The Combined Effect of Tacrolimus Intrapersonal Variability and Donor-specific HLA Antibodies on Kidney Allograft Outcomes: Implications for CYP3A5 Genotyping

[1,2]Eric Ho, [2]Bora Pajo, [2]Gail Frankle, [1]Elaine Silvia, [1]E. Rodica Vasilescu, [1]George Vlad, [1]Nicole Suciu-Foca, [2]Lewis Chongwony

1. Columbia University, Department of Pathology & Cell Biology, NY, NY. 2. Franklin University, School of Public and Health Administration, Columbus, OH.

Aim:

This study investigates the impact of intrapersonal variability (IPV) in tacrolimus trough concentrations and the development of donor-specific HLA antibodies (DSAs) on allograft survival in kidney transplant recipients. Additionally, it aims to determine whether the combination of high IPV (≥30%) and the presence of DSAs further compromises graft survival outcomes.

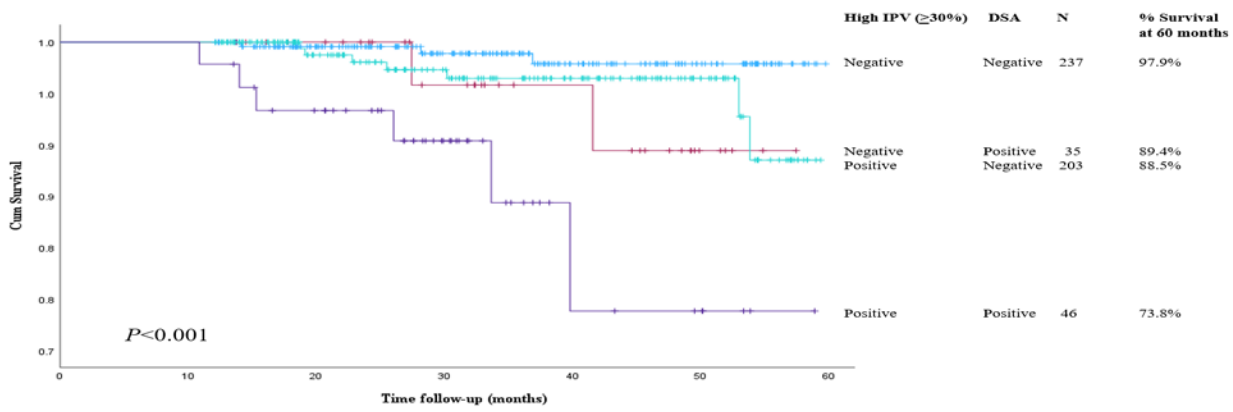
Methodology:

This observational retrospective cohort study employs a stratified sampling technique followed by a cluster sampling strategy to create a more homogeneous study population. A total of 521 adult patients who underwent kidney transplantation at Columbia University Irving Medical Center (CUIMC) were included between January 1, 2015, and December 31, 2018, as shown in Table 1.

Table 1. The summary of patients' demographics and characteristics in this study

			N	%
Patients' demograpghics				
Gender	Male		322	38.2
	Female		199	61.8
Race	Caucasians		213	40.9
	African Americans		72	13.8
	Hispanics		146	28.0
	Others		90	17.3
Age at the time of transplant		Mean±SD = 50.8±14.3		
Patients' characteristics				
History of transplant	Primary graft		448	86.0
	Regraft		73	14.0
Type of transplant	Living donor		286	54.9
	Deceased donor		235	45.1
HLA-A, B, C, DR, DQ mismatches	0 MM		29	5.7
	1 MM		8	1.5
	2 MM		12	2.3
	3 MM		32	6.1
	4 MM		48	9.2
	5 MM		69	13.2
	6 MM		73	14.0
	7 MM		83	15.9
	8 MM		98	18.9
	9 MM		50	9.6
	10 MM		19	3.6
cPRA at the time of transplant		Mean±SD = 46.3±299.0		
Donor-specific antibodies, post-transplantation	Positive		81	15.5
	Negative		440	84.5
Tacrolimus level measurements		Mean±SD = 10.9±11.3		
IPV		Mean±SD = 31.7±16.0		

Figure 1. Impact of High Tacrolimus IPV and Donor-Specific Antibodies on Graft Survival in Kidney Transplant Recipients



Results:

- IPV and DSAs were both significant predictors of kidney allograft failure.
  - Cox Regression Analysis: Higher IPV was associated with increased risk of graft loss (HR = 1.029, 95% CI [1.006–1.052], $P = 0.014$)
  - Presence of DSA increased the risk over fourfold (HR = 4.443, 95% CI [1.728–11.428], $P < 0.002$)
- Threshold Definition: High IPV was defined as ≥30%, based on literature consensus.
  - Kaplan-Meier Survival Analysis: Patients with both high IPV and DSA (IPV+/DSA+) had the lowest graft survival. Statistically significant difference in survival compared to patients without either risk factor (IPV−/DSA−), $P < 0.001$, as shown in Figure 1.

Conclusion:

High tacrolimus IPV and presence of DSAs are significant, independent predictors of poorer kidney allograft survival. Patients with both high IPV and DSA experienced the worst outcomes. CYP3A5 genotyping may help identify patients at risk for high IPV. Personalized tacrolimus dosing based on genotype could: reduce IPV, minimize DSA development, and improve long-term graft outcome.