



# A Half-Century 3000 Cases of Kidney Transplant Experiences in a Single Hospital: the Longest Registry in Korea

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## ABSTRACT

**Background.** This study aims to analyze the entire registry of kidney transplant over the past 50 years and understand the clinical significance.

**Methods.** From the data on 3012 kidney transplants performed at our center between March 1969 and September 2018, we analyzed retrospectively clinical variables.

**Results.** Until September 2018, there have been 3012 kidney transplants performed. The number of primary transplant cases was 2755 (91.8%), which included 16 cases of simultaneous liver-kidney transplant, and the number of repeated transplants was 245 (225 second transplants [7.5%] and 20 third transplants [0.7%]). There were 3 simultaneous pancreas kidney transplants, and 3 small bowel-kidney transplants, one of them being transplanted at the same time. There was a single simultaneous heart-kidney transplant. The viability rates of a transplanted kidney for 1, 5, 10, 20, and 30 years were 97%, 92%, 90%, 51%, and 36%, respectively, and the patient survival rates were 96%, 89%, 82%, 64%, and 52%, respectively. Five-year graft survival rate of the first 1000 cases was 64.6%; those of the 1001st to 2000th cases and 2001<sup>st</sup> to 3012th cases were 87.6% and 88.8%, respectively. There are statistically significant differences among the groups.

**Conclusion.** This study has identified the appropriate selection or control of immunotherapy, based on the risk level of kidney transplant recipient, is needed to minimize chronic rejection, which is the key cause of transplanted kidney failure.

**K**IDNEY transplant is one of the best treatments possible for end-stage renal disease (ESRD). In 1956, Harrison [1] and Merrill [2] attempted renal homotransplants in identical twins and succeeded for the first time. In addition, the first live donor kidney transplant was successfully performed at our center in 1969. Since the first successful kidney transplant from a deceased (brain-dead) donor at another center, the development of immunosuppressants and surgical techniques have led to studies reporting a  $\geq 90\%$  overall success rate of kidney transplant

in Korea. In 1999 and 2010, the legislation on organ transplants to improve organ donor-recipient matching and distribution process was passed and amended. With an

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Total 3012 cases between March 1969 and September 2018

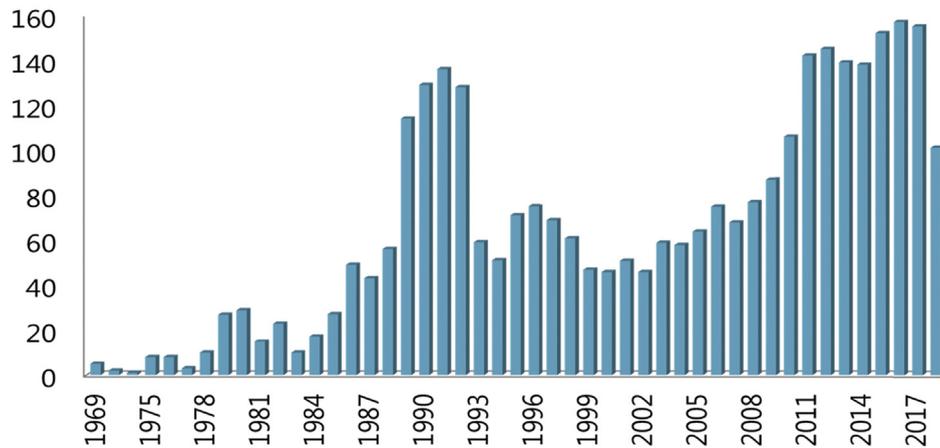


Fig 1. No. of KT in Seoul St. Mary's Hospital. Abbreviation: KT, kidney transplant.

**Table 1. Demographics and Clinical Characteristics of Kidney Recipients**

Recipients	N = 3012
Age, mean (SD)	41.88 (12.25)
Sex, M:F (%)	1874 (62.2):1138 (37.8)
BMI	28.73 (5.32)
Renal replacement therapy before KT, No. (%)	
Preemptive	287 (9.5)
HD	2171 (72.1)
PD	554 (18.4)
KT, No. (%)	
1	2755 (91.8)
2	225 (7.5)
3	20 (0.7)
Blood group, No. (%)	
O	813 (26.9)
A	1042 (34.6)
B	805 (26.7)
AB	352 (11.6)
HLA mismatch, No. (%)	
0-2	435 (14.4)
3-4	1182 (39.2)
5-6	1395 (46.4)
Cause of ESRD in recipients, No. (%)	
Chronic glomerulonephritis	1647 (54.9)
Diabetes nephropathy	382 (12.7)
Hypertensive nephrosclerosis	288 (9.6)
Polycystic kidney disease	89 (2.9)
Lupus nephritis	56 (1.8)
Others (Gout/Tbc, etc.)	45 (1.5)
Pyelointerstitial nephritis	28 (0.9)
Vesicoureteral reflux	14 (0.4)
Hereditary nephropathy	6 (0.2)
Unknown	428 (13.9)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ESRD, end stage renal disease; HD, hemodialysis; KT, kidney transplant; PD, peritoneal dialysis; Tbc, tuberculosis.

active development in the field of organ transplantation in Korea, in 2012, there were 1783 kidney transplants and 1283 liver transplants performed in 87 different centers within Korea. Since the first successful Korean kidney transplant performed in 1969, Korea has developed into a country with a world-class kidney transplant history and techniques.

**Table 2. Demographics and Clinical Characteristics of Kidney Donors**

Donors	N = 3012
Age, mean (SD), y	51.88 (12.97)
Sex, M:F, (%)	1659 (55.1):1353 (44.9)
BMI, mean (SD)	29.73 (6.33)
HTN, No. (%)	1345 (44.6)
DM, No. (%)	1144 (37.9)
Blood group, No. (%)	
O	1118 (37.2)
A	954 (31.6)
B	741 (24.6)
AB	199 (6.6)
Donor-recipient relation, No. (%)	
LRD	1936 (64.2)
LUD	451 (15.0)
DD	625 (20.8)
Cause of brain death, No. (%)	
CVA	294 (47.1)
Traumatic	225 (36.0)
Others	106 (16.9)
Kidney retrieval method, No. (%)	
Open nephrectomy	2180 (72.3)
Laparoscopic nephrectomy	832 (27.7)
Cold ischemia time, mean (SD), min	310 (196.8)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CVA, cerebrovascular accident; DD, deceased donor; DM, diabetes mellitus; HTN, hypertension; LRD, living related donor; LUD, living unrelated donor.

**Table 3. Graft survival Rate by Donor Type**

Duration, y	1	5	10	15	20	30
LD, % (n = 2387)	97.6	82.3	75.8	64.8	59.7	55.6
DD, % (n = 625)	94.8	82.1	71.6	61.1	50.1	

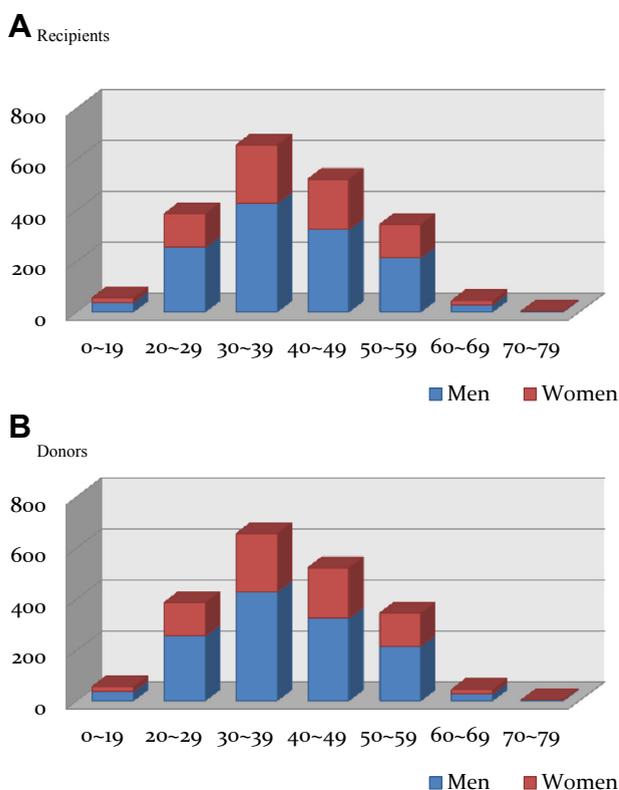
Abbreviations: DD, deceased donor; LD, living donor.

According to the US report on the use of donor kidneys, the half-life of a donor kidney from a deceased (brain-dead) patient has remarkably increased by ~50% from 10.6 years in 1989 to 15.5% years in 2005. This trend is similarly observed in live donor kidney transplant as well.

Previous studies have attempted the analysis of long-term survival data up to 25 years, but there has not been a study based on a registry from ~50 years of history. This study aims to analyze the entire registry of kidney transplant over the past 50 years and understand the clinical significance.

## MATERIALS AND METHODS

From the data on 3000 kidney transplants performed at our center between March 1969 and November 2018, we have assessed the following: sex and age distribution of the donor and the recipient, the number of kidney transplants in each year, the relationship between the donor and the recipient, the causative disease of chronic renal failure, complications, transplanted kidney viability and the patient survival, and the risk factors affecting transplanted kidney viability. Among different diagnostic



**Fig 2.** Age and sex distribution of the kidney transplant recipients and donors.

standards used to assess the functional status of a transplanted kidney, we have used the following for post-transplant recovery: the patients with a normal renal function within 2 weeks of the transplant were defined to exhibit an early graft function, while the patients with normal renal function after 2 weeks of transplant were defined to exhibit slow graft function. The patients who required dialysis within 1 week of transplant were defined to exhibit delayed graft function.

For transplant rejection, which is the most important aspect of post-transplant condition in the transplant recipient, the patients who exhibited suspicious clinical symptoms (ie,  $\geq 25\%$  increase in blood creatinine level and decreased urine volume) were further assessed for ultrasonography of the transplanted kidney. The patients with resistive index of  $\geq 75\%$  were suspected of transplant rejection, and the diagnosis was confirmed via biopsy.

The key purpose of the induction therapy is to reduce the risk of acute transplant rejection. Induction therapy has been performed using different agents throughout the history, starting from steroid to interleukin 2 receptor antagonist (IL2RA) and T lymphocyte-depleting rabbit-derived antithymocyte globulin.

The main immunosuppressants used were azathioprine, cyclosporine A, or FK506. Two-medication therapy involved the use of the main immunosuppressant and a steroid, while 3-medication therapy involved combined use of cyclosporine A or FK506, steroid, and mycophenolate mofetil.

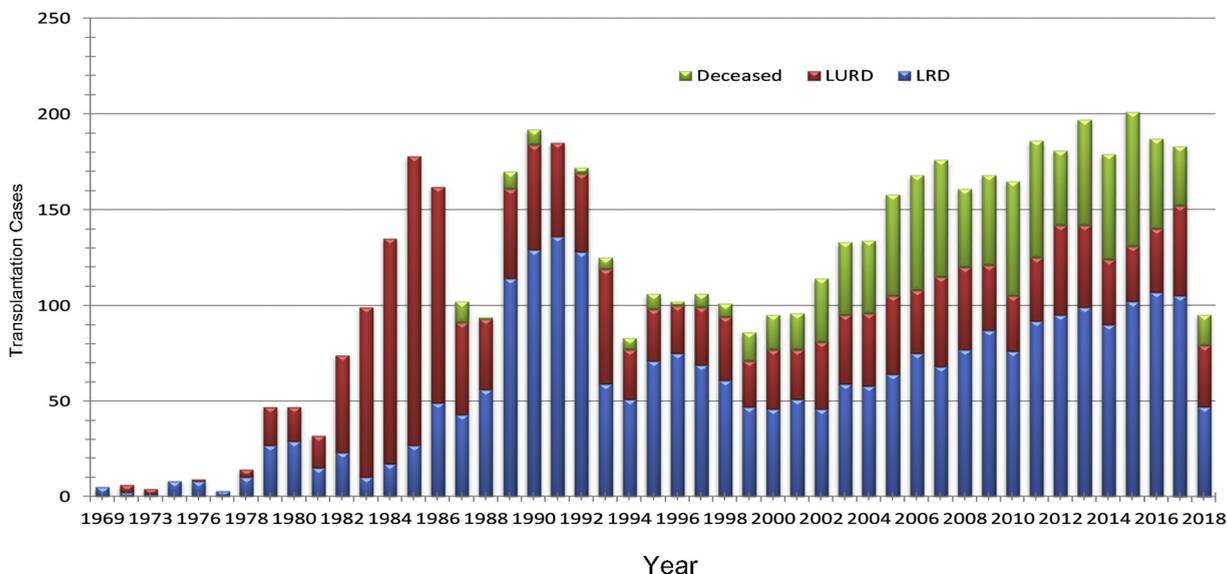
For outcome analysis, *t* test was used for continuous variables, and Fisher exact test or  $\chi^2$  test was used for noncontinuous variables. To assess the risk factors affecting the transplanted kidney viability, we performed univariate and multivariate analysis using Cox proportional hazard model (forward method). Kaplan-Meier survival curves and log-rank test were used to statistically analyze the transplanted kidney viability and patient survival rate according to various factors. The software used for statistical analysis was SPSS version 21.0 (IBM, Armonk, NY, United States), and outcomes with  $P < .05$  were considered statistically significant.

## RESULTS

### Number of Kidney Transplants in Each Year

In 1969, the first kidney transplant in Korea was performed. In addition, there were 5 cases of live donor kidney transplant cases performed in the same year. Until 1977, there have been only 3 to 4 kidney transplants per year, but the number has dramatically increased to  $\geq 10$  cases per year as of 1978 with the initiation of the National Health Insurance system in Korea. Since 1990, the number of cases has been rapidly increasing, and there have been  $\geq 100$  transplants performed annually. Until September 2018, there have been 3012 kidney transplants performed. The number of kidney transplants in each year is shown in Fig 1.

The number of primary transplants was 2755 (91.8%), which included 16 cases of simultaneous liver-kidney transplant, and the number of repeated transplants was 245 (225 second transplants [7.5%] and 20 third transplants [0.7%]). There were 3 simultaneous pancreas-kidney (SPK) transplants. There were 3 small bowel-kidney transplants, 1 of them being transplanted at the same time. There was single case of simultaneous heart-kidney transplant in our registry.

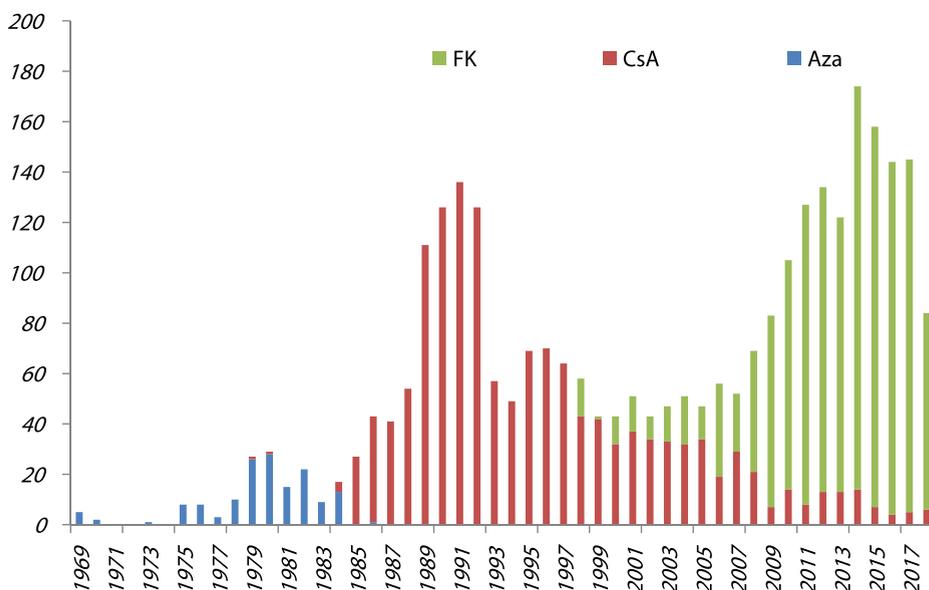


**Fig 3.** Annual changes of recipient-donor relation type in the kidney transplant. Abbreviations: LRD, living related donor; LURD, living unrelated donor.

**Characteristics of the Kidney Transplant Recipients and Donors**

*Age and sex distribution.* The mean age and sex (male:female) ratio of kidney transplant recipients were 41.88 years (range, 10–79 years) and 1874:1138 (62%/38%), respectively (Table 1). The mean age and sex (male:female) ratio of kidney transplant donors were 51.88 years (range, 4–74 years) and 1659:13531 (55.1%/44.9%), respectively (Table 2). For the age distribution of the kidney transplant recipients and donors (Fig 2), most individuals were in their 30s.

*Causative kidney disease and pretransplant dialysis.* Chronic glomerulonephritis was the most common causative disease (1647 cases, 54.9%) followed by diabetes (382 cases, 12.7%) and hypertension (288 cases, 9.6%). Pretransplant peritoneal dialysis was performed in 554 cases (18.4%), and hemodialysis was performed in 2171 cases (72.1%) (Table 1). The mean duration of the pretransplant dialysis was 19 months. Urgent hemodialysis because of severe uremic symptoms, including nausea, vomiting, and simultaneous elevated blood urea nitrogen level, was required in 186 (6.2%) cases using catheter.



**Fig 4.** Main immunosuppressant drug in the kidney transplant. Abbreviations: Aza, azathioprine; CsA, cyclosporine A; FK, FK506.

**Table 4. Graft Survival Rate While Acute Rejection Postoperative Within 1 Year**

Duration, y	1	5	10	15	20	30
No AR, % (n = 2176)	96.9	92.4	80.1	70.3	60.1	51.2
AR within 1 year, % (n = 624)	91.1	78.4	61.2	51.0	40.1	

Abbreviation: AR, acute rejection.

**Donor.** The most common relationship between the kidney transplant recipient and the donor was living relatives (1938 cases, 64.5%) followed by unrelated donors (449 cases, 31.8%) and deceased donors (625 cases, 10.4%). The annual changes of donor type in the kidney transplant are shown in Fig 3. Over the years, deceased donor kidney transplant was elevated after the 2000s. Prior to 1985, there was a remarkably higher number of living donors compared with deceased donors. However, with strict regulations on commercial organ trading, the proportion of unrelated donors is being maintained at around 10%. The proportion of deceased donors since the first successful transplant surgery in 1979 was ~10% of all kidney transplants until 1998; this then increased to 20% to 40% until 2000 and is being maintained at 15% to 20% (Fig 3).

#### Immunosuppressant Therapy

Among patients using an immunosuppressant, 172 patients (5.7%) were using azathioprine, 1286 patients (42.7%) were using cyclosporine A, and 1542 patients (51.2%) were using FK506. Two-medication therapy was used in 1290 cases (42.8%) and 3-medication therapy was used in 1722 cases (57.2%). The main immunosuppressant drug in the kidney transplant is shown in Fig 4.

#### Acute Transplant Rejection and its Frequency

After kidney transplant, acute rejection was observed in 824 cases (27.4%). Among acute rejection grafts, 624 cases (75.7%) exhibited the first rejection within 1 year of transplant (Table 4). In most cases, acute rejection was a 1-time event (536 cases, 17.8%), but there were cases of more than 2 times (94 cases, 3.1%) (Table 5). Acute rejections within the first year and multiple times of acute rejection were statistically significant for survival curve of transplanted graft. Steroid shock therapy was performed in patients with acute rejection symptoms, and 225 patients (7.4%) received OKT3 monoclonal antibody or consecutive antithymocyte globulin rescue therapy.

**Table 5. Graft Survival Rate Based on No. of Acute Rejection Episodes**

Duration, y	1	5	10	15	20	30
No AR, % (n = 2382)	98.0	90.3	78.4	66.1	59.3	50.1
AR = 1 event, % (n = 536)	92.7	79.6	65.4	55.4	50.2	
AR ≥ 2 events, % (n = 94)	81.6	60.1	50.5	29.1	25.6	

Abbreviation: AR, acute rejection.

#### Functionality and Viability of the Transplanted Kidney

Of 3012 total kidney transplants, 1750 cases (58.1%) had a normal renal function maintained, while 795 cases (26.4%) exhibited a loss of renal function and required dialysis; among them, 201 cases exhibited loss of follow-up or patient death, and 596 cases are still under follow-up. In addition, 572 cases (18.9%) involved patient death, and 361 cases (11.7%) involved the transfer to a different center or loss of follow-up. The maximum survival period for a transplanted kidney procedure patient is 412 months, and this patient still has a normal renal function.

**Causes of transplanted kidney failure and patient death.** There were 1169 cases of transplanted kidney failure, and the main causes of death were the following: 490 cases (41.9%) of deaths unrelated to the transplant; 87 cases (7.4%) due to acute rejection; 442 cases (37.8%) due to chronic rejection; 55 cases (4.7%) due to the recurrence of a causative kidney disease; and 65 cases (5.5%) due to non-compliant patients (Table 6). There were 654 cases of patient mortality, mainly caused by various infections (183 cases, 27.9%), cerebrovascular diseases (98 cases, 14.9%), cardiovascular complications (91 cases, 13.9%), respiratory diseases, liver failure, malignant tumor, urinary tract disease, and other diseases (Table 6).

**Transplanted kidney viability and patient survival.** The overall viability rates of a transplanted kidney for 1, 5, 10, 20, and 30 years were 97%, 92%, 90%, 51% and 36%, (Table 3) respectively, and the patient survival rates were 96%, 89%, 82%, 64%, and 52%, respectively (Fig 5). Graft survival of every 1000 cases is shown in Fig 6. Five-year graft survival rate of the first 1000 cases was 64.6%; those of the 1001st to the 2000th cases and the 2001st to the 3012th cases were 87.6% and 88.8%, respectively. There are statistically significant differences among the groups (Fig 6).

**Risk factors affecting the transplanted kidney viability.** We have analyzed the following factors for their effect on the transplanted kidney viability: the age of the kidney transplant donor and recipient, causative kidney disease, form of pre-transplant dialysis, dialysis duration, history of blood transfusion prior to the transplant, repeated transplant, type of donor, number of unmatched HLA, number of unmatched HLA-DR antigen, main immunosuppressants, number of immunosuppressants, and the presence of transplant rejection within 3 months. From the univariate analysis, the age of the donor and the recipient, the number of unmatched HLA antigen, and transplant rejection within 3 months had a significant effect on the transplanted kidney viability. Subsequent multivariate analysis of the above 4 factors showed that the age of donor, the number of unmatched HLA antigens, and transplant rejection within 3 months were the factors with significant outcomes.

#### DISCUSSION

In this study, we analyzed 3000 kidney transplants performed in a single center in 50 years and assessed the

**Table 6. Causes of Transplanted Kidney Failure and Patient Death**

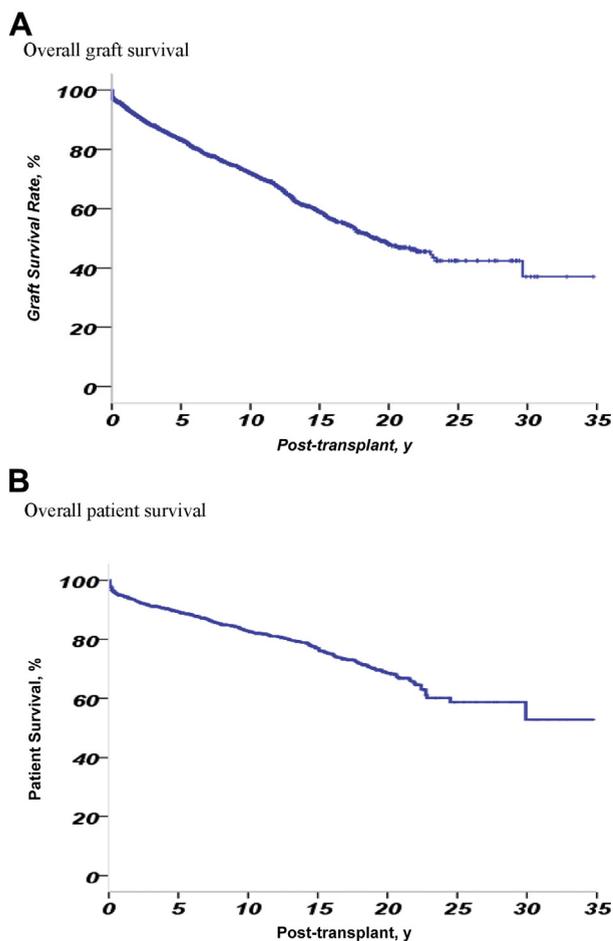
Cause of transplanted kidney failure	N = 1169	Cause of patient death	N = 654
Death with functioning graft, No. %	490 (41.9)	Infection	183 (27.9)
Chronic rejection, No. %	442 (37.8)	Cerebrovascular	98 (14.9)
Acute rejection, No. %	87 (7.4)	Cardiovascular	91 (13.9)
Noncompliance, No. %	65 (5.5)	Pulmonary	52 (7.9)
Recurrence of primary disease, No. %	55 (4.7)	Hepatobiliary	50 (7.6)
Graft infection, No. %	19 (1.6)	Malignancy	49 (7.5)
Vascular or urologic complications, No. %	6 (0.5)	Urologic	31 (4.7)
Removal of functioning graft, No. %	5 (0.4)	Others	100 (15.2)

characteristics and prognosis of these kidney transplants. In addition, we assessed the risk factors affecting the viability of the transplanted kidney and evaluated their clinical significance to establish an index for the future development of transplant surgery. The outcome that needs to be highlighted from this study is improved transplanted kidney viability. Comparison of transplanted kidney viability in 10-year terms has demonstrated that the viability has been steadily increasing, which is likely because of already-known factors including the changes in immunosuppressants,

development in surgical techniques, management of infection rate, improvement of pretransplant patient condition, and an improved accuracy of pretransplant examinations. The factors previously associated with the long-term maintenance of transplanted kidney function included the sex of donors, the ages of recipients and donors, pretransplant dialysis duration, prevalence of diabetes, type of donor, the number of unmatched HLA-DR, and history of acute rejection within 1 year. In our study, the factors associated with the functionality of a transplanted kidney were strongly correlated with acute rejection more than 2 times, history of acute rejection within 1 year, and type of main immunosuppressant.

From this study, the proportion of glomerulonephritis has decreased from 54.9%. On the other hand, the proportion of diabetic nephropathy has been 12.7%. A total of 25% of all patients enrolled in ESRD programs had diabetes; diabetic nephropathy is the most common cause of ESRD in the world including Europe, Japan, and the United States [3,4]. There was a cohort study showing patients with chronic kidney disease with diabetes and HbA<sub>1c</sub> levels < 6% and ≥ 9% were associated with higher risk for death [5]. About 3% of patients with newly diagnosed type 2 diabetes mellitus already have overt nephropathy, but in patients with type 1 diabetes mellitus, it is rare to find diabetic nephropathy [6]. Based on the fact that almost 40% of all ESRD patients have diabetes and higher risk for morbidities and mortality, a more aggressive attitude toward kidney transplant in diabetic patients is needed.

A noticeable change in kidney transplant donors is the remarkable reduction in the number of unrelated donors. In total, there were 1938 cases of live related donors, which was still 4-fold greater than the 449 cases of unrelated donors. However, the number of unrelated donors has rapidly decreased since 2000 (Fig 3). This phenomenon is likely due to the strict selection process of commercial donors and strengthened role of the Korean Network for Organ Sharing in our university, leading to a more transparent process of donor selection [7]. There were 1169 cases involving the failure of a transplanted kidney, and mortalities unrelated to the transplant (41.9%) and chronic rejection (37.8%) were accountable for the majority of failures. Meanwhile, there were 654 cases involving patient mortality, mainly caused by cardiovascular and cerebrovascular complications (Table 6). Although a previous study

**Fig 5.** Overall graft and patient survival.

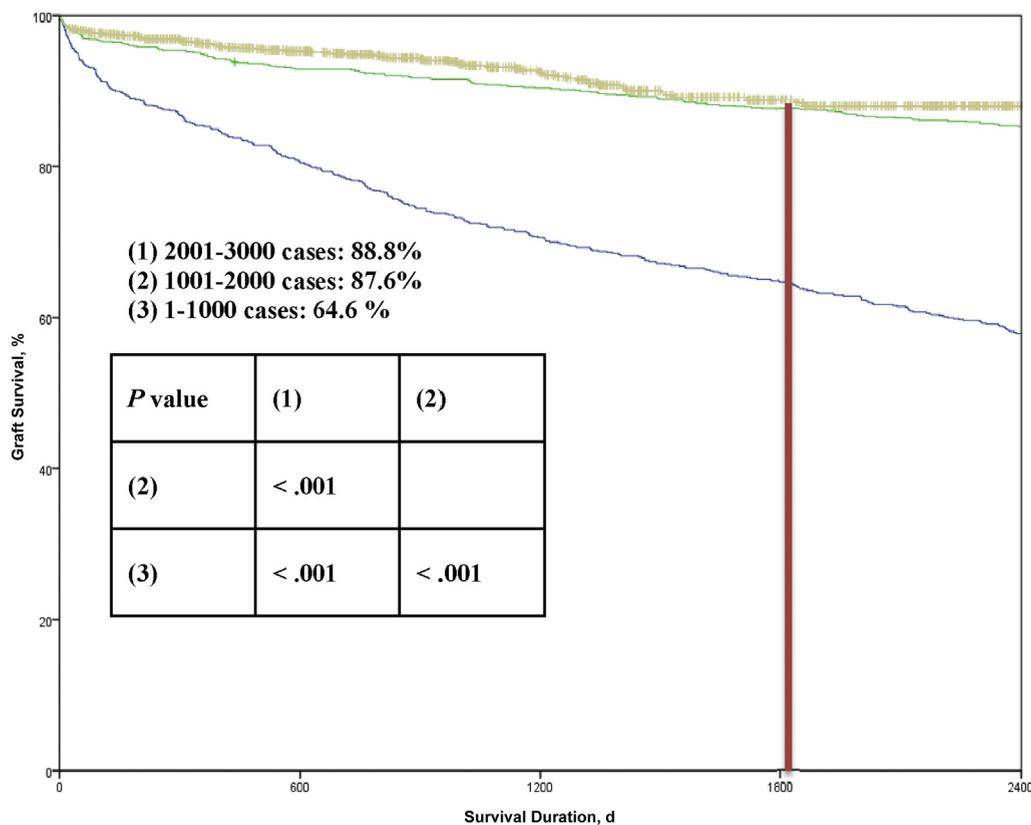


Fig 6. Graft survival every 1000 cases.

has suggested that repeated transplants result in a relatively reduced transplanted kidney viability compared with the primary transplant surgery [8], there was no significant difference in the transplanted kidney viability or the patient survival in our study, and this is likely because of the improved immunosuppression therapy and increased number of live donor transplants. As mentioned previously, the transplanted kidney viability and the recipients have improved every 10 years. These improvements are reportedly caused by the use of cyclosporine [8], tacrolimus [9], and mycophenolate mofetil [10]. In our study, the use of a calcineurin inhibitor resulted in a greater patient survival rate than the use of azathioprine, and there was no difference compared with the tacrolimus or cyclosporine groups. However, the difference in patient survival according to the main immunosuppressant may be affected by other factors, as azathioprine was used in earlier transplants while the calcineurin inhibitor was used in more recent transplants. Although 2-medication therapy and 3-medication therapy did not have a significant effect on the transplanted kidney viability, an additional reassessment should be made in the future as the number of patients in 3-medication therapy group was small and their follow-up period was relatively shorter. From the analysis

of the transplanted kidney viability according to the donor, we observed a significant difference in the viability of the transplanted kidney and the recipient between related and unrelated donors, but no significant difference was observed between live and deceased donors. The 5-year graft survival every 1000 cases shows the great differences from the 1st through the 1000th case vs later cases. Although these rates are slightly lower compared with some of the other domestic transplant centers [11,12], this is likely because of the poor environment for kidney transplant surgery during earlier periods and a frequent failure of the transplanted kidney due to acute rejection with a limited injection of immunosuppressants—in fact, the transplanted kidney viability recently has been remarkably higher. There is an ongoing controversy on the effect of tissue-specific antigen matching on the viability of transplanted kidney, although there have been studies reporting that the HLA, especially HLA-DR antigen matching, is an important prognostic factor of successful kidney transplant [13]. In our study, the patients with complete HLA matching exhibited a higher transplanted kidney viability and patient survival. The degree of HLA-DR matching did not exhibit a statistically significant effect on the transplanted kidney viability or the patient survival; HLA-DQ

mismatches are associated with acute rejection, independent of HLA-ABDR mismatches and initial immunosuppression. A recent study showed the potential importance of HLA-DQ matching in the assessment of immunologic risk in kidney transplant recipients [14].

Studies have suggested that an older age of the recipients is not correlated with a lower transplanted kidney viability [11,15]. In our study, the age of the kidney transplant recipient was a significant factor of the transplanted kidney viability in the univariate analysis but not in the multivariate analysis. It is also known that donor age is a risk factor of transplanted kidney viability, and the outcome of our study was in agreement with this previous observation as the donors who were 40 years or older exhibited a higher risk of transplanted kidney failure.

Several studies have reported acute rejection as an important risk factor of the viability of the transplanted kidney [16]. In our center, we have been performing a biopsy of the transplanted kidney in patients exhibiting normal renal function during the initial period after the transplant for 10 years on day 14 after the transplant surgery. The patients who did not exhibit acute rejection during the initial period after the transplant had 1-year survival of 97.9%, which was significantly higher than the group of patients with acute rejection (88.4%). This difference became more pronounced with the prolonged survival period of the transplanted kidney: there was a 20% difference in 5-year survival (95.9% vs 77.8%) and a 30% difference in 10-year survival (93.7% vs 62.3%) [17]. The multivariate analysis in our study also suggested that the history of acute rejection within 1 year of transplant has resulted in a higher risk of transplanted kidney failure. Therefore, the acute rejection of the transplanted kidney during the initial period and its recovery appear to be the decisive factor of long-term viability of the transplanted kidney. Consequently, an aggressive treatment against acute rejection during the initial period is absolutely essential to improve the viability of the transplanted kidney.

## CONCLUSIONS

This study has assessed 3000 cases of kidney transplants performed in the past 50 years at the Catholic University of Korea Seoul St. Mary's Hospital and identified the following: (1) With the development of immunosuppressant, the viability of transplanted kidney has been steadily improving. In addition, the age of the kidney transplant recipient has also been steadily increasing as well as the proportion of patients with hypertension and diabetes. (2) The proportion of deceased donor kidney transplant has increased since organ donation registration was established. (3) The major causes of transplanted kidney failure were mortalities unrelated to the transplant and chronic rejection, and the main causes of patient mortality were infection

and cerebrovascular and cardiovascular diseases. (4) The 1-year and 30-year viability of transplanted kidneys was 97% and 51%, respectively, while the 1-year and 30-year patient survival rate was 96% and 52%, respectively. (5) In the future, the appropriate selection or control of immunotherapy, based on the risk level of kidney transplant recipient, is needed to minimize chronic rejection, which is the key cause of transplanted kidney failure. In addition, a multidimensional effort is needed to improve the shortage of organ donors.

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