Analysis of risk factors for donation after circulatory death kidney transplantation in Japan

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Abstract
Background In Japan, donations after circulatory death kidney transplantation are widely performed due to legislation delays. The number of donations after brain death kidney transplantations is increasing, but the target remains unmet. We reviewed the outcomes of donation after circulatory death in Japan.

Methods We analyzed 2923 deceased kidney transplantations (2239: donation after circulatory death (DCD), 684: donation after brain death (DBD)) performed in Japan from 2000 to 2019. The outcomes of the DCD and DBD groups were compared. We examined the risk factors for graft loss in the DCD group.

Results The 5-year patient survival and death-censored graft survival rates of the DCD group, obtained by propensity score matching, were 93.6% and 95.2%, respectively, which were equivalent to 94.2% and 93.8%, respectively, obtained in the DBD group. Older donors (≥ 50 years) and prolonged cold ischemia time (≥ 12 h) were risk factors for graft loss; in the presence of these, graft survival was lower in the DCD group.

Conclusions Older donors and prolonged cold ischemia time reduced graft survival in the DCD group. Proper evaluation of donors and careful preparation for transplant surgery are, therefore, essential to ensure good transplant outcomes.

Keywords Kidney transplantation · Donation after circulatory death · Cold ischemia time

Abbreviations
DCD Donation after circulatory death
DBD Donation after brain death
CIT Cold ischemic time
WIT Warm ischemia time
CVD Cerebrovascular disorder

Introduction

Kidney transplantation is a widely performed and established treatment option for chronic renal failure. In Japan, legislation permitting the donation of brain-dead organs was enacted in 1997 [1]. However, because brain-dead organ donation requires the donor to make their intention clear before brain death, for approximately 10 years following its enaction, brain-dead organ transplantation was performed in very few patients every year [2]. On the other hand, living-donor kidney transplantation and kidney transplantation from donation after circulatory death (DCD) have been widely performed in Japan [3].

Most DCDs performed in Japan are Maastricht category IV and uncontrolled DCDs [4]. This is because active termination of treatment, such as respiratory withdrawal, is not preferred in the country. Under these severe conditions, renal transplantation with uncontrolled DCD is being performed in Japan in patients with chronic renal failure. Although donation after brain death (DBD) increased after revision of the law in 2010, the target remains unmet, and it is necessary to continue DCD kidney transplantation in Japan.

DCD kidney transplantation was considered to have poor outcomes, similar to donations from expanded criteria donors [5, 6]. Recently, many DCDs have been performed due to donor shortage, and many reports have suggested the usefulness of DCD kidney transplantation [7, 8]. Some reports have suggested that DCD outcomes are similar to DBD outcomes [9, 10]. However, this cannot be considered
true for Japanese donors, since they have different backgrounds than donors from other countries. The large difference in end-stage circulatory dynamics is due to differences in end-stage care and the degree of organ injury. Prolonged end-of-life hypotension, which is common in Japan, causes a decrease in renal blood flow and severe organ damage. Ischemia–reperfusion injury worsens in cases of prolonged blood pressure levels below 80 mmHg [11]. It is also assumed that the cold ischemic time (CIT) is longer, because the time of cardiac arrest is always unknown. A prolonged ischemia time may cause poor graft outcomes [12, 13].

DCD needs to be continued in Japan, and the key to this continuation is the analysis of transplantation outcomes and risk factors for graft loss. This study assessed the transplantation outcomes and risk factors of the graft loss in DCD transplantation of Japan.

Patients and methods

Study population

This study used data from the Japan Transplant Society for Transplantation registry. This was a retrospective analysis of kidney transplantations performed in Japan between 2000 and 2018. To compare the kidney transplantation outcomes exclusively, patients with multiple organ transplantations were excluded. A total of 2923 deceased kidney donors were included: 2239 were DCD cases, and 684 were DBD cases.

Donation after cardiac arrest in Japan

If brain death could not be diagnosed legally, donations were performed after cardiac arrest. The following measures were followed for organ retrieval after cardiac arrest: arterial cannulation could be performed before cardiac arrest when brain death was diagnosed clinically. Heparin injection was allowed, but ventilator arrest was not recommended before cardiac arrest. Surgeons waited for cardiac arrest from fluid reduction or tapering of catecholamines in the intensive care unit. Perfusion was initiated from the cannula after the declaration of death. If arterial cannulation could not be performed before cardiac arrest, cardiopulmonary resuscitation (CPR) after cardiac arrest was performed until the start of operation.

Only few records of the presence or absence of pre-cardiac arrest cannulation and CPR were available; this was not the focus of this study.

Data collection and study content

The variables of interest included characteristics of the recipients (age, sex, preoperative dialysis period) and donors (age, sex, cause of death), CIT, and transplantation outcomes (patient survival period and graft survival period), which were collected from the database. The transplantation outcomes and background characteristics of the DCD group were compared with those of the DBD group. To further examine the transplantation outcomes of the DCD group, the relationship between DCD outcomes and the above-mentioned variables was assessed.

Statistical analysis

All continuous variables are presented as mean ± standard deviation. The survival rate was calculated using the Kaplan–Meier method and analyzed using the log rank test. The propensity score was calculated using recipients’ characteristics, donors’ characteristics, and CIT. A one-to-one score matching was performed. A multivariate analysis was performed using the Cox proportional hazards model. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [14]. A P value < 0.05 was considered statistically significant.

Ethical considerations

All the study participants provided informed consent to the committee of the Japanese kidney transplant registry, and information on the opt-out procedure was published on the Fujita Health University website (http://www.fujita-hu.ac.jp). The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Fujita Health University (HM20-127).

Results

DCD vs. DBD—before propensity score matching

The background characteristics of both groups are shown in Table 1. The mean age of the recipients in the DCD and DBD groups was 48.4 ± 12.8 and 48.5 ± 15.9 years, respectively; there was no statistically significant difference. The number of male recipients was higher in the DCD group than in the DBD group (65.7% vs. 60.7%, P = 0.019). The duration of dialysis did not differ between the two groups (16.5 ± 7.6 vs. 17.1 ± 7.4 years, P = 0.087). Regarding donors’ characteristics, there were several significant differences. The mean age of the donors in the DCD group was 50.0 ± 15.4 years; the DCD group was significantly older than the DBD group (P < 0.001). The main cause of death in both groups was cerebrovascular disorders (CVDs). However, the prevalence of CVDs was 56.1% in the DCD group.
and 50.8% in the DBD group; the difference was statistically significant \( (P=0.005) \). Furthermore, CIT was significantly longer in the DCD group \( (11.5 \pm 5.2 \text{ vs. } 8.2 \pm 3.2 \text{ h}, P < 0.001) \).

Figure 1 shows the patient and graft survival rate. The 1-year \( (96.6\% \text{ vs. } 98.6\%) \), 3-year \( (93.9\% \text{ vs. } 95.6\%) \), and 5-year patient survival \( (90.4\% \text{ vs. } 92.8\%) \) were lower in the DCD group (Fig. 1A). The 1-year, 3-year, and 5-year overall graft survival rate were significantly lower in the DCD group \( (93.2 \text{ vs. } 97.4, 88.7 \text{ vs. } 93.5, 83.8 \text{ vs. } 88.3, P=0.009, \text{ Fig. 1B}) \). The death-censored graft survival rate was lower in the DCD group at 1 year \( (96.3\% \text{ vs. } 98.6\%) \), 3 years \( (93.8\% \text{ vs. } 97.3\%) \), and 5 years \( (91.5\% \text{ vs. } 93.9\%) \) (Fig. 1C).

Since there was a significant difference in the characteristics of the donors between both groups, we adjusted for background factors (recipient age and sex, duration of dialysis, donor age and sex, cause of death, and CIT) using propensity score matching before comparing the two groups.

**DCD vs. DBD—after propensity score matching**

The characteristics of the two groups after matching are shown in Table 1. A total of 394 pairs were extracted from both groups by matching. The donors’ ages were lower, and the CIT was shorter in the DCD group than before matching; this resulted in no significant difference in the background characteristics of the donors between the two groups. The patient survival in both groups is shown in Fig. 1D. The 1-year, 3-year, and 5-year survival rates of the DCD and DBD groups were 99.4 vs. 99.0%, 97.3 vs. 96.9%, and 93.6 vs. 94.2%, respectively (Fig. 1D). The 1-year-, 3-year-, and 5-year overall graft survival rates of both groups were 98.3% vs. 98.2%, 94.1% vs. 94.7%, and 89.7% vs. 89.2%, respectively (Fig. 1E). The 1-year, 3-year, and 5-year death-censored graft survival rates of both groups were 98.7% vs. 99.3%, 96.7% vs. 97.4%, and 95.2% vs. 93.8%, respectively (Fig. 1F). There were no significant differences in the patient and graft survival between the two groups.

From these results, DCD and DBD transplantation outcomes are similar under certain conditions. However, the results changed significantly after propensity score matching, suggesting that the outcomes are dependent on background characteristics, especially those of the donors. Thus, we further investigated each donor characteristic in the DCD group.

**Analysis of donors’ characteristics in the DCD group**

**Donor age**

The mean age of the DCD donors (50.0 years) was higher than that of the DBD donors. DCD donors were divided into four groups according to their age (< 40, 40–49, 50–59, and ≥ 60 years). Figure 2 shows the Kaplan–Meier curve of the death-censored graft survival of each group. Five-year death-censored graft survival rates worsened significantly with age \( (P=0.0173) \). The difference between those aged ≥ 50 years and < 50 years was significantly large. From the receiver operating characteristic curve for graft loss within 5 years, the cutoff value was 51 years (area under the curve = 0.649).

### Table 1  Background characteristics of both groups

| Variables                        | Pre-matching |                                     | Post-matching |                                     |
|----------------------------------|--------------|--------------------------------------|---------------|--------------------------------------|
|                                  | DCD          | DBD                                  | \( p \) value | DCD                                  | DBD      | \( p \) value |
| Recipients’ characteristics      |              |                                       |               |                                       |          |               |
| Age (years)                      | n = 2239     | n = 684                              | 0.924         | n = 394                              | n = 394  | 0.506         |
| Sex (male, %)                    | 1465 (65.7)  | 415 (60.7)                           | 0.019         | 236 (59.9)                           | 242 (61.4)| 0.715         |
| Duration of dialysis (years)     | 16.51 (7.62) | 17.12 (7.43)                         | 0.087         | 17.43 (9.44)                         | 17.30 (7.07)| 0.832         |
| Donors’ characteristics          |              |                                       |               |                                       |          |               |
| Age (years)                      | n = 394      | n = 394                              | <0.001        | n = 394                              | n = 394  | 0.622         |
| Sex (male, %)                    | 727 (61.0)   | 391 (59.7)                           | 0.621         | 222 (56.3)                           | 218 (55.3)| 0.83          |
| Cause of death (%)               |              |                                       | 0.005         |                                       |          | 0.198         |
| Trauma                           | 374 (18.1)   | 164 (19.4)                           | 0.75          | 75 (19.0)                            | 74 (18.8)|               |
| Cerebrovascular disorder         | 1158 (56.1)  | 429 (50.8)                           | 0.628         | 195 (49.5)                           | 200 (50.8)|               |
| Cardiovascular disorder          | 91 (4.4)     | 22 (2.6)                             | 0.17          | 17 (4.3)                             | 12 (3.0) |               |
| Hypoxia                          | 194 (9.4)    | 111 (13.1)                           | 0.50          | 50 (12.7)                            | 67 (17.0)|               |
| Other                            | 248 (12.0)   | 119 (14.1)                           | 0.57          | 57 (14.5)                            | 41 (10.4)|               |
| CIT (hours)                      | 11.52 (5.16) | 8.17 (3.19)                          | <0.001        | 8.29 (3.21)                          | 8.25 (3.05)| 0.868         |

\( p \) values < 0.05 in bold show significant difference between groups.

*DCD* donation after circulatory death, *DBD* donation after brain death, *CIT* critical ischemic time.
Cause of donor death

Figure 3A shows the causes of death in the DCD group. CVD was the most common cause of death. Moreover, the rate of death-censored graft loss within 5 years was significantly higher when CVD was the cause of death (P < 0.001). Figure 3B shows the percentage of donors aged ≥ 50 years in the CVD and non-CVD groups. Most donors who died from CVDs were ≥ 50 years. Figure 3C shows the Kaplan–Meier curve of death-censored graft survival showing the differences between the CVD and non-CVD donors. The graft survival rate after transplantations of kidneys from CVD donors was significantly lower than that of non-CVD donors (P = 0.0048).

Cold ischemic time

The mean CIT in the DCD group was 11.5 h. The cutoff value was set at 12 h, by referring to a previous report [15]. Figure 4 shows the death-censored graft survival rate of the two groups (CIT < 12 h, CIT ≥ 12 h). The death-censored graft survival rate was significantly lower in the ≥ 12 h group than in the < 12 h group (P = 0.0486).

Multivariate analysis

A Cox proportional hazards analysis of the death-censored graft survival was performed using recipient and donor factors.

Recipient sex, donor age, cause of death, and CIT (≥ 12 h) were significant factors in the univariate analysis (Table 2). A multivariate analysis using these factors and recipient age identified donor age and CIT (≥ 12 h) as independent risk factors.

Examination using risk factors

Table 3 shows the comparison of background characteristics of the DBD and DCD groups according to age. In both groups, the most prevalent cause of death among the older donors was CVD. In contrast, the rate of CVD was lower in younger donors in both groups. To further examine the difference in graft survival due to this factor, the death censored...
The usefulness of uncontrolled DCD was elucidated in this Japanese data-based study. This study’s results are pertinent in a setting like Japan, where the number of DBD is small, and the need for DCD is high. After propensity score matching, there was no difference in both patient and graft survival rates between the DBD and DCD groups. This suggests that uncontrolled DCD in Japan is acceptable under certain conditions. However, there was a significant difference in the characteristics of DCD and DBD before propensity score matching. Before matching, there were significant differences in background characteristics, such as donor age and cause of death, which are generally referred to as risk factors for graft loss. These differences can explain the differences.

Discussion

The usefulness of uncontrolled DCD was elucidated in this Japanese data-based study. This study’s results are pertinent in a setting like Japan, where the number of DBD is small, and the need for DCD is high. After propensity score matching, there was no difference in both patient and graft survival rates between the DBD and DCD groups. This suggests that uncontrolled DCD in Japan is acceptable under certain conditions. However, there was a significant difference in the characteristics of DCD and DBD before propensity score matching. Before matching, there were significant differences in background characteristics, such as donor age and cause of death, which are generally referred to as risk factors for graft loss. These differences can explain the differences.

Fig. 3 Graft survival rate according to cause of death. A shows the frequency of the cause of death and the percentage of graft failure within 5 years. Cerebrovascular disorders (CVD) were the commonest cause, and the rate of graft loss was also high in CVD donors. B shows the percentage of donors aged ≥ 50 years in the CVD and non-CVD groups. CVD accounted for a higher percentage of patients. C shows the death-censored graft survival rate of the CVD and non-CVD groups. The death-censored graft survival rate was significantly lower in the CVD group.
in graft survival. Therefore, we concluded that DCD outcomes may be poor under certain conditions.

In the DCD group, donor age and CIT were risk factors for graft loss. The cause of donor death, which is known as a risk factor for graft loss [16], was a significant risk factor in the univariate analysis, but not in the multivariate analysis. Furthermore, in the sub-analysis, it was revealed that CVD affected graft survival only in elderly donors. This indicates that donor age and CIT in patients with uncontrolled DCD should be the areas of focus. The fact that donor age is a risk factor suggests that kidney function deteriorates with age. In fact, the kidneys of older donors undergo arteriosclerosis, and have lower nephron counts. Furthermore, it is thought that the kidneys of elderly donors are more vulnerable to ischemia–reperfusion injury than those of younger donors [17]. Therefore, to improve transplant outcomes from older donors, it is necessary to reduce perioperative graft injury. One of the ways of reducing ischemia–reperfusion injury is shortening the CIT. This idea resonates with our result, that the CIT is crucial, especially for older donors. Sampaio et al. also reported the importance of shortening the CIT in

![Fig. 4](Image)

**Fig. 4** Graft survival rate according to critical ischemic time. The death-censored graft survival rate was significantly lower in the ≥ 12 h group than in the < 12 h group.

| Table 2 | Results of the analysis of the death-censored graft survival using a Cox proportional hazards model |
| Factor                          | Univariate analysis |          | Multivariate analysis |          |
|                                 | HR (95% CI) | p value | HR (95% CI) | p value |
| Recipient factor                |              |          |              |          |
| Age (years)                     | 0.9961 (0.990–1.006) | 0.448 | 0.9899 (0.973–1.007) | 0.245 |
| Sex (male, %)                   | 1.358 (1.006–1.833) | **0.0453** | 1.175 (0.696–1.983) | 0.546 |
| Duration of dialysis (years)    | 0.9945 (0.976–1.013) | 0.562 |              |          |
| Donor factor                    |              |          |              |          |
| Age (≥ 50 years)                | 1.021 (1.005–1.038) | **<0.001** | 1.744 (1.014–2.999) | **0.0443** |
| Sex (male, %)                   | 0.9397 (0.591–1.495) | 0.793 |              |          |
| Cause of death (CVD)            | 1.709 (1.267–2.305) | **<0.001** | 1.421 (0.812–2.485) | 0.215 |
| CIT (≥ 12 h)                    | 1.32 (1.002–1.741) | **0.0487** | 1.737 (1.065–2.83) | **0.0268** |

*p values < 0.05 in bold show significant difference between groups*

**HR** hazard ratio, **CI** confidence interval, **CIT** critical ischemic time, **CVD** cerebrovascular disorders

| Table 3 | Background characteristics of the two groups classified according to donor age in years |
| Variables                          | DCD <50 | ≥ 50 | DBD <50 | ≥ 50 |
| *n* = 453  | *n* = 545 | *n* = 308 | *n* = 201 |
| Recipients’ characteristics        |        |        |        |        |
| Age (years)                        | 48.8 ± 14.8 | 50.2 ± 12.0 | 46.6 ± 16.9 | 50.0 ± 15.1 |
| Sex (male, %)                      | 165 (36.6) | 185 (33.9) | 108 (35.1) | 85 (42.3) |
| Duration of dialysis (years)       | 17.1 ± 8.1  | 17.7 ± 7.6  | 16.8 ± 7.7  | 17.1 ± 7.0  |
| Donor factor                       |        |        |        |        |
| Age (years)                        | 39.3 ± 11.5 | 61.5 ± 6.3  | 35.0 ± 12.2 | 59.4 ± 5.9  |
| Sex (male, %)                      | 167 (36.9) | 221 (40.7) | 115 (37.3) | 101 (50.2) |
| Cause of death (cerebrovascular disorders) | 175 (42.8) | 322 (63.5) | 109 (42.9) | 113 (62.1) |
| CIT (hours)                        | 11.7 ± 6.0  | 12.2 ± 6.2  | 8.0 ± 3.1  | 8.4 ± 3.1  |

*DCD* donation after circulatory death, *DBD* donation after brain death, *CIT* critical ischemic time
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Kidney transplantation from marginal donors. They clarified that minimizing CIT improved transplant outcomes when the Kidney Donor Profile Index, which was created based on risk factors including donor age and DCD status, was over 85% [15]. Shortening of CIT can be achieved not only with technical improvements, but also with improved coordination. In Japan, regional systems for prefectures have been adopted for kidney donations. As a result, the CIT of DCD is shorter than that in several reports [18–21]. However, the CIT in the DCD group was approximately 3 h longer than that of the DBD group in this study. This suggests that the exact time for transplant surgery in uncontrolled DCD transplantation cannot be estimated. It is difficult to accurately predict when cardiac arrest will occur. Proper coordination from procurement to transplantation is important in DCD transplantation.

While such risk factors were clarified in the DCD group, there was no significant decrease in the graft survival rate in the DBD group, even with the two risk factors. The major difference between uncontrolled DCD and DBD is hemodynamic instability in the terminal stage. Gill et al. showed that there was a difference in the graft survival rate after prolonged warm ischemia time (WIT), depending on whether the CIT was 12 h or more [22]. This suggests that organ injury due to prolongation of the WIT is reversible for a short CIT. Peters-Sengers et al. also reported that long periods of CIT exacerbated graft damage due to warm ischemia in DCD kidney transplantation [23]. In our study, the graft survival rate was relatively good if the CIT was < 12 h, even if the donor was older. Similarly, graft injury is reversible if the CIT is short. Thus, CIT is very important in uncontrolled DCD, and the CIT target should be < 12 h.

This study had some limitations. First, this was a retrospective observational study with probable bias in donor and recipient selection. There was a large difference between the two groups. Therefore, a propensity score matching was performed, and the groups were compared. Second, the background characteristics of DBD performed in Japan were slightly different from those of DCD. In Japan, the Organ Transplant Law was amended in 2010, and the rate of DBD transplantation increased; therefore, DBD transplantation has been enforced. Nevertheless, the results of DCD after propensity score matching were almost similar to those of DBD; therefore, the outcomes of DCD in Japan, most of which is uncontrolled DCD, is very good. In addition, the data used in this study were registered in the database of the Japan Society for Transplantation. The registered data items were limited, which hindered examination of the data in detail.

Fig. 5 Differences between the four subgroups classified according to donor age and cause of death in the DCD group. There was no difference in the cause of death in those < 50 years, but the survival rate was low in those aged ≥ 50 years when the cause of death was CVD.

Fig. 6 Differences between the four subgroups classified according to donor age and critical ischemic time (CIT). A In the DCD group, the graft survival rate was significantly lower when the donor age was ≥ 50 years and the CIT ≥ 12 h. B In the DBD group, the differences in graft survival with CIT or the donor age are not shown.
In conclusion, the results of DCD in Japan are almost similar to those of DBD. Uncontrolled DCD can be continued without any issues in Japan. However, since donors aged ≥ 50 years and CIT (≥ 12 h) were significant risk factors for poor graft survival, proper evaluation of donors and careful coordination from the stage of procurement until transplantation are required.

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Data availability The data that support the findings of this study are available from the Japan Society for Transplantation, but restrictions apply to the availability of these data, which were used under license for the current study and are not publicly available. Data are available from the authors upon reasonable request and with permission of the Japan Society for Transplantation.

Declarations

Conflict of interest The authors declare no conflict of interest.

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