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Drug–drug interaction between tacrolimus and caspofungin in Chinese kidney transplant patients with different *CYP3A5* genotypes

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Abstract

Background: The effect of drug–drug interaction between tacrolimus and caspofungin on the pharmacokinetics of tacrolimus in different *CYP3A5* genotypes has not been reported in previous studies.

Objectives: To investigate the effect of caspofungin on the blood concentration and dose of tacrolimus under different *CYP3A5* genotypes.

Design: We conducted a retrospective cohort study in The First Affiliated Hospital of Shandong First Medical University and Shandong Provincial Qianfoshan Hospital from January 2015 to December 2022. All kidney transplant patients were divided into the combination or non-combination group based on whether tacrolimus was combined with caspofungin or not. Patients were subdivided into *CYP3A5* expressers (*CYP3A5*1/*1* or *CYP3A5*1/*3*) and *CYP3A5* non-expressers (*CYP3A5*3/*3*).

Methods: Data from the combination and the non-combination groups were matched with propensity scores to reduce confounding by SPSS 22.0. A total of 200 kidney transplant patients receiving tacrolimus combined with caspofungin or not were enrolled in this study. Statistical analysis was conducted on the dose-corrected trough concentrations (C_0/D) and dose requirements (D) of tacrolimus using independent sample two-sided t-test and nonparametric tests to investigate the impact on patients with different.

Results: In this study, the C_0/D values of tacrolimus were not significantly different between the combination and non-combination groups ($p = 0.054$). For *CYP3A5* expressers, there was no significant difference in tacrolimus C_0/D or D values between the combination and non-combination groups ($p = 0.359$; $p = 0.851$). In *CYP3A5* nonexpressers, the C_0/D values of tacrolimus were significantly lower in the combination than in the non-combination groups ($p = 0.039$), and the required daily dose of tacrolimus was increased by 11.11% in the combination group.

Conclusion: Co-administration of caspofungin reduced tacrolimus blood levels and elevated the required daily dose of tacrolimus. In *CYP3A5* non-expressers, co-administration of caspofungin had a significant effect on tacrolimus C_0/D values. An approximate 10% increase in the weight-adjusted daily dose of tacrolimus in *CYP3A5* non-expressers is recommended to ensure the safety of tacrolimus administration.

Plain language summary

Differential drug interactions of caspofungin on tacrolimus in Chinese kidney transplant patients with different CYP3A5 genotypes

Why was the study done? Currently, there have been studies reporting the effect of caspofungin on tacrolimus blood concentrations, but the conclusions are conflicting, and

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no study has focused on the effect of *CYP3A5* genotypes on the drug-drug interaction. We explored a number of research questions: 1. Does caspofungin have an effect on the pharmacokinetics of the immunosuppressant tacrolimus? 2. How does *CYP3A5*3*, which affects tacrolimus metabolism significantly, affect tacrolimus blood concentration levels? 3. How should the dose of tacrolimus be adjusted when combined with caspofungin?

What did the researchers do? By reviewing literature, we understood the problems related with the kidney transplant patients better, which led to the development of strict inclusion and exclusion criteria. The patients (from January 2015 to December 2022) were categorized into combination and non-combination groups according to whether they were co-administered with caspofungin or not. The results of the study were analyzed using SPSS 22.0.

What did the researchers find? The study finally included 200 patients. We found no statistically significant differences in the dose-corrected trough concentrations (C_0/D) and dose requirements (D) of tacrolimus between the combination and non-combination groups. However, in patients with *CYPA5*3/*3* genotype, tacrolimus C_0/D values were significantly lower in the combination group than in the non-combination group, and the required daily tacrolimus dose was increased.

What do the findings mean? This study has found that co-administration of caspofungin in patients with *CYP3A5*3/*3* genotype resulted in a significant decrease in the C_0/D value of tacrolimus, therefore, an appropriate increase in the daily dose of tacrolimus is recommended. The implication is that it is important and necessary to monitor the concentrations of tacrolimus and the *CYP3A5* genotypes, and adjust the dose when combined or discontinuing with caspofungin in kidney transplant patients.

Keywords: caspofungin, *C_0/D*, CYP3A5, kidney transplant, tacrolimus

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Introduction

Tacrolimus, a calcineurin inhibitor with a 23-element macrolide structure, is currently widely used as a first-line immunosuppressive agent after kidney transplantation to reduce the incidence of graft rejection.[1,2] The triple immunosuppressive regimen of tacrolimus/mycophenate/glucocorticoid is the primary treatment for preventing rejection after kidney transplantation. Tacrolimus has a very narrow therapeutic window. Blood concentrations above the upper limit of the therapeutic window may increase the risk of adverse reactions and even toxicity, while concentrations below the therapeutic window may lead to insufficient immunosuppression or graft rejection.[3,4] Therefore, monitoring tacrolimus concentrations is particularly important for predicting the outcomes of pharmacotherapy in kidney transplant recipients and has become a routine protocol in clinical practice. Tacrolimus is mainly metabolized by cytochrome P450 (CYP) 3A family. Previous studies reporting *POR*28* and *ABCB1* are limited or with contradictory conclusions.[5] In the *CYP3A* family, *CYP3A4* and *CYP3A5* are thought to be relevant in adults. *CYP3A7* is only expressed in fetal liver, and *CYP3A43* is of uncertain significance.[5] For *CYP3A4* gene variants, *CYP3A4*22* and *CYP3A4*1B* are not suitable for evaluating their effect on tacrolimus efficacy in Chinese due to their near-zero mutation rate in Asian populations,[6,7] and *CYP3A4*18B* was dependent on *CYP3A5* genotype.[8] *CYP3A5* gene is highly polymorphic in the East Asian population[9] and is one

of the important factors affecting the blood concentrations of tacrolimus.[10,11] Among them, the frequency of the *CYP3A5*3* allele is about 0.742, while the gene frequencies of both *CYP3A5*6* and *CYP3A5*7* alleles are less than 0.001 in Asian populations, so only the *CYP3A5*3* genotype was considered in this study.[5] Individuals carrying at least one functional allele are referred to as *CYP3A5* expressers (*CYP3A5*1/*1* and *CYP3A5*1/*3* genotypes), while those carrying two non-functional alleles are referred to as *CYP3A5* non-expresser (*CYP3A5*3/*3* genotype). The Clinical Pharmacogenetics Implementation Consortium (CPIC) recommends that kidney transplant recipients be individualized tacrolimus therapy based on *CYP3A5* genotypes.[5] In addition, other factors such as drug–drug interactions (DDIs) and the patient's characteristics including body mass index (BMI), days post-transplant, and hematocrit (HCT) may also influence tacrolimus plasma concentrations.[12,13]

Invasive fungal infection (IFI) is an important cause of morbidity and mortality in solid organ transplant recipients because of the use of immunosuppressants and postoperative health deterioration. Invasive *Candidiasis* (53%) and invasive *Aspergillosis* (19%) were the most common pathogens of IFI.[14] Echinocandins have been widely used for fungal infection in kidney transplant patients due to their good safety and efficacy.[15] Caspofungin, the first echinocandin agent on the market with a strong antifungal effect against azole-resistant *Candida*, is highly recommended for the treatment of invasive *Candidiasis* (including Candidemia in neutropenic and non-neutropenic patients).[16] Caspofungin is a poor substrate for CYP450 enzymes. Although interactions of echinocandins are generally rare, caspofungin has greater interactions with other drugs than micafungin and anidulafungin.[17] Studies have shown that the maximum blood concentration (Cmax) of tacrolimus can be reduced (up to 20%) when caspofungin is used in combination, which may also require adjustment of the tacrolimus dose.[18] However, little is known about the effects of caspofungin on tacrolimus drug interactions under different genotypes of *CYP3A5*. Therefore, the purpose of this study was to evaluate the effect of caspofungin on tacrolimus blood concentrations and daily doses in kidney transplant patients with different genotypes of *CYP3A5* and to further guide the dose adjustment of tacrolimus when combined with caspofungin.

Methods

Study design

This single-center retrospective cohort study was conducted in The First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[19] In-patients receiving kidney transplants in the Department of Urology from January 2015 to December 2022 were included. The inclusion criteria were as follows: (1) at least 18 years old, (2) first kidney transplant, and (3) taking a tacrolimus-based triple immunosuppressive regimen (tacrolimus + mycophenolate sodium + glucocorticoids). Exclusion criteria were as follows: (1) patients with multiple organ transplants, (2) patients receiving drugs that affect the blood concentrations of tacrolimus (e.g. strong enzyme inhibitors or inducers of cytochrome 450 enzyme including rifampin, phenytoin sodium, carbamazepine, azoles or Wuzhi capsules), (3) patients with severe hepatic dysfunction [serum alanine aminotransferase (ALT) levels >3 times of the upper normal limit or total bilirubin (TBIL) >2 mg/dL, or known hepatic cirrhosis, etc.] or severe gastrointestinal disease (e.g. severe gastric ulcer, gastric perforation, ulcerative colitis, gastric bypass, banding or gastric sleeve), (4) patients who were pregnant or breastfeeding, and (5) patients with the significant rejection of transplanted organs or death from other causes within 1–2 months after the operation.

The enrolled kidney transplant patients were divided into combination groups or non-combination groups based on whether caspofungin was used in combination with tacrolimus or not.

Data collection and patient treatment

The data were collected from the HIS (Hospital Information System). Demographic and biochemical characteristics of patients in both groups were collected, including male, age, height, weight, days post-transplant, ALT, aspartate aminotransferase, TBIL, serum creatinine (Cr), estimated glomerular filtration rate (eGFR), red blood cell count (RBC), albumin (ALB), hemoglobin (HGB), HCT, *CYP3A5* genotypes, trough concentration (C_0) and dose (D) of tacrolimus after combined with caspofungin, and drug use in

combination at each trough measurement. eGFR was calculated by the CKD-EPI formula based on the serum creatinine at the start of caspofungin treatment [For women with a plasma creatinine ≤ 0.7, (plasma creatinine/0.7)$^{-0.329}$ × (0.993)^{age} (× 166 if black; × 144 if white or other); for women with a plasma creatinine >0.7, (plasma creatinine/0.7)$^{-1.209}$ × (0.993)^{age} (× 166 if black; × 144 if white or other); for men with a plasma creatinine ≤ 0.9; (plasma creatinine/0.9)$^{-0.411}$ × (0.993)^{age} (× 163 if black; × 141 if white or other); for men with a plasma creatinine >0.9, (plasma creatinine/0.9)$^{-1.209}$ × (0.993)^{age} (× 166 if black; × 144 if white or other)]. Hepatic dysfunction was defined as the serum ALT higher than three times the upper normal limit, TBIL higher than 2 mg/dL, or known hepatic cirrhosis at the time of being enrolled. The patients' blood was collected in the morning before taking tacrolimus to ensure that the measured values were trough concentrations. Measurement of tacrolimus trough values was performed in our hospital laboratory using a uniform fluorescence polarization immunoassay, usually at 1- to 2-day intervals. The relative standard deviation of the results was less than 6%. The trough concentrations measured at least 3 days after the administration or dose adjustment of tacrolimus were chosen for the non-combination group because tacrolimus concentrations generally reach to a steady state 2–3 days after the dosage. The C_0 values of tacrolimus in the combination group were recorded when 1 week of treatment with co-administered caspofungin was completed and tacrolimus concentrations had reached a steady state.

Patients were treated with a post-transplant immunosuppression protocol according to *The Kidney Disease: Improving Global Outcomes Clinical Practice Guideline*.[20] More specifically, intravenous methylprednisolone sodium succinate was administered the day after transplantation with an initial dose of 500 mg/day, which was evenly tapered to 40 mg/day during the first week. During the second week, methylprednisolone tablets were given sequentially at 40 mg/day, which was gradually reduced to 16 mg/day as the maintenance dose. Immunosuppression was maintained with oral mycophenolate sodium 720 mg, twice daily. Tacrolimus was taken orally twice a day at an initial dose of 0.05–0.25 mg/kg/day. Dosages were adjusted based on tacrolimus C_0 of the patients and clinical situation. Target tacrolimus trough levels in the first month following kidney transplantation were 6–15 ng/mL, 8–15 ng/mL in the first 2–3 months, 7–12 ng/mL in the 4–6 months after transplantation, and 5–10 ng/mL after the first 6 months.[21] For the patients in the combination group, the dosage of caspofungin was 70 mg intravenous injection once on the first day after surgery and 50 mg intravenous injection once a day starting from the second day. The patient's medication was strictly monitored by the nursing team to ensure good adherence.

Genotyping

The presence of *CYP3A5*3* was detected using a TaqMan real-time polymerase chain reaction (RT-PCR) assay (Applied Biosystems, Foster City, CA, USA). Genomic deoxyribonucleic acid was extracted from the blood samples using the TIANamp Blood DNA Kit (DP348; TIANGEN Biotech, Beijing, China) according to the manufacturer's instructions. The primers and sequences for *CYP3A5*3* are as follows: forward primers (5′-CCTGCCTTCAATTTTCACT-3′); reverse primers (5′-GGTCCAAACAGGGAAG AGGT-3′). To validate the RT-PCR results, *CYP3A5*3* (rs776746) was confirmed *via* Sanger sequencing using a 3730XL Genetic Analyzer (Applied Biosystems, Foster City, CA, USA).

Statistical analysis

The method of propensity score matching was used to match the baseline data of kidney transplantation patients in the combination and non-combination groups at 1:1, to obtain a new dataset with successful matching. Normality was tested using the Shapiro–Wilk test. Continuous data with normal distributions were represented as mean ± standard deviation (SD), and comparison between groups was performed by independent sample two-sided *t*-test. The median and interquartile range were used to represent continuous data with abnormal distributions, and a nonparametric test was used to compare between groups. Categorical data were expressed as frequency and percentages, and the chi-square test was used for comparison between groups. $p < 0.05$ represents a significant difference. All analyses were performed using the International Business Machine Statistical Product Service Solutions software package SPSS 22.0. Figures were generated using the Microsoft Office software package Microsoft Visio (version 2013) and the GraphPad Software package GraphPad Prism (version 8).

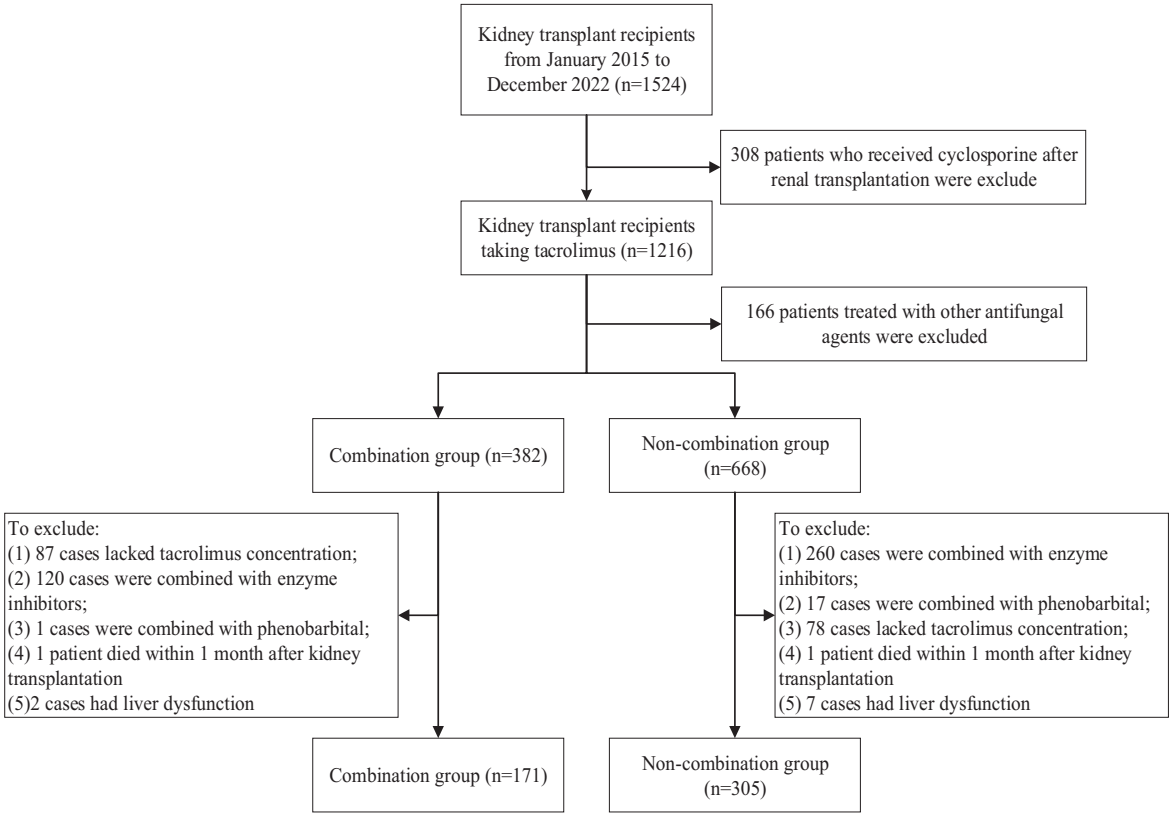

Figure 1. Flow chart of participants in the study.

Results

Patient recruitment and baseline information

A total of 1524 patients who underwent kidney transplantation were screened, of which 308 were excluded due to receiving the immunosuppressive regimen without tacrolimus, and 166 were excluded for not receiving caspofungin for fungal infection. In the remaining patients, those who lacked data of C_0 of tacrolimus, combined with strong cytochrome enzyme inhibitors or inducers, suffered from severe liver dysfunction or died within 1 month after kidney transplantation were excluded. Finally, 476 kidney transplant recipients were enrolled in this study, among whom 171 were for the combination group and 305 for the non-combination group. The enrolling process is shown in Figure 1.

The combination and the non-combination groups were matched with propensity scores to reduce confounding by SPSS 22.0. Sex of birth, age, BMI, *CYP3A5*3*, days post-transplant, ALB, HCT, HGB, and RBC were strongly correlated with the C_0/D values of tacrolimus,[22–26] so these variables were used as covariates for propensity score matching. Finally, 100 cases were successfully matched in the combination and non-combination groups, respectively. In the combination group, there were 76 males, aged 39.00 (30.00, 50.00) years old with a BMI of 23.43 (20.76, 25.36) kg/m^2. In the non-combination group, there were 72 males, aged 38.50 (31.00, 48.00) years old and an average BMI of 23.16 (20.98, 26.18) kg/m^2. The groups were not significantly different when comparing the recipient age, male, BMI, days post-transplant, liver, and renal function at the baseline. The demographic and baseline characteristics of both groups are shown in Table 1.

CYP3A5 *genotyping*

The genotype frequencies of the *CYP3A5*3* polymorphisms of the recruited patients are summarized in Table 2. Among the 200 kidney transplant recipients, 3 (1.50%) recipients exhibited the *CYP3A5*1/*1* genotype, 64 (32.00%) carried *CYP3A5*1/*3*, and 133 (66.50%) carried *CYP3A5*3/*3*. Therefore, the allelic frequencies

Table 1. Baseline clinical characteristics of the study population.

Indicators	Combination group ($n=100$)	Non-combination group ($n=100$)	p Value
Sex of birth (male/female)	76/24	72/28	0.519
Age (years)	39.00 (30.00, 50.00)[b]	38.50 (31.00, 48.00)[b]	0.769
BMI (kg/m^2)	23.43 (20.76, 25.36)[b]	23.16 (20.98, 26.18)[b]	0.582
Days post-transplant	9.00 (7.00, 23.50)[b]	10.00 (8.00, 19.50)[b]	0.291
Organ dysfunction			
Hepatic dysfunction	0	0	/
eGFR (mL/min/1.73 m^{-2})	58.46 ± 28.09[a]	58.53 ± 25.33[a]	0.985
ALB	38.20 (36.30, 41.20)[b]	38.50 (35.60, 41.95)[b]	0.736
RBC (10^{12}/L)	3.44 (3.07, 3.87)[b]	3.55 (3.08, 3.88)[b]	0.524
HGB (g/L)	106.00 (95.00, 118.50)[b]	108.00 (93.00, 119.00)[b]	0.658
HCT (%)	0.33 (0.30, 0.37)[b]	0.33 (0.30, 0.37)[b]	0.516
PPI combination (n)	68	58	0.143
Primary disease (n)			
Diabetes nephropathy	26	23	0.622
PKD	2	4	0.678
IgA nephropathy	17	15	0.700
Glomerulonephritis	48	52	0.572
Congenital solitary kidney	2	0	0.477
Other	5	5	1.000

[a]Mean ± SDs.
[b]Median and interquartile range.
ALB, albumin; BMI, body mass index; CRF, chronic renal failure; eGFR, estimated glomerular filtration rate; HCT, hematocrit; HGB, hemoglobin; IgA, immunoglobulin A; PKD, polycystic kidney disease; PPI, proton pump inhibitor; RBC, red blood cell count.

Table 2. The *CYP3A5* genotype distribution of kidney transplant patients.

n	Genotype (n/%)			Allele Frequency (%)		p
	CYP3A5*1/*1	***CYP3A5*1/*3***	***CYP3A5*3/*3***	***CYP3A5*1***	***CYP3A5*3***	
200	3/1.50	64/32.00	133/66.50	17.50	82.50	0.126

of *CYP3A5*1* and *CYP3A5*3* were 17.50% (70/400) and 82.50% (330/400), respectively. The allele distribution of *CYP3A5* was consistent with the Hardy-Weinberg equilibrium ($\chi^2=2.343$; $p=0.126$).

Effect of caspofungin on tacrolimus concentrations

Table 3 shows the effect of caspofungin on the required daily doses of tacrolimus under different *CYP3A5* genotypes. To maintain tacrolimus C_0

Table 3. Effect of caspofungin on the required daily dose of tacrolimus under different *CYP3A5* genotypes.

Patients	Tacrolimus daily dose (mg/kg/day)			*p*
	Non-combination group	Combination group	% Change in dose	
Total (*n* = 200)	0.096 (0.065, 0.113)	0.100 (0.070, 0.119)	+4.17	0.544
*CYP3A5*1/*1* or **1/*3* (*n* = 67)	0.105 (0.071, 0.123)	0.110 (0.081, 0.123)	+4.76	0.851
*CYP3A5*3/*3* (*n* = 133)	0.090 (0.063, 0.108)	0.100 (0.066, 0.111)	+11.11	0.449

in the ideal ranges, the required daily dose of tacrolimus was 4.17% higher in the combination group compared to the non-combination group ($p = 0.544$). Further analysis based on *CYP3A5* genotypes showed that for patients with *CYP3A5*1/*1* or *CYP3A5*1/*3* genotype, the required daily dose of tacrolimus was 4.76% higher in combination group than in non-combination group ($p = 0.851$), whereas for patients with *CYP3A5*3/*3* genotype, the required daily dose of tacrolimus was 11.11% higher in combination group than in non-combination group ($p = 0.449$).

No significant difference in the C_0/D values of tacrolimus was found between the combination and the non-combination groups [109.71 (74.03, 134.00) ng/mL/(mg/kg/day) *versus* 118.93 (85.65, 157.39) ng/mL/(mg/kg/day), $p = 0.054$]. Further analysis based on *CYP3A5* genotypes showed that in patients with *CYP3A5*1/*1* or *CYP3A5*1/*3* genotype, there was no significant difference in the C_0/D of tacrolimus between the combination and non-combination groups [91.58 (67.29, 131.36) ng/mL/(mg/kg/day) *versus* 100.80 (70.20, 138.45) ng/mL(mg/kg/day), $p = 0.359$], either; while for patients with *CYP3A5*3/*3* genotype, the C_0/D values of tacrolimus were significantly lower in the combination group than in the non-combination group [116.21 (81.11, 134.00) ng/mL/(mg/kg/day) *versus* 126.50 (101.34, 158.18) ng/mL/(mg/kg/day), $p = 0.039$], as shown in Figure 2.

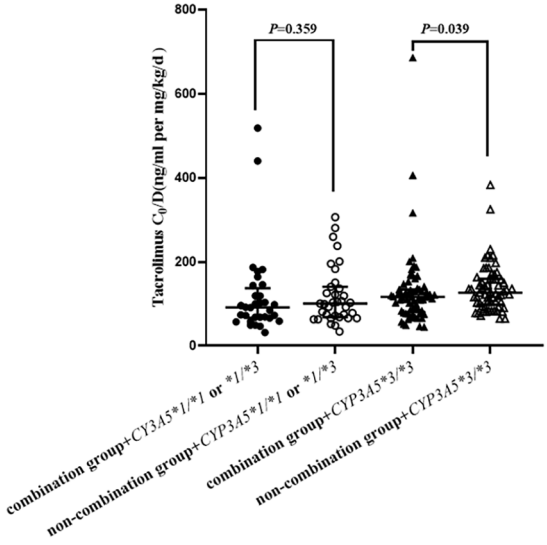

Figure 2. Tacrolimus dose-adjusted trough concentrations between combination and non-combination groups with different *CYP3A5* genotypes ($p < 0.05$ denotes a significant difference between corresponding data).
Solid circle or triangle means tacrolimus combined with caspofungin, and hollow means no combination. ●/○: *CYP3A5* expresser: *CYP3A5*1/*1* or **1/*3* genotypes. ▲/△: *CYP3A5* non-expresser: *CYP3A5*3/*3* genotype.

In patients with *CYP3A5*3/*3* genotype, the C_0/D values of tacrolimus were significantly lower in the combination group than in the non-combination group ($p = 0.039$), while in patients with *CYP3A5*1*, no statistical difference was found between the two groups ($p = 0.359$).

Discussion

In this study, we found that caspofungin decreased the blood concentrations of tacrolimus. The DDI between tacrolimus and caspofungin was stronger in *CYP3A5* non-expressers than in *CYP3A5* expressers, and the required daily dose of tacrolimus in combination with caspofungin was higher than in the non-combination group for *CYP3A5* non-expressers.

The results obtained in the present study are consistent with those in studies in allogeneic hematopoietic stem cell, liver, and lung transplant recipients.[27–29] Data from these studies suggested that co-administration of caspofungin reduced

the blood concentrations of tacrolimus. This might be because caspofungin is mainly metabolized as an inactive substance in the liver and serves as an inducer of liver drug-metabolizing enzymes, which can increase the metabolism of tacrolimus,[29] thereby reducing the concentration of tacrolimus[18,30] and increase the required dose of tacrolimus.[31] But no statistically significant difference was found. By contrast, Cheng *et al.*[21] obtained statistically significant results in their study, indicating that co-administration of caspofungin significantly reduced tacrolimus blood concentrations.

In addition, our study also examined the DDI between tacrolimus and caspofungin according to *CYP3A5* genotyping. For *CYP3A5* non-expressers, the C_0/D values of tacrolimus were significantly lower in patients treated with caspofungin than in patients without caspofungin, while we did not find such a difference in *CYP3A5* expressers. As a result, the required daily dose of tacrolimus was elevated more in *CYP3A5* non-expressers than in *CYP3A5* expressers, indicating that the DDI between tacrolimus and caspofungin was stronger in *CYP3A5* non-expressers. The results above suggest that enhanced monitoring of tacrolimus blood concentration levels is needed to better adjust the individual regimen of kidney transplant patients receiving caspofungin in combination with tacrolimus.

This study was characterized by propensity score matching to match the baseline data of the combination and non-combination groups to minimize the interference of confounding factors. In addition, this study is the first observational study to combine the DDI of tacrolimus with caspofungin and the *CYP3A5* genotype in kidney transplant patients.

Limitations

There are some limitations to this observational study. First, the sample size of our study was conducted in a single center, which limits the generality of our findings. Second, the study only evaluated a Chinese kidney transplant population, so it is not clear whether the findings apply to other populations that may have other *CYP3A5* variants. Third, only selected *CYP3A5*3* for the study in an Asian population.

Conclusion

Co-administration of caspofungin is associated with accelerated tacrolimus metabolism, which decreases tacrolimus blood levels and increases tacrolimus dosage. For *CYP3A5* expressers, co-administration of caspofungin had a minor effect on tacrolimus C_0/D values. For *CYP3A5* non-expressers, co-administration of caspofungin significantly decreased tacrolimus C_0/D values, thereby elevating tacrolimus D values. Therefore, in kidney transplant patients with the *CYP3A5*3/*3* genotype, it is recommended to consider increasing the dose of tacrolimus by approximately 10% when co-administration of caspofungin and to strengthen the monitoring of tacrolimus concentrations to ensure the safety of tacrolimus administration.

Declarations

Ethics approval and consent to participate

The Ethics Committee of The First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital approved the research protocol [YXLL-KY-2023(018)]. The need for informed consent was waived by The First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital.

Consent for publication

This study was retrospective and an informed consent waiver was obtained at the time of ethical application.

Author contributions

Yundi Zhang: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Bowen Shen: Investigation; Methodology; Writing – review & editing.

Yue Li: Investigation; Writing – review & editing.

Huiying Zong: Investigation; Writing – review & editing.

Xiaoming Zhang: Investigation; Writing – review & editing.

Xiaohong Cao: Investigation; Writing – review & editing.

Fengxi Liu: Investigation; Writing – review & editing.

Yan Li: Conceptualization; Investigation; Methodology; Project administration; Software; Supervision; Validation; Visualization; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The data sets used and/or analyzed during this study are available from the corresponding author upon reasonable request.

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