PROFESIONAL HEALTH JOURNAL
Volume 8, No. 1, December 2026 (Page. 166-178)
Available Online at https://www.ojsstikesbanyuwangi.com/index.php/PHJ/index
E-ISSN 2715-6249
DOI: https://doi.org/10.54832/phj.v8i1.1371

The Effect of CYP3A4, CYP3A5 and ABCB1 Polymorphisms on Tacrolimus Dose Requirements in Adult Kidney Transplant Patients

Khusnul Khotimah [a]* | Lolita [b] | Lalu Muhammad Irham [c]
[a,b,c] Faculty of Pharmacy, Ahmad Dahlan University
*Corresponding Author: lolita@pharm.uad.ac.id

ARTICLE INFORMATION

Article history
Received (14 December 2025)
Revised (30 December 2025)
Accepted (31 December 2025)

Keywords
Keywords must contain at least three to five keywords representing the main content of the article

ABSTRACT

Introduction: *Polymorphisms in the CYP3A4, CYP3A5, and ABCB1 genes play a significant role in the response to tacrolimus therapy in kidney transplant patients. Tacrolimus, a commonly used immunosuppressant, has a narrow therapeutic index and is highly influenced by individual genetic variation. These genetic polymorphisms significantly affect the response to tacrolimus therapy in patients undergoing kidney transplantation. Inaccurate dosing can lead to serious consequences: a tacrolimus dose that is too low increases the risk of acute rejection, while a dose that is too high can cause nephrotoxicity and other serious side effects. Therefore, accurate initial dosing of tacrolimus is critical in the clinical practice of kidney transplantation..*
Methods: *The article search was conducted using the CrossRef database, which provides access to a wide range of scientific journals. The research focused on studies published within the last five years, ensuring that only those addressing polymorphisms related to the CYP3A4, CYP3A5, and ABCB1 genes in the context of tacrolimus were included. A total of 18 studies met the inclusion criteria and were subjected to further analysis.*
Results: *Previous analyses revealed that CYP3A5 polymorphisms are the most consistent genetic factors influencing tacrolimus metabolism. Individuals with the *1/*1 or *1/*3 genotypes express the enzyme and metabolize tacrolimus more rapidly, requiring higher doses—initial recommendations range from 0.14 to 0.18 mg/kg/day for immediate-release formulations and up to 0.2 mg/kg/day for extended-release formulations. Consequently, expressers often require higher maintenance doses to maintain therapeutic baseline concentrations. Studies suggest that they may need doses up to 50% higher than non-expressors to achieve similar blood levels, with the average daily dose for expressers being approximately 0.151 mg/kg, compared to 0.089 mg/kg for non-expressors. Meanwhile, non-expressors with the *3/*3 genotype experience a greater risk of toxicity with increasing baseline concentrations, although the contributions of CYP3A4 and ABCB1 vary by ethnicity and transplant stage.*
Conclusions: *From the results of this review, it can be concluded that CYP3A5 gene polymorphisms are the primary predictors of tacrolimus dose requirements. Recommendations for implementing CYP3A5 genotyping before transplantation may enhance the efficacy of immunosuppression and reduce the risk of toxicity. Further research is necessary to develop more adaptive, pharmacogenetic-based dosing models and to evaluate the clinical factors influencing tacrolimus pharmacokinetics.*

Introduction

Tacrolimus is the primary immunosuppressant drug most widely used in kidney transplantation to prevent organ rejection; however, its clinical use is characterized by marked interindividual variability, largely driven by genetic factors. This variability in drug exposure increases the risk of graft rejection or drug-related toxicity. Tacrolimus metabolism is predominantly mediated by the cytochrome P450 enzymes CYP3A4 and CYP3A5, while its intestinal absorption and distribution are influenced by the P-glycoprotein transporter encoded by the ABCB1 gene (Mukkavilli et al., 2024a). Genetic polymorphisms in these genes can substantially alter tacrolimus pharmacokinetics and consequently affect individual dose requirements, underscoring the importance of personalized dose optimization to achieve therapeutic drug concentrations. Therefore, the objective of this narrative review is to evaluate and synthesize current evidence on the combined influence of CYP3A5, CYP3A4, and ABCB1 genetic polymorphisms on tacrolimus dosage requirements and clinical outcomes in kidney transplant recipients, with the aim of supporting genotype-guided dosing strategies.

PROFESIONAL HEALTH JOURNAL
Volume 8, No. 1, December 2026 (Page. 166-178)
Available Online at https://www.ojsstikesbanyuwangi.com/index.php/PHJ/index
E-ISSN 2715-6249
DOI: https://doi.org/10.54832/phj.v8i1.1371

This variability is primarily influenced by genetic factors that modulate the pharmacokinetics of tacrolimus. The metabolism of this drug depends on the CYP3A4 and CYP3A5 enzymes, while its distribution and transport are largely influenced by P-glycoprotein, which is encoded by the ABCB1 gene (Cusinato, Lacchini, Romão, et al., 2014; Mukkavilli et al., 2024a). Polymorphisms in these three genes have been shown to cause differences in dosage requirements among patients. CYP3A5 is the most consistent predictor, with patients carrying the *1/*1 or *1/*3 genotype (expressors) requiring higher doses of tacrolimus to achieve target therapeutic levels compared to those with the *3/*3 genotype (non-expressors), who are more susceptible to toxicity due to higher drug exposure (D. A. Brazeau et al., 2020; Htun et al., 2020a; Mukkavilli et al., 2024b). Additionally, CYP3A4 polymorphisms, particularly *1B, have been shown to influence dose requirements in certain populations (Hannachi et al., 2024a). Variants of ABCB1, such as C3435T and 2677G>T, are associated with altered tacrolimus absorption and clearance, thereby impacting both efficacy and the risk of toxicity (D. Brazeau, 2025a; Kwakyi et al., 2023a).

The clinical implications of genetic variations in CYP3A4, CYP3A5, and ABCB1 are significant, as they directly influence tacrolimus blood levels, initial and maintenance dose requirements, and the risk of organ rejection and toxicity in kidney transplant patients. Tacrolimus, as a primary immunosuppressant, undergoes complex metabolism influenced by multiple genetic factors that influence its pharmacokinetics. Studies have shown that genetic variations, particularly in CYP3A5, result in significant differences in tacrolimus levels and efficacy. Individuals with the CYP3A53/3 genotype (non-expressers) exhibit a higher area under the curve (AUC) for tacrolimus compared to expressers with the CYP3A51/3 or CYP3A51/1 genotype in the early post-transplant phase (Mukkavilli et al., 2024a; Rotarescu et al., 2024a). Some alleles, particularly CYP3A53, are known to be common variants that can cause variation in enzyme expression in the population. Studies have shown that individuals with the active allele of CYP3A5 (CYP3A51) require higher doses of tacrolimus to achieve therapeutic concentrations compared to CYP3A5 non-expressers (CYP3A5*3)(D. A. Brazeau et al., 2020; Htun et al., 2020b). This dose increase is often associated with an increased risk of side effects and acute rejection in post-transplant patients (Kwakyi et al., 2023b; Mukkavilli et al., 2024a; Seligson et al., 2024a). Research conducted by Srinivas et al., showed that CYP3A53 is a major determinant of tacrolimus concentrations and can be used to build a genotype-based dose prediction model (Srinivas et al., 2021)

Although CYP3A5 has a more significant influence on tacrolimus metabolism, genetic variation in CYP3A4 also plays a crucial role (Hannachi et al., 2024a)(Li et al., 2014). The CYP3A4*1B polymorphism, while less impactful than CYP3A5 variations, may affect tacrolimus dosage requirements, particularly in specific populations such as Black individuals (Provenzani, 2011). Research indicates that accounting for genetic variations, including polymorphisms in CYP3A4, is essential to reducing the risk of therapy failure (Li et al., 2014)(D. Brazeau, 2025b). ABCB1, which encodes P-glycoprotein (P-gp), serves as the primary transporter of tacrolimus and plays a role in the drug's absorption in the gastrointestinal tract and clearance from the bloodstream (Rotarescu et al., 2024b). Polymorphisms such as C3435T and 2677G>T in the ABCB1 gene have been significantly associated with tacrolimus metabolism and efficacy (Kwakyi et al., 2023c). Individuals with variants in the P-gp gene may experience altered tacrolimus bioavailability, necessitating dose adjustments to achieve optimal therapeutic concentrations (D. Brazeau, 2025b).

A study suggests that genetic variation in ABCB1 may contribute to side effects and treatment responses in the context of kidney transplantation (Pallio et al., 2020). Furthermore, combined polymorphisms in CYP3A5 and ABCB1 appear to correlate with higher dose requirements and may impact overall transplant outcomes (Seligson et al., 2024b)(Cusinato, Lacchini, Romao, et al., 2014). The functionality of the P-glycoprotein transporter encoded by

PROFESIONAL HEALTH JOURNAL
Volume 8, No. 1, December 2026 (Page. 166-178)
Available Online at https://www.ojsstikesbanyuwangi.com/index.php/PHJ/index
E-ISSN 2715-6249
DOI: https://doi.org/10.54832/phj.v8i1.1371

the ABCB1 gene is crucial in this context. Since tacrolimus is a substrate of P-gp, genetic variations in ABCB1 may influence plasma tacrolimus levels. These differences can affect tacrolimus excretion by renal cells, thereby contributing to the risk of renal toxicity in transplant recipients. Low-function ABCB1 genotypes may increase the likelihood of kidney damage due to elevated levels of unutilized tacrolimus within renal cells.

Therefore, calculating doses based solely on body weight without considering an individual's genetic profile can lead to inaccuracies in dose determination, ultimately hindering therapeutic success. A personalized dosing approach based on pharmacogenetic principles is essential for optimizing immunosuppressive effectiveness while reducing the risk of toxicity and organ rejection (Mukkavilli et al., 2024a; Srinivas et al., 2021). However, most previous studies have primarily analyzed the contribution of each gene separately, despite the fact that tacrolimus metabolism and distribution involve complex processes with simultaneous interactions between CYP3A4, CYP3A5, and ABCB.

To address this gap, the objective of this narrative review is to systematically synthesize and compare current evidence on the contributions of the CYP3A4, CYP3A5, and ABCB1 genes to tacrolimus dosing requirements and clinical outcomes in kidney transplant patients. By integrating findings from pharmacogenetic and clinical studies, this review aims to clarify the relative and combined influence of these genes on interindividual variability in tacrolimus response and to strengthen the scientific rationale for implementing personalized medicine approaches in tacrolimus therapy within clinical practice.

Methods

A comprehensive literature search was conducted using the CrossRef database to identify key articles on the influence of genetic polymorphisms on tacrolimus metabolism and their clinical implications in kidney transplant patients. The search took place on November 17, 2025, using the medical keywords: “immunosuppressant,” “kidney transplantation,” “gene polymorphisms,” “therapeutic,” and “tacrolimus.” Filters were applied to extract articles from clinical trials and randomized controlled trials involving adult participants (>18 years), limiting the results to full-text English-language publications. Additional studies were identified through manual reference searches of the selected articles.

Inclusion criteria for study selection were as follows: publication between 2020 and 2025; English-language articles; original research evaluating the association between genetic polymorphisms and tacrolimus therapy response in kidney transplant patients; participants who were adult kidney transplant recipients (>18 years of age); and studies reporting the impact of genetic variation on tacrolimus therapy outcomes, including initiation, drug level stability, efficacy, and clinical safety. Exclusion criteria included in vitro studies, animal studies, non-peer-reviewed articles, editorials, conference abstracts, and non-systematic reviews.

Since this study is a narrative review, no formal protocol registration or systematic screening was conducted following PRISMA guidelines. The selection process prioritized scientific relevance and methodological quality, facilitating a comprehensive synthesis of the current evidence. It involved reviewing titles, abstracts, and full texts of potential studies. Data from the eligible studies were descriptively extracted, focusing on the following variables: study characteristics (design, location, sample size); intervention details (the relationship of CYP3A4, CYP3A5, and ABCB1 polymorphisms to tacrolimus pharmacokinetics); clinical outcomes (graft function, incidence of acute rejection, nephrotoxicity, infections, and other adverse events); and key findings along with the clinical implications of pharmacogenetics.

The findings from the identified literature were narratively synthesized using a comparative and integrative analytical approach, in which studies were systematically examined and grouped into key clinical domains, including graft function, tacrolimus concentration stability, patient and graft survival, and adverse events. Rather than performing a

PROFESIONAL HEALTH JOURNAL
Volume 8, No. 1, December 2026 (Page. 166-178)
Available Online at https://www.ojsstikesbanyuwangi.com/index.php/PHJ/index
E-ISSN 2715-6249
DOI: https://doi.org/10.54832/phj.v8i1.1371

meta-analysis, which was not feasible due to heterogeneity in study designs, genetic analysis methods, and outcome reporting, a qualitative cross-study analysis was conducted to identify consistent patterns, contrasts, and clinically relevant trends across different populations and post-transplant phases. The results were then critically interpreted to evaluate both the individual and combined contributions of CYP3A5, CYP3A4, and ABCB1 polymorphisms in determining tacrolimus pharmacokinetics, dose requirements, and clinical response in kidney transplant recipients.

Results

Out of the 990 articles identified through the literature search process in the CrossRef database, 816 articles were excluded during the initial screening stage due to incompleteness and duplication. Subsequently, 174 articles were selected based on the relevance of their titles and abstracts. A full-text evaluation was then conducted using established inclusion and exclusion criteria. Sixty-six articles were excluded because they did not discuss kidney transplantation, 48 articles did not focus on the CYP3A4, CYP3A5, and ABCB1 genes, and 42 articles were inaccessible. Ultimately, a total of 18 articles met the eligibility criteria and were included in the final analysis. This selection process is illustrated in Figure 1 below

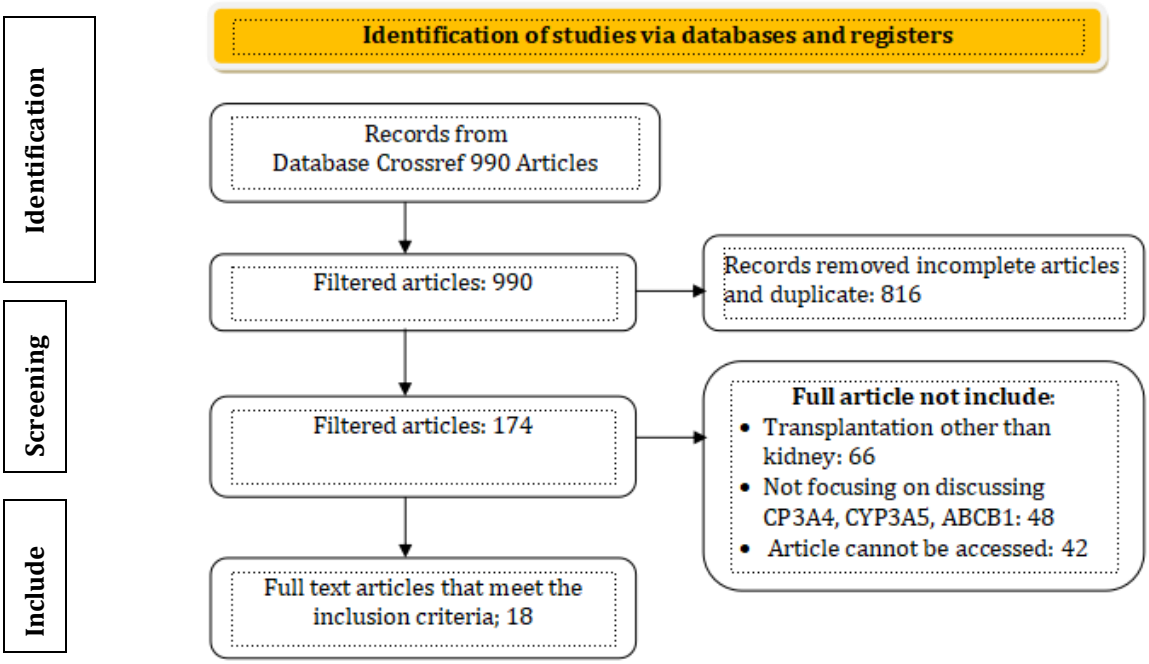

Figure 1. Flowchart of article search and identification

In this narrative review, we present the results of an analysis of the association between the CYP3A4, CYP3A5, and ABCB1 genes and tacrolimus dose requirements and concentrations in patients undergoing kidney transplantation, as summarized in Table 1. This table provides an overview of recent studies that explore the polymorphisms of CYP3A4, CYP3A5, and ABCB1 genes and their impact on tacrolimus pharmacokinetics.

Table 1. Relationship of CYP3A5, CYP3A4, and ABCB1 Genes with Tacrolimus Dose Requirements.

No	Authors	Country /	Genes Studied	Design and	Results	Genes Main	Study

PROFESIONAL HEALTH JOURNAL
Volume 8, No. 1, December 2026 (Page. 166-178)
Available Online at https://www.ojsstikesbanyuwangi.com/index.php/PHJ/index
E-ISSN 2715-6249
DOI: https://doi.org/10.54832/phj.v8i1.1371

	(Year)	Population		Number	Described	Findings	Weaknesses
1	Hannachi *et al* (2024)	Tunisia / Healthy subjects & Kidney transplant patients	CYP3A4*1B, CYP3A4*22, and CYP3A5*3	Cross-sectional; 101 kidney transplant patients + 102 healthy subjects	Distribution of CYP3A4, CYP3A5 polymorphisms & metabolizer status	The dominant alleles in Tunisian ethnicity were CYP3A4*1B (0.87), CYP3A4*22 (0.975), and CYP3A5*3 (0.82). Important information for predicting TAC dose based on ethnic group	No direct correlation with C0/D or clinical outcome
2	Jia *et al* (2024)	China/kidney transplant patients	CYP3A5*1/*1, *1/*3	Retrospective correlational, 105 patients	CYP3A5 polymorphism & acute immune rejection events	Expresser genotypes (*1/*1 or *1/*3) were more common in the acute rejection group; there was a significant correlation between CYP3A5 polymorphisms and rejection risk, even though TAC levels were similar between groups.	Single center, moderate sample size, did not explore other clinical factors in depth
3	Hirai *et al* (2022)	Japan/ kidney transplant patients	CYP3A5(*1/*1, *1/*3) expressers vs CYP3A5(*3/*3) non-expressers	Retrospective cohort, 42 patients	Correlation between C/D Ratio and HbA1c levels with TAC at 7 days, 6 and 12 months	Non-expressers had higher C/D and HbA1c, with significant increases in C/D. CYP3A5 and glycemic control explained long-term TAC variability.	Small sample, only 1 center and 1 dosage form (controlled-release).
4	Tanaka *et al* (2021)	Japan/Kidney transplant patients	Expressors (CYP3A5*1/*1 and *1/*3) vs. non-expressors (CYP3A5*3/*3)	Observational, 48 patients	Pre-transplant TAC C/D and iPTH levels	CYP3A5 non-expressors (higher TAC C/D); high iPTH also increases C/D. CYP3A5 and iPTH play a role in TAC dose adjustment before transplantation	Pre-transplant phase only and limited generalization
5	Muller *et al* (2020)	South African/Multi-Ethnic Kidney	rs776746A>G (CYP3A5). rs776746A>G (CYP3A5*3).	Retrospective Cohort. 43 patients (35% Black	C0/TAC Dose, IPV, Differences Between	CYP3A5 expressers required approximately	The small sample size for each ethnic subgroup is a limitation of

PROFESIONAL HEALTH JOURNAL
Volume 8, No. 1, December 2026 (Page. 166-178)
Available Online at https://www.ojsstikesbanyuwangi.com/index.php/PHJ/index
E-ISSN 2715-6249
DOI: https://doi.org/10.54832/phj.v8i1.1371

		Recipients		African, 44% Mixed Ancestry, 21% White)	Ethnicities	twice the tacrolimus (TAC) dose compared to non-expressers. Non-expressers (genotype *3/*3) exhibited higher concentrations-to-dose ratios (C/D) and greater interindividual variability (IPV). The frequency of expression was higher among individuals of Black ethnicity, necessitating a higher initial dose.	the study.
6	Brazeau *et al* (2020)	United States/Black & Caucasian kidney transplant patients	CYP3A5*3(rs776746), *6(10264272), *7(41303343) composite (Extensive, Intermediate, Poor Metabolizer). ABCB1 1236C > T (rs1128503), 2677G > T/A (rs2032582), and 3435C > T (rs1045642).	Cross-sectional PK/PGx. 65 patients.	The effect of CYP3A5 and ABCB1 polymorphisms on tacrolimus dose and area under the curve (AUC) is significant.	The ABCB1 3435C > T allele significantly reduced tacrolimus clearance across all three CYP3A5 metabolizer composite groups (*3, *4, and *5). Genetic factors contribute to interpatient variability in tacrolimus pharmacokinetics between White and Black individuals.	The sample size is relatively small, emphasizing pharmacokinetics (PK) rather than long-term clinical outcomes.
7	Srinivas *et al* (2021)	South India/kidney transplant patients	CYP3A5*3, CYP3A4*1B, CYP3A4*1G, ABCB1 G2677T, and ABCB1 C3435T)	Prospective observational, 145 patients	C0/D TAC on day 6, 6 months, 1 year; rejection & NODAT	CYP3A5*3 was the single factor most closely associated with the determination of tacrolimus concentration to dose ratio (C0/D) in blood at all three time points ($p < 0.001$).	For the Kerala population specifically, external validation is not yet available.
8	Kwakyi *et al* (2023)	Ghana/ESRD (dialysis and some transplant	CYP3A5*3 (6986A G), CYP3A4*1B (-290A G) and	Cross-sectional, 87 patients	The influence of polymorphisms (SNPs) on	A small proportion of patients are homozygous for	Only 5 transplant patients, so for PK analysis is limited.

PROFESIONAL HEALTH JOURNAL
Volume 8, No. 1, December 2026 (Page. 166-178)
Available Online at https://www.ojsstikesbanyuwangi.com/index.php/PHJ/index
E-ISSN 2715-6249
DOI: https://doi.org/10.54832/phj.v8i1.1371

		patients)	MDR1		tacrolimus dose requirements.	the CYP3A53 gene (4.6%), while the majority (79.31%) are homozygous for the CYP3A41B gene (-290A > G), which influences the dose requirements for potential tacrolimus (TAC) recipients.	
9	Wang *et al* (2020)	China/kidney transplant patients	CYP3A5 and 15 other SNPs	Clinical study, 406 patients	The effect of HB levels and polymorphisms on tacrolimus concentration	CYP3A5 genotype and Hb level were the most significant predictors of C0/D.	Single ethnicity (Chinese), needs validation in other populations
10	Zhang *et al* (2020)	Japan/kidney transplant patients	CYP3A5 recipient and donor	Prospective observational, 52 patients, 74 biopsies	Intrarenal TAC concentration (Ctissue) & C0; donor CYP3A5 genotype	Ctissue correlated weakly but significantly with C0; however, it was not associated with the donor CYP3A5 genotype. Intrarenal exposure was more influenced by systemic levels than by donor genetic factors.	Small sample, did not assess patient genotype.
11	Mukkavilli *et al* (2024)	India/kidney transplant patients	CYP3A4 (−392 G>A), CYP3A5 (6986 A>G), ABCB1 (3435 T>C)	Prospective cohort 327 patients	Tacrolimus levels, C/D, C/D/BB, rejection events & toxicity	CYP3A5 polymorphisms are associated with tacrolimus metabolism and risk of rejection.	In only one country have drug interactions been explored in detail. CYP3A4 and ABCB1 did not show a significant association.
12	Rotarescu *et al* (2024)	Romania / kidney transplant patients	ABCB1 (3435C>T, 1236C>T, 2677G>T/A)	Retrospective, 162	Tacrolimus levels, genotype, haplotype, and diplotype	ABCB1 gene polymorphisms are associated with TAC levels; genetic variations affect TAC metabolism.	Small sample size for some gene variants; single-center study design
13	Chang *et al* (2025)	Taiwan/kidney transplant patients	CYP3A5*1/*1 vs non*3/*3	Retrospective cohort, 431 patients	Initial tacrolimus dose	Non-expressers (*3/*3) required the greatest dose	Prospective trials of the dosage algorithm

PROFESIONAL HEALTH JOURNAL
Volume 8, No. 1, December 2026 (Page. 166-178)
Available Online at https://www.ojsstikesbanyuwangi.com/index.php/PHJ/index
E-ISSN 2715-6249
DOI: https://doi.org/10.54832/phj.v8i1.1371

					requirements and simulation based on genotype	adjustments and experienced the most overexposure (±34%). Simulations showed that genotype based dosing reduced the risk of overexposure (±69%).	have not been performed.
15	Prasad et al, (2020)	North India/kidney transplant patient	CYP3A5*1*1 CYP3A5*1*3 CYP3A5*3*3	Prospective observational, 248 patients	TAC dose requirements, C0/D, combination with MDR1	CYP3A5 expressers require higher tacrolimus (TAC) doses, and the combination of CYP3A5 expressers with the MDR1 G2677T/A variant has the highest daily TAC dose requirement. In contrast, non-expressers require lower doses and exhibit higher concentrations-to-dose ratios (C/D).	Early post-transplant focus, limited long-term outcome follow-up.
16	Zhang *et al* (2023)	China/kidney transplant patients	CYP3A5*1/*1, *1/*3 (ekspreser) vs *3/*3	Multicenter prospective observational cohort, 145 patients	Time and proportion reaching target and mean dose of tacrolimus	Non-expressers were faster and more likely to reach target TAC levels.	Initial focus one month, not yet assessing long-term effects (rejection, survival).
17	Cheng *et al* (2021)	China/kidney transplant patients	CYP3A5, CYP3A4*1B, CYP3A4*22, ABCB1, ABCC2, POR*28, or PXR.	Retrospective, single center, 201 patients	C0/D TAC, outcome (AR, PTDM, diarrhea)	CYP3A5 is clearly associated with TAC C0/D; other genes are inconsistent. Clinical factors (RBC, Hb, albumin) and Wuzhi capsule also influence C0/D. High TAC concentrations are associated with increased diarrhea and	There is no genotype-based dosing intervention.

PROFESIONAL HEALTH JOURNAL
Volume 8, No. 1, December 2026 (Page. 166-178)
Available Online at https://www.ojsstikesbanyuwangi.com/index.php/PHJ/index
E-ISSN 2715-6249
DOI: https://doi.org/10.54832/phj.v8i1.1371

						PTDM, not acute rejection.	
18	Chen *et al* (2021)	China/early post-transplant kidney patients	CYP3A5 6986A>G (expresser) and IL-10 -819C>T	Retrospective cohort; 188 patients	C0/D TAC day 5,10,15,30	CYP3A5 non-expressors + IL-10 low activity (TT) genotype: C0/D TAC was highest, while the combination of IL-10 and CYP3A5 influenced TAC dose requirements early post-transplant.	Only an initial phase, not yet linked in detail to long-term clinical outcomes.

*concentration/dose-normalized by body weight (C/D), tacrolimus (TAC), acute rejection (AR), trough levels (C0), dose-adjusted tacrolimus trough concentration (C0/D), intra-patient variability (IPV). new-onset diabetes mellitus after transplantation (NODAT)

Discussion

The findings of this narrative review consistently demonstrate that CYP3A5 gene polymorphisms are the most influential genetic determinants of tacrolimus metabolism and dose requirements in kidney transplant recipients (Hannachi et al., 2024b; Khan et al., 2025; Srinivas et al., 2021). Patients carrying at least one functional CYP3A5*1 allele (*1/*1 or *1/3), classified as expressers, exhibit faster tacrolimus metabolism, lower trough concentrations, and consequently require higher doses to achieve therapeutic targets. In contrast, individuals with the CYP3A53/*3 genotype (non-expressers) show slower metabolism, higher dose-adjusted exposure, and lower dose requirements, but are at increased risk of overexposure and toxicity (Khan et al., 2025; Mendrinou et al., 2020). Across multiple studies, optimal starting doses for non-expressers generally range from 0.08–0.10 mg/kg/day, whereas expressers typically require 0.14–0.18 mg/kg/day, confirming that tacrolimus dosing based solely on body weight is insufficient (Birdwell et al., 2015; Mendrinou et al., 2020; Qu et al., 2017).

Ethnic differences further modulate these observations, with studies reporting a higher prevalence of CYP3A5 expressers among Black and certain Asian populations, who may require up to twofold higher doses compared to predominantly White non-expressor populations (D. Brazeau, 2025a; D. A. Brazeau et al., 2020; Mendrinou et al., 2020). Prospective and cohort studies, including those conducted in South Asia, have consistently shown that the CYP3A5*3 genotype is a strong predictor of the concentration-to-dose ratio (C0/D) at early and late post-transplant time points (Srinivas et al., 2021). These findings reinforce the robustness of CYP3A5 as a predictor of tacrolimus exposure across diverse clinical settings.

In addition to genetic factors, clinical parameters such as hemoglobin levels, glycemic status (HbA1c), intact parathyroid hormone (iPTH), and intra-patient variability (IPV) have been shown to significantly influence tacrolimus pharmacokinetics (Hirai et al., 2023; Muller et al., 2020; Tanaka et al., 2021). Elevated HbA1c and iPTH levels, particularly in CYP3A5 non-expressers, are associated with higher C0/D ratios, indicating increased systemic exposure (Hirai et al., 2023; Tanaka et al., 2021). High IPV further complicates long-term therapy, reflecting fluctuations in tacrolimus exposure over time and underscoring the dynamic nature of dose requirements beyond the initial post-transplant period (D. Brazeau, 2025a; Qin et al., 2024).

From a pharmacokinetic perspective, the observed differences in dose requirements between CYP3A5 expressers and non-expressers can be explained by variations in drug

PROFESIONAL HEALTH JOURNAL
Volume 8, No. 1, December 2026 (Page. 166-178)
Available Online at https://www.ojsstikesbanyuwangi.com/index.php/PHJ/index
E-ISSN 2715-6249
DOI: https://doi.org/10.54832/phj.v8i1.1371

clearance and systemic exposure (Chen & Prasad, 2018). While therapeutic drug monitoring based on trough concentration (C0) remains the standard of care, accumulating evidence suggests that C0 alone may not accurately reflect intrarenal tacrolimus exposure or immunological activity (Van Gelder et al., 2014). This limitation supports theoretical models proposing that AUC-based monitoring may offer a more precise assessment of tacrolimus exposure, particularly in patients with high variability or discordant C0/D ratios (Cheng et al., 2022; Couette et al., n.d.).

Although CYP3A5 exerts the most consistent and clinically relevant effect, variants in CYP3A4 and ABCB1 also contribute to tacrolimus pharmacokinetics in a population- and time-dependent manner (Mukkavilli et al., 2024a; Muller et al., 2020). Evidence regarding CYP3A4*1B and ABCB1 polymorphisms remains inconsistent, likely due to ethnic differences, linkage disequilibrium, and interactions with clinical covariates (Kwakyi et al., 2023b; Mukkavilli et al., 2024a). These findings suggest that while CYP3A4 and ABCB1 may modify tacrolimus exposure in specific contexts, their influence is generally secondary to that of CYP3A5.

Taken together, these data indicate that genotype-guided tacrolimus dosing represents a rational strategy to improve early attainment of therapeutic drug levels, particularly by identifying patients who require substantially higher or lower doses at treatment initiation (Birdwell et al., 2015; Srinivas et al., 2021). However, genotype-based dosing should be viewed as a complement rather than a replacement for therapeutic drug monitoring, as ongoing dose adjustments remain necessary to account for temporal changes in pharmacokinetics and clinical status (Brunet & Pastor-Anglada, 2022).

Several limitations should be acknowledged. Most available studies have been conducted in single populations, limiting generalizability across diverse ethnic groups. Furthermore, many investigations focus on one or two genetic variants, whereas tacrolimus metabolism is influenced by a complex interplay of multiple genes and clinical factors (Khan et al., 2025; Shi et al., 2015). Future research should therefore prioritize multiethnic, multigene studies integrating pharmacogenetic data with dynamic clinical variables to refine individualized dosing algorithms.

From a clinical standpoint, CYP3A5 expressers appear to be at greater risk of acute rejection due to rapid tacrolimus clearance and subtherapeutic exposure, while non-expressers are more susceptible to nephrotoxicity, infections, and post-transplant diabetes mellitus as a result of higher drug exposure (Hannachi et al., 2024b; Srinivas et al., 2021). Consequently, pre-transplant CYP3A5 genotyping can guide initial dose selection, whereas continued therapeutic monitoring remains essential during maintenance therapy to optimize long-term graft and patient outcomes (Birdwell et al., 2015).

Conclusion

This narrative review confirms that polymorphisms in the CYP3A5 gene are major determinants of tacrolimus metabolism and, importantly, of dose requirements in kidney transplant recipients. Patients who carry at least one functional CYP3A5*1 allele (expressors) consistently demonstrate faster tacrolimus clearance and lower concentration-to-dose ratios, necessitating higher initial and maintenance doses to achieve therapeutic trough levels. In contrast, CYP3A5 non-expressors (*3/*3) exhibit slower metabolism and higher dose-adjusted exposure, which requires lower doses to avoid overexposure and toxicity. Although variants in CYP3A4 and ABCB1 also influence tacrolimus pharmacokinetics, their impact on dosing appears less consistent and is modulated by ethnicity and the post-transplant phase. Clinical factors such as hemoglobin levels, parathyroid hormone, and glycemic status further modify dose requirements and therapeutic responses. Collectively, these findings support the pretransplant genotyping of CYP3A5 as a practical strategy for guiding initial tacrolimus dosing, improving the

PROFESIONAL HEALTH JOURNAL
Volume 8, No. 1, December 2026 (Page. 166-178)
Available Online at https://www.ojsstikesbanyuwangi.com/index.php/PHJ/index
E-ISSN 2715-6249
DOI: https://doi.org/10.54832/phj.v8i1.1371

early attainment of target drug levels, and reducing the risks of rejection and adverse events. Given that most available evidence is derived from East Asian, South Asian, and European populations, pharmacogenetic studies focusing on Indonesian populations and diverse sub-ethnic groups across the archipelago are urgently needed to develop population-specific dosing strategies and optimize tacrolimus therapy.

References

Birdwell, K. A., Decker, B., Barbarino, J. M., Peterson, J. F., Stein, C. M., Sadee, W., Wang, D., Vinks, A. A., He, Y., Swen, J. J., Leeder, J. S., Van Schaik, R. H. N., Thummel, K. E., Klein, T. E., Caudle, K. E., & MacPhee, I. A. M. (2015). Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for CYP3A5 genotype and tacrolimus dosing. *Clinical Pharmacology and Therapeutics*, *98*(1), 19–24. https://doi.org/10.1002/cpt.113

Brazeau, D. (2025a). Association of Metabolic Genotype Composite <i>CYP3A5*3</I> And <i>CYP3A4*1B</I> to Tacrolimus Pharmacokinetics in Stable Black and White Kidney Transplant Recipients. *Clinical and Translational Science*, *18*(10). https://doi.org/10.1111/cts.70370

Brazeau, D. (2025b). Association of Metabolic Genotype Composite <i>CYP3A5*3</I> And <i>CYP3A4*1B</I> to Tacrolimus Pharmacokinetics in Stable Black and White Kidney Transplant Recipients. *Clinical and Translational Science*, *18*(10). https://doi.org/10.1111/cts.70370

Brazeau, D. A., Attwood, K., Meaney, C. J., Wilding, G. E., Consiglio, J. D., Chang, S. S., Gundroo, A., Venuto, R. C., Cooper, L., & Tornatore, K. M. (2020). Beyond Single Nucleotide Polymorphisms: CYP3A5∗3∗6∗7 Composite and ABCB1 Haplotype Associations to Tacrolimus Pharmacokinetics in Black and White Renal Transplant Recipients. *Frontiers in Genetics*, *11*(August), 1–13. https://doi.org/10.3389/fgene.2020.00889

Brunet, M., & Pastor-Anglada, M. (2022). Insights into the Pharmacogenetics of Tacrolimus Pharmacokinetics and Pharmacodynamics. In *Pharmaceutics* (Vol. 14, Issue 9). https://doi.org/10.3390/pharmaceutics14091755

Chen, L., & Prasad, G. V. R. (2018). CYP3A5 polymorphisms in renal transplant recipients: Influence on tacrolimus treatment. *Pharmacogenomics and Personalized Medicine*, *11*, 23–33. https://doi.org/10.2147/PGPM.S107710

Cheng, F., Li, Q., Cui, Z., Wang, Z., Zeng, F., & Zhang, Y. (2022). Tacrolimus Concentration Is Effectively Predicted Using Combined Clinical and Genetic Factors in the Perioperative Period of Kidney Transplantation and Associated with Acute Rejection. *Journal of Immunology Research*, *2022*. https://doi.org/10.1155/2022/3129389

Couette, A., Tron, C., Golbin, L., Franck, B., Houssel-Debry, P., Frouget, T., Morin, M.-P., Brenier, H., Rayar, M., & Verdier, M.-C. (n.d.). Area under the curve of tacrolimus using microsampling devices: towards precision medicine in solid organ transplantation? *European Journal of Clinical Pharmacology*, *2023*(11). https://doi.org/10.1007/s00228-023-03566-5ï

Cusinato, D. A. C., Lacchini, R., Romao, E. A., Moysés-Neto, M., & Coelho, E. B. (2014). Relationship of CYP3A5 genotype and ABCB1 diplotype to tacrolimus disposition in Brazilian kidney transplant patients. *British Journal of Clinical Pharmacology*, *78*(2), 364–372. https://doi.org/10.1111/bcp.12345

Cusinato, D. A. C., Lacchini, R., Romão, E. A., Neto, M. M., & Coelho, E. B. (2014). Relationship Of<i><scp>CYP3A5</Scp></I>genotype And<i><scp>ABCB1</Scp></I>diplotype to Tacrolimus Disposition in Brazilian Kidney Transplant Patients. *British Journal of Clinical Pharmacology*, *78*(2), 364–372. https://doi.org/10.1111/bcp.12345

Hannachi, I., Chadli, Z., Kerkeni, E., Chaabane, A., Ben-Fredj, N., Boughattas, N. A., & Aouam, K. (2024a). Distribution of CYP3A4 and CYP3A5 Polymorphisms and Genotype Combination Implicated inTacrolimusMetabolism. *Tunisie Medicale*, *102*(9), 537–542. https://doi.org/10.62438/tunismed.v102i9.4969

Hannachi, I., Chadli, Z., Kerkeni, E., Chaabane, A., Ben-Fredj, N., Boughattas, N. A., & Aouam, K. (2024b). Distribution of CYP3A4 and CYP3A5 Polymorphisms and Genotype Combination Implicated inTacrolimusMetabolism. *Tunisie Medicale*, *102*(9), 537–542. https://doi.org/10.62438/tunismed.v102i9.4969

PROFESIONAL HEALTH JOURNAL
Volume 8, No. 1, December 2026 (Page. 166-178)
Available Online at https://www.ojsstikesbanyuwangi.com/index.php/PHJ/index
E-ISSN 2715-6249
DOI: https://doi.org/10.54832/phj.v8i1.1371

Hirai, T., Morikawa, Y., Onishi, R., Nakatani, Y., Nishikawa, K., Inoue, T., & Iwamoto, T. (2023). Impact of glycaemic control and CYP3A5 polymorphisms on tacrolimus trough concentrations after adult kidney transplantation. *British Journal of Clinical Pharmacology*, *89*(6), 1852–1861. https://doi.org/10.1111/bcp.15662

Htun, Y. Y., Than, N. N., & Swe, H. K. (2020a). Effect of Cytochrome P450 3A5 Polymorphism on the Pharmacokinetics of Tacrolimus in Renal Transplant Recipients. *Korean Journal of Transplantation*, *34*(1), 24–30. https://doi.org/10.4285/kjt.2020.34.1.24

Htun, Y. Y., Than, N. N., & Swe, H. K. (2020b). Effect of Cytochrome P450 3A5 Polymorphism on the Pharmacokinetics of Tacrolimus in Renal Transplant Recipients. *Korean Journal of Transplantation*, *34*(1), 24–30. https://doi.org/10.4285/kjt.2020.34.1.24

Khan, A., Zaidi, S., Hassan, S., & Hanif Article, E. (2025). Impact of CYP3A5 Gene Polymorphisms on Tacrolimus Pharmacokinetics and Renal Allograft Rejection in Kidney Transplant Recipients: A Meta-Analysis Across Ethnic Populations. *Research Square*. https://doi.org/10.21203/RS.3.RS-7490941/V1

Kwakyi, E., Nartey, E. T., Otabil, M. K., Asiedu-Gyekye, I., Ahorhorlu, S. Y., Bioma, V., & Kudzi, W. (2023a). *Genetic Polymorphisms and Tacrolimus Dose Requirements: Potential Implications for Ghanaian patients with End-stage renal disease*. https://doi.org/10.21203/rs.3.rs-3595318/v1

Kwakyi, E., Nartey, E. T., Otabil, M. K., Asiedu-Gyekye, I., Ahorhorlu, S. Y., Bioma, V., & Kudzi, W. (2023b). *Genetic Polymorphisms and Tacrolimus Dose Requirements: Potential Implications for Ghanaian patients with End-stage renal disease*. https://doi.org/10.21203/rs.3.rs-3595318/v1

Kwakyi, E., Nartey, E. T., Otabil, M. K., Asiedu-Gyekye, I. J., Ahorhorlu, S. Y., Bioma, V., & Kudzi, W. (2023c). *Genetic Polymorphisms and Tacrolimus Dose Requirements: Potential Implications for Ghanaian Patients With End-Stage Renal Disease*. https://doi.org/10.21203/rs.3.rs-3595318/v1

Li, C., Li, L., Lin, L., Jiang, H., Zhong, Z., Li, W.-M., Zhang, Y., Zheng, P., Tan, X.-H., & Zhou, L. (2014). Impact of the CYP3A5, CYP3A4, COMT, IL-10 and POR Genetic Polymorphisms on Tacrolimus Metabolism in Chinese Renal Transplant Recipients. *Plos One*, *9*(1), e86206. https://doi.org/10.1371/journal.pone.0086206

Mendrinou, E., Mashaly, M. E., Al Okily, A. M., Mohamed, M. E., Refaie, A. F., Elsawy, E. M., Saleh, H. H., Sheashaa, H., & Patrinos, G. P. (2020). CYP3A5 Gene-Guided Tacrolimus Treatment of Living-Donor Egyptian Kidney Transplanted Patients. *Frontiers in Pharmacology*, *11*. https://doi.org/10.3389/fphar.2020.01218

Mukkavilli, K. K., Khan, M. S. A., Donakonda, A. K., Gopal Gangisetty, S. R., & Poojaveli, D. (2024a). Influence of Cyp3A4, Cyp3A5 and ABCB1 Polymorphisms on Tacrolimus Concentrations and Rejection Risk in Indian Kidney Transplant Recipients. *Indian Journal of Transplantation*, *18*(1), 42–45. https://doi.org/10.4103/ijot.ijot_76_23

Mukkavilli, K. K., Khan, M. S. A., Donakonda, A. K., Gopal Gangisetty, S. R., & Poojaveli, D. (2024b). Influence of Cyp3A4, Cyp3A5 and ABCB1 Polymorphisms on Tacrolimus Concentrations and Rejection Risk in Indian Kidney Transplant Recipients. *Indian Journal of Transplantation*, *18*(1), 42–45. https://doi.org/10.4103/ijot.ijot_76_23

Muller, W. K., Dandara, C., Manning, K., Mhandire, D., Ensor, J., Barday, Z., & Freercks, R. (2020). CYP3A5 polymorphisms and their effects on tacrolimus exposure in an ethnically diverse South African renal transplant population. *South African Medical Journal*, *110*(2), 159–166. https://doi.org/10.7196/SAMJ.2020.v110i2.13969

Pallio, G., Irrera, N., Bitto, A., Mannino, F., Minutoli, L., Rottura, M., Pallio, S., Altavilla, D., Alibrandi, A., Marciano, M. C., Righi, M., Mannucci, C., Arcoraci, V., & Squadrito, F. (2020). Failure of Achieving Tacrolimus Target Blood Concentration Might Be Avoided by a Wide Genotyping of Transplanted Patients: Evidence From a Retrospective Study. *Journal of Personalized Medicine*, *10*(2), 47. https://doi.org/10.3390/jpm10020047

Provenzani, A. (2011). Influence of CYP3A5 and ABCB1 Gene Polymorphisms and Other Factors on Tacrolimus Dosing in Caucasian Liver and Kidney Transplant Patients. *International Journal of Molecular Medicine*. https://doi.org/10.3892/ijmm.2011.794

Qin, K., Qing, J., Wang, Q., & Li, Y. (2024). Epidemiological shifts in chronic kidney disease: a 30-year global and regional assessment. *BMC Public Health*, *24*(1). https://doi.org/10.1186/s12889-024-21065-9

Qu, L., Lu, Y., Ying, M., Li, B., Weng, C., Xie, Z., Liang, L., Lin, C., Yang, X., Feng, S., Wang, Y., Shen, X., Zhou, Q., Chen, Y., Chen, Z., Wu, J., Lin, W., Shen, Y., Qin, J., … Huang, H. (2017). Tacrolimus dose requirement

PROFESIONAL HEALTH JOURNAL
Volume 8, No. 1, December 2026 (Page. 166-178)
Available Online at https://www.ojsstikesbanyuwangi.com/index.php/PHJ/index
E-ISSN 2715-6249
DOI: https://doi.org/10.54832/phj.v8i1.1371

based on the CYP3A5 genotype in renal transplant patients. In *Oncotarget* (Vol. 8, Issue 46). www.impactjournals.com/oncotarget/

Rotarescu, C. A., Maruntelu, I., Rotarescu, I., Constantinescu, A. E., & Constantinescu, I. (2024a). Analysis of ABCB1 Gene Polymorphisms and Their Impact on Tacrolimus Blood Levels in Kidney Transplant Recipients. *International Journal of Molecular Sciences*, *25*(20). https://doi.org/10.3390/ijms252010999

Rotarescu, C. A., Maruntelu, I., Rotarescu, I., Constantinescu, A. E., & Constantinescu, I. (2024b). Analysis of ABCB1 Gene Polymorphisms and Their Impact on Tacrolimus Blood Levels in Kidney Transplant Recipients. *International Journal of Molecular Sciences*, *25*(20). https://doi.org/10.3390/ijms252010999

Seligson, N. D., Zhang, X., Zemanek, M., Johnson, J. A., VanGundy, Z., Wang, D., Phelps, M. A., Roddy, J., Hofmeister, C. C., Li, J., & Poi, M. (2024a). CYP3A5 Influences Oral Tacrolimus Pharmacokinetics and Timing of Acute Kidney Injury Following Allogeneic Hematopoietic Stem Cell Transplantation. *Frontiers in Pharmacology*, *14*. https://doi.org/10.3389/fphar.2023.1334440

Seligson, N. D., Zhang, X., Zemanek, M., Johnson, J. A., VanGundy, Z., Wang, D., Phelps, M. A., Roddy, J., Hofmeister, C. C., Li, J., & Poi, M. (2024b). CYP3A5 Influences Oral Tacrolimus Pharmacokinetics and Timing of Acute Kidney Injury Following Allogeneic Hematopoietic Stem Cell Transplantation. *Frontiers in Pharmacology*, *14*. https://doi.org/10.3389/fphar.2023.1334440

Shi, W., Tang, H., & Zhai, S. (2015). Effects of the CYP3A4*1B Genetic Polymorphism on the Pharmacokinetics of Tacrolimus in Adult Renal Transplant Recipients: A Meta-Analysis. *Plos One*, *10*(6), e0127995. https://doi.org/10.1371/journal.pone.0127995

Srinivas, L., Gracious, N., & Nair, R. R. (2021). Pharmacogenetics Based Dose Prediction Model for Initial Tacrolimus Dosing in Renal Transplant Recipients. *Frontiers in Pharmacology*, *12*(November), 1–9. https://doi.org/10.3389/fphar.2021.726784

Tanaka, R., Suzuki, Y., Watanabe, H., Fujioka, T., Hirata, K., Shin, T., Ando, T., Ono, H., Tatsuta, R., Mimata, H., Maruyama, T., & Itoh, H. (2021). Association of CYP3A5 polymorphisms and parathyroid hormone with blood level of tacrolimus in patients with end-stage renal disease. *Clinical and Translational Science*, *14*(5), 2034–2042. https://doi.org/10.1111/cts.13065

Van Gelder, T., Van Schaik, R. H., & Hesselink, D. A. (2014). Pharmacogenetics and immunosuppressive drugs in solid organ transplantation. *Nature Reviews Nephrology*, *10*(12), 725–731. https://doi.org/10.1038/nrneph.2014.172