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**Impact of tacrolimus intra-patient variability in adverse outcomes after organ transplantation**

Morais MC *et al*. Tac-IPV and outcomes after organ transplantation

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**Abstract**

Tacrolimus (Tac) is currently the most common calcineurin-inhibitor employed in solid organ transplantation. High intra-patient variability (IPV) of Tac (Tac IPV) has been associated with an increased risk of immune-mediated rejection and poor outcomes after kidney transplantation. Few data are available concerning the impact of high Tac IPV in non-kidney transplants. However, even in kidney transplantation, there is still a controversy whether high Tac IPV is indeed detrimental in respect to graft and/or patient survival. This may be due to different methods employed to evaluate IPV and distinct time frames adopted to assess graft and patient survival in those reports published up to now in the literature. Little is also known about the influence of high Tac IPV in the development of other untoward adverse events, update of the current knowledge regarding the impact of Tac IPV in different outcomes following kidney, liver, heart, lung, and pancreas transplantation to better evaluate its use in clinical practice.

**Key Words:** Tacrolimus; Intra-patient variability; Rejection; Organ transplantation; Graft survival; Outcomes

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**Core Tip:** Tacrolimus is widely used after solid organ transplantation. High intra-patient variability of tacrolimus (Tac IPV) has been associated with poor graft and patient survival. This review summarizes current evidence regarding the impact of high Tac IPV in several outcomes after kidney, liver, heart, lung and pancreas transplantation.

**INTRODUCTION**

Tacrolimus (Tac) is nowadays the most common immunosuppressive drug employed in solid organ transplantation and has replaced cyclosporin as the most common calcineurin inhibitor used worldwide in immunosuppressive regimens[1,2]. Tac exhibits a peculiar pharmacokinetic profile with large inter-patient and intra-patient variability (IPV) of whole blood drug levels over time, even when doses remain unchanged. This is usually ascribed to overlapping factors, such as ethnicity, pharmacogenomics, food-drug and drug-drug interactions, non-adherence, enhanced Tac absorption or impaired drug excretion due to either diarrhea or cholestasis, assays variability for Tac levels determinations or even alternate use of Tac compounds or its generic formulations[3-5]. Due to its narrow therapeutic window, therapeutic drug monitoring of trough levels (Cmin) is required to attain target levels of immunosuppression over time, as well as avoidance of undesired Tac side effects such as infections, neurotoxicity and nephrotoxicity, which are usually related to higher drug exposure[1].

High Tac IPV or time in the therapeutic range (TTR) of Tac has been associated with an increased risk of immune-mediated rejection and poor outcomes after kidney transplantation (KT)[5,6]. Few data are available concerning the impact of high Tac IPV in non-kidney transplants[7]. However, even in KT, there is still a controversy whether high Tac IPV is indeed detrimental in respect to graft and/or patient survival[5,6]. This may be due to different methods employed to evaluate IPV and distinct time frames adopted to assess graft and patient survival in the reports published up to now. Little is also known about the influence of high Tac IPV in the development of other harmful adverse events associated with immunosuppression, such as infections, chronic kidney disease, type 2 diabetes, metabolic syndrome and *de novo* or recurrent cancer. The purpose of this review is to provide an update of current knowledge regarding the impact of Tac IPV in different outcomes following KT, liver (LT), heart (HT), lung, kidney/pancreas and bone marrow (BMT) transplantation to better evaluate its use in clinical practice.

**STUDY SELECTION**

To identify and select studies for this review, research was made in the MedLine/PubMed database, using the following terms: Tacrolimus; intra-patient; variability; transplant; transplantation; rejection; and graft loss. These terms were obtained from Medical Subject Headings (MeSH), using the Booleans “AND” and “OR”, from various search algorithms in PubMed.

Search 1: ((“tacrolimus”[MeSH Terms] OR “tacrolimus”[All Fields]) AND “intra”[All Fields] AND (“patient s”[All Fields] OR “patients”[MeSH Terms] OR “patients”[All Fields] OR “patient”[All Fields] OR “patients s”[All Fields]) AND (“variabilities”[All Fields] OR “variability”[All Fields] OR “variable”[All Fields] OR “variable s”[All Fields] OR “variables”[All Fields] OR “variably”[All Fields])) AND (y\_10[Filter]). Search 2: ((((((tacrolimus[Title/Abstract]) AND (variability[Title/Abstract])) OR (intrapatient variability[Title/Abstract])) AND (transplant[Title/Abstract])) OR (transplantation[Title/Abstract])) AND (rejection[Title/Abstract])) OR (graft loss[Title/Abstract]).

Subsequently, an active manual search of studies was carried out through carefully selected articles in gray literature.

The research was completed on May 17th, 2023. A total of 43 articles were included in the present study, 376 studies were found in PubMed database, and after careful reading of abstracts, 15 were included in our final review (references No. 3, 7, 24, 31, 33, 37, 38, 57, 60, 62, 65-67, 69, and 70). The excluded works did not satisfactorily meet the theme proposed for the present work. Furthermore, 28 studies different from the ones previously selected in PubMed database were identified in our active manual research in gray literature, all of which were included in this review.

**METHODS USED TO ASSESS TAC IPV**

Intra-patient variability of Tac over time has been calculated using different methods, particularly[5-7]: Mean levels and standard deviation (SD) of Tac whole-blood Cmin levels, also expressed as the medication level variability index (MLVI).

Mean absolute deviation (MAD), based on the formula MAD (%) = {[(Xmean - X1) + (Xmean - X2)… + (Xmean - Xn)]/n of Cmin results}, where X is the Tac Cmin level.

Coefficient of variation (CV), calculated according to the formula CV (%) = σ/μ, where σ is the standard deviation, and μ is the mean Tac Cmin levels of all available samples of the individual. CV may be corrected or not by the corresponding Tac dose (C0/D) or defined as time-weighted coefficient of variability using time-weighted standard deviation divided by the mean drug levels.

Tac TTR, calculated by the Rosendaal method[8].Standard deviation or MLVI are expressed as numbers, classes, or dichotomized intervals, whereas CV and TTR are expressed as percentages, tertiles and dichotomized intervals usually at the median split. There are no universally accepted recommended target levels for each one of those parameters used to assess Tac IPV. It is important to highlight that target levels of Tac Cmin usually vary over time according to the type of organ transplant, donor and recipient risk factors for rejection, comorbidity, occurrence of side effects and local immunosuppression protocols. The TTR may also vary sharply according to adopted Tac Cmin thresholds used by distinct centers in different time frames after organ transplantation[5-7].

**FACTORS INFLUENCING TAC IPV**

Interpatient variability of Tac has been attributed to interindividual pharmacokinetics variability which may be induced by several factors including drug-food and drug-drug interactions, concurrent clinical events such as diarrhea, cholestasis or liver dysfunction, ethnicity and pharmacogenetics[3,9-13]. In this regard, polymorphisms in CYP3A5, CYP3A4, and SLC and ABC transporter encoding genes have been shown to influence the area under the curve of tacrolimus, leading either to rejection or even toxicity in transplant recipients[4,13].

Tac IPV, on the other hand, has been additionally ascribed to non-adherence after organ transplantation, pre-analytical and analytical variables to measure Cmin in different commercially available biochemical assays and administration of different Tac formulations, including generic substitutions[3,5-7]. However, non-adherence is a common reason reported in medical literature to explain the observed deleterious effect of Tac IPV on patient and graft survival in organ transplantation by some[14-19],but not all authors[20,21].

Several approaches have been proposed to assess IPV, with most studies being retrospective, with different methodologies, considering pediatric and adult populations, with no organ-specific approach. Despite these limitations, IPV provides a sign that patients are at risk.

**TAC IPV IN HEART TRANSPLANTATION**

Four studies evaluating the influence of Tac IPV on HT outcomes were performed in adult patients using Tac CV[22-24] and Tac TTR[25], and in pediatric subjects using Tac SD/MLVI[26,27].

Concerning pediatric LT, Pollock-Barziv *et al*[26] associated Tac IPV with late rejection as well as worse patient and graft survival, but it is worth to mention that few heart transplant recipients were included in this study. Sirota *et al*[27] found similar results for rejection, but the authors also linked Tac SD/MLVI, particularly when higher than 3, to cardiac allograft vasculopathy and patient survival. In adults, Gueta *et al*[22] described an association of Tac IPV in the first year after HT with rejection after 12 but not between three and 12 mo after HT. On the other hand, Shuker *et al*[23] found no increase in the frequency of either early or late acute rejection or even cardiac allograft vasculopathy in heart transplant recipients. Both authors ascribed the lack of association of Tac IPV with early acute rejection[20] and overall rejection[23] to a higher immunosuppression exposure frequently observed in those heart transplant recipients. González-Vílchez *et al*[24] studied the largest cohort up to now. The authors found an effect of Tac IPV, assessed between four to 12 mo after HT, on the frequency of rejection after one year. Using Tac TTR, Baker *et al*[25] found no effect of Tac IPV on acute rejection within the first 30 d after HT. None of those studies in adults reported other outcomes such as mortality or Tac-related adverse events in association with Tac IPV[22-25]. The main findings related to HT are depicted in Table 1[22-27].

**TAC IPV IN LUNG TRANSPLANTATION**

Four studies have investigated the impact of Tac IPV in the frequency of acute and chronic rejection or chronic lung allograft dysfunction (CLAD) after lung transplantation in adults using Tac SD/MLVI[28], Tac CV[29] and Tac TTR[29-31]. Gallagher *et al*[28] demonstrated that higher Tac SD/MLVI between 6-12 mo after lung transplantation was associated with development of CLAD with an adverse impact on survival. Acute rejection, on the other hand was not associated with Tac SD/MLVI[28]. Ensor *et al*[30] evaluated retrospectively the role of Tac TTR in 292 Lung transplant recipients the development of acute and chronic rejection. Tac TTR was measured in the first year after lung transplantation. The authors observed a lower likelihood for acute rejection and CLAD whenever Tac TTR was increased by 10%. Lower rates of infection and mortality was also linked to high Tac TTR. Other authors failed to demonstrate higher frequency of acute rejection after lung transplantation when Tac IPV was assessed by either Tac CV or Tac TTR in the first 6 mo after surgery[29]. On the other hand, more recently Japanese investigators disclosed an association of acute rejection with Tac TTR calculated in the first six month after lung transplantation[31]. The main findings related to lung transplantation are depicted in Table 2.

**TAC IPV IN LIVER TRANSPLANTATION**

Impact of Tac IPV on different outcomes after LT, including allograft rejection, postoperative complications and survival was evaluated in pediatric[26,32-35] and adult[36-42] transplant recipients using SD/MLVI[26,32-34], CV[35-41], and TTR[42].

Most studies performed in children associated higher SD/MLVI to biopsy-proven acute rejection (BPAR) at least six months after LT[42-34].Defrancq *et al*[35] found similar results in another cohort of children using Tac CV one year after surgery. The authors reported an association between high Tac CV and BPAR and correlated Tac CV with albumin and bilirubin levels in different time frames after LT as well as with missed outpatient consultations, possibly reflecting immunosuppression adherence[33]. Decreased survival was also related to high Tac IPV in just one of those reports including few patients submitted to LT[26].

Up to now, seven reports were published in the medical literature concerning the effect of Tac IPV on post-LT outcomes in adults. In this regard, Christina *et al*[36] disclosed an association between Tac SD/MLVI and BPAR in patients submitted to LT. Similar findings were reported by Del Bello *et al*[37] who reported higher Tac CV measured just after LT discharge with BPAR, as well as with the occurrence of *de novo* anti-donor specific antibodies (*dn*DSA). No impact was seen in patient survival[37]. Van der Veer *et al*[39] evaluated the influence of Tac CV measured between six to 18 mo after LT in adult subjects. The authors were unable to disclose any association between Tac CV and immune mediated graft injury. Rayar *et al*[38] investigated the influence of Tac CV measured in the first 30 d after LT on postoperative outcomes. The authors found an increased frequency of acute kidney injury as well as cardiovascular and neurologic complications in patients with higher Tac CV. Most importantly, shortened graft and patient survival rates were also associated with Tac IPV[38]. Other authors investigated whether Tac CV, assessed between three to six months after LT, could be associated with worse graft and patient long-term outcomes[40]. In this study, lower long-term survival and poorer renal function were similarly observed in those subjects with high Tac CV. Another group of investigators also linked higher Tac IPV using CV with hepatocellular carcinoma (HCC) recurrence after LT[41]. Only one study up to now assessed the impact of Tac IPV after LT employing TTR[42]. The authors found that lower TTR in those subjects, irrespectively of Tac CV, was associated with a higher risk for *dn*DSA and long-term death-censored graft loss. The main findings related to LT are depicted in Table 3.

**TAC IPV IN KIDNEY TRANSPLANTATION**

Most of the studies published thus far demonstrated an adverse impact of Tac IPV on KT outcomes (Table 4)[43-68]. Most of them were performed in adult recipients using MLVI/SD[44], MAD[45-48,62,66], CV[49-60,63,64,67-68],TTR[61] or other methods[65]. In this regard, several authors have associated higher Tac IPV, usually measured more than 6 mo after KT, with BPAR[44-46],long-term graft loss or dysfunction[47-55,58,59,68] as well as with lower survival[50,51].In some, but not all reports[62], higher Tac IPV was associated with the development of *dn*DSA[53,67], chronic active antibody mediated rejection[47] and chronic histological lesions in kidney grafts[54,56].Most authors attributed those Tac IPV-related outcomes to non-adherence[43] and some[57-59] but not others[60] to genetic predisposition. Two other reports compared TTR[61] and a novel Tac variability score (TVS)[64] to conventional IPV measures and found that both were more reliable in their ability to predict worse outcomes after KT.

Concerning pediatric transplant recipients, Pollock-Barziv *et al*[26] were one of the first authors to show a significant association of higher Tac IPV and late graft rejection or loss. Similar findings were subsequently reported by other investigators who reported and association of higher Tac IPV with BPAR and graft loss beyond one year in children and adolescents submitted to KT[66-68].

**TAC IPV IN KIDNEY AND PANCREAS, AND BONE MARROW TRANSPLANTATION**

Two studies have evaluated the impact of Tac IPV in the frequency of *dn*DSA, BPAR and graft loss in adult kidney and pancreas recipients[69,70] and in the occurrence of graft *vs* host disease after bone marrow transplantation[70]. The first report failed to disclose an association of Tac IPV with BPAR in adult recipients of kidney and pancreas transplants, but the main purpose of the study was to compare Tac IPV and graft function in groups of patients receiving two different Tac formulations[69]. Davis *et al*[38] on the other hand, demonstrated that Tac TTR was associated to a very high risk of *dn*DSA and a 4-fold risk of graft loss by five years, independently of Tac CV.

In respect to bone marrow transplant recipients, Marco *et al*[70] correlated high Tac IPV, measured by CV, with the occurrence of acute graft *vs* host disease in the first month after BMT (Table 5).

**CONCLUSION**

Altogether, available data up to now suggest that Tac IPV, possibly due to non-adherence and/or genetic, pharmacologic, or clinically significant factors, is associated with adverse outcomes after organ transplantation, particularly KT. The heterogeneity observed in the results obtained in the reports thus far are probably due to the retrospective design of most studies, the distinct methods used to assess Tac IPV, utilization of different immunosuppression protocols, distinct observation time frames and endpoints. Refinement or combination of different scores may improve usage of Tac IPV in clinical practice in the future.

**REFERENCES**

1 **Ong SC**, Gaston RS. Thirty Years of Tacrolimus in Clinical Practice. *Transplantation* 2021; **105**: 484-495 [PMID: 32541562 DOI: 10.1097/TP.0000000000003350]

2 **Staatz CE**, Tett SE. Clinical pharmacokinetics and pharmacodynamics of tacrolimus in solid organ transplantation. *Clin Pharmacokinet* 2004; **43**: 623-653 [PMID: 15244495 DOI: 10.2165/00003088-200443100-00001]

3 **Shuker N**, van Gelder T, Hesselink DA. Intra-patient variability in tacrolimus exposure: causes, consequences for clinical management. *Transplant Rev (Orlando)* 2015; **29**: 78-84 [PMID: 25687818 DOI: 10.1016/j.trre.2015.01.002]

4 **Brunet M**, Pastor-Anglada M. Insights into the Pharmacogenetics of Tacrolimus Pharmacokinetics and Pharmacodynamics. *Pharmaceutics* 2022; **14** [PMID: 36145503 DOI: 10.3390/pharmaceutics14091755]

5 **Kuypers DRJ**. Intrapatient Variability of Tacrolimus Exposure in Solid Organ Transplantation: A Novel Marker for Clinical Outcome. *Clin Pharmacol Ther* 2020; **107**: 347-358 [PMID: 31449663 DOI: 10.1002/cpt.1618]

6 **Schumacher L**, Leino AD, Park JM. Tacrolimus intrapatient variability in solid organ transplantation: A multiorgan perspective. *Pharmacotherapy* 2021; **41**: 103-118 [PMID: 33131078 DOI: 10.1002/phar.2480]

7 **Coste G**, Lemaitre F. The Role of Intra-Patient Variability of Tacrolimus Drug Concentrations in Solid Organ Transplantation: A Focus on Liver, Heart, Lung and Pancreas. *Pharmaceutics* 2022; **14** [PMID: 35214111 DOI: 10.3390/pharmaceutics14020379]

8 **Rosendaal FR**, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost* 1993; **69**: 236-239 [PMID: 8470047]

9 **Giza P**, Ficek R, Dwulit T, Chudek J, Woźniak I, Więcek A, Kolonko A. Number of Regularly Prescribed Drugs and Intrapatient Tacrolimus Trough Levels Variability in Stable Kidney Transplant Recipients. *J Clin Med* 2020; **9** [PMID: 32575525 DOI: 10.3390/jcm9061926]

10 **Jacobo-Cabral CO**, García-Roca P, Romero-Tejeda EM, Reyes H, Medeiros M, Castañeda-Hernández G, Trocóniz IF. Population pharmacokinetic analysis of tacrolimus in Mexican paediatric renal transplant patients: role of CYP3A5 genotype and formulation. *Br J Clin Pharmacol* 2015; **80**: 630-641 [PMID: 25846845 DOI: 10.1111/bcp.12649]

11 **Taber DJ**, Su Z, Fleming JN, McGillicuddy JW, Posadas-Salas MA, Treiber FA, Dubay D, Srinivas TR, Mauldin PD, Moran WP, Baliga PK. Tacrolimus Trough Concentration Variability and Disparities in African American Kidney Transplantation. *Transplantation* 2017; **101**: 2931-2938 [PMID: 28658199 DOI: 10.1097/TP.0000000000001840]

12 **Campagne O**, Mager DE, Tornatore KM. Population Pharmacokinetics of Tacrolimus in Transplant Recipients: What Did We Learn About Sources of Interindividual Variabilities? *J Clin Pharmacol* 2019; **59**: 309-325 [PMID: 30371942 DOI: 10.1002/jcph.1325]

13 **Tron C**, Lemaitre F, Verstuyft C, Petitcollin A, Verdier MC, Bellissant E. Pharmacogenetics of Membrane Transporters of Tacrolimus in Solid Organ Transplantation. *Clin Pharmacokinet* 2019; **58**: 593-613 [PMID: 30415459 DOI: 10.1007/s40262-018-0717-7]

14 **Shemesh E**, Fine RN. Is calculating the standard deviation of tacrolimus blood levels the new gold standard for evaluating non-adherence to medications in transplant recipients? *Pediatr Transplant* 2010; **14**: 940-943 [PMID: 20887400 DOI: 10.1111/j.1399-3046.2010.01396.x]

15 **Herblum J**, Dacouris N, Huang M, Zaltzman J, Prasad GVR, Nash M, Chen L. Retrospective Analysis of Tacrolimus Intrapatient Variability as a Measure of Medication Adherence. *Can J Kidney Health Dis* 2021; **8**: 20543581211021742 [PMID: 34188946 DOI: 10.1177/20543581211021742]

16 **Gokoel SRM**, Zwart TC, Moes DJAR, van der Boog PJM, de Fijter JW. No Apparent Influence of Nonadherence on Tacrolimus Intrapatient Variability in Stable Kidney Transplant Recipients. *Ther Drug Monit* 2020; **42**: 702-709 [PMID: 32941396 DOI: 10.1097/FTD.0000000000000772]

17 **Kostalova B**, Mala-Ladova K, Sulkova SD, Denhaerynck K, De Geest S, Maly J. Comparison of different methods to assess tacrolimus concentration intra-patient variability as potential marker of medication non-adherence. *Front Pharmacol* 2022; **13**: 973564 [PMID: 36313323 DOI: 10.3389/fphar.2022.973564]

18 **Lieber SR**, Volk ML. Non-adherence and graft failure in adult liver transplant recipients. *Dig Dis Sci* 2013; **58**: 824-834 [PMID: 23053889 DOI: 10.1007/s10620-012-2412-0]

19 **Stuber ML**, Shemesh E, Seacord D, Washington J 3rd, Hellemann G, McDiarmid S. Evaluating non-adherence to immunosuppressant medications in pediatric liver transplant recipients. *Pediatr Transplant* 2008; **12**: 284-288 [PMID: 18331387 DOI: 10.1111/j.1399-3046.2008.00923.x]

20 **Leino AD**, King EC, Jiang W, Vinks AA, Klawitter J, Christians U, Woodle ES, Alloway RR, Rohan JM. Assessment of tacrolimus intrapatient variability in stable adherent transplant recipients: Establishing baseline values. *Am J Transplant* 2019; **19**: 1410-1420 [PMID: 30506623 DOI: 10.1111/ajt.15199]

21 **Ko H**, Kim HK, Chung C, Han A, Min SK, Ha J, Min S. Association between medication adherence and intrapatient variability in tacrolimus concentration among stable kidney transplant recipients. *Sci Rep* 2021; **11**: 5397 [PMID: 33686160 DOI: 10.1038/s41598-021-84868-5]

22 **Gueta I**, Markovits N, Yarden-Bilavsky H, Raichlin E, Freimark D, Lavee J, Loebstein R, Peled Y. High tacrolimus trough level variability is associated with rejections after heart transplant. *Am J Transplant* 2018; **18**: 2571-2578 [PMID: 29989311 DOI: 10.1111/ajt.15016]

23 **Shuker N**, Bouamar R, Hesselink DA, van Gelder T, Caliskan K, Manintveld OC, Balk AH, Constantinescu AA. Intrapatient Variability in Tacrolimus Exposure Does Not Predict The Development of Cardiac Allograft Vasculopathy After Heart Transplant. *Exp Clin Transplant* 2018; **16**: 326-332 [PMID: 28969528 DOI: 10.6002/ect.2016.0366]

24 **González-Vílchez F**, Crespo-Leiro MG, Delgado-Jiménez J, Pérez-Villa F, Segovia-Cubero J, Díaz-Molina B, Mirabet-Pérez S, Arizón Del Prado JM, Blasco-Peiró T, Martínez-Sellés M, Almenar-Bonet L, Garrido-Bravo I, Rábago G, Vázquez de Prada JA. Impact of intrapatient blood level variability of calcineurin inhibitors on heart transplant outcomes. *Rev Esp Cardiol (Engl Ed)* 2022; **75**: 129-140 [PMID: 33744197 DOI: 10.1016/j.rec.2021.02.001]

25 **Baker WL**, Steiger S, Martin S, Patel N, Radojevic J, Darsaklis K, O'Bara L, Kutzler H, Dougherty J, Feingold A, Hammond J, Fusco D, Gluck JA. Association Between Time-in-Therapeutic Tacrolimus Range and Early Rejection After Heart Transplant. *Pharmacotherapy* 2019; **39**: 609-613 [PMID: 30892740 DOI: 10.1002/phar.2262]

26 **Pollock-Barziv SM**, Finkelstein Y, Manlhiot C, Dipchand AI, Hebert D, Ng VL, Solomon M, McCrindle BW, Grant D. Variability in tacrolimus blood levels increases the risk of late rejection and graft loss after solid organ transplantation in older children. *Pediatr Transplant* 2010; **14**: 968-975 [PMID: 21040278 DOI: 10.1111/j.1399-3046.2010.01409.x]

27 **Sirota M**, Heyrend C, Ou Z, Masotti S, Griffiths E, Molina K. Impact of tacrolimus variability on pediatric heart transplant outcomes. *Pediatr Transplant* 2021; **25**: e14043 [PMID: 34390091 DOI: 10.1111/petr.14043]

28 **Gallagher HM**, Sarwar G, Tse T, Sladden TM, Hii E, Yerkovich ST, Hopkins PM, Chambers DC. Erratic tacrolimus exposure, assessed using the standard deviation of trough blood levels, predicts chronic lung allograft dysfunction and survival. *J Heart Lung Transplant* 2015; **34**: 1442-1448 [PMID: 26186804 DOI: 10.1016/j.healun.2015.05.028]

29 **Kao CC**, Segraves J, Parulekar AD. Tacrolimus monitoring parameters are not associated with acute cellular rejection following lung transplantation. *Eur J Clin Pharmacol* 2021; **77**: 63-69 [PMID: 32803287 DOI: 10.1007/s00228-020-02976-z]

30 **Ensor CR**, Iasella CJ, Harrigan KM, Morrell MR, Moore CA, Shigemura N, Zeevi A, McDyer JF, Venkataramanan R. Increasing tacrolimus time-in-therapeutic range is associated with superior one-year outcomes in lung transplant recipients. *Am J Transplant* 2018; **18**: 1527-1533 [PMID: 29513387 DOI: 10.1111/ajt.14723]

31 **Katada Y**, Nakagawa S, Itohara K, Suzuki T, Kato R, Endo H, Sugimoto M, Yonezawa A, Nakagawa T, Ohsumi A, Nakajima D, Date H, Terada T. Association between time in therapeutic range of tacrolimus blood concentration and acute rejection within the first three months after lung transplantation. *J Pharm Health Care Sci* 2022; **8**: 25 [PMID: 36180948 DOI: 10.1186/s40780-022-00256-9]

32 **Venkat VL**, Nick TG, Wang Y, Bucuvalas JC. An objective measure to identify pediatric liver transplant recipients at risk for late allograft rejection related to non-adherence. *Pediatr Transplant* 2008; **12**: 67-72 [PMID: 18186891 DOI: 10.1111/j.1399-3046.2007.00794.x]

33 **Shemesh E**, Bucuvalas JC, Anand R, Mazariegos GV, Alonso EM, Venick RS, Reyes-Mugica M, Annunziato RA, Shneider BL. The Medication Level Variability Index (MLVI) Predicts Poor Liver Transplant Outcomes: A Prospective Multi-Site Study. *Am J Transplant* 2017; **17**: 2668-2678 [PMID: 28321975 DOI: 10.1111/ajt.14276]

34 **de Oliveira JTP**, Kieling CO, da Silva AB, Stefani J, Witkowski MC, Smidt CR, Mariano da Rocha CR, Hirakata VN, Grossini MDG, Zanotelli ML, Gonçalves Vieira SM. Variability index of tacrolimus serum levels in pediatric liver transplant recipients younger than 12 years: Non-adherence or risk of non-adherence? *Pediatr Transplant* 2017; **21** [PMID: 29034612 DOI: 10.1111/petr.13058]

35 **Defrancq C**, De Wilde N, Raes A, Van Biervliet S, Vande Velde S, Van Winckel M, De Bruyne R, Prytuła A. Intra-patient variability in tacrolimus exposure in pediatric liver transplant recipients: Evolution, risk factors, and impact on patient outcomes. *Pediatr Transplant* 2019; **23**: e13388 [PMID: 30916883 DOI: 10.1111/petr.13388]

36 **Christina S**, Annunziato RA, Schiano TD, Anand R, Vaidya S, Chuang K, Zack Y, Florman S, Shneider BL, Shemesh E. Medication level variability index predicts rejection, possibly due to nonadherence, in adult liver transplant recipients. *Liver Transpl* 2014; **20**: 1168-1177 [PMID: 24931127 DOI: 10.1002/lt.23930]

37 **Del Bello A**, Congy-Jolivet N, Danjoux M, Muscari F, Lavayssière L, Esposito L, Hebral AL, Bellière J, Kamar N. High tacrolimus intra-patient variability is associated with graft rejection, and *de novo* donor-specific antibodies occurrence after liver transplantation. *World J Gastroenterol* 2018; **24**: 1795-1802 [PMID: 29713132 DOI: 10.3748/wjg.v24.i16.1795]

38 **Rayar M**, Tron C, Jézéquel C, Beaurepaire JM, Petitcollin A, Houssel-Debry P, Camus C, Verdier MC, Dehlawi A, Lakéhal M, Desfourneaux V, Meunier B, Sulpice L, Bellissant E, Boudjema K, Lemaitre F. High Intrapatient Variability of Tacrolimus Exposure in the Early Period After Liver Transplantation Is Associated With Poorer Outcomes. *Transplantation* 2018; **102**: e108-e114 [PMID: 29315140 DOI: 10.1097/TP.0000000000002052]

39 **van der Veer MAA**, Nangrahary N, Hesselink DA, Erler NS, Metselaar HJ, van Gelder T, Darwish Murad S. High Intrapatient Variability in Tacrolimus Exposure Is Not Associated With Immune-mediated Graft Injury After Liver Transplantation. *Transplantation* 2019; **103**: 2329-2337 [PMID: 30801539 DOI: 10.1097/TP.0000000000002680]

40 **Dopazo C**, Bilbao I, García S, Gómez-Gavara C, Caralt M, Campos-Varela I, Castells L, Hidalgo E, Moreso F, Montoro B, Charco R. High intrapatient variability of tacrolimus exposure associated with poorer outcomes in liver transplantation. *Clin Transl Sci* 2022; **15**: 1544-1555 [PMID: 35373449 DOI: 10.1111/cts.13276]

41 **Kim HJ**, Lee J, Lee JG, Joo DJ, Kim MS. Clinical association between tacrolimus intra-patient variability and liver transplantation outcomes in patients with and without hepatocellular carcinoma. *Sci Rep* 2022; **12**: 16169 [PMID: 36171260 DOI: 10.1038/s41598-022-20636-3]

42 **Davis S**, Gralla J, Klem P, Stites E, Wiseman A, Cooper JE. Tacrolimus Intrapatient Variability, Time in Therapeutic Range, and Risk of De Novo Donor-Specific Antibodies. *Transplantation* 2020; **104**: 881-887 [PMID: 32224815 DOI: 10.1097/TP.0000000000002913]

43 **Gonzales HM**, McGillicuddy JW, Rohan V, Chandler JL, Nadig SN, Dubay DA, Taber DJ. A comprehensive review of the impact of tacrolimus intrapatient variability on clinical outcomes in kidney transplantation. *Am J Transplant* 2020; **20**: 1969-1983 [PMID: 32406604 DOI: 10.1111/ajt.16002]

44 **Sapir-Pichhadze R**, Wang Y, Famure O, Li Y, Kim SJ. Time-dependent variability in tacrolimus trough blood levels is a risk factor for late kidney transplant failure. *Kidney Int* 2014; **85**: 1404-1411 [PMID: 24336032 DOI: 10.1038/ki.2013.465]

45 **Ro H**, Min SI, Yang J, Moon KC, Kim YS, Kim SJ, Ahn C, Ha J. Impact of tacrolimus intraindividual variability and CYP3A5 genetic polymorphism on acute rejection in kidney transplantation. *Ther Drug Monit* 2012; **34**: 680-685 [PMID: 23149441 DOI: 10.1097/FTD.0b013e3182731809]

46 **Whalen HR**, Glen JA, Harkins V, Stevens KK, Jardine AG, Geddes CC, Clancy MJ. High Intrapatient Tacrolimus Variability Is Associated With Worse Outcomes in Renal Transplantation Using a Low-Dose Tacrolimus Immunosuppressive Regime. *Transplantation* 2017; **101**: 430-436 [PMID: 26950724 DOI: 10.1097/TP.0000000000001129]

47 **Borra LC**, Roodnat JI, Kal JA, Mathot RA, Weimar W, van Gelder T. High within-patient variability in the clearance of tacrolimus is a risk factor for poor long-term outcome after kidney transplantation. *Nephrol Dial Transplant* 2010; **25**: 2757-2763 [PMID: 20190242 DOI: 10.1093/ndt/gfq096]

48 **Shuker N**, Shuker L, van Rosmalen J, Roodnat JI, Borra LC, Weimar W, Hesselink DA, van Gelder T. A high intrapatient variability in tacrolimus exposure is associated with poor long-term outcome of kidney transplantation. *Transpl Int* 2016; **29**: 1158-1167 [PMID: 27188932 DOI: 10.1111/tri.12798]

49 **O'Regan JA**, Canney M, Connaughton DM, O'Kelly P, Williams Y, Collier G, deFreitas DG, O'Seaghdha CM, Conlon PJ. Tacrolimus trough-level variability predicts long-term allograft survival following kidney transplantation. *J Nephrol* 2016; **29**: 269-276 [PMID: 26374111 DOI: 10.1007/s40620-015-0230-0]

50 **Goodall DL**, Willicombe M, McLean AG, Taube D. High Intrapatient Variability of Tacrolimus Levels and Outpatient Clinic Nonattendance Are Associated With Inferior Outcomes in Renal Transplant Patients. *Transplant Direct* 2017; **3**: e192 [PMID: 28795143 DOI: 10.1097/TXD.0000000000000710]

51 **Rozen-Zvi B**, Schneider S, Lichtenberg S, Green H, Cohen O, Gafter U, Chagnac A, Mor E, Rahamimov R. Association of the combination of time-weighted variability of tacrolimus blood level and exposure to low drug levels with graft survival after kidney transplantation. *Nephrol Dial Transplant* 2017; **32**: 393-399 [PMID: 28025383 DOI: 10.1093/ndt/gfw394]

52 **Rahamimov R**, Tifti-Orbach H, Zingerman B, Green H, Schneider S, Chagnac A, Mor E, Fox BD, Rozen-Zvi B. Reduction of exposure to tacrolimus trough level variability is associated with better graft survival after kidney transplantation. *Eur J Clin Pharmacol* 2019; **75**: 951-958 [PMID: 30762079 DOI: 10.1007/s00228-019-02643-y]

53 **Rodrigo E**, Segundo DS, Fernández-Fresnedo G, López-Hoyos M, Benito A, Ruiz JC, de Cos MA, Arias M. Within-Patient Variability in Tacrolimus Blood Levels Predicts Kidney Graft Loss and Donor-Specific Antibody Development. *Transplantation* 2016; **100**: 2479-2485 [PMID: 26703349 DOI: 10.1097/TP.0000000000001040]

54 **Mo H**, Kim SY, Min S, Han A, Ahn S, Min SK, Lee H, Ahn C, Kim Y, Ha J. Association of Intrapatient Variability of Tacrolimus Concentration With Early Deterioration of Chronic Histologic Lesions in Kidney Transplantation. *Transplant Direct* 2019; **5**: e455 [PMID: 31321291 DOI: 10.1097/TXD.0000000000000899]

55 **Süsal C**, Döhler B. Late intra-patient tacrolimus trough level variability as a major problem in kidney transplantation: A Collaborative Transplant Study Report. *Am J Transplant* 2019; **19**: 2805-2813 [PMID: 30859672 DOI: 10.1111/ajt.15346]

56 **Vanhove T**, Vermeulen T, Annaert P, Lerut E, Kuypers DRJ. High Intrapatient Variability of Tacrolimus Concentrations Predicts Accelerated Progression of Chronic Histologic Lesions in Renal Recipients. *Am J Transplant* 2016; **16**: 2954-2963 [PMID: 27013142 DOI: 10.1111/ajt.13803]

57 **Seibert SR**, Schladt DP, Wu B, Guan W, Dorr C, Remmel RP, Matas AJ, Mannon RB, Israni AK, Oetting WS, Jacobson PA. Tacrolimus trough and dose intra-patient variability and CYP3A5 genotype: Effects on acute rejection and graft failure in European American and African American kidney transplant recipients. *Clin Transplant* 2018; **32**: e13424 [PMID: 30318646 DOI: 10.1111/ctr.13424]

58 **Stefanović NZ**, Veličković-Radovanović RM, Danković KS, Mitić BP, Paunović GJ, Cvetković MB, Cvetković TP. Combined Effect of Inter- and Intrapatient Variability in Tacrolimus Exposure on Graft Impairment Within a 3-Year Period Following Kidney Transplantation: A Single-Center Experience. *Eur J Drug Metab Pharmacokinet* 2020; **45**: 749-760 [PMID: 32886348 DOI: 10.1007/s13318-020-00644-2]

59 **Stefanović N**, Veličković-Radovanović R, Danković K, Pavlović I, Catić-Đorđević A, Bašić J, Despotović M, Jevtović-Stoimenov T, Mitić B, Cvetković T. Effect of the Interrelation between CYP3A5 Genotype, Concentration/Dose Ratio and Intrapatient Variability of Tacrolimus on Kidney Graft Function: Monte Carlo Simulation Approach. *Pharmaceutics* 2021; **13** [PMID: 34834385 DOI: 10.3390/pharmaceutics13111970]

60 **Nuchjumroon A**, Vadcharavivad S, Singhan W, Poosoonthornsri M, Chancharoenthana W, Udomkarnjananun S, Townamchai N, Avihingsanon Y, Praditpornsilpa K, Eiam-Ong S. Comparison of Tacrolimus Intra-Patient Variability during 6-12 Months after Kidney Transplantation between CYP3A5 Expressers and Nonexpressers. *J Clin Med* 2022; **11** [PMID: 36362548 DOI: 10.3390/jcm11216320]

61 **Song T**, Yin S, Jiang Y, Huang Z, Liu J, Wang Z, Li L, Zeng J, Fan Y, Wang X, Li X, Lin T. Increasing Time in Therapeutic Range of Tacrolimus in the First Year Predicts Better Outcomes in Living-Donor Kidney Transplantation. *Front Immunol* 2019; **10**: 2912 [PMID: 31921171 DOI: 10.3389/fimmu.2019.02912]

62 **Sablik KA**, Clahsen-van Groningen MC, Hesselink DA, van Gelder T, Betjes MGH. Tacrolimus intra-patient variability is not associated with chronic active antibody mediated rejection. *PLoS One* 2018; **13**: e0196552 [PMID: 29746495 DOI: 10.1371/journal.pone.0196552]

63 **Park Y**, Lee H, Eum SH, Kim HD, Ko EJ, Yang CW, Chung BH. Intrapatient Variability in Tacrolimus Trough Levels Over 2 Years Affects Long-Term Allograft Outcomes of Kidney Transplantation. *Front Immunol* 2021; **12**: 746013 [PMID: 34659243 DOI: 10.3389/fimmu.2021.746013]

64 **Yin S**, Wang X, Huang Z, Fan Y, Song T, Lin T. Tacrolimus variability score outperforms coefficient of variation in predicting clinical outcomes of living kidney transplantation. *Br J Clin Pharmacol* 2022; **88**: 75-83 [PMID: 33899267 DOI: 10.1111/bcp.14876]

65 **Kim EJ**, Kim SJ, Huh KH, Kim BS, Kim MS, Kim SI, Kim YS, Lee J. Clinical significance of tacrolimus intra-patient variability on kidney transplant outcomes according to pre-transplant immunological risk. *Sci Rep* 2021; **11**: 12114 [PMID: 34108576 DOI: 10.1038/s41598-021-91630-4]

66 **Gold A**, Tönshoff B, Döhler B, Süsal C. Association of graft survival with tacrolimus exposure and late intra-patient tacrolimus variability in pediatric and young adult renal transplant recipients-an international CTS registry analysis. *Transpl Int* 2020; **33**: 1681-1692 [PMID: 32881096 DOI: 10.1111/tri.13726]

67 **Baghai Arassi M**, Gauche L, Schmidt J, Höcker B, Rieger S, Süsal C, Tönshoff B, Fichtner A. Association of intraindividual tacrolimus variability with *de novo* donor-specific HLA antibody development and allograft rejection in pediatric kidney transplant recipients with low immunological risk. *Pediatr Nephrol* 2022; **37**: 2503-2514 [PMID: 35166920 DOI: 10.1007/s00467-022-05426-3]

68 **Pizzo HP**, Ettenger RB, Gjertson DW, Reed EF, Zhang J, Gritsch HA, Tsai EW. Sirolimus and tacrolimus coefficient of variation is associated with rejection, donor-specific antibodies, and nonadherence. *Pediatr Nephrol* 2016; **31**: 2345-2352 [PMID: 27286686 DOI: 10.1007/s00467-016-3422-5]

69 **Torabi J**, Konicki A, Rocca JP, Ajaimy M, Campbell A, Azzi Y, Pynadath C, Liriano-Ward L, Akalin E, Kinkhabwala M, Graham JA. The use of LCP-Tacrolimus (Envarsus XR) in simultaneous pancreas and kidney (SPK) transplant recipients. *Am J Surg* 2020; **219**: 583-586 [PMID: 32122660 DOI: 10.1016/j.amjsurg.2020.02.027]

70 **Marco DN**, Salas MQ, Gutiérrez-García G, Monge I, Riu G, Carcelero E, Roma JR, Llobet N, Arcarons J, Suárez-Lledó M, Martínez N, Pedraza A, Domenech A, Rosiñol L, Fernández-Avilés F, Urbano-Ispízua Á, Rovira M, Brunet M, Martínez C. Impact of Early Intrapatient Variability of Tacrolimus Concentrations on the Risk of Graft-Versus-Host Disease after Allogeneic Stem Cell Transplantation Using High-Dose Post-Transplant Cyclophosphamide. *Pharmaceuticals (Basel)* 2022; **15** [PMID: 36558980 DOI: 10.3390/ph15121529]

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**Table 1 Tacrolimus intra-patient variability in heart transplantation: Main findings**

|  |
| --- |
| **Heart transplantation** |
| **Ref.** | **Sample size** | **Donor type** | **Tac-IPV, assessment** | **Outcome** |
| Gueta *et al*[22], 2018 | 72 | Deceased | CV | High trough level variability is associated with higher rates of graft rejection, and trough level variability during the first year is associated with increased risk of rejection after HT |
| Shuker *et al*[23], 2018 | 86 | Deceased | MAD | A high IPV was not associated with the development and progression of cardiac allograft vasculopathy or development of acute cellular rejection |
| González-Vílchez *et al*[24], 2022 | 1581 | Deceased | CV | IPV levels had limited influence on mid-term outcomes in heart transplant, however high IPV may predispose to rejection in initially stable patients |
| Baker *et al*[25], 2019 | 67 | Deceased | TTR | Higher TTR was not associated with a lower rate of Acute Cellular Rejection within the first 30 d after heart transplant |
| Pollock-Barziv *et al*[26], 2010 | 144 | Deceased | SD | Associated Tac IPV with late rejection as well as worse patient and graft survival, but it is worth to mention that few heart transplant recipients were included in this study |
| Sirota *et al*[27],2021 | 118 | Deceased | SD | SD ≥ 3 is associated with increased risk of poor outcomes |

CV: Coefficient of variability; HT: Heart transplant; MAD: Mean absolute deviation; TTR: Time in therapeutic range; SD: Standard deviation.

**Table 2 Tacrolimus intra-patient variability in lung transplantation: main findings**

|  |
| --- |
| **Lung transplantation** |
| **Ref.** | **Sample size** | **Donor type** | **Tac-IPV assessment** | **Outcome** |
| Gallagher *et al*[28], 2015 | 110 | Non specified | SD | Patients with highly variable trough tacrolimus levels in the second half of the first post-transplant year will likely have similar variability in the second year and are at high risk for subsequent chronic lung allograft dysfunction and death |
| Kao *et al*[29], 2021 | 157 | Non specified | CV and TTR | The results suggest that tacrolimus TTR, time in therapeutic range, and variability are not related to the presence of ACR in LTRs |
| Ensor *et al*[30], 2018 | 292 | Non specified | TTR | Tacrolimus TTR was predictive of clinical outcomes of ACR, CLAD, infection, and death in lung transplant recipients at 1 yr in this investigation after adjusting for potential confounders |
| Katada *et al*[31], 2022 | 90 | Living and deceased | TTR | A lower tacrolimus TTR is a predictor of late acute rejection |

SD: Standard deviation; TTR: Time in therapeutic range; ACR: Acute cellular rejection; LTR: Lung transplant rejection; CLAD: Chronic lung allograft dysfunction.

**Table 3** **Tacrolimus intra-patient variability and liver transplantation: Main findings**

|  |
| --- |
| **Liver transplantation** |
| **Ref.** | **Sample size** | **Donor** | **Tac-IPV assessment** | **Outcome** |
| Lieber*et al*[18], 2013 | 988 | Not specified | SD | Non-adherence among liver transplant recipients is associated with increased risk of graft failure |
| Stuber *et al*[19], 2008 | 96 | Not specified | SD | The SD has utility of monitoring routine tac blood levels in pediatric recipients for detecting non-adherence prior to clinical rejection |
| Venkat *et al*[32], 2008 | 101 | Not specified | SD | Variations in tac blood levels is associated with an increased risk of late allograft rejection in pediatric recipients |
| Shemesh *et al*[33], 2017 | 400 | Both living and deceased donor | SD; MLVI | MLVI predicts late acute rejection in pediatric liver transplantation recipients |
| de Oliveira *et al*[34], 2017 | 50 | Both living and deceased donor | SD; MLVI | MLVI may be a nice indicator of the risk of medication non-adherence in child-age |
| Defrancq *et al*[35], 2019 | 41 | Both living and deceased donor | CV | High Tac IPV may be associated with adverse patient outcomes. Also, there is some impact of biological factors on IPV and therapy adherence |
| Christina *et al*[36], 2014 | 150 | Not specified | SD; MLVI | The MLVI is associated with and can predict rejection, possibly related to non-adherence in adult recipients |
| Del Bello *et al*[37], 2018 | 116 | Deceased donor only | CV | Tac IPV could be useful to identify patients with a greater risk of graft rejection and pf developing *de novo* DSA after liver transplantation |
| Rayar *et al*[38], 2018 | 812 | Deceased donor only | CV | High CV of Tac concentrations was found to be predictive of Tac-related toxicity and poorer survival |
| van der Veer *et al*[39], 2019 | 326 | Both living and deceased donor | CV | High IPV in Tac exposure beyond 6 mo after liver transplantation was not associated with imune-mediated graft injury |
| Dopazo *et al*[40], 2022 | 140 | Deceased donor only | CV | High IPV between the third and sixth months appears to be an early and independent predictor of poorer liver transplant outcomes |
| Kim *et al*[41], 2022 | 636 | Both living and deceased donor | CV | High Tac IPV was associated with increased risks of overall mortality and HCC recurrence in liver transplantation recipients with HCC |

SD:Standarddeviation;CV:Coefficientofvariation;MLVI:Medicationlevelvariabilityindex;DSA:Donor-specificantibodies;HCC:Hepatocellularcarcinoma.

**Table 4** **Tacrolimus intra-patient variability and kidney transplantation: Main findings**

|  |
| --- |
| **Kidney transplantation** |
| **Ref.** | **Sample size** | **Donor type** | **Tac-IPV assessment** | **Outcomes** |
| Borra *et al*[47], 2010 | 297 | Both living and deceased donor | MAD | Significant relationship between high Tac-IPV and long-term graft failure |
| Ro *et al*[45], 2012 | 249 | Both living and deceased donor | MAD | TAC IPV had a significant impact on rejection-free survival. The effect was influenced by CYP3A5 polymorphism |
| Sapir-Pichhadze *et al*[44], 2014 | 356 | Both living and deceased donor | MLVI/SD | Increased time-dependent TAC SD may be an independent risk factor for adverse kidney transplant outcomes |
| O’Regan *et al*[49], 2016 | 394 | Both living and deceased donor | CV | Inferior renal allograft survival was observed in recipients with higher Tac-IPV |
| Rodrigo *et al*[53], 2016 | 310 | Deceased donor only | CV | Tacrolimus level variability is a strong risk factor for dnDSA development and death-censored graft loss |
| Whalen *et al*[46], 2017 | 376 | Both living and deceased donor | MAD | Highly variable tacrolimus levels predict worse out- comes postrenal transplantation |
| Shuker *et al*[48], 2016 | 808 | Both living and deceased donor | MAD | A high tacrolimus IPV is an independent risk factor for adverse kidney transplant outcomes that can be used as an easy monitoring tool to help identify high-risk RTRs |
| Vanhove *et al*[56], 2016 | 220 | Both living and deceased donor | CV  | High IPV is related to accelerated progression of chronic histologic lesions before any evidence of renal dysfunction |
| Rozen-Zvi *et al*[51], 2017 | 803 | Both living and deceased donor | CV | The combination of high CV and exposure to low drug levels might identify high-risk patients in the early post-transplantation period |
| Goodall *et al*[50], 2017 | 688 | Both living and deceased donor | CV | High tacrolimus IPV and clinic nonattendance are associated with inferior allograft survival |
| Sablik *et al*[62], 2018 | 248 | Both living and deceased donor | MAD | A high Tac IPV per se does not predispose to the development of chronic active antibody mediated rejection (c-aABMR) but is associated with inferior graft survival once c-aABMR is diagnosed |
| Seibert *et al*[57], 2018 | 1472 | Both living and deceased donor | CV | High variability of TAC dose increases risk of acute rejection. High variability of TAC trough increases risk of graft failure |
| Mo *et al*[54], 2019 | 671 | Both living and deceased donor | CV | High IPV of Tac is associated with early deterioration of chronic histologic lesions as well as poorer long-term outcomes |
| Song *et al*[61], 2019 | 1241 | Living donor only | TTR | Increasing the TTR of tacrolimus in the first year was associated with improved long-term outcomes in living kidney transplants, and TTR may be a novel valuable strategy to monitor tacrolimus exposure |
| Süsal *et al*[55], 2019 | 6638 | Deceased donor only | CV | Even in patients with good outcome during the first 3 post-transplant years, a high IPV was associated with inferior graft survival, indicating that a fluctuating tacrolimus trough level at years 1, 2 and 3 post-transplant is a major problem in kidney transplantation |
| Rahamimov *et al*[52], 2019 | 878 | Both living and deceased donor | CV | Monitoring CV can help detect the high-risk patients |
| Gold *et al*[66], 2020 | 1419 | Deceased donor only | MAD | A more intense and less variable exposure to tacrolimus could improve graft survival strongly in patients with high TAC IPV |
| Stefanović *et al*[58], 2020 | 104 | Both living and deceased donor | CV | Combined assessment of tacrolimus IPV and tacrolimus C0/D may categorize patients towards risk of graft deterioration in the long-term post-transplantation period |
| Stefanović *et al*[59], 2021 | 103 | Both living and deceased donor | CV | Simultaneous assessment of Tac IPV, C0/D, and CYP3A5 genotype may identify patients at risk of deterioration of graft function in the long-term post-transplantation period |
| Kim *et al*[65], 2021 | 1080 | Both living and deceased donor | CV | High tacrolimus IPV significantly increases the risk of graft failure and antibody mediated rejection in patients with high immunological risk |
| Park *et al*[63], 2021 | 1143 | Both living and deceased donor | CV | TAC-IPV can significantly affect allograft outcomes even with a high mean TAC-C0 |
| Yin *et al*[64], 2022 | 1343 | Living donor only | CV | Tac variability score is a novel measure of Tac IPV with higher correlation with graft survival and more convenience in clinical use than CV after kidney transplantation |
| Baghai Arassi *et al*[67], 2022 | 48 | Both living and deceased donor | CV | High Tac IPV is associated with an increased risk of dnDSA development and rejection episodes > year 1 posttransplant even in patients with low immunological risk profile |
| Nuchjumroon *et al*[60], 2022 | 188 | Both living and deceased donor | CV | No evidence that the CYP3A5 polymorphisms significantly influence tacrolimus IPV during the 6 to 12 mo after kidney transplantation |

SD: Standard deviation; CV: Coefficient of variation; MLVI: Medication level variability index; DSA: Donor-specific antibodies; TTR: Time in therapeutic range.

**Table 5 Tacrolimus intra-patient variability in pancreas and bone marrow transplantation: Main findings**

|  |
| --- |
| **Kidney and pancreas, and bone marrow transplant** |
| **Ref.** | **Sample size** | **Donor type** | **Tac-IPV Assessment** | **Outcome** |
| Torabi *et al*[69], 2020 | 39 | Both living and deceased donor | CV | The once daily LCPT dosing may facilitate medication adherence and result in improved long-term outcomes |
| Marco *et al*[70], 2022 | 128 | Living donor only | CV | Determination of Tac IPV soon after alloHSCT could be useful in identifying greater risks of aGVHD |

CV:Coefficientofvariation;LCPT:LCP-tacrolimus;alloHSCT:Allogeneicstemcelltransplantation;aGVHD: Acutegraft-vesus-hostdisease.



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