed the causes of donation failure. A total of 756 donors among 1,658 potential living donors succeeded in donating their kidneys (45.6%) and 756 living donor kidney transplantation were performed for 1,273 recipients

(59.4%). The average number of potential donors that received donor work-up was 1.30 ± 0.66 per a recipient. Among LDKT patients, 75.1% received kidneys after work-up of the first potential donor and 24.9% needed work-up of two or more potential donors. Among 1,658 potential living kidney donors, 902 (54.4%) failed to donate kidneys. Donor-related factors (n=444, 49.2%) were the most common causes of donation failure. Recipient-related factors and immunologic or size mismatches between donors and recipients caused donation failure in 146 (16.2%) and 229 (25.4%) cases, respectively.

An early study reviewed the consequences of kidney donation on the health of living kidney donors[11]. Living kidney donors did not have a higher risk of death compared to the general healthy population. There was a risk of accelerating eGFR loss, but the ESKD risk was very low[11]. There was no evidence of an increased risk of ESRD for living kidney donors compared to the general population; however, living kidney donors were at an increased risk of ESKD compared to healthy non-donors, although the absolute increase in the ESRD risk attributable to donation was minimal[12-14]. Based on these data, evaluation and minimization of post-donation ESRD risk have been a priority in screening potential living kidney donors[15]. It is essential to balance between the most suitable kidney for the beneficiary and the safety of a single kidney donor for the rest of their life in the donor selection process. The proportions of donors who violated absolute or relative contraindications in the screening process may vary from center to center. A study conducted in Australia and New Zealand found that 767 (26%) of 2932 donors disregarded at least one relative contraindication according to the Caring for Australians with Renal Impairment (CARI) guidelines, 268 patients (9%) proceeded to kidney donation by violation of at least one absolute contraindication, and there was no clear change in donor risk profile over time[16]. However, no living kidney donor who violated the absolute contraindications proceeded to kidney transplantation in this study. The donor screening process should be improved and systematized.

Our donor evaluation program consists of three sequential steps to minimize unnecessary testing. Based on this stepwise approach, 76.2% of all donation failure cases occurred at the first step, suggesting efficiency of our evaluation system. For causes of donation failure, donor-related factors were the most common causes. However, criteria for donor-related factors has been made more flexible, due to severe organ shortage[4,5]. Living donors with the relative contraindications, such as impaired fasting blood glucose, controlled hypertension without evidence of target organ damage, and positive hepatitis B virus surface antigen (HBsAg) without clinical and laboratory evidence of hepatitis, have tried to donate their kidneys. Of course, further long-term studies should confirm safety of these expanded criteria living donors after donation. We excluded five potential donors due to positive HBsAg in this study; however, we have recently changed this policy and have started to accept these donors in recipients with protective anti-HBs antibody. Eight potential donors failed to donate their kidneys due to their advanced age. However, the average age of living kidney donors has steadily increased in Korea with increase in the expected lifespan.[9] Therefore, henceforth, advancing age will not be a cause of donation failure as far as the donors is physically healthy.

Immunologic or size mismatch between donor and recipients were also important causes of donation failure. In parallel, the number of potential donors that received donor work-up in sensitized recipients was higher than that in recipients without DSA or ABO-incompatible donors. Presence of DSA and positive cross-match test results used to contraindications to donation as they can induce hyperacute or severe acute antibody-mediated rejection in sensitized recipients; thus, 22.0% of potential donors failed to donate their kidneys.. However, waiting time of sensitized recipients for deceased donor transplantation is also longer than that of wait-listed patients without sensitization[17]. Since living donor kidney transplantation after desensitization led to better patient survival than waiting for deceased donor transplantation in the United States and Korea[18,19], active application of desensitization to highly sensitized recipients is expected to increase utilization of these mismatched donors. On the other hand, 14 potential donors failed to donate their kidneys due to ABO-incompatibility and high titer of anti-ABO antibodies in this study. However, development of effective desensitization technology has markedly improved outcomes of ABO-incompatible living donor kidney transplantation worldwide[20-23]. The number of ABO-incompatible living donor kidney transplantations in Korea has rapidly increased from 78 cases in 2010 to 709 cases in 2019, which corresponds to 16.4% of all living donor kidney transplantation[9]. In parallel with this trend, our results also include ABO-incompatible living donor transplantation in 103 cases (13.6%) in this study, no longer regarding an ABO-incompatibility as a contraindication to living kidney donation.

Recipient-related factors, including malignancy and cardiovascular diseases, also interfered with living donor kidney transplantation. A European guideline recommends malignancy screening in potential living kidney donors and recipients according to the recommendations that apply to the general population and suggests that cases with current or previous cancer be discussed with an oncologist on a case-by-case basis[24]. Although Korea is implementing a nationwide cancer health screening program, living donor kidney transplantation did not proceed due to a recipient's malignancy (3.1%) in this study. Therefore, we need periodic and more detailed screening programs for malignancy in ESKD or advanced chronic kidney disease patients in addition to a national screening program.

Interestingly, withdrawal of donation will (12.5%) was the most common cause of donation failure as a single cause. This suggests that many potential donors had experienced pressure from the recipient and hesitated to donate their kidneys. It also emphasizes the need for repeated education to help potential donors consider the pros and cons of donation sufficiently and the importance of providing an opportunity of voluntary decision without external pressure at any step of donor evaluation. On the other hand, many recipients refused to receive living kidneys from their potential donors because they did not want to give harm to their potential donors, this being the most common cause among the recipient-related factors. Refusal of donor family consent also contributed to donation failure because the donor family did not want their offspring or spouse to experience potential harm by donating their kidneys. Overall, these results demonstrate that non-biomedical factors, in addition to biomedical factors, play an important role in donation failure. Therefore, sufficient education of potential donors and recipients along with their family before donor evaluation testing is essential to enhance efficiency of LDKT process.

Previous studies on living kidney donors have primarily focused on absolute and relative contraindication criteria to minimize a donor risk. The barriers of potential living kidney donors have not been sufficiently investigated yet. This study is expected to contribute to improvement of the LDKT preparation process by helping the medical staff understand causes of donation failure more systematically as well as to provide objective data to potential donors and recipients for their better preparation and for informed decision making.

In conclusion, nearly half of the potential living donors did not proceed to living donor kidney transplantation. Donor-related factors were the most common causes of donation failure, followed by immunologic or size mismatch between donors and recipients and recipient-related factors. In addition to biomedical factors, non-biomedical factors also played an important role in donation failure. Understanding of barriers to living kidney donation could contribute to more efficient and safer living kidney donation.

Declarations

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Author Contributions

K.M., H.Y.H, and J.Y. contributed to the design of the study. K.M., and T.Y.K. participated in the data collection. K.M., T.Y.K., H.Y.H, and J.Y. participated in the data analysis. K.M., T.Y.K., and J.Y. participated in the writing of the paper.

Competing Interests

The authors declare no competing interests.

References

1. Agency KOD. Statistical Yearbook 2019 https://www.koda1458.kr/home.do.

2. Yi, M. S. The pattern of decision making to donate a living kidney. *J Korean Acad Nurs* **30**, 47-59 (2000). 10.4040/jkan.2000.30.1.47.

3. Kim, M. H., Kwon, O. J. & Kang, C. M. The quality of life for living donors after kidney transplantation. *J Korean Soc Transplant* **26**, 15-22; 10.4285/jkstn.2012.26.1.15 (2012).

4. Lafranca, J. A., Spoon, E. Q. W., van de Wetering, J., IJzermans, J. N. M. & Dor, F. J. M. F. Attitudes among transplant professionals regarding shifting paradigms in eligibility criteria for live kidney donation. *PLoS One* **12**, e0181846; 10.1371/journal.pone.0181846 (2017).

5. Ahmadi, A. R., *et al*. Shifting paradigms in eligibility criteria for live kidney donation: A systematic review. *Kidney Int* **87**, 31-45; 10.1038/ki.2014.118 (2015).

6. LaPointe Rudow, D., *et al* Consensus conference on best practices in live kidney donation: Recommendations to optimize education, access, and care. *Am J Transplant* **15**, 914-922; 10.1111/ajt.13173 (2015).

7. Perlis, N. *et al.* Evaluating potential live-renal donors: Causes for rejection, deferral and planned procedure type, a single-centre experience. *Can Urol Assoc J* **7**(1-2), 41-45; 10.5489/cuaj.216 (2013).

8. Taormina, S. P., Galloway, M. P. & Jain, A. Barriers to live donor kidney transplants in the pediatric population: A single-center experience. *Pediatr Transplant* **21**, e12852; 10.1111/petr.12852 (2017).

9. Sharing, K. NfO. Statistical Yearbook of Organ Transplantation and Human Tissue Donation 2021 https://www.konos.go.kr/konosis/common/bizlogic.jsp (2020).

10. World Health Organization. The global Observatory on donation and transplantation: WHO GODT statistics 2019 http://www.transplant-observatory.org (2021).

11. Delanaye, P., *et al*. Outcome of the living kidney donor. *Nephrol Dial Transplant* **27**, 41-50; 10.1093/ndt/gfr669 (2012).

12. Ibrahim, H. N., *et al*. Long-term consequences of kidney donation. *N Engl J Med* **360**, 459-469; 10.1056/NEJMoa0804883 (2009).

13. Mjøen, G., *et al*. Long-term risks for kidney donors. *Kidney Int* **86**, 162-167; 10.1038/ki.2013.460 (2014).

14. Muzaale, A. D., *et al*. Risk of end-stage renal disease following live kidney donation. *JAMA* **311**, 579-586; 10.1001/jama.2013.285141 (2014).

15. Claisse, G., Gaillard, F. & Mariat, C. Living kidney donor evaluation. *Transplantation* **104**(12), 2487-2496; 10.1097/TP.0000000000003242 (2020).

16. Clayton, P. A., *et al*. Risk-factor profile of living kidney donors: The Australia and New Zealand dialysis and transplant living kidney donor registry 2004-2012. *Transplantation* **100**, 1278-1283; 10.1097/TP.0000000000000877 (2016).

17. Fehrman-Ekholm, I., Elinder, C. G., Stenbeck, M., Tydén, G. & Groth, C. G. Kidney donors live LONGER1. *Transplantation* **64**, 976-978; 10.1097/00007890-199710150-00007 (1997).

18. Montgomery, R. A., *et al*. Desensitization in HLA-incompatible kidney recipients and survival. *N Engl J Med* **365**, 318-326; 10.1056/NEJMoa1012376 (2011).

19. Koo, T. Y., *et al*. Presence of a survival benefit of HLA-incompatible living donor kidney transplantation compared to waiting or HLA-compatible deceased donor kidney transplantation with a long waiting time. *Kidney Int* **100**, 206-214; 10.1016/j.kint.2021.01.027 (2021).

20. Okumi, M., *et al*. ABO-incompatible living kidney transplants: Evolution of outcomes and immunosuppressive management. *Am J Transplant* **16**, 886-896; 10.1111/ajt.13502 (2016).

21. Opelz, G. *et al.* Three-year outcomes following 1420 ABO-incompatible living-donor kidney transplants performed after ABO antibody reduction: Results from 101 centers. *Transplantation* **99**, 400-404; 10.1097/TP.0000000000000312 (2015).

22. de Weerd, A. E. & Betjes, M. G. H. ABO-incompatible kidney transplant outcomes: A meta-analysis. *Clin J Am Soc Nephrol* **13**, 1234-1243; 10.2215/CJN.00540118 (2018).

23. Massie, A. B., *et al*. Impact of ABO-incompatible living donor kidney transplantation on patient survival. *Am J Kidney Dis* **76**, 616-623; 10.1053/j.ajkd.2020.03.029 (2020).

24. Pascual, J., *et al*. European renal best practice guideline on the management and evaluation of the kidney donor and recipient. *Nefrologia* **34**, 293-301; 10.3265/Nefrologia.pre2014.Feb.12490 (2014).

Tables

Due to technical limitations, table 1-3 is only available as a download in the Supplemental Files section.

Figures

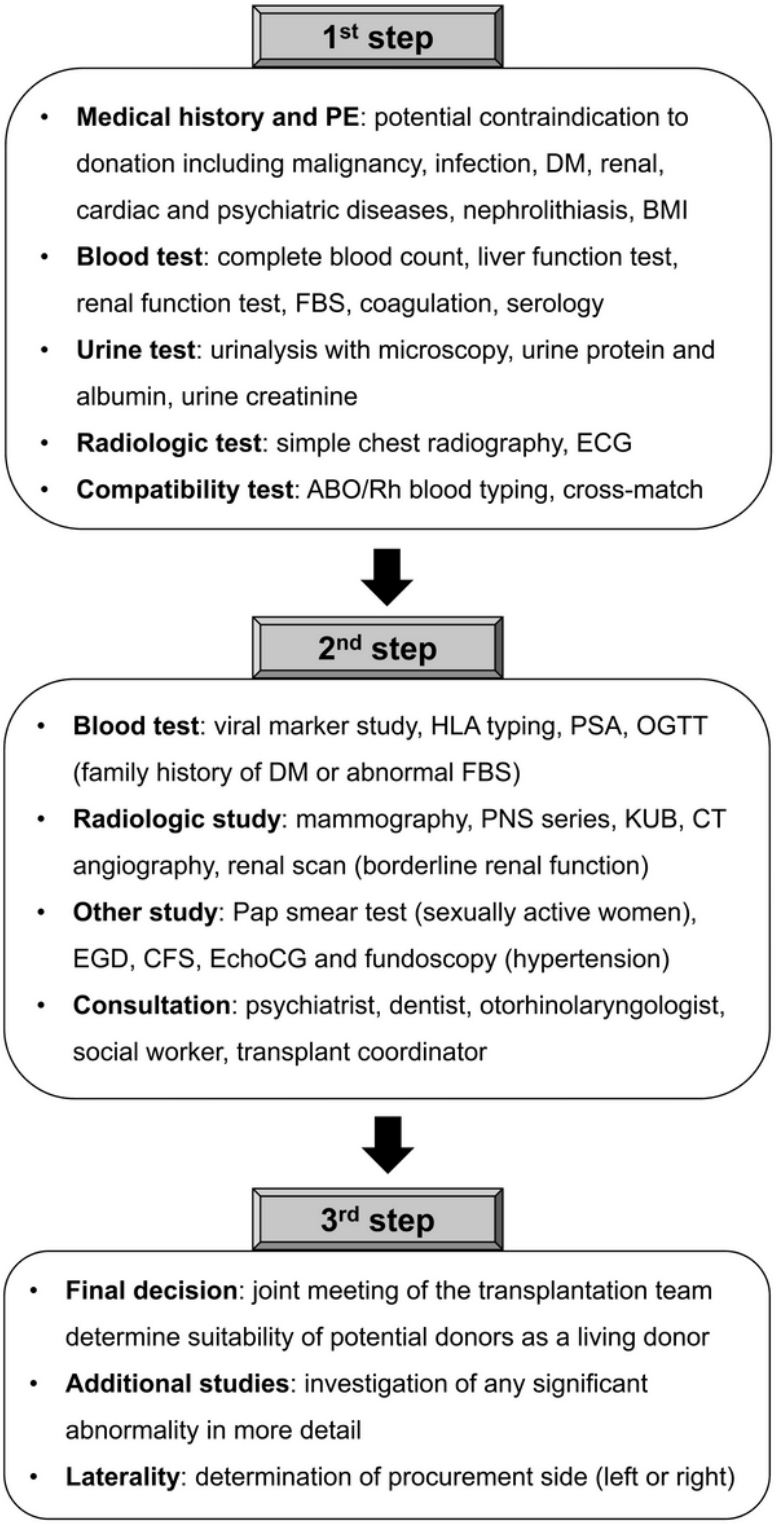

Figure 1

The Stepwise Screening Processes for Potential Living Kidney Donors. The evaluation for potential living kidney donors consists of three steps. BMI, body mass index; CFS, colonofiberscopy; DM, diabetes mellitus; ECG, electrocardiogram; EchoCG, echocardiography; EGD, esophagogastroduodenoscopy; FBS, fasting blood sugar; KUB, kidney, ureter, and bladder; OGTT, oral glucose tolerance test; PE, physical examination; PNS, paranasal sinus.

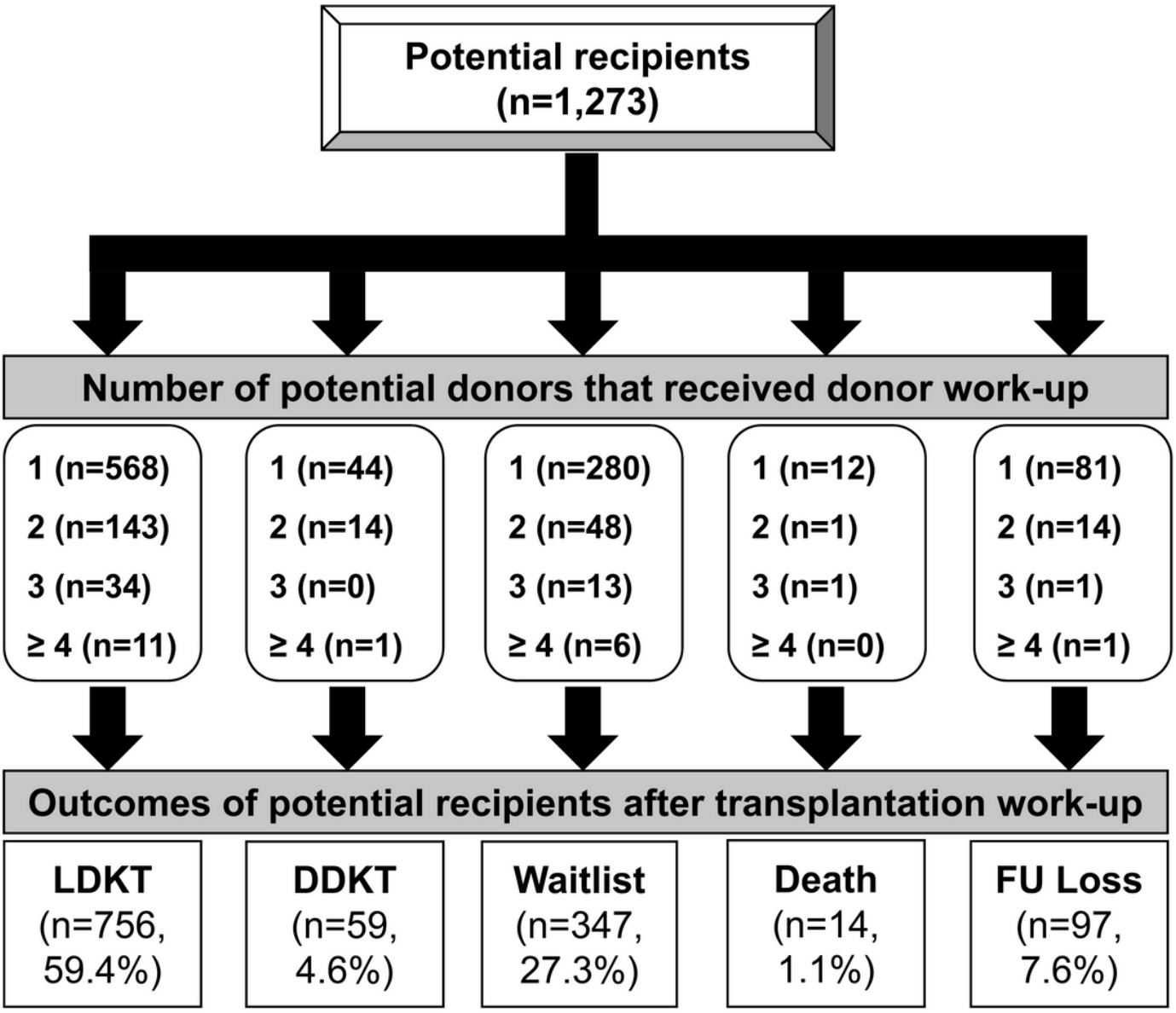

Figure 2

Number of Potential Donors per Recipient that Received Donor Work-up and Outcomes of Potential Recipients after Transplantation Work-up. In total, 1,273 potential recipients were cross-matched with 1,658 potential donors. After transplantation work-up, potential recipients received LDKT (n=756) or DDKT (n=59) were still on the waitlist for DDKT (n=347), died (n=14), or were lost to follow-up (n=97). DDKT, deceased donor kidney transplantation; FU, follow-up; LDKT, living donor kidney transplantation.

Supplementary Files

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- Tables.pdf