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Original article

# Recipient ABCB1, donor and recipient CYP3A5 genotypes influence tacrolimus pharmacokinetics in liver transplant cases

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ABSTRACT

*Background:* Effective immunosuppression through optimization of trough levels tacrolimus reduces post-transplant mortality rate in liver transplant cases.
*Methods:* Meta-analysis was carried out to evaluate how donor/recipient CYP3A5 (n = 678) and recipient ABCB1 (n = 318) genotypes influence tacrolimus pharmacokinetics till one-month of transplantation.
*Results:* The donor CYP3A5*3/*3 genotype exhibited higher concentration/dose (C/D) ratio of tacrolimus in week 1 (mean difference: 65.04, 95% CI: 15.30–114.79 ng/ml/mg/kg), week 2 (mean difference: 21.7, 95% CI: 12.6–30.9 ng/ml/mg/kg) and week 4 (mean difference: 43.28, 95% CI: 17.09 – 69.49 ng/ml/mg/kg) compared to *1/*1 and *1/*3 genotypes. The recipient CYP3A5 *3/*3 genotype did not showed significant difference in tacrolimus C/D ratio in week 1 compared to other two genotypes. However, week 2 (mean difference: 44.16, 95% CI: 3.68–84.65 ng/ml/mg/kg) and week 4 (mean difference: 43.74, 95% CI: 12.50–75.00 ng/ml/mg/kg) availability was higher in *3/*3 mutant recipients. However, the recipient ABCB1 3435 C > T polymorphism has no significant influence on tacrolimus pharmacokinetics till one month of transplant.
*Conclusions:* The donor and recipient CYP3A5*3 polymorphism influences tacrolimus pharmacokinetics in the first month post-transplantation, whereas the association with recipient ABCB1 3435 C > T is inconclusive.
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## Introduction

Liver transplantation is a life saving therapeutic option in end stage liver disease; and it is also effective in curing certain metabolic disorders, hepatocellular carcinoma and hepatoblastoma. In the last three decades, the survival rate following liver transplantation has significantly improved [1]. Tacrolimus is a calcineurin inhibitor used at a dose of 0.1 to 0.15 mg/kg per day to maintain immunosuppression following liver transplantation. Tacrolimus is being preferred over cyclosporine due to its high potency, minimized cardiovascular adverse effects, less acute cellular rejection [2]. The survival rate after liver transplantation was shown to reduce in subjects whose trough levels were less than 5 ng/ml [3]. The optimal trough levels were expected to be between 5–10 ng/ml for a better survival [3].

The P-Glycoprotein encoded by the ATP Binding Cassette Subfamily B Member 1 (ABCB1) gene influences the intestinal absorption and transport of tacrolimus across the membranes within the hepatocytes [4]. Tacrolimus is metabolized by CYP3A5 predominantly and to a lesser extent by CYP3A4 [5]. Several studies explored ABCB1, CYP3A4, CYP3A5 genetic variants as possible pharmacogenetic determinants of tacrolimus concentration/dose (C/D) ratio and clearance [6–11].

The tacrolimus concentration/dose (C/D) ratio was reported to have an inverse association with the intestinal mRNA level of ABCB1 [6]. High levels of ABCB1 were shown to increase the risk for acute cellular rejection before day 10 of transplant and with poor survival during the first postoperative year [7]. The tacrolimus C/D ratios were reported to be lower in recipients harboring ABCB1 3435 CC-genotype while higher C/D ratios were observed when donor exhibited CYP3A5*3/*3-genotype [8]. Minimum drug levels

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were not attained in the early days after transplant in the presence of the CYP3A5*3 allele in both donor and recipient [9]. The ABCB1 3435C > T polymorphism was reported to influence tacrolimus C/D ratio in the first days after liver transplantation while no significant difference was shown after one to three months post-transplant [10]. Recipient CYP3A5 *1/*1-genotype was reported to contribute towards lower trough and C/D ratio than CYP3A5*3/*3 genotype in the first-week post-transplant while donor CYP3A5 genotypes have shown to influence the trough and C/D after three months of transplant [11].

The existing literature thus highlights that time after transplantation, recipient and donor genotypes as the possible pharmacogenetic determinants of tacrolimus C/D ratio. In view of inconsistencies in the existing literature about the possible role of these variants, we have aimed to conduct a meta-analysis to evaluate whether the recipient ABCB1 and donor CYP3A5 variants influence the tacrolimus C/D ratio in week 1, week 2 and week 4 post-liver transplant.

## Materials and methods

### *Data collection*

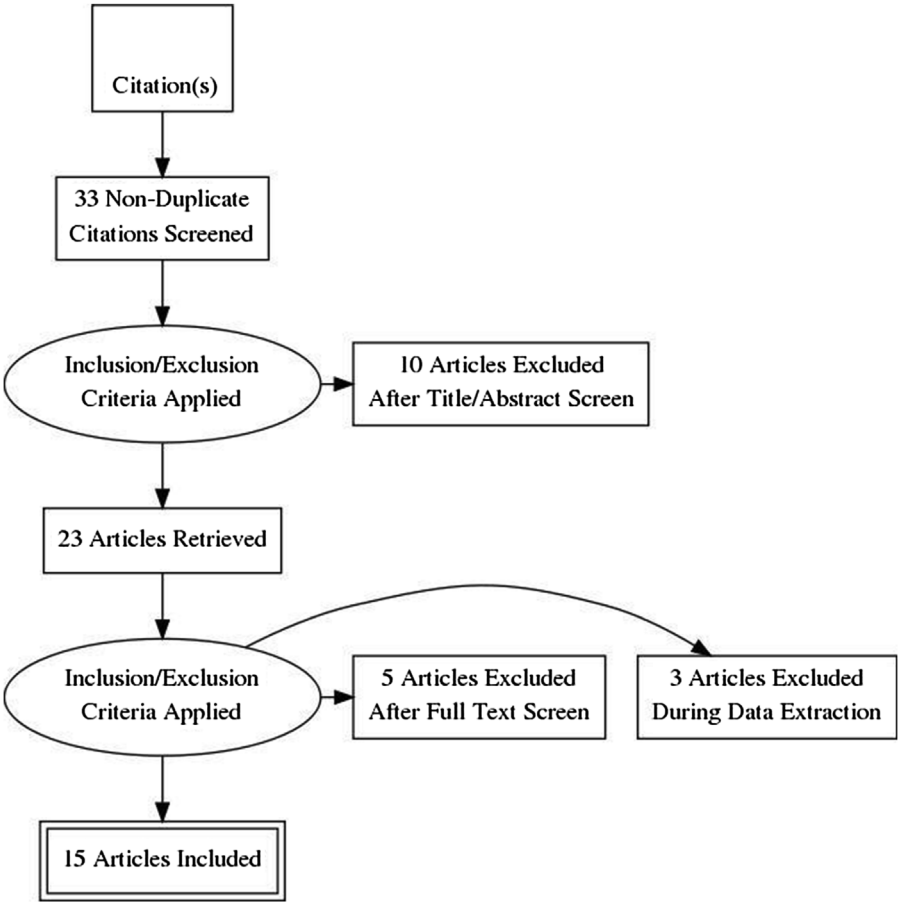
All the published studies till May 2018 were retrieved using the keywords, 'tacrolimus', 'CYP3A5', 'ABCB1', 'MDR1', 'liver transplant' from PubMed, Medline and Google Scholar databases. The inclusion criteria were: i) accessibility of the manuscript; and ii) presentation of data on the C/D ratio of tacrolimus according to genotype with respect to first four weeks of post-transplant. Studies without the details of C/D ratio according to genotype and those that have taken to account different timelines after 1 month of transplant were excluded. Author name, year of publication, ethnicity, C/D ratio of tacrolimus (mean, standard deviation and number of subjects) according to genotype and the timeline post-transplant was documented. The PRISMA flowchart depicts different stages of data extraction (Scheme 1).

### *Meta-analysis of means*

The meta-analysis was performed on a set of two-group, continuous-scale studies using recessive allelic model. For CYP3A5, *3/*3 genotype was considered as treatment group while *1/*1 and *1/*3 were considered as control group. For ABCB1, CC-genotype was considered as treatment group while CT + TT-genotypes were considered as control group. Each study's results in terms of tacrolimus C/D ratio were summarized by the sample size (n), mean, and standard deviation for each of the two groups.

Hedges 'g' value was calculated as a measure of effect size. It is the ratio of the difference in mean and pooled and weighted standard deviation. A g-value of $\leq$0.2 indicate small effect, >0.2 $\leq$ 0.5 indicate medium effect and >0.5 to 0.8 indicate a large effect.

Effect-Equality (Heterogeneity) Test was carried out using Cochran's Q Test. Cochran's Q-value was used to measure heterogeneity in the meta-analysis. It is calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies. The 'p' values were obtained by comparing the statistics with a $\chi^2$ distribution with κ-1° of




**Scheme 1.** PRISMA flow chart showing the steps in data collection for meta-analysis. This illustrates different stages in the meta-analysis wherein out of 33 articles, 15 were considered for the final data extraction.

freedom (κ= number of studies). $P < 0.05$ was considered to be an indicator of heterogeneity. As the Q-test performance depends on the number of studies, $I^2$ also calculated as it describes the percentage of total variation across studies. A value of 0% indicates no heterogeneity and larger values show increasing heterogeneity. These tests were used in choosing between the use of fixed effect (homogeneous) and random effects (heterogeneous model). Egger's test was performed to calculate publication bias.

## Results

### *Influence of donor CYP3A5*3 on the C/D ratio of tacrolimus*

#### *Week 1*

As shown in Fig. 1, six studies from China [8,12–16], two studies from Spain [9,17], one each from Egypt [18], Japan [19], and Singapore [20] were included in the meta-analysis. Cochran's Q-test revealed significant heterogeneity in the association of CYP3A5*3 variant with tacrolimus C/D ratio (Q: 154.5, $p = 0.0000$; $I^2 = 93.53\%$). The random effect model was considered due to heterogeneity in the association. The Egger test was not significant for publication bias ($p = 0.08$). A study by Liu et al. deviated significantly from the rest of the studies [15]. Among the remaining studies, except for Liao et al who reported large differences between means of tacrolimus C/D ratio in CYP3A5 *3/*3 *vs.* CYP3A5 *1/*1 and *1/*3 genotypes [16], rest of the studies are distributed more homogeneously in terms of 1/standard error *vs.* Z-statistics (suppl. Fig. 1). Based on Hedges' g-value and pooled standard deviation, the mean difference in tacrolimus C/D ratio between CYP3A5 *3/*3 *vs.* CYP3A5 *1/*1 and *1/*3 was 65.04 (15.30–114.79) ng/ml/mg/kg.

#### *Week 2*

As shown in Fig. 1, six studies from China [8,12–16], two studies from Spain [9,17] and one study from Egypt [18] were included in the meta-analysis. Cochran's Q-test revealed significant heterogeneity in the association of CYP3A5*3 variant with tacrolimus C/D ratio (Q: 24.14, $p = 0.002$, $I^2$: 66.85%). The random effect model was considered due to heterogeneity in the association. The Egger test for publication bias was not statistically significant ($p = 0.15$). A study by Barrera-Pulido deviated significantly from the rest of the

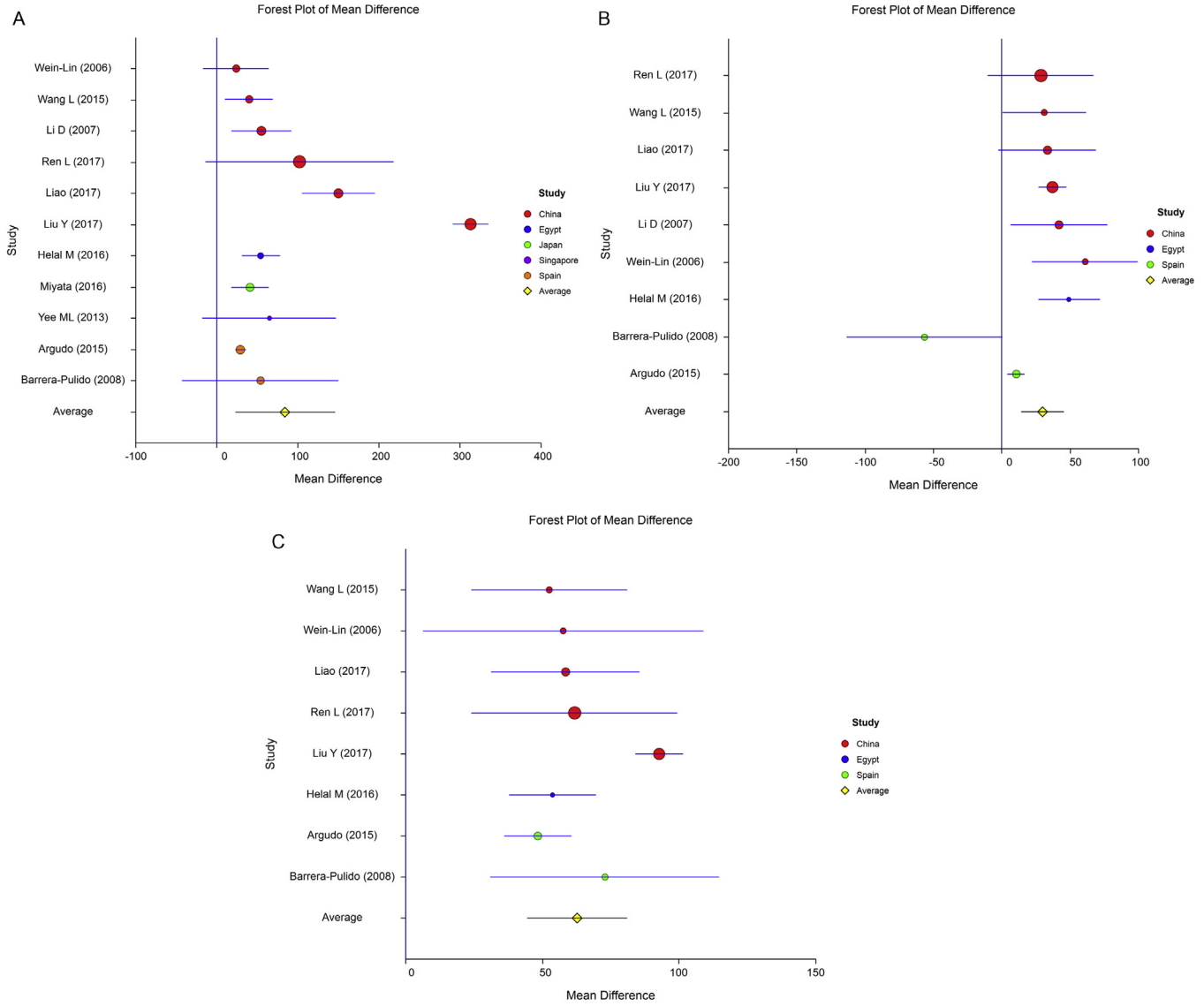



**Fig. 1.** Association of donor CYP3A5 genotypes with tacrolimus concentration/dose ratio during first one month after transplantation. Recessive genetic model (*3/*3 *vs.* *1/*1 and *1/*3) was used to study the mean differences in tacrolimus concentration/dose ratio during first one-month after transplantation across eleven published studies representing 678 liver transplant cases: (A) week 1; (B) week 2; (C) week 4.

studies [9]. Among the remaining studies, except for Argudo et al. who reported minimal differences between means of tacrolimus C/D ratio in CYP3A5 *3/*3 *vs.* CYP3A5 *1/*1 and *1/*3 genotypes [17], rest of the studies are distributed more homogeneously in terms of 1/standard error *vs.* Z-statistics (Suppl. Fig. 1). Based on Hedges' g-value and pooled standard deviation, the mean difference in tacrolimus C/D ratio between CYP3A5 *3/*3 *vs.* CYP3A5 *1/*1 and *1/*3 was 21.78 (12.6–30.9) ng/ml/mg/kg.

*Week 4*

As shown in Fig. 1, five studies from China [8,12–16], two studies from Spain [9,17] and one study from Egypt [18] were included in the meta-analysis. Cochran's Q-test revealed significant heterogeneity in the association of CYP3A5*3 variant with tacrolimus C/D ratio (Q: 99.06,$p = 0.0000$, $I^2$: 92.93%). The random effect model was considered due to heterogeneity in the association. The Egger test was not statistically significant for publication bias ($p = 0.26$). Except for Liu et al. who reported larger differences between means of tacrolimus C/D ratio in CYP3A5 *3/*3 *vs.* CYP3A5 *1/*1 and *1/*3 genotypes [15], rest of the studies are distributed more homogeneously in terms of 1/standard error *vs.* Z-statistics (Suppl. Fig. 1). Combined meta-analysis revealed that the mean difference in tacrolimus C/D ratio between CYP3A5 *3/*3 *vs.* CYP3A5 *1/*1 and *1/*3 as 43.28 (17.09–69.49) ng/ml/mg/kg. (Suppl. Table 1)

*Influence of recipient ABCB1 c.3435C > T on the C/D ratio of tacrolimus*

*Week 1*

As shown in Fig. 2, one study each from China [8], Egypt [18], France [10], Iran [21], Japan [19], and Singapore [20] were included for the meta-analysis. Cochran's Q-test revealed significant heterogeneity (Q: 9.36, $p = 0.096$, $I^2$: 46.55%). The random effect model was considered due to heterogeneity in the association. The Egger test was not statistically significant for publication bias ($p = 0.84$). Mean differences between ABCB1 3435 CC *vs.* ABCB1 3435 CT + TT were not found to be statistically significant in the combined analysis: 8.00 (−0.42 – 16.86) ng/ml/mg/kg.

*Week 4*

As shown in Fig. 2, one study each from China [8], Egypt [18], Iran [21], and Jordan [22] were included for the meta-analysis. Cochran's Q-test revealed no heterogeneity (Q: 3.33, $p = 0.54$). The fixed effect model was considered due to heterogeneity in the association. Except for study by Rahsaz et al. [21], all other studies were homogenous as per the 1/standard error *vs.* Z-statistics (Suppl. Fig. 2). Mean differences between ABCB1 3435 CC *vs.* ABCB1 3435 CT + TT were not found to be statistically significant in the combined analysis: 5.15 (1.29–9.27) ng/ml/mg/kg (Suppl. Table 2).

*Influence of recipient CYP3A5*3 on the C/D ratio of tacrolimus*

*Week1*

As shown in Fig. 3, a total of eight studies covering 548 liver transplant cases were included for the meta-analysis. Four studies were from China [13–16] and one study each from Iran [21], Singapore [20], Japan [23] and Egypt [18]. Significant heterogeneity was observed in the association of recipient CYP3A5 with tacrolimus (Q: 99.63, $p = 0.0000$, $I^2$: 92.97%). Hence, the random effect model was considered. The Egger test showed no statistical significance for publication bias ($p = 0.41$). Mean difference in tacrolimus C/D ratio between *3/*3 *vs.* *1/*3 and *1/*1 were 58.39 (−6.63–123.40) ng/ml/mg/kg.

*Week 2*

As shown in Fig. 3, a total of six studies covering 431 liver transplant cases were included for the meta-analysis. Four studies were from China [13–16] and one study each from Japan [23] and Egypt [18]. Significant heterogeneity was observed in the association of recipient CYP3A5 with tacrolimus (Q: 76.61, $p = 0.0000$, $I^2$: 93.47%). Hence, the random effect model was considered. The Egger test showed no statistical significance for publication bias ($p = 0.11$). Mean difference in tacrolimus C/D ratio between *3/*3 *vs.* *1/*3 and *1/*1 were 44.16 (3.68–84.65) ng/ml/mg/kg.

*Week 4*

As shown in Fig. 3, a total of seven studies covering 531 liver transplant cases were included for the meta-analysis. Four studies were from China [13–16] and one study each from Iran [21], Japan [23] and Egypt [18]. Significant heterogeneity was observed in the association of recipient CYP3A5 with tacrolimus (Q: 55.81, $p = 0.0000$, $I^2$: 89.25%). Hence, the random effect model was considered. The Egger test showed no statistical significance for publication bias ($p = 0.13$). Mean difference in tacrolimus C/D ratio between *3/*3 *vs.* *1/*3 and *1/*1 were 43.74 (12.50–75.00) ng/ml/mg/kg (Suppl. Table 3).

In order to maintain the tacrolimus tough level as 10 ng/ml, the dose of tacrolimus required (mg/kg) was calculated based on cumulative data with relevance to donor and recipient CYP3A5 genotypes as shown in Fig. 4. This showed that donor CYP3A5*1 expression increases tacrolimus required dose by 0.028 at first, 0.016 at second and 0.041 mg/kg/day at the fourth week of transplantation. Similarly, the recipient CYP3A5*1 expression increases tacrolimus required dose by 0.018 at first, 0.039 at second and 0.034 mg/kg/day at the fourth week of transplantation.

## Discussion

The current meta-analysis demonstrates that donor and recipient CYP3A5 genotypes influence tacrolimus C/D ratio while recipient ABCB1 genotype has no statistically significant influence on the tacrolimus C/D ratio. CYP3A5 *3/*3 genotype in both donor and recipient increase the C/D ratio than *1/*1 and *1/*3 genotypes. Hence, the required doses of tacrolimus to attain optimal trough levels will be higher if the donor or recipient has CYP3A5*1 allele.

CYP3A5*3 (6986 A > G) creates a cryptic splice site in intron 3, which leads to an insertion from intron 3 thus altering the reading frame and causes a premature termination codon and a non-functional protein [24] and hence has a significant influence on the tacrolimus metabolism.

A meta-analysis by Hendijani et al. revealed that donor CYP3A5*1 expression increases tacrolimus required dose by 0.024 at first, 0.035 at third, and 0.032 mg/kg/day at sixth month [25]. A meta-analysis by Buendia et al. revealed that recipient CYP3A5*1 allele has the greatest influence on tacrolimus pharmacokinetics in the immediate post-transplant period while donor CYP3A5*1 allele is more important with increasing time after transplant [26]. A meta-analysis by Rojas et al. is consistent with our observation in documenting donor CYP3A5 genotype as the important determinant of tacrolimus pharmacokinetics in the recipient [27]. However, this meta-analysis was based on only 254 liver transplant cases while our meta-analysis included 678 liver transplant cases thus increasing the power of association. A meta-analysis by Tang et al. revealed that tacrolimus daily dose requirements vary with CYP3A5 genotype, ethnicity, the time of post-transplantation [28]. A meta-analysis by Liu et al. revealed that recipient ABCB1 3435 CT-genotype had higher C/D ratio of tacrolimus than those with CC and TT genotypes at different post-transplantation times [29]. In the current meta-analysis, we have observed no significant association of ABCB1 3435C > T with C/D ratio of tacrolimus during the first week and fourth week of transplantation using recessive genetic model (CC *vs.* CT + TT).

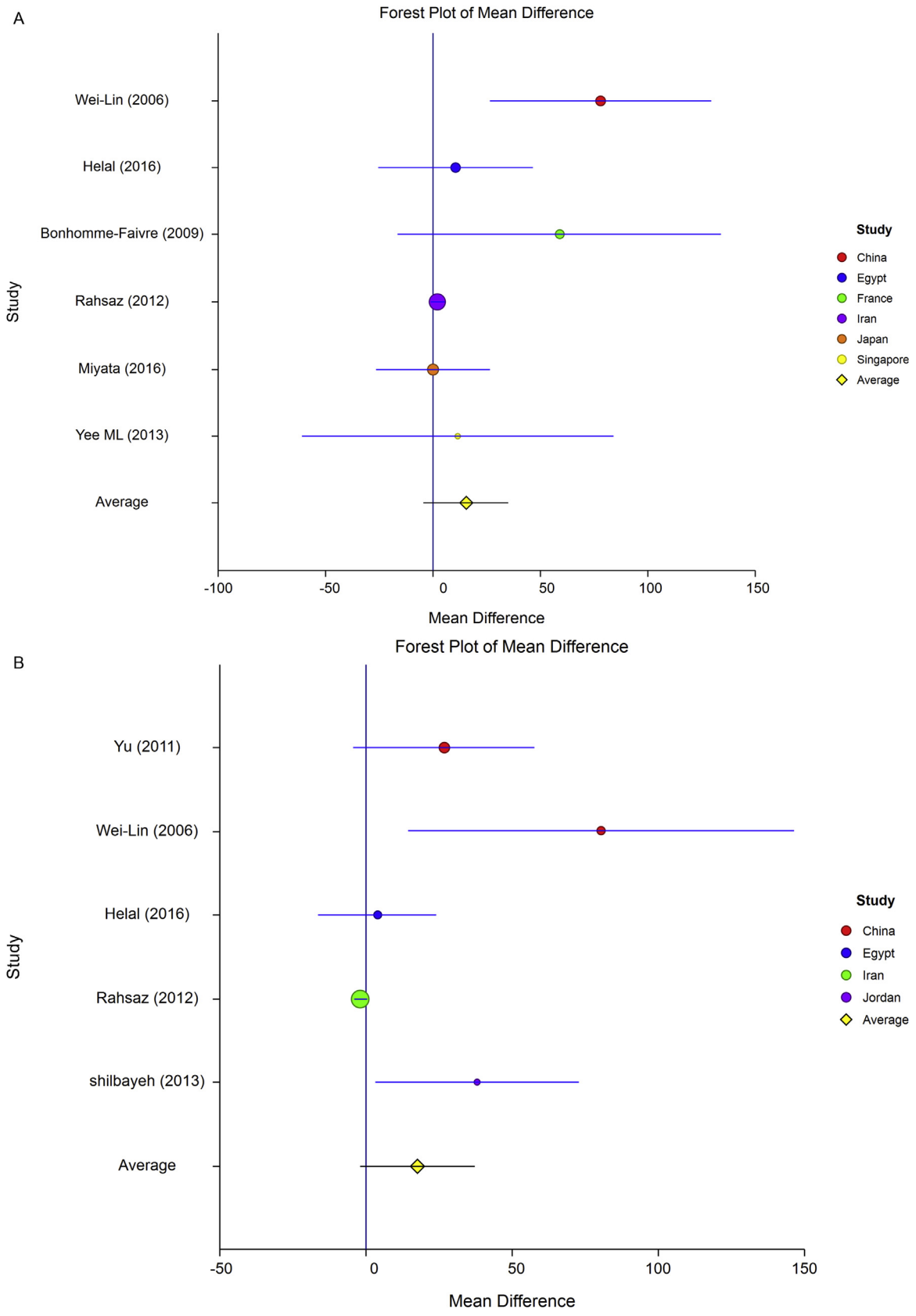



**Fig. 2.** Association of recipient ABCB1 3435 genotypes with tacrolimus concentration/dose ratio during first one month after transplantation. Recessive genetic model (CC *vs.* CT and TT) was used to study the mean differences in tacrolimus concentration/dose ratio during first one month of transplantation across six published studies representing 318 liver transplant cases: (A) week 1; (B) week 4.

When recipient and donor have different genotypes of CYP3A5, liver grafts were reported to exhibit significant differences in the distribution of G and A-alleles of CYP3A5*3 following live donor liver transplantation [30]. When a recipient with AA-genotype received a liver graft from a donor from GG-genotype, the liver graft biopsy indicated a proportional increase in A and decrease in G at two different time points *i.e.* 1.5 months and 4 months after LDLT [30]. However, RFLP-based analysis cannot identify these changes whereas pyrosequencing is effective in elucidating these changes. A study from Japan has indicated no significant impact of recipient and donor CYP3A5 genotypes on infection and rejection following one year of post LDLT [31]. They suggested that CYP3A5 genotypes of recipient and donor mainly affect tacrolimus pharmacokinetics during the early postoperative period but not late phase after the operation.

The strength of the current meta-analysis is its sample size and consideration of genotype and time of transplant in the analysis. Limitations are i) non-inclusion of donor ABCB1 for the meta-analysis; ii) other confounding factors such as cadaver *vs.* live donor, pediatric *vs.* adult patients, *etc.* were not studied.

The role of CYP3A5*3 genetic polymorphism as a pharmacogenetic determinant of tacrolimus dose is well documented. However, in live donor liver transplantation, the donor and recipient CYP3A5 genotypes will have variable effects on the metabolism of tacrolimus. It is reported that in the early phases of transplant, donor genotype will have the major effect. However, with time, the recipient genotype predominates due to the homogeneous phenomenon. This meta-analysis contributes to the existing literature by demonstrating weekly changes in the concentration/dose ratio of tacrolimus in relation to recipient ABCB1 and donor/recipient CYP3A5 genotypes in early phases of transplantation. Based on this data, it also suggested the tacrolimus doses.

To conclude, the donor CYP3A5 genotype influences tacrolimus pharmacokinetics from week 1 to week 4 of transplantation. Although the recipient CYP3A5 genotypes were not shown to have a statistical significant association with tacrolimus

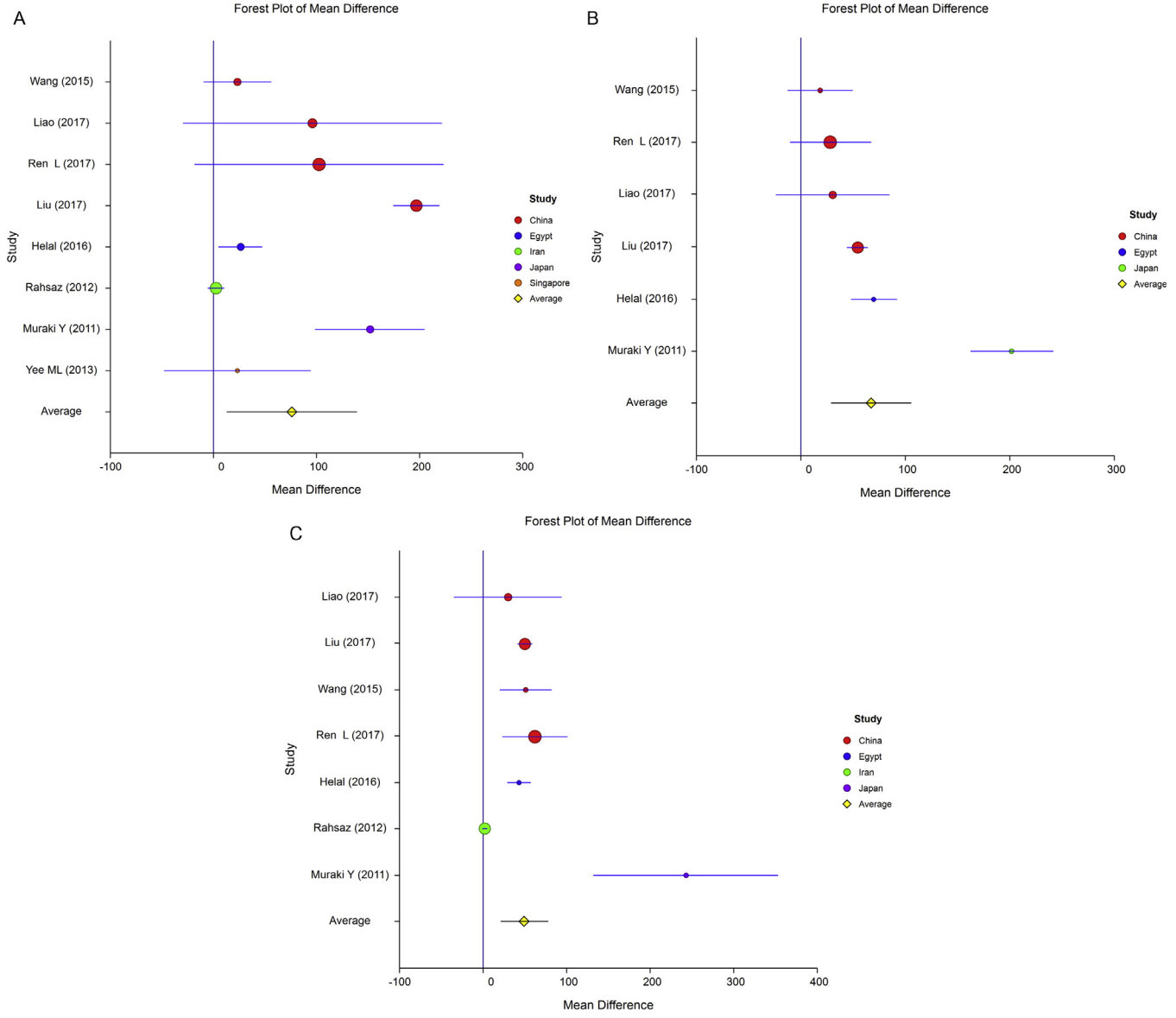



**Fig. 3.** Association of recipient CYP3A5 genotypes with tacrolimus concentration/dose ratio during first one month after transplantation. Recessive genetic model (*3/*3 *vs.* *1/*1 and *1/*3) was used to study the mean differences in tacrolimus concentration/dose ratio during first one-month after transplantation across eight published studies representing 548 liver transplant cases: (A) week 1; (B) week 2; (C) week 4.

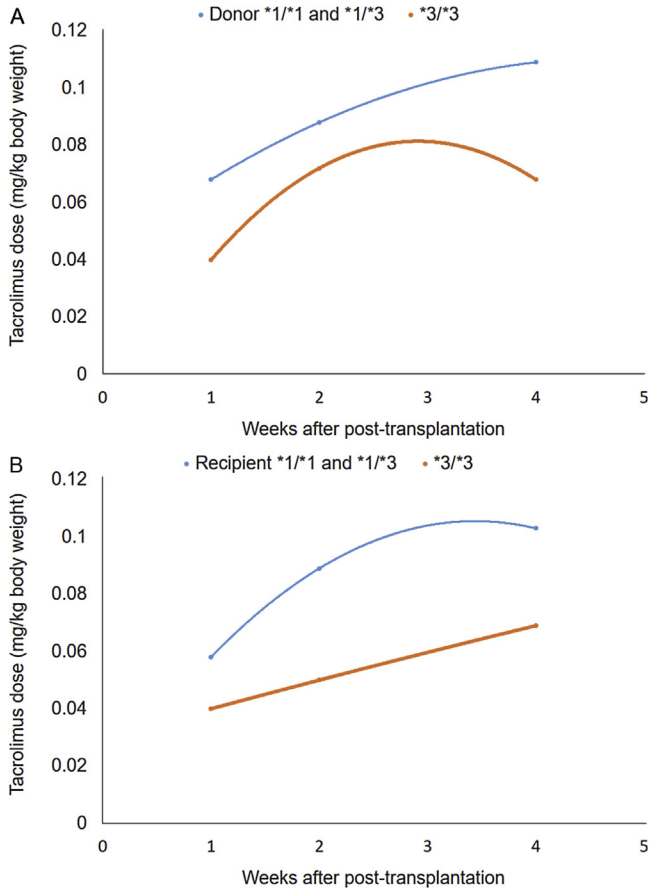



**Fig. 4.** Influence of donor and recipient CYP3A5 genotypes on tacrolimus dose requirements. (A) Donor (B) Recipient CYP3A5 genotypes influence tacrolimus dose requirement.

pharmacokinetics during the first week of transplant, during $2^{nd}$ and $4^{th}$ week, they also influence the pharmacokinetics of tacrolimus. The role of recipient ABCB1 genotype on tacrolimus concentration/dose ratio is not significant in the first month of transplantation. A better understanding of various factors contributing to tacrolimus pharmacokinetics through integrated OMIC approach encompassing drug metabolomics, pharmacogenomics, and proteomics-based evaluation of calcineurin signaling might facilitate more specific and precise dose optimization of tacrolimus in liver transplant cases.

## Conflicts of interest

All the authors hereby declare no conflicts of interest.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.pharep.2019.01.006.

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