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ORIGINAL ARTICLE

# Japanese national survey on declined liver allografts from brain-dead donors: High decline rate but promising outcomes in allografts with moderate steatosis

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## Abstract

**Aim:** Liver allografts from brain-dead donors, which were declined and were eventually not transplanted due to accompanying marginal factors, have never been surveyed in Japan. We surveyed the declined allografts and discussed the graft potential focusing on various marginal factors.

**Methods:** We collected data on brain-dead donors between 1999 and 2019 from the Japan Organ Transplant Network. We divided their liver allografts into declined (non-transplanted) and transplanted ones, and then characterized declined ones focusing on their timepoints of decline and accompanying marginal factors. For each marginal factor, we calculated the decline rate from the number of declined and transplanted allografts, and assessed the 1-year graft survival rate from transplanted allografts.

**Results:** A total of 571 liver allografts were divided into 84 (14.7%) declined and 487 (85.3%) transplanted ones. In the declined allografts, a majority was declined after laparotomy ($n = 55$, 65.5%), most of which had steatosis and/or fibrosis ($n = 52$). Out of the moderate steatotic (without $F \geq 2$ fibrosis) allografts ($n = 33$), 21 were declined and 12 were transplanted, leading to a 63.6% decline rate. The latter 12 achieved

a 92.9% 1-year graft survival rate after transplantation. Comparison of donor background showed no significant difference between the declined and transplanted allografts.

**Conclusion:** Pathological abnormalities of steatosis/fibrosis seem to be the most common donor factor leading to graft decline in Japan. Allografts with moderate steatosis were highly declined; however, transplanted ones achieved promising outcomes. This national survey highlights the potential utility of liver allografts with moderate steatosis.

**KEYWORDS**
deceased-donor liver transplantation, donor selection, fibrosis, graft survival, steatosis

## 1 | INTRODUCTION

In Japan, the first brain-dead liver transplantation under the Organ Transplant Law was performed in 1999, and the number of organ donations increased after the revision of the Organ Transplant Law in 2010. In recent years, deceased-donor liver transplantation (DDLT) has become an established treatment option, along with living donor liver transplantation, accounting for 10%–20% of liver transplants in Japan.[1] We have previously conducted a national survey on DDLT in Japan and reported that the most recent 1-year graft survival rate from 2015 to 2019 reached 94%, which is superior to that in other countries globally.[2–5] In the study, we identified prognostic factors for adult DDLT and developed a unique risk index for 1-year graft loss termed the "Japan Risk Index." We can now use the index to identify marginal donors who are considered to be at high risk for postoperative graft failure and understand whether marginal liver allografts could be transplantable, depending on the recipient conditions or ischemic time.[2]

Although the shortage of brain-dead donors remains a serious issue in DDLT in Japan,[6,7] there were declined liver allografts due to donor conditions. To save the lives of more patients with endstage liver disease, it is essential to distinguish transplantable and nontransplantable allografts among declined ones, and reduce the number of declined grafts appropriately. In addition, an overestimation or misunderstanding of donor risk could have resulted in excessive decline. However, deceased donors whose liver allografts were not transplanted because of marginal factors have never been surveyed in Japan.

Therefore, in the present study, using data from all brain-dead donors from the Japan Organ Transplant Network (JOTNW), we discuss the transplantability of declined liver allografts focusing on various marginal factors. We first characterized declined liver allografts focusing on representative marginal factors and timepoints of decline. Subsequently, we investigated the various marginal factors, by assessing decline frequency and graft survival following transplantation. Finally, we attempted to identify marginal factors that frequently led to a decline but did not have serious adverse impacts on the outcome following transplantation, and discuss the transplant potential of liver allografts based on these factors.

## 2 | MATERIALS AND METHODS

### 2.1 | Data collection from the nationwide JOTNW databases and group definition

We collected data on donor characteristics and recipient survival status from the JOTNW database. We assessed liver allografts from donors who were diagnosed as brain dead for organ donation by the JOTNW between January 1999 and March 2019. We excluded liver allografts from donors whose families did not consent to donation of the liver and who had no organs transplanted for any reason after diagnosis of brain death. Liver allografts were categorized into declined and transplanted ones, depending on whether the graft was actually transplanted to a recipient.

This study was approved by the Japanese Liver Transplantation Society (JLTS) Project Committee and the Institutional Review Board of Keio University School of Medicine (#20180301). The JOTNW data were provided for this study with the approval of the Institutional Review Board of JOTNW (#4). Written informed consent was not required from any patient, given the nature of the study.

### 2.2 | Donor acceptance system in Japan

The allocation system before 2019 in Japan has been reported in detail.[2,8,9] JOTNW consistently mediates organ allocation. Waiting patients are ranked based on blood type, medical urgency, and waiting period. After a donor candidate is diagnosed as brain-dead legally, JOTNW offers transplant institutions detailed donor data according to the ranking of the waiting list. The transplant institution has the right to decide whether to accept or decline liver allografts from the donor on the first call (first decision). If one of the transplant institutes accepts the donor, transplant surgeons at the recipient hospital visit the donor hospital, directly examine the donor's condition before procurement, and decide whether to proceed to procurement (second decision). After laparotomy, the surgeons still have the right to accept or decline the donor based on the macroscopic findings on the liver and microscopic findings from a liver biopsy, which is

performed in some donor hospitals (third decision). After returning to the recipient hospital, the doctors of the procurement and recipient teams make the final decision to transplant the liver graft. The liver allograft is transplanted after being accepted based on the above four decisions.

### 2.3 | Decline rate over the years

The decline rate was calculated by dividing the number of declined liver allografts by the number of both declined and transplanted allografts. We assessed the annual decline rates from 1999 to 2019 and calculated the decline rates in the two periods of 1999–2010 and 2011–2019.

### 2.4 | Characteristics of declined and transplanted liver allografts

Basic and representative characteristics were compared between declined and transplanted liver allografts. An average alcohol intake ≥60 g/day was defined as a positive alcohol history, and a Brinkman index ≥100 was defined as a positive smoking history. The duration of respirator support was used as an indicator of long-term donor management. The catecholamine level at procurement was calculated using the catecholamine index, which was defined as dopamine + dobutamine + (adrenaline + noradrenaline) × 100 μg/kg/min.[10] For blood biochemical tests, the maximum value from admission to procurement and the last value before procurement were collected. An image finding of steatosis was referred from the abdominal ultrasonography and computed tomography (CT) reports, which were described by a medical consultant, who is entrusted by JOTNW to evaluate and manage donated organs at the donor hospital. It was also defined as positive if any or both of the ultrasonography and CT showed findings suggesting steatosis, such as hepato-renal echo contrast, and negative if no particular findings were described. Pathological data regarding the status of fibrosis (degree indicated by the Inuyama classification)[11] and steatosis were collected from the biopsy report if an intraoperative biopsy was performed during procurement. For the degree of steatosis, the pathologically assessed percentage of macrosteatosis was recorded as the representative value for this study. If the percentage was described as a range in the report at procurement, the median value of range was recorded. Microsteatosis was not considered in the present study. The number of times that transplanted liver allografts were declined for donor reasons rather than recipient or institutional reasons before acceptance was counted and the graft survival rates were calculated by the number of declines. As for the split-liver transplantations, we only included DDLTs, with higher-priority-ranked recipients as representative of the corresponding donor. The Japan Risk Index for donor (JRI-D) was calculated using a previously reported formula.[2] The graft survival status of the recipients as of March 2020 was recorded.

### 2.5 | Characteristic marginal factors in declined liver allografts by each declined timing

The reasons for the decline were then examined for each decision stage. Japanese transplant institutions are required to report the reasons for decline when they decline at the second, third, or final decision but are not required to report details of the exact reasons for decline at the first decision. Thus, in cases of decline at the first decision, we inferred the reason for the decline by examining representative marginal factors as follows: age, comorbidity, alcohol history, body mass index (BMI), catecholamine, underlying liver disease, laboratory abnormality, and radiological abnormality.[2,12,13]

### 2.6 | Decline and 1-year graft survival rates for donors with liver steatosis and fibrosis

Liver allografts that were biopsied intraoperatively were plotted in a scatterplot, depending on the severity of steatosis (*y* axis) and fibrosis (*x* axis). Declined and transplanted liver allografts were discriminated as white circles and black diamonds, respectively. They were divided into subgroups with vertical and horizontal borders representing the severity of steatosis and fibrosis, respectively. The borders were established according to the following severities: mild <30%, moderate 30%–60%, and severe >60% in steatosis,[14] and mild ≤F1, moderate F2, and severe ≥F3 in fibrosis.[11] The area separated by the borders was defined as a "Gate" as follows: Gate A: mild steatosis and mild fibrosis, Gate B: moderate steatosis and mild fibrosis, Gate C: mild steatosis and moderate fibrosis, Gate D: moderate steatosis and moderate fibrosis, and Gate E: severe steatosis or severe fibrosis. In each gate, the decline rate and 1-year graft survival rate in DDLT from transplanted liver allografts were examined. Donor characteristics were compared between the declined and transplanted liver allografts in Gates A, B, and C.

### 2.7 | Association between pathologically diagnosed steatotic rate and image findings of steatosis

We categorized the liver allografts that were biopsied intraoperatively into two groups of presence or absence of image findings of steatosis and compared the pathological steatotic rates between the groups.

### 2.8 | Decline and 1-year graft survival rates for donors with nonpathological marginal factors

With regard to nonpathological marginal factors (donor age, catecholamine index at procurement, maximum serum sodium, maximum total bilirubin, last aspartate aminotransferase [AST], and alanine aminotransferase [ALT]), donors were divided into four subgroups representing the severity of the marginal factors. In each group, the decline rate and 1-year graft survival rate in DDLT from transplanted liver allografts were examined and compared.

### 2.9 | Statistical analyses

Continuous data are represented as median values and ranges, while categorical data are presented as numbers and percentages. The Mann–Whitney *U* test was used to compare continuous data, and the chi-square test was used to compare categorical data. Graft survival (GS) rates were calculated using the Kaplan–Meier method, and the log-rank test was applied to compare 1-year graft survival between groups. $p$ values $<0.05$ were considered statistically significant. A jittered scatterplot was used to avoid overlapping points. IBM SPSS Statistics 27 software (IBM Corp.) was used for all statistical analyses.

## 3 | RESULTS

### 3.1 | Study population, decline rate, and characteristics of declined and transplanted liver allografts

Figure 1 shows the scheme used in this study. Among a total of 591 liver allografts from brain-dead donors, those from donors without consent to donate the liver ($n = 15$) and those from donors who had no organs transplanted (malignant disease, $n = 2$, bacteremia, $n = 2$, and other reason, $n = 1$) were excluded. In total, 571 liver allografts were included in this study. Of these, 84 (14.7%) liver allografts were declined at all decisions for graft acceptance and not transplanted, and 487 (85.3%) were transplanted. The transplanted ones yielded a total of 523 DDLTs (whole liver graft, $n = 451$ and split liver graft, $n = 72$).

The decline rate varied from 0% to 50% in 1999–2010, but remained constant within the 10%–20% range in 2011–2019 (Figure 2). The decline rates during 1999–2010 and 2011–2019 were 20.5% and 13.3%, respectively.

The demographic and clinical characteristics of the grafts are summarized in Table 1. Declined grafts were significantly different from transplanted ones based on age, diabetes mellitus, alcohol history, BMI, catecholamine index, sodium, liver function parameters, and steatotic findings on the radiological test. The number of declines in transplanted liver allografts revealed that more than 20% of the grafts were declined multiple times. Survival curves for declines are shown in Figure S1. The 1-year graft survival rate was ≥80% in DDLT with grafts that were declined up to nine times, and 70.6% in DDLT with grafts that were declined ≥10 times.

### 3.2 | Characteristic marginal factors in declined liver allografts based on each declined timing

The scheme for the timing of the decline is shown in Figure 3A. Figure 3B shows the number of declines and the representative marginal factors recognized for each decision (presumed reasons for decline). The largest number of declines occurred after laparotomy (third decision, $n = 55$), followed by declines based on donor data

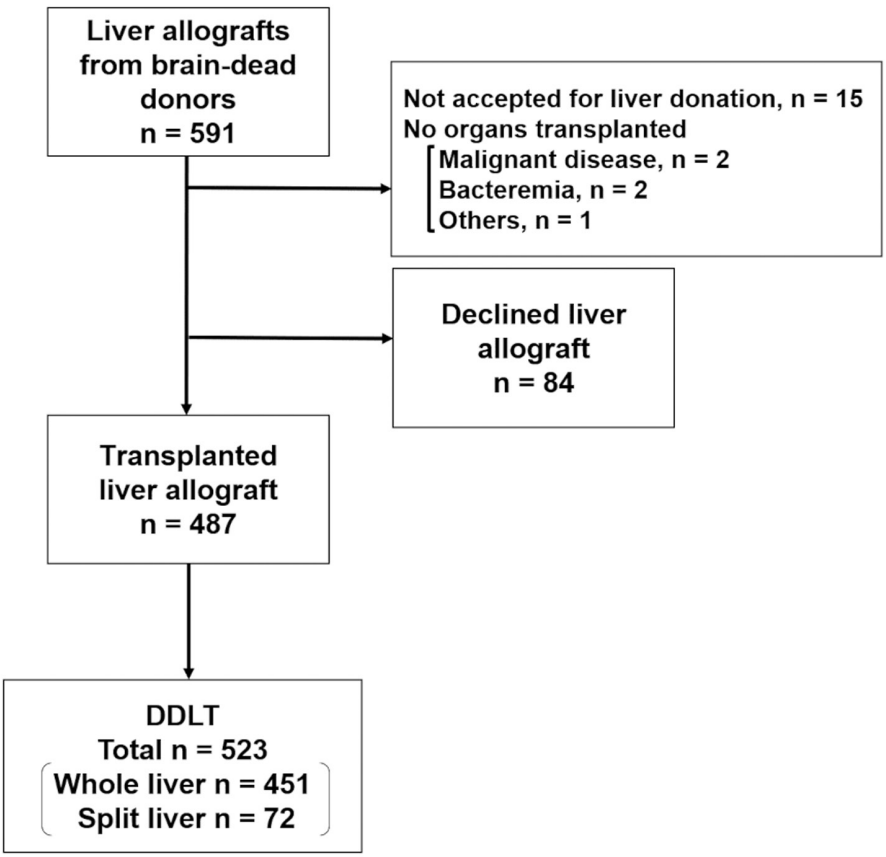


FIGURE 1 Study population. Among 591 liver allografts from brain-dead donor candidates, 571 liver allografts were included in this study. Out of these, 84 (14.7%) were declined and 487 (85.3%) were transplanted. DDLT, deceased-donor liver transplantation.

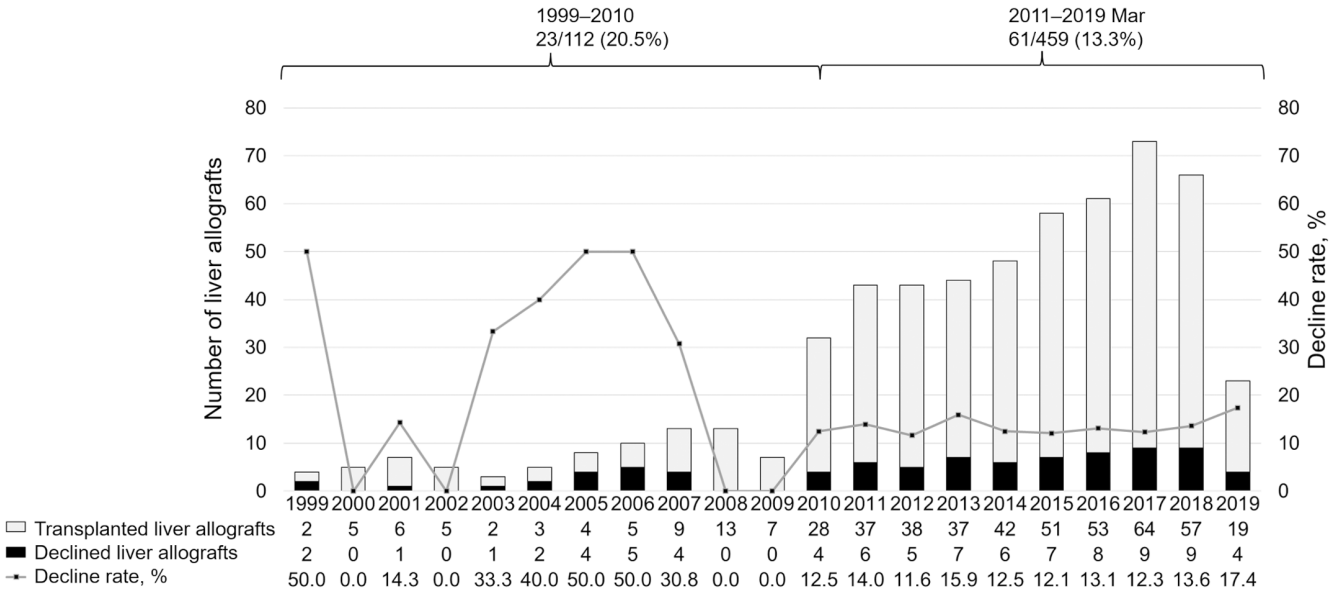


**FIGURE 2** Summary of declined liver allografts from brain-dead donors by year. The decline rate varied from 0% to 50% in 1999–2010, but remained constant within the 10%–20% range in 2011–2019. The average decline rates in 1999–2010 and 2011–2019 were 20.5% and 13.3%, respectively.

(first decision, $n = 25$) and declines just before laparotomy (second decision, $n = 4$). No liver allograft was declined after procurement (final decision). In the first decision, elderly donors, a high catecholamine index, underlying liver disease, abnormal liver function parameters, and radiological abnormalities were commonly observed. In the third decision, liver steatosis and/or fibrosis were the major reasons for decline.

### 3.3 | Decline and 1-year graft survival rates for donors with liver steatosis and fibrosis

The distribution of steatosis and fibrosis in each graft is shown in a scatterplot (Figure 4A). All grafts with severe steatosis or fibrosis (Gate E) were declined. Figure 4B shows the rate of decline in each gate. Over 60% of grafts in Gate B (moderate steatosis and mild fibrosis) were declined at a significantly higher rate than that of the control group (Gate A). Conversely, the 1-year graft survival rate in Gate B was 92.9%, which was not significantly different from that in Gate A (Figure 4C). Out of the 14 DDLT cases in Gate B, only one case with a transplanted donor aged ≥60 years and total bilirubin ≥5.0 mg/dL was recorded as a 1-year graft loss. Similarly, we also found that donors in Gate C (moderate fibrosis with mild steatosis) were declined at a significantly higher rate than those in Gate A; however, five of six (83.3%) cases had a 1-year graft survival in Gate A.

Table 2 presents a comparison of donor characteristics in Gates A, B, and C between the declined and transplanted liver allografts. In Gate B, there was no significant difference in variables between the groups. In Gate C, there were no grafts aged ≥60 years in the transplanted group, whereas there were four (57.1%) donors aged ≥60 years in the declined group.

### 3.4 | Association between pathologically diagnosed steatotic rate and image findings of steatosis

The pathologically diagnosed steatotic rate (median, range) was 20 (0%–90%) and 0 (0%–75%) in the image-finding positive and negative groups, respectively. There was a significant difference between the groups ($p < 0.001$) (Figure 5). Notably, 14 (5.3%) grafts in the negative group were diagnosed with ≥30% steatosis, and 25 (39.6%) grafts in the positive groups were diagnosed with ≤10% steatosis.

### 3.5 | Decline and 1-year graft survival rates for donors with nonpathological marginal factors

The distributions of representative marginal factors (donor age, catecholamine index, maximum serum sodium, maximum total bilirubin, AST, and ALT at the last value) in declined and transplanted liver allografts are illustrated in Figure S2. Some marginal factors showed excellent graft survival in Groups B, C, and D, which were comparable to those in Group A. Some of the marginal factors showed a significantly higher decline rate in Groups B, C, and D than in Group A. Very few grafts had extreme marginal factors (Group D): $n = 7$ aged ≥70 years, $n = 6$ with catecholamine index ≥50, $n = 17$ with serum sodium ≥180 mEq/L, $n = 8$ with total bilirubin ≥10.0 mg/dL, $n = 6$ with AST ≥500 IU/L, and $n = 9$ with ALT ≥500 IU/L. The decline rate/1-year graft survival rates in Group D were 28.6%/40.0%, 50.0%/66.7%, 11.8%/80.0%, 50.0%/50.0%, 50.0%/33.3%, and 55.6%/100.0% in liver allografts with age ≥70 years, catecholamine index ≥50.0, maximum sodium ≥180 mEq/L, maximum total bilirubin ≥10.0 mg/dL, AST ≥500 IU/L, and ALT ≥500 IU/L, respectively.

**TABLE 1** Characteristics of declined and transplanted liver allografts.

| | Declined liver allografts $n = 84$ | Transplanted liver allografts $n = 487$ | $p$ Value |
|---|---|---|---|
| Sex (male) | 48 (57.1) | 284 (58.3) | 0.84 |
| Age, years old | **49 (20–76)** | **44 (1–73)** | **<0.001** |
| Hypertension | 18 (21.4) | 86 (17.9) | 0.44 |
| Diabetes mellites | **8 (9.5)** | **14 (2.9)** | **0.004** |
| Height, cm | 162 (147–180) | 165 (73–190) | 0.58 |
| BMI, kg/m$^2$ | **23.8 (16.6–43.8)** | **22.0 (12.8–42.3)** | **<0.001** |
| Alcohol history | **18 (20.9)** | **20 (4.2)** | **<0.001** |
| Smoking history | 45 (52.3) | 206 (43.5) | 0.13 |
| Antihepatitis B core antibody positive | 4 (4.9) | 50 (10.3) | 0.11 |
| Cause of death | | | |
| Trauma | 17 (20.2) | 95 (19.5) | 0.19 |
| Cerebrovascular disease | 48 (57.1) | 229 (47.0) | |
| Anoxia | 19 (22.6) | 157 (32.2) | |
| Others | 0 (0.0) | 6 (1.2) | |
| Temporary cardiac arrest | 35 (41.7) | 242 (49.7) | 0.17 |
| Duration on respirator, days | **6.0 (2–31)** | **8.0 (2–325)** | **<0.001** |
| Catecholamine index | **6.0 (0.0–68.0)** | **3.9 (0–109.4)** | **0.003** |
| Sodium max, mEq/L | 154 (138–181) | 156 (135–202) | 0.44 |
| Sodium last, mEq/L | **144.5 (126–175)** | **141 (114–176)** | **0.002** |
| Total bilirubin max, mg/dL | **1.6 (0.5–19.7)** | **1.4 (0.3–24.7)** | **0.01** |
| Total bilirubin last, mg/dL | **1.4 (0.2–16.7)** | **1.0 (0.1–17.3)** | **<0.001** |
| AST max, IU/L | 144 (22–6910) | 141 (20–9004) | 0.60 |
| AST last, IU/L | **53 (9–5883)** | **42 (11–2096)** | **<0.001** |
| ALT max, IU/L | 83 (7–7092) | 86 (6–5737) | 0.87 |
| ALT last, IU/L | 38 (4–7092) | 35 (3–784) | 0.81 |
| Image findings of steatosis | **36 (47.4)** | **46 (9.8)** | **<0.001** |
| Number of times declined for donor reason | | | |
| Never declined | | 382 (78.4) | |
| Once | | 44 (9.0) | |
| Twice | | 21 (4.3) | |
| 3–4 times | | 19 (3.9) | |
| 5–9 times | | 4 (0.8) | |
| ≥10 times | | 17 (3.5) | |
| Japan Risk Index for donor (JRI-D)[a] | 1.3 (1.0–3.4) | 1.0 (1.0–7.8) | 0.58 |

*Note*: Data presented as median values (range) and numbers (%) for continuous and categorical variables, respectively. The Mann–Whitney *U* test was performed for continuous variables and the chi-square test was performed for categorical variables to compare variance between groups. Bold emphasis indicates statistical significance ($p < 0.05$).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DDLT, deceased-donor liver transplantation.

[a]JRI-D = exp [(0.390 if donor age 60–69) + (0.869 if donor age ≥70) + (0.262 if catecholamine index 10.0–29.9) + (0.642 if catecholamine index ≥30.0) + (0.518 if donor maximum sodium ≥180 mEq/L) + (0.079 if donor maximum total bilirubin 3.0–4.9 mg/dL) + (0.544 if donor maximum total bilirubin ≥5.0 mg/dL)].

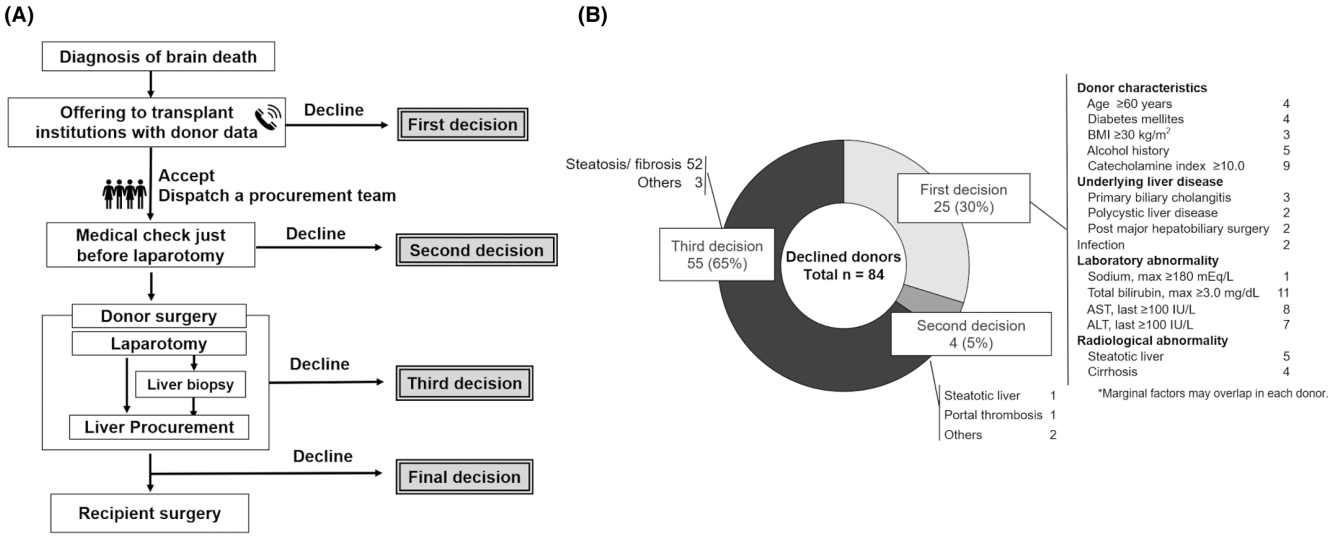


FIGURE 3 Characteristic marginal factors in declined liver allografts by each decline timing. (A) The scheme of the timing of decline. (B) The timing of decline and the representative marginal factors in each decision. The largest number of declines occurred after laparotomy (third decision, $n = 55$), followed by declines based on donor data (first decision, $n = 25$) and just before laparotomy (second decision, $n = 4$). ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index.

## 4 | DISCUSSION

To the best of our knowledge, this is the first national survey to investigate liver allografts from brain-dead donors that were declined and eventually not transplanted due to accompanying marginal factors in Japan. This survey identified 84 declined liver allografts from 571 donor candidates, and investigated how often and why transplant institutes declined the grafts. Based on the outcomes of the transplanted grafts, the probability of liver allografts with marginal factors was speculated. Together with the recent national survey that proposed the original Japanese risk index for transplanted donors,[2] this study provides data that could help transplant surgeons to decide to accept marginal grafts.

Notably, the decline rates changed greatly after the revision of the Organ Transplant Law in 2010 (Figure 2). After the revision of the law, the number of donated organs under brain death increased slightly, and the decline rate stabilized in the 10% range. The decline rate of 13.3% is slightly lower than that in the United States, but slightly higher than that in some European countries.[15,16] For a country with extremely few deceased donors, reducing the number of liver allografts that are not transplanted is an urgent issue. Therefore, we investigated the characteristics of the declined liver allografts.

Of the 487 grafts subsequently transplanted, 105 had a history of being declined at first decision. It is noteworthy that grafts with such a history of decline achieved a 1-year survival rate comparable to grafts without a history of decline if the number of declines was nine or less (Table 1, Figure S1). Eighty-four grafts were never accepted by any institution. These declined liver allografts had inferior values compared to those of transplanted grafts in multiple variables that were previously reported as marginal factors (Table 1).[2,15,16] In the absence of a national survey on nontransplanted liver allografts, Japanese transplant surgeons may have made donor selections based on their experience, previous reports, and general medical knowledge, resulting in significant differences in the characteristics between declined and transplanted grafts. However, there is no consensus on whether the declined grafts with these marginal features are actually nontransplantable in Japan.

We examined when the decline occurred from the first call of donor information to recipient surgery to clarify their reason for decline. The most frequent timepoint for decline was after laparotomy (third decision, 65%), followed by the time of the first call (first decision, 30%). In the declines at the first call of donor information, elderly donors, high-dose catecholamine use, abnormal laboratory values, and previously known liver disease were prominent features. As for the declines after laparotomy of procurement surgery, pathological abnormalities of steatosis and fibrosis were highly likely the major reason for decline. Given the results, it is presumed that donor factors such as age, catecholamine use, laboratory values, and pathological findings are the main issues reducing nontransplanted donors in Japan.

To explore the potential utility (transplantability) of declined grafts, we assessed the survival rates of DDLT from transplanted liver allografts that were equivalent to the corresponding declined allografts, based on one marginal factor. Interestingly, graft survival in marginal groups (Gates/Groups B–D in Figure 4 and Figure S2) was comparable to that in Group A based on some of the investigated factors. The decline rate varied, depending on the type of marginal factor. The observations indicate that the criteria for graft decline in Japan and consensus among transplant surgeons have not been established. Regrettably, nontransplanted liver allografts could have been declined due to a misunderstanding of the graft's original status. Among the analyses of marginal factors, the results of steatosis and fibrosis were of particular interest (Figure 4). Only <50% liver allografts whose intraoperative liver biopsy showed 30%–60%

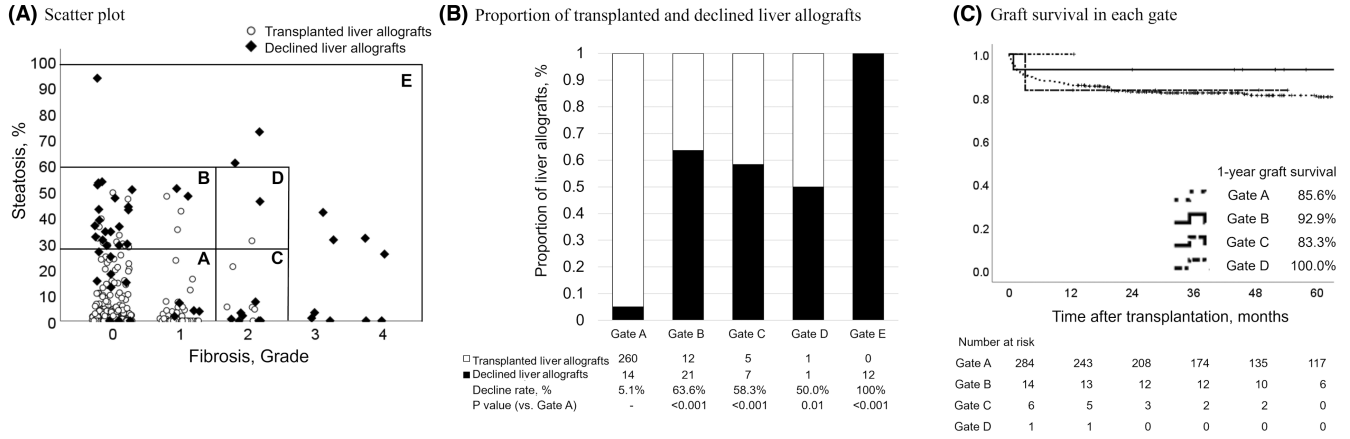


**FIGURE 4** Decline rates for steatotic and/or fibrotic liver allografts and 1-year graft survival rate of DDLT upon use. (A) Scatterplot showing the distribution of steatosis and fibrosis in each donor. (B) Decline rate in each gate. All cases in Gate E were declined and ≥50% of grafts in Gates B–D were declined at a significantly higher rate than that of the control group (Gate A). (C) The 1-year graft survival in Gates A–D was 85.6%, 92.9%, 83.3%, and 100% (only one case), respectively. The 1-year graft survival in Gate B was not significantly different from that in Gate A. DDLT, deceased-donor liver transplantation.

steatosis and/or F2 fibrosis (Gates B–D) were transplanted; however, allografts transplanted with equivalent abnormalities achieved favorable outcomes. The imbalance between the favorable outcomes of transplanted donors and the high decline rates suggests that Japanese transplant surgeons are confused with regard to the potential utility of grafts with steatosis and fibrosis. Living donors, the major donor source in Japan, are usually determined to be ineligible if diagnosed with steatosis or fibrosis; consequently, transplant surgeons do not have much experience with liver transplantation using steatotic and fibrotic grafts. They sometimes hesitate to accept marginal liver allografts since the Japanese allocation system currently does not allocate liver grafts to recipients with graft loss within 1 year after transplantation. Therefore, it would be effective to allow allocation to graft loss above or establish a preferential allocation system of retransplantation for acceptors of extreme marginal grafts to promote marginal donor usage. However, the question is whether the current number of donated organs in Japan can support such compensatory allocation.

Steatosis is a pathologically reversible condition; however, the transplantability of steatotic liver grafts has not been widely reported. Several studies on DDLT using severe steatotic liver allografts showed unfavorable 1-year graft survival rates, at around 25%–40%.[17,18] However, in recent years there has been a growing number of reports showing better results of DDLT even with severe steatotic liver allograft if the condition of the recipient is appropriate and ischemic time is short.[19] We also reported that adult DDLT using steatotic (≥30%) and fibrotic (F2) liver allografts achieved 100% 1-year graft survival according to a Japanese national survey; however, the outcomes were under favorable conditions, with no cases of prolonged ischemic time and hyperbilirubinemia.[2] In the present study, the analysis focusing on Gate B (grafts with 30%–60% steatosis and F0-1 fibrosis) showed that characteristics of declined liver allografts did not differ from those of transplanted ones (Table 2), suggesting that steatosis was the only distinct feature from the transplanted allografts in the majority of declined liver allografts. Although the number of DDLTs in this category is very small in Japan, recent studies and the results of Gate B calls draw our attention to the possibility that the liver allografts declined due to moderate steatosis could be uneventfully transplanted to relatively low-risk recipients who are waiting at neighboring institutions. The discussions on introducing a regional system in Japan have not yet been concluded. According to this study, preoperative image diagnosis of steatosis is underdeveloped to determine the direction of allocation. Therefore, it is expected to establish a reasonable risk adjustment method according to the marginal condition and improve preoperative diagnostic performance.

The donor candidates with F2 and <30% steatosis (Gate C) also raised similar issues regarding the transplantability as described above. Fibrosis is generally considered an irreversible condition, and moderately fibrotic liver is also considered a nonapplicable donor criterion in the Organ and Procurement Transplant Network in the U.S.[20] Very few papers have attempted to report the transplantability of moderate fibrosis. Martini et al.[21] reported a favorable short-term outcome for a hepatitis C virus–positive liver allograft with moderate fibrosis by minimizing cold ischemia time and careful recipient selection. Although this study was a favorable proposal as a proof-of-concept, we did not find any subsequent reports of actual results based on the concept. Wadhera et al.[22] reported that recipients with liver allograft fibrosis achieved excellent outcomes comparable to those with no fibrosis. However, out of the 101 cases of allografts with fibrosis, only three had moderate-stage fibrosis and most had early-stage fibrosis, providing insufficient information on the transplantability of moderate fibrosis allografts. Due to the lack of evidence regarding grafts with moderate fibrosis, declining allografts from elderly donors seems reasonable (Table 2). Although the outcomes in DDLT using transplanted grafts in Gate C (83.3% of 1-y survival) encouraged the study of the conditions under which fibrotic grafts can be transplanted,

**TABLE 2** Comparison of donor characteristics between declined and transplanted liver allografts in Gates A, B, and C.

| | Gate A | | | Gate B | | | Gate C | | |
|---|---|---|---|---|---|---|---|---|---|
| | Declined liver allografts, $n = 14$ | Transplanted liver allografts, $n = 260$ | $p$ Value | Declined liver allografts, $n = 21$ | Transplanted liver allografts, $n = 12$ | $p$ Value | Declined liver allografts, $n = 7$ | Transplanted liver allografts, $n = 5$ | $p$ Value |
| Sex (male) | 7 (50.0) | 159 (61.2) | 0.41 | 13 (61.9) | 6 (50.0) | 0.51 | **4 (57.1)** | **0 (0.0)** | **0.04** |
| Age ≥ 60 years | 4 (28.6) | 42 (16.2) | 0.23 | 3 (14.3) | 3 (25.0) | 0.44 | **4 (57.1)** | **0 (0.0)** | **0.04** |
| BMI ≥ 25 kg/m$^2$ | 6 (42.9) | 70 (26.9) | 0.20 | 12 (57.1) | 4 (33.3) | 0.19 | 1 (14.3) | 1 (20.0) | 0.67 |
| Alcohol history | 0 (0.0) | 13 (5.2) | 0.38 | 5 (23.8) | 1 (8.3) | 0.27 | 0 (0.0) | 1 (20.0) | 0.22 |
| Cause of death | | | | | | | | | |
| Trauma | 3 (21.4) | 51 (19.6) | 0.97 | 2 (9.5) | 2 (16.7) | 0.08 | **2 (28.6)** | **0 (0.0)** | **0.01** |
| Cerebrovascular disease | 7 (50.0) | 120 (46.2) | | 14 (66.7) | 8 (66.7) | | **1 (14.3)** | **5 (100)** | |
| Anoxia | 4 (28.6) | 87 (33.5) | | 5 (23.8) | 0 (0.0) | | **4 (57.1)** | **0 (0.0)** | |
| Others | 0 (0.0) | 2 (0.8) | | 0 (0.0) | 2 (16.7) | | **0 (0.0)** | **0 (0.0)** | |
| Temporary cardiac arrest | 6 (42.9) | 132 (50.8) | 0.56 | 11 (52.4) | 3 (25.0) | 0.13 | 6 (85.7) | 2 (40.0) | 0.10 |
| Duration on respirator ≥7 days | 1 (7.1) | 143 (55.0) | <0.001 | 7 (33.3) | 3 (25.0) | 0.62 | 2 (28.6) | 4 (80.0) | 0.08 |
| Catecholamine index | | | | | | | | | |
| 10.0–29.9 | 4 (28.6) | 42 (16.2) | 0.01 | 4 (19.0) | 3 (25.0) | 0.84 | 1 (14.3) | 1 (20.0) | 0.67 |
| ≥30.0 | 2 (14.3) | 6 (2.3) | | 3 (14.3) | 1 (8.3) | | 1 (14.3) | 0 (0.0) | |
| Serum sodium, max ≥180 mEq/L | 0 (0.0) | 12 (4.6) | 0.41 | 1 (4.8) | 0 (0.0) | 0.44 | 0 (0.0) | 1 (20.0) | 0.22 |
| Total bilirubin, max | | | | | | | | | |
| 3–5 mg/dL | 1 (7.1) | 25 (9.6) | 0.61 | 0 (0.0) | 0 (0.0) | 0.18 | 0 (0.0) | 0 (0.0) | |
| ≥5 mg/dL | 0 (0.0) | 15 (5.8) | | 0 (0.0) | 1 (8.3) | | 0 (0.0) | 0 (0.0) | |
| AST, last ≥100 IU/L | 1 (7.1) | 3 (1.2) | 0.07 | 4 (19.0) | 1 (8.3) | 0.41 | 1 (14.3) | 1 (20.0) | 0.79 |
| ALT, last ≥100 IU/L | 1 (7.1) | 5 (1.9) | 0.19 | 2 (9.5) | 2 (16.7) | 0.55 | 0 (0.0) | 1 (20.0) | 0.22 |
| Number of times declined for donor reasons | | | | | | | | | |
| Never declined | | 209 (80.4) | | | 6 (50.0) | | | 4 (80.0) | |
| Once | | 25 (9.6) | | | 3 (25.0) | | | 0 (0.0) | |
| Twice | | 9 (3.5) | | | 2 (16.7) | | | 0 (0.0) | |
| 3–4 times | | 7 (2.7) | | | 0 (0.0) | | | 1 (20.0) | |
| 5–9 times | | 2 (0.8) | | | 1 (8.3) | | | 0 (0.0) | |
| ≥10 times | | 8 (3.1) | | | 0 (0.0) | | | 0 (0.0) | |

TABLE 2 (Continued)

| | Gate A | | | Gate B | | | Gate C | | |
|---|---|---|---|---|---|---|---|---|---|
| | Declined liver allografts, $n = 14$ | Transplanted liver allografts, $n = 260$ | $p$ Value | Declined liver allografts, $n = 21$ | Transplanted liver allografts, $n = 12$ | $p$ Value | Declined liver allografts, $n = 7$ | Transplanted liver allografts, $n = 5$ | $p$ Value |
| Japan Risk Index for donor (JRI-D)[a] | 1.3 (1.0–2.8) | 1.0 (1.0–7.8) | 0.24 | 1.3 (1.0–1.9) | 1.0 (1.0–3.3) | 0.96 | 1.5 (1.0–2.8) | 1.0 (1.0–1.7) | 0.34 |

*Note*: Data presented as median values (range) and numbers (%) for continuous and categorical variables, respectively. The Mann–Whitney *U* test was performed for continuous variables and the chi-square test was performed for categorical variables to compare variance between groups. Bold emphasis indicates statistical significance ($p < 0.05$).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DDLT, deceased-donor liver transplantation.

[a]JRI-D = exp [(0.390 if donor age 60–69) + (0.869 if donor age ≥70) + (0.262 if catecholamine index 10.0–29.9) + (0.642 if catecholamine index ≥30.0) + (0.518 if donor maximum sodium ≥180 mEq/L) + (0.079 if donor maximum total bilirubin 3.0–4.9 mg/dL) + (0.544 if donor maximum total bilirubin ≥5.0 mg/dL)].

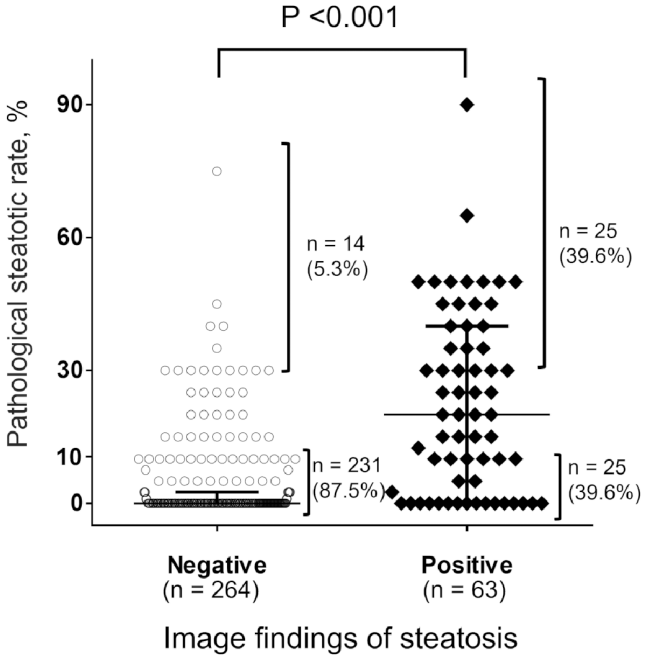


**FIGURE 5** Pathologically diagnosed steatotic rate and image findings of steatosis. The pathologically diagnosed steatotic rate in the image-finding positive group was significantly higher than that in the negative group ($p < 0.001$). Even if the diagnosis is positive on imaging, 39.6% of the liver allograft were pathologically diagnosed with ≤10% steatosis. Similarly, even if the image diagnosis is negative, 5.3% of the liver allografts were pathologically ≥30% steatosis.

The present study had some limitations. Since the reason for the graft decline was not systematically recorded, we evaluated the representative features of declined liver allografts according to the timing of the decline. However, the actual circumstances leading to decline might be more multifactorial and difficult to evaluate. Second, although we collected all past cases of declined and transplanted liver allografts in Japan, the total number of cases is still small and the statistical power might be limited. Particularly, the number of transplanted cases in Gates C and D was minimal, and it was difficult to discuss the transplantability in this study. Third, there are limits to the universality and accuracy of intraoperative pathological information. Pathological diagnoses of biopsied livers vary, depending on the pathologists in each donor hospital, and there is neither a standardized format for recording diagnosed findings nor a system of collecting specimens for later pathological verification. Therefore, these issues should be resolved in the future. Finally, assessing the potential utility of declined liver allografts is methodologically difficult. We explored the transplantability of one population of declined liver allografts by studying two populations of declined and transplanted allografts with one common marginal factor. However, it is difficult to accurately compare the backgrounds of the two populations, because declined liver allografts may have some marginal factors that are not shared with transplanted ones and were not investigated in the present study.

In conclusion, a national survey of declined liver allografts revealed various characteristics of declined allografts in Japanese DDLT. Notably, more than 10% of organ donations are still declined in Japan, a country where organ donations are severely limited. Among the various marginal factors examined, steatosis, the leading reason for decline, deserves special attention as an unrecognized expandable graft source. The number of livers declined for this reason is notable. Considering the promising outcome following transplantation and similar backgrounds of declined and transplanted allografts, allografts declined in the past due to moderate steatosis might be uneventfully transplanted. The actual transplantability of allografts with moderate steatosis should be investigated to reduce the number of livers discarded as much as possible. The results of the present study could facilitate decision-making among Japanese transplant surgeons as well as prospective studies on marginal donors.

## AUTHOR CONTRIBUTIONS

Authors Yusuke Takemura, Masahiro Shinoda, Yasushi Hasegawa, Yohei Yamada, Hideaki Obara, Minoru Kitago, Mureo Kasahara, Susumu Eguchi, Hideki Ohdan, Yuko Kitagawa, and Hiroto Egawa contributed to the study conception and design. Authors Yusuke Takemura, Masahiro Shinoda, Koji Umeshita, and Hiroto Egawa managed this study and collected data and interpreted the results. Authors Yusuke Takemura and Masahiro Shinoda drafted the article. All authors reviewed and approved the final version of the article.

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## CONFLICT OF INTEREST STATEMENT

Author Yuko Kitagawa is Editor in Chief of Annals of Gastroenterological Surgery. Author Hideki Ohdan and Susumu Eguchi are current Editors of Annals of Gastroenterological Surgery. Author Yuko Kitagawa received lecture fees from Asahi Kasei Pharma Co., AstraZeneca K.K., Ethicon Inc., Ono Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Factory Inc., Olympus Corporation, Nippon Covidien Inc., Shionogi & Co., Ltd., Taiho Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Bristol-Myers Squibb K.K., MSD K.K., Smith & Nephew K.K., Kaken Pharmaceutical Co., Ltd., ASKA Pharmaceutical Co., Ltd., Miyairisan Pharmaceutical Co., Ltd., Toray Industries, Inc., Daiichi Sankyo Company, Ltd., Chugai Foundation for Innovative Drug Discovery Science, and Nippon Kayaku Co., Ltd. Author Yuko Kitagawa was supported by grants from Chugai Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd, Yakult Honsha Co., Ltd., Asahi Kasei Pharma Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Tsumura & Co., Kaken Pharmaceutical Co., Ltd., Sumitomo Pharma Co., Ltd., EA Pharma Co., Ltd., Eisai Co., Ltd., Otsuka Pharmaceutical Factory Inc., Medicon Inc., Kyouwa Hakkou Kirin Co., Ltd., Takeda Pharmaceutical Co., Ltd., Teijin Pharma Ltd., and Nippon Covidien Inc. Author Yuko Kitagawa held an endowed chair provided by Chugai Pharmaceutical Co., Ltd. and Taiho Pharmaceutical Co., Ltd., outside the submitted work.

## DATA AVAILABILITY STATEMENT

The datasets used in this study are available from the corresponding author on reasonable request.

## ETHICAL APPROVAL

This study was approved by the JLTS Project Committee and the Institutional Review Board of Keio University School of Medicine (#20180301). The JOTNW data were provided for this study with the approval of the Institutional Review Board of JOTNW (#4). Written informed consent was not required from any patient, given the nature of the study.

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## SUPPORTING INFORMATION

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

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