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Research Article

Both donor and recipient CYP3A5 gene polymorphisms represent as significant factors influencing Tacrolimus weight-dose adjusted concentration in the early phase after living donor liver transplantation

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ABSTRACT

Several factors are considered for individualized Tacrolimus (Tac) dosing in transplant patients, including CYP3A5 genotype as a major one. However, previous studies about the effect of CYP3A5 polymorphism on Tac exposure in living donor liver transplant (LDLT) patients remain inconclusive, largely due to the contribution difference of donor and recipient CYP3A5 genotypes. This study aimed to assess the combined impact of both donor and recipient CYP3A5 genetic polymorphism on Tacrolimus weight-dose adjusted trough level (C0/D) during the first 4 weeks after LDLT. This retrospective, single-center study included 65 adults LDLT patients. Patients with CYP3A5*1*1 or CYP3A5*1*3 are defined as CYP3A5 expressors (E), and those with CYP3A5*3*3 are referred to as non-expressors (N). Bayesian Model Averaging method was used to screen potential factors affecting C0/D, including recipient (R) and donor (D) CYP3A5 genotypes, graft-to-recipient weight ratio, patients' demographic and subclinical characteristics at day 7, 14, 21 and 28 post-transplant. The selected significant factors were then analysed in multiple linear regression models to evaluate their impact on C0/D. To further explore effect of combined R-D genotype on Tac exposure, C0/D were evaluated among 4 groups (R_ED_E, R_ED_N, R_ND_E, R_ND_N) at each time points. In the study population, a high prevalence of CYP3A5 expressors was witnessed, with 61.5% in recipients and 55.5% in donors. In multiple linear regression models, the effect of the recipient CYP3A5 genotype on C0/D was significantly observed throughout the timeline ($p < 0.01$). Significant impacts were also seen in donor CYP3A5 genotype at three out of four time points (except for day 7). Of note, R_ND_N group had consistently highest C0/D, meanwhile, the lowest C0/D was observed in R_ED_E patients ($p < 0.05$). In conclusion, both recipient and donor CYP3A5 genetic polymorphisms influence Tac C0/D in the first 28 days after transplantation. Personalized Tac dosing after LDLT should be based on combined donor-recipient CYP3A5 genotype.

Keywords:
tacrolimus, CYP3A5 genetic polymorphism, liver transplantation, personalized medicine

1. INTRODUCTION

Graft rejection is a primary concern after solid organ transplantation[1]. The cornerstone of graft rejection prevention lies in immunosuppressive therapy, in which Tacrolimus (Tac) plays a pivotal role in the regimen[2]. However, Tac is recognized as a medicine with narrow therapeutic range and severe toxicity[3,4]. Low Tac concentration might deprive the ability to prevent rejection while high exposure could lead to severe nephrotoxicity. Additionally, Tac has great inter-individual and intra-individual pharmacokinetic variability, especially in the

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immediate period after transplant when function of the transplanted organ and patients' condition are not yet stabilized[3,5]. Therefore, Tac usage management through therapeutic drug monitoring (TDM) approach has been routinely conducted in many transplant centers[3,6].

To optimize Tac dosage, previous studies have investigated several factors potentially affecting Tac pharmacokinetic properties, such as patient demographics, graft features, laboratory test results, drug interactions, and patients' genotype[7-11]. Among these factors, the newest European consensus on Tac Therapeutic Drug Monitoring (TDM) suggests pharmacogenetics as a potential approach for Tac monitoring[3]. After oral administration, Tac is metabolized by gastrointestinal and hepatic cytochrome P450 (CYP) 3A isoenzymes, with CYP3A5 playing a major role[12,13]. However, a high prevalence of CYP3A5 genetic polymorphism has been recorded, with the frequency of the CYP3A5*3 mutation at 94% for the European, 80% for the Mixed American, and 68% for the South Asian[3]. Individuals with homozygous CYP3A5*3 genotype are considered to have a CYP3A5 non-expression genotype, resulting in poor Tac metabolism. Conversely, normal metabolic function is attributed to CYP3A5*1 allele, also defined as expression genotype[13,14]. It is consistently reported that patients with CYP3A5*1 allele (CYP3A5*1*1 or CYP3A5*1*3) demonstrate a lower Tac concentration (C0) than those with CYP3A5*3*3 in kidney, lung and heart transplantation. Therefore, CYP3A5*1 allele carriers are suggested to require 1.5 – 2 times higher Tac dose than CYP3A5*3*3 carriers[15].

However, in living-donor liver transplantation (LDLT), the influence of CYP3A5 genotype is more complicated as donor liver graft also exhibits Tac hepatic metabolism function, while the intestinal metabolism is still determined by recipients[16]. Therefore, both recipient and donor genotypes must be considered. While some studies have documented significant influences of both recipient and donor genotypes on Tac C0/D[17,18], others have suggested a greater contribution from the donor[19-21]. Otherwise, Buendia et al. demonstrated the impact of the recipient's intestinal genotype at the immediate postoperative period, whereas the donor's liver allograft appeared to exert influence after the first few weeks[22]. Admittedly, there is still conflicting evidence regarding the differential contributions of recipient and donor CYP3A5 genotypes in LDLT.

In Vietnam, liver transplantation is the second most common type of solid organ transplantation, following renal transplantation. Previous studies have demonstrated the influence of CYP3A5 genotype on Tac pharmacokinetic properties in renal transplant patients[23,24], but its impact on the liver transplant population remained unidentified. Additionally, the frequency of CYP3A5 genetic polymorphism in Vietnamese population also remains high[24]. Therefore, this research aimed to investigate the combined impact of recipient and donor CYP3A5 genotype on Tacrolimus weight-adjusted dose concentration in Vietnamese patients undergoing living donor liver transplantation.

2. METHODS

Study design and population

This retrospective, single-center study included patients undergoing living-donor liver transplantation from January 2019 to December 2023 at 108 General Hospital, Hanoi, Vietnam. The inclusion criteria were patients above 18 years old receiving Tacrolimus as a primary component in the immunosuppressive regimen. The study excluded retransplantation patients, those who were not followed up for at least 4 weeks after transplant, and those or their donors' lacking identification of CYP3A5 genotype.

As CYP3A5 genotyping has not yet been included in our instituiton's liver transplant protocol, the gene identification was conducted retrospectively and was currently used for research purposes.

Tacrolimus sampling & Data collection

In this study, Tacrolimus was immediate-released type (Prograf, taken orally twice daily every 12 hours). Tacrolimus concentrations (C0) were sampled prior to the administration of morning dose as part of the TDM routine. The Tac TDM procedure followed the hospital liver transplant protocol with Tac C0 target at 2 – 4 ng/mL on day 2, 4 – 6 ng/mL on day 3, 6 – 8 ng/mL on day 4, 8 – 10 ng/mL on day 5 and 10 – 12 ng/mL from day 6 onward after transplant.

Plasma tacrolimus concentrations were quantified by using luminescent micromolecular immunochemistry (CMIA, analyzed on Architect i2000, Abbott Diagnostics, USA). The limit of quantification of analyzing method is 0.8 ng/mL. The tacrolimus C/D ratio [(ng/mL)/(mg/kg/day)] was calculated as Tac C0 in ng/mL divided by the weight-adjusted dose (mg/kg/day).

Patients' information was collected in order to investigate their influence on Tac exposure. The data included: demographic data (age, gender), graft feature (graft to recipient weight), subclinical characteristics (serum creatinine (SCr), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), albumin (ALB), total bilirubin, direct bilirubin, urea, hematocrit (HCT), hemoglobin (HGB)) and concomitant medications. Recipient and donor CYP3A5 genotypes were also collected to be analyzed.

CYP3A5 identification

Before transplant, whole blood samples of donors and recipients were stored according to the hospital protocol. After receiving approval from the Hospital Ethical Committee, we retrospectively retrieved these stored blood samples to identify the CYP3A5 genotype. Two single nucleotide polymorphisms of CYP3A5, namely CYP3A5*1 and CYP3A5*3, were ascertained through direct sanger sequencing (CFX96 Real-Time PCR Detection System, USA).

Recipient and donor carrying CYP3A5*1*1 or CYPA5*1*3 were defined as CYP3A5 expressors (R_E, D_E), and those with CYP3A5*3*3 were refered to as CYP3A5 non-expressors (R_N, D_N). To identify the influence of combined recipient – donor genotype, we categorized patients into 4 groups: recipient expressors/ donor expressors group (R_ED_E), recipient expressors/ donor non-expressors group (R_ED_N), recipient non-expressors/ donor expressors group (R_ND_E), and recipient non-expressors/ donor non-expressors group (R_ND_N)

Table 1. General characteristics of living-donor liver transplant recipients & donors.

Feature	N = 65
Recipient	
Male, n (%)	54 (83.1)
Age (years), mean ± SD	51.2 ± 12.4
Weight (kg), mean ± SD	63.2 ± 9.48
Viral hepatitis, n (%)	
HBV	34 (32.5)
HCV	5 (7.7)
HBV + HCV	1 (1.5)
Donor	
Male, n (%)	50 (76.9)
Age (years), mean ± SD	33.8 ± 7.5
Weight (kg), mean ± SD	68.6 ± 8.1
Type of transplant, n (%)	
Living related	12 (18.5)
Living unrelated	53 (81.5)
Deceased	0
Graft feature	
Graft volumn (mL), mean ± SD	836.2 ± 162.1
Graft to Recipient Weight ratio (%), mean ± SD	1.312 ± 0.297
Tacrolimus dosage & TDM	
Intial Tacrolimus dose (mg/day), n (%)	
2	44 (67.7)
3	2 (3.1)
4	19 (29.2)
Initial Tacrolimus dose by weight (mg/kg/day), mean ± SD	0.044 ± 0.003
Day starting Tacrolimus, n (%)	
POD 0	5 (7.7)
POD 1	48 (73.8)
POD 2	5 (7.7)
POD 3	3 (4.6)
POD 4	4 (6.2)
Number of Tac C0 samples	1193
Number of Tac C0 samples per patient	18.4
Tac C0 within 4 weeks (ng/mL), mean ± SD	8.8 ± 3.5

Abbreviation: C0: trough concentration, HBV: Hepatitis B virus, HCV: Hepatitis C virus, TDM: therapeutic drug monitoring, POD: post-operative day, SD: standard deviation

Statistical analysis

Normal distribution data was presented as mean ± standard deviation (SD), and non-normal distribution data was presented as median with interquartile range (IQR). Hardy–Weinberg Equilibrium analysis for allele and genotype frequency was determined using the chi-squared ($\chi 2$) test.

Bayesian Model Averaging (BMA) method was used to screen potential factors affecting C0/D at day 7, 14, 21, 28 after transplant. Potential factors included in the study were those previously examined in other research and those recorded in medical records. Those factors include patients' demographic, graft feature, patients' subclinical characteristics, concomitant medications, and recipient and donor CYP3A5 genotypes. BMA method is a Bayesian approach that considers multiple possible models based on observed data and accounts for the model uncertainty[25]. The suitability of a model is indicated by posterior model probability and Bayesian Information Criterion (BIC) value. Model with the smallest BIC and highest posteriori probability is selected. The factors in that model are considered the correlated factors, which are then analysed in multiple regression analysis to quantify their impact on Tac C0/D at each time point.

In Tac C0/D comparision between 4 groups, one-way analysis of variance, followed by TuKey post-hoc test was used for normal distribution data, otherwise Kruskal-Wallis tests, followed by Dunn's post-hoc test, was used for non-normal distribution data. A p value less than 0.05 was considered to be statistically significant. Statistical analysis was conducted by Microsoft Excel 365 and R version 4.3.2.

3. RESULTS

Participant characteristics

In total, 168 patients underwent LDLT in the period. Due to missing samples, only 94 recipients and 89 donors had their CYP3A5 genotype identified. Total 69 recipient-donor pairs were fully identified for the CYP3A5 genotype in both recipient and donor, of which 4 pairs were excluded because the recipients died within 4 weeks post-transplant. Consequently, 65 recipient – donor pairs remained for further investigation.

Table1 depicts general characteristics of recipients and donors in the study. A total of 65 recipient-donor pairs were included, with an average age of 51.2 years old in recipients and 33.8 years old in donors. Males comprised the majority of LDLT cases. Approximately 81.5% of donors were not biologically related to the recipients. The graft-to-recipient weight ratio averaged around 1.3%.

Majority of patients (73.9%) started using Tac at day 1 post-transplant. The most common Tac initial dose was 2 mg/day (used in 67.7% of patients), followed by a dosage of 4 mg/day (29.2%). Only 2 patients started Tac with a dose of 3 mg/day. In terms of Tac monitoring, a total of 1193 trough concentration points were collected during the study, with an average of 18.4 points per patient. The mean Tac trough concentration (C0) was 8.8 ng/mL over the study period.

Frequency of CYP3A5 genetic polymorphisms

Table 2 shows the CYP3A5 genotype distribution in the study population. Individuals with CYP3A5*1*1 genotype accounted for the lowest proportion in both recipient and donor. Meanwhile, the percentage of CYP3A5 non-expression genotype (CYP3A5*3*3) in recipient and donor was 38.5% and 44.6%, respectively. Among the four combined genotype groups, R_ND_N had the lowest count, comprising only 8 pairs (12.3%). There were no significant deviations from Hardy–Weinberg Equilibrium in CYP3A5 genotypes and alleles for recipients and donors ($P > 0.05$), indicating the consistency of study data with the gene balance in general population.

Table 2. Frequency of CYP3A5 genotype in study population.

	Genotype	Frequency, n (%)
Recipient CYP3A5	*1*1	7 (10.7)
	*1*3	33 (50.8)
	*3*3	25 (38.5)
Donor CYP3A5	*1*1	9 (13.9)
	*1*3	27 (41.5)
	*3*3	29 (44.6)
Combined Recipient – Donor	R_ED_E	19 (29.2)
	R_ED_N	21 (32.3)
	R_ND_E	17 (26.2)
	R_ND_N	8 (12.3)

Tac C0/D by Recipient and Donor Genotypes

Tac C0/D ratio of different genotype in recipient or donor was demonstrated in **Figure 1**. Regarding recipient genetic polymorphisms only, those who were CYP3A5 non-expressors (R_N) consistently exhibited higher C0/D values than CYP3A5 expressors (R_E) over the course of 28 days. However, when considering different genotypes solely in donors, it was only after 7 days that patients with non-expressor donors (D_N) demonstrated higher C0/D values compared to expressor donors (D_E). During initial 7 days, the trend line showed relatively equal values in both D_E and D_N.

Multiple linear regression analysis

After screening with Bayesian Averaging Method, four correlated factors were identified: recipient CYP3A5 genotype, donor CYP3A5 genotype, hematocrit (HCT), and serum creatinine (SCr). In multiple linear regression models, the impact of these 4 factors on Tac C0/D was quantified at each time point.

Overall, genetic factors exhibited a greater contribution than non-genetic factors. The effect of recipient CYP3A5 genotype was observed at all time points, whereas donor genotype significantly influenced C0/D only at days 14, 21, and 28 ($p < 0.05$). Among the non-genetic factors, HCT and SCr were the only two associated factors. HCT correlated with C0/D at days 7 and 21, while SCr had an impact at days 7 and 28 ($p < 0.05$). Both factors showed a positive correlation with C0/D (coefficient >0*)*

Tac CO/D comparision between groups

As the influence of recipient and donor genotype was determined during the study period (**Figure 1**, **Table 3**), we proceed to analyze the combined effect of both Recipient-Donor on Tac C0/D (**Figure 2**). Patients with both CYP3A5 non-expression genotypes (R_ND_N) consistently exhibited the highest median C0/D, whereas the lowest C0/D values were observed in the R_ED_E groups accross various time points. Notably, the most significant difference was noted between these 2 groups with the C0/D ratio of R_ND_N being 1.7 – 3 times higher than that of R_ED_E.

When comparisions were conducted between pairs with same donor genotype but different recipient one (R_ED_E vs R_ND_E; R_ED_N vs R_ND_N), patients with recipient non-expressor had higher C0/D than recipient expressor ($R_ND_E > R_ED_E$; $R_ND_N > R_ED_N$). The statistically significant difference was observed in nearly all time points for both pairs ($p < 0.05$), only except for $R_ED_N – R_ND_N$ at day 28 ($p > 0.05$).

The relatively similar trending was also witnessed when the donor genotype was different and recipient was the same ($R_ED_N > R_ED_E$; $R_ND_N > R_ND_E$). Regarding the comparison between R_ND_N and R_ND_E, statistical differences were observed only on day 14, while $R_ED_N – R_ED_E$ pair showed statistical differences at days 14, 21, and 28. On day 7, both comparisons' differences were not statistically significant.

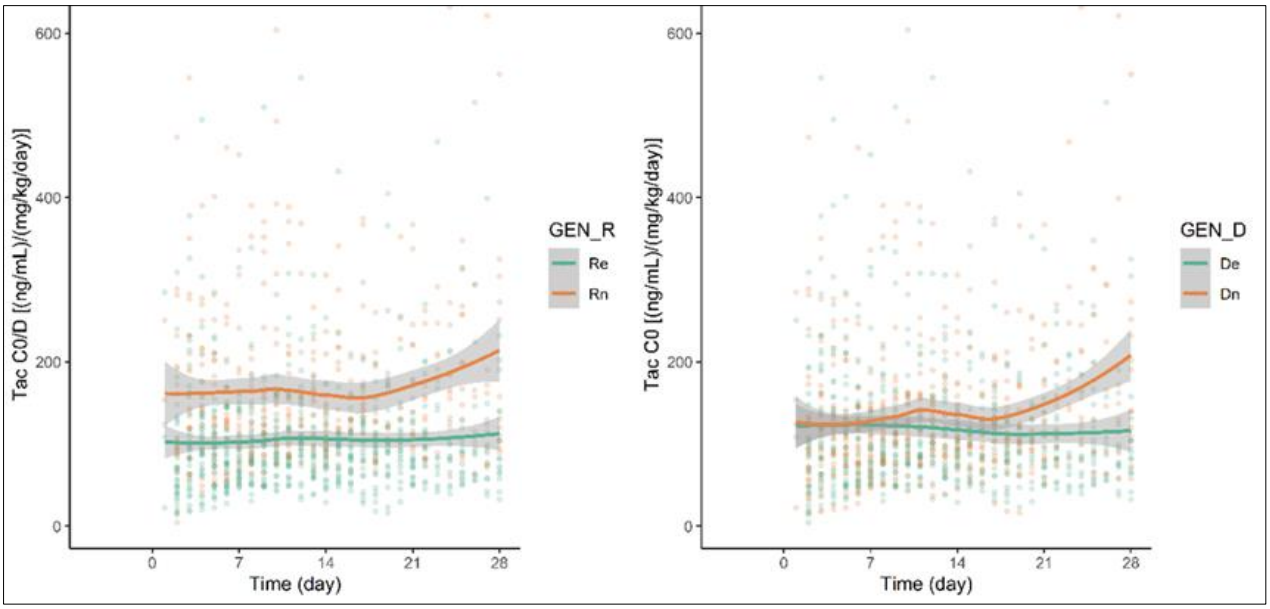

Figure 1. Tacrolimus weight-dose adjusted concentration by recipient and donor genotype. The straight lines represent median C0/D, the shade gray represents 95% confidence interval. *Abbreviation:* C0/D: weight-adjusted dose concentration; R_E: recipient with expression genotype; R_N: recipient with non-expression genotype; D_E: donor with expression genotype; D_N: donor with non-expression genotype.

Table 3. Multiple linear regression analysis of factors influencing Tac C0/D

POD	Covariates	Coefficient	Standard error	P value
7	Creatinin	0.68	0.26	0.0109
	Hematocrit	5.19	2.40	0.0344
	Recipient genotype	55.59	17.91	0.0029
	Donor genotype	-	-	ns
14	Recipient genotype	44.93	14.55	0.0031
	Donor genotype	36.79	14.24	0.012
21	Creatinin	0.27	0.06	<0.001
	Recipient genotype	62.11	12.05	<0.001
	Donor genotype	34.76	11.84	<0.01
28	Hematocrit	3.98	1.76	0.028
	Recipient genotype	83.03	20.71	<0.001
	Donor genotype	74.29	20.63	<0.001

Abbreviation: POD: post-operative day; ns: not significant

4. DISCUSSION

The present study evaluated the impact of CYP3A5 genetic polymorphisms on Tac C0/D in patients after living-donor liver transplatation. Generally, both recipient and donor genotypes were observed to influence Tac C0/D during the first 28 days after transplant.

High polymorphism of the CYP3A5 genotype has been reported in many studies, with 25 allelic variants of CYP3A5 (alleles numbered 1–9)[26]. While CYP3A5*1 is the wildtype allele with normal CYP3A5 function, CYP3A5*3 has been identified as the most common nonfunctional variant of CYP3A5. This is caused by a SNP *(single nucleotide polymorphism)* at nucleotide 22893 in intron 3 of CYP3A5*3, which creates a cryptic splice site, alters mRNA splicing and results in a premature stop codon. Other alleles such as *2, *6, and 7 have also been investigated for their mechanisms leading to the loss of CYP3A5 expression[26]. However, the frequency of these alleles has been reported to be low, especially in the Asian population. Additionally, no other CYP3A5 allele, other than *1 and *3, has been detected in previous studies in Vietnam. Previous studies and guidelines have also focused solely on the impact of CYP3A5*1 and *3 alleles on Tac exposure[3]. Therefore, studying CYP3A5*1 and *3 would be of greater importance than other variants for our population.

In our study, the frequency of the CYP3A5*3*3 was 38.5% in recipient and 44.6% in donor (**Table 2**), aligning with the frequencies observed in the Asian population[27]. This frequency is much lower compared to European countries and white populations, where homozygous CYP3A5*3 individuals constitute approximately 80–85% of the population[3,20,28]. These data clearly indicate that in white populations, CYP3A5 non-expressors are predominant, with CYP3A5 expressors being the minority. Conversely, the prevalence of CYP3A5 expressors in the Asian population, including Vietnam, is relatively high. Due to these differences in CYP3A5 polymorphism frequency, we suggest that for Asian population, alternative approaches based on individual genotypes, rather than following standard dose regimen of Europe, would be more effective for Tac monitoring.

Overall, we observed the consistent impact of recipient genotype on Tac C0/D across all time points during the initial 28 days post-transplantation. The median Tac C0/D trended higher in recipients with non-expresion genotype (R_N) compared to those with expression genotype (R_E) (**Figure 1**), confirmed with statistically significant correlation through multiple regression linear analysis result (**Table 3**). Given the same donor genotype, Tac C0/D levels were also higher in R_ND_E and R_ND_N groups than in R_ED_E and R_ED_N groups, respectively (**Figure 2**). This finding aligns with previous research. A study by Miwa (2017), involving 400 Japanese patients, highlighted the significant influence of recipient intestinal CYP3A5 genotype, rather than that of the donor liver, on Tac C0/D ratio within the first 5 weeks postoperative[29]. Similarly, another study involving 373 Chinese LDLT patients also demonstrated the impact of recipient genotype upto 3 months[30]. However, conflicting results have been reported in some studies. Argudo (2020) found no

influence of recipient CYP3A5 polymorphisms on Tacrolimus metabolism within the initial 90 days, which could be attributed to the study's inclusion of patients undergoing full liver transplants[30]. As a full-sized liver would have different physiological recovery from a partial one, study with full liver transplants may exhibit a more pronounced influence of donor genotype over recipient genotype.

In terms of donor influence, the trend in Tac C0/D, as depicted in **Figure 1**, along with results of the multiple linear regression analysis presented in **Table 3**, suggested that only after day 7 post-transplant did the impact of donor genotype become significant. While it is reported that the influence of the donor genotype tends to increase over time following transplantation, the exact timing of this initial impact remains uncertain.

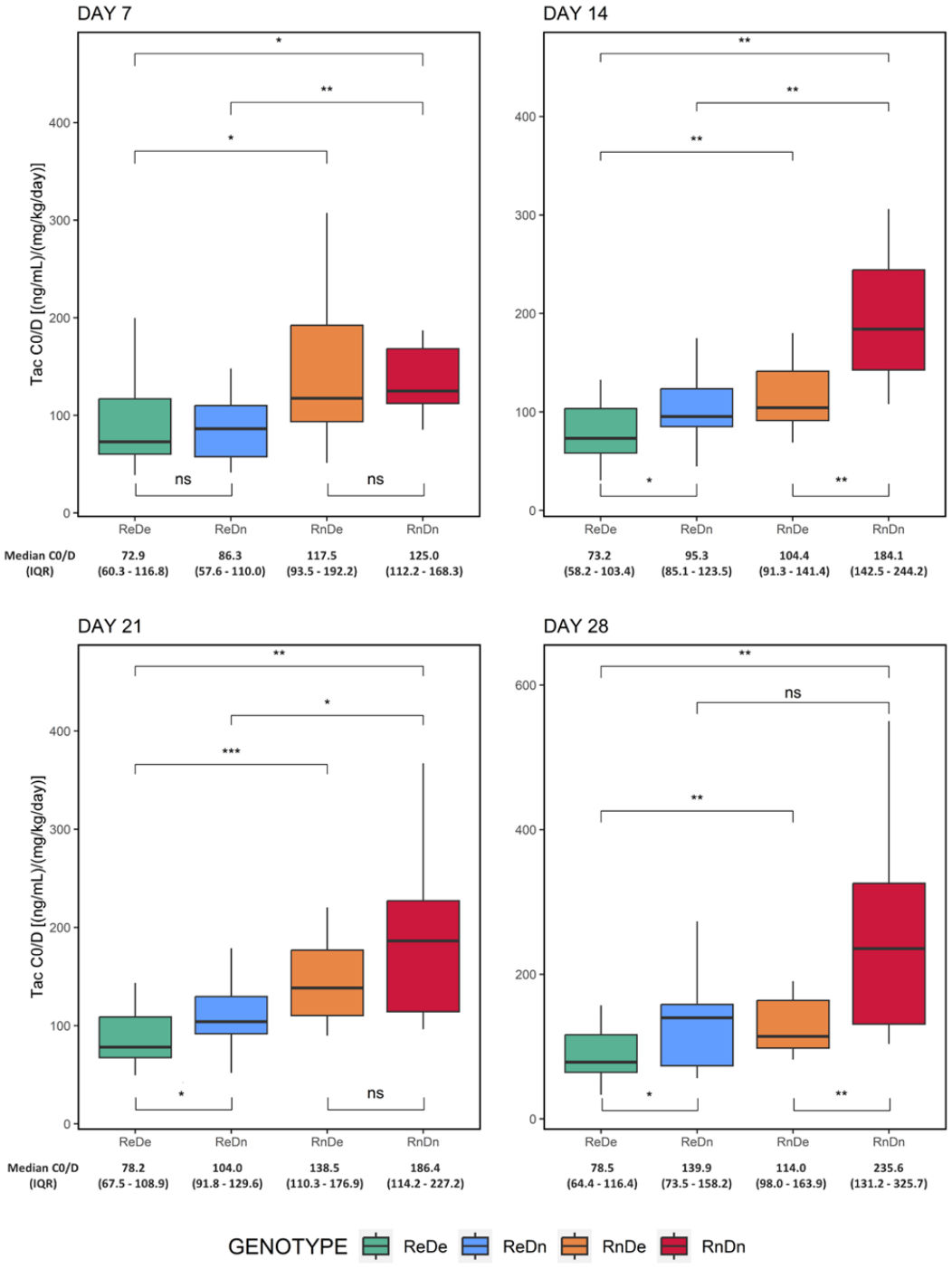

Figure 2. The effect of combined recipient – donor CYP3A5 genotype on Tac C0/D. Patient were divided into 4 groups (R_ED_E, R_ED_N, R_ND_E, R_ND_N). The bars represent the median C0/D and the boxes indicate 25th and 75th percentiles of the data. *Abbreviation*: R_ED_E: recipient expressors/ donor expressors group; R_ED_N: recipient expressors/ donor non-expressors group; R_ND_E: recipient non-expressors/ donor expressors group; R_ND_N: recipient non-expressors/ donor non-expressors group; IQR: interquartile range; *p <0.05; **p <0.01; ***p <0.001; ns: not significant.

Liu et al. indicated the influence of the donor genotype from the onset of Tacrolimus, while Goto et al. suggested the impact became apparent only after 1 month of treatment[30,31]. Mechanistically, the impact of donor genotype would depend on the recovery of liver allograft. A partial grafted liver would require time to regain normal function, and this duration depends on various factors such as ischemic injury, graft size, immunosuppression, steatosis, donor age and viral hepatitis[32]. These diverse characteristics may explain the differing results regarding the initial impact of donor genotype. In relation to our study population, we hypothesized that the donor genotype would require more than a week to begin influencing Tac metabolism. However, for a more definitive conclusion, further studies involving a larger number of patients should be conducted.

Among the four combined genotype groups, CYP3A5 expressors with expression grafted liver (R_ED_E) observed the lowest C0/D, meanwhile the highest value belonged to CYP3A5 non-expressors with non-expression grafted liver (R_ND_N) across study duration. These results corroborate the impact of both recipient - donor influences and align with finding of other research[18]. Consequently, patients in R_ED_E groups initally should receive a higher dosage, while a lower dosage could be considered for R_ND_N patients. The Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for CYP3A5 genotype indicate that the starting dose of TAC for R_ED_E should be 1.5 to 2 times higher than that for R_ND_N[15]. As the relative ratio of Tac C0/D between R_ND_N and R_ED_E was approximately 1.7 at day 7 **(Figure 2)**, the appropriate Tac initial dosage in our institution could follow the suggestion of CPIC Guildlines for R_ED_E and R_ND_N groups. Nevertheless, to recommend precise doses for each group, further research, such as population pharmacokinetic modeling and dosage simulation studies, is needed.

Regarding intermediate groups (R_ED_N, R_ND_E), the CPIC guidelines, however, do not recommend specific dosages due to inconsistent results in these two groups[15]. Shao (2020) indicated that their impact on Tac clearance was equivalent, and suggested a similar dosage for both the R_ED_N and R_ND_E groups, with the dose being the same as for R_ND_N[33]. However, in Ji study, R_ED_N group was recommended a moderate dosage between R_ED_E and R_ND_N, while R_ND_E dosage was similar to that of R_ND_N[34]. Our study found no statistically significant difference in Tac C0/D between the R_ND_E and R_ND_N groups at two of the four time points (**Figure 2**). Meanwhile, R_ED_N differed from both R_ED_E and R_ND_N ($R_ED_E < R_ED_N < R_ND_N$). Consequently, we propose that Tac dosage in our population could follow a similar pattern as in Ji's study, with a standard dose for R_ND_E (equal dose as R_ND_N) and a moderate dose for R_ED_N. However, as we have mentioned above, further study should be conducted to investigate precise doses for each group.

Regarding non-genetic factors, we explored the significant association of hematocrit (HCT) and serum creatinine (SCr) with Tac C0/D, although their influence was found to be less pronounced compared to the CYP3A5 genotype (**Table 3**). Both factors showed positive correlations with Tac C0/D at certain time points. The association between HCT and Tac levels has been well-documented in previous research[11,35]. Given Tacrolimus's strong affinity for red blood cells, higher HCT values likely result in a larger fraction of Tac bound to red blood cells, leading to reduced Tac metabolism in plasma and consequently higher Tac concentrations. Consequently, HCT has been included in several population pharmacokinetic models to suggest Tac dosage[36,37]. Furthermore, our study also examined the impact of renal function on Tac concentration, as reflected by serum creatinine levels. However, this effect was relatively minor, with a 1 μmol/L increase in serum creatinine associated with only around 0.3 unit increase in Tac C0/D (**Table 3**). Sam et al. reported relatively similar finding, indicating that a 1 μmol/L increase in serum creatinine resulted in a 0.6% reduction in Tac clearance (CL/F)[38]. However, they also suggested that dose adjustment based on serum creatinine levels might be unnecessary, given that only a small fraction of Tac and its metabolites are eliminated through the kidneys. Conversely, Chen et al. observed that patients with a creatinine clearance of 30 mL/min exhibited a 12% decrease in Tac clearance compared to those with normal renal function[39]. This suggests that individuals with severe renal impairment may indeed require Tac dosage adjustments. Previous studies have indicated that other factors such as drug interactions and liver function can influence Tac concentration. However, our study did not find significant associations between these factors and Tac levels. This lack of observed effect may be due to the small sample size and the limited follow-up period of only 4 weeks. Consequently, longer follow-up and larger sample sizes may be necessary to fully understand the impact of these factors on Tac concentration.

To the best of our knowledge, this is the first study to evaluate the impact of the CYP3A5 genotype on Tac exposure in the Vietnamese population following LDLT. Conducted at one of Vietnam's largest organ transplant centers, these findings could provide valuable evidence to enhance Tac monitoring in clinical practice. Given findings in our study, applying routine CYP3A5 genotype testing for recipients and donors before transplant could support the concept of Tac dosage individualization. In our hospital, Tac dosing is still followed traditional weight-based dosage and the

experience of physicians, while other factors, particularly CYP3A5 genotype, are not yet considered. Our results demonstrate the pivotal role of CYP3A5 genotype in Tacrolimus exposure, paving the way for further research to incorporate the CYP3A5 genotype into a population pharmacokinetic (PopPK) model for personalized Tacrolimus dosing. Indeed, the concept of utilizing pharmacogenetic and population pharmacokinetic (PK/PG) for Tac TDM has been highlighted in the latest European consensus of 2019[3]. Additionally, a randomized, controlled trial in China indicated that CYP3A5 genotype-based dosing using PopPK model significantly improved the percentage of patients reaching target range, as well as reduced the number of dose adjustments, compared to traditional weight-based dosage[40]. Based on these positive evidences, this study is expected to be the first step in our ongoing research aimed at optimizing Tacrolimus usage.

However, there remains certain limitations in our study. Firstly, due to the retrospective nature of our study, fewer participants were identified CYP3A5 than expected, resulting in relatively small sample size. Further research with a larger cohort could be carried out to enhance the statistical power and representativeness of general population. Secondly, since we focused on the CYP3A5 genotype, other genetic factors were not investigated. Few studies have reported the influence of ABCA1 genetic polymorphisms on Tac absorption, which are also prevalent in the Asian population, but the results remain inconclusive in the liver transplant population[3]. Including other genes in future studies could provide a more comprehensive view of pharmacogenomics for Tac. Lastly, as the present study focused mainly in the early phase after transplantation, we suggested that longer-term research could be conducted to investigate the enduring impact of recipient and donor genotypes.

5. CONCLUSION

Our study found that both recipient and donor CYP3A5 genotype influence Tac C0/D during the first 28 days after LDLT. The level of impact was evaluated in multiple linear regression models. R_ND_N group exhibited the highest C0/D, while the lowest C0/D was observed in R_ED_E patients. Personalized Tac dosing after LDLT should be based on combined donor-recipient CYP3A5 genotype.

6. ACKNOWLEDGMENT

Conflict of interest
The authors declare that they have no conflict of interest.

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Ethics approval
This research was reviewed and approved by the 108 General Hospital Ethical Committee, under the approval number 863/GCN-BV.

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