science, engineering and health studies

Research Article

Science, Engineering and Health Studies
https://lio1.tci-thaijo.org/index.php/sehs
ISSN (Online): 2630-0087

Clinically relevant drug-drug interactions of tacrolimus in the first week post-kidney transplantation recipients

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***Received**: 25 September 2023*
***Revised**: 1 November 2023*
***Accepted**: 13 November 2023*
***Published**: 31 December 2023*

***Citation**:
Musa, A. B., Youngkong, S., Tragulpiankit, P., Hustrini, N. M., and Nosoongnoen, W. (2023). Clinically relevant drug-drug interactions of tacrolimus in the first week post-kidney transplantation recipients. Science, Engineering and Health Studies, 17, 23050025.

ABSTRACT

This retrospective observational study aimed to investigate the prevalence and associated risk factors of clinically relevant drug-drug interactions of tacrolimus in kidney transplantation (KT) recipients during the first week post-transplantation. Medical records of tacrolimus-treated KT recipients were reviewed and DDIs were determined using two drug interaction programs. The presence of clinically relevant DDIs was confirmed by evaluating tacrolimus levels (C_0) and adverse drug events through the drug interaction probability scale. This study enrolled 142 eligible KT recipients with mean potential DDIs in each patient of 7.8 and a standard deviation of 2.4. The majority type of potential DDIs was in the moderate category (84.0%). The prevalence of clinically relevant DDIs of tacrolimus was 18.6% (95% confidence interval: 11.4%–27.7%). Logistic regression analysis revealed that the number of potential DDIs significantly affected the likelihood of clinically relevant DDIs with tacrolimus, increasing the odds of experiencing clinically relevant immunosuppressant DDIs by 56%. These results provided compelling evidence for the substantial prevalence of clinically relevant DDIs of tacrolimus one-week post-KT and emphasized the importance of a comprehensive understanding of associated risk factors.

Keywords: drug-drug interactions; kidney; transplantation

1. INTRODUCTION

Kidney transplantation (KT) was the preferred treatment for end-stage kidney disease (ESKD) and provided significant benefits for patients in terms of improved quality of life and long-term outcomes. KT recipients required long-term immunosuppressive therapy to prevent rejection and maintain graft function (Kidney Disease: Improving Global Outcomes Transplant Work Group, 2009). However, the concomitant use of multiple medications in KT recipients posed a risk for drug-drug interactions (DDIs), resulting in suboptimal therapeutic outcomes and potential adverse effects (Bril et al., 2016). Previous studies investigated DDIs in various patient populations, including geriatric patients and those with chronic kidney disease (Ramadaniati et al., 2016; Wulandari et al., 2018). However, more data that explicitly focused on immunosuppressant DDIs, particularly in Indonesian KT recipients, were required. According to the growing number of KT procedures performed in Indonesia (Marbun et al., 2022) and the increasing complexity of medication regimens in KT recipients (Stemer and Lemmens-Gruber, 2010), understanding the prevalence and associated risk factors of immunosuppressant DDIs during the early post-KT period is crucial (Amkreutz et al., 2017). This study filled the knowledge gap by identifying

the prevalence of clinically relevant immunosuppressant DDIs focusing on tacrolimus and determining the risk factors associated with an increased likelihood of such interactions in KT recipients the first week after transplantation to consider the safety and effectiveness of immunosuppressive therapy.

2. MATERIALS AND METHODS

2.1 Study design

This retrospective observational approach collected data from January 2018 to December 2022 by reviewing the medical records of KT recipients, focusing on the first week post transplantation. Comprehensive drugs and medical information were recorded for the DIPS scoring to identify clinically relevant immunosuppressant DDIs.

2.2 Study setting

The study was conducted at the 1,000-bed capacity academic hospital, Dr. Cipto Mangunkusumo National Hospital (RSCM), Jakarta, Indonesia. All KT recipients received the same initial immunosuppressive protocol (Indonesian Society of Nephrology, 2013), in which tacrolimus was initially administered at 0.15–0.3 mg/kg/day with subsequent adjustments based on tacrolimus levels and kidney function. The initial targeted tacrolimus predose concentration (C_0) was 6–8 ng/mL. The immediate-release tacrolimus was administered twice daily (08.00 a.m. and 08.00 p.m.), whereas the extended-release tacrolimus was given once daily (09.00 a.m.). Methylprednisolone of 500 mg was intravenously given once daily for three consecutive days, with the first dose administered intraoperatively and subsequent doses at 24 and 48 h. It was changed to oral from the fourth day onward with a reduced dosage of 16 mg/day. Mycophenolate was administered as the primary antiproliferative drug using mycophenolate mofetil at a recommended dose of 1000 mg twice daily or mycophenolic acid at a recommended dose of 720 mg twice daily. Whole blood samples were collected from KT recipients at time 0 to measure the first tacrolimus C_0 levels at three days post-KT. Subsequently, the second measurement was performed three days after the first investigation. The chemiluminescent microparticle immunoassay method on the Architect iSR2000 system from Abbott Laboratories was used to determine the tacrolimus levels. The assay had lower and upper limits of quantification of 2 ng/mL and 30 ng/mL, respectively (Dasgupta, 2016).

2.3 Ethical considerations

The Health Research Ethics Committee, Faculty of Medicine, Universitas Indonesia, and RSCM (HREC-FMUI/CMH) (certification of approval number KET-423/UN2.F1/ETIK/PPM.00.02/2023), and the Institutional Review Board (IRB) of Faculty of Dentistry and Faculty of Pharmacy, Mahidol University, Bangkok, Thailand (letter of authorization transfer to local IRB of HREC-FMUI/CMH No. 78.0319/EC.092) approved this study. Information of all participants was kept confidential.

2.4 Inclusion and exclusion criteria

The inclusion criteria were *de novo* KT recipients admitted to RSCM, aged≥18 years, and being treated with tacrolimus as part of an immunosuppressive maintenance regimen. Data analysis excluded incomplete medical records from these participants during the first week of the observation period.

2.5 Data collection of DDIs

The medical records of KT recipients treated with tacrolimus were retrieved from the manual and electronic medical record system of RSCM and reviewed to achieve the inclusion criteria. Relevant guidelines and strategies for data collection from medical records were conducted to ensure the validity and accuracy of data collection (Gregory and Radovinsky, 2012; Jansen et al., 2005), including regular meetings and training with data collectors to encourage communication, resolve data conflicts, and clarify questions. Further, continuous monitoring and periodic reviews were performed.

The clinical pharmacist then collected, extracted, and filled the study data in the designed data collection format. Data were investigated until one-week post-KT. Demographic data, including age, gender, etiology of ESKD, predominant modality treatment before KT, total length of hospital stay (LOS), and comorbidities were recorded. The participant's age was determined upon hospital admission. Comorbidities and etiology of ESKD were included to characterize the participant population.

DDIs and severity levels were identified from the participant's drug treatment list using the RSCM's drug interaction program and the Lexicomp® Drug Interactions database (Lexicomp® Drug Interactions). The DDIs were categorized as severe (contraindicated), major, moderate, minor, or none for category analysis. The most severe category was selected when more than one category was identified from drug interaction programs. To evaluate the clinically relevant immunosuppressant effects of the categorized DDIs, the clinical pharmacist reviewed the participants' medical records to confirm the outcomes of tacrolimus pre-dose concentration (C_0) or tacrolimus metabolism rate (C_0/D ratio) fluctuation and/or adverse drug events (ADEs) generated by DDIs. Laboratory data or participants' subjective data were used to confirm the clinical manifestation of DDIs. The C_0/D ratio was calculated using the given dose on the third day before withdrawing blood samples to reach the steady-state tacrolimus concentration. The previous dose was used in the calculation if the current dose was changed in less than three days. The DIPS tool (Horn et al., 2007) was then used to assess the likelihood of a causal relationship between DDIs and events by discussing with a nephrologist if a clinical pharmacist identified a change in the C_0 and/or an ADE outcome. The probability of DDIs was categorized from DIPS scoring as doubtful (<2), possible (2–4), probable (5–8), or highly probable (>8). The terms "probable" or "highly probable" DDIs indicated that the total score from the 10 questions in the DIPS tool was sufficiently high to indicate a causal relationship between the interaction and the patient's event. Therefore, they were considered clinically relevant immunosuppressant DDIs in this study. Figure 1 presents the process of data collection.

2.6 Data analysis

Descriptive and inferential statistics were used to analyze demographic and clinical data. The Shapiro-Wilk normality test was used to evaluate data normality. The median and

interquartile range were calculated for continuous variables, such as total LOS and dialysis duration before KT, whereas mean and standard deviation (SD) were calculated for the age, body weight, and number of medications per patient per day. Frequency and percentage tables were utilized to describe the distribution of categorical variables, such as gender, etiology of ESKD, and comorbidities. Logistic regression was used to investigate the association between demographic characteristics, comorbidities, predominant modality treatment before KT, number of medications per day, number of potential DDIs with tacrolimus, and clinically relevant immunosuppressant DDIs (yes/no). The likelihood ratio test was used to compare models with different sets of independent variables. The Hosmer-Lemeshow goodness-of-fit test was performed to assess the fit of the logistic regression model with the data. The degree of association was calculated using the odds ratio and the confidence interval of 95% (95% CI). The statistical analysis was performed using statistical package for the social sciences (SPSS) version 18 (IBM Corp.). Each variable with a p value of <0.05 was statistically significant and considered a risk factor for clinically relevant immunosuppressant DDIs.

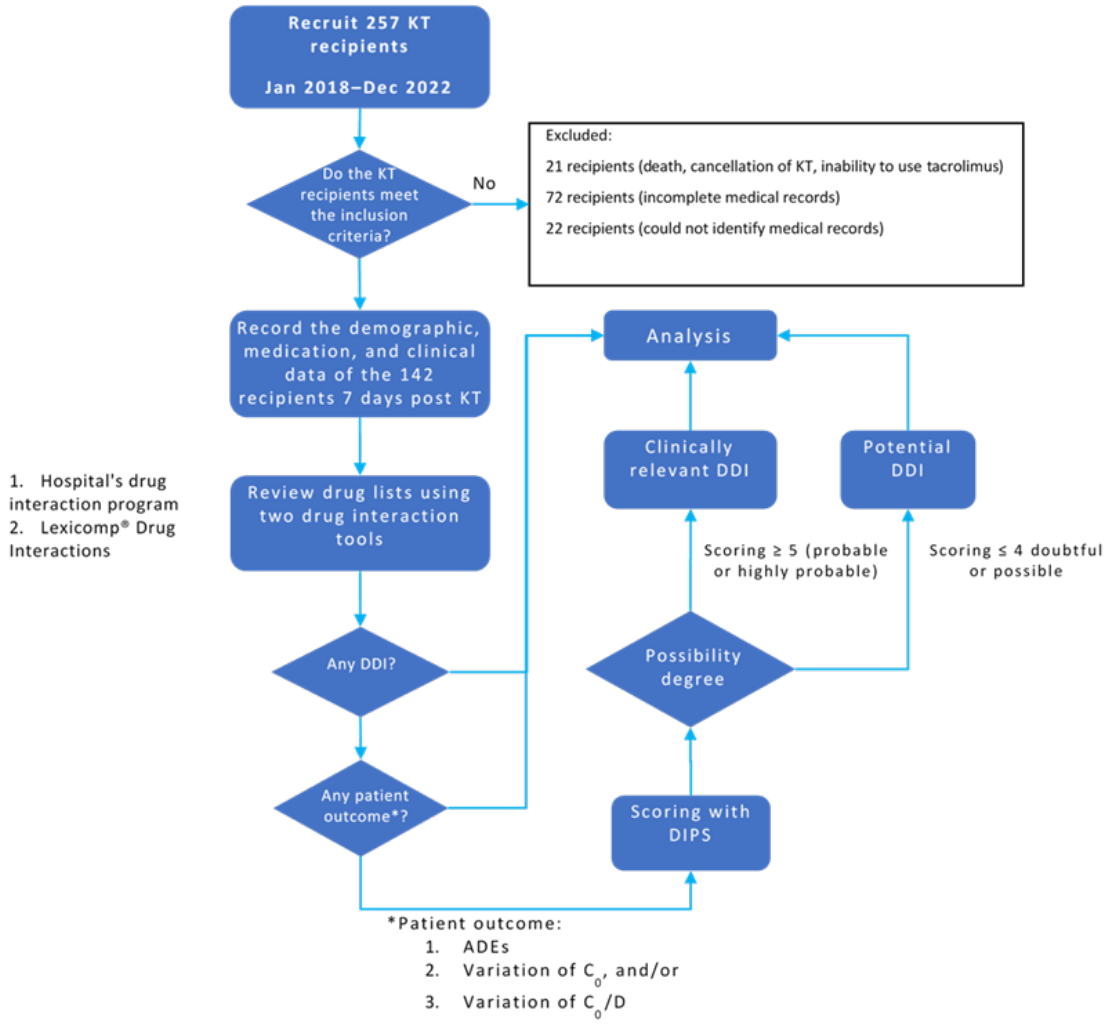

Figure 1. Process of data collection

3. RESULTS

3.1 Demographic data

During the study period, 257 KT recipients were recruited. This study excluded 21 participants because of death, KT cancellation, or inability to use tacrolimus; 72 because of incomplete medical records; and 22 because of unidentified medical records. Therefore, this study included 142 KT recipients, including 86 (60.6%) males, with a mean±SD age of 41.5±11.8 years. All KT were from living donors with 9.2% performed preemptively. Hypertension caused ESKD in 54.2% (n = 77) of participants. Hemodialysis was the predominant modality treatment prior to transplantation in 83.8% (n = 119) of participants with a median dialysis duration of 18 months. The mean±SD number of medications per patient per day was 9.8±1.6. The top three prescribed non-immunosuppressant medications included –acetaminophen (97.9%, n = 139), omeprazole (94.4%, n = 134), and cefoperazone (78.9%, n = 112). Table 1 presents the clinical and demographic characteristics.

Table 1. Socio-demographic characteristics of nurses

Characteristic	Value
Total, n	142
Gender	
Male, *n* (%)	86 (60.6)
Female, *n* (%)	56 (39.4)
Age (years) median (IQR; range)	41 (19, 21–69)
LOS (days) median (IQR; range)	13 (1, 10–24)
Etiology of ESKD, *n* (%)	
Hypertension	77 (54.2)
Glomerular disease (primary or secondary)	17 (12.0)
Diabetes mellitus	16 (11.3)
Recurrent kidney stone disease	6 (4.2)
Certain medications*	4 (2.8)
ADPKD	4 (2.8)
Unknown	11 (7.8)
Other causes	7 (4.9)
Had at least one comorbidity	
Yes, *n* (%)	135 (95.1)
No, *n* (%)	7 (4.9)
Comorbidities, *n* (%)	
Hypertension	130 (71.4)
Diabetes	21 (11.5)
Cardiovascular disease	10 (5.5)
Infectious diseases**	8 (4.9)
Autoimmune diseases	7 (3.9)
Chronic lung disease	2 (1.1)
Hyperuricemia	2 (1.1)
Hyperthyroid	1 (0.6)
Treatment modalities before KT, *n* (%)	
HD	119 (83.8)
CAPD	10 (7.0)
Pre-emptive KT	13 (9.2)
Duration of dialysis before KT (months) Median (IQR; range)	18 (20; 1–124)
Number of medications per patient per day, Mean±SD	9.8±1.6
Most common medications (other than immunosuppressive therapy), *n* (%)	
Acetaminophen	139 (97.9)
Omeprazole	134 (94.4)
Cefoperazone	112 (78.9)

Note: *including NSAIDs and other nephrotoxic agents; **chronic hepatitis C or TB. LOS: length of hospital stay; ESKD: end-stage kidney disease; IQR: interquartile range; HD: hemodialysis; CAPD: continuous ambulatory peritoneal dialysis; KT: kidney transplantation; SD: standard deviation; ADPKD: autosomal dominant polycystic kidney disease.

All participants received the maintenance immunosuppressant regimen of tacrolimus-methylprednisolone-mycophenolate. Among participants, 99 (69.7%) received the immediate-release, whereas the remaining received the extended-release tacrolimus. Concerning the antiproliferative agent, mycophenolate mofetil was prescribed to 84 (59.2%) participants, mycophenolic acid was prescribed to 45 (31.7%) participants, and mycophenolate mofetil initially started but subsequently switched to mycophenolic acid due to gastrointestinal discomfort in 13 (9.2%) participants. All participants received 500 mg of intravenous methylprednisolone once daily for the first three days post-KT, subsequently switching to the oral daily dose of 16 mg until discharge. The initial tacrolimus dose of 8 mg (97.9%, *n* = 139) with a median weight-based dose of 0.13 mg/kg was administered in most cases. Ninety-seven (68.3%). One-week post-KT, participants underwent two measurements of tacrolimus C_0, whereas the remaining underwent a single measurement, especially for the extended-release tacrolimus. Table 2 presents the data.

Table 2. Maintenance immunosuppressant drug used

Immunosuppressant characteristic	Value
Methylprednisolone 500 mg IV D1–D3, 16 mg oral D4, and onwards, ***n*** (%	142 (100.0)
Tacrolimus	
TAC-IR, *n* (%)	99 (69.7)
TAC-ER, *n* (%)	43 (30.3)
Mycophenolate	
MMF, *n* (%)	84 (59.2)
MPA, *n* (%)	45 (31.7)
MMF-MPA, n (%)	13 (9.2)
Initial tacrolimus dose (mg), *n* (%)	
8	139 (97.9)
10	3 (2.1)
Weight-based tacrolimus dose, mg/kg	
Initial dose, Median (IQR; range)	0.13 (0.04, 0.09–0.21)
Adjusted dose, Median (IQR; range)	0.13 (0.04, 0.00–0.26)
Tacrolimus C_0 measurements, *n* (%)	
Single C_0 measurement	45 (31.7)
Two C_0 measurements	97 (68.3)

Note: TAC-IR: immediate-release tacrolimus; TAC-ER: extended-release tacrolimus; IQR: interquartile range; MMF: mycophenolate mofetil; MPA: mycophenolic acid; D: day

3.2 Potential DDIs

All potential DDIs were determined, with an average of 7.8 and an SD of 2.4 per patient. A total of 1,106 potential DDIs with immunosuppressants were identified, including 75 different drug interaction pairs, of which 802 (72.5%) involved tacrolimus as the perpetrator or the victim drug presenting 49 different drug interaction pairs. Data are shown in the supplementary Table S1. The moderate category was the most common type (84.0%), followed by the major category (11.8%) and the minor category (4.2%), respectively. However, the severe category was not found. The most potential DDIs were pharmacokinetic (71.2%), whereas the remaining were classified as pharmacodynamic DDIs.

3.3 Clinically relevant DDIs of tacrolimus

Comprehensive evaluations of medical records revealed 54 potential DDIs that involved tacrolimus along with their respective outcomes. Among these potential DDIs, 40 cases were classified to be pharmacokinetic with 25 demonstrating a decrease in tacrolimus C_0 and metabolism rate (C_0/D ratio) from 35% to 56% and from 1.4– to 2.7–fold, respectively, and 15 presenting an increase in tacrolimus C_0 and metabolism rate (C_0/D ratio) from 31% to 79% and from 1.5– to 2.2–fold, respectively, as shown in Table 3. Additionally, 14 cases were identified as pharmacodynamic DDIs related to early post-KT hyperglycemia, as shown in Table 4.

Table 3. Potential pharmacokinetic DDIs involving tacrolimus that showed various patient outcomes

Subject	1st C_0 to 2nd C_0 (ng/mL) (% change of C_0)		1st C_0/D ratio to 2nd C_0/D ratio, (ng/mL)/mg (the fold change)		*CYP3A* inducer	*CYP3A* inhibitor	Patient outcome	Alternative cause (s)	DIPS score
C_0 decreased ≥ 30% or C_0/D ratio decreased ≥ 1.3–fold; Proposed mechanism: *CYP3A* induction									
S36	7.3 to 4	(–45.2%)	0.91 to 0.5	(1.83)	MP	Omeprazole	(a)*	(c)	5
S77	30 to 10.6		3.75 to 2.65	(1.42)	MP, clobazam (weak)	Omeprazole	(b)	Unknown	5
S79	11.5 to 5.7		1.44 to 0.81	(1.77)	MP	Omeprazole, nifedipine	(b)	Unknown	5
S91	4.6 to 3.9		0.58 to 0.39	(1.47)	MP	Omeprazole, nifedipine	(b)**	(c)	5
S127	10 to 5.5		1.25 to 0.92	(1.36)	MP	Esomeprazol, diltiazem	(b)	Unknown	5
S1	5.2 to 4.4		0.65 to 0.44	(1.48)	MP	Omeprazole, alprazolam (weak)	(b)	(c)	4
S6	3.9 to 1.9	(–51.3%)	0.49 to 0.24	(2.05)	MP	Omeprazole (80 mg/day), esomeprazole (40 mg/day)	(a)	(c), (d)	4
S9	16.3 to 4.6		2.04 to 1.15	(1.77)	MP clobazam (weak)	Omeprazole, nifedipine	(b)	(c), (d)	4
S15	4.4 to 3		0.55 to 0.3	(1.83)	MP	Omeprazole	(b)	(c)	4
S20	5 to 2.7		0.63 to 0.23	(2.78)	MP, rifampicin	Omeprazole, isoniazid (weak)	(b)	(c)	4
S26	11.4 to 4.8		1.43 to 0.8	(1.78)	MP	Omeprazole	(b)	(c)	4
S29	12.8 to 6		1.6 to 1	(1.60)	MP	Omeprazole	(b)	(c), (e)	4
S30	12.1 to 4.7		1.51 to 0.78	(1.93)	MP	Omeprazole, amlodipine	(b)	(e)	4
S41	7 to 4.6	(–34.3%)	0.88 to 0.58	(1.52)	MP	Amlodipine, alprazolam (weak)	(a)	(c)	4
S49	10.4 to 5.1	(–51.0%)	1.3 to 0.64	(2.04)	MP	Omeprazole, amlodipine	(a)	(c)	4
S52	10.7 to 6.4		1.34 to 0.91	(1.46)	MP	Omeprazole	(b)	(c)	4
S60	13.6 to 7.1		1.7 to 1.18	(1.44)	MP	Omeprazole	(b)	(c)	4
S62	13 to 7.3		1.63 to 1.04	(1.53)	MP	Omeprazole, amlodipine	(b)	(f55)	4
S67	8.1 to 5.3	(–34.6%)	1.01 to 0.66	(1.53)	MP	Omeprazole	(a)	(e)	4

Table 3. (Continued)

Subject	1st C_0 to 2nd C_0 (ng/mL) (% change of C_0)		1st C_0/D ratio to 2nd C_0/D ratio, (ng/mL)/mg (the fold change)		*CYP3A* inducer	*CYP3A* inhibitor	Patient outcome	Alternative cause (s)	DIPS score
S86	13.5 to 6.7		1.69 to 1.12	(1.51)	MP	Omeprazole, nifedipine	(b)	(c)	4
S87	11.8 to 6.8		1.48 to 0.97	(1.52)	MP	Omeprazole	(b)	(c)	4
S94	8.7 to 5.6	(–35.6%)	1.09 to 0.7	(1.55)	MP	Omeprazole	(a)	(c)	4
S131	7.9 to 3.5	(–55.7%)	0.99 to 0.44	(2.26)	MP	Esomeprazole	(a)	(e)	4
S132	13.4 to 5.9		1.68 to 0.98	(1.70)	MP	Omeprazole, amlodipine	(b)	(c)	4
S140	16.6 to 8		2.08 to 1.14	(1.82)	MP	Omeprazole, nifedipine, diltiazem	(b)	(c)	4
C_0 increased ≥ 30% or C_0/ D ratio increased ≥ 1.3–fold or high initial C_0; Proposed mechanism: *CYP3A* inhibition									
S37	6.6 to 11.8	(78.8%)	0.83 to 1.48	(1.79)	MP	Omeprazole	(g)***	Unknown	6
S65	9 to 13.6	(51.1%)	1.13 to 1.7	(1.51)	MP	Omeprazole, amlodipine	(g)****	Unknown	6
S4	30 to 14.8		3.75 to 7.4	(1.97)	MP	Omeprazole	(h)	Unknown	5
S23	3.4 to 9.5		0.43 to 0.95	(2.24)	MP	Omeprazole	(h)	Unknown	5
S44	4.3 to 9.3		0.54 to 0.93	(1.73)	MP	Omeprazole	(h)	Unknown	5
S55	4.5 to 10.4		0.56 to 1.04	(1.85)	MP	Omeprazole	(h)	Unknown	5
S58	8.3 to 11.9	(43.4%)	1.04 to 1.49	(1.43)	MP	Omeprazole	(g)	Unknown	5
S61	4.2 to 10.2		0.53 to 1.02	(1.94)	MP	Omeprazole, amlodipine	(h)	Unknown	5
S64	12.6 to 20.8	(65.1%)	1.58 to 2.6	(1.65)	MP	Omeprazole, amlodipine	(g)	Unknown	5
S68	5 to 11.3		0.63 to 1.13	(1.81)	MP	Omeprazole, amlodipine	(h)	Unknown	5
S81	27.2 to 10.7		3.4 to 3.57	(1.05)	MP	Omeprazole, diltiazem, nifedipine	(i)	Unknown	5
S130	10.5 to 13.8	(31.4%)	1.31 to 1.73	(1.31)	MP	Esomeprazol, amlodipine	(g)	Unknown	5
S138	6.1 to 10.8	(77.0%)	0.76 to 1.35	(1.77)	MP	Omeprazole, alprazolam (weak)	(g)	Unknown	5

Table 3. (Continued)

Subject	1st C_0 to 2nd C_0 (ng/mL) (% change of C_0)	1st C_0/D ratio to 2nd C_0/D ratio, (ng/mL)/mg (the fold change)		*CYP3A* inducer	*CYP3A* inhibitor	Patient outcome	Alternative cause (s)	DIPS score
S10	4.6 to 8.7	0.58 to 0.87	(1.51)	MP	Omeprazole	(h)	(e), (j)	4
S83	2.1 to 5.2	0.26 to 0.52	(1.98)	MP, rifampicin	Omeprazole, amlodipine, isoniazid (weak)	(h)	(k)	4

Note: MP: methylprednisolone, (a) C_0 decreased by ≥30%, (b) the C_0/D ratio decreased by ≥1.3–fold, (c) lower hematocrit value, (d) changed in proton pump inhibitors, (e) difference in time intervals for blood withdrawal, (f) laxative used, (g) C_0 increased ≥30%, (h) the C_0/D ratio increased ≥1.3–fold, (i) high initial C_0, (j) missed dose, (k) low initial C_0 due to strong inducer.

*signs of graft rejection

**serum creatinine increased and worsened hypertension

***signs of infection

****nephrotoxicity

Table 4. Potential pharmacodynamic DDIs involving tacrolimus that showed early post-KT hyperglycemia

Subject	Antidiabetic agents	Alternative cause	DIPS score
S18	Insulin aspart, ansulin glargine	a, c	4
S25	Insulin aspart	a, b, c	4
S48	Insulin aspart, insulin glargine	a, b, c	4
S53	Insulin aspart, insulin glargine	a, b, c	4
S63	Insulin lispro	a, c	4
S85	Insulin aspart	a, b, c	4
S99	Gliclazide, linagliptin, insulin aspart, insulin glargine	a, b, c	4
S105	Insulin aspart	a, b, c	4
S111	Insulin aspart	a, b, c	4
S113	Insulin aspart, insulin glargine	a, b, c	4
S117	Insulin aspart, insulin glargine	a, b, c	4
S132	Insulin aspart, metformin	a, b, c	4
S134	Insulin aspart, insulin glargine	a, b, c	4
S135	Insulin aspart, insulin glargine	a, b, c	4

The DIPS criteria investigation classified 18 potential DDIs to be clinically relevant immunosuppressant DDIs. However, the remaining 36 cases were classified as possible DDIs. Therefore, the prevalence of clinically relevant immunosuppressant DDIs related to tacrolimus, which is the proportion of patients with a DIPS score of ≥5 among subjects with two C_0 measurements, was 18.6% (95% CI: 11.4%–27.7%). Furthermore, 4 (22.2%) of 18 clinically relevant immunosuppressant DDIs presented significant ADEs, as shown in Table 5.

3.4 Risk variables linked to an increased likelihood of clinically relevant DDIs

Logistic regression analysis was conducted to determine the effect of gender, age, body weight, at least one comorbidity, the predominant modality treatment before KT, the number of medications per day, and the number of potential DDIs with tacrolimus on the likelihood of clinically relevant immunosuppressant DDIs related to tacrolimus. Results revealed that gender (p = 0.564), age (p = 0.461), body weight (p = 0.099), at least one comorbidity (p = 0.071), the predominant modality treatment before KT (p = 0.936), and the number of medications per day (p = 0.290) did not significantly affect the model. However, the number of potential DDIs with tacrolimus (p = 0.027) significantly influenced the model. Subsequently, this variable was determined as a predictor of clinically relevant immunosuppressant DDIs and presented the odds ratio of 1.56 (95% CI: 1.05–2.32). Table 6 shows the comparison of demographic and clinical characteristics between participants with and without clinically relevant immunosuppressant DDIs.

4. DISCUSSION

This study used the DIPS criteria to evaluate potential DDIs and their corresponding outcomes for KT recipients. A total of 54 potential DDIs with outcomes were found. However, based on the DIPS criteria, 18 clinically relevant immunosuppressant DDIs represented a prevalence rate of 18.6% (95% CI: 11.4%–27.7%) among 97 KT recipients who underwent two C_0 measurements. This result closely aligned with a previous study that presented a prevalence rate of 21.7% for real DDIs (Gago-Sánchez et al., 2021), indicating that approximately one out of five KT recipients experienced clinically relevant DDIs of tacrolimus. Furthermore, of the 18 cases with clinically relevant immunosuppressant DDIs, 4 presented significant outcomes of ADEs (Table 5). These ADEs included signs of graft rejection (S36), a decline in kidney function accompanied by worsening hypertension (S91), signs of infection (S37), and delayed graft function associated with nephrotoxicity (S65). These results highlighted the importance of closely monitoring drug combinations with tacrolimus. This study confirms the prevalence and implications of clinically relevant immunosuppressant DDIs in KT recipients who underwent tacrolimus therapy and emphasizes the need for vigilant monitoring to optimize patient safety and treatment outcomes. Methylprednisolone was the only identified perpetrator drug that caused a lower tacrolimus C_0 or C_0/D ratio, considering cases S36 and S91. It induced the activity of *CYP3A4/5* isoenzymes and influenced the calcineurin inhibitor metabolism of cyclosporine and tacrolimus (Dashti-Khavidaki et al., 2021). Corticosteroid withdrawal regimens revealed a significant increase in tacrolimus C_0 within seven days of discontinuation (Shihab et al., 2013). Additionally, tacrolimus clearance was strongly related (R = 0.94) to corticosteroid dose in KT recipients (Undre and Schäfer, 1998). Moreover, the tacrolimus single therapy treatment increased the tacrolimus AUC by approximately 41% higher than the tacrolimus and corticosteroid combination treatment (Anglicheau et al., 2003; Kim et al., 2005). Tacrolimus C_0 was reduced by approximately 27% after high-dose corticosteroid administration in liver transplant recipients who expressed the *CYP3A5* enzyme, indicating the effect of genetic polymorphisms (Hosohata et al., 2014). In case S37, the concomitant use of proton pump inhibitors elevated tacrolimus C_0 by approximately 78.8% which was consistent with previous reports (Hosohata et al., 2008; Moreau et al., 2006; Takahashi et al., 2007). Additionally, a recent study revealed that a single dose of omeprazole significantly increased tacrolimus concentration at the 26–h time point compared to the 2–h time point (Miedziaszczyk, 2023). However, a study that included KT recipients revealed no differences in the tacrolimus C_0/D ratio with the concurrent use of omeprazole (Pascual et al., 2005). Individual patient factors, such as *CYP2C19* and/or *CYP3A5* genotypes, affected the severity of this interaction. Omeprazole was metabolized primarily in the liver by *CYP2C19* through 5–

hydroxylation with a minor contribution from *CYP3A*. However, the use of high-dose omeprazole (40 mg/day) demonstrated the saturation of *CYP2C19* in extensive or poor metabolizers. Therefore, *CYP3A* became the dominant enzyme for omeprazole metabolism (Maguire et al., 2012). In case S65, the combination use of amlodipine and omeprazole could potentially act as perpetrator drugs to increase tacrolimus C_0 by approximately 51% and cause delayed graft function associated with nephrotoxicity. Additionally, tacrolimus was seen to dramatically increase serum creatinine and directly harm the kidneys related to delayed graft function (Ponticelli et al., 2022). The effect of amlodipine on tacrolimus metabolism demonstrated that amlodipine increased tacrolimus AUC from 2.4–fold to 4–fold in healthy Chinese volunteers who expressed *CYP3A5*. However, no significant differences in tacrolimus pharmacokinetic parameters were observed when amlodipine and tacrolimus were administered in the volunteers who did not express *CYP3A5* (Zuo et al., 2013).

All potential DDIs associated with pairs of tacrolimus-antidiabetic agents were investigated to present a DIPS score of 4, indicating possible DDIs. However, tacrolimus administration was indicated as a potential contributor to early post-KT hyperglycemia characterized by dose-dependent β-cell toxicity that reduced insulin secretion, exacerbated insulin resistance, and removed the GLUT4 transporter from the cell surface (Iqbal et al., 2022). Directly evaluating the pharmacodynamic interactions between tacrolimus and antidiabetic agents is challenging because several common alternatives may cause hyperglycemia such as the use of high-dose corticosteroids, preexisting diabetes, and postoperative stress.

Table 5. Clinically relevant DDIs with ADEs

No.	ADEs (Subject's code)	*n*	Perpetrator drug	Severity	Tacrolimus PK change	DIPS score
1	Signs of graft rejection (S36)	1	MP	moderate	C_0 decreased 7.3 to 4 (−45.2%)	5
2	Serum creatinine increased and worsened hypertension (S91)	1	MP	moderate	C_0/D ratio decreased 0.58 to 0.39 (−1.47)	5
3	Nephrotoxicity (S65)	1	Omeprazole, amlodipine	moderate	C_0 increased 9 to 13.6 (51.1%)	6
4	Signs of infection (S37)	1	Omeprazole	moderate	C_0 increased 6.6 to 11.8 (78.8%)	6

Table 6. Comparison of demographic and clinical characteristics between patients with and without clinically relevant DDIs

Variable	Patients without clinically relevant DDIs, (*n*=124)	Patients with clinically relevant DDIs, (*n*=18)	OR (95% CI) [*p* value]
Gender			
Male, *n* (%)	75 (60.5)	11 (61.1)	0.69 (0.19–2.47) [0.564]
Female, *n* (%)	49 (39.5)	7 (38.9)	
Age (years)			
Mean±SD	41.3±12.0	42.9±10.3	1.02 (0.97–1.07) [0.461]
Body weight (kg)			
Mean±SD	63.3±13.6	59.5±10.9	0.96 (0.91–1.01) [0.099]
Had at least one comorbidity			
Yes, *n* (%)	119 (96.0)	16 (88.9)	5.85 (0.86–39.77) [0.071]
No, *n* (%)	5 (4.0)	2 (11.1)	
Treatment modalities			
CAPD, *n* (%)	9 (7.3)	1 (5.6)	
HD, *n* (%)	104 (83.9)	15 (83.3)	0.59 (0.04–10.08) [0.716]
Pre-emptive, *n* (%)	11 (8.9)	2 (11.1)	0.84 (0.15–4.77) [0.844]
Number of medications per day			
Median (IQR)	9.6 (3)	10.0 (2)	0.80 (0.52–1.22) [0.290]
Range	6–14	7–12	
Number of potential DDIs with tacrolimus			
Median (IQR)	5 (2)	6 (3)	1.56 (1.05–2.32) [0.027]*
Range	3–11	4–9	

Our study revealed a high proportion of potential pharmacokinetic DDIs in approximately 71.2% of patients, which correlated with the previous DDI study on KT patients in outpatient settings (Moradi et al., 2020). Notably, all identified clinically relevant DDIs of tacrolimus were classified as pharmacokinetic DDIs. This result highlights the importance of closely monitoring tacrolimus levels and intensively considering the drug interaction caused by polymedication.

Tacrolimus C_0 was the pharmacokinetic parameter to assess the safety and efficacy of using tacrolimus in transplant centers in Indonesia (Indonesian Society of Nephrology, 2013). However, the tacrolimus C_0/D ratio was also used as an alternative evaluation method to

assess drug interactions and their associations with patient outcomes in recent years (Mori et al., 2012; van Gelder et al., 2020). Patients with a low C_0/D ratio (<1.05) require a high dose of tacrolimus, which results in high tacrolimus levels in their system. The increased exposure to tacrolimus and its metabolite was associated with a risk of death-censored graft loss that was increased by a factor of 2.26 in the multivariate analysis (Jouve et al., 2020). The present study revealed that the use of the C_0/D ratio approach was beneficial for ADE monitoring in KT recipients, who underwent the dose adjustments. However, this parameter was not used to predict ADEs because the change in the C_0/D ratio may be caused by the dose modification of tacrolimus or other factors that influenced potential DDIs.

Furthermore, logistic regression analysis was used to investigate the association between several variables, including age, gender, the predominant modality treatment before KT, comorbidity, number of prescribed medications, number of potential DDIs with tacrolimus, and the probability of clinically relevant immuno-suppressant DDIs one-week post-KT (yes/no). The results revealed that KT recipients one-week post-KT were exposed to a higher number of potential DDIs when compared to the general population of KT recipients in the previous study with values of 7.8 and 5.6 DDIs, respectively (Bril et al., 2016). Additionally, each additional potential DDI with tacrolimus increased the odds of experiencing clinically relevant immuno-suppressant DDIs by 56%. This information supported our result that clinical pharmacists should provide special attention to concern ADE prevention in recipients one-week post-KT. However, our results slightly differed from previous research, which emphasized the impact of the number of prescribed drugs as a strong predictor of such interaction (Gago-Sánchez et al., 2021). This discrepancy result from the use of drug interaction programs and types of transplant procedures in our study, which were dissimilar to the other studies. The results of our study offer the prevalence of clinically relevant DDIs of tacrolimus in KT recipients one-week post-KT and underscore the importance of a comprehensive understanding of associated risk factors to provide the safety and effectiveness of immunosuppressive therapy.

This is the first study to investigate the occurrence of clinically relevant DDIs of tacrolimus in KT recipients in Indonesia, particularly within the first week post-transplant. Various risk factors associated with these DDI events were analyzed. Notably, our study could represent individual KT recipients from various regions of Indonesia and enhance the generalizability of the findings to a larger population as enrolled participants were from a single KT center, RSCM in Jakarta. Unfortunately, the main limitation was incomplete medical records. Further, the tacrolimus measurement from TAC-ER could not provide two tacrolimus C_0. These limitations caused the exclusion of certain data. Therefore, comprehensive data collection approaches are crucial for future research. This study could represent the foundational information for further prospective KT study with tacrolimus to obtain a comprehensive dataset by improving data collection approaches, creating strengthened validity, and generating the study findings for a huge population, despite the data availability constraints. Moreover, the potential influence of polymorphism among subjects was acknowledged as a significant factor in determining associated risk factors. However, polymorphism was not included in the analysis due to the unavailability of relevant data. Additionally, formal validation, specifically for this context, remains lacking although the DIPS score has been used to assess immunosuppressant DDIs. This emphasizes the necessity for future research to validate the accuracy of this instrument.

5. CONCLUSION

This retrospective observational study aimed to investigate the prevalence and associated risk factors of clinically relevant DDIs of tacrolimus in 142 KT recipients one-week post-transplantation. A significant number of potential DDIs was determined with an average of 7.8±2.4 potential DDIs per patient. Various potential DDIs were observed along with their respective outcomes, including a decrease in tacrolimus C_0 and metabolism rate (C_0/D ratio) of 35%–56% and 1.4– to 2.7–fold, respectively, An increase in tacrolimus C_0 and metabolism rate (C_0/D ratio) of 31%–79% and 1.5– to 2.2–fold, respectively, were also observed. The prevalence of clinically relevant DDIs was 18.6% according to the DIPS criteria (95% CI: 11.4%–27.7%). Furthermore, the results revealed that each additional potential DDI that involved tacrolimus increased the odds of experiencing clinically relevant immunosuppressant DDIs by 56%. Other significant outcomes, such as signs of graft rejection, elevated serum creatinine, worsening hypertension, signs of infection, and nephrotoxicity, were also investigated and presented in approximately 22.2% of identified clinically relevant DDIs. Therefore, this study filled the knowledge gap by investigating the prevalence of clinically relevant DDIs of tacrolimus and identifying the risk variables associated with an increased likelihood of such interactions one-week post-KT in Indonesian recipients to provide the safety and effectiveness of immune-suppressive therapy.

ACKNOWLEDGMENT

The authors would like to thank all staff members of RSCM, Jakarta, Indonesia, for their support and coordination throughout this study. We sincerely acknowledge Anita Natasya and Fitriani Syawalia Naisya Buri for their invaluable contributions as data collectors.

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SUPPLEMENTARY MATERIALS

Table S1. Drug pairs involved in potential DDIs with immunosuppressant

No	Perpetrator drug	Victim drug	DDIs Category	PK/PD	Potential outcome	*n*	%
1	alprazolam	tacrolimus	moderate	PK	Increased tacrolimus levels	8	5.6%
2	amlodipine	tacrolimus	moderate	PK	Increased tacrolimus levels	48	33.8%
3	calcium carbonate	MP	major	PK	Decreased MP levels	13	9.2%
4	carvedilol	tacrolimus	moderate	PK	Increased tacrolimus levels	4	2.8%
5	cilostazol	tacrolimus	moderate	PK	Increased tacrolimus levels	1	0.7%
6	clobazam	tacrolimus	moderate	PK	Decreased tacrolimus levels	3	2.1%
7	clonidine	tacrolimus	minor	PK	Increased tacrolimus levels	33	23.2%
8	daclatasvir	tacrolimus	moderate	PK	Increased tacrolimus levels	1	0.7%
9	diltiazem	tacrolimus	moderate	PK	Increased tacrolimus levels	6	4.2%
10	esomeprazole	MMF/MPA	moderate	PK	Decreased MPA levels	7	4.9%
11	esomeprazole	tacrolimus	moderate	PK	Increased tacrolimus levels	7	4.9%
12	isoniazid	tacrolimus	moderate	PK	Increased tacrolimus levels	3	2.1%
13	isoniazid	MP	moderate	PK	Increased MP levels	3	2.1%
14	lansoprazole	MMF/MPA	moderate	PK	Decreased MPA levels	1	0.7%
15	lansoprazole	tacrolimus	moderate	PK	Increased tacrolimus levels	1	0.7%
16	levofloxacin	MMF/MPA	moderate	PK	Decreased MPA levels	2	1.4%
17	loratadine	tacrolimus	moderate	PK	Increased tacrolimus levels	1	0.7%
19	metoclopramide	tacrolimus	moderate	PK	Increased tacrolimus levels	22	15.5%
19	MP	tacrolimus	moderate	PK	Decreased tacrolimus levels	142	100.0%
20	MP	acetylsalicylic acid	moderate	PD	GI bleeding	1	0.7%
21	MP	calcitriol	moderate	PD	Decreased calcitriol efficacy	1	0.7%
22	MP	furosemide	moderate	PD	Hypokalemia	70	49.3%
23	MP	gliclazide	moderate	PD	Hyperglycemia	2	1.4%
24	MP	insulin aspart	moderate	PD	Hyperglycemia	19	13.4%
25	MP	insulin detemir	moderate	PD	Hyperglycemia	2	1.4%
26	MP	insulin glargine	moderate	PD	Hyperglycemia	12	8.5%
27	MP	insulin lispro	moderate	PD	Hyperglycemia	6	4.2%
28	MP	insulin regular	moderate	PD	Hyperglycemia	1	0.7%
29	MP	levofloxacin	moderate	PD	Tendon rupture	2	1.4%
30	MP	linagliptin	moderate	PD	Hyperglycemia	2	1.4%
31	MP	metformin	moderate	PD	Hyperglycemia	1	0.7%
32	MP	salbutamol	minor	PD	Hypokalemia	1	0.7%
33	MMF/MPA	tacrolimus	moderate	PK	Increased tacrolimus levels	142	100.0%
34	nicardipine	tacrolimus	moderate	PK	Increased tacrolimus levels	15	10.6%
35	nifedipine	tacrolimus	moderate	PK	Increased tacrolimus levels	10	7.0%
36	omeprazole	MMF/MPA	moderate	PK	Decreased MPA levels	134	94.4%
37	omeprazole	tacrolimus	moderate	PK	Increased tacrolimus levels	134	94.4%
38	pantoprazole	MMF/MPA	moderate	PK	Decreased MPA levels	9	6.3%
39	pantoprazole	tacrolimus	moderate	PK	Increased tacrolimus levels	9	6.3%
40	perindopril and amlodipine	tacrolimus	moderate	PK	Increased tacrolimus levels	1	0.7%
41	pyrazinamide	tacrolimus	minor	PK	Decreased tacrolimus levels	2	1.4%
42	rabeprazole	MMF/MPA	moderate	PK	Decreased MPA levels	2	1.4%
43	rabeprazole	tacrolimus	moderate	PK	Increased tacrolimus levels	2	1.4%
44	rifampin	MMF/MPA	major	PK	Decreased MPA levels	3	2.1%
45	rifampin	MP	major	PK	Decreased MP levels	3	2.1%
46	rifampin	tacrolimus	major	PK	Decreased tacrolimus levels	3	2.1%
47	schisandra	MP	moderate	PK	Increased MP levels	1	0.7%
48	schisandra	tacrolimus	moderate	PK	Increased tacrolimus levels	1	0.7%
49	sodium bicarbonate	MP	major	PK	Decreased MP levels	4	2.8%
50	sofosbuvir	tacrolimus	moderate	PK	Increased tacrolimus levels	1	0.7%

Table S1. (Continued)

No	Perpetrator drug	Victim drug	DDIs Category	PK/PD	Potential outcome	*n*	%
51	tacrolimus	amiodarone	moderate	PD	QT-prolongation	1	0.7%
52	tacrolimus	atorvastatin	moderate	PK	Increased statin levels	2	1.4%
53	tacrolimus	candesartan	moderate	PD	Hyperkalemia	15	10.6%
54	tacrolimus	chlorpromazine	moderate	PD	QT-prolongation	1	0.7%
55	tacrolimus	digoxin	moderate	PK	Increased digoxin effect or levels	1	0.7%
56	tacrolimus	domperidone	minor	PD	QT-prolongation	8	5.6%
57	tacrolimus	gliclazide	moderate	PD	Hyperglycemia	2	1.4%
58	tacrolimus	granisetron	moderate	PD	QT-prolongation	3	2.1%
59	tacrolimus	haloperidol	moderate	PD	QT-prolongation	4	2.8%
60	tacrolimus	insulin aspart	moderate	PD	Hyperglycemia	19	13.4%
61	tacrolimus	insulin detemir	moderate	PD	Hyperglycemia	2	1.4%
62	tacrolimus	insulin glargine	moderate	PD	Hyperglycemia	12	8.5%
63	tacrolimus	insulin lispro	moderate	PD	Hyperglycemia	6	4.2%
64	tacrolimus	insulin regular	moderate	PD	Hyperglycemia	1	0.7%
65	tacrolimus	irbesartan	moderate	PD	Hyperkalemia	6	4.2%
66	tacrolimus	levofloxacin	moderate	PD	QT-prolongation	2	1.4%
67	tacrolimus	linagliptin	moderate	PD	Hyperglycemia	2	1.4%
68	tacrolimus	loperamide	moderate	PD	QT-prolongation	1	0.7%
69	tacrolimus	metformin	moderate	PD	Hyperglycemia	1	0.7%
70	tacrolimus	ondansetron	major	PD	QT-prolongation	105	73.9%
71	tacrolimus	ramipril	moderate	PD	Hyperkalemia	1	0.7%
72	tacrolimus	risperidone	moderate	PD	QT-prolongation	1	0.7%
73	tacrolimus	telmisartan	moderate	PD	Hyperkalemia	2	1.4%
74	tacrolimus	valsartan	moderate	PD	Hyperkalemia	4	2.8%
75	telmisartan	MMF/MPA	minor	PK	Decreased MPA levels	2	1.4%
		major:	11.8%	PK:	71.2%	Total:	1,106
		moderate:	84.0%	PD:	28.8%	Avg.:	7.8±2.4
		minor:	4.2%				

Note: MMF: mycophenolate mofetil; MP: methylprednisolone; MPA: mycophenolic acid; PK: pharmacokinetic; PD: pharmacodynamic; DDIs: drug-drug interactions