

Association of Tacrolimus Variability and Adherence in Kidney Transplant Recipients: A Systematic Review and Meta-Analysis

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Article Info

Submitted: 30-10-2024

Revised: 10-07-2025

Accepted: 16-07-2025

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ABSTRACT

Tacrolimus has a narrow therapeutic window and exhibits high intra-patient variability (IPV) in its pharmacokinetics. Kidney transplant recipients with high IPV in tacrolimus exposure are at increased risk of graft rejection and failure. One potential contributor to tacrolimus IPV is drug adherence. However, the relationship between tacrolimus IPV and drug adherence remains unclear. The aim of this study is to determine the association between tacrolimus IPV and adherence among stable kidney transplant recipients by performing systematic review and meta-analysis. PubMed, Embase, Cochrane, OpenGrey, Scopus, Clinicaltrial.gov, Web of Science, CINAHL, and medRxiv were searched from inception through October 23, 2024. The focus was on observational studies and randomized controlled trials comparing tacrolimus IPV in adherence and non-adherence groups. To account for differences between studies, we used a random-effects model to analyze tacrolimus IPV, with standardized mean difference (SMD) and a 95% confidence interval (95%CI). Four studies were included for meta-analysis. All of which are observational studies with a pooled sample size of 790, divided into 655 participants in adherence group and 135 participants in non-adherence group. The pooled estimate found a statistically significant difference of tacrolimus IPV between adherence and non-adherence group (SMD -0.24, 95% CI: -0.44, -0.04; $p=0.017$; $I^2=0.0\%$). Recent observational research indicates a relationship between variability in tacrolimus concentration and adherence among stable kidney transplant recipients. However, due to the quality concerns and their limited number of these studies, it is important to exercise caution in interpreting these results.

Keywords: Tacrolimus, kidney transplantation, intra-patient variability, medication adherence

INTRODUCTION

Tacrolimus, an immunosuppressive drug, is widely used in preventing kidney transplant rejection through targeted suppression of T-cell

activation. (Ekberg et al., 2007) However, it has a narrow therapeutic index and exhibits high intra-patient variability (IPV) in pharmacokinetics, even with consistent dosing (Stift et al., 2014). High

tacrolimus IPV is associated with de novo donor-specific Human leukocyte antigen (HLA) antibody production, graft fibrosis, acute rejection, and nephrotoxicity (Gonzales et al., 2020; Kim et al., 2021, 2023; Kuypers, 2020; Süsal & Döhler, 2019), necessitating careful monitoring of blood concentration. Various factors contribute to IPV in tacrolimus levels among kidney transplant recipients, including genetic differences, drug formulation, analytical methodology, potential drug interactions, dietary intake, and gastrointestinal disturbances, such as diarrhea (Larpparisuth et al., 2021; Shuker et al., 2015). Additionally, non-adherence to immunosuppressive regimens following transplantation is associated with an elevated risk of graft rejection and decreased graft survival.

Non-adherence is a common problem in transplant recipients (Massey, 2016), with rates increasing significantly over time post-transplant (Low et al., 2019). Non-adherence may be linked to higher IPV. A previous study suggested that enhancing adherence to immunosuppressive therapy significantly reduced IPV among transplant recipients (McGillicuddy et al., 2020). Conversely, independent studies by Ko et al. and Herblum et al. found no statistically significant association between adherence and IPV reductions (Herblum et al., 2021; Ko et al., 2021). In light of previous conflicting evidence, this study conducts a systematic review and meta-analysis to rigorously assess the relationship between medication adherence and IPV of tacrolimus in stable kidney transplant recipients.

METHODS

This systematic review and meta-analysis was carried out and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (Page et al., 2021). By adhering to the PRISMA guidelines, we aimed to provide a clear and comprehensive account of the review process. To further ensure transparency and minimize the risk of reporting bias, this research was registered in the international prospective register of systematic reviews (PROSPERO) under the registration number: CRD42024522833.

Data sources and search strategy

This study reviewed observational and randomized controlled trials (RCTs) investigating the relationship between medication adherence and IPV of tacrolimus blood levels in stable kidney

transplant recipients. A systematic literature search was conducted across databases, including PubMed, Embase, Cochrane, OpenGrey, Scopus, ClinicalTrials.gov, Web of Science, CINAHL, and medRxiv, from their inception to October 23, 2024. Search terms included Medical Subject Headings (MeSH), Emtree terms, and relevant free-text terms, including "Kidney transplantation," "Tacrolimus," "Compliance," "Patient compliance," and "Medication adherence." Boolean operators (AND, OR) were applied to combine search terms to optimize comprehensiveness: (Kidney transplantation OR Tacrolimus) AND (Patient compliance OR Compliance OR Medication adherence). Additional searches were performed using reference lists and appendices from relevant studies to identify further pertinent research. The full details of our literature search are provided in Supplementary TableS1. All identified studies were imported into the Rayyan ® program for further processing.

Study selection

The study selection process began with screening titles and abstracts. Full-text articles were then assessed based on pre-defined inclusion and exclusion criteria. In cases where sufficient data was unavailable, corresponding authors were contacted for further information. Two independent reviewers conducted the study selection process, with a third reviewer resolving any discrepancies. Inclusion criteria were as follows: (1) observational studies or randomized controlled trials (RCTs); (2) stable kidney transplant recipients receiving tacrolimus for at least six months after transplant; (3) studies with both adherent and non-adherent groups; and (4) assessment of intra-patient pharmacokinetic variability of tacrolimus blood levels. Exclusion criteria included: (1) studies where participants were taking tacrolimus concurrently with other medications known to affect tacrolimus pharmacokinetics (drugs that obviously affected CYP3A and ABCB1 function, i.e., verapamil, clarithromycin, phenytoin, and amiodarone) except for the use of medication cost assistance (diltiazem and fluconazole) (van Gelder, 2002); and (2) studies involving transplant recipients of organs other than the kidney. (3) animal studies and those studies not presented as original research, such as reviews, comments, editorials, expert opinions, surveys, letters, conference meeting abstracts, case reports, case series, systematic reviews and meta-analysis.

Data extraction and quality assessment

Two independent reviewers extracted data and conducted a systematic review of the literature, recording the information in a standardized data extraction form. The following data were collected: demographic and baseline characteristics, type of adherence assessment tool used, and IPV of tacrolimus levels.

The methodological quality of the studies included was assessed by two independent reviewers, with a third reviewer resolving any disagreements. For observational studies, the Risk of Bias in Non-randomized Studies of Exposure (ROBINS-E) tool was used. This tool assesses seven domains of bias: (1) confounding, (2) exposure measurement, (3) participant selection, (4) post-exposure interventions, (5) missing data, (6) outcome measurement, and (7) selective reporting. Each domain is rated as low risk, some concerns, high risk, or very high risk. The overall assessment is considered "low risk" if all domains are rated as low risk, "some concerns" if all domains are rated as low risk or some concerns, "high risk" if any domain is rated as high risk and none as very high risk, and "very high risk" if any domain is rated as very high risk (Higgins et al., 2024).

For randomized controlled trials (RCTs), the Risk of Bias (RoB 2.0) tool was employed. This tool assesses five domains of bias: (1) selection bias, (2) performance bias, (3) attrition bias, (4) detection bias, and (5) reporting bias. Each domain is rated as low risk, high risk, or some concerns. The assessment of heterogeneity between studies was also conducted. The overall assessment is considered "low risk" if all domains are rated as low risk, "high risk" if any domain is rated as high risk or if there is more than one domain with some concerns, and "some concerns" if any domain is rated as some concerns and no domain is rated as high risk (Sterne et al., 2019).

Data synthesis and statistical analysis

Heterogeneity between studies was assessed using Cochrane's Q test at a significance level of 0.1. The degree of heterogeneity was quantified using the I^2 statistic, categorized as low (<25%), moderate (25-75%), or high (>75%) (Higgins et al., 2003). A fixed-effect model was used to pool results if no significant heterogeneity was detected; otherwise, a random-effects model was employed (Clarke et al., 2010; Kanters, 2022).

The standard mean difference (SMD) in tacrolimus IPV between adherent and non-adherent groups was calculated for each study.

Studies reporting IPV as median values and interquartile range, were converted to mean and standard deviation before analysis in order to pool results in a consistent format (Wan et al., 2014). This method incorporated sample size and greatly improved the estimation performance providing a nearly unbiased estimate of the true sample standard deviation for normal data and a slightly biased estimate for skewed data. Pooled results were presented in a forest plot with 95% confidence intervals (CIs). To ensure consistency in the type of adherence measure used for the pooled analysis, data based on self-report assessments of adherence were used from each included study. When studies reported multiple adherence measures, the categorization (adherent vs. non-adherent) based on a self-report instrument was prioritized for extraction and analysis.

Publication bias was assessed using a funnel plot, with the SMD of tacrolimus IPV on the horizontal axis and the standard error (SE) of the MD on the vertical axis. Egger's test was used to test the symmetry of the funnel plot (Egger et al., 1997). All statistical analyses were performed using STATA® version 18 (StataCorp LLC, 2023), with a significance level of $p < 0.05$.

RESULTS AND DISCUSSION

Identification of relevant studies

The literature search yielded a total of 15,322 studies. After removing duplicates from 9 databases and registers, 9,299 unique studies remained. Following title and abstract screening based on the inclusion and exclusion criteria, 43 potentially relevant studies were identified. Full-text review of these studies resulted in the exclusion of 20 studies that did not meet the inclusion criteria, 17 studies that were conference abstracts without full text available, 2 studies not published in English, and none of the exclusions were due to the drug interaction criteria. None of the 252 studies identified via medRxiv were eligible for further analysis. Ultimately, 4 studies were included in the qualitative synthesis (Figure 1).

Study characteristics

All eligible studies were observational studies published between 2020 and 2022, and conducted in four distinct countries: Canada, South Korea, the Netherlands, and the United States. The total sample size across all studies was 790 participants, with 655 in the adherent group and 135 in the non-adherent group.

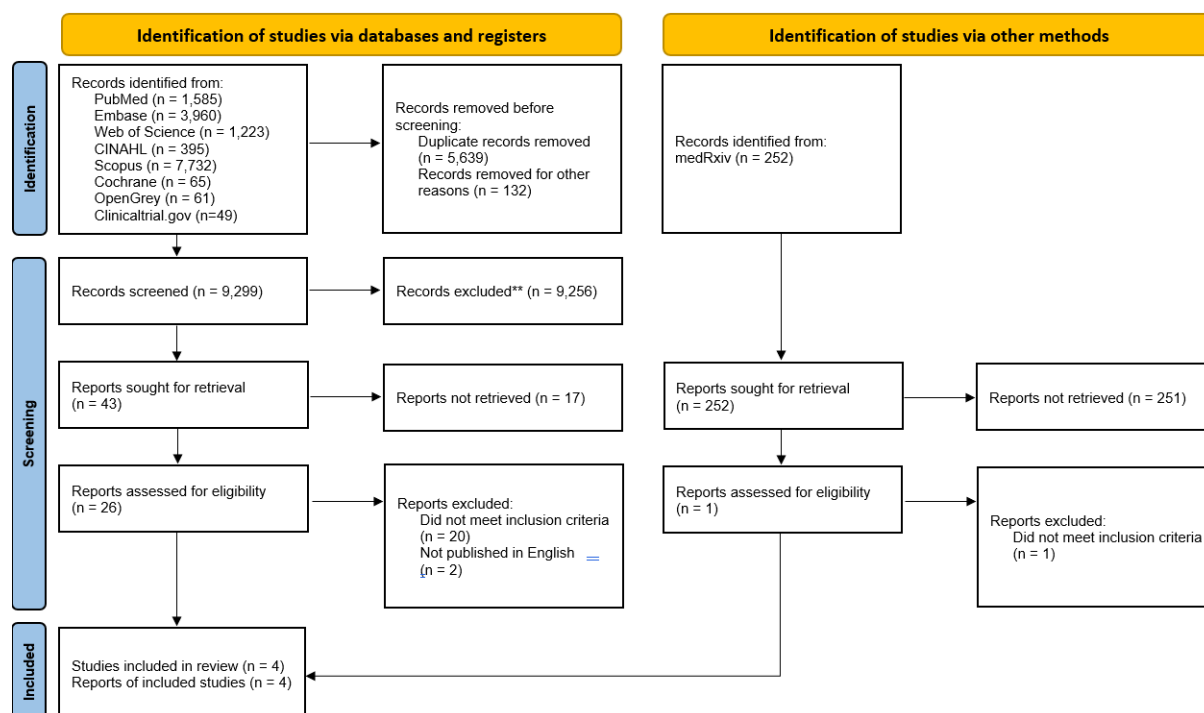


Figure 1. Flow diagram for identification of relevant studies.

Table I. General characteristics of the studies included in the final analysis.

Study/ country	Type of study	N	Time post- transplant (year)	Adherence assessment method	Tacrolimus concentration quantification method	Number of tacrolimus concentration*
(Herblum et al., 2021) Canada	Retrospective cohort	525	Ad = 5.8±3.7 Non-ad = 6.3±3.5	- Modified BAASIS questionnaire	HPLC-MS	>=3
(Ko et al., 2021) South Korea	Retrospective cohort	92	Ad = 1.7 (IQR 1.1-3.2) Non-ad = 1.8 (IQR 1.1, 3.9)	- EM - BAASIS questionnaire	HPLC-MS	>=4
(Gokoel et al., 2020) Netherlands	Prospective cohort	64	5.4	- EM - ITAS - Physician rating - TTR-C0 - CAS	HPLC-MS	5
(Leino et al., 2022) United State of America	Retrospective cohort	144	n/a	- Self-report (pharmacist assessment) - Laboratory monitoring	n/a	5

Ad: Adherent group; Non-ad: Non-adherent group, BAASIS; The Basel Assessment of Adherence to Immunosuppressive Medication Scale, EM; electronic monitoring, IQR; interquartile range, ITAS; Immunosuppressant Therapy Adherence Scale, TTR-C0; tacrolimus trough concentrations, CAS; composite adherence score, HPLC-MS; high-performance liquid chromatography-mass spectrometry.* Number of tacrolimus concentration measurements per patient used for IPV calculation.

The patient populations in these studies comprised stable kidney transplant recipients (more than 1 year post transplant for all 4 included trials), indicating a focus on patients who had successfully undergone transplantation and were in a relatively stable post-transplant phase. This selection criterion aimed to minimize the potential confounding effects of acute post-transplant complications on tacrolimus IPV. All the included studies utilized self-report methods to assess medication adherence, with two studies also employing electronic monitoring (EM) for a more objective measure of adherence. The specific self-report measures employed varied across the studies (Table I).

Quality of studies

All four studies included in the qualitative synthesis were observational studies, and therefore, their methodological quality was assessed using the ROBINS-E tool. Among the studies evaluated for risk of bias, Ko et al. (2021) had a low risk of bias, Gokoel et al. (2020) had some concerns, while Herblum et al. (2021) and Leino et al. (2022) were classified as high risk. All studies demonstrated a low risk of bias in the domain of selective reporting (Figure 2).

The study by Herblum et al., which employed a retrospective design, did not specify any measures to prevent selection bias, leading to a high risk of bias in participant selection. Additionally, there was a high risk of bias due to post-exposure interventions, as the study did not address how non-adherence was managed when identified in patients. The study by Leino et al. had a high risk of bias arising from the measurement of exposure and did not outline procedures for handling missing data, resulting in a high risk of bias due to missing data (Figure 3).

The Herblum et al. study had a risk of allocation bias due to the use of a modified 3-item BAASIS questionnaire, for which reliability data were not available. There was also a high risk of bias due to post-exposure interventions, as the retrospective design meant that pharmacists or nurses in the transplant clinic might have provided counseling according to standard practice if non-adherence was identified, potentially influencing the intra-patient pharmacokinetic variability of tacrolimus blood levels (Herblum et al., 2021).

The Ko et al. study utilized data from a randomized controlled trial with a 6-month follow-up period. It had a clear methodology, controlled for confounding factors, used validated tools, and

had a low risk of missing data, resulting in a low overall risk of bias (Ko et al., 2021). Similarly, the prospective observational study by Gokoel et al. also had a low risk of bias, except for the control of confounding factors, which is a limitation inherent to observational studies (Gokoel et al., 2020). The Leino et al. study had a high risk of bias because it did not use a standardized tool to assess adherence, and the assessors also incorporated clinical judgment in their evaluations without providing justifications (Leino et al., 2022).

All included studies, except for Leino et al., used HPLC-MS to measure tacrolimus concentrations, a method known for its high accuracy. Other controlled factors included food intake and drug interactions. In the Ko et al. study, participants were advised to take their medication one hour after or two hours before meals and to be cautious about using medications that could affect tacrolimus pharmacokinetics. The Leino study excluded patients with inappropriate blood sampling times or drug interactions. However, the Gokoel et al. and Herblum et al. studies did not specify clear guidelines for controlling confounding factors. Additionally, reporting of tacrolimus dose adjustment protocols varied: Gokoel et al. and Ko et al. mentioned targeting C₀ or AUC, while two others did not specify. This heterogeneity in approach or reporting is a limitation that could affect IPV and confound results. Genetic factors (e.g., *CYP3A5* polymorphisms) affecting tacrolimus IPV vary in prevalence across ethnic groups, potentially correlating with IPV differences (e.g., higher IPV in African American recipients) (Lieber et al., 2018; Seibert et al., 2018; Taber et al., 2019). The lack of data on ethnicity or specific genetic markers in the included studies precluded analysis of these underlying influences. Other factors that may influence IPV include meal timing and fat content, and changes in hemoglobin levels. These factors may not be adequately controlled in observational studies.

Association between tacrolimus IPV and adherence

The assessment of heterogeneity between studies, which is used to select the appropriate model for data analysis, revealed an I^2 value of 0.0% and a p -value of 0.956. It is important to consider that the I^2 test for heterogeneity may be less reliable in meta-analyses with a limited number of studies (Von Hippel, 2015). Despite this potential limitation, a fixed-effect model was chosen for the analysis of the pooled results.

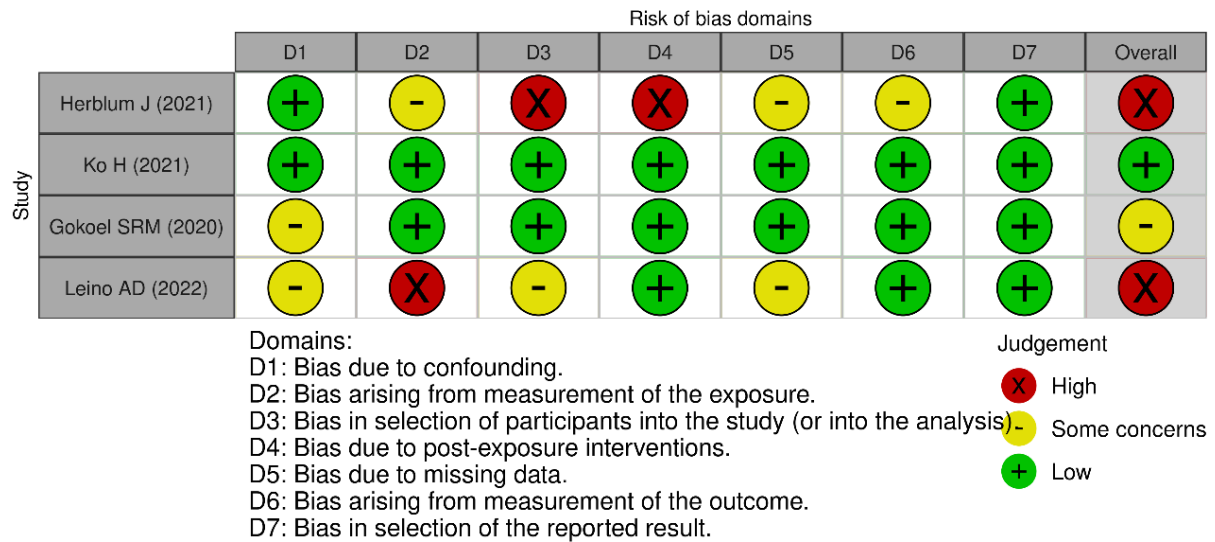


Figure 2. Traffic-light plot illustrating the risk of bias assessment for each study

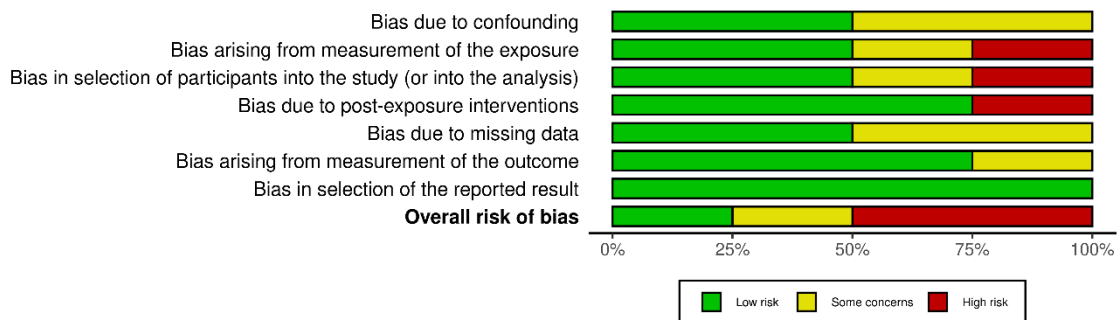


Figure 3. Summary plot illustrating the risk of bias across studies, categorized by assessment question.

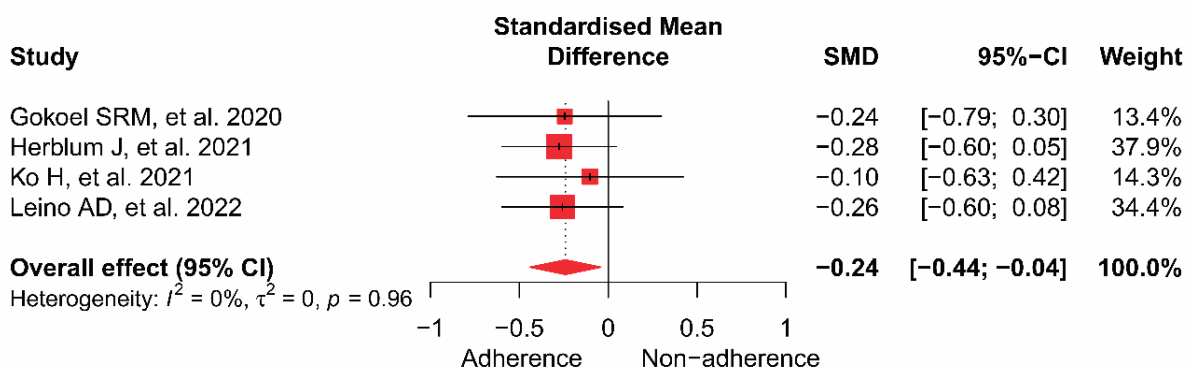


Figure 4. Forest plot illustrating the mean difference in tacrolimus IPV between adherent and non-adherent groups.

The analysis of the relationship between tacrolimus IPV and adherence, as assessed by self-report, revealed a statistically significant difference in IPV between the adherent and non-adherent groups (SMD -0.24, 95% CI: -0.44, -0.04; $p=0.017$). Interestingly, this meta-analysis finds a significant association while the individual included studies did not. Combination of the studies in this meta-analysis increases the overall sample size leading to greater statistical power to detect an association between IPV and adherence. The study by Herblum et al., with the largest sample size of 525 participants, contributed the most weight to the results (37.90%). Although the Leino et al. study had a smaller sample size of 144, its narrow distribution of IPV values resulted in a substantial weight of 34.43% (Figure 4). To assess the impact of study quality, we performed a sensitivity analysis excluding the two studies with a high risk of bias. The remaining studies showed a similar trend to the primary result (2 studies, $n=121$; SMD -0.17, 95% CI: -0.55 to 0.20; $p=0.709$; $I^2=0.0\%$), though the finding was not statistically significant (Supplementary figure S1). This indicates that while adherent patients generally had lower IPV, the statistical significance of the pooled result depended heavily on the inclusion of higher-risk studies. These findings highlight the need for cautious interpretation and emphasize the importance of future high-quality research.

There is strong evidence suggesting that IPV exceeding 20-30% is associated with acute and chronic rejection, de novo donor-specific antibodies, and renal fibrosis. Thus, IPV serves as a reliable surrogate marker for clinical outcomes. Previous research has also indicated that IPV may be a surrogate marker for non-adherence (Goodall et al., 2017; Pizzo et al., 2016). McGillicuddy et al. found that interventions promoting tacrolimus adherence significantly reduced IPV from baseline ($p=0.046$) (McGillicuddy et al., 2020). This contradicts the findings of the included studies in this meta-analysis, which showed no difference in IPV between adherent and non-adherent groups. This discrepancy may be attributed to insufficient sample sizes in individual studies. However, when data were pooled for a larger sample size, a significant association between IPV and adherence emerged.

The prevalence of non-adherence, as assessed by self-report, was less than 10% in the Herblum et al. study (Herblum et al., 2021), while the other three studies reported similar and higher prevalence rates ranging from 25% to 36.7%

(Gokoel et al., 2020; Ko et al., 2021; Leino et al., 2022). When adherence was assessed using electronic monitoring (EM), the prevalence increased, highlighting the significant impact of different adherence assessment methods on prevalence estimates, which may influence the analysis of the relationship with tacrolimus IPV.

Gokoel et al. observed that using different adherence cut-off values altered the number of patients in the adherent and non-adherent groups, affecting the mean IPV (Gokoel et al., 2020). However, there is no consensus on the optimal cut-off point for clinically relevant outcomes such as rejection. The prevalence of non-adherence based on EM and composite adherence score (CAS) was similar. Moreover, the prevalence of non-adherence based on CAS was higher than in previous studies. The tacrolimus trough concentrations (TTR-C0) criterion may involve healthcare provider factors, as some patients may have individualized target trough concentrations (C0) that deviate from standard guidelines. For example, patients with opportunistic infections may have lower target C0 values (affecting IPV SD prevalence). However, even after using individualized target C0 values, no association was found between CAS and IPV. Therefore, using different criteria or cut-off points to classify patients into adherent and non-adherent groups may lead to varying results. Once again, to ensure consistency in the type of adherence measure used for the pooled analysis, data based on self-report assessments of adherence were used from each included study. Additionally, the patients in this study exhibited high adherence levels, with an average of only one missed dose every two weeks.

Assessment of publication bias

Publication bias is a potential concern in any meta-analysis. To assess the potential for publication bias in this meta-analysis, we employed two complementary methods: visual inspection of a funnel plot and Egger's test. The assessment revealed a symmetrical distribution of points on the funnel plot (Figure 5). While the funnel plot suggests no substantial publication bias, the low number of studies limits the reliability of this assessment. Egger's test yielded a p -value of 0.708, indicating no evidence of publication bias. This result, in conjunction with the visual inspection of the funnel plot, provides reassurance that publication bias is unlikely to have significantly influenced the findings of this meta-analysis.

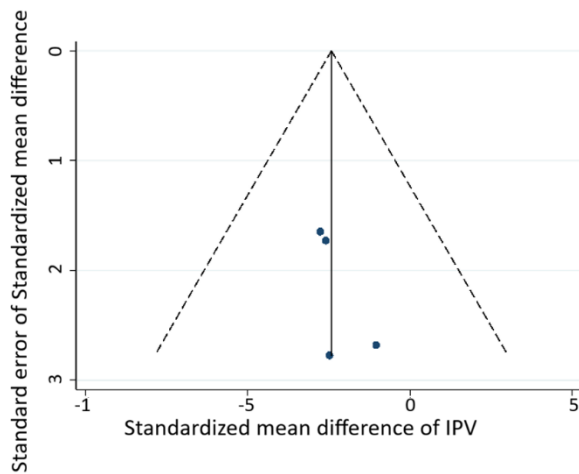


Figure 5. Funnel plot illustrating the standard mean difference of IPV and standard error between adherent and non-adherent groups.

While the meta-analysis examined the direct relationship between medication adherence and tacrolimus intra-patient variability (IPV), a complementary systematic review of the identified studies highlights a multifactorial framework influencing IPV and its implications for graft outcomes.

Pharmacological and biological factors

Beyond behavioral adherence, several pharmacological factors contribute to fluctuations in tacrolimus trough levels. The impact of drug formulation is a significant area of research; while conversion from twice-daily immediate-release tacrolimus (IR-Tac) to once-daily extended-release formulations (ER-Tac) often simplifies regimens, its effect on IPV is heterogeneous (Bunthof et al., 2022; Del Bello et al., 2021; Kamińska et al., 2020; Lai et al., 2022; Larpparisuth et al., 2019; Mohammed Ali et al., 2025).

The oral bioavailability of tacrolimus is notoriously low and inconsistent, primarily due to its extensive pre-systemic metabolism and the influence of external factors like dietary intake (Baraldo, 2016; van Gelder, 2002). Food intake, particularly high-fat meals, has been shown to significantly decrease the rate and extent of tacrolimus absorption, which can lead to unpredictable fluctuations in trough concentrations (Larpparisuth et al., 2019; van Gelder, 2002). These dietary interactions create "pharmacological noise" that can be easily misidentified as behavioral non-adherence during routine monitoring (Kuypers, 2020; Shuker et al.,

2015). Furthermore, circadian modulations in gastric emptying and intestinal transit times result in different pharmacokinetic profiles for morning versus evening doses (Hwang et al., 2021; Prado-Velasco et al., 2020). Maintaining a consistent dosing schedule relative to meals is therefore critical to minimizing intra-patient variability and ensuring stable immunosuppression (Gokoel et al., 2020; Ko et al., 2021).

Biological factors such as CYP3A5 and CYP3A4 genetic polymorphisms significantly influence tacrolimus clearance, although their direct relationship with IPV remains a subject of ongoing debate. (Chai et al., 2025; Choi et al., 2022; Gongor et al., 2025; Koudijs et al., 2025; Nuchjumroon et al., 2022; Stefanović et al., 2020). While the CYP3A5 genotype is a well-known determinant of tacrolimus dose requirements, other genetic modifiers also play a significant role in drug exposure stability (Prytuła & van Gelder, 2019; Seibert et al., 2018). Genetic polymorphisms in the ABCB1 gene, which encodes the P-glycoprotein efflux transporter, can influence the intracellular concentration and overall variability of tacrolimus (Gongor et al., 2025; Pashae et al., 2011). Additionally, variations in the CYP3A4 gene, such as the CYP3A422* allele, have been found to work in tandem with CYP3A5 to affect the metabolic rate and the risk of overexposure (Koudijs et al., 2025; Stefanović et al., 2020). The combined effect of these inter- and intra-patient genetic variabilities often complicates the attainment of target trough levels in the early post-transplant period (Larpparisuth et al., 2021; Stefanović et al., 2020). Understanding this complex genetic landscape is essential for personalizing therapy and distinguishing between biological predispositions and poor adherence (Nuchjumroon et al., 2022; Pashae et al., 2011).

Digital health and mHealth Interventions

The role of technology in monitoring and mitigating high IPV has expanded significantly. Recent randomized controlled trials have explored information and communication technology (ICT)-based systems that provide real-time alarms for missed doses (Jung et al., 2020).

Research into mHealth interventions for kidney transplant recipients indicates that while digital tools show promise for reducing tacrolimus intra-patient variability (IPV), current evidence is inconsistent. High tacrolimus variability is a critical risk factor for graft rejection and loss. Some clinical trials have found success; for instance, a

pharmacist-led mHealth intervention significantly decreased tacrolimus IPV over 12 months (Fleming et al., 2021), and a 6-month study using an app and electronic medication tray significantly reduced the mean tacrolimus coefficient of variation (CV) (McGillicuddy et al., 2020). Conversely, a study utilizing smartwatches and the "Transplant Hero" app found no significant differences in CV levels at the 3-month mark (Levine et al., 2019). A 2025 meta-analysis suggests that these conflicting results may stem from low-quality evidence and high heterogeneity in how digital interventions are designed and measured (Zhou et al., 2025).

To address these inconsistencies, the SmartNTx-study is evaluating whether embedding a certified app within a holistic telemedical framework—featuring bidirectional data transfer and regular clinician visits—can more effectively lower tacrolimus IPV as part of a comprehensive clinical endpoint. This approach aims to move beyond stand-alone apps by integrating healthcare professionals to better manage complex therapeutic regimens (Schiffer et al., 2025).

Socioeconomic factors and health literacy

Socioeconomic status and health literacy are critical, yet often overlooked, determinants of tacrolimus intra-patient variability. Limited health literacy is common among transplant recipients and is significantly correlated with increased healthcare utilization and more frequent outpatient visits during the first-year post-transplant (Haubrich et al., 2025; Patzer et al., 2016). Socioeconomic barriers, including lower income, unemployment, and minority race, are also independently associated with higher rates of hospitalization and poor medication understanding (Belaiche et al., 2017; Patzer et al., 2016). Conversely, some studies suggest that high-quality prerenal transplant education and evaluation programs can mitigate these risks by establishing robust social support systems and improving longitudinal tacrolimus stability (Jesse et al., 2022; Taber et al., 2019).

Adherence assessment

Accurate adherence assessment is vital for preventing graft rejection and ensuring optimal clinical outcomes (Anthony et al., 2019; Krause et al., 2021; Williams et al., 2016). While various methods exist, including pill counts and pharmacy refill records, self-report remains the most common tool due to its low cost and ease of use in clinical settings (Belaiche et al., 2017; Lieb et al.,

2020; Williams et al., 2016). Validated instruments like the Basel Assessment of Adherence to Immunosuppressive Medication Scale (BAASIS) or the Immunosuppressant Therapy Adherence Scale (ITAS) are frequently used to identify "taking" and "timing" non-adherence (Gokoel et al., 2020; Krause et al., 2021; Vaisbourd et al., 2023). However, these subjective measures are prone to social desirability and recall biases, which may lead to an underestimation of true non-adherence rates (Belaiche et al., 2017; Herblum et al., 2021; Lieb et al., 2020).

Electronic medication monitoring devices (EMDs) are considered the gold standard because they provide objective, real-time data on dosing patterns. Although EMDs often reveal higher "taking" adherence compared to "timing" adherence, their implementation is limited by high costs and potential interference with a patient's daily routine (Jung et al., 2020; Krause et al., 2021; Williams et al., 2016). Interestingly, some studies have found a moderate-to-high concordance between self-reports and electronic data, suggesting that well-designed questionnaires can be adequate surrogates in resource-limited settings (Gokoel et al., 2020; Krause et al., 2021; Lieb et al., 2020).

Non-adherence is a multifactorial issue influenced by younger age, male gender, and socioeconomic factors like unemployment or low health literacy (Belaiche et al., 2017; Mella et al., 2023; Patzer et al., 2016). Complex drug regimens and the frequency of daily intakes further exacerbate the risk of missed doses (Baraldo, 2016; Mella et al., 2023). Consequently, a multi-modal assessment approach combining self-reports with objective metrics like tacrolimus intra-patient variability (IPV) or the immunosuppressant possession ratio (IPR) is recommended to accurately identify high-risk patients (Chambord et al., 2023; Gavcovich et al., 2025).

IPV as a predictor of graft rejection

A high degree of fluctuation in tacrolimus whole-blood concentrations is now recognized as a potent risk factor for acute cellular and antibody-mediated rejection (Shuker et al., 2015). Research consistently demonstrates that high intra-patient variability (IPV), defined as fluctuations occurring while the drug dose remains unchanged—predisposes kidney transplant recipients to alloimmune-mediated injury (Kuypers, 2020). This is evidenced by studies showing that patients receiving immediate-release tacrolimus may

exhibit higher coefficient of variation (CV) at one-year post-transplant compared to those on extended-release formulations, which correlates with significantly higher episodes of acute rejection (Torabi et al., 2020). Recent multicenter data indicate that high IPV, specifically a coefficient of variation (CV%) exceeding 23% between months 6 and 12 post-transplant, is significantly associated with an increased risk of rejection episodes beyond the first year (Baghai Arassi et al., 2025).

This risk of rejection is particularly pronounced in patients categorized as "rapid metabolizers" or those with a low concentration-to-dose (C/D) ratio. In these cohorts, a low C/D ratio during the first six months post-transplant has been associated with a three-fold higher risk of rejection between months 6 and 12 (Baghai Arassi et al., 2025). Furthermore, patients who achieve target trough levels (C₀) only through very low doses may have a low peak and low overall area under the curve (AUC), potentially leading to underexposure. Conversely, those with a low C₀/dose ratio may experience unexpectedly high peak concentrations after oral administration, which further complicates the balance between preventing rejection and inducing toxicity (van Gelder et al., 2025).

IPV and long-term graft survival

Beyond the immediate risk of acute rejection, high tacrolimus IPV serves as a critical marker for long-term allograft survival. The underlying pathophysiology linking high variability to graft loss includes the development of de novo donor-specific anti-HLA antibodies (dnDSA) and progressive, irreversible fibrotic damage to the renal parenchyma (Kuypers, 2020).

Studies have shown that individual-specific variability is a superior metric for predicting long-term adverse events compared to simple mean trough levels. Patients with higher CV loading parameters face a significantly higher hazard of developing dnDSA, which serves as an early warning sign of graft failure (Campbell et al., 2021). Furthermore, the stability of the tacrolimus formulation itself may play a role in long-term outcomes, as switching between different formulations is associated with a higher frequency of trough level excursions. This instability often necessitates more frequent therapeutic drug monitoring and subsequent dose adjustments (Schwartz et al., 2019). Because high IPV tracks consistently with inferior graft survival, its quantification is recommended as a standard tool

in everyday clinical practice to identify high-risk patients who may benefit from more sophisticated monitoring, such as AUC-based assessments (Marquet, 2025).

Clinical impact on special populations

The clinical consequences of high IPV are particularly pronounced in pediatric and adolescent populations, who are at a higher risk for non-adherence during the vulnerable period of transition to adult care (Annunziato et al., 2015; Fernandez et al., 2019; Holmberg, 2019). Adolescent age at the time of transplant has been recognized as a significant risk factor for renal allograft loss (Fernandez et al., 2019). High variability in these cohorts is a robust predictor of late acute cellular rejection (LACR) and the development of de novo donor-specific antibodies (dnDSA) (Abu Bakar et al., 2019; Holmberg, 2019; Pizzo et al., 2016). Furthermore, a high standard deviation in serial tacrolimus concentrations is associated with an increased hazard of graft loss in pediatric organ transplant recipients (Pollock-Barziv et al., 2010).

Recent evidence also suggests that high IPV may be associated with early subclinical graft injury, as evidenced by elevated donor-derived cell-free DNA (dd-cfDNA) levels within the first-year post-transplant (Kopfman et al., 2024). In pediatric recipients, a tacrolimus coefficient of variation (CV%) exceeding 31% has been found to maximize the classification of biopsy-proven rejection (Pizzo et al., 2016). Additionally, while adolescents do not always show higher variability than younger children, those who experience late acute rejection consistently demonstrate higher CV% levels (Prytula et al., 2012). Implementing specialized transition programs and multidisciplinary support is essential to maintain low variability and protect graft function in these high-risk young populations (Feddersen et al., 2021; Holmberg, 2019).

Clinical cut-off points and thresholds for tacrolimus IPV

Establishing standardized cut-off points for tacrolimus intra-patient variability (IPV) is essential for identifying kidney transplant recipients at high risk for adverse outcomes (Kuypers, 2020; Shuker et al., 2015). While various metrics are used, the coefficient of variation (CV%) is the most frequently applied index for defining these therapeutic thresholds (Baghai Arassi et al., 2025; Kuypers, 2020). Current evidence suggests a

"danger zone" for graft health when the CV% exceeds a range of 25% to 31% (Cheng et al., 2025; Mira et al., 2021).

In adult populations, a tacrolimus IPV threshold of $\geq 25.6\%$ has been identified as a significant predictor of biopsy-proven acute rejection and a doubling of serum creatinine within the first year post-transplant (Cheng et al., 2025; Javed et al., 2025). Similarly, receiver operating characteristic (ROC) curve analyses have determined a specific intra-patient variability cut-off point of 28.3% for predicting acute graft rejection in recipients maintained on prolonged-release formulations (Mira et al., 2021; Taber et al., 2023). For long-term survival, a CV% greater than 30% has been independently associated with death-censored graft loss and the development of de novo donor-specific antibodies (dnDSA) (Kuypers, 2020; Rodrigo et al., 2016). Furthermore, some studies utilize a more stringent threshold of 15%, noting that maintaining variability below this level, combined with trough concentrations above 7 ng/mL, can significantly improve 24-month graft function in adherent patients (Leino et al., 2019; Nafar et al., 2024).

Thresholds for pediatric populations often require higher cut-offs due to age-related pharmacokinetic differences (Hsiau et al., 2011; Prytuła & van Gelder, 2019). Multicenter data from the CERTAIN registry established a pediatric-specific IPV cut-off of 23%, identifying it as a predictive marker for graft rejection beyond 12 months post-transplant (Baghai Arassi et al., 2025; Feddersen et al., 2021). Other pediatric studies have suggested that a tacrolimus CV% of 31% maximizes the sensitivity and specificity for classifying biopsies as rejection (Hsiau et al., 2011; Pizzo et al., 2016). In addition to the CV%, the mean absolute deviation (MAD) has been proposed as a robust metric, with a threshold of 26% serving as a clinical marker for late acute cellular rejection (LACR) (Abu Bakar et al., 2019; Ko et al., 2021). Collectively, these data indicate that while specific values may vary by population and calculation method, a CV% consistently exceeding 30% or a MAD above 26% should trigger immediate clinical intervention and adherence support (Abu Bakar et al., 2019; Rodrigo et al., 2016).

Advanced TDM and Statistical Methods

The limitations of relying solely on trough concentrations (C₀) have led to the development of more sophisticated therapeutic drug monitoring

(TDM) strategies (Marquet, 2025; van Gelder et al., 2025). Estimation of the area under the concentration-time curve (AUC) using limited sampling strategies (LSS) or Bayesian forecasting provides a more accurate reflection of total drug exposure (Andrews et al., 2017; Marquet, 2025). These advanced statistical methods can help identify patients who are underexposed despite having "normal" trough levels, thereby reducing the risk of subclinical rejection (Andrews et al., 2017; van Gelder et al., 2025). Additionally, individual-specific random error terms in longitudinal models have been shown to be superior to simple mean values for predicting the hazard of developing de novo donor-specific antibodies (Campbell et al., 2021; Javed et al., 2025). Implementing these technology-enabled and data-driven approaches in clinical routine could significantly optimize long-term graft survival (Ky et al., 2022; Marquet, 2025).

LIMITATIONS OF THE STUDY

The first major limitation of this study is the quality and limited number of included studies, all of which were observational, although some utilized data from randomized controlled trials. Therefore, the authors rightly recommend future researches with more rigorous designs, such as RCTs, to confirm the findings. The second limitation is the heterogeneity in study designs, including the use of different adherence assessment tools and the presentation of IPV as median and interquartile range values, necessitating data conversion that may introduce inaccuracies. However, the converted values are expected to deviate by only 1% if the data are normally distributed (Wan et al., 2014). The third limitation is the reliance on self-reported adherence measures, which may be subject to memory bias or social desirability, potentially leading to an underestimation of non-adherence and affecting patient grouping and CV% values for each group. A subgroup or sensitivity analysis based on different types of adherence assessment (e.g., self-report vs. electronic monitoring) was considered but deemed not feasible due to the limited number of studies reporting data for non-self-report methods. Nevertheless, previous research has shown good agreement between self-reported and EM-measured adherence (Lieb et al., 2020). Additionally, self-report is a convenient and cost-effective tool suitable for practical use.

CONCLUSION

This study represents the first systematic review and meta-analysis investigating the relationship between medication adherence and intra-patient pharmacokinetic variability (IPV) of tacrolimus levels in stable kidney transplant recipients. The investigation into the relationship between tacrolimus IPV and adherence in stable kidney transplant recipients revealed that the adherent group exhibited significantly lower IPV compared to the non-adherent group. However, this finding should be interpreted cautiously as all included studies were observational in nature, and their results may be confounded by uncontrolled factors. Moreover, some studies demonstrated a high risk of bias. Therefore, a definitive causal relationship between adherence and tacrolimus IPV cannot be established based on the current evidence.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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