



Survival of Heart Transplant Candidates in Japan

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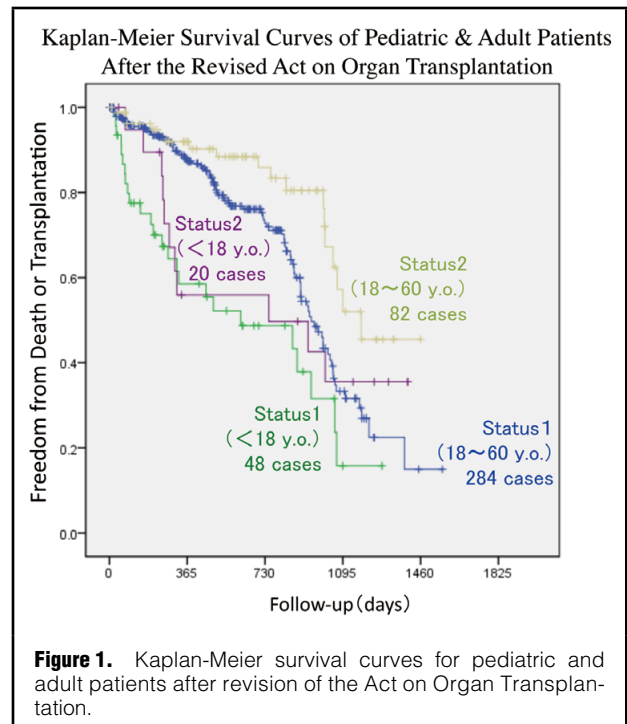
Background: In Japan, there are more patients waiting for heart transplants (HTXs) than available organs.

Methods and Results: Since July 2010, 68 pediatric and 366 adult patients aged <60 years applied for HTX candidacy with the Japanese Circulation Society's HTX Committee. No significant differences in freedom from death or HTX were observed between pediatric Status 1 and Status 2 patients. More adult Status 1 patients reached the endpoint of death or HTX than adult Status 2 patients. Pediatric patients (Status 1 and 2) did not have better survival than adult Status 1 or Status 2 patients.

Conclusions: Pediatric patients should be prioritized over adult patients for HTX.

Key Words: Heart transplantation; Japan; Survival; Waiting list status

Heart transplantation (HTX) improves the length and quality of life in patients with severe heart disease.¹ Prior to 2006, approximately 40 patients per year applied for a decision on whether HTX is indicated from the HTX Committee (HTC) in Japan. The number increased to 148 in 2014² after implementation of the revised Act on Organ Transplantation (AOT) in 2010, approval of insurance coverage for implantable ventricular assist devices (VADs) in 2011, and an increase in the age limit from 60 to 65 years at the time of application in 2013. Although the number of HTXs performed annually in Japan increased from approximately 6 to 37 after the AOT was revised,² there are 10 times as many patients waiting for HTX under the current system.³ Consequently, patients in Japan wait approximately 900 days for HTX; many patients die while waiting.² The revised AOT also allows for pediatric HTX. However, there are fewer pediatric donors than adult donors. According to the allocation system in Japan, pediatric Status 1 patients are prioritized if a donor is younger than 18 years. However, second priority is given to Status 1 patients aged 18 years or older, followed by Status 2 patients younger than 18 years. As of the end of 2014, only 8 HTXs had been performed in children aged less than 18 years in Japan; only 2 donors were aged less than 6 years. Given the circumstances in Japan, we think it is time to reconsider the allocation system for cardiac transplantation. We



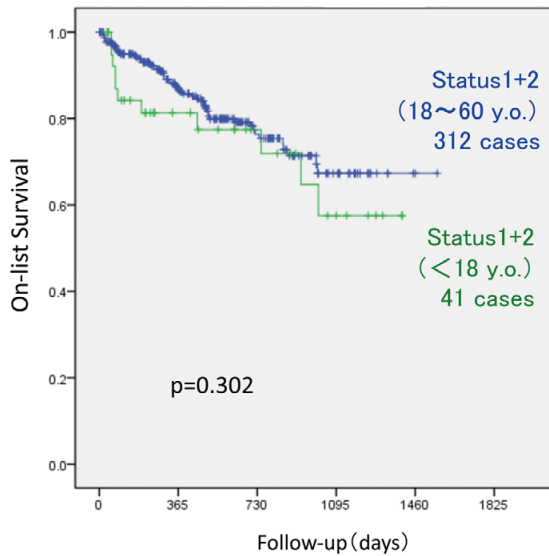
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A Kaplan-Meier On-list Survival Curves of Pediatric & Adult Patients
After the Revised Act on Organ Transplantation



B Kaplan-Meier On-list Survival Curves of Pediatric & Adult Patients
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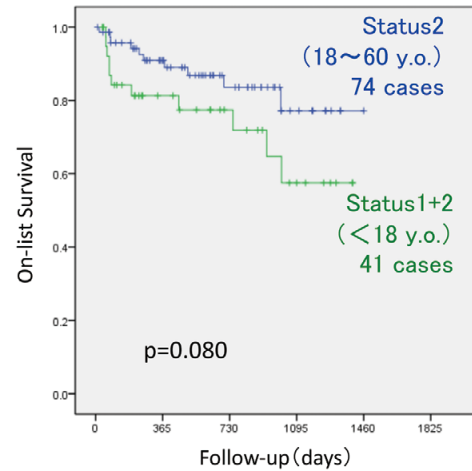
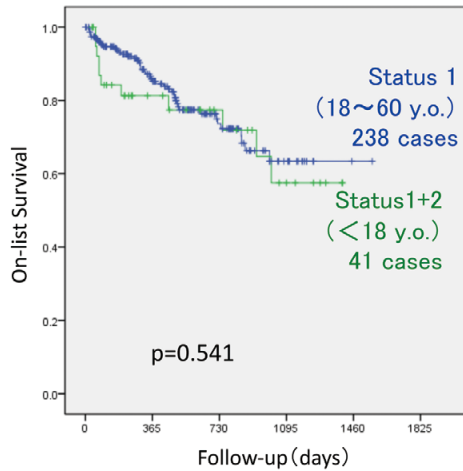


Figure 2. (A) Kaplan-Meier curves for on-list survival for pediatric and adult patients after revision of the Act on Organ Transplantation. (B) Kaplan-Meier on-list survival curves for pediatric and adult patients by status after revision of the Act on Organ Transplantation. Kaplan-Meier curves for all pediatric patients vs. adult Status 1 (Left) and adult Status 2 patients (Right) are shown.

retrospectively examined the prognosis of patients for whom the HTC had determined that a HTX is indicated and the patient prioritization status.

Methods

We included patients who applied for HTC determination after implementation of the revised AOT who were less than 60 years of age at the time of application.

On October 31 of every other year, the HTC conducts a survey on the prognosis of patients approved for HTX. Written informed consent for survey participation was

obtained from each patient or patient's parent at the time of application. In the present study, we included patients who applied during the 51.5-month period from July 17, 2010, the date that the revised AOT came into effect, to October 31, 2014.

We generated Kaplan-Meier curves for the following groups of patients with the composite endpoint of death or HTX: patients between 18 and 60 years of age at the time of application classified as Status 1 for medical urgency (284 patients; mean age \pm SD, 40.5 \pm 11.9 years), patients between 18 and 60 years of age at the time of application classified as Status 2 (82 patients; 43.3 \pm 11.2 years), patients

younger than 18 years at the time of application classified as Status 1 (48 patients; 9.1±6.2 years), and patients younger than 18 years at the time of application classified as Status 2 (20 patients; 5.8±4.7 years).

In addition, we compared survival without HTX (on-list survival) of all pediatric patients (<18 years; 4 patients; mean age±SD, 8.0±6.1 years) vs. all adult patients (18–60 years of age; 312 patients; 41.8±11.6 years), adult Status 1 patients (238 patients; 41.3±11.6 years), and adult Status 2 patients (74 patients; 43.7±11.6 years), respectively.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics, version 19 (IBM, Armonk, NY, USA). The Kaplan-Meier method was used to assess survival. Differences between Kaplan-Meier curves were compared using the log-rank test. $P < 0.05$ was considered statistically significant.

Results

Freedom from death or HTX was examined using Kaplan-Meier survival analysis (**Figure 1**). In children younger than 18 years at the time of application, no significant differences were observed between those classified as Status 1 vs. 2 at the time of application ($P=0.3$).

Among patients between 18 and 60 years of age at the time of application, the probability of survival free from death or HTX was significantly lower among Status 1 patients than Status 2 patients ($P=0.005$). However, the Kaplan-Meier curve for Status 2 patients showed a sudden drop around 1,100 days after application, mostly because of HTX.

Pediatric Status 1 patients had worse event-free survival than adult Status 1 patients ($P=0.001$). Similarly, pediatric Status 2 patients had significantly worse event-free survival than adult Status 2 patients ($P=0.03$). Pediatric Status 2 patients had similar survival as adult Status 1 patients ($P=0.748$) (**Figure 1**).

Regarding on-list survival without HTX in Japan and abroad (**Figure 2**), pediatric patients (Status 1 and 2) did not have better survival than adult Status 1 (**Figure 2B, Left**) and Status 2 patients (**Figure 2B, Right**); however, these differences were not statistically significant.

Discussion

Implementation of the revised AOT beginning July 2010 and approval of insurance coverage for implantable VADs in 2011 made the social environment surrounding HTX in Japan similar to that in the USA and many European countries. However, currently there are still relatively few donors in Japan. According to the Japan Organ Transplant Network (JOT), approximately 400 patients are waiting for HTX, which is approximately 10 times the annual number of HTX procedures. The average waiting time exceeds 800 days.²

In Japan, if a donor is younger than 18 years, pediatric Status 1 patients are prioritized for HTX. If there are no

pediatric Status 1 patients, second priority is given to Status 1 patients aged 18 years or older, followed by Status 2 patients younger than 18 years. In this system, many pediatric HTX candidates might die waiting for transplant in Japan or consider going abroad for HTX. Our data showed that pediatric HTX candidates do not have better survival than adult counterparts. Reasons include uncertainty about the efficacy of β -blockers and ACE inhibitors⁴ and the limited use of VADs in pediatric patients. Eurotransplant has already begun to prioritize pediatric patients as organ recipients from pediatric donors.⁵ One limitation of this study is that we were not able to show statistically significant differences in the Kaplan-Meier survival analysis because of the small number of pediatric patients compared with adult patients; however, we were able to show that pediatric patients waiting for HTX do not have a better prognosis than adult patients. Therefore, it is time to reconsider revising the current allocation system to allow pediatric patients, whether Status 1 or 2, to have priority for organs from donors younger than 18 years of age.

The Kaplan-Meier survival curve for freedom from death or HTX in adult Status 1 patients showed a precipitous fall at approximately 900 days after application, partially because of HTX. The curve for adult Status 2 patients also drops rapidly after another 200 days, around 1,100 days after application. Thus, our results showed that 900–1,100 days is a critical HTX waiting period for patients registered with JOT. Our study included fewer pediatric patients than adults, limiting the statistical analysis; however, further analysis should be performed with more patients. Further investigations should be performed to improve organ allocation for HTX in Japan, but increasing the number of donors will be the most powerful solution.

Acknowledgement

See **Supplementary Appendix**.

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Supplementary Files

Please find supplementary file(s);
<http://dx.doi.org/10.1253/circj.CJ-17-0024>