Early Changes in Donor Fraction Cell-free DNA in Newly Transplanted Heart Transplant Patients

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Background

- Heart transplantation is a well established therapy for end-stage heart failure in children and young adults.
- The highest risk for graft loss remains in the first 60 days post transplant
- Donor fraction (DF) cell-free DNA (cfDNA) measurement is a highly sensitive marker of graft injury.
- Early changes in DF cfDNA post-transplant have not been previously studied in patients after heart transplantation

Aims and Hypothesis

- **Aim**: evaluate the association between early changes in DF cfDNA and transplant outcomes.
- **Hypothesis**: Patients with rising DF cfDNA following transplantation will have increased rates of graft loss compared to those with falling levels.

Methods

- Single center review of early post-transplant DF cfDNA levels in children and young adults after heart transplantation.
- DF cfDNA testing was performed by Tai Diagnostics.
- Data reviewed included demographics and key operative characteristics including ischemic time and bypass time.
- Recipient & graft outcomes were analyzed for patients with 3 DF cfDNA results.
- Declination curves were created for each patient based on the DF cfDNA data using an estimation modeling approach.

Results

- 17 patients were identified with at least two DF cfDNA levels drawn in the peri-operative period (within 8 days of transplant).
- 10 patients had levels drawn on days 0, 4, and 8 allowing further analysis.
- In general, each day post-transplant was associated with a significant decrease in DF cfDNA ($p < 0.001$) by POD #8.

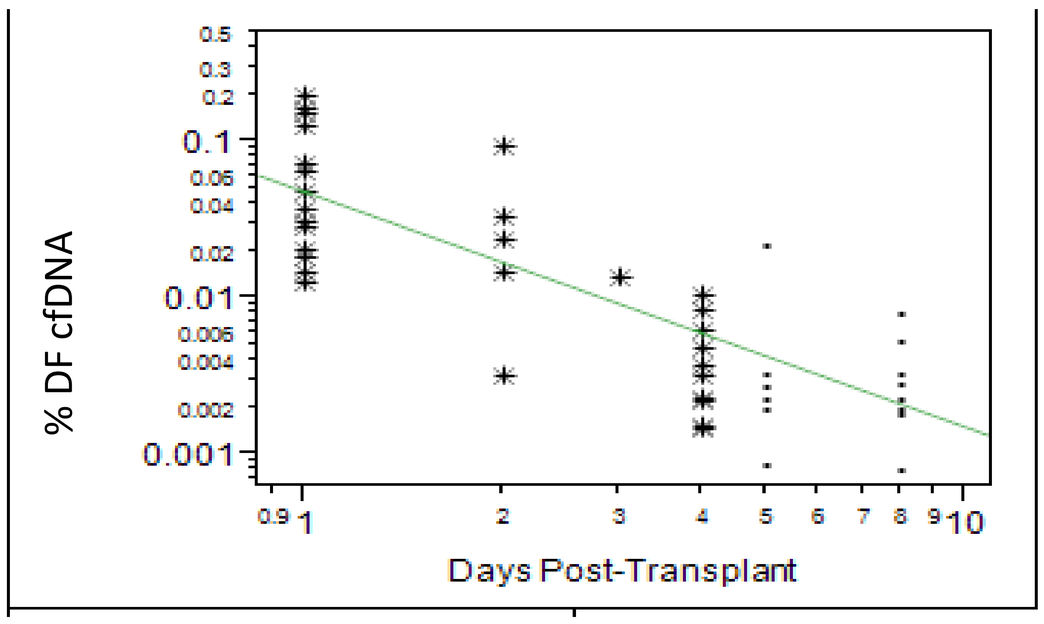
Authors listed will not discuss any off label use and/or investigational use of drugs/devices.

Results

Patient Characteristics

	Patients (n = 17)
Mean age at transplant (years)	7.8 years (0.2 – 23.8)
Percent Male	65%
Percent Congenital Heart Disease	59%

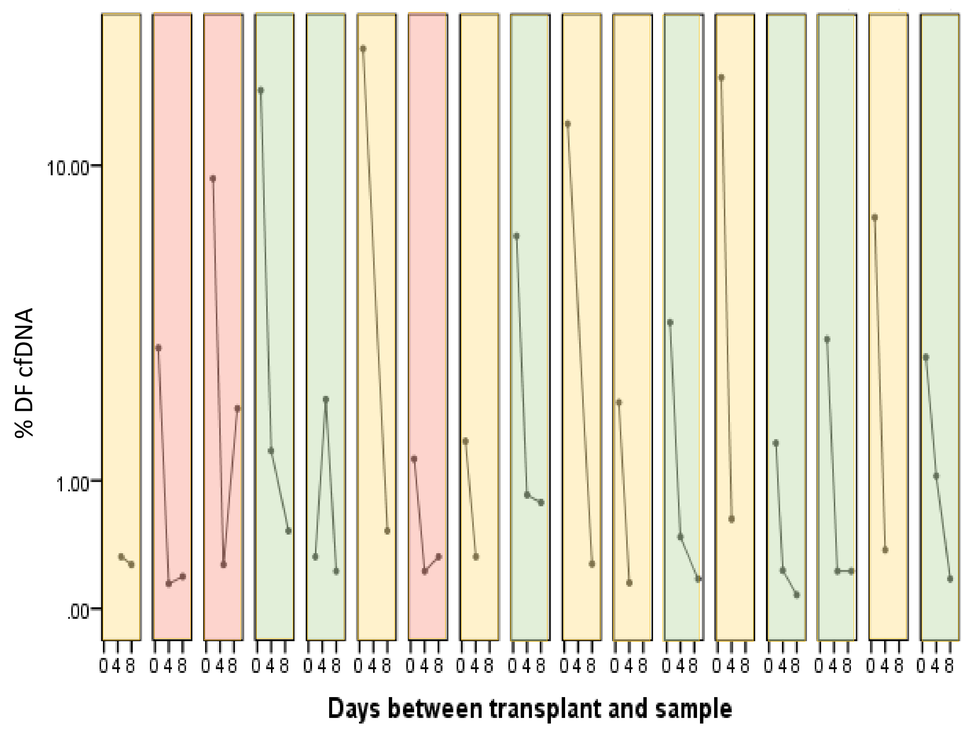
Figure 1. Association of Percent DF cfDNA to Days Post-Transplant



Association between percent DF cfDNA (calculated as concentration of DF cfDNA divided by concentration of total cfDNA) and time on a log-log scale. DF cfDNA levels declined significantly over the first 8 days post-transplant ($p < 0.001$).

Results

Figure 2. Declination Curves for 17 Patients with Multiple Observations



Declination curves for all 17 patients with at least two DF cfDNA samples within 8 days of transplantation. Curves shaded in **yellow** correspond to patients with only 2 samples collected in this time period. Those shaded in **green** had decline of their DF cfDNA from day 4 to day 8 and those shaded in **red** had an increase in DF cfDNA from day 4 to day 8.

Results

- 7 of 10 patients had a decline in their DF cfDNA levels from POD #4 to POD #8
  - None died within 60 days of transplant
- 3 of 10 patients had an increase in DF cfDNA levels from POD #4 to POD #8
  - All three died within 60 days of transplant
- 1 of 10 patients had an increase in DF cfDNA from POD 0 to POD #4.
  - This increase corresponded to a short ischemic time (115 minutes) and an episode of acute hypotension on POD #3.
  - The patient had a decline in DF cfDNA by day 8 and a negative biopsy on POD #9

Discussion and Recommendations

- DF cfDNA is a very sensitive marker of graft injury following heart transplantation.
- Early monitoring of DF cfDNA may allow for detection of clinically important events signaling risk to the graft.
- Serial monitoring of DF cfDNA may provide important clinical information on graft health or injury.
- While these preliminary findings suggest the utility of DF cfDNA as a non-invasive marker of graft injury, larger studies are needed prior to implementation in routine patient care pathways.

Conclusions

- DF cfDNA appears to significantly decline by day 8 post heart transplant.
- A rise in the level of DF cfDNA from POD#4 to POD#8 is associated to peri-transplant graft survival.

Future Directions

- Prospective confirmation of this preliminary study via a larger data set.
- Further statistical modeling to determine clinically significant trends in DF cfDNA levels in the peri-operative period that may signal risk of graft loss.

Author Disclosures

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