Impact of Metabolic Variability of Tacrolimus on Post-Transplant Clinical Outcomes in Kidney Transplant Recipients

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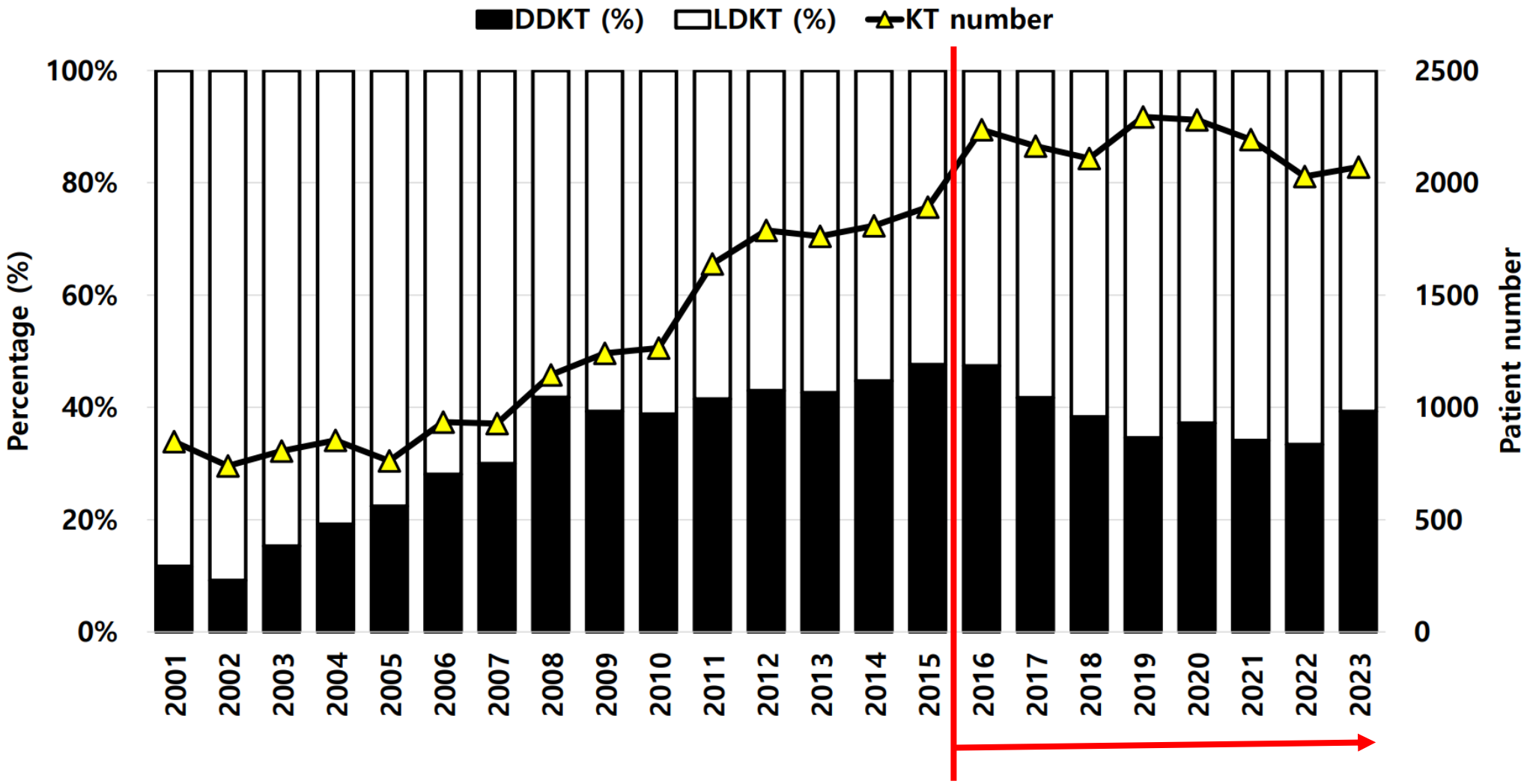
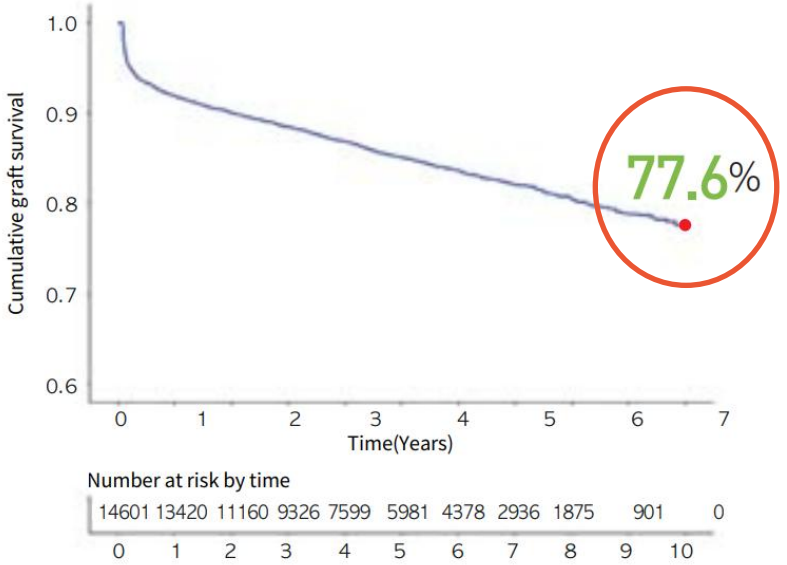
Current Status of Kidney Transplantation in South Korea



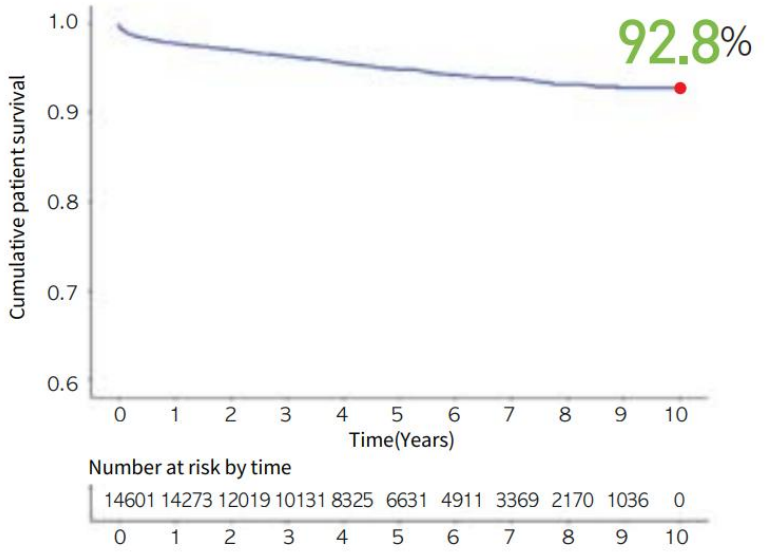
2024 KORDS annual report

10-year survival rate in kidney transplant recipients in South Korea

10-year death-censored graft survival rate



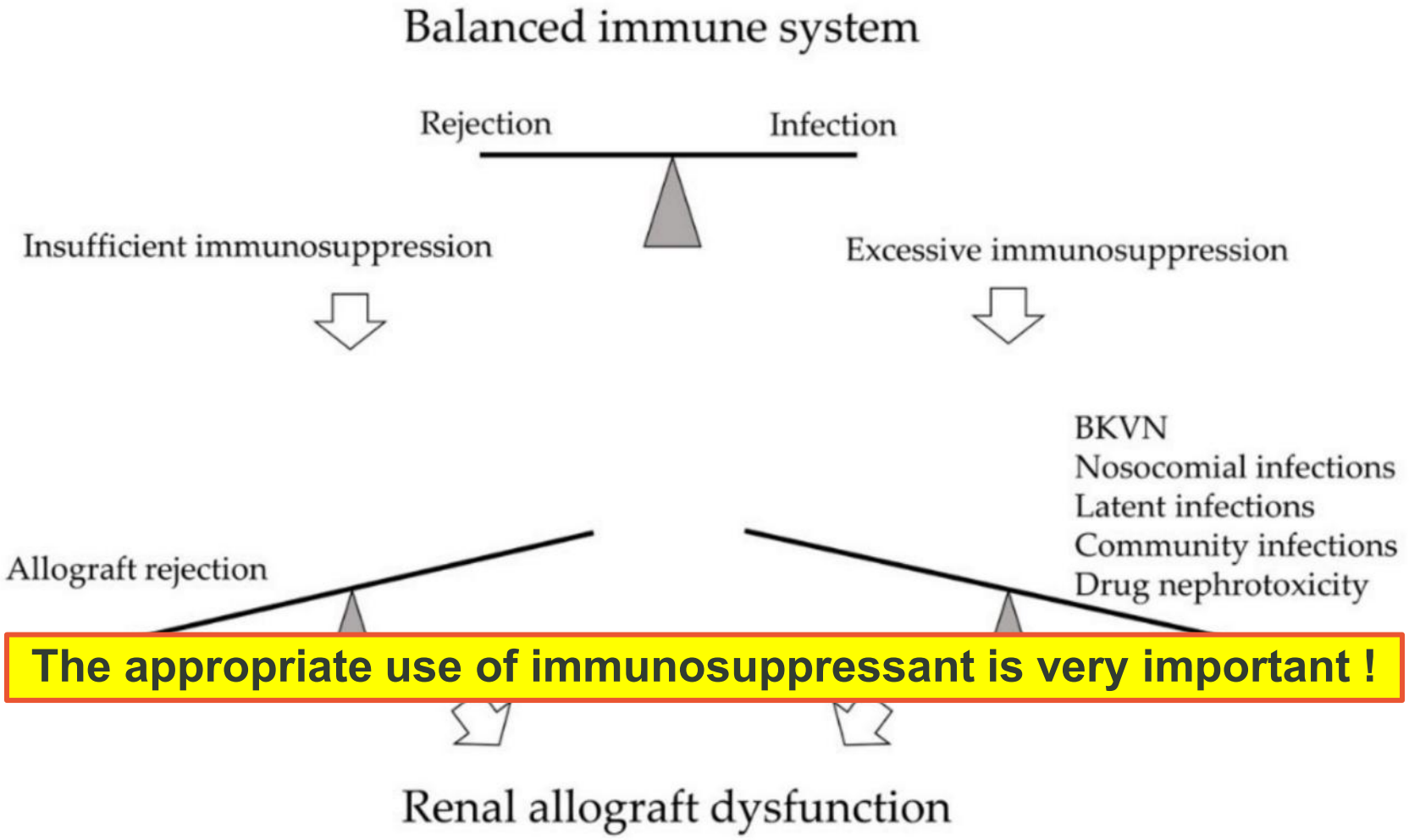
10-year patient survival rate



Short-term graft and patient survival rates are good, but long-term graft survival rate is poor.

2024 KORDS annual report

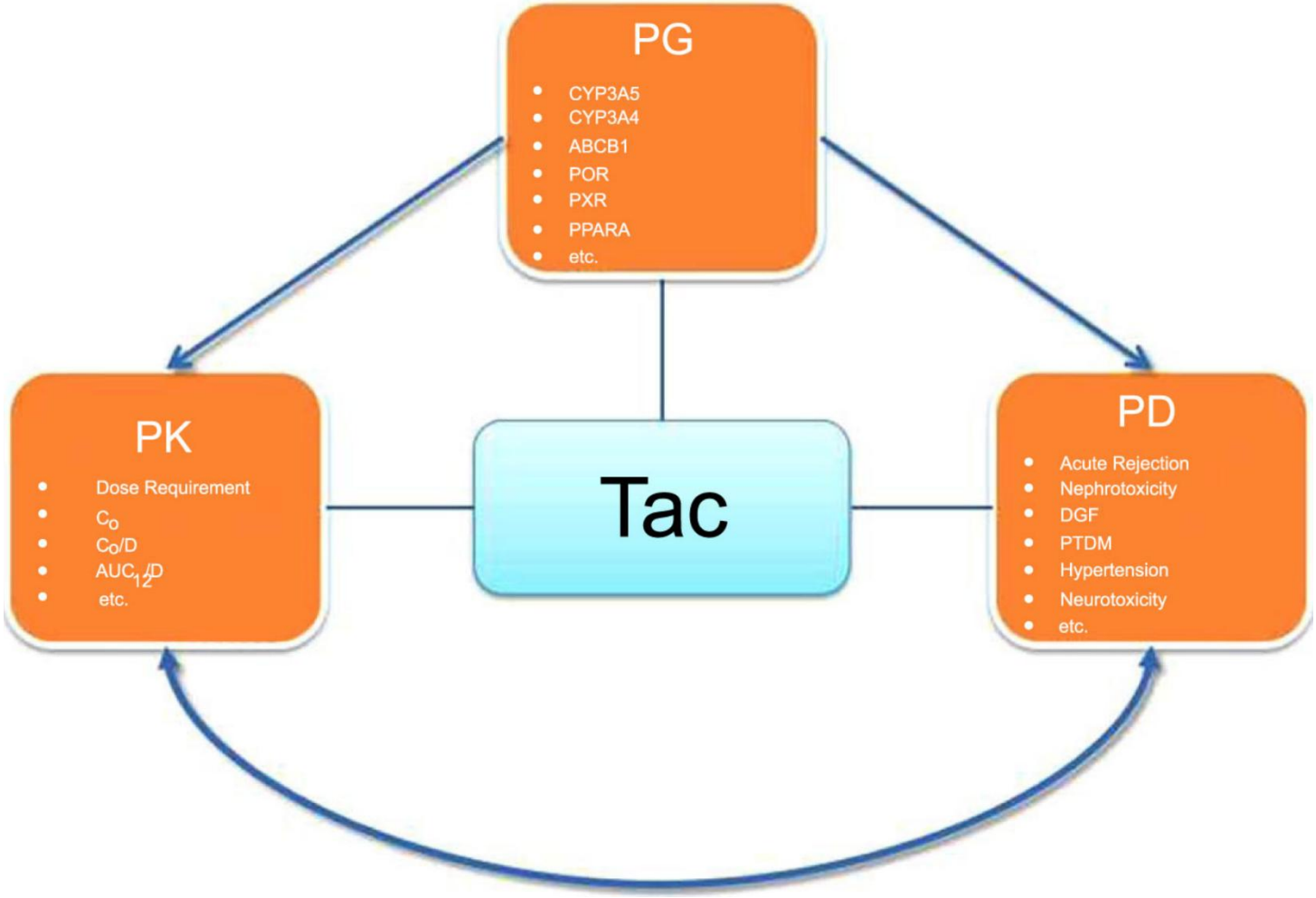
The immune system of kidney transplant recipients is balanced between rejection and infection



The appropriate use of immunosuppressant is very important !

Viruses 2021, 13, 487

Pharmacokinetics, pharmacogenetics, pharmacodynamics of tacrolimus in kidney transplantation



Current Drug Metabolism, 2018, 19, 513-522

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP3A5 Genotype and Tacrolimus Dosing

Table 2 Dosing recommendations for tacrolimus based on *CYP3A5* phenotype

CYP3A5 phenotype[a]	Implications for tacrolimus pharmacologic measures	Therapeutic recommendations[b]	Classification of recommendations[c]
Extensive metabolizer (CYP3A5 expresser) **CYP3A5 *1/*1**	Lower dose-adjusted trough concentrations of tacrolimus and decreased chance of achieving target tacrolimus concentrations.	Increase starting dose 1.5–2 times recommended starting dose.[d] Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Strong
Intermediate metabolizer (CYP3A5 expresser) **CYP3A5 *1/*3**	Lower dose-adjusted trough concentrations of tacrolimus and decreased chance of achieving target tacrolimus concentrations.	Increase starting dose 1.5–2 times recommended starting dose.[a] Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Strong
Poor metabolizer (CYP3A5 nonexpresser) **CYP3A5 *3/*3**	Higher ("normal") dose-adjusted trough concentrations of tacrolimus and increased chance of achieving target tacrolimus concentrations.	Initiate therapy with standard recommended dose. Use therapeutic drug monitoring to guide dose adjustments.	Strong

[a]Typically, with other CYP enzymes, an extensive metabolizer would be classified as a "normal" metabolizer, and, therefore, the drug dose would not change based on the patient's genotype. However, in the case of CYP3A5 and tacrolimus, a CYP3A5 expresser (i.e., CYP3A5 extensive metabolizer or intermediate metabolizer) would require a

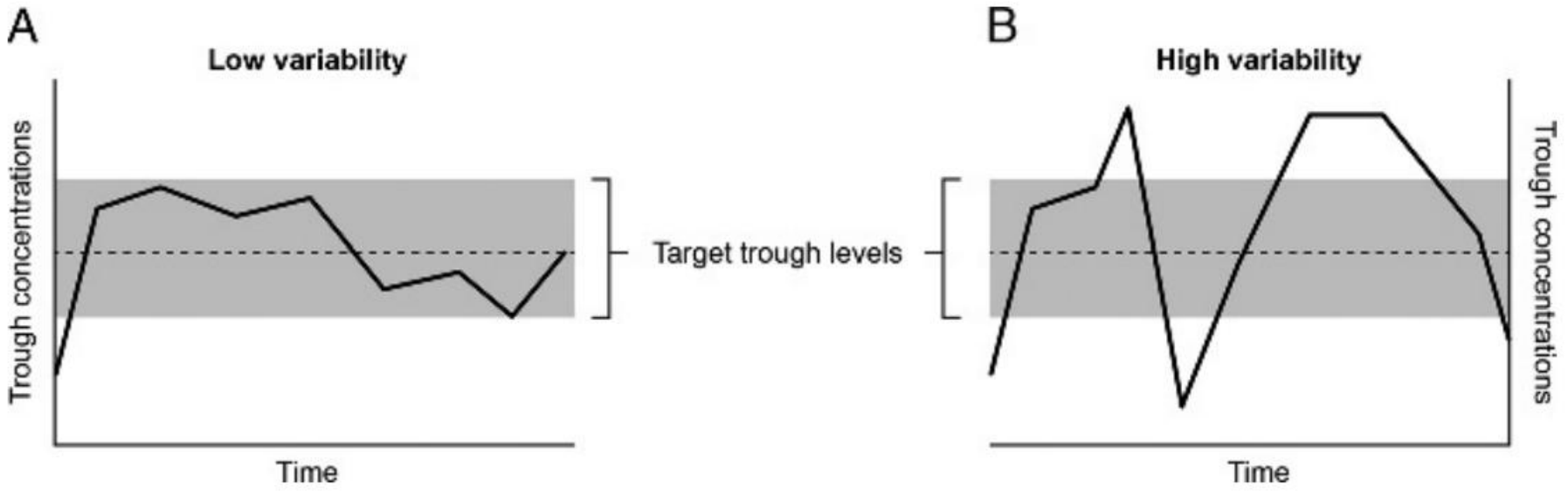
Acute rejection

Nephro-toxicity

Identifying the genotype and the dose adjustment of tacrolimus is important to maintain the balance between acute rejection and nephrotoxicity.

Clin Pharmacol Ther. 2015 Jul;98(1):19-24.

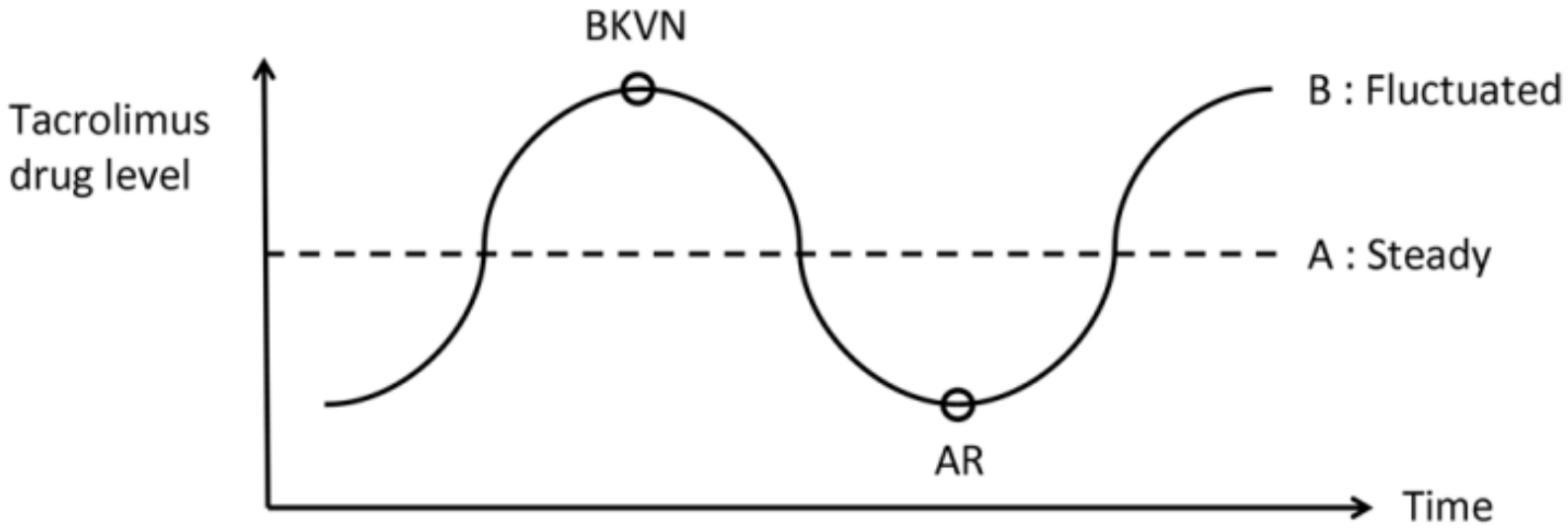
Intra-patient variability of tacrolimus exposure



In tacrolimus nephrotoxicity or acute rejection, not only the tacrolimus dose but also the tacrolimus variability important to maintain stable target trough levels.

Transplantation. 2017 Apr;101(4S Suppl 2):S1-S56.

Proposed model for the pathogenesis of coexisting BKVN and AR

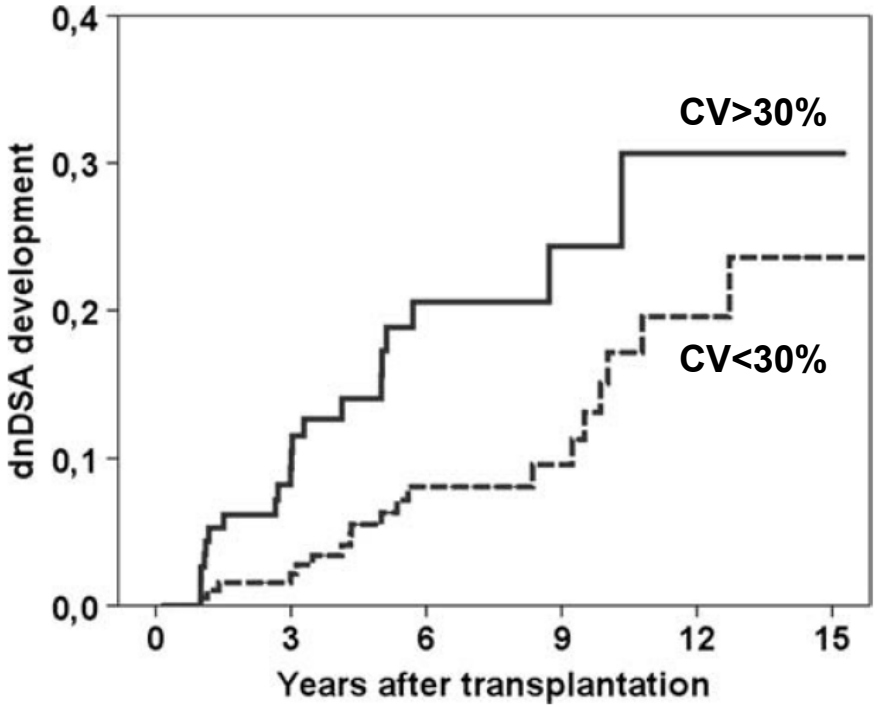


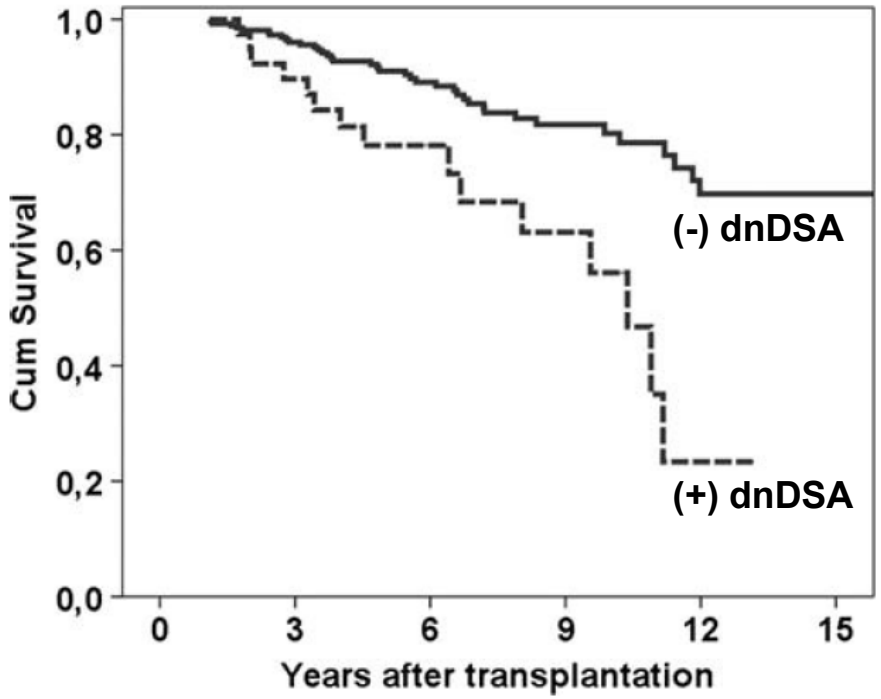
Tacrolimus trough level >10 ng/mL is associated with BKPyV infection after kidney transplantation.

A higher variability of tacrolimus trough level may be associated with the coexistence of BKVN and acute rejection.

Wiebe C et al. Am J Transplant 15: 2921–2930, 2015

De novo DSA detection according to the variability of CNI levels





CV: coefficient of variation

A higher tacrolimus intra-patient variability is related to the risk factor for dnDSA development and lower graft survival rate.

Rodrigo E et al. Transplantation. 100(11):2479-2485, 2016

Purpose

- We aimed to investigate the appropriate markers for the metabolic variability of tacrolimus in kidney transplant recipients.
- Primary outcome: Death-censored graft survival rate
- Secondary outcomes:
  - Comparison of clinical outcomes based on the tacrolimus metabolic variability
  - Comparison of pathologic findings based on the tacrolimus metabolic variability
  - Risk factors associated with death-censored graft failure in kidney transplantation

Methods and Materials

- We enrolled 100 patients performed KT between 2013 and 2020.
- Tacrolimus metabolism rate was defined as the blood concentration normalized by its daily dose (the C/D ratio).
- Based on the Tac C/D ratio, patients with a C/D ratio <1.05 ng/mL x 1/mg were defined as fast metabolizers and patients with a C/D ratio of >1.05 ng/mL x 1/mg were defined as slow metabolizers.

C/D ratio (ng/mL X 1/mg) = Blood Tac trough concentration (ng/mL)/Daily Tac dose (mg)

- We analyzed the incidence of delayed graft function (DGF), de novo donor specific antibody (DSA), acute rejection, infection, graft function and graft survival based on the tacrolimus metabolism.
- We also checked the coefficient of variation (CV) of tacrolimus for tacrolimus metabolism variability.

Results

Comparison of clinical parameters based on the tacrolimus metabolic variability

	Total (n=100)	Fast metabolizer (n=41)	Slow metabolizer (n=59)	*P*-value
Recipient age at kidney transplantation, years	43.9 ± 10.2	40.8 ± 9.9	46.0 ± 10.0	0.012
Donor age at kidney transplantation, years	38.8 ± 14.0	39.0 ± 12.8	38.6 ± 14.9	0.900
Recipient male gender, n (%)	50 (50)	25 (61.0)	25 (42.4)	0.103
Donor male gender, n (%)	57 (43)	21 (51.2)	36 (61.0)	0.412
Type of kidney transplantation, n (%)				1.000
Deceased donor kidney transplantation	50 (50)	21 (51.2)	29 (49.2)	
Living donor kidney transplantation	50 (50)	20 (48.8)	30 (50.8)	
Kidney transplantation number, n (%)				0.456
First	76 (76)	32 (78.0)	44 (74.6)	
Second	24 (24)	9 (21.9)	15 (25.4)	
Dialysis type before kidney transplantation, n (%)				0.154
Hemodialysis	72 (72)	33 (80.5)	39 (66.1)	
Peritoneal dialysis	19 (19)	4 (9.8)	15 (25.4)	
None	9 (9)	4 (9.8)	5 (8.5)	
Cause of end-stage renal disease, n (%)				0.167
Glomerulonephritis	80 (80)	33 (80.5)	47 (79.7)	
Diabetes mellitus	11 (11)	2 (4.9)	9 (15.3)	
Hypertension	2 (2)	1 (2.4)	1 (1.7)	
Autosomal dominant polycystic kidney disease	2 (2)	2 (4.9)	0	
Others	5 (5)	3 (7.3)	2 (3.4)	
HLA mismatch number	3.4 ± 1.7	3.1 ± 1.7	3.6 ± 1.6	0.141
Induction immunosuppressant, n (%)				1.000
Basiliximab	100 (100)	41 (100)	59 (100)	
Allograft function (eGFR, ml/min/1.73m^2)				
Discharge after kidney transplantation	84.3 ± 21.0	82.5 ± 21.2	85.6 ± 21.0	0.467
1 year after kidney transplantation	78.0 ± 24.7	76.2 ± 25.3	79.3 ± 24.5	0.545
3 years after KT	85.5 ± 28.4	83.5 ± 28.1	86.9 ± 28.8	0.564
Follow-up duration, months	133.6 ± 21.3	133.4 ± 21.0	133.7 ± 21.5	0.940

Values are expressed as means ± SDs, n (%). HLA = human leukocyte antigen; eGFR = estimated glomerular filtration rate

Relationship of tacrolimus dose-exposure-variability between fast and slow metabolizers in kidney transplant recipients

Tacrolimus dose

	Fast metabolizer	Slow metabolizer	*P*-value
Post-op day 7	8.88 ± 2.59	4.92 ± 1.62	<0.001
Post-op day 14	9.39 ± 2.81	4.96 ± 1.66	<0.001
Post-op day 21	8.98 ± 2.76	4.69 ± 1.55	<0.001
One month	8.24 ± 2.67	4.38 ± 1.55	<0.001
Three months	6.70 ± 2.46	3.53 ± 1.28	<0.001
Six months	5.72 ± 2.38	3.03 ± 1.13	<0.001
Twelve months	4.95 ± 2.09	2.91 ± 1.12	<0.001

Tacrolimus trough level

	Fast metabolizer	Slow metabolizer	*P*-value
Post-op day 7	**5.74 ± 1.98**	**8.69 ± 2.17**	**<0.001**
Post-op day 14	7.91 ± 2.46	7.82 ± 2.40	0.851
Post-op day 21	8.33 ± 2.23	8.43 ± 2.98	0.861
One month	8.97 ± 2.67	9.29 ± 3.70	0.636
Three months	7.14 ± 2.13	7.62 ± 2.10	0.276
Six months	7.06 ± 1.70	6.66 ± 2.09	0.320
Twelve months	6.29 ± 1.90	5.86 ± 1.88	0.273

Tacrolimus C/D ratio

	Fast metabolizer	Slow metabolizer	*P*-value
Post-op day 7	0.69 ± 0.23	1.92 ± 0.69	<0.001
Post-op day 14	0.97 ± 0.62	1.72 ± 0.70	<0.001
Post-op day 21	1.05 ± 0.59	1.91 ± 0.77	<0.001
One month	1.21 ± 0.54	2.39 ± 1.39	<0.001
Three months	1.22 ± 0.60	2.52 ± 1.36	<0.001
Six months	1.50 ± 0.89	2.54 ± 1.41	<0.001
Twelve months	1.58 ± 1.07	2.52 ± 2.06	0.004

Tacrolimus coefficient of variation

	Fast metabolizer	Slow metabolizer	*P*-value
One month	**34.57 ± 24.11**	**24.98 ± 23.27**	**0.049**
Three months	20.90 ± 14.71.	19.89 ± 17.68	0.765
Six months	21.21 ± 17.79	25.33 ± 25.95	0.381
Twelve months	**19.40 ± 16.83**	**30.66 ± 24.01**	**0.011**

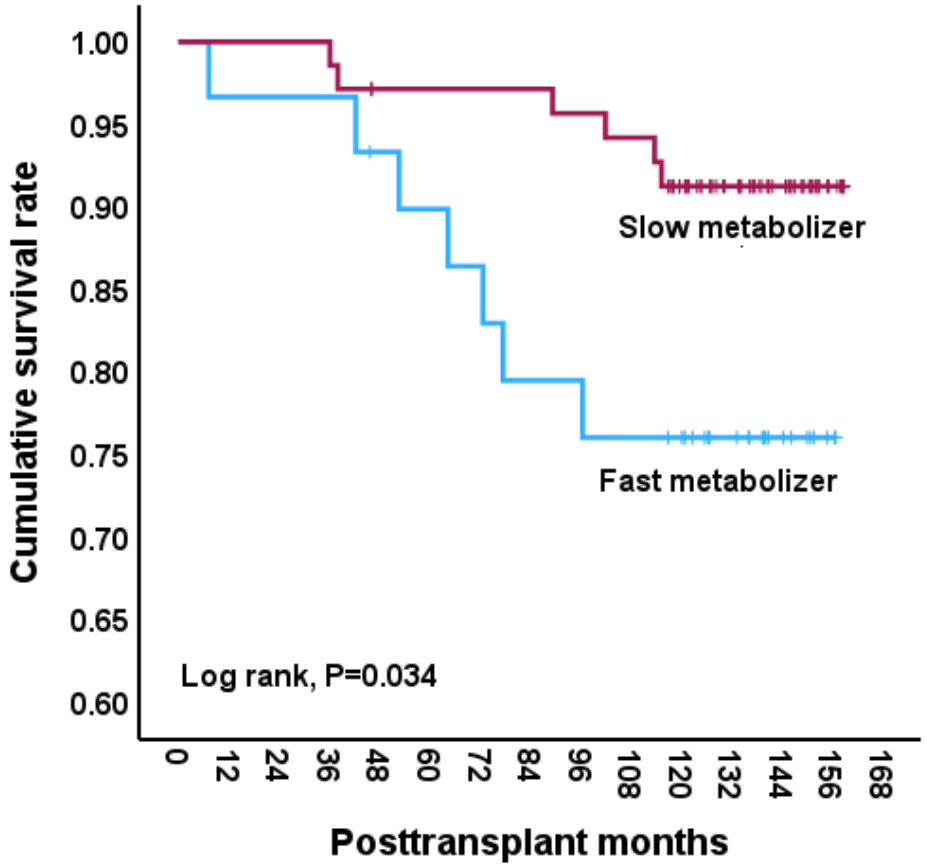
Values are expressed as means ± SDs, n (%).

Clinical and pathologic findings by tacrolimus metabolic variability

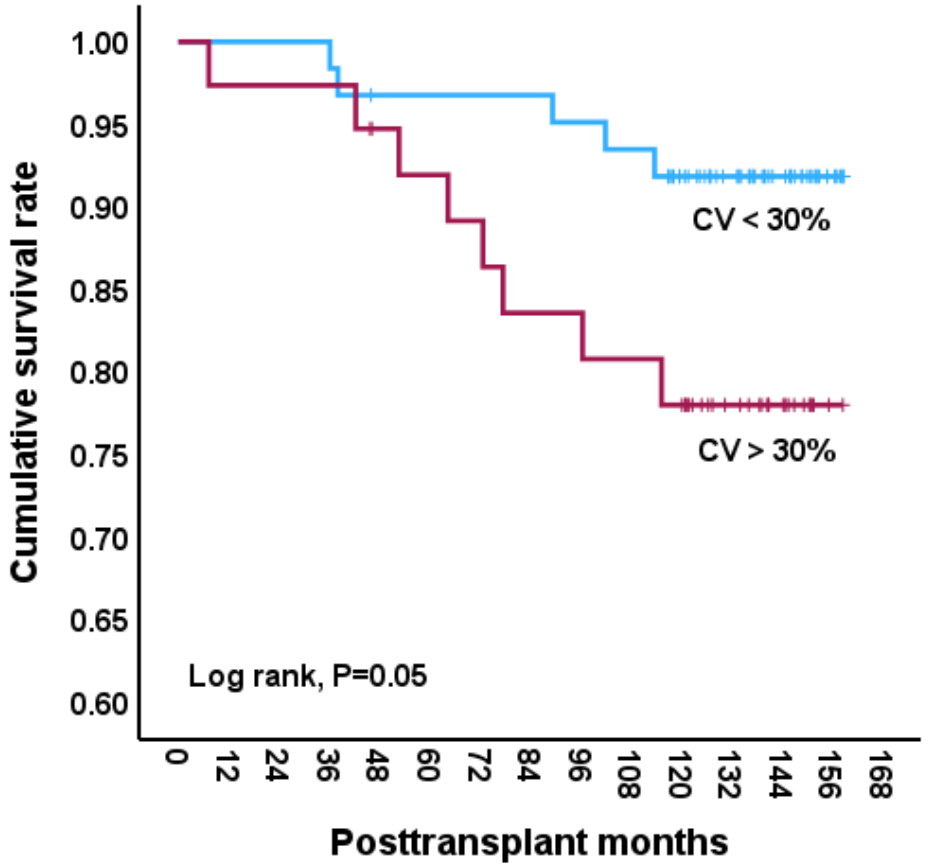
	Fast metabolizer	Slow metabolizer	*P*-value
Clinical findings			
Acute rejection within 1 year after KT, n (%)	3 (7.3)	4 (6.8)	1.000
Delayed recovery of graft function, n (%)	0	3 (9.1)	0.274
De novo donor specific antibody, n (%)	**5 (20.0)**	**2 (5.3)**	**0.103**
Cytomegalovirus infection, n (%)	19 (46.3)	30 (50.8)	0.689
BK virus-associated nephropathy, n (%)	1 (2.4)	0	0.410
Urinary tract infection, n (%)	**1 (2.4)**	**10 (16.9)**	**0.025**
Pneumonia, n (%)	4 (9.8)	2 (3.4)	0.224
Herpes zoster, n (%)	2 (4.9)	3 (5.1)	1.000
Pathologic findings			
Nonspecific change, n (%)	1 (2.4)	2 (3.4)	1.000
Borderline, n (%)	0	3 (3.4)	0.511
aTCMR, n (%)	3 (7.3)	4 (6.8)	1.000
AAMR, n (%)	1 (2.4)	4 (6.8)	0.646
CAMR, n (%)	2 (4.9)	1 (1.7)	0.566
Recurrent GN, n (%)	5 (12.2)	3 (5.1)	0.267
CNI toxicity, n (%)	1 (2.4)	4 (6.8)	0.646
Transplant glomerulopathy, n (%)	1 (2.4)	1 (1.7)	1.000
BKVAN, n (%)	1 (2.4)	0	0.410

Values are expressed as means ± SDs, n (%). KT = kidney transplantation; TCMR, T cell mediated rejection; AAMR, acute antibody-mediated rejection; CAMR, chronic antibody-mediated rejection; GN, glomerulonephritis; CNI, calcineurin inhibitor; BKVAN, BK virus nephropathy

Death censored graft survival rate based on the metabolic variability and the coefficient of variation



Death censored graft survival rate based on the metabolic variability



Death censored graft survival rate based on the coefficient of variation

Risk factors associated with death-censored graft failure in kidney transplantation

Variables	Univariate			Multivariate*		
	HR	95% C.I.	*P*-value	HR	95% C.I.	*P*-value
Female	6.394	1.416 - 28.872	0.016			
Delayed recovery of graft function	7.342	1.464 - 36.827	0.015			
Deceased donor kidney transplantation	3.720	1.023 - 13.531	0.046	37.318	5.036 - 276.523	<0.001
Cytomegalovirus infection	8.220	2.258 - 29.917	0.001			
BK virus-associated nephropathy	19.084	2.229 - 163.375	0.007			
Acute rejection within 1 year after KT	9.130	2.790 - 29.871	<0.001	27.006	2.020 - 361.08	0.013
Fast metabolizer	3.065	1.029 - 9.128	0.044			
High coefficient of variation	2.904	0.949 - 8.883	0.062	17.220	1.028 - 288.390	0.048

HR = hazard ratio, C.I. = confidence interval; KT = kidney transplantation

Conclusions

- Tacrolimus drug-level monitoring is important in post-transplant care because of the pharmacological properties: non-linear concentration effect relationship, narrow therapeutic window, and nephrotoxicity.
- Intra-patient variability (IPV) of tacrolimus should be considered when choosing target trough levels because tacrolimus IPV may cause fluctuation of blood tacrolimus level even with stable prescription dosage.
- Our findings suggest that not only tacrolimus trough levels but also C/D ratio and CV should be evaluated simultaneously to appropriately assess tacrolimus exposure and related clinical risks.

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