

Absolute quantification of donor-derived cell-free DNA as a marker of rejection and graft injury in kidney transplantation: Results from a prospective observational study

Oellerich M, Shipkova M, Asendorf T, et al. (2019) Am J Transplant 19(11):3087.

Practical Clinical Utility

The absolute quantity of dd-cfDNA (cp/mL) is a more accurate marker for the assessment of graft health than the fractional abundance of dd-cfDNA (%).

dd-cfDNA (cp/mL) may aid in determining the minimum effective immunosuppressive dose for kidney transplant patients.

Droplet digital PCR (ddPCR) can be used to effectively measure dd-cfDNA with a one-day turnaround time.

Endpoints and Goals

Directly compare the diagnostic performance of dd-cfDNA absolute quantification (cp/mL), dd-cfDNA fraction (%), and plasma creatinine (mg/dL) for detection of graft injury.

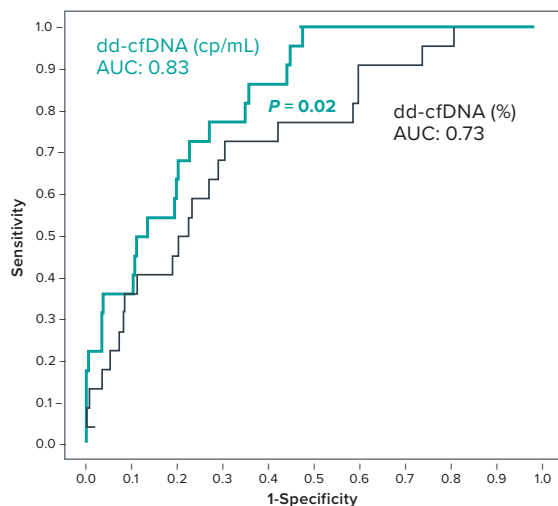
Methods

- Prospective, non-interventional, blinded, single-center study to evaluate **189 adult kidney transplant patients with 1,641 samples** for one year following transplantation
- dd-cfDNA (%) and dd-cfDNA (cp/mL) were directly compared along with additional laboratory values from routine monitoring (creatinine, white blood cell count, eGFR, and ISD)

- Following kidney transplantation, patients were put on standard immunosuppression and plasma samples from patients were collected daily for the first 2 weeks, then patients were assigned to the closest scheduled sampling time points of: 3W (weeks), 4W, 2M (months), 3M, 4M, 5M, 6M, 8M, 10M, and 1Y (year)
- Longitudinal samples from patients were assigned to one of six subgroups: "Non-rejecting Phase," "Stable Phase," "Negative Biopsy," "Borderline TCMR," "Biopsy-proven Rejection (BPR)," and "Interstitial fibrosis/tubular atrophy (IF/TA)"

Results

Receiver Operating Characteristic (ROC) curve comparison of dd-cfDNA (cp/mL) and dd-cfDNA (%)



Absolute dd-cfDNA (cp/mL) allowed for better discrimination than dd-cfDNA (%) of kidney transplant patients with BPR

- Median dd-cfDNA (cp/mL) was 3.3-fold higher in BPR patients (N=15) than in Stable Phase patients (N=83) without rejection, whereas median dd-cfDNA (%) was only 2.0-fold higher

ROC curve for dd-cfDNA (cp/mL) increased significantly by 14% compared to dd-cfDNA (%) in discriminating Stable Phase (n=395) to BPR (n=22) with a 98% NPV*

There were a significantly higher proportion of samples with elevated dd-cfDNA (cp/mL) and lower tacrolimus levels (<8 µg/L) compared to the samples with higher tacrolimus concentrations.

*Calculated at a 12% prevalence.

N = number of patients | n = number of samples

Conclusion

In a direct comparison, dd-cfDNA (cp/mL) absolute values significantly outperformed dd-cfDNA (%) for the discrimination

of acute rejection from stable phase in kidney transplant patients. Absolute values were not confounded by changes in total cfDNA.