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Review Article

A systematic review and meta-analysis recite the efficacy of Tacrolimus treatment in renal transplant patients in association with genetic variants of *CYP3A5* gene

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Abstract: Tacrolimus is an immunosuppressant with a narrow therapeutic index and pharmacokinetic variability. This variability may be attributed to genetic variants in gene *CYP3A5* associated with Tacrolimus metabolism. Studies focusing on genetic variants in the *CYP3A5* gene associated with Tacrolimus metabolism have been published, a meta-analysis of these published articles may provide a direction that can change the future research and clinical management of renal transplant patients. In this systematic review and meta-analysis, we have reviewed and analyzed the studies and clinical trials conducted to determine the association between genetic variants of *CYP3A5* and Tacrolimus metabolism from the PubMed database and clinical trials (www.clinicaltrials.gov). This meta-analysis also assessed the correlation of *CYP3A5* genotype (rs776746) with concentration/dose (C_o/D) of Tacrolimus in renal transplant patients. The 59 published articles on genetic association of the *CYP3A5* on Tacrolimus doses were reviewed for this systematic review. Meta-analysis showed that the Tacrolimus C_o/D ratio is significantly lower in the *CYP3A5* expressor group as compared with non-expressor in Asian, European as well as in mixed populations at any post-transplant period (P<0.0001). Our study further confirmed that the *CYP3A5* variant (rs776746) is clinically relevant for the dose determination of Tacrolimus. Variations in Tacrolimus C_o/D have been found to be significantly linked to the patient's *CYP3A5* genetic variant (rs776746). The addition of other genetic variants involved in the pharmacokinetic of Tacrolimus may determine efficient regimen for drug dose. Our meta-analysis confirmed that the *CYP3A5* genetic variant (rs776746) analysis is relevant in personalizing the Tacrolimus dose determination in renal transplant patients.

Keywords: Tacrolimus, renal transplantation, pharmacokinetic, *CYP3A5*, polymorphism, Egger's and Begg's tests

Introduction

Tacrolimus, a calcineurin antagonist, is an immunosuppressive agent used in solid organ transplantation. It improved graft survival rates and reduced the acute rejection chances in transplant recipients. Its use has been set back due to notable inter- and intra-variability in its pharmacokinetics [1]. This fluctuation can be reduced by modifying the dose and monitoring Tacrolimus blood levels. Despite this personalized strategy, the risk of graft rejection (8-15%) and patient survival remains static [2]. Although, Tacrolimus associated adverse drug events do precipitate even after its therapeutic blood-level.

CYP (Cytochrome P450) enzymes control around 75% of metabolic reactions [3]. The *CYP3A* (Cytochrome P450 Family 3 Subfamily A) gene family is a known phase I metabolism-related gene family. The *CYP3A* family has four major

genes, *CYP3A4*, *CYP3A5*, *CYP3A7*, and *CYP-3A43*. The *CYP3A4* and *CYP3A5* genes are involved in several drug-related reactions such as the deactivation and activation of drug compounds and excretion of drug compounds [4]. It has been reported that *CYP3A4* and *CYP3A5* genetic variants affect the treatment of diseases by altering the drug metabolism [5-7]. Several genetic variants have been identified in *CYP3A4* and *CYP3A5* genes. Genetic variants of these genes are responsible for diverse gene expressions, which are associated with variable drug response. A genetic variant of the *CYP3A5* gene is implicated in Tacrolimus drug response, which explains around 50% of the variability in Tacrolimus metabolism and clearance [8]. *CYP3A5* gene (rs776746) single nucleotide polymorphism (SNP) located in the 3rd intronic region at 6986 position results in the transition of A>G nucleotide creating a cryptic splice site, regulates the expression and metabolic activity of the *CYP3A5*, affecting Tacrolimus pharmacokinetics [9].

*CYP3A5*3* allele forms an altered protein by alternative splicing of the *CYP3A5* mRNA. *CYP3A5**3-altered protein activity is known to be associated with low Tacrolimus dose requirement [10]. The *CYP3A5*1* has been associated with an increase of *CYP3A5* activity and may allow renal function after renal transplantation [11]. Several studies have shown that *CYP3A5* expressors (*CYP3A5*1* homozygous or heterozygous allele) require 50-100% higher Tacrolimus doses compared to *CYP3A5* non-expressors (*CYP3A5*3*) homozygous variant alleles [12, 13].

GWAS (Genome-wide Association study) could be a promising way to discover new SNPs by associating it with disease development and drug pharmacokinetics. NGS (Next generation sequencing) serves as a powerful tool for the identification of novel pathogenic genotypes. As a result, these approaches are anticipated to aid in the identification of novel genetic alterations that can be applied to accurately determine the Tacrolimus pharmacokinetics. Furthermore, a patient's clinical status can influence Tacrolimus pharmacokinetics, therefore clinical considerations or lab parameters related to Tacrolimus pharmacokinetics are required for estimation of Tacrolimus trough concentration by dose ratio (C_0/D) [14].

The goal of this systematic review and meta-analysis is to provide a brief scenario on current pharmacogenomics studies of Tacrolimus metabolizers and their involvement in drug response variability among renal transplant patients. Pre-determine pharmacogenetics markers will be useful for designing personalized immunosuppressive regimens.

Tacrolimus pharmacology, pharmacokinetic and pharmacodynamic

Tacrolimus forms a complex by binding to immunophilin called FK-binding protein-12 (*FKBP12*). This complex of drug-immunophilin interacts with calcineurin and blocks phosphatase activity. As a consequence, translocation of nuclear factor of activated T-cells (*NF-AT*) to the nucleus is inhibited by decreasing the transcription of cytokine genes-Interleukin (*IL-2*), tumor necrosis factor-alpha (*TNF-α*), *IL-3, IL-4, CD40L* (Cluster of differentiation 40 ligand), granulocyte-macrophage colony-stimulating factor, interferon-gamma and T-lymphocyte [15].

Tacrolimus is useful for improving kidney graft survival and reduces the incidence of graft rejection in renal transplant patients. Tacrolimus is accompanied with a wide range of adverse effects, especially nephrotoxicity, neurotoxicity, and post-transplant diabetes mellitus (PTDM). Hypertension, Cardiomyopathy, alopecia, hyperkalemia, hypertriglyceridemia, hypomagnesemia, hirsutism, Hemolytic uremic syndrome (HUS), and gingival hyperplasia, lymphoproliferative disorders have also been documented [16]. Nephrotoxicity caused by Tacrolimus can be non-reversible and may lead to loss of kidney graft [17]. The *CYP3A5* nonexpressor recipient may show to have a higher risk of CNI nephrotoxicity as they are slow metabolizers and may require comparatively lower dose to maintain the allograft, while the expressor recipient may be more likely to have acute rejection due to their fast-metabolizing nature and thus they require higher dose for long-term graft survival [18].

Tacrolimus pharmacokinetic profile is diverse among patients. Mostly, plasma drug concentration peaks within 0.5-1 hr of oral administration. Bioavailability ranges from 4 to 89% due to first-pass metabolism and efflux mechanism. The half-life ($t_{1/2}$) is 3.5-40.5 hrs. 99% of the Tacrolimus binds to plasma protein (Alpha-1-

acid glycoprotein (AAG), Albumin). Its immunosuppressive effect can be achieved when drug reaches the lymphatic area. CL/F (drug apparent clearance) is 9.3 ± 0.96 L/hr, V_d/F (distribution volume) is 101 ± 2 L, and $t_{½β}$ (elimination half-life) is 7.5 hrs. After biotransformation in the liver, approx. 15 metabolites are produced with primary metabolite, 13-0-Demethyl-Tacrolimus having 10% of the property of its parent drug. The *CYP3A* family is the key player for metabolism. *CYP3A5*1* is a wild-type allele that has normal enzyme activity. It is important to note that *CYP3A5*1/1* and *CYP3A5*1/3* carriers are fast metabolizers of Tacrolimus, whilst **3/3* carriers are slow metabolizers. *CYP3A4*, *CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP2E1, CYP3A43,* and *CYP3A7* also contribute to Tacrolimus metabolism. Kidney clearance contributes for less than 1% while 99% of drug is eliminated through feces [19].

Tacrolimus undergoes extensive hepatic clearance, genetic variations in enzyme coding for its metabolism may account for some variability in its pharmacokinetics. Numerous research has been conducted in recent years to investigate the association between *CYP* genetic variants and Tacrolimus trough blood concentration (C_o), with the results compared and discussed in multiple publications. Despite the hurdles in determining the clinical effects of various genetic polymorphisms, these investigations concur that gene polymorphisms influence the distribution and metabolic activity of *CYP3A5*. 80% of the Caucasian population were found to be **3/*3* carriers which resulted in suppressed expression of the functional protein [9]. It is the most utilized pharmacogenetic predictive marker for determining the Tacrolimus dosage. Expression of *CYP3A4* is regulated by *CYP3A4*22* polymorphism (rs-35599367 C>T in intron 6), decreasing expression of enzyme and increasing Tacrolimus blood level [18]. Hence, a combined study of *CYP3A5* and *CYP3A4,* along with other metabolizing genes could be of great use to design a personalized Tacrolimus therapy.

Relevance of pharmacogenetics of metabolizers

Phases of metabolism

Different xenobiotics follow varied pathways of metabolism, either phase 1 and/or phase 2. Furthermore, certain medications are transformed directly into non-toxic metabolites, which are easily removed from the body because most of these inactive metabolites are aqueous. Metabolites are eliminated through urine (the most common route), bile, breathe, or perspiration, depending on their chemical makeup. While a few agents are transformed to intermediate metabolite (functional/toxic), which is further converted to aqueous form for its excretion. In comprehension, drug biotransformation converts the drug into a water-soluble form for its elimination. Because the enzymes involved in drug metabolism (primarily the *CYP450* family) are proteins, so they are susceptible to genetic variations [21].

75-80% of xenobiotics are metabolized by a large group of enzymes called *CYP450*s. 3 prominently involved sub-families of *CYP450* in drug metabolism are *CYP1, CYP2*, and *CYP3* [20].

Pharmacogenetic relevance of metabolizers

Metabolizers convert the drug into its metabolite (active/inactive), regulating drug efficacy, and elimination pathway. They are abundantly expressed in hepatocytes, regulating the metabolism of drugs.

Inter-individual heterogeneity in metabolizers functionality is a significant aspect to consider when explaining the drug actions. As many 'variable' factors like age, disorder, drug-drug interactions, or environmental substance interplay, the functionality of proteins might alter throughout the patient's life [22]. Furthermore, genetic polymorphism might affect drug metabolism accounting for drug response variations.

And so, metabolizer pharmacogenetics is a major field for clinical pharmacology to examine and integrate it into personalising therapy. Although pharmacogenetic researches have focused primarily on polymorphisms of metabolic enzymes in recent years, the scientific community has also clearly pointed out the concerns for the same. Furthermore, several SNPs have been discovered for *CYP3A5*, *CYP-3A4*, and *CYP3A7* genes. Many of them are now regarded as clinically relevant for the prediction of drug actions (**Table 1**).

Table 1. SNPs identified in *CYP3A5* gene [26]

Allele	rs ID	Nucleotide and amino acid change	Tacrolimus metabolism
*1	-	Wild type	Normal function
*2	rs28365083	27289G>T (T398N)	Limited/no data
*3A	rs776746	6986T>C (splicing defect)	Decreased
*3B	rs28383468	3705C>T (H30Y)	Decreased
*3D	rs56244447	7249T>G (L82R)	Decreased
*3F	rs28365085	31551T>C (I488T)	Decreased
*3K	rs41279854	29753T>C (F446S)	Decreased
*3L	rs72552791	3775A>G (Y53C)	Decreased
*4	rs56411402	14665T>C (Q200R)	Limited/no data
*5	rs55965422	12952A>G (splice defect)	Limited/no data
*6	rs10264272	14690C>T (splice defect)	Function loss/neutral
*7	rs41303343	27131_27132insA (346frameshift)	Function loss
*8	rs55817950	3699G>A (R28C)	Decreased
*9	rs28383479	19386C>T (A337T) 6986T>C	Decreased

Tacrolimus pharmacokinetic is strongly influenced by metabolic pathways. Metabolizers (*CYP3A*) may also affect the delivery of Tacrolimus to the graft at targeted concentration. An SNP in the *CYP3A5* gene (rs776746; 6986 A>G) causes a variation in *CYP3A5* protein enzymatic properties, which influences Tacrolimus therapeutic level. *CYP3A5**1 (wild-type) allele encodes for functional enzyme protein. Homozygous AA (**1/*1*) or heterozygous AG (**1/*3*) carriers are characterized as fast/intermediate metabolizers (expressors) due to enhanced metabolic activity while the homozygous GG (**3/*3*) genotype decreases the Tacrolimus metabolism and is thus referred as a non-expressor [19, 23].

The presence of the *CYP3A5* variants, ethnicity, and post-transplantation duration can all affect Tacrolimus pharmacokinetics. The studies found that patients with the *CYP3A5* (GG or **3/*3*) polymorphism, i.e., non-expressor, had prominently increased Tacrolimus C_o/D than patients with the expressors, at various post-transplant periods [17]. As there are no pooled trials with identical clinical variables, ethnicity, or post-transplantation length, these analyses have certain limitations.

To characterize an individualized therapy of Tacrolimus it is important to understand the significant diversity in its response among recipients. Other genes influencing Tacrolimus pharmacokinetic are *CYP3A4*, ATP-binding cassette sub-family B1 (*ABCB1*), Cytochrome P450 oxidoreductase (*POR*), Pregnane X receptor (*PXR*), UDP-glucuronosyltransferase-1 (*UGT1*), and *CYP3A7* [19]. Multiple gene variation analysis can derive a better predictive value for drug responsiveness as well as its dose requirement. Hence, covering the whole range of genes influencing Tacrolimus pharmacokinetics can broader the window of drug dose determination and patient care. These could be important biomarkers that should be included in future scientific research to establish their correlation for individualizing immunosuppressive regimens in transplanted recipients.

CYP3A5 (cytochrome P450 family 3 subfamily A member 5)

Tacrolimus is a major substrate for *CYP3A5* encoded by the *CYP3A5* gene on chromosome 7q21.1. It is a 52.5-kDa (Kilodaltons) protein expressed in the prostate and liver [24]. Approximately 50% of xenobiotics are metabolized by *CYP3A5,* including several macrolide antibiotics, immune modulators, antivirals, calcium channel blockers, statins, neoplastic agents, anti-depressants, hormones [22]. Out of several polymorphs of *CYP3A5*, **3/3* (rs776746, 6986 A>G) resulting in non-functional protein is the most extensively studied [19].

Different SNPs shown in **Table 1** [26] are identified for the *CYP3A5* gene found to be responsible for influencing Tacrolimus metabolism. *1 is

a naturally existing wild-type allele with optimum metabolic activity. It is distributed in 5-15% Caucasians, 73% African Americans, and 15-35% of 26 Asians [25].

Method

A PubMed search of the studies on *CYP3A5* genetic variants and its association with Tacrolimus was collected in between January 2010 to December 2022. Out of 125 publications, 59 were included in this review to accommodate the analysis points. Keywords used were 'Tacrolimus' 'renal transplant', '*CYP3A5*' 'Pharmacokinetics'. Clinical trials carried out for genetic association of *CYP3A5* on Tacrolimus were obtained from www.ClinicalTrial.gov. 29 different trials were found, 14 trials were excluded due to search criteria (drug-drug interactions, method development for Tacrolimus concentration estimation, comparison of different formulations on pharmacokinetics and dynamics of Tacrolimus). High throughput screening methods (HTS), GWAS were collected from the PubMed database with 7 outcomes. keywords- 'Tacrolimus' 'high throughput screening studies', 'Genome-wide association studies', 'renal transplant'. Additional keywords used for PubMed search: 'Tacrolimus' 'Single nucleotide polymorphism', 'metabolism', 'pharmacogenetics', 'pharmacogenomics', '*CYP3A5*' 'outcome', 'renal transplant'.

Association of CYP3A5 genotype with Tacrolimus pharmacokinetics

Tacrolimus is prominently metabolized by *CYP3A5* [25]. Any mutation in this enzyme will alter Tacrolimus metabolism as well as clearance and, ultimately its bioavailability. Different variants of this enzyme are responsible for alterations in its therapeutic concentration [26]. SNP in *CYP3A5* cause 40-50% variations in Tacrolimus biotransformation and elimination [29]. Transition of Adenine to Guanine (A>G) nucleotide at 6986 positions located at the 3rd intronic region will develop a defected splice site in mRNA generating abnormal stop codon, responsible for non-functional *CYP3A5* gene (rs776746) in hepatic tissues. Individual carrying one/several replica of *CYP3A5*1* (wild type) generates functional gene and wider expression in hepatic tissues. Those individuals are characterized as *CYP3A5* expressors/fast metabolizers. One carrying *CYP3A5**3 variant is classified as *CYP3A5* non-expressors/homozygous/slow metabolizers as they express a low amount of active *CYP3A5* enzymes [30].

Polymorphisms in the *CYP3A5* gene are observed commonly and are found to be correlating to Tacrolimus dose requirement and pharmacokinetics. A large number of studies (**Table 2**) from different populations concluded that homozygous carriers require low strength to maintain therapeutic concentration and attain elevated Tacrolimus C_o in blood. They are also associated with late attainment of C_o during the early period of post-transplantation.

As per the discussion and studies shown in **Table 2**, the genetic association of *CYP3A5* genotypes and haplotypes with Tacrolimus dosing can be postulated. These genotypes are one of the responsible factors contributing to drug response variabilities. Determination of these genetic variants and their actions on the pharmacokinetics of the drug will ameliorate the therapeutic drug actions, reduce the adverse outcomes associated with Tacrolimus, and minimize the over-exposure of the drug in patients [59]. It can also help clinicians to design an optimized immunosuppressive therapy to overcome the over-exposure of the drug.

High-throughput screening (HTS) studies

The use of automated equipment to analyze hundreds to millions of samples for biological activity is known as high throughput screening (HTS). HTS approaches help to filter many genes (e.g., GWAS) and are proved to be more appropriate for determining interlinked SNPs affecting Tacrolimus pharmacokinetics. This type of study should give the perception of the complexities of the biological interactions [60]. These studies found novel SNPs of interest that gene candidate techniques had previously missed. A genetics research method known as a genome-wide association study (GWAS) is used to correlate certain genetic variations to specific diseases. This process scans the genome of huge samples to identify genetic markers that can be used to predict disease. Once such genetic markers have been identified, they can be used to understand the genetic association with disease progression and to design more effective preventative and treatment methods [14].

Table 2. Association studies of *CYP3A5* variants and Tacrolimus pharmacokinetics in renal transplant patients

Genotype	rs ID	Nucleotide	Study outcomes	Effect on metabolism	References
*3/*3 (CC)	rs776746	6986T>C	Higher C_o	Decreased	[31]
			Higher C_o	Slower	[32]
			Lower CL/F	Reduced elimination	[33]
			Broad $AUC_{0\text{-}12\ h}$ with Proton pump inhibitors (PPIs)	It increased Tacrolimus blood level	[34]
			Elevated C_o at day 3 of post-transplant	Decreased elimination	[35]
			Increased Tacrolimus levels	Lower metabolic rate	[36]
			Lower doses were required	Slow metabolism	[37]
			Lower doses required, higher risk of organ rejection, and nephrotoxicity	Suppressed metabolism	[38]
			Lower mean dose	Slow metabolism	[39]
			Increased $AUC_{0\text{-}24\ h}$, C_{max} and C_{min} than expressors	Decreased metabolism	[40]
			Higher Tacrolimus blood level	Slow elimination	[40]
			Average C_o was beyond the therapeutic range	Slow excretion of Tacrolimus	[41]
			Greater C_o than expressors	Decreased metabolism	[42]
			Increased Tacrolimus exposure in blood and fewer doses are required	Suppressed metabolic and excretion rate	[43]
			Higher C_{min} than *1/*1	Depressed biotransformation	[44]
			Increased trough levels	Low metabolic rate	[45]
			Greater AUC, lower dose, C_{max} and clearance	Lower metabolic and elimination rate	[46]
*1/*1 (TT)	Wild-type (rs776746)		Higher doses, elevated clearance and C_{max}, lower $AUC_{0\text{-}12\ h}$	Increased clearance and metabolism	[46]
			Less C_o/D ratio compared to non-expressers	Elevated metabolism	[27]
			It decreased C_o at day 3 of post-transplant, higher doses requirement	Increased metabolism and clearance	[35]
			Depressed Tacrolimus levels, high Tacrolimus dose required	It increased the metabolic profile	[28]
			Risk of delayed graft functions (DGF)	It increased metabolic activity	[36]
			Doses required were higher	Elevated biotransformation	[38]
			43.3% reduced C_o than non-expressors	Excessive metabolism	[29]
			Two times increased CL/F ratio than *3/*3	Excessive elimination	[47]
			36.3% enhanced Tacrolimus dose needed. Reduced C_o/D	Excessive excretion and metabolism	[48]
			Lower bioavailability in single day dosing (QD) compared to non-expressers	Tacrolimus C_o was below the therapeutic window due to rapid clearance of the drug	[49]
			Higher doses were needed for desired C_{max}, dose-adjusted C_o, and $AUC_{0\text{-}12\ h}$	Higher metabolism	[50]
			Higher doses are required	Rapid elimination	[51]
			The elevated dose needed, 33.9% advanced C_{max}	Fast metabolism	[52]
			Lower C_o than the therapeutic range	Faster excretion	[41]
			Narrow $AUC_{0\text{-}24\ h}$ than homozygotes	A rapid removal of drugs from the body	[53]
			Increased excretion of a drug by 1.88 factor	Rapid removal	[54]
			More Tacrolimus dose required in case of once a daily dosing	Eliminates quickly	[55]

*1/*3 (TC)	rs776746	1.5 times increased CL/F ratio than *3/*3	Rapid elimination	[47]
		Increased CL/F or lower Km	Easy excretion	[56]
		1.74-factor elevation in Tacrolimus elimination	Elimination is enhanced	[54]
		66% increased elimination of once-daily prolonged-release Tacrolimus	Rapid clearance	[57]
(TT, CT, CC)	rs15524	C_0/D was more in TT genotype than CC and CT	Increased elimination in TT carriers than CC and CT carriers	[58]

66 outcomes were obtained for HTS studies on pharmacogenomics of Tacrolimus from year 1999-2022. 7 studies were included in the review (**Table 3**).

Clinical trials on pharmacogenetic study on Tacrolimus

29 clinical trials were reported from clinicaltrials.gov worldwide to date, which intends to study the association of *CYP3A5* genotype with Tacrolimus dose and concentration. Keywords used for the search were Renal transplantation, "Tacrolimus" and "*CYP3A5*" Out of 29 trials, 14 clinical trials were removed due to unmet search criteria (drug-drug interactions, method development for Tacrolimus concentration estimation, comparison of different formulations on pharmacokinetics and pharmacodynamics of Tacrolimus).

Clinical trials were mainly focused on the determination of the initial dosing strategy based on genotyping of *CYP3A5* genetic variants. The primary objective of the 3 studies (NCT00935298, NCT04825262, and NCT00552201) belonging from China, Singapore, and France, respectively, was to design an optimized initial dosing strategy of Tacrolimus which is the utmost step to avoid Tacrolimus-related adverse outcomes. As per the studies, genotyping of *CYP3A5* will allow physicians to know the patient's genotype and their dose requirement. Prior genotyping will surpass the burden of drugs as well as the economy, improving graft and patient survival rates. Moreover, these findings might also help to potentiate Tacrolimus efficacy, safety, and rapid attainment of its therapeutic concentration in blood.

Five trials intended to study the impact of multigene on Tacrolimus pharmacokinetics. A study from the University of IOWA, US (NCT01288521) evaluated the effect of haplotypes formed from 3 SNPs of *ABCB1* gene (C1236T, G2677T, C3435T) to anticipate the possibility of drug-drug interaction (DDI) between Tacrolimus and ketoconazole. *CYP3A5* non-expressors were divided based on ABCB1 haplotypes (CGC vs. TTT) with and without ketoconazole treatment. These findings can help to identify drug-drug interactions (DDIs) predictive genomic markers and help physicians to modify drug prescribing patterns. The influence of *CYP3A5*, 3A4, and p-gp on Tacrolimus and cyclosporin pharmacokinetics was studied among Egyptian renal transplant patients (NCT03830255). Prevalence of these variants with patients' therapeutic outcomes at the post-Tx (Transplantation) period was also noted. A cumulative study (NCT02707822) on the association of multigene including *CYP3A5*, *3A4, ABCB1*, and *POR* on Tacrolimus ADME (Absorption, Distribution, Metabolism, and Excretion) properties was carried out on Taiwan renal recipients. They also analyzed the association of other factors such as absolute protein and bilirubin, *AST* (Aspartate aminotransferase), *ALT* (Alanine aminotransferase), sex, age, and DDI with Tacrolimus dose and concentration. A study (NCT03465410) from Spain developed a pharmacokinetic model for identifying *CYP3A4*22* and *CYP3A5*3* SNPs and hematocrit as responsible variables for Tacrolimus inter-variability outcomes. The study planned to implement a pharmacogenomics approach to de-novo patients, which will help to tailor the personalized treatment for each patient based on the targeted C_0 values and the patients with *CYP3A4*22* and *CYP3A5*3* SNPs. A pharmacokinetic study (NCT00411944) from Belgium studied the influence of multi-gene including *CYP3A5*1*, *CYP3A4*1B, MDR1* G2677T/A and C3435T SNPs on Tacrolimus availability to understand the interplay between *CYP3A5*, *CYP3A4* and *MDR1*, Tacrolimus-associated ADRs (Adverse drug reactions).

Table 3. High throughput screening (HTS) approach for determining the influence of *CYP3A5* SNPs in Tacrolimus pharmacokinetics

Sr. no	No. of patients	Outcomes	Site	References
1.	1446	Prominent SNPs were detected on chromosome 7 according to the Manhattan plot. rs35599367 (P=2.21e17), was known to decrease functional variation among *CYP3A4* gene (*CYP3A4**22). In our population, the minor allele frequency (MAF) for the *CYP3A4**22 variation was 0.054. 11 more SNPs were found to be important on chromosome 7.	Deterioration of Kidney Allograft Function (DeKAF) genomics study	[61]
2.	1979	Out of 17 SNPs, rs776746, rs10264272, and rs41303343 were found to be significant for influencing pharmacokinetic of Tacrolimus.		[62]
3.	1133	GWAS and rare variant analysis was conducted for frequent variants only in cohort 1 (n=346). *CYP3A5**3 (rs776746) was found to be statistically relevant for influence on Tacrolimus pharmacokinetics. Its *p*-value at 7-day, 1-Mon, and 3-Mon were 4.8×10^{-16}, 9.6×10^{-31}, and 1.6×10^{-37} respectively.	Republic Korea	[63]
4.	853	30 variations within 12 genes were included in the GWAS panel. Results concluded that most of the patients were carriers of 3/4 Diplotypes while 17.4% had 5/>5 Diplotypes.		[64]
5.	455	25 SNPs showed association with Tacrolimus levels ($P<10^5$), with 8 of these being significant as GWAS ($P<1.025*10^{-7}$). SNPs found to be correlated were having MAF of 0.07 to 0.35 out of 25, 21 were located on chromosome 7, with 14 of them mapped to pharmacogenes (*CYP3A4*, *CYP3A5*, CYP3A7, and CYP3A7-CYP3AP1) as per GWAS Manhattan plot. Significant SNP was rs776746 ($P=9.71*10^{-13}$).	7 centres of Canada	[65]
6.	357	28 of the variations had *p*-values of $1*10^5$, and five of them were significant at the genome-wide level ($P<5*10^8$). The pseudogene CYP3AP2 (rs17161880, $P=9.29*10^{14}$, and rs34880695, $P=1.03*10^{12}$) has the most significant variants (rs17161880, $P=149.26*10^{14}$, and rs34880695, $P=141.03*10^{12}$). *CYP3A5**3 was the most significant SNP.	DeKAF study	[66]
7.	229	PSL1&2 strategies were defined for diversity in dose and follow-up. All the operations were statistically significant (P<0.001). *CYP3A5* and 3A4 were found to be associated at all the time points in the model. In PSL2 model, 7 SNPs of *CYP3A4*, *CYP3A5*, CYP3A7, *CYP3A4*3 and ATP binding cassette C8 (ABCC8) showed influence on C_o/D.	Tactique cohort study, France	[67]

A pilot study (NCT01655563) was conducted on Canadian pediatric renal, cardiac, and liver transplant recipients to establish a genetic association with rapid Tacrolimus concentration achievement and age and genotype. The study concluded that dose decided as per age and genotyping rapidly and precisely attained desired Tacrolimus concentration compared to the conventional method. Additionally, they also found age- and genotyping-guided dosing regimens helped to minimize the period of recovery (examined by the ability of kidneys to eliminate creatinine from blood) and ADRs [57].

A prospective study (NCT03173820) from Thailand studied the association of *CYP3A5* in both the induction and maintenance phase of Tacrolimus to know whether the implementation of genotype-based dosing can allow attaining therapeutic concentration rapidly in both the phases. The study will also assess the effect of *CYP3A5* on post-Tx outcomes. A similar kind of study (NCT03020589) was conducted at California, US studied the direct correlation of *CYP3A5* genotype with Tacrolimus C_o and post-Tx outcomes.

Influence of *CYP3A5* on Tacrolimus level and rejection rate at early post-Tx period was studied among Thai renal recipients (NCT02377791). As per the trial, identification of *CYP3A5* variants can allow for ease in reaching initial Tacrolimus dose, concentration and improves Tacrolimus outcome. A comparative study of correlation of *CYP3A5* genotype on Tacrolimus OD (Once a day) and BID (Twice a day) (NCT01884480) was performed on Canadian kidney transplant patients. They found the patients who required higher doses after conversion from BID to OD were *CYP3A5* non-expressors. This study might lead to better dosing strategy for OD of Tacrolimus. A study (NCT02356146) from Thailand found a significant correlation was found between *CYP3A5*

gene, Tacrolimus C_o, and dose. A study from Belgium (NCT02311010) with an objective to optimize the Tacrolimus therapy in combination with mycophenolic acid and corticosteroids on basis of *CYP3A5* genotype of an individual. As per the study Tacrolimus C_o level can be an indicator to identify if the drug has attained its therapeutic level.

Meta-analysis

Literature survey

Publications were searched from PubMed database. Keywords used for the survey were *CYP3A5* polymorphism, renal transplantation, kidney transplantation, Tacrolimus (FK506/Prograf), and graft rejection. There were no language restrictions in the search, and only studies based on humans were included. Cross references were investigated further to broaden the scope of the relevant article search. Two researchers worked independently on the database search.

Data selection and eligibility criteria

According to the eligibility criteria, the selected papers were checked for data relevancy. Two independent researchers examined the articles, and disagreements were settled through conversation. The first author's name, year of publication, total number of cases/controls, drug C_o/D, and *CYP3A5* genotyping (*CYP3A5*1/*1*, *CYP3A5*1/*3*, and *CYP3A5*3/*3*) among renal transplant patients are taken from each study. C_o/D was collected for week-1, months 1, 3, 6, and 12.

Studies included in the review were: a) research papers with systematic data, b) renal transplant recipient studies, and c) Tacrolimus C_o/D correlated with *CYP3A5* genotype. Studies were excluded on basis of inappropriate data, reviews, and patients with other transplant cases.

Statistical analysis

Tacrolimus pharmacokinetics studies were plotted on forest plot using MedCalc (version 20.007) software. Association of *CYP3A5* with Tacrolimus C_o/D was calculated using standard mean difference (SMD). As per the heterogeneity test, the fixed/random effect model was decided to determine the size of the study. In the case of P≤0.05 (Cochran's Q-test), random model was selected with an inconsistency coefficient [I^2 (95% uncertainty intervals)]. Moreover, the variance between the studies was determined by Tau^2 random model. Publication bias was detected by Egger's test and Begg's test. P≤0.05 was considered a statistically significant bias.

Results

Publication selection

The pattern of study selection related to impact of *CYP3A5* variants with Tacrolimus C_o/D is represented in figure (**Figure 1**). Electronic datasets were explored using above keywords, and 13,812 publications were obtained. Each article was inserted in Mendeley desktop for title and abstract screening. The studies involved in meta-analysis include the studies of *CYP3A5* gene polymorphism and Tacrolimus pharmacokinetics (n=18). Studies involved in the review were from 2010-2022.

Out of 13,812 publications, 13,794 studies were excluded due to undefined time-points for association of Tacrolimus C_o/Dwith *CYP3A5*1/*1, *1/*3, *3/*3*, association of Tacrolimus C_o/D with multiple genes, graphical presentation of Tacrolimus C_o/D vs. *CYP3A5* expressors and non-expressors, comparative metabolic studies of Tacrolimus and other immunosuppressive agents, and impact of other drugs on Tacrolimus pharmacokinetics. The goal of the present meta-analysis is to correlate the *CYP3A5* genotype with Tacrolimus metabolism (n=18). Publications were selected from 2010-2022 PubMed.

Tacrolimus C_o/D studies

Out of 18 studies, 2 studies belonged to Spain, 2 from China, 2 from Korea, 3 from India, 2 from France, and single studies from The Netherlands, Japan, Thailand, Argentina, and Poland, and 2 from Italy. 6 studies belonged to Caucasian population and 12 studies included Asian population. 3 cohorts included a mixed population-Caucasian (76-94%), Asian (2-10%), and African (4-14%). Ethnicity of one study group was unknown. Each study was cohort and was conducted at hospital/institute premises. N1 and N2 represents the *CYP3A5* nonex-

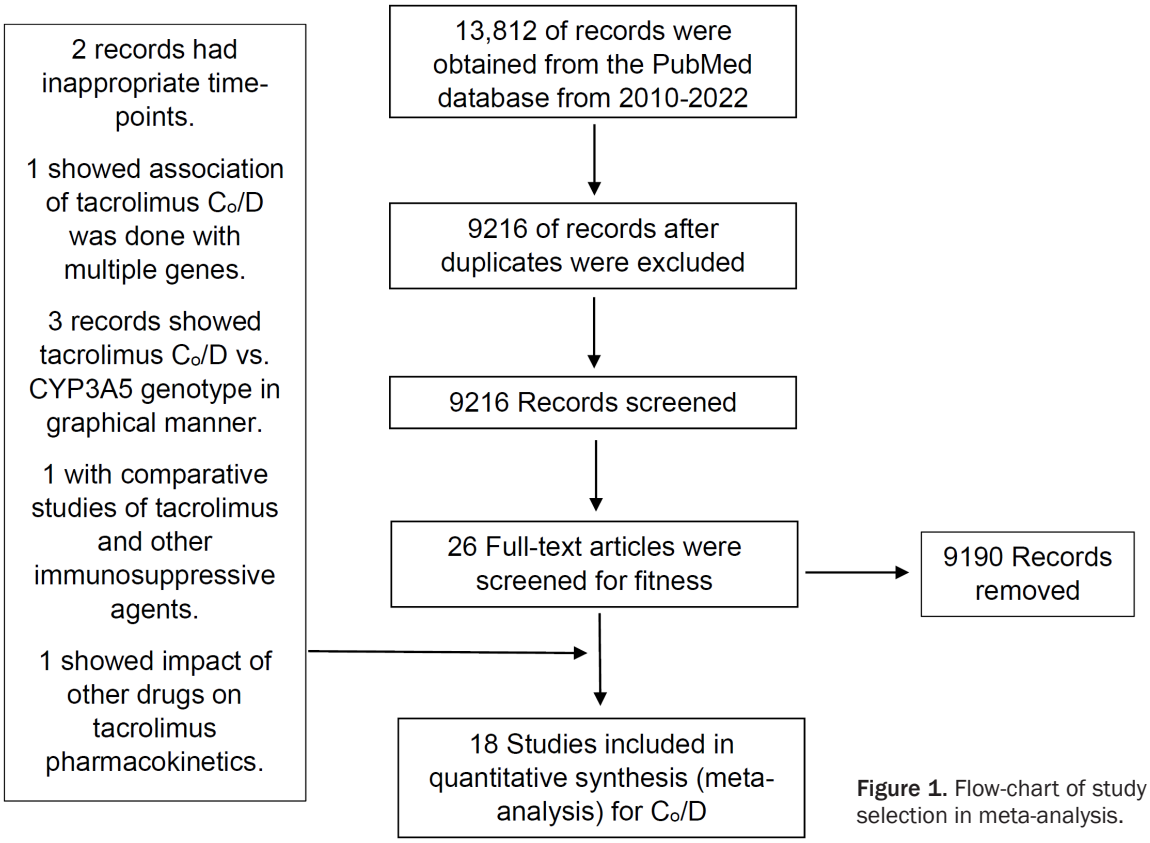


Figure 1. Flow-chart of study selection in meta-analysis.

pressors (*CYP3A5*3/*3*) and *CYP3A5* expressors (*CYP3A5*1/*1, *1/*3*) respectively.

Tacrolimus C_o/D studies in Asian group

There were 12 studies consisting of the Asian population (n=12). Time points considered for Asian population Tacrolimus C_o/D were on week 1, and months 1, 3, 6, and 12. There was no significant variation in the mean differences of Tacrolimus C_o/D among Asian groups, according to the findings. At all-time points, a considerably low SMD (-1.54, -1.87, -1.012, -0.928, and -0.900) revealed a significantly lowered collective C_o/D ratio in Asian *CYP3A5* expressors (**Figure 2**). Percentage of *CYP3A5* expressors and non-expressors found among Asian population was found to be 63.94% and 36.71% respectively. The publication bias was tested by Egger's rank correlation and Begg's regression tests. Begg's test was insignificant at all time points, whereas Egger's test was also insignificant at all time points except at 12 months. Therefore, our study does not have publication bias in studied time point (**Figure 2**).

Tacrolimus C_o/D studies in Caucasian group

There were 8 studies consisting of the Caucasian population (n=8). Time points considered for Caucasian population Tacrolimus C_o/D were on week 1, and months 1, 3, 6, and 12. There was no significant variation in the mean differences of Tacrolimus C_o/Din Caucasian groups, according to the findings. At all-time points, a considerably low SMD (-0.09, -0.57, -0.501, -0.245, and -1.94) revealed a significantly lowered collective C_o/D among Asian *CYP3A5* expressors (**Figure 2**). Percentage of *CYP3A5* expressors and non-expressors found among Caucasian population was found to be 81.44% and 18.55% respectively. No publication bias was observed while analyzing Egger's and Begg's tests (**Figure 2**).

Discussion

CYP3A5 is an isoenzyme belonging to the cytochrome P450 monooxygenase family abundantly distributed in hepatic tissues and converts Tacrolimus to its metabolites via oxidative and reductive pathways. Genetic variants of

Week 1

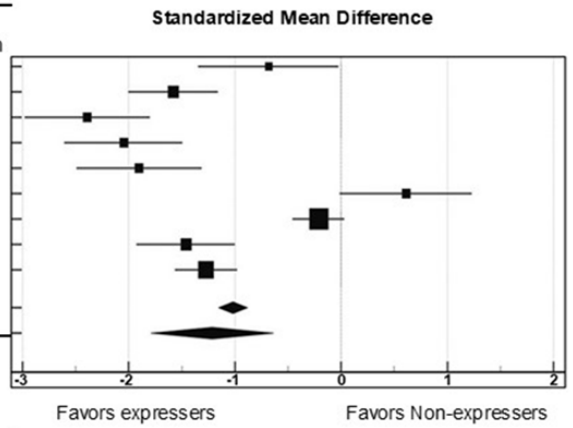
Study	N1	N2	Total	SMD	SE	95% CI	t	P	Weight (%) Fixed	Weight (%) Random
(Gervasini et al., 2012) [20]	10	93	103	-0.68	0.334	-1.345 to -0.0213			4.39	10.49
(Zhang et al., 2005) [79]	48	70	118	-1.58	0.213	-2.003 to -1.160			10.81	11.41
(Chandel et al., 2009) [10]	32	47	79	-2.39	0.296	-2.980 to -1.801			5.58	10.8
(Chandel et al., 2009) [10]	32	47	79	-2.05	0.279	-2.605 to -1.492			6.27	10.93
(Chen et al., 2009) [12]	38	29	67	-1.9	0.294	-2.488 to -1.314			5.66	10.82
(Kurzawski et al., 2014) [35]	127	11	138	0.611	0.315	-0.0118 to 1.233			4.94	10.65
(Tavira et al., 2011) [68]	80	320	400	-0.21	0.125	-0.458 to 0.0337			31.31	11.87
(Srinivas et al., 2021) [61]	42	50	92	-1.46	0.234	-1.926 to -0.997			8.94	11.27
(Phupradit et al., 2018) [53]	106	110	216	-1.27	0.149	-1.566 to -0.979			22.09	11.77
Total (fixed effects)	515	777	1292	-1.02	0.0699	-1.156 to -0.881	-14.561	<0.001	100	100
Total (random effects)	515	777	1292	-1.21	0.294	-1.791 to -0.638	-4.135	<0.001	100	100

N1=Non-expresser, N2=Expresser, SMD= Standard mean difference, SE=Standard error

Heterogeneity: chi square=127.00, DF=8, I^2=93.70% (90.13 to 95.98), P<0.0001

Egger's test: p=0.26,

Begg's test: Kendall's tau=-0.22, p=0.40,



1 Month

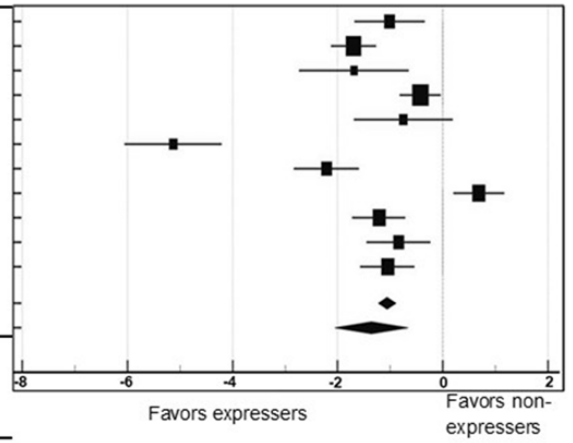
Study	N1	N2	Total	SMD	SE	95% CI	t	P	Weight (%) Fixed	Weight (%) Random
(Gervasini et al., 2012) [24]	10	93	103	-1.01	0.338	-1.679 to -0.339			6.44	9.08
(Zhang et al., 2005) [83]	48	70	118	-1.69	0.216	-2.123 to -1.266			15.7	9.55
(Turolo et al., 2010) [76]	6	20	26	-1.69	0.508	-2.739 to -0.642			2.85	8.22
(Quteineh et al., 2008) [56]	34	102	136	-0.43	0.199	-0.823 to -0.0375			18.63	9.6
(Alessio Provenzani, 2011) [1]	5	45	50	-0.75	0.47	-1.693 to 0.197			3.33	8.43
(Chandel et al., 2009) [10]	32	47	79	-5.13	0.467	-6.057 to -4.198			3.37	8.44
(Chandel et al., 2009) [10]	38	29	67	-2.21	0.31	-2.829 to -1.592			7.67	9.2
(Kurzawski et al., 2014) [35]	213	18	231	0.686	0.247	0.200 to 1.172			12.07	9.45
(Singh et al., 2009) [59]	31	42	73	-1.22	0.255	-1.723 to -0.706			11.31	9.42
(Thervet et al., 2003) [70]	13	67	80	-0.84	0.307	-1.454 to -0.230			7.78	9.21
(Cho et al., 2012) [14]	26	44	70	-1.05	0.26	-1.569 to -0.531			10.85	9.4
Total (fixed effects)	456	577	1033	-1.06	0.0857	-1.229 to -0.892	-12.371	<0.001	100	100
Total (random effects)	456	577	1033	-1.36	0.353	-2.052 to -0.666	-3.846	<0.001	100	100

N1=Non-expresser, N2=Expresser, SMD= Standard mean difference, SE=Standard error

Heterogeneity: chi square=161.31, DF=10, I^2=93.80% (90.75 to 95.85), P<0.0001

Egger's test: p=0.16,

Begg's test: Kendall's tau=-0.24, p=0.31,



3 Month

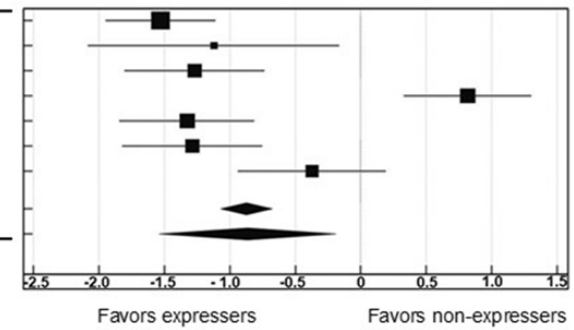
Study	N1	N2	Total	SMD	SE	95% CI	t	P	Weight (%) Fixed	Weight (%) Random
(Zhang et al., 2005) [81]	48	70	118	-1.53	0.211	-1.945 to -1.109			22.78	15.03
(Alessio Provenzani, 2011) [1]	5	45	50	-1.12	0.477	-2.082 to -0.162			4.45	12.19
(Chen et al., 2009) [12]	38	29	67	-1.27	0.267	-1.801 to -0.734			14.21	14.53
(Kurzawski et al., 2014) [37]	217	18	235	0.818	0.247	0.330 to 1.305			16.58	14.72
(Singh et al., 2009) [61]	31	42	73	-1.33	0.259	-1.843 to -0.811			15.16	14.62
(Cho et al., 2012) [14]	26	44	70	-1.29	0.268	-1.819 to -0.751			14.16	14.53
(Hesselink et al., 2003) [28]	17	45	62	-0.37	0.283	-0.939 to 0.193			12.66	14.38
Total (fixed effects)	382	293	675	-0.87	0.101	-1.071 to -0.675	-8.664	<0.001	100	100
Total (random effects)	382	293	675	-0.87	0.344	-1.539 to -0.190	-2.515	0.012	100	100

N1=Non-expresser, N2=Expresser, SMD= Standard mean difference, SE=Standard error

Heterogeneity: chi square=67.34, DF=6, I^2=91.09% (84.22 to 94.97), P<0.0001

Egger's test: p=0.92,

Begg's test: Kendall's tau=0.33, p=0.30,



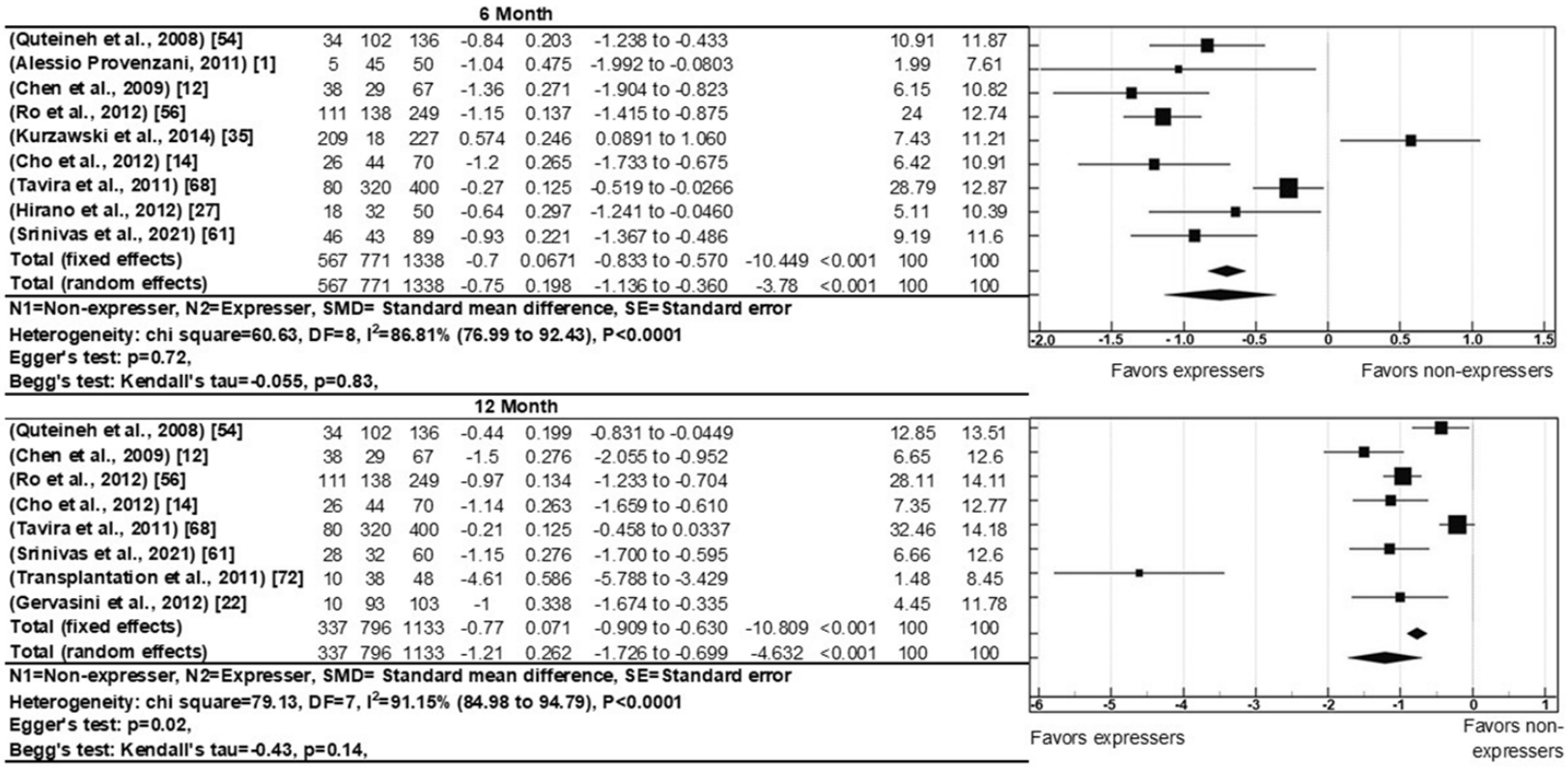


Figure 2. Association of tacrolimus C_o/D ratio with CYP3A5 variants at Week 1, Month 1, 3, 6, and 12 of post-transplant.

CYP3A5 gene results in variations of its metabolic functions and are classified as *CYP3A5* expressors (*CYP3A5*1/*1, *1/*3*) and *CYP3A5* nonexpressors (*CYP3A5*3/*3*) [68]. The *CYP3A5*3* allele results due to transition of A>G at 6986 position creates a cryptic splice site, forming a non-functional protein, which has found to be an important driver in Tacrolimus metabolism [69]. Diversity in attaining Tacrolimus blood concentration during the initial post-transplant period is dependent on *CYP3A5* genetic makeup. These variations are also an attributing factor for graft rejection or Tacrolimus-associated toxicities. As per the correlation of *CYP3A5* genotype and Tacrolimus pharmacokinetics, *CYP3A5*1/*1* and **1/*3* carriers require increased doses to attain targeted concentration to prevent graft rejection while *CYP3A5*3/*3* is recommended with lower doses to avoid adverse drug events [12, 18].

In the present meta-analysis, the association of *CYP3A5* expresser and non-expresser with Tacrolimus C_o/D has been shown. Out of 18 studies considered, the prevalence of *CYP3A5* expressors in Asian population was found to be 63.94%, while in Caucasian population, it showed 81.44% [70, 74, 78]. *CYP3A5* nonexpressors were prevalent among Asians compared to Caucasians due to lower expression of *CYP3A5*3/*3* genotype [73, 77]. The primary conclusion from meta-analysis was a significant decrement in Tacrolimus C_o/D ratio in case of *CYP3A5* expressors due to increased metabolic rate than non-expressors. Our study depicts the stringent dose monitoring in *CYP3A5* expressors to prevent renal graft rejection.

Maintenance of an optimal C_o with changeable Tacrolimus dosages by Therapeutic drug monitoring (TDM) has been a prominent difficulty in transplantation throughout the starting phase. The first Tacrolimus dosage is determined by body weight and then changed as per the C_o. Various studies have published the data on association of *CYP3A5* genotype with Tacrolimus response [37, 71, 76, 82]. Instead of a body weight, consideration of the *CYP3A5* genotypes prior to initiating Tacrolimus therapy may aid in obtaining an early target Tacrolimus level. This method is thought to reduce the incidence of rejection and drug-induced events, as well as provide clinical advantages at short- and long-term post-transplantation [79, 83].

The strength of our meta-analysis states the broad literature survey using selection criteria. Moreover, we included relative studies showing correlation of *CYP3A5* with Tacrolimus pharmacokinetics from 2010 to 2022. We have some shortcomings, firstly, we have only included the genetic association of *CYP3A5* with Tacrolimus pharmacokinetic [80, 81]. Secondly, genetic association with the onset and progression of drug-induced adverse events such as nephrotoxicity, neurotoxicity, and acute graft rejection were not included in the review. Studies and data regarding graft rejection and multiple genetic effects on Tacrolimus were not included. We divided our data as per the Asian and Caucasian groups to identify the genetic association of *CYP3A5* on Tacrolimus concentration in both populations. Ethnicity is thought to be one of the important factors for genetic distribution. The frequency of the *CYP3A5* functional (A) allele in kidney recipients has been documented in various ethnicities. The *CYP3A5* expressors were prevalent among Africans (47%), Asians (22-28%), and Europeans (8-11%), as per our meta-analysis [72, 75]. The clinical studies should be designed which covers the genetic polymorphism affecting all aspects of pharmacokinetics and ethnicity using advance sequencing methods such as whole exome sequencing and GWAS studies in future which may provide a better prediction of Tacrolimus trough concentration. An Artificial intelligence model can also be developed which might help in designing better personalized Tacrolimus therapy based on multiple gene variants and ethnic variability.

Conclusion

In conclusion, there are a few gene variations known as drugmetabolizers. Variations in Tacrolimus C_o/D have been found to be significantly linked to patient's genetic makeup. Although there are considerations that promote exploration of the influence of *CYP3A5* isoenzyme, where *CYP3A5* polymorphisms are of special importance in understanding Tacrolimus variabilities in pharmacokinetics and pharmacodynamics. As a result, it's likely that the pharmacogenomis approach of studying polymorphisms of metabolizers may help in predicting drug concentrations in blood and its response which may help in tailoring personalized treatment and preventing renal graft rejection.

Understanding of distribution of *CYP3A5* in various ethnic populations among kidney recipients may aid clinicians in achieving targeted Tacrolimus dose.

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Disclosure of conflict of interest

None.

Abbreviations

CYP, Cytochrome P450; *CYP3A,* Cytochrome P450 Family 3 Subfamily; SNP, Single Nucleotide Polymorphism; GWAS, Genome-Wide Association Studies; NGS, Next generation sequencing; C_o/D, Trough concentration/Dose ratio; HTS, High-throughput screening; *FKBP12*, FK-binding protein-12; *NF-AT*, Nuclear factor of activated T-cells; *IL-2*, Interleukin-2; *TNF-α*, Tumour necrosis factor-alpha; CD40L, Cluster of differentiation 40 ligand; PTDM, Post-transplant diabetes mellitus; HUS, Hemolytic uremic syndrome; $t_{1/2}$, Half-life; AAG, Alpha-1-acid glycoprotein; CL/F, Drug apparent clearance; V_d/F, Distribution volume; $t_{½β}$, Elimination half-life; C_o, Trough blood Concentration; *ABCB1,* ATP-binding cassette sub-family B1; *POR,* Cytochrome P450 oxidoreductase; *PXR,* Pregnane X receptor; *UGT1*, UDP-glucuronosyltransferase-1; kDa, Kilodaltons; DDI, Drug-drug interaction; Tx, Transplantation; ADME, Absorption, Distribution, Metabolism and Excretion; *AST*, Aspartate aminotransferase; *ALT*, Alanine aminotransferase; ADRs, Adverse drug reactions; OD, Once a day; BID, Twice a day; FK506, Tacrolimus; SMD, Standard Mean Deviation; TDM, Therapeutic Drug Monitoring.

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