LETTER TO THE EDITORS

Impact of kidney transplant type and previous transplant on baseline donor-derived cell free DNA

Kalathil K. Sureshkumar[1], Shelly Lyons[2] & Bhavna Chopra[1]

1 Division of Nephrology and Hypertension, Medicine Institute, Allegheny General Hospital,Allegheny Health Network, Pittsburgh, PA, USA

2 Surgery Institute, Allegheny General Hospital,Allegheny Health Network, Pittsburgh, PA, USA

E-mail: Kalathil.sureshkumar@ahn.org

Dear Editors,

Donor-derived-cell free DNA (dd-cfDNA) is a biomarker now available to predict acute rejection in renal allografts [1–3]. The technology utilizes targeted next-generation sequencing and does not require donor genotyping [1]. dd-cfDNA levels ≥1% suggest allograft injury usually from acute rejection [2]. It is less clear whether baseline dd-cfDNA levels are affected by the presence of failed previous allograft and differ by the type of transplant (deceased vs. living donor). We aimed to evaluate to see if differences exist in baseline dd-cfDNA values based on the type (deceased vs. living donor) and number(repeat vs. first-time) of kidney transplants.

The study protocol was approved by the Institutional Review Board. Our center started checking serial dd-cfDNA (AlloSure; CareDx, Brisbane, CA, USA) as surveillance in high-immunological risk patients since January 2018. We identified patients who underwent kidney transplantation at our center between April 2018 and June 2019 and had measurement of dd-cfDNA at multiple time-points beyond 2 weeks post-transplantation. A dd-cfDNA value ≥1.0% was considered abnormal and prompted allograft biopsy. If there was evidence of rejection or other injury on allograft biopsy, that patient's dd-cfDNA values were excluded from the analysis since we aimed to compare baseline values. Baseline dd-cfDNA values were compared for patients who underwent deceased versus living donor and repeat versus first-time kidney transplants.

There were 72 patients with first-time and 13 with repeat-kidney transplants during the study period who underwent dd-cfDNA measurements. Twelve patients from first-time and one patient from repeat-transplant groups were excluded from the analysis since they had allograft biopsies showing evidence for rejection or other injury. The final analysis included 196 measurements of dd-cfDNA among 60 first-time and 44 dd-cfDNA measurements among 12 repeat-transplant recipients (11 patients with two and one with three kidney allografts in situ). Among first-time transplants, there were 32 deceased donor (with 112 dd-cfDNA values) and 28 living donor (with 84 dd-cfDNA values) kidney recipients. There were no significant differences in dd-cfDNA values for either deceased versus living donor ($0.39 \pm 0.42\%$ vs. $0.37 \pm 0.20\%$, $P = 0.35$) or repeat versus first-time ($0.34 \pm 0.07\%$ vs. $0.39 \pm 0.43\%$, $P = 0.36$) transplants (Fig. 1).

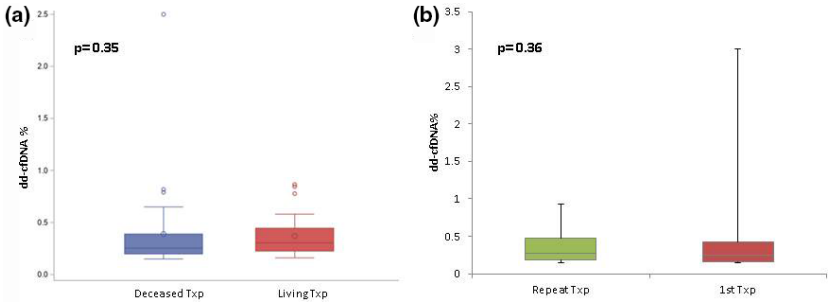

Figure 1 Box plots showing dd-cfDNA levels stratified by donor type (deceased vs. living, a) and number of transplants (repeat vs. first-time transplant, b).

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Our findings suggest that a previously failed kidney transplant does not significantly affect the baseline dd-cfDNA values. A recent study showed significantly higher dd-cfDNA value in repeat-kidney compared to first-time kidney recipients (0.29% vs. 0.19%, $P < 0.001$) but well within the established 1% dd-cfDNA rejection threshold [4]. One possible explanation for these seemingly contradictory findings could be the difference in the number of viable cells in the failed allografts between the studies that were capable of generating dd-cfDNA. Based on these analyses, it appears reasonable to use dd-cfDNA to predict rejection in repeat-kidney transplants. To our knowledge, our analysis is the first to compare baseline dd-cfDNA levels between deceased and living donor kidney recipients. The values were similar between the groups despite the possibility that kidney from deceased donor is susceptible to higher levels of ongoing injury from factors such as ischemia-reperfusion and higher degrees of immunological mismatch. Relatively small sample size is a study limitation. Our findings warrant further studies.

Conflicts of interest

Kalathil Sureshkumar has received grant/research support and honoraria from CareDx. Shelly Lyons: None. Bhavna Chopra: has received grant/research support from CareDx.

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REFERENCES

1. Grskovic M, Hiller DJ, Eubank LA, *et al*. Validation of a clinical-grade assay to measure donor-derived cell-free DNA in solid organ transplant recipients. *J Mol Diagn* 2016; **18**: 890.
2. Bloom RD, Bromberg JS, Poggio ED, *et al*. Cell-free DNA and active rejection in kidney allografts. *J Am Soc Nephrol* 2017; **28**: 2221.
3. Haung E, Sethi S, Peng A, *et al*. Early clinical experience using donor-derived cell-free DNA to detect rejection in kidney transplant recipients. *Am J Transplant* 2019; **19**: 1663.
4. Mehta SG, Chang JH, Alhamad T, *et al*. Repeat kidney transplant recipients with active rejection have elevated donor-derived cell-free DNA. *Am J Transplant* 2019; **19**: 1597.