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Short Communication

The effect of ABCB1 C3435T polymorphism on pharmacokinetics of tacrolimus in liver transplantation: A meta-analysis

Yuan-Yuan Liu [a,1], Changping Li [a,1], Zhuang Cui [a,1], Xiaomeng Fu [a], Shu Zhang [a], Lin-Lin Fan [a], Jun Ma [a,*], Guang Li [b,**]

[a] Department of Health Statistics, School of Public Health, Tianjin Medical University, 22 Qi-Xiang-Tai Road, Heping District, Tianjin 300070, China
[b] Department of Biology, School of Basic Medical, Tianjin Medical University, 22 Qi-Xiang-Tai Road, Heping District, Tianjin 300070, China

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ABSTRACT

Objectives: The effect of ABCB1 C3435T SNP on the pharmacokinetics of immunosuppressive drug tacrolimus in different studies was conflicting. So a meta-analysis was employed to study the correlation of ABCB1 C3435T SNP and the pharmacokinetics of tacrolimus at different post-transplantation times.
Method: Several studies about ABCB1 C3435T polymorphism and the pharmacokinetics of tacrolimus were collected through the search on PubMed and the Cochrane Library. After the extraction of pharmacokinetic parameters from these studies, a meta-analysis was performed on the software STATA version11.0.
Results: A total of 9 studies were adopted including 558 liver transplant recipients. For the dose of tacrolimus, the subjects with wild-type CC had a significantly higher tacrolimus dose than homozygous mutated genotype TT within 1 week (WMD = 0.01 (0.00, 0.02), $P = 0.014$) and the similar result in recipients with heterozygous CT compared with TT after transplantation for 1 month (WMD = 0.01 (0.00, 0.02), $P = 0.002$). For the tacrolimus concentration/dose ratio, subjects with CT had higher C/D ratio than those with CC and TT at different post-transplantation times. A subgroup analysis based on different ethnic populations was also carried out. Donors' genotypes were also considered in this meta-analysis.
Conclusion: Through this meta-analysis for the including studies about the pharmacokinetics of tacrolimus and ABCB1 C3435T SNP, several significant associations were obtained. Particularly, the Caucasians showed more significant associations between the C/D ratio and ABCB1 C3435T polymorphism; however, the correlations were not steady at different post-transplantation times.

1. Introduction

Solid organ transplantation including liver transplantation, kidney transplantation and lung transplantation, as an effective treatment for patients with end-stage diseases, receives great attention. However, due to immune rejection of human beings, the survival rate is limited for patients after transplantation. In order to improve this situation, immunosuppressants are employed. Among them, calcineurin inhibitors, such as tacrolimus and cyclosporine, are widely used for preventing from organ rejection after transplantation. Tacrolimus, which is a macrolide antibiotic compound, can effectively decrease rejection rates and relieve renal complications in liver transplantation (Cholongitas et al., 2011) and its potency is almost 100 times greater on a molar level (Geissler and Schlitt, 2009) than that of cyclosporine. Due to its superiority, tacrolimus is used more extensively. However, how to use this drug scientifically is crucial, because low blood concentrations of tacrolinus can lead to rejection, and high blood concentration can lead to infection or toxicosis (Schwartz et al., 1995). To avoid the rejection and adverse reaction, achieving the desired target blood concentration is very important (Venkataramanan et al., 1995). As a result of narrow therapeutic index and variable pharmacokinetics of tacrolimus, monitoring its blood concentration is very necessary (Venkataramanan et al., 2001), especially in the early time after liver transplantation (Zahir et al., 2004). So the research about the pharmacokinetics of tacrolimus has become a key issue in recent years. In the intestinal bioavailability process of tacrolimus, cytochrome P4503A (CYP3A) and P-glycoprotein (P-gp) play important roles. Many works about the association of CYP3A polymorphism and tacrolimus pharmacokinetics have been accomplished (Dai et al., 2001, 2006; Sai et al., 2003; Staatz et al., 2010b; Tang et al., 2011; Thiebaut et al., 1987).

Tacrolimus is a substrate of P-gp, which is expressed as the product of gene ABCB1. Up to date, more than 50 single nucleotide polymorphisms (SNPs) in human ABCB1 coding region have been reported by National Center for Biotechnology Information (NCBI) (Fung and Gottesman, 2009). Studies about ABCB1 SNPs mainly involve the exon

Abbreviations: CI, confidence intervals; P-gp, P-glycoprotein; SNPs, single nucleotide polymorphisms; WMD, weighted mean differences.

* Corresponding author. Tel./fax: +86 22 83336660.
** Corresponding author. Tel./fax: +86 22 83336839.
E-mail addresses: junma@tijmu.edu.cn (J. Ma), lig@tijmu.edu.cn (G. Li).

[1] These authors contributed equally to this work.

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Table 1
Basic characteristics of the studies included in this meta-analysis.

Study: first author, year	Country	Ethnicity	Cases/ male (*n*)	Age (years)	Body weight (kg)	Immunosuppressive protocol	Genotype method	Method of concentration measured	Donors
Goto M., 2002	Japan	Asian	69/28	Range (0.6–59.6)	–	–	PCR-RFLP	–	Living
Goto M., 2004	Japan	Asian	Recipients: 181/84 Donors: 114/57	Recipients: 10(0.3–70) Donors: 35(18–64)	Recipients: 25(5–92.1)	–	PCR-RFLP	MEIA	Living
Jin J., 2005	China	Asian	50/48	44.36 ± 8.46	59.89 ± 10.60	Tac, MMF, steroid	PCR	IMx analyzer	Cadaveric
Bonhomme-Faivre L., 2009	France	Caucasian	42/31	54 ± 12	–	Tac and corticosteroids, or add MMF	PCR	MEIA	Cadaveric
Provenzani A., 2009	Italy	Caucasian	Recipients: 32/24 Donors: 32/13	Recipients: 53.53 ± 12.38 Donors: 39.25 ± 18.99	–	Tac/Tac, steroids and/or MMF	PCR-RFLP	EMIT	–
Provenzani A., 2011	Italy	Caucasian	Recipients: 51/39 Donors: 51/25	Recipients: 54 ± 12.30 Donors: 42.80 ± 20.30	–	Tac/Tac, steroids and/or MMF	PCR-RFLP	EMIT	–
Yu X., 2011	China	Asian	62/57	46.6 ± 9.3	66.4 ± 8.4	Tac, steroid	PCR-RFLP	IMx analyzer	–
de Wildt S.N., 2011	Canada	Caucasian	42/–	1.5(0.05–14.8)	10.9(2.6–64)	Tac, MMF, methylprednisolone, or add basiliximab or thymoglobulin	Taqman allelic discrimination assay	LC–MS–MS	–
Rahsaz M., 2012	Iran	Caucasian	100/64	35.1 ± 17.55	49.17 ± 18.14	Tac, cyclosporine or MMF, steroids	PCR-RFLP	EMIT	Living and cadaveric

PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; Tac: tacrolimus; MMF: mycophenolate mofetil; MEIA: microparticle enzyme immunoassay; EMIT: enzyme multiplied immunologic technique; LC–MS: liquid chromatography–mass spectrometry.

11 (G1199A), exon 12 (C1236T), exon 21 (G2677T/A) and exon 26 (C3435T). Among these regions, C3435T SNP is a silent polymorphism; however, its polymorphism may be in linkage disequilibrium with some non-synonymous SNP of ABCB1, such as G2677T/A, which causes a serine–alanine substitution and results in a low expression of intestinal P-gp (Anglicheau et al., 2003). Also, according to the recent research, C3435T may reduce ABCB1 mRNA stability in the liver (Wang et al., 2005). So the expression and function of P-gp were affected (Saeki et al., 1993; Sakaeda et al., 2003), as a result of the mutation of C>T in the region of ABCB1. P-gp is the transporter of tacrolimus in the metabolism process of this immunosuppressant, which has great effect on pharmacokinetics of tacrolimus. Thus, ABCB1 C3435T has been studied more extensively, compared with other three exons. Although several studies show no significance between donors' ABCB1 genotypes and tacrolimus pharmacokinetics in liver transplant recipients (Jin et al., 2005; Provenzani et al., 2009, 2011), the influence of ABCB1 polymorphisms on pharmacokinetics of tacrolimus in liver transplant recipients has not reached a consensus. The reasons of the controversial results may be the low numbers of sample size and the genetic linkage between the ABCB1 SNPs, yet a confirmed result is of importance for the clinical treatment of liver transplantation. Thus, a systematic review about this controversy is necessary.

In order to summarize the influence of ABCB1 C3435T polymorphism on tacrolimus pharmacokinetics, several studies about this were collected to form a relatively bigger sample size, and the meta-analysis is employed to systematically review the existing evidences which discuss the relationship of ABCB1 C3435T polymorphisms and tacrolimus pharmacokinetics in liver transplant recipients.

2. Materials and methods

2.1. Search strategy

The studies were searched in the databases of PubMed (1977–2012) and the Cochrane Library (2012) until November 2011, and relevant studies were extracted, which referred to the association between ABCB1 C3435T polymorphism and pharmacokinetics of tacrolimus in liver transplant recipients. This electronic search was performed without language restrictions. The following search terms were used as follows: (liver transplant OR liver transplantation) AND tacrolimus AND (MDR1 OR ABCB1 OR p-glycoprotein OR P-gp) AND (polymorphism OR polymorphisms OR genotype).

2.2. Inclusion/exclusion criteria

Two reviewers (Yuan-Yuan Liu and Lin-Lin Fan) evaluated the titles, abstracts and the full texts of the candidate articles (n = 35) independently. Studies were considered for inclusion when they met the following criteria: (a) it explored the association between ABCB1 C3435T polymorphism and pharmacokinetics of tacrolimus in liver transplant recipients; (b) ABCB1 C3435T polymorphism was described as CC, CT and/or TT; (c) the postoperative time was defined clearly; and (d) the pharmacokinetic parameters were expressed as dose (mg/kg per day) or concentration (ng/ml) or concentration/dose (ng/ml per mg/kg).

The decision to exclude any of these studies was made by the consensus of two reviewers. The effort to contact with the corresponding authors was made, when the article which met the inclusion criteria, provided insufficient pharmacokinetic data.

2.3. Data extraction

Data of the eligible studies were extracted by two reviewers (Yuan-Yuan Liu and Lin-Lin Fan) independently. The basic information which included first author, year of publication, country, ethnicity, number of total cases and male cases, age, body weight, immunosuppressive protocol, genotype method, tacrolimus concentration measured method and the sources of donors, was listed in Table 1. Furthermore, the postoperative time, cases number of ABCB1 C3435T genotypes of recipients and the tacrolimus pharmacokinetic parameters such as dose, concentration and concentration/dose (C/D) ratio were extracted

Table 2
Characteristics of tacrolimus pharmacokinetic parameters of the eligible studies included in the meta-analysis for recipients' ABCB1 C3435T polymorphism.

Study: first author, year	Postoperative time	Cases (*n*) (CC/CT/TT)	Dose (mg/kg per day)			Concentration (ng/ml)			Concentration/dose (ng/ml per mg/kg)		
			CC	CT	TT	CC	CT	TT	CC	CT	TT
Goto M., 2002	1 week	46 (15/22/9)							152.7 ± 22.4	170.4 ± 20.6	155.6 ± 26.2
Goto M., 2004	1 week	143 (40/76/27)							158.5 ± 77.9	160.2 ± 94.5	147.4 ± 81.2
Jin J., 2005	1 week	50 (8/35/7)	0.097 ± 0.037	0.063 ± 0.022	0.062 ± 0.015				66.86 ± 14.26	137.41 ± 68.17	183.10 ± 81.92
	2 weeks	50 (8/35/7)	0.126 ± 0.034	0.068 ± 0.027	0.053 ± 0.026				73.00 ± 21.33	131.66 ± 76.74	134.07 ± 56.74
	1 month	50 (8/35/7)	0.124 ± 0.026	0.060 ± 0.024	0.042 ± 0.013				52.40 ± 10.23	125.10 ± 92.75	171.72 ± 84.48
Bonhomme-Faivre L., 2009	1–3 days	42 (10/23/9)	0.107 ± 0.05	0.081 ± 0.039	0.083 ± 0.049	10.2 ± 7.9	9.1 ± 4.9	16.0 ± 7.4	104 ± 74	131 ± 108	236 ± 119
	1 month	42 (10/23/9)	0.123 ± 0.078	0.13 ± 0.074	0.109 ± 0.061	13.08 ± 5.69	10.4 ± 4.52	10.6 ± 3.15	162 ± 136	104 ± 66	136 ± 114
	3 months	42 (10/23/9)	0.091 ± 0.067	0.094 ± 0.073	0.093 ± 0.048	10.43 ± 2.98	8.34 ± 3.44	7.97 ± 1.73	156 ± 92	127 ± 84	106 ± 57
Provenzani A., 2009	1 month	32 (5/19/8)	0.079 ± 0.030	0.078 ± 0.035	0.099 ± 0.059	6.72 ± 2.86	8.07 ± 3.21	7.93 ± 4.22	93.29 ± 57.54	121.54 ± 64.38	85.78 ± 41.53
	3 months	32 (5/19/8)	0.077 ± 0.033	0.063 ± 0.045	0.065 ± 0.029	8.57 ± 3.27	8.47 ± 3.28	7.33 ± 2.60	125.04 ± 61.16	216.46 ± 205.76	125.06 ± 56.28
	6 months	32 (5/19/8)	0.058 ± 0.032	0.051 ± 0.038	0.046 ± 0.022	7.19 ± 2.06	8.17 ± 2.34	6.09 ± 1.53	151.12 ± 73.87	274.95 ± 274.51	159.63 ± 78.64
Provenzani A., 2011	1 month	51 (9/26/16)	0.089 ± 0.05	0.086 ± 0.035	0.102 ± 0.060	7.50 ± 2.37	9.00 ± 3.64	8.24 ± 3.67	114.50 ± 88.70	121.28 ± 64.05	91.15 ± 41.26
	3 months	51 (9/26/16)	0.073 ± 0.03	0.061 ± 0.040	0.063 ± 0.036	8.29 ± 2.70	8.44 ± 3.03	7.93 ± 2.42	139.35 ± 75.76	208.54 ± 188.34	151.56 ± 70.54
	6 months	51 (9/26/16)	0.054 ± 0.02	0.048 ± 0.033	0.044 ± 0.017	7.69 ± 1.87	8.31 ± 2.53	7.13 ± 2.38	170.99 ± 96.89	270.92 ± 247.58	186.76 ± 85.06
Yu X., 2011	1 month	62 (7/24/31)							117.54 ± 23.16	137.95 ± 49.83	150.20 ± 48.05
de Wildt S.N., 2011	2 weeks	32 (10/15/7)	0.130 ± 0.045[a]	0.125 ± 0.063 [a]	0.205 ± 0.058 [a]	9.70 ± 2.35 [a]	11.78 ± 1.84 [a]	11.60 ± 1.75 [a]	194.37 ± 84.82 [a]	986.50 ± 476.65 [a]	125.51 ± 42.19 [a]
Rahsaz M., 2012	1 week	100 (16/51/33)	0.171 ± 0.018	0.167 ± 0.018	0.163 ± 0.015	4.9 ± 3.6	5.2 ± 3.3	5.1 ± 4.2	29.19 ± 3.1	31.19 ± 4.1	31.29 ± 9.1
	1 month	100 (16/51/33)	0.185 ± 0.021	0.193 ± 0.021	0.184 ± 0.014	7.9 ± 3.5	9.2 ± 2.5	8.8 ± 3.4	37.01 ± 2.1	6.21 ± 3.1	35.19 ± 4

[a] The mean and standard deviation were calculated from min and max (Jiang et al., 2008).

Table 3
Characteristics of tacrolimus pharmacokinetic parameters of the eligible studies included in the meta-analysis for donors' ABCB1 C3435T polymorphism.

Study: first author, year	Postoperative time	Cases (*n*) (CC/CT/TT)	Dose (mg/kg per day)			Concentration (ng/ml)			Concentration/dose (ng/ml per mg/kg)		
			CC	CT	TT	CC	CT	TT	CC	CT	TT
Jin J., 2005	1 week	50 (15/29/6)	0.071 ± 0.038	0.069 ± 0.022	0.055 ± 0.010				124.63 ± 69.61	120.70 ± 61.28	209.37 ± 88.93
	2 weeks	50 (15/29/6)	0.079 ± 0.039	0.076 ± 0.034	0.060 ± 0.040				106.80 ± 59.14	123.29 ± 76.78	158.88 ± 64.02
	1 month	50 (15/29/6)	0.068 ± 0.041	0.069 ± 0.030	0.063 ± 0.039				100.38 ± 52.73	121.52 ± 100.96	120.00 ± 89.47
Provenzani A., 2009	1 month	32 (10/15/7)	0.075 ± 0.032	0.081 ± 0.035	0.101 ± 0.060	7.88 ± 3.50	6.88 ± 2.61	9.77 ± 4.18	112.55 ± 43.71	103.86 ± 75.19	111.24 ± 43.88
	3 months	32 (10/15/7)	0.063 ± 0.031	0.071 ± 0.048	0.059 ± 0.034	7.41 ± 1.82	8.26 ± 2.55	9.21 ± 5.12	176.68 ± 190.47	162 ± 110.2	220.2 ± 241.38
	6 months	32 (10/15/7)	0.053 ± 0.026	0.055 ± 0.040	0.039 ± 0.0235	8.13 ± 2.03	7.35 ± 2.15	6.90 ± 2.84	245 ± 290.46	186.63 ± 103.45	288.75 ± 307.81
Provenzani A., 2011	1 month	51 (12/26/13)	0.087 ± 0.05	0.089 ± 0.048	0.102 ± 0.047	8.12 ± 3.25	8.19 ± 3.31	9.10 ± 3.50	106.71 ± 43.78	115.97 ± 76.11	96.31 ± 37.00
	3 months	51 (12/26/13)	0.068 ± 0.03	0.066 ± 0.043	0.061 ± 0.026	7.76 ± 1.86	8.37 ± 2.22	8.50 ± 4.15	167.97 ± 174.78	167.45 ± 100.13	176.03 ± 181.08
	6 months	51 (12/26/13)	0.054 ± 0.02	0.048 ± 0.033	0.041 ± 0.017	8.29 ± 2.01	8.17 ± 2.53	6.73 ± 2.26	226.29 ± 267.65	222.50 ± 116.48	224.60 ± 230.63

and presented in Table 2. These data about donors were also extracted and shown in Table 3. All the pharmacokinetic parameters were demonstrated by the form of mean ± SD. The method which was reported by Jiang et al. (2008) was applied to estimate the mean and standard deviation if the studies only provided minimum and maximum instead.

2.4. Statistical analysis

Weighted mean differences (WMD), 95% confidence intervals (CI) of tacrolimus dose and tacrolimus C/D ratio between different C3435T genotypes (CC/CT/TT) were reported respectively, according to their postoperative time. Heterogeneity was tested by χ^2 test which was based on Cochran's Q test, and quantified with I^2 (Cochran, 1954), and the forest plots. The variation in WMD attributed to heterogeneity was represented by I^2. A random effects model (DerSimonian and Laird method) was applied, when I^2 was more than 50%, which implied statistically significant heterogeneity (DerSimonian and Laird, 1986). Otherwise, a fixed effects model (Inverse Variance method) was applied. And Z-test was used to determine the statistical significance of pooled WMD and the results would be considered significant with $P < 0.05$. Subgroup analysis based on ethnicity was also performed.

All statistical analyses were conducted using STATA version11.0 (Stata Corp., College Station, TX, USA).

3. Results

3.1. Literature search

A total of 35 studies which were searched from both PubMed and the Cochrane Library were identified by our initial search. After screening the titles and abstracts, 7 studies were removed. Among them, 6 studies were review (Gijsen et al., 2012; Hawwa and McElnay, 2011; Marquet et al., 2007; Masuda and Inui, 2006; Staatz et al., 2010a; Utecht et al., 2006) and one study was case report (Provenzani et al., 2012). The remaining 28 studies were further evaluated with the full texts. Finally, 19 studies were excluded due to some reasons as follows: nine of them did not focus on the association between tacrolimus pharmacokinetics and ABCB1 C3435T (Fu et al., 2008; Fukudo et al., 2006, 2008; Li et al., 2007a, 2012b; Mourad et al., 2008; Uesugi et al., 2006; Wu et al., 2009; Yamauchi et al., 2002); four studies did not provide the numerical value of the parameters or showed the data as figures (Barrera-Pulido et al., 2008; Hawwa et al., 2009; Jin et al., 2009; Li et al., 2007b); two studies did not defined the postoperative time clearly with their corresponding data (Jun et al., 2009; Shi et al., 2013); one article studied the haplotypes of ABCB1 combined by G2677T/A and C3435T without the single polymorphism (Hosohata et al., 2009); and one article described the dose as geometric means (Elens et al., 2007). There were two studies that investigated the genotypes as CC and CT + TT (Wei-lin et al., 2006; Zhang et al., 2011), and one of them (Zhang et al., 2011) provided data as figures. The effort to contact with the corresponding authors was made, but in vain. So article by Wei-lin et al. (2006) was excluded because it was the only one which assessed the genotype combined as CT + TT. The flow chart described the process of our search strategy (Fig. 1).

As a result, 9 studies which included 558 liver transplant recipients were identified in this meta-analysis. And the variation of tacrolimus dose and concentration/dose ratio based on ABCB1 C3435T polymorphisms was analyzed respectively at different post-transplant time. There were 3 studies involving 133 liver donors which providing the association of ABCB1 C3435T polymorphism with tacrolimus dose and concentration/dose ratio among 9 studies, and also in all studies, only 3 studies gave the data about donors.

3.2. Association between recipients' ABCB1 C3435T polymorphism and tacrolimus dose

A total of 6 studies (Bonhomme-Faivre et al., 2009; Jin et al., 2005; Provenzani et al., 2009, 2011; Rahsaz et al., 2012; Wildt et al., 2011) involving 307 liver transplant recipients evaluated the association between ABCB1 C3435T polymorphism and tacrolimus dose. There were three studies (Bonhomme-Faivre et al., 2009; Jin et al., 2005; Rahsaz et al., 2012) examining the tacrolimus dose within a week. Two studies provided the data at postoperative time of 2 weeks (Jin et al., 2005; Wildt et al., 2011). Five of them gave the results at postoperative time of 1 month (Bonhomme-Faivre et al., 2009; Jin et al., 2005; Provenzani et al., 2009, 2011; Rahsaz et al., 2012). Three studies (Bonhomme-Faivre et al., 2009; Provenzani et al., 2009, 2011) presented the data at postoperative time of 3 months and two of them also gave the data at postoperative time of 6 months (Provenzani et al., 2009, 2011). Among them, only one study was conducted in Asian (Jin et al., 2005) when the post-transplant time was 1 week and 1 month, while the remaining studies were conducted in Caucasians. So subgroup analysis based on ethnicity, was performed only in Caucasian at the time of 1 week and 1 month after transplantation. Tacrolimus doses of different post-transplant time were summarized in Table 2.

Through heterogeneity test, random effects model was applied at the time of 1 week, 2 weeks and 1 month, because the value of I^2 showed heterogeneity ($I^2 > 50\%$) in tacrolimus dose in the comparison of genotypes CC and CT. Meta-analysis of the postoperative time of 3 months and 6 months was calculated by fixed effects model. On the basis of these principles, WMDs and 95% CIs were computed in different groups, respectively.

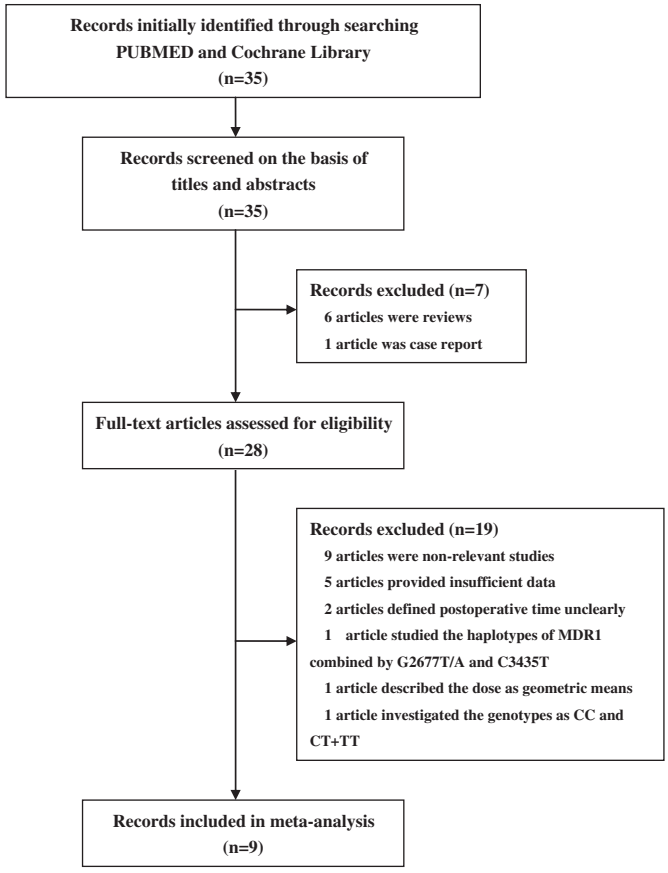

Fig. 1. Search strategy flow chart.

Results of meta-analysis which assessed the influence of ABCB1 C3435T polymorphism on tacrolimus dose were listed in Table 4 and presented in Fig. 2. Results showed that recipients with wild-type CC had a significantly higher tacrolimus dose than homozygous mutated genotype TT within 1 week (WMD = 0.01 (0.00, 0.02), $P = 0.014$). Similarly, recipients with heterozygous CT also had a significantly higher dose administration compared with TT after transplantation for 1 month (WMD = 0.01 (0.00, 0.02), $P = 0.002$). When subgroup analysis was performed, no significant association was detected except that subjects with CT genotype showed higher dose administration, compared with TT genotype in Caucasian after transplantation for 1 month (WMD = 0.01 (0.00, 0.01), $P = 0.046$) (Table 4 and Fig. 3).

3.3. Association between recipients' ABCB1 C3435T polymorphism and tacrolimus concentration/dose ratio

Nine studies, which included 558 liver transplant recipients, were presented in Table 2. The effect of ABCB1 C3435T polymorphism on tacrolimus C/D ratio has been estimated in these studies. According to the postoperative time in each study, five studies (Bonhomme-Faivre et al., 2009; Goto et al., 2002, 2004; Jin et al., 2005; Rahsaz et al., 2012) reported the results at 1 week after transplantation. Furthermore, three of them were conducted in Asians (Goto et al., 2002, 2004; Jin et al., 2005), and other two studies were conducted in Caucasians (Bonhomme-Faivre et al., 2009; Rahsaz et al., 2012). Also, two studies gave the data at the time of 2 weeks (Jin et al., 2005; Wildt et al., 2011). Six studies (Bonhomme-Faivre et al., 2009; Jin et al., 2005; Provenzani et al., 2009, 2011; Rahsaz et al., 2012; Yu et al., 2011) discussed the association in 1 month after transplantation. Among them, two studies were about Asians (Jin et al., 2005; Yu et al., 2011), and the remaining four studies were conducted in Caucasians (Bonhomme-Faivre et al., 2009; Provenzani et al., 2009, 2011; Rahsaz et al., 2012). As the same as the researches about tacrolimus dose, three studies (Bonhomme-Faivre et al., 2009; Provenzani et al., 2009, 2011) explored the effect in 3 months, while two of them included the time of 6 months (Provenzani et al., 2009, 2011). Subgroup analysis based on ethnicity was performed in groups of post-transplant within 1 week and 1 month.

For the tacrolimus C/D ratio, the choice of effects model was the same as the principles described above.

The results which were listed in Table 5, showed that subjects with CC genotype had lower C/D ratio, compared with recipients carrying genotype CT in 6 months (WMD = −109.54 (−197.92, −21.16), $P = 0.015$). Subjects with heterozygous genotype CT had higher C/D ratio than those with genotype homozygous TT in 3 months (WMD = 40.51 (1.12, 79.91), $P = 0.044$) and 6 months (WMD = 95.76 (13.44, 178.07), $P = 0.023$) (Fig. 4). Results of subgroup analysis based on ethnicity revealed that in Caucasian subjects with CC genotype had lower C/D ratio, compared with CT within 1 week (WMD = −2.02 (−3.91, −0.13), $P = 0.036$), but had higher C/D ratio than subjects with CT (WMD = 30.76 (29.42, 32.09), $P < 0.001$) and TT genotype (WMD = 1.85 (0.14, 3.55), $P = 0.034$) in 1 month (Fig. 3).

Table 4
Results of meta-analysis of the influence of ABCB1 C3435T polymorphism on tacrolimus dose in liver transplant recipients.

Subjects	Studies	Effects model	WMD (95% CI)	Test of heterogeneity		I^2	Z	P
				Chi-squared	P			
≤1 week								
All studies								
CC vs CT	Jin J., 2005*; Bonhomme-Faivre L., 2009; Rahsaz M., 2012	Random	0.02 (−0.00, 0.04)	5.23	0.073	61.8%	1.62	0.105
CC vs TT		Fixed	0.01 (0.00, 0.02)	3.47	0.176	42.4%	2.46	0.014
CT vs TT	Jin J., 2005; Bonhomme-Faivre L., 2009; Rahsaz M., 2012	Fixed	0.00 (−0.00, 0.01)	0.24	0.889	0%	1.01	0.314
Caucasian								
CC vs CT	Bonhomme-Faivre L., 2009; Rahsaz M., 2012	Fixed	0.01 (−0.00, 0.02)	1.41	0.235	29.2%	1.15	0.249
CC vs TT		Fixed	0.01 (−0.00, 0.02)	0.47	0.493	0%	1.73	0.083
CT vs TT		Fixed	0.00 (−0.00, 0.01)	0.10	0.747	0%	1.06	0.289
2 weeks								
All studies								
CC vs CT	Jin J., 2005*; de Wildt S.N., 2011	Random	0.03 (−0.02, 0.09)	4.44	0.035	77.5%	1.30	0.192
CC vs TT		Random	0.00 (−0.14, 0.15)	23.70	<0.001	95.8%	0.01	0.995
CT vs TT	Jin J., 2005; de Wildt S.N., 2011	Random	−0.03 (−0.12, 0.06)	10.46	0.001	90.4%	0.62	0.538
1 month								
All studies								
CC vs CT	Jin J., 2005*; Provenzani A., 2009; Provenzani A., 2011;	Random	0.01 −(-0.02, 0.05)	38.62	<0.001	89.6%	0.69	0.492
CC vs TT	Bonhomme-Faivre L., 2009; Rahsaz M., 2012	Random	0.01 (−0.03, 0.06)	50.55	<0.001	92.1%	0.65	0.517
CT vs TT		Fixed	0.01 (0.00, 0.02)	6.24	0.182	35.9%	3.13	0.002
Caucasian								
CC vs CT	Provenzani A., 2009; Provenzani A., 2011;	Fixed	−0.01 (−0.02, 0.00)	0.56	0.905	0%	1.14	0.255
CC vs TT	Bonhomme-Faivre L., 2009; Rahsaz M., 2012	Fixed	−0.00 (−0.01, 0.01)	1.20	0.753	0%	0.08	0.936
CT vs TT		Fixed	0.01 (0.00, 0.01)	4.08	0.253	26.5%	1.99	0.046
3 months								
All studies								
CC vs CT	Provenzani A., 2009; Provenzani A., 2011;	Fixed	0.01 (−0.01, 0.03)	0.32	0.852	0%	1.09	0.275
CC vs TT	Bonhomme-Faivre L., 2009	Fixed	0.01 (−0.01, 0.03)	0.20	0.903	0%	0.89	0.371
CT vs TT		Fixed	−0.00 (−0.02, 0.02)	0.02	0.992	0%	0.18	0.855
6 months								
All studies								
CC vs CT	Provenzani A., 2009; Provenzani A., 2011	Fixed	0.01 (−0.01, 0.02)	0.00	0.958	0%	0.77	0.443
CC vs TT		Fixed	0.01 (−0.00, 0.02)	0.01	0.912	0%	1.46	0.144
CT vs TT		Fixed	0.00 (−0.01, 0.02)	0.01	0.943	0%	0.67	0.505

* The results showed statistically significant ($P < 0.05$) in the original texts which were included.

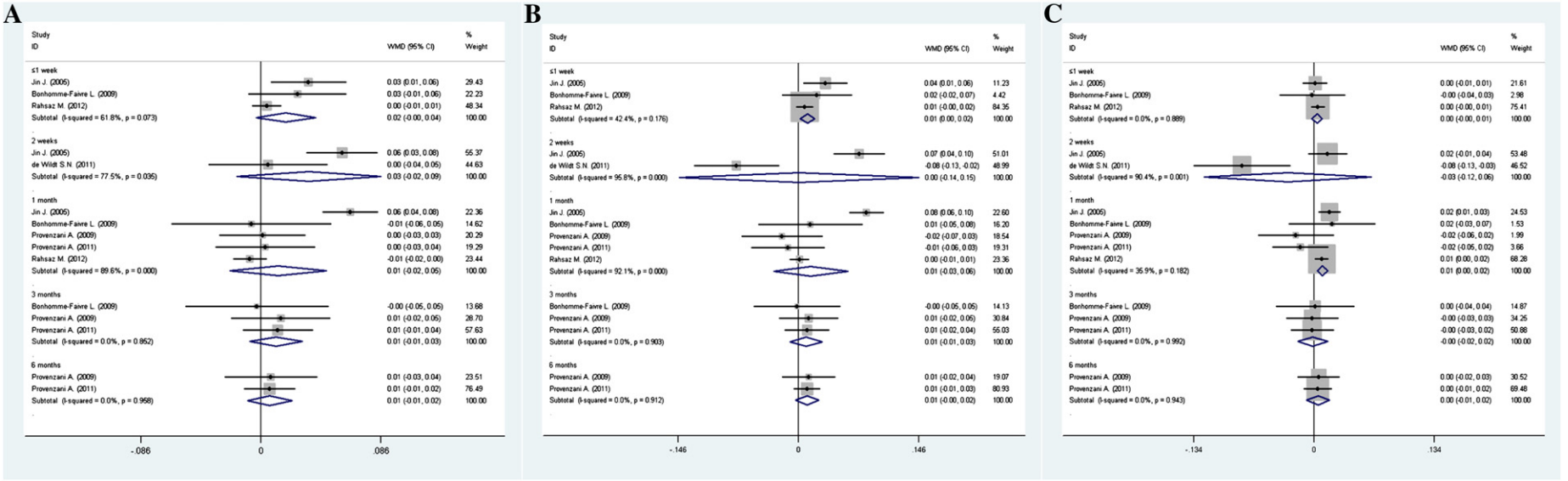

Fig. 2. Forest plots of the association between ABCB1 C3435T polymorphism and tacrolimus dose. (A) CC vs. CT; (B) CC vs. TT; (C) CT vs. TT. The center of each square represents the WMD. The area of the square is the number of sample and thus the weight used in the meta-analysis, and the horizontal line indicates the 95% CI.

3.4. Association of donors' ABCB1 C3435T polymorphism with tacrolimus dose and concentration/dose ratio

A total of 3 studies (Jin et al., 2005; Provenzani et al., 2009, 2011) involving 133 liver transplant donors evaluated the association between ABCB1 C3435T polymorphism and tacrolimus dose. There were one study (Jin et al., 2005) examining the tacrolimus dose at the time of a week and two weeks. All of them provided the data at postoperative time of 1 month. And two studies gave the results at postoperative time of 3 months and 6 months (Provenzani et al., 2009, 2011). Among them, only one study was conducted in Asian (Jin et al., 2005) as the post-transplant time was 1 week, 2 weeks and 1 month, while the remaining studies were conducted in Caucasians at postoperative time of 1 month, 3 months and 6 months. So subgroup analysis based on ethnicity was performed only in Caucasian within 1 month after transplantation. Tacrolimus doses of different post-transplant time were summarized in Table 3.

Through heterogeneity test, fixed effects model was applied in all groups of different postoperative time.

Results of meta-analysis which assessed the influence of ABCB1 C3435T polymorphism of donors on tacrolimus dose were listed in Table 6. Results showed that recipients receiving livers of donors with heterozygous CT, had higher tacrolimus dose than that with homozygous TT within 1 month (WMD = 0.01 (0.00, 0.02), $P = 0.047$). The group receiving organs with wild-type CC had higher tacrolimus dose at the post-operative time of 6 months (WMD = 0.01 (0.00, 0.03), $P = 0.036$), compared with recipients receiving livers with TT genotype.

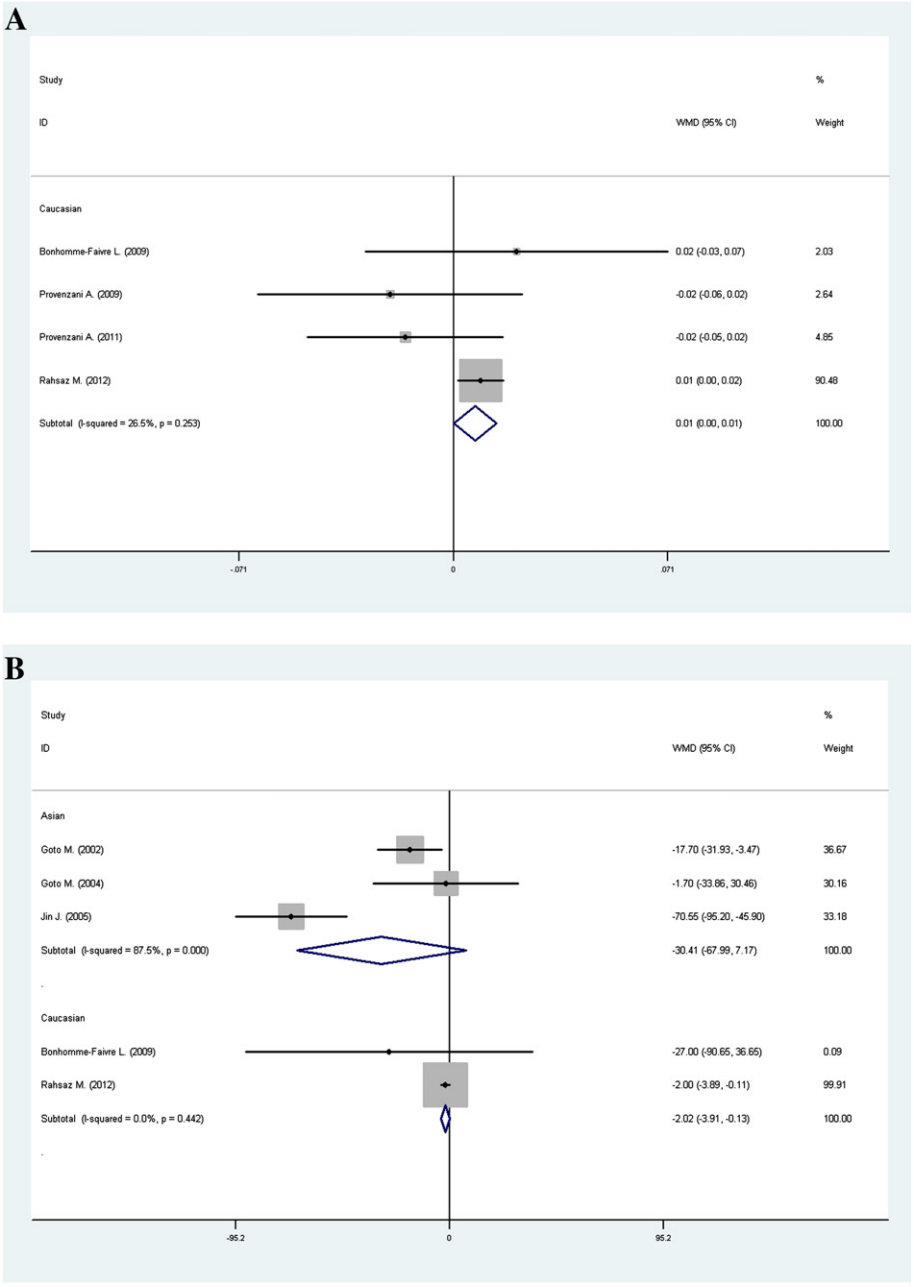

Fig. 3. Forest plots of the association between ABCB1 C3435T polymorphism and tacrolimus pharmacokinetic parameters by subgroup analysis of ethnicity. (A) Tacrolimus dose at 1 month after liver transplantation in Caucasian (CT vs. TT); (B) tacrolimus concentration/dose ratio within 1 week after liver transplantation (CC vs. CT); (C) tacrolimus concentration/dose ratio at 1 month after liver transplantation (CC vs. CT); (D) tacrolimus concentration/dose ratio at 1 month after liver transplantation (CC vs. TT).

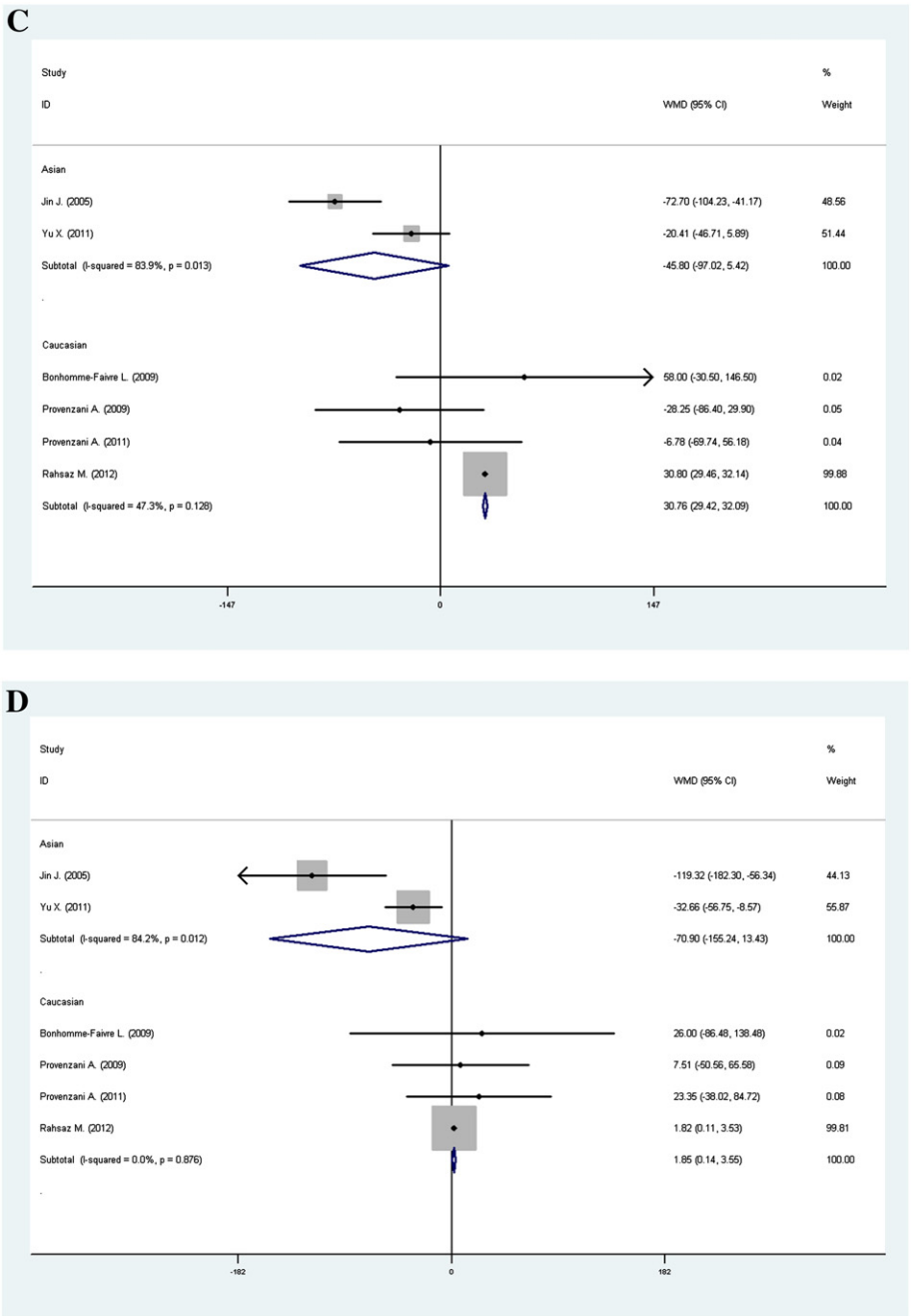

Fig. 3 (*continued*).

For the association between donors' ABCB1 C3435T polymorphism and tacrolimus C/D ratio, the detail of adopted literatures and model was the same as above. Tacrolimus C/D ratios of different post-transplant time were summarized in Table 3.

Results of meta-analysis which assessed the influence of ABCB1 C3435T polymorphism on tacrolimus C/D ratio were listed in Table 7. Results showed that there were no significant influences of C3435T SNPs in donors, either in subgroup analysis.

4. Discussion

Immunosuppressive regimens are very crucial for patients to achieve successful allograft function and suppress rejection. Nevertheless, adverse side effects, for example infection, cancer, diabetes and anemia, were accompanied (Halloran, 2004). As a result, the establishment of individual immunosuppression protocol is absolutely important and necessary. But it is a challenge to identify the dose requirements of individual immunosuppressant therapy after transplantation, especially for tacrolimus, because there are so many factors that may act on drugs which are substrates of P-glycoprotein. In recent years, evidences indicated that some important SNPs, such as CYP3A5 6986A>G, influenced tacrolimus pharmacokinetics (Staatz et al., 2010b), extremely. Researches about the functions, activity and expressions of CYP3A and P-glycoprotein were helpful to know how the polymorphisms affected metabolism. The results were introduced to explain association between polymorphisms and variation of interindividual pharmacokinetics. And ABCB1 SNPs, particularly C3435T, proved to be another important factor that may explain the variation. Knowing the characterization of ABCB1 polymorphisms and the effect of pharmacogenetics may be used as an

Table 5
Results of meta-analysis of the influence of ABCB1 C3435T polymorphism on tacrolimus concentration/dose ratio in liver transplant recipients.

Subjects	Studies	Effects model	WMD (95% CI)	Test of heterogeneity		I^2	Z	P
				Chi-squared	P			
≤1 week								
All studies								
CC vs CT	Jin J., 2005*; Bonhomme-Faivre L., 2009; Rahsaz M., 2012;	Random	−22.44 (−45.78, 0.89)	34.46	<0.001	88.4%	1.89	0.059
CC vs TT	Goto M., 2002; Goto M., 2004	Random	−24.70 (−53.70, 4.30)	21.57	<0.001	81.5%	1.67	0.095
CT vs TT	Jin J., 2005; Bonhomme-Faivre L., 2009*; Rahsaz M., 2012; Goto M., 2002; Goto M., 2004	Random	−0.97 (−19.72, 17.78)	9.95	0.041	59.8%	0.10	0.919
Asian								
CC vs CT	Jin J., 2005*; Goto M., 2002; Goto M., 2004	Random	−30.41 (−67.99, 7.17)	16.01	<0.001	87.5%	1.59	0.113
CC vs TT		Random	−29.12 (−85.15, 26.91)	13.05	0.001	84.7%	1.02	0.308
CT vs TT	Jin J., 2005; Goto M., 2002; Goto M., 2004	Fixed	10.49 (−5.99, 26.97)	3.10	0.212	35.5%	1.25	0.212
Caucasian								
CC vs CT	Bonhomme-Faivre L., 2009; Rahsaz M., 2012	Fixed	−2.02 (−3.91, −0.13)	0.59	0.442	0%	2.10	0.036
CC vs TT	Bonhomme-Faivre L., 2009*; Rahsaz M., 2012	Random	−58.90 (−185.19, 67.40)	7.94	0.005	87.4%	0.91	0.361
CT vs TT		Random	−42.65 (−143.60, 58.30)	5.28	0.022	81.1%	0.83	0.408
2 weeks								
All studies								
CC vs CT	Jin J., 2005*; de Wildt S.N., 2011	Random	−414.73 (−1133.22, 303.75)	33.43	<0.001	97.0%	1.13	0.258
CC vs TT		Random	2.14 (−125.15, 129.42)	11.33	0.001	91.2%	0.03	0.974
CT vs TT	Jin J., 2005; de Wildt S.N., 2011	Random	420.74 (−425.21, 1266.69)	46.51	<0.001	97.8%	0.97	0.330
1 month								
All studies								
CC vs CT	Jin J., 2005*; Provenzani A., 2009; Provenzani A., 2011;	Random	−9.99 (−53.46, 33.47)	61.36	<0.001	91.9%	0.45	0.652
CC vs TT	Bonhomme-Faivre L., 2009; Rahsaz M., 2012; Yu X., 2011*	Random	−17.35 (−48.51, 13.80)	22.69	<0.001	78.0%	1.09	0.275
CT vs TT	Jin J., 2005; Provenzani A., 2009; Provenzani A., 2011; Bonhomme-Faivre L., 2009; Rahsaz M., 2012; Yu X., 2011	Random	−5.52 (−32.82, 21.79)	24.58	<0.001	79.7%	0.40	0.692
Asian								
CC vs CT	Jin J., 2005*; Yu X., 2011*	Random	−45.80 (−97.02, 5.42)	6.23	0.013	83.9%	1.75	0.080
CC vs TT		Random	−70.90 (−155.24, 13.43)	6.34	0.012	84.2%	1.65	0.099
CT vs TT	Jin J., 2005; Yu X., 2011	Fixed	−16.49 (−40.97, 7.99)	0.82	0.366	0%	1.32	0.187
Caucasian								
CC vs CT	Provenzani A., 2009; Provenzani A., 2011;	Fixed	30.76 (29.42, 32.09)	5.69	0.128	47.3%	45.18	<0.001
CC vs TT	Bonhomme-Faivre L., 2009; Rahsaz M., 2012	Fixed	1.85 (0.14, 3.55)	0.69	0.876	0%	2.12	0.034
CT vs TT		Random	2.92 (−39.95, 45.79)	22.80	<0.001	86.8%	0.13	0.894
3 months								
All studies								
CC vs CT	Provenzani A., 2009; Provenzani A., 2011;	Random	−36.18 (−114.38, 42.03)	4.98	0.083	59.9%	0.91	0.365
CC vs TT	Bonhomme-Faivre L., 2009	Fixed	10.35 (−26.98, 47.68)	1.93	0.381	0%	0.54	0.587
CT vs TT		Fixed	40.51 (1.12, 79.91)	1.72	0.423	0%	2.02	0.044
6 months								
All studies								
CC vs CT	Provenzani A., 2009; Provenzani A., 2011	Fixed	−109.54 (−197.92, −21.16)	0.07	0.795	0%	2.43	0.015
CC vs TT		Fixed	−12.54 (−69.00, 43.92)	0.02	0.900	0%	0.44	0.663
CT vs TT		Fixed	95.76 (13.44, 178.07)	0.13	0.720	0%	2.28	0.023

* The results showed statistically significant ($P < 0.05$) in the original texts which were included.

efficient tool for optimizing efficacy and minimizing toxicity in patients after liver transplantation. Thus, knowledge which achieved in researches provided guidance to improve clinical outcomes. Although studies on relationship of ABCB1 SNPs and pharmacokinetics of their substrates were mostly focus on C3435T, the conclusions did not reach a consensus. The aim of this meta-analysis is to evaluate the effect of C3435T on tacrolimus pharmacokinetic parameters in liver transplant recipients.

As an important characteristic of C3435T SNP, its allele frequency varies in different human populations. In this meta-analysis, frequency of CC, CT and TT genotypes in liver transplant recipients showed 23.26%, 52.16%, and 24.58% in Asian and 19.46%, 52.14%, and 28.40% in Caucasian, respectively. The percentage of CC genotype was lower in Asian liver transplant patients than healthy Asians, and percentage of CT and TT genotype was little higher, while the similar trend was observed in Caucasian liver transplant patients (Fung and Gottesman, 2009).

Li et al. (2012a) has demonstrated that different postoperative times affected tacrolimus pharmacokinetics in subjects with different ABCB1 C3435T SNPs. The pharmacokinetic parameters were all calculated excluding the influence of body weight. Through the review of 6 studies involving 307 liver transplant patients (Table 2), it was observed that higher tacrolimus dose for the subjects with genotype CC after transplantation within 1 week was used, compared with subjects possessing genotype TT (Table 4 and Fig. 2(B)). At a month after transplantation, the recipients with heterozygous CT presented higher tarcolimus dose than the patients with homozygous mutated genotype TT (Fig. 2(C)). This is consistent with the report, which was carried out by Hoffmeyer et al. (2000). They observed high intestinal absorption of tacrolimus due to low P-gp expression in individuals with TT. Goto et al. (2004) also reported that the pharmacokinetics of tacrolimus was affected by excretion via P-glycoprotein in the intestine during the first week. Furthermore, the similar conclusion has been obtained in renal transplant recipients by Li et al. (2012a), which implied that the relationship of tacrolimus pharmacokinetics and ABCB1 C3435T polymorphism showed the same rule in different solid organ transplant recipients.

Several studies have explored the dose requirements of tacrolimus in liver transplant recipients in different ethnicity. Some of them indicated lower concentration/dose ratio in recipients with

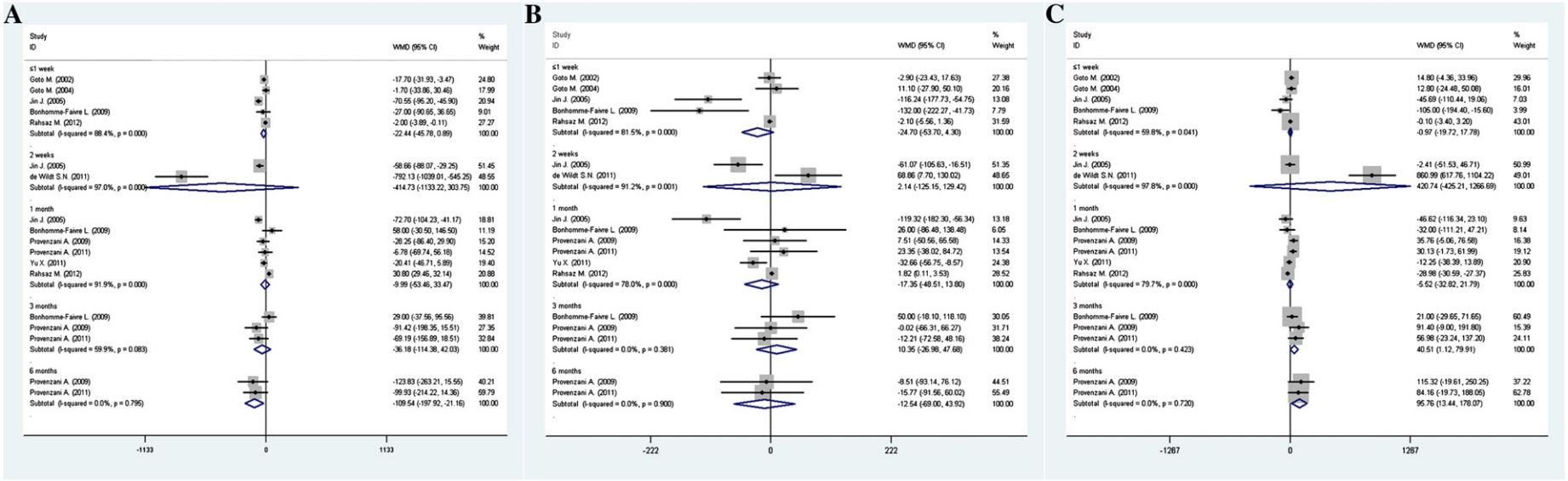

Fig. 4. Forest plots of the association between ABCB1 C3435T polymorphism and tacrolimus concentration/dose ratio. (A) CC vs. CT; (B) CC vs. TT; (C) CT vs. TT.

Table 6
Results of meta-analysis of the influence of ABCB1 C3435T polymorphism on tacrolimus dose in liver transplant donors.

Subjects	Studies	Effect model	WMD [95% conf. interval]	Test of heterogeneity		I^2	Z	P
				Chi-squared	P			
≤1 month								
All studies								
CC vs CT	Jin J., 2005; Provenzani A., 2009; Provenzani A., 2011	Fixed	−0.00 (−0.01, 0.01)	0.31	0.989	0%	0.04	0.967
CC vs TT		Fixed	0.01 (−0.01, 0.02)	4.16	0.384	3.9%	0.92	0.358
CT vs TT		Fixed	0.01 (0.00, 0.02)	4.21	0.379	4.9%	1.99	0.047
Caucasian								
CC vs CT	Provenzani A., 2009; Provenzani A., 2011	Fixed	−0.00 (−0.03, 0.02)	0.03	0.855	0%	0.42	0.675
CC vs TT		Fixed	−0.02 (−0.05, 0.01)	0.12	0.727	0%	1.25	0.210
CT vs TT		Fixed	−0.02 (−0.04, 0.01)	0.06	0.811	0%	1.13	0.260
3 months								
All studies								
CC vs CT	Provenzani A., 2009; Provenzani A., 2011	Fixed	−0.00 (−0.02, 0.02)	0.25	0.615	0%	0.18	0.860
CC vs TT		Fixed	0.01 (−0.01, 0.02)	0.02	0.879	0%	0.65	0.515
CT vs TT		Fixed	0.01 (−0.01, 0.03)	0.11	0.739	0%	0.74	0.461
6 months								
All studies								
CC vs CT	Provenzani A., 2009; Provenzani A., 2011	Fixed	0.00 (−0.01, 0.01)	0.26	0.613	0%	0.50	0.621
CC vs TT		Fixed	0.01 (0.00, 0.03)	0.00	0.944	0%	2.09	0.036
CT vs TT		Fixed	0.01 (0.00, 0.02)	0.32	0.569	0%	1.35	0.177

wild-type CC in Asian (Jin et al., 2005; Yu et al., 2011), while others showed insignificant association between C3435T polymorphism and tacrolimus dose administration (Goto et al., 2002, 2004). And no significant association was detected in Caucasian, only except for Bonhomme-Faivre's report (Bonhomme-Faivre et al., 2009). Interestingly, results of subgroup analysis based on ethnicity revealed no evidence was found to support this association in Asian, but in Caucasian subjects, the recipients possessing heterozygous CT needed higher tacrolimus dose than those with homozygous genotype TT at 1 month after transplantation (Table 4 and Fig. 3(A)). The result was the same as the result which was obtained from all subjects.

For the tacrolimus C/D ratio, 9 studies involving 558 liver transplant patients were adopted, and the statistical significant correlations were listed as follows (Table 5 and Fig. 4): (1) At the time of 3 months after the operation, the C/D ratio of TT patients was lower than those of CT. (2) After 6 post-operative months, the C/D level of the subjects with genotype CT was higher than those of the recipients with homozygous CC and TT, respectively. Additionally, according to subgroup analysis on different race, several significant associations in Caucasians were summarized in the first post-transplantation month. In detail, the Caucasian subjects with genotype CC showed lower C/D ratio than those with genotype CT at the first week after transplantation, while at 1 month after transplantation, the C/D ratio of Caucasian subjects carrying CC allele was higher than that of genotypes CT and TT (Figs. 3(B)–(D)). The C/D ratio for all subjects within a month did not reflect statistical significance, which may be due to ethnic differences (Asian and Caucasian) (Jiang et al., 2008). In fact, because adopted studies were all about Caucasians, the C/D ratios of 3 months and 6 months for all subjects were also the results of Caucasians. So generally, the C/D ratios in different post-transplantation time for Caucasian subjects seemed more significant. This phenomenon was similar with the report by Chowbay et al. (2005). However, the correlation between ABCB1 C3435T polymorphism and C/D ratio of tacrolimus was not steady. This indicated that C3435T may be not the only polymorphism affecting the expression of P-glycoprotein (Li et al., 2012a).

Table 7
Results of meta-analysis of the influence of ABCB1 C3435T polymorphism on tacrolimus concentration to dose ratio in liver transplant donors.

Subjects	Studies	Effect model	WMD [95% conf. interval]	Test of heterogeneity		I^2	Z	P
				Chi-squared	P			
≤1 month								
All studies								
CC vs CT	Jin J., 2005; Provenzani A., 2009; Provenzani A., 2011	Fixed	−7.21 (−26.12, 11.71)	1.29	0.863	0%	0.75	0.455
CC vs TT		Fixed	−9.58 (−31.13, 11.96)	7.24	0.124	44.8%	0.87	0.383
CT vs TT		Fixed	−7.42 (−30.86, 16.01)	7.74	0.102	48.3%	0.62	0.535
Caucasian								
CC vs CT	Provenzani A., 2009; Provenzani A., 2011	Fixed	−2.04 (−31.67, 27.60)	0.34	0.560	0%	0.13	0.893
CC vs TT		Fixed	7.11 (−18.37, 32.58)	0.11	0.737	0%	0.55	0.585
CT vs TT		Fixed	10.61 (−18.35, 39.56)	0.75	0.388	0%	0.72	0.473
3 months								
All studies								
CC vs CT	Provenzani A., 2009; Provenzani A., 2011	Fixed	6.15 (−76.19, 88.50)	0.03	0.869	0%	0.15	0.884
CC vs TT		Fixed	−18.62 (−135.54, 98.30)	0.07	0.786	0%	0.31	0.755
CT vs TT		Fixed	−20.56 (−112.61, 71.49)	0.20	0.651	0%	0.44	0.661
6 months								
All studies								
CC vs CT	Provenzani A., 2009; Provenzani A., 2011	Fixed	26.44 (−94.34, 147.22)	0.19	0.663	0%	0.43	0.668
CC vs TT		Fixed	−12.58 (−175.40, 150.24)	0.06	0.800	0%	0.15	0.880
CT vs TT		Fixed	−26.56 (−142.27, 89.14)	0.53	0.466	0%	0.45	0.653

In previous reports (Jin et al., 2005; Provenzani et al., 2009, 2011), for donors' ABCB1 genotypes, no significant association was observed with tacrolimus dose and C/D ratio. However, through this meta-analysis, several significant associations were obtained. Within 1 month and at 6 months after operation, recipients with donors' organ of CT and CC genotype presented higher tacrolimus dose, respectively, compared with recipients with donors' organ with homozygous TT genotype (Table 6). Donors' genotype of TT always required lower tacrolimus dose, which may be also due to high intestinal absorption of tacrolimus, because of low P-gp expression in individuals with TT genotype (Hoffmeyer et al., 2000).

However, limitations of this meta-analysis also should be detailed. First, as the result of the absence of available original data, several eligible articles were excluded. The exclusion of these articles may have an impact on this meta-analysis. Second, one of the included articles provided the minimum and maximum of the parameters, instead of mean and standard deviation. Though the mean and standard deviation were calculated according to the literature (Jiang et al., 2008), the results may still be influenced. Third, because of the discrepancy of postoperative time, the number of articles in some subgroup analysis was limited, and the sample size was small, simultaneously. Thus, our conclusion should be interpreted with caution.

5. Conclusion

In conclusion, through the meta-analysis for the including studies about the pharmacokinetics of tacrolimus and ABCB1 C3435T SNP, several significant associations were observed. The tacrolimus dose of subjects with homozygous mutated genotype TT was in lower level, relative to other subjects with genotypes CC and CT. This was the result of the higher adsorption rate of tacrolimus due to the lower expression of P-glycoprotein in TT subject group. According to the results of subgroup analysis on the basis of ethnicity, the Caucasians presented more significant correlations between the tacrolimus C/D ratio and ABCB1 C3435T polymorphism; however, these correlations did not show robust rules with C3435T polymorphism. It implied that the expression of P-glycoprotein was controlled by multi-genes, so the correlations were not steady in different post-transplantation time.

Conflict of interest

No conflict of interest to disclose.

Acknowledgment

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