Impact of Donor-derived Cell-free DNA Fraction Assessment in Monitoring Kidney Transplant Recipients: Insights from a European Prospective Cohort Study

Angelica Pagliazzi[1], Karolien Wellekens[1], Henriette de Loor[1], Thibaut Vaulet[1], Thierry Viard[2], Narin Tangprasertchai[2], Sílvia Casas Fontdevila[2], Robert Woodward[2], Maarten Naesens[1,3]

1 KU Leuven, Nephrology and Renal Transplantation Research Group, Leuven, Belgium, 2 CareDx Inc., Brisbane, California, United States, 3 UZ Leuven, Department of Nephrology and Renal Transplantation, Leuven, Belgium.

Donor-derived cell-free DNA (dd-cfDNA) is a promising non-invasive biomarker for monitoring kidney transplant (KT) recipients. We aim to evaluate its clinical utility in a prospective, and unselected, cohort of 500 cases.

Since July 2022, we prospectively collect plasma from each KT recipient immediately prior to renal biopsy, to measure dd-cfDNA, using a locally implemented standardized assay (AlloSeq cfDNA, CareDx, CA), and correlate %dd-cfDNA with allograft and recipient status. Dd-cfDNA results remain blind to the clinical team.

Of the 430/500 samples collected so far, %dd-cfDNA has been already measured in 229, with 92.1% of samples passing quality control. The %dd-cfDNA <14 days post-TX (0.71% [0.53-0.85]) was significantly higher than >14 days post-TX (0.21% [0.12-0.32]; p=5.3x10-7, Fig.1A). Dd-cfDNA was increased in deceased donor (DD) kidneys, both DBD (0.24% [0.16-0.38]; p=0.004) and DCD (0.24% [0.12-0.4]; p=0.03), compared to living donation (LD) (0.13% [0.1- 0.25], Fig.1B), but not different between DBD and DCD kidneys. The difference between DD and LD kidneys persisted >14 days post-TX (DBD 0.21% [0.15-0.31]; DCD 0.22% [0.11-0.32]; LD 0.13% [0.10-0.25]). Dd-cfDNA level was significantly higher at the time of indication biopsies (0.41% [0.26-0.85]) than at surveillance biopsies (0.18% [0.11-0.30]; p=2.8x10-10). 13.3% of cases had (borderline) allograft rejection (AR). Dd-cfDNA was higher in AR (0.80% [0.47-1.64]) versus no rejection (0.31% [0.25-0.70]; p=0.016, Fig.1C) in indication biopsies only, which also showed more cases of full-blown AR than surveillance biopsies (17% vs 3%, respectively). Within 14 days post-TX, the inherently higher %dd-cfDNA masked the association between dd-cfDNA and AR. In indication biopsies performed >14 days post-TX, AR was associated with higher %dd-cfDNA (1.19% [0.32-2.00] vs 0.28% [0.23-0.44] in AR vs no rejection, Fig.1D).

We anticipate completing %dd-cfDNA measurements for the entire prospective cohort, comprising 500 samples, by February 2024. Meanwhile, this interim analysis indicates that, when measured >14 days post-TX, dd-cfDNA could guide whether to perform an indication biopsy. However, within <14 days post-TX, the injury/healing process occurring after TX masks the ability of dd-cfDNA to uncover ongoing AR. The impact of donor type on %dd-cfDNA persists >14 days post-TX. The clinical utility of dd-cfDNA for subclinical AR will be addressed upon study completion on the full prospective cohort.

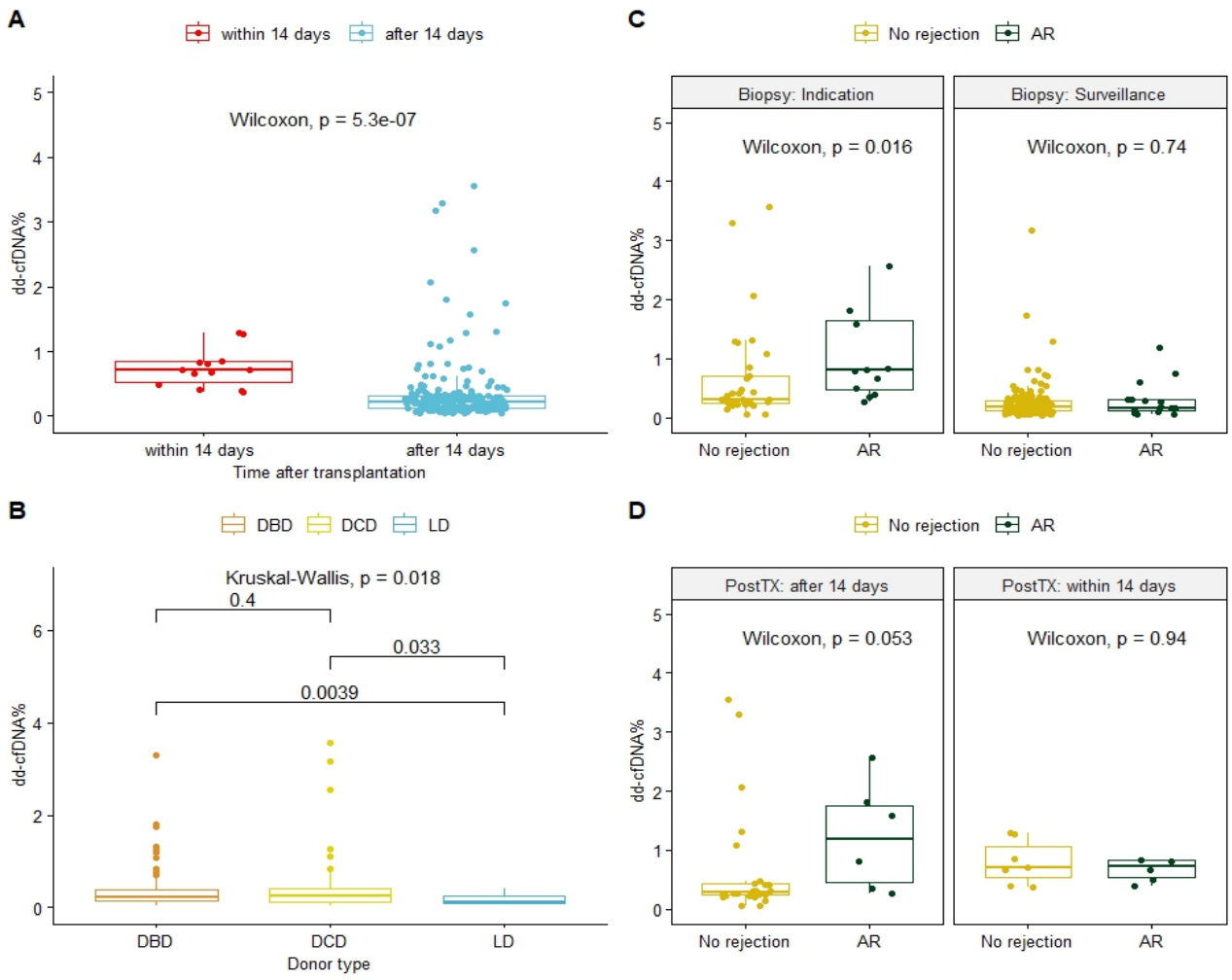

Figure 1: A. Box and whisker plot showing %dd-cfDNA median levels within and after 14 days post-transplantation. **B.** Box and whisker plot showing %dd-cfDNA median levels in kidney transplant recipients from deceased (DBD and DCD) and living (LD) donation. **C.** Box and whisker plot showing %dd-cfDNA median levels in patients with and without allograft rejection (AR) at the time of indication and surveillance biopsies. **D.** Box and whisker plot showing %dd-cfDNA median levels in patients with and without allograft rejection at the time of indication biopsies performed within and after 14 days post-transplantation. DBD=donor after brain death; DCD=donor after cardiac death.