ORIGINAL ARTICLE

Outcomes in kidney transplantation with mycophenolate mofetil-based maintenance immunosuppression in China: a large-sample retrospective analysis of a national database

Liping Chen, Hongwei Bai, Hailong Jin, Tianyu Zhang, Bingyi Shi, Ming Cai & Yudi Wang

Kidney Transplant Quality Control Center of National Health Commission, The 8th Medical Center of Chinese People's Liberation Army General Hospital, Beijing, China

Correspondence
Bingyi Shi, No.17, Heishanhu Road, Haidian District, Beijing, China.
Tel.: +86-010-66775460;
fax: +86-010-51520594;
e-mail: paradiselily@163.com

Liping Chen and Hongwei Bai contributed equally to this study.

Correction added on 04 March 2020, after first online publication: Table 1 and Supplementary Table 1 have been updated to reflect the correct values for warm ischemia time.

SUMMARY

There is no large data analysis reporting the outcome of Chinese kidney transplant patients using mycophenolate mofetil (MMF). This study analyzed 6719 patients from the Chinese Scientific Registry of Kidney Transplantation using MMF, which included 1153 from donation after cardiac death (DCD), 1271 from donation after brain and cardiac death (DBCD), and 4295 from living donor (LD). Compared with the transplants from deceased donor (DD), better outcomes including 3-year graft survival probabilities (LD = 95.8% vs. DD = 91.3%), incidence of delayed graft function (DGF, LD = 2.4% vs. DD = 17.7%), infection (LD = 10.7% vs. DD = 20.7%), graft loss (LD = 2.3% vs. DD = 6.3), and death (LD = 1.3% vs. DD = 3.2%) were shown in the LD group, with similar incidences of acute rejection (AR, LD = 3.7% vs. DD = 4.7%), hyperuricemia (LD = 21.7% vs. DD = 22.2%) within postoperative 1 year, and serum creatinine (Scr) >133 μmol/l at 1 year (LD = 18.8% vs. DD = 18.6%). Nonsignificant differences were found between the DCD and DBCD group. The 5-year survival of patient and graft in the LD group were 97.5% and 93.0%. Adjusted Cox model for graft loss showed significant associations with DGF [hazard ratio 3.7 (95% CI: 2.4, 5.8)], AR [2.8 (1.7, 4.6)], Scr >133 μmol/l at 1 year [2.6 (1.5, 4.2)], hyperuricemia [2.3 (1.6, 3.3)], and DD [1.6 (1.1, 2.4)].

Transplant International 2020; 33: 718–728

Key words
kidney transplantation, mycophenolate mofetil, risk factor, survival

Received: 10 July 2019; Revision requested: 27 August 2019; Accepted: 18 December 2019;
Published online: 12 January 2020

Introduction

Kidney transplantation is an effective treatment for end-stage renal disease (ESRD), and by the end of 2017 in China, 524 467 hemodialysis patients had been reported. In the same year, 30 502 patients were in the kidney transplant waiting list but only 10 793 underwent kidney transplantation, which means a considerable donor organ shortfall exists in China [1]. Since organ procurement from executed prisoners was banned by the Chinese government in 2015 to ensure sustainable and healthy development of organ transplantation, voluntary organ donation has been the only source of organ transplantation in

doi:10.1111/tri.13566

China, among which deceased donation (DD) plays a dominant role [2]. In China clinical practice, DD could be categorized into donation after brain death (DBD), donation after cardiac death (DCD), or donation after brain and cardiac death (DBCD) [3]. However, laws defining brain death have not been approved yet because the populace acknowledge death only when one's heart arrests. Therefore, the DBCD category consists of potential donors who meet both criteria of brain death and cardiac arrest before organ donation is initiated. Encouragingly, DBCD has been universally regarded as a suitable strategy that respects national, cultural, and social beliefs in China [4].

Potent immunosuppression agents that prevent organ rejection have contributed to the success of organ transplantation considerably [5]. At present, the most common triple immunosuppressive (IS) regimen involve the combination of mycophenolate mofetil (MMF), calcineurin inhibitor (preferring tacrolimus to cyclosporine in China), and steroid. MMF is an inhibitor of inosine monophosphate dehydrogenase and has been used in organ transplantation for more than 20 years to suppress cell-mediated and humoral immune responses in transplantation [6]. In China, more than 80% kidney transplant recipients apply an MMF-based IS regimen and the efficacy of MMF in improving graft and patient survival has been well established [7]; however, no clinical outcome based on large national kidney transplant database has been reported yet.

The Chinese Scientific Registry of Kidney Transplantation (CSRKT) is an only official and national data acquisition system for kidney transplantation, which is held and supervised by the National Health Commission of the People's Republic of China. By October 30, 2019, there had been 135 tertiary hospitals authorized to perform kidney transplantation, each of which reports transplant-related data to this registry mandatorily. CSRKT provides not only the foundation for national regulatory authorities to formulate relevant transplantation policies and regulations, but also scientific management tools of kidney transplant recipients for transplant centers in Mainland of China. Nowadays, CSRKT has become the most critical information systems in kidney transplantation and academic exchange platforms for kidney transplantation in China.

Taking use of this national registry, we retrospectively analyzed the clinical outcome of DCD, DBCD, and related-living donor (LD) transplant recipients with an initial MMF-based IS regimen. Risk factors of all-cause graft loss were also explored.

Patients and methods

Data source and patient population

It is reported that the total kidney transplants from large transplant centers (defined as >100 kidney transplants per year) have exceeded 80% of nation's total number in 2017 in China [1]. As it is generally considered that large transplant centers are more experienced in the management of transplantation and do better in postoperative follow-up, after evaluating data quality according to the uniform scoring rule of CSRKT, we screened 41 large organ transplant centers across 21 cities in China to achieve representative and comprehensive kidney transplant-related data. A total of 9040 cases who underwent DCD, DBCD, or LD kidney transplantation between January 2010 and December 2016 were initially screened. Patients were included with age >18 years and an MMF (CellCept, Roche)-based IS strategy. Patients who converted from MMF to EC-MPA or other maintenance therapy during follow-up were also enrolled in this analysis. As China banned the use of prisoners' organs in 2015, DCD and DBCD transplants between January 2010 and December 2014 were excluded. Patients with previous kidney transplantation, multiple transplant organs, and ABO-incompatible transplant organs were also excluded. Finally, a total of 6719 recipients were included and analyzed, and the patient selection process was presented (Fig. 1). Follow-up information was reported manually at postoperative 1, 3, 6, and 12 months, after which the data were reported every 6 months. This study was approved by the National Health Commission of the People's Republic of China. No data sourced from executed prisoner's' donation was included in this study in accordance with international human rights guidelines of the Declaration of Helsinki and the Declaration of Istanbul.

Outcomes and variable definition

The primary outcomes of this study were patient and graft survival. The secondary outcomes included the incidences of major complications within 1 year post-transplant such as delayed graft function (DGF), acute rejection (AR), primary nonfunction (PNF), hyperuricemia, and renal function assessed by serum creatinine (Scr) levels. All-cause graft loss was defined as patient death, graft failure (a return to chronic dialysis), nephrectomy, and re-transplantation. Graft survival is the time from transplantation to graft loss, patient death, or last follow-up (August 1st, 2018), whichever

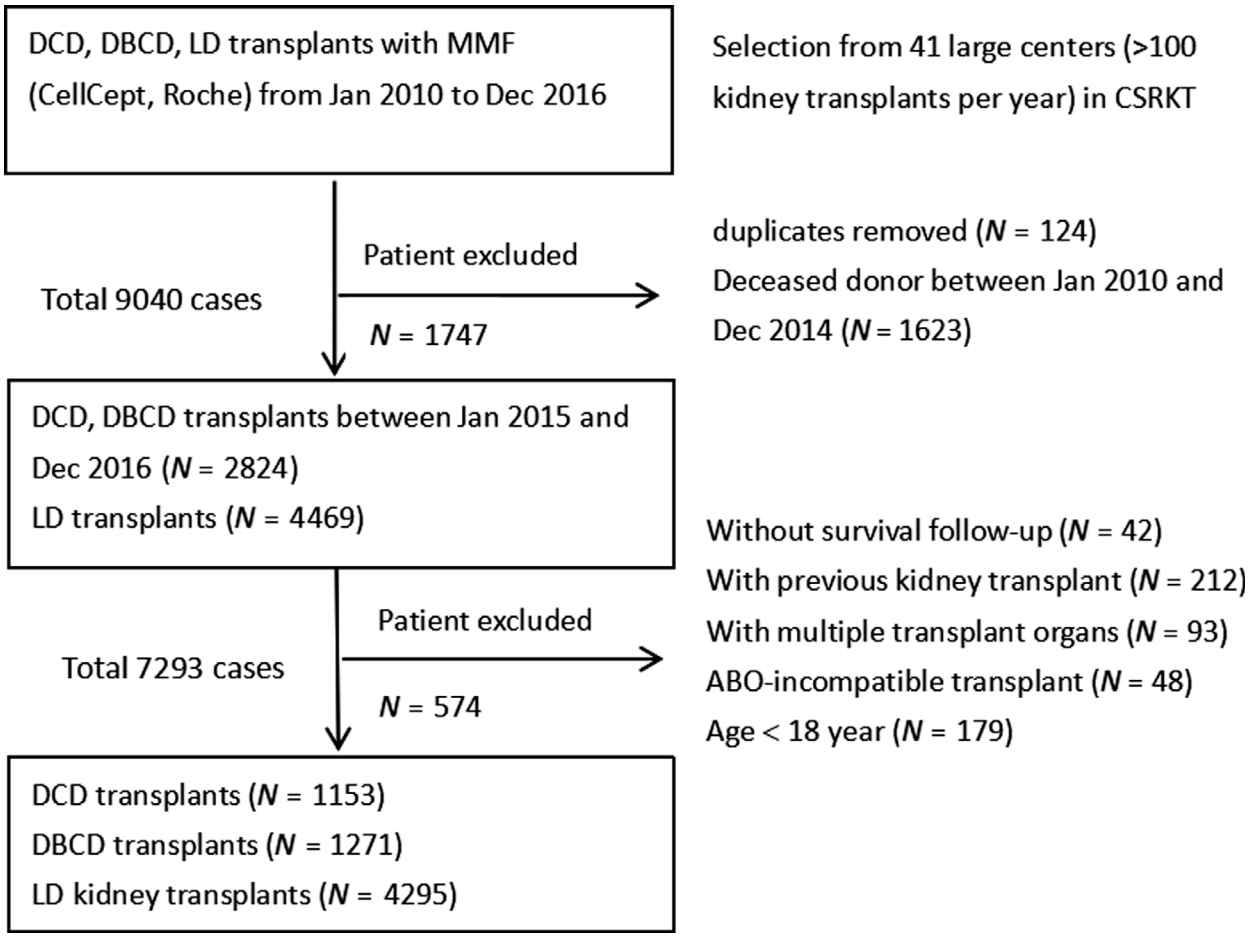

Figure 1 Defining the study population. We reviewed the medical records of 9040 individuals and collected data from 7293 recipients. According to the exclusion criterion, 6719 patients remained in the final analysis.

occurred first. Three-year survival probability was comparatively evaluated in DCD, DBCD, and LD kidney transplants, while 5-year survival probability was additionally explored in LD transplants between January 2010 and December 2016. Sensitivity analyses and comparation were performed in the LD subgroups (transplantation in 2015–2016 vs. in 2010–2014). AR was defined by the need for antirejection treatment, with or without biopsy confirmation on the CSRKT follow-up form. Primary nonfunction (PNF) was defined as graft not functioning from the time of transplantation, excluding premature graft failure from known causes [8]. DGF was defined as need for dialysis in the first week after transplantation [9] and Scr were examined in patient with a functioning graft. Infection was diagnosed by clinical manifestation, imaging, or laboratory examination but urinary tract infection excluded. Postoperative hyperuricemia was biologically defined as mean serum uric acidic (calculated from uric acid values tested for multiple times after transplant in order to assure UA exposure) >420 μmol/l regardless of gender [10]. Dyslipidemia was defined as serum total cholesterol (TC) ≥6.2 mol/l, or low-density lipoprotein cholesterol (LDL-C) ≥4.1 mol/l, or high-density lipoprotein cholesterol (HDL-C) <1.0 mol/l, or triglyceride (TG) ≥2.3 mol/l. HLA mismatches were calculated as the sum of the mismatches in A, B, and DR. Patients lacking biopsy-proven primary kidney disease for uremia but only having a history of glomerular nephritis, are classified as "non-biopsy-proven glomerular nephritis" in CSRKT.

Potential risk factors for graft loss

The baseline characteristics potentially associated with all-cause graft loss include: (i) patient characteristics: age, gender, body mass index, primary disease for transplantation, duration of dialysis before transplantation, dialysis technique, hyperuricemia history, dyslipidemia history, diabetes history; (ii) donor

Transplant International 2020; 33: 718–728

characteristics: age, gender, male recipient of a female donor, donor type (DD or LD); and (iii) transplant-related variables: ischemia time, human leukocyte antigen (HLA) mismatches, antibody induction, initial concomitant IS agents (cyclosporine or tacrolimus). Except for regarding DGF as a baseline variable, the transplant outcomes such as AR (yes/no), postoperative hyperuricemia (yes/no), Scr >133 μmol/l at 1 year post-transplant (yes/no), were also explored the impacts on the graft loss as time-dependent variables. However, patient with PNF were excluded in the process of risk factor evaluation.

Statistical method

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Descriptive summaries included count, sample size, and categorical variables which were shown in groups by donor type. Continuous variables were summarized using mean, standard deviation or median, minimum, and maximum. Mann–Whitney rank sum tests and Pearson's chi-squared tests were used to compare continuous and categorical variables respectively between groups. The Kaplan–Meier method was used to determine the graft survival probability, tested with the log-rank statistics. Cox proportional hazards regression model was used to assess variables associated with graft loss based on the 6719 recipients which were eligible for this study. Missing observations were assumed to be missing at random, and partial deletion was used to handle missing observations. The exploratory analysis of univariable Cox regression used all possible data (i.e., information from patients with both complete and incomplete data) to screen potential influencing factors of graft survival, but the formal univariable and multivariable analysis involved cases that were evaluable for each single variable only. The hypothesis of proportional hazards was checked with graphical diagnostics and a test based on the scaled Schoenfeld-weighted residuals, which showed no evidence of non-proportionality of hazards. The selection of variables into the multivariable model was based on the forward selection method with an entry P value of 0.1. The inclusion of interaction terms was checked based on the P values of all possible interaction terms. No interaction terms will be included if none of the interaction term is statistically significant. Hazard ratios (HRs) and their 95% confidence intervals (CIs) are calculated, and statistical significance was defined as a two-sided P value <0.05.

Results

Baseline characteristics

This study consisted of 6719 transplant patients, including 1153 cases of DCD, 1271 of DBCD, and 4295 of LD kidney transplants. Baseline characteristics were described and compared by donor type (Table 1). Compared with the DD group (DCD and DBCD transplant patients combined), the LD group presented better physical states and donor kidney qualities overall, including younger recipient age, shorter dialysis duration and ischemia time, less proportion of high HLA mismatches (>4), and fewer concomitant diseases such as diabetes, preoperative hyperuricemia, and dyslipidemia. Compared with the DD group, the LD group had more donor aged >60 years, female donors, and male transplant recipients from female donors. Most patients used tacrolimus as a concomitant IS agent instead of cyclosporine, especially in the DD group. It was notable that immune-induction therapy was more commonly used in the DD group than in the LD group, particularly antihuman thymocyte globulin (ATG). The LD subgroups (transplantation in 2015–2016 vs. in 2010–2014) had comparable demographic characteristics (Table S1).

Outcome of transplantation

13.2% (912/6719) of patients with initial MMF usage switched to EC-MPA (10%, 676/6719), mizoribin (3.3%, 219/6719), and azathioprine (0.25%, 17/6719) before the last follow-up data were acquired. Gastrointestinal reaction, leukopenia, and cytomegalovirus infection were the most common reasons for MMF discontinuation. The survival probabilities of graft and patient in the LD group within 3 years after transplant was higher than the DD group (Table 2, Fig. 2a,b), and the 5-year survival probabilities of graft and patient were 93.0% and 97.5% in the LD group (Fig. 3), respectively. Compared with the DD group, the LD group showed lower incidences of DGF, PNF, graft loss, death, and infection within 1 year post-transplant, but similar morbidity of AR, hyperuricemia, and Scr >133 μmol/l at postoperative 1 year (Table 3). Compared with the DD group, renal function indicated by Scr were similar at postoperative 1, 2 years but slightly elevated in the LD group at 3 years, and maintained stable after that (Table 4). No significant differences in clinical outcomes mentioned above were found between the DCD and the DBCD group. Sensitivity analyses showed that the LD subgroups had similar post-transplant outcomes (Table S2–S4).

Table 1. Transplant-related characteristics by donor types.

	DCD (n = 1153)	DBCD (n = 1271)	DD (n = 2424)	LD (n = 4295)	*P* value (LD versus DD)
Recipient					
Median follow-up time (day), [range]	571 [2,1251]	640 [1,1266]	596 [1,1266]	1461 [1,3062]	<0.001
Age (year) ± SD	41.7 ± 11.4	41.0 ± 11.5	41.3 ± 11.4	32.3 ± 8.5	<0.001
>60 year *n* (%)	76/1153 (6.6)	60/1271 (4.7)	136/2424 (5.6)	11/4295 (0.3)	<0.001
Body mass index (kg/m^2) ± SD	22.2 ± 3.6	22.0 ± 3.4	22.1 ± 3.5	21.3 ± 3.0	<0.001
Male, *n* (%)	783/1153 (67.9)	879/1271 (69.2)	1662/2424 (68.6)	3322/4295 (77.3)	<0.001
Male recipient from female donor, *n* (%)	97/1153 (8.4)	103/1271(8.1)	200/2424 (8.3)	2220/4295 (51.7)	<0.001
Male recipient from male donor, *n* (%)	686/1153 (59.5)	776/1271(61.1)	1462/2424 (60.3)	1102/4295 (25.6)	
Primary disease for transplantation					
Non-biopsy-proven glomerular diseases, *n* (%)	645/1153 (55.9)	614/1271 (48.3)	1259/2424 (51.9)	3019/4295 (70.3)	<0.001
Biopsy-proven glomerular diseases, *n* (%)	411/1153 (35.6)	502/1271(39.5)	913/2424 (37.7)	1236/4295(28.8)	<0.001
IgA nephropathy	262/1153 (22.7)	313/1271 (24.6)	575/2424 (23.7)	747/4295 (17.4)	<0.001
Membranous nephropathy	61/1153 (5.3)	53/1271 (4.2)	114/2424 (4.7)	137/4295 (3.2)	0.002
Focal segmental glomerulosclerosis	36/1153 (3.1)	60/1271 (4.7)	96/2424 (4.0)	172/4295 (4.0)	0.929
Other glomerular diseases	52/1153 (4.5)	76/1271 (6.0)	128/2424 (5.3)	180/4295 (4.2)	0.040
Diabetes nephropathy, *n* (%)	32/1153 (2.8)	39/1271 (3.1)	71/2424 (2.9)	4/4295 (0.1)	<0.001
Hypertensive nephropathy, *n* (%)	42/1153 (3.6)	50/1271 (3.9)	92/2424 (3.8)	1/4295 (0)	<0.001
Other primary disease, *n* (%)	24/1153 (2.1)	66/1271(5.2)	90/2424 (3.7)	34/4295 (0.8)	<0.001
Median duration of dialysis (day), [range]	519 [4, 5355]	536 [3, 4775]	528 [3, 5355]	282 [1, 4865]	<0.001
Dialysis technique (HD versus Peritoneal, *n*)	1153/0	1271/0	2424/0	4166/129	<0.001
Hyperuricemia history, *n* (%)	603/994 (60.7)	623/1056 (59.0)	1226/2050 (59.8)	1983/3593 (55.2)	0.001
Dyslipidemia history, *n* (%)	290/502 (57.8)	154/271 (56.8)	444/773 (57.4)	807/1740 (46.4)	<0.001
Diabetes history, *n* (%)	202/1153 (17.5)	236/1271 (18.6)	438/2424 (18.1)	94/4295 (2.2)	<0.001
Donor					
Age (year) ± SD	39.0 ± 16.5	34.8 ± 15.9	37.0 ± 16.4	50.0 ± 8.8	<0.001
>60 year, *n* (%)	84/1153 (7.3)	42/1271 (3.3)	126/2424 (5.2)	490/4295 (11.4)	<0.001
Male, *n* (%)	980/1153 (85.0)	1101/1271 (86.6)	2081/2424 (85.8)	1447/4295(33.7)	<0.001
Transplant					
Cold ischemia time (h) ± SD	6.0 ± 3.6	6.0 ± 4.9	6.1 ± 4.4	1.4 ± 0.5	<0.001
>12 h, *n* (%)	58/1145 (5.1)	77/1258 (6.1)	135/2403 (5.6)	133/4108 (3.2)	<0.001
Warm ischemia time (min) ± SD	7.1 ± 6.0	9.4 ± 8.1	8.5 ± 7.4	3.7 ± 3.3	<0.001
>30 min, *n* (%)	3/1132 (0.3)	14/1235 (1.1)	17/2367 (0.7)	1/4018 (0)	<0.001
Negative PRA, *n* (%)	688/735 (93.6)	732/803 (91.2)	1402/1538 (92.3)	1868/1927 (96.9)	<0.001
HLA mismatches >4, *n* (%)	346/771 (44.9)	382/1010 (37.8)	728/1781 (40.9)	126/2690 (4.7)	<0.001
Antibody induction, *n* (%)	1000/1153 (86.7)	1053/1271(82.8)	2053/2424 (84.7)	2277/3930 (57.9)	<0.001
ATG	604/1153 (52.4)	540/1271 (42.5)	1144/2424 (47.2)	1000/3930 (25.4)	<0.001
IL-2 RA	317/1153 (27.5)	351/1271 (27.6)	668/2424 (27.6)	1036/3930 (26.4)	0.296
ALG	57/1153 (4.9)	142/1271(11.2)	199/2424 (8.2)	100/3930 (2.5)	<0.001
Other	22/1153 (1.9)	20/1271 (1.6)	42/2424 (1.7)	141/3930 (3.6)	<0.001

Table 1. Continued.

	DCD (n = 1153)	DBCD (n = 1271)	DD (n = 2424)	LD (n = 4295)	*P* value (LD versus DD)
None induction, *n* (%)	153/1153 (13.3)	218/1271 (17.2)	371/2424 (15.3)	1653/3930 (42.1)	<0.001
CsA + MMF + steroids, *n* (%)	69/1153 (6.0)	35/1271 (2.8)	104/2424 (4.3)	677/4285 (15.8)	<0.001
Tac + MMF + steroids, *n* (%)	900/1153 (78.1)	920/1271 (72.4)	1820/2424 (75.1)	2747/4285 (64.1)	<0.001
Other or none report, *n* (%)	184/1153 (15.9)	316/1271(24.8)	500/2424 (20.6)	861/4285 (20.1)	0.602

ALG, anti-lymphocyte immunoglobulin; ATG, antithymocyte immunoglobulin; DBCD, donation after brain death followed by circulatory death; DCD, donation after cardiac death; DD, DCD, and DBCD transplant patients combined; HD, hemodialysis; HLA, human leukocyte antigen; IL-2 RA, interlukin-2 receptor antagonist; LD, living donor; MMF, mycophenolate mofetil; SD, standard deviation.

Patients with missing data are deleted for calculation. All the comparison between the DD and LD groups were statistical significance, with the exception of incidences of focal segmental glomerulosclerosis, IL-2 RA use, other or none report of immunosuppressive regimen.

Risk factor for graft loss

Univariate Cox analysis showed that diabetes history of recipients, HLA-mismatches >4, DD (versus LD), no use of cyclosporine, DGF, AR, Scr >133 μmol/l at 1 year, hyperuricemia negatively impacted the graft survival. After adjustment for major time-dependent and fixed confounding factors, multivariate stepwise Cox regression analysis retained DD, DGF, AR, Scr >133 μmol/l at 1 year, postoperative hyperuricemia as the independent factors associated with all-cause graft loss (Table 5). Table S5 showed that the characteristics of the complete cases ($n = 2488$) resembled the total dataset ($n = 6719$).

Discussion

Since the beginning of the voluntary organ donation trial in 2010 and banning on the use of prisoners' organs in 2015 [11], the Chinese government has been striving to establish a legal, ethical and sustainable system in organ donation and transplantation and has made a successful transformation, with opportunity and challenge coexisting. This study is a comprehensive analysis of outcomes in kidney transplant recipients from DCD, DBCD, LD, and risk factor for all-cause graft loss, providing some notable findings that with Chinese characteristics, especially patient demographics and transplant characteristics. First, more than half of transplant candidates have non-biopsy-proven primary kidney disease, which might because that currently, pathological diagnosis is not a routine diagnostic process for patient with ESRD from a variety of reasons in China. Second, cold ischemia time of graft is short on death donors, which might because that donated organs are usually procured and allocated regionally and the Chinese government has established the green channel for human organs transport since May 2016 to shorten the cold ischemia time and avoid unnecessary organ damage or waste. Third, compared with the USA, the proportion of high HLA-antigen mismatches is comparable in DD transplants [12] but lower in LD transplants, which might be attributed to the legal prohibition of unrelated living donor transplant in China [13].

This study also revealed promising clinical outcomes in kidney transplants with MMF-based IS strategy in China. It was reported that the 1- and 3-year graft survival probabilities were 95.7%, 92.4% [14] in a Chinese study of 71 DCD transplants, and 97.7%, 94.5% in another study of 128 DBCD transplants [15]. Our results revealed a similar 1-, 3-year graft survival in the DCD transplants (93.9%, 91.6%) but a slightly lower graft survival in the DBCD group (93.6%, 91.1%), while the

Table 2. Graft and patient survival probabilities by Kaplan–Meier analysis (%, 95% CI).

	DCD (n = 1153)	DBCD (n = 1271)	DD (n = 2424)	LD in 2010–2016 (n = 4295)
Graft survival				
1 year	93.9 [92.3–95.2]	93.6 [92.1–94.9]	93.8 [92.7–94.7]	97.7 [97.2–98.1]
2 year	92.8 [91.0–94.3]	92.0 [90.2–93.5]	92.4 [91.2–93.4]	96.9 [96.3–97.4]
3 year	91.6 [89.3–93.6]	91.1 (88.9–92.9)	91.3 (89.7–92.7)	95.8 [95.2–96.4]
P value	0.600 (DCD versus DBCD)		<0.001 (DD versus LD)	
Patient survival				
1 year	97.2 [96.0–98.1]	96.1 [94.9–97.1]	96.7 [95.8–97.3]	98.8 [98.4–99.0]
2 year	96.9 [95.7–97.8]	95.1 [93.6–96.2]	96.0 [95.0–96.7]	98.5 [98.1–98.8]
3 year	96.3 [94.2–97.6]	95.1 [93.6–96.2]	95.6 [94.4–96.6]	98.2 [97.7–98.5]
P value	0.058 (DCD versus DBCD)		<0.001 (DD versus LD)	

CI, confidence interval.

probabilities were higher than the results previously reported from the UK [16]. Undoubtedly, the LD group had much better survival outcomes than the DD group within 3-year follow-up, and the 5-year survival probabilities for patients and grafts were satisfying (97.5% and 93.0%, respectively). Although overall survival outcomes in LD kidney transplantation were optimistic, it is clear that considerable variability exists between different studies. For example, an analysis of 3124 LD transplant patients in the UK Transplant Registry reported 5-year survival probabilities of patients and grafts as 97% and 89%, respectively [17]. Another Chinese study of 1109 LD kidney transplants reported a 5-year patient survival probability of 97%, which was similar to ours [18].

Studies have shown that clinical outcomes within 1 year after transplantation are essential parameters that can influence long-term graft survival [19]. In China, some single-center studies have shown different clinical outcomes between DCD and DBCD kidney transplantation. For instance, Xue *et al.* [20] reported that the incidence of DGF in DBCD group was significantly lower than in DCD group (12% vs. 27%), and the incidence of AR within postoperative 1 year was lower in DBCD transplants than DCD transplants (6% vs. 18%). However, another Chinese retrospective analysis [21] of 338 DBCD kidney transplants reported a DGF incidence of 19.3%. Variations in the definition of DGF and demographic variables might explain the fluctuation of these

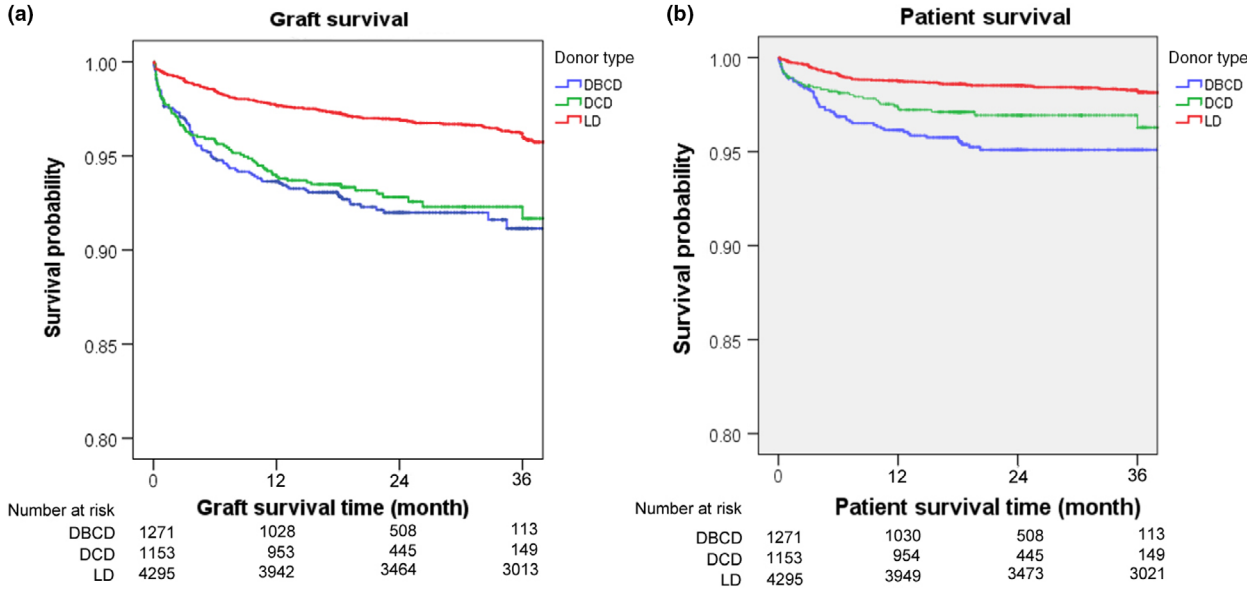

Figure 2 Graft and patient survival of the donation after cardiac death (DCD), donation after brain and cardiac death (DBCD), and living donor (LD) transplants. (a). There are no significant difference in 3-year graft survival between DCD (n = 1153) and DBCD group (n = 1271), but much better graft survival in the LD group (n = 4295). (b). Similar results are shown at the 3-year patient survival.

Transplant International 2020; 33: 718–728

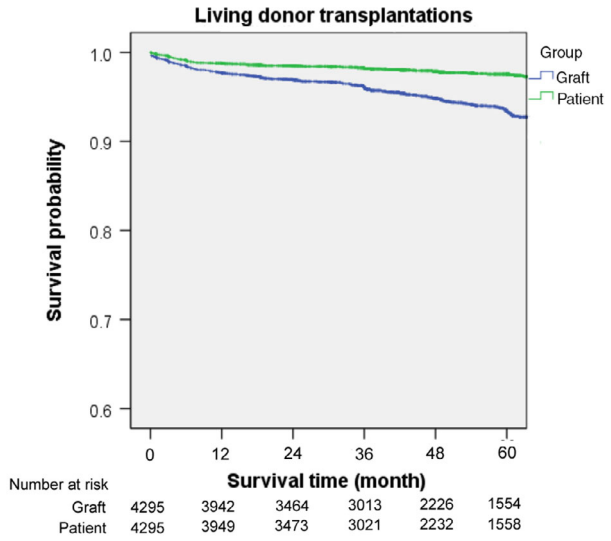

Figure 3 Graft and patient survival of the living donor transplants (n = 4295). The 5-year survival probabilities for grafts and patients were 93.0% and 97.5%, respectively.

previously reported [22]. In this study, DGF incidence in the DD group was much higher than in the LD group (17.7% vs. 2.4%). PNF incidence in the DD group was about 1%, which was slightly lower than the incidence reported previously [23], and was rarely encountered in the LD group.

Taken in to consideration of better survival probabilities and fewer complications (i.e., DGF, PNF, graft loss, death, and infection) within 1 year after transplant, our result demonstrated a much better clinical outcomes of the LD group. However, it seemed that there is no superiority from AR, hyperuricemia, Scr >133 μmol/l in the LD group over the DD group. As shown in Table 1, the large age difference is another prominent characteristic of living donor kidney transplantation in China, which might associate with the large proportion of donation between parents and their children. However, it was reported that kidney transplant from an older donor to a younger recipient had a higher risk of acute rejection early after transplant, but did not affect graft or patient survivals [24]. On the other hand, a high percentage of recipients of the DD group in this study received aggressive induction regimens, which could account for the low AR incidence. Scr at 1 and 2 years after transplant were comparable between groups, with a slight ascending in the LD group but a descending in the DD group at postoperative 3 years. This might be attributed to individual variability and older donor age in the LD group, which suggests that more extended observations are required to further understand long-term clinical outcomes [25].

In this study, patients showed good tolerance to MMF that only about 13% of patients withdrew MMF. Although some studies have reported better gastrointestinal tolerance of enteric-coated mycophenolate sodium than MMF, there is no evidence from blinded studies confirming this advantage, suggesting that other demographic factors may account for these results [26]. For example, tacrolimus is associated with a higher incidence of gastrointestinal adverse events compared to cyclosporine [27]. Hence, in this nonrandomized, large-sample, real-world study, it is difficult to identify the MMF-related adverse events.

Factors associated with outcomes of kidney transplants are well studied but varied in many studies. To our knowledge, this is the first large-sample study based on a China national database, evaluating the potential factors influencing outcome in kidney graft survival. After multivariable adjustment for major time-varying and fixed confounding factors in the large cohort of transplant patients with initial MMF use, the result showed that the independent risk factors for all-cause graft loss were DD, DGF, AR, hyperuricemia, and Scr >133 μmol/l at 1 year post-transplant. Some researches demonstrated that DGF and AR are important risk factors for graft failure in both young and old renal

Table 3. Outcomes of transplantation within 1 year after transplant, n (%).

	DCD (n = 1153)	DBCD (n = 1271)	DD (n = 2424)	LD (n = 4295)	P value (LD versus DD)
DGF	212/1153 (18.4)	217/1271 (17.1)	429/2424 (17.7)	96/3980 (2.4)	<0.001
PNF	12/1153 (1.0)	15/1271 (1.2)	27/2424 (1.1)	2/3980 (0.1)	<0.001
AR	69/1153 (6.0)	44/1271 (3.5)	113/2424 (4.7)	159/4295 (3.7)	0.055
Infection	252/1153 (19.5)	220/1271 (21.9)	472/2424 (20.7)	427/3989 (10.7)	<0.001
Hyperuricemia	254/1039 (24.4)	223/1108 (20.1)	477/2147 (22.2)	864/3983 (21.7)	0.920
Graft loss	71/1153 (6.2)	82/1271 (6.4)	153/2424 (6.3)	99/4295 (2.3)	<0.001
Death	30/1153 (2.6)	48/1271 (3.8)	78/2424 (3.2)	56/4295 (1.3)	<0.001
Scr >133 μmol/l at 1 year	156/864 (18.0)	185/969 (19.1)	341/1833 (18.6)	668/3545 (18.8)	0.831

AR, acute rejection; DGF, delayed graft function; PNF, primary nonfunction; Scr, serum creatinine.

Table 4. Serum creatinine levels in patient with a functioning graft by donor type (μmol/l, *n*).

Postoperation (year)	DCD (*n* = 1153)	DBCD (*n* = 1271)	DD (*n* = 2424)	LD (*n* = 4295)	*P* value (LD versus DD)
1	110.6 ± 58.8 (854)	116.1 ± 61.9 (971)	112.3 ± 55.6 (1825)	113.2 ± 60.1 (3390)	0.348
2	114.7 ± 61.1 (407)	112.0 ± 65.9 (498)	113.2 ± 63.7 (902)	113.8 ± 48.5 (2239)	0.262
3	107.9 ± 33.3 (170)	105.4 ± 43.4 (190)	106.5 ± 38.8 (360)	117.4 ± 63.9 (2612)	<0.001
4	Unavailable	Unavailable	Unavailable	117.6 ± 51.8 (1174)	
5	Unavailable	Unavailable	Unavailable	116.7 ± 48.2 (1372)	

Patients with missing data or with a nonfunctioning graft are deleted for calculation. Scr values at 4 and 5 years in DD group are unavailable owing to the limited follow-up duration.

transplant patients [28], although others showed that AR has no association with graft loss [29]. Our findings show that DGF and AR are strongly associated with graft loss, presumably because DGF and AR can result in functional and structural damage to the graft, which subsequently causes poor graft outcomes. Previous analyses have demonstrated that renal function, measured by Scr at 1 year post-transplant, is a consistent predictor of graft survival, patient survival, and cardiovascular mortality [30]. Here, we used a cutoff point of 133 μmol/l to evaluate the impact of renal function on graft survival and showed that Scr >133 μmol/l at 1 year post-transplant was an independent risk factor for graft loss [31]. This indicates a potential association between Scr absolute level and graft survival probabilities.

Serum uric acid concentration increases in chronic kidney disease and is associated with kidney function. Kidney transplant recipients, particularly those with impaired kidney function, often have abnormal uric acid [32]. These were practically confirmed in our study that hyperuricemia occurred in more than 50% of kidney transplant candidates and about 20% of transplant recipients within postoperative 1 year. However, we did not see significant difference in the morbidities of hyperuricemia between the DD and LD groups. The association between hyperuricemia and kidney graft outcome remains controversial. Kim *et al.* [33] have previously suggested that uric acid level is associated with the risk of total graft failure, but not as an independent risk factor. Nevertheless, studies also showed that post-transplant

Table 5. Cox regression analysis for graft loss free survival with evaluable covariate values (*n* = 2488).

	Univariable		Multivariable	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Recipient				
Gender (M/F)	1.1 [0.8–1.6]	0.500		
Diabetes history of recipient (Y/N)	1.9 [1.2–3.1]	0.005		
HLA mismatches >4 (Y/N)	1.8 [1.3–2.6]	0.001		
Duration of dialysis per year increase	1.1 [1.0–1.2]	0.098		
Donor				
DD versus LD	2.3 [1.6–3.3]	<0.001	1.6 [1.1–2.4]	0.012
CIT >12 h (Y/N)	1.0 [0.4–2.7]	0.986		
Transplant related				
Antibody induction (Y/N)	1.3 [0.9–1.9]	0.136		
Cyclosporine (Y/N)	0.7 [0.5–0.9]	0.009		
Tacrolimus (Y/N)	1.3 [0.9–1.9]	0.142		
DGF (Y/N)	6.2 [4.4–10.1]	<0.001	3.7 [2.4–5.8]	<0.001
AR (Y/N)	4.5 [2.8–7.3]	<0.001	2.8 [1.7–4.6]	<0.001
Scr >133 μmol/l at 1 year (Y/N)	3.6 [2.2–6.0]	<0.001	2.6 [1.5–4.2]	<0.001
Hyperuricemia (Y/N)	3.3 [2.4–4.8]	<0.001	2.3 [1.6–3.3]	<0.001

CIT, cold ischemia time; HR, hazard ratio; Scr, serum creatinine; Y/N, Yes/No.

Cox regression analysis only involves data that are evaluable for each single variable. Percentage of censored was 93.6%, and the number of graft loss was 160.

Transplant International 2020; 33: 718–728

elevation of serum uric acid is an independent predictor of long-term graft survival and graft function [34], which might because that hyperuricemia plays a role in progression of cardiovascular event and renal disease at cellular and molecular level [35]. Accordingly, our analysis also revealed that hyperuricemia was an independent predictor of all-cause graft loss.

One of major advantages of this study is that up to now, this is the first large-sample, real-world study based on the China's national database to analyze the detailed clinical outcomes of DCD, DBCD, and LD kidney transplantation. However, limitations always exist. First, missing data and incomplete records of donor demographic characteristics or recipient follow-up events in the CSRKT should not be ignored. It will influence the assessment of patient outcomes, increase the complexity of the analysis, and cause bias of results and so on. This also includes complicating cardiac and cerebrovascular events, potential drug nephrotoxicity, tumor, metabolic diseases, and viral infections (especially cytomegalovirus and BK virus), which may also influence the observed associations between independent risk factors and graft survival. Second, details of IS therapy adjustment are not analyzed in this study and we are unable to precisely comment on the relationship between IS regimen and outcomes. Third, there was a large proportion of nonbiopsy-proven glomerular nephritis in our cohort, which is a potential confounder given the association between primary kidney disease and graft survival.

In summary, this large-sample and retrospective study based on China's national database indicates good outcomes after DCD, DBCD, and LD kidney transplant with initial MMF-based IS regimen. Patient and graft survival, as well as the overall morbidities of major complications within 1 year after transplant, were comparable between DCD and DBCD kidney transplants, but higher than those in the LD group. DGF, AR, and Scr >133 μmol/l at 1 year post-transplant, hyperuricemia, and DD were identified as independent risk factors for graft survival.

Authorship

LC and HB: designed the study and wrote paper. TZ: collected the data. HJ and YW: analyzed the data and generated the tables. MC and BS: revised the manuscript. All authors have read and approved the final version of the manuscript for publication.

Funding

This study was supported by the National Natural Science Foundation project of China (No. 81770647).

Conflict of interest

The authors declare no conflict of interests. The results presented in this paper have not been published previously in whole or part, except in abstract format.

Acknowledgements

The authors are grateful to all the transplant centers in China that contributed the data on which the article is based.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Transplant-related characteristics by era and donor type.

Table S2. Graft and patient survival probabilities by Kaplan-Meier analysis (%, 95% CI).

Table S3. Postoperative complications within 1 year by era and donor type, *n* (%).

Table S4. Serum creatinine levels in patient with a functioning graft by ear and donor type (mol/l, *n*).

Table S5. Comparison of multiple variables in the complete cases by type donor, *n* (%).

REFERENCES

1. National Health Commission of the People's Republic of China. *National Medical Service and Quality Safety Report 2018*. Beijing: Scientific and Technological Documentation Press, 2019: 606 pp. [in Chinese].
2. Guo Y. The, "Chinese Mode" of organ donation and transplantation: moving towards the center stage of the world. *Hepatobiliary Surg Nutr* 2018; **7**: 61.
3. Sun R. A study of cadaveric organ donation in China. *J Sichuan Univ Arts Sci* 2014; **24**: 47.
4. Sun Q, Gao X, Wang H, Ko DS, Li XC. A new era for organ transplantation in China. *Lancet* 2014; **383**: 1971.
5. Newell KA, Turka LA. Tolerance signatures in transplant recipients. *Curr Opin Organ Transplant* 2015; **20**: 400.
6. European Mycophenolate Mofetil Cooperative Study Group. Placebo-controlled study of mycophenolate mofetil combined with cyclosporin and

corticosteroids for prevention of acute rejection. *Lancet* 1995; **345**: 1321.
7. Wu JY, Chen JH, Wang YM, He Q, Wu DB. Improved clinical outcomes in Chinese renal allograft recipients receiving lower dose immunosuppressants. *Transplantation* 2004; **78**: 713.
8. Bell R, Farid S, Pandanaboyana S, Upasani V, Baker R, Ahmad N. The evolution of donation after circulatory death renal transplantation: a decade of experience. *Nephrol Dial Transplant* 2019; **34**: 1788.
9. Sert I, Colak H, Tugmen C, *et al*. The effect of cold ischemia time on delayed graft function and acute rejection in kidney transplantation. *Saudi J Kidney Dis Transpl* 2014; **25**: 960.
10. Branch of Kidney Physicians of Chinese Physicians Association. Guidelines for the diagnosis and treatment of hyperuricemia in renal diseases in China (2017 edition). *Natl Med J China* 2017; **97**: 1927.
11. Huang J, Millis JM, Mao Y, Millis MA, Sang X, Zhong S. A pilot programme of organ donation after cardiac death in China. *Lancet* 2012; **379**: 862.
12. Williams RC, Opelz G, McGarvey CJ, Weil EJ, Chakkera HA. The risk of transplant failure with HLA mismatch in first adult kidney allografts from deceased donors. *Transplantation* 2016; **100**: 1094.
13. Williams RC, Opelz G, Weil EJ, McGarvey CJ, Chakkera HA. The risk of transplant failure with HLA mismatch in first adult kidney allografts 2: living donors, summary, guide. *Transplant Direct* 2017; **3**: e152.
14. Chen GD, Shiu-Chung Ko D, Wang CX, *et al*. Kidney transplantation from donors after cardiac death: an initial report of 71 cases from China. *Am J Transplant* 2013; **13**: 1323.
15. Na N, Li K, Huang Z, *et al*. Posttransplant outcomes of kidneys donated after brain death followed by circulatory death: a cohort study of 128 Chinese patients. *Transplant Direct* 2017; **3**: e189.
16. Summers DM, Johnson RJ, Allen J, *et al*. Analysis of factors that affect outcome after transplantation of kidneys donated after cardiac death in the UK: a cohort study. *Lancet* 2010; **376**: 1303.
17. Fuggle SV, Allen JE, Johnson RJ, *et al*. Factors affecting graft and patient survival after live donor kidney transplantation in the UK. *Transplantation* 2010; **89**: 694.
18. Song T, Fu L, Rao Z, *et al*. Kidneys from older living donors provide excellent short and intermediate outcomes – a single China center's experience. *Transplantation* 2015; **99**: e81.
19. Park WY, Kang SS, Jin K, Park SB, Han S. Is the clinical outcome good or bad in patients hospitalized within 1 year after kidney transplantation? *Transplant Proc* 2018; **50**: 1001.
20. Xue W, Tian P, Xiang H, *et al*. Outcomes for primary kidney transplantation from donation after Citizens' death in China: a single center experience of 367 cases. *BMC Health Serv Res* 2017; **17**: 250.
21. Sun Q, Huang Z, Zhou H, *et al*. New factors predicting delayed graft function: a multi-center cohort study of kidney donation after brain death followed by circulatory death. *Kidney Blood Press Res* 2018; **43**: 893.
22. Siedlecki A, Irish W, Brennan DC. Delayed graft function in the kidney transplant. *Am J Transplant* 2011; **11**: 2279.
23. Hamed MO, Chen Y, Pasea L, *et al*. Early graft loss after kidney transplantation: risk factors and consequences. *Am J Transplant* 2015; **15**: 1632.
24. Lee YJ, Chang JH, Choi HN, *et al*. Donor-recipient age difference and graft survival in living donor kidney transplantation. *Transplant Proc* 2012; **44**: 270.
25. Xiong Y, Jiang J, Zhang H, *et al*. Higher renal allograft function in deceased-donor kidney transplantation rather than in living-related kidney transplantation. *Transplant Proc* 2018; **50**: 2412.
26. Budde K, Durr M, Liefeldt L, Neumayer HH, Glander P. Enteric-coated mycophenolate sodium. *Expert Opin Drug Saf* 2010; **9**: 981.
27. Helderman JH, Goral S. Gastrointestinal complications of transplant immunosuppression. *J Am Soc Nephrol* 2002; **13**: 277.
28. Faravardeh A, Eickhoff M, Jackson S, *et al*. Predictors of graft failure and death in elderly kidney transplant recipients. *Transplantation* 2013; **96**: 1089.
29. Morales JM, Marcén R, del Castillo D, *et al*. Risk factors for graft loss and mortality after renal transplantation according to recipient age: a prospective multicentre study. *Nephrol Dial Transplant* 2012; **27**(Suppl. 4): iv39.
30. Hariharan S, McBride MA, Cherikh WS, Tolleris CB, Bresnahan BA, Johnson CP. Renal function as a predictor of long-term graft survival in renal transplant patients. *Nephrol Dial Transplant* 2003; **18**(Suppl. 1): i3.
31. Pascual J, Marcén R, Ortuño J. Renal function: defining long-term success. *Nephrol Dial Transplant* 2004; **19** (Suppl. 6): vi3.
32. Mazali FC, Mazzali M. Uric acid and transplantation. *Semin Nephrol* 2011; **31**: 466.
33. Kim ED, Famure O, Li Y, Kim SJ. Uric acid and the risk of graft failure in kidney transplant recipients: a re-assessment. *Am J Transplant* 2015; **15**: 482.
34. Haririan A, Metireddy M, Cangro C, *et al*. Association of serum uric acid with graft survival after kidney transplantation: a time-varying analysis. *Am J Transplant* 2011; **11**: 1943.
35. Zhang K, Gao B, Wang Y, *et al*. Serum uric acid and renal transplantation outcomes: at least 3-year post-transplant retrospective multivariate analysis. *PLoS ONE* 2015; **10**: e0133834.