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RESEARCH ARTICLE

Effect of CYP3A5 genotype on hospitalization cost for kidney transplantation

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Abstract

Background Dosage quantities of tacrolimus (TAC) vary according to cytochrome P450 3A5 (*CYP3A5*) genotype. Genotyping is expected to optimize the response to TAC response and to minimize adverse effects. In Thailand, kidney transplantation is reimbursable with the same diagnosis-related group payment regardless of patient's *CYP3A5* genotype. *Objective* This study aimed to determine the costs of TAC administration, therapeutic drug monitoring (TDM), and hospitalization for kidney transplantation across *CYP3A5*1/*1, *1/*3, and *3/*3* genotypes. *Setting* A single transplant center in a university hospital. *Method* This is an observational study that collected data from patients pooled from both arms of a randomized controlled trial that tested initial doses of TAC. Main outcome measure TAC and TDM cost and hospitalization cost for transplantation were compared between genotypes. *Results* The *CYP3A5*1/*1* patients had the highest median combined TAC–TDM cost and hospitalization cost ($1062 and $9097), followed by *CYP3A5*1/*3* ($859 and $6467) and *CYP3A5*3/*3* patients ($761 and $5604). The *CYP3A5*1/*1* patients had a higher hospitalization cost by $2787 over the *CYP3A5*1/*3* patients, despite marginal significance. The *CYP3A5*1/*1* patients had a significantly higher cost of TAC plus TDM (by $309) and hospitalization cost (by $3275) than the *CYP3A5*3/*3* patients. Both study costs were significantly higher in patients with delayed graft functioning than in patients with instant or slow graft functioning. *Conclusion* The benefits of genotype detection in patients with *CYP3A5*1/*1* should be considered for a higher reimbursement rate because of the substantial differences in total hospitalization cost for kidney transplantation among patients with different *CYP3A5* genotypes.

Keywords *CYP3A5* · Kidney transplantation · Surgical cost · Tacrolimus · Thailand

Impacts on practice

- Patients undergoing kidney transplantation should be genotyped for *CYP3A5* because *CYP3A5*1/*1* is associated with a higher total hospitalization cost than *CYP3A5*3/*3*.
- In Thailand, the reimbursement for total hospitalization cost in patients with the *CYP3A5*1/*1* genotype should be increased by $3275.

Introduction

Kidney transplantation is the best option for patients with end stage kidney disease, resulting in improvements in quality of life. In Thailand, the cost of transplant surgery and hospitalization ranges from US$6250 to $11,765; however, complications after the transplant are not uncommon and can incur additional costs ranging from US$676 to $14,500 [1]. Immunosuppressive drugs are crucial therapies to prevent allograft rejection after a kidney transplant. At present, tacrolimus (TAC), a calcineurin inhibitor, is one of the cornerstone immunosuppressants and is increasingly used despite its highly variable pharmacokinetics and narrow therapeutic window. Graft rejection can occur when the levels of TAC

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in plasma are too low, and nephrotoxicity can result when the levels are too high. Theoretically, achieving the target therapeutic TAC level to prevent complications requires dose adjustments, which are guided by therapeutic drug monitoring (TDM) of TAC levels.

At day 3 after transplantation, the TAC level is normally in a steady state. Therefore, achieving the target blood concentration of TAC at day 3 is used as a parameter in pharmacokinetic and pharmacogenetic studies to examine the impact of the cytochrome P450 3A5 (*CYP3A5*) polymorphism on TAC concentration [2–4]. A rapid attainment of the target therapeutic level would decrease the risk of graft rejection, which is high during the initial period after transplantation, as well as decrease adverse events and drug costs. In one study of kidney transplants in patients who were given the same dose of TAC, those who had experienced delayed graft function in the first week were found to have a higher blood concentration of TAC at day 4 than those who had not experienced such complications [5]. Moreover, a TAC blood concentration greater than 15 ng/mL was reported to be associated with an increased risk of developing new-onset diabetes after transplantation and delayed graft function during the first week after the transplant [6]. Therefore, an appropriate dose that guided by the TDM of TAC is the key to manage the risk of complications after transplantation.

TAC is primarily metabolized by the *CYP3A* subfamily, which primarily includes *CYP3A4* and *CYP3A5* in the liver and intestine. The prevalence of *CYP3A5* genotypes differs across ethnicity. Approximately 1% and 17% of Caucasians are *CYP3A5* expressers compared with 14% and 43% of Thais (*CYP3A5*1/*1* and *CYP3A5*1/*3* genotypes, respectively). The prevalence of *CYP3A5*3/*3* was reported to be 86% in Caucasians and 44% in Thai populations [7]. The patients who are characterized by the *CYP3A5*3/*3* genotype require a lower TAC dose to reach the target concentration compared to patients with the *CYP3A5*1/*1* genotype. Patients who are *CYP3A5* expressers have a higher clearance rate (0.679 ± 0.195 L/h/kg) than those who have the *CYP3A5*3/*3* genotype (0.355 ± 0.091 L/h/kg) [7]. From a previous study in Thailand, the average dose of TAC for the induction phase in those who had the *CYP3A5*3/*3* genotype was lower than that of patients with the *CYP3A5*1/*3* and *CYP3A5*1/*1* genotypes (0.077, 0.097, and 0.142 mg/kg/day, respectively) [8]. When receiving the same dose of TAC, patients with the *CYP3A5*1/*1* and *CYP3A5*1/*3* genotypes had a higher rate of acute graft rejection (i.e., early T cell mediated rejection) than those with the *CYP3A5*3/*3* genotype, as confirmed by renal biopsy at day 10 after the transplant [9]. Another study in French patients who had undergone kidney transplantation reported that 29% of patients in the fixed dose group (0.2 mg/kg/day) and 43% of patients in the genotype-guided dose groups achieved the target therapeutic TAC level at day 3 after transplantation. However, acute graft rejection and glomerular filtration rates did not differ between the two groups [4].

Genotyping to detect the *CYP3A5* allele has become a popular test in transplant centers in Thailand due to its affordable cost. The application of genotype testing is expected to optimize TAC treatment responses and to minimize adverse effects. The Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline has recommended a genotype-guided initial TAC dose followed by TDM-guided dose adjustment [10]. Although the clinical benefits of the genotype-guided initial TAC doses for kidney transplantation are controversial with respect to acute graft rejection and delayed graft function, the dosage quantities of TAC varied according to gene allele [10]. There is limited evidence regarding the costs of hospitalization in patients with different *CYP3A5* genotypes. It is expected that patients with the *CYP3A5*1/*1* genotype would have higher treatment costs than other genotypes because they need a higher dose of TAC to reach the therapeutic level, but this higher dose also increases the risk of acute kidney injury. Currently, hospital reimbursement for inpatient care in Thailand is based on diagnosis related groups (DRGs). Genetic information is not included in the algorithm for classification to a particular DRG. Patients receiving kidney transplants are classified to the same DRG regardless of their *CYP3A5* genotype, and they receive the same reimbursement rate.

Aim of the study

The aim of this study was to determine the TAC and TDM cost and total hospitalization cost for kidney transplantation across the *CYP3A5*1/*1*, **1/**3, and **3/*3* genotypes. These cost findings could provide additional information to justify the inclusion of *CYP3A5* genotyping into the reimbursement system, despite the fact that its clinical outcomes remain controversial.

Ethics approval

The study was approved by the Ethics Committee for Human Research, Khon Kaen University.

Method

Study patients

Eligible patients were 18 years or older who were first-time kidney transplant patients at a single transplant center in a university hospital. The exclusion criteria were patients

with aspartate transaminase (AST) and alanine transaminase (ALT) ≥ 2 times of normal limit or total bilirubin ≥ 1.5 mg/mL. Female patients who were either pregnant or breastfeeding were also excluded.

Study design

This is an observational study that collected the data from patients who were pooled from both arms of a randomized controlled trial (RCT) that compared a conventional fixed dose and genotype-guided dose of TAC during the first 3 days of transplantation. The RCT detailed protocol can be found at the Clinicaltrials.gov (ID No. NCT03173820). All patients who were included in the RCT had genotype testing conducted while they were on the transplant waiting list. The main outcomes in the present study included costs of TAC and TDM and the hospitalization cost incurred during hospitalization for the transplant.

An initial loading dose of oral TAC (Prograf®) was given 2–6 h before the surgery, depending on the time of transplantation. The first dose was 0.1 mg/kg/day in the conventional group, while the dose in the genotype-guided group was 0.125, 0.1, and 0.08 mg/kg/day for patients with the *CYP3A5*1/*1*, **1/*3*, and **3/*3* genotypes, respectively. The second dose at half of the first doses was administered at the next appropriate time after surgery, at approximately 8.00 AM or 8.00 PM. After the second dose, the next four equal doses were continued every 12 h. After day 3, the doses were adjusted based on the trough level. The target blood concentration was 5–8 ng/mL for the first 4 weeks and 5 ng/mL from weeks 5–12. From weeks 13–24, the target level was reduced to 3–5 ng/mL. Both the conventional fixed dose and genotype-guided dose groups received the same standard immunosuppressive regimens except for the initial dosing of TAC, as described above. On the day of transplantation (day 0), induction therapy with intravenous methylprednisolone (1000 mg) and basiliximab (20 mg if clinically indicated) were given. Methylprednisolone was continued in the reduced doses until day 3 and then substituted by oral prednisolone (60 mg/day) on day 4. The third immunosuppressive drug was either mycophenolate mofetil (1500 mg/day) or mycophenolic acid (1080 mg/day), and this was added within 24–48 h after the transplant when the refunctioning of bowel absorption occurred. The dose of prednisolone was tapered to 5 mg within 3 months.

Genotype analysis and therapeutic drug monitoring

DNA was extracted from peripheral blood leucocytes (QIAamp Blood Mini Kit, QIAGEN, Hilden, Germany). Genotyping of *CYP3A5* was performed with real time polymerase chain reaction (PCR) (The Applied Biosystems ViiA 7 system, Life Technologies, USA) by sequence-specific PCR primers and probes to identify single nucleotide polymorphisms. The *CYP3A5*1/*1*, **1/*3*, and **3/*3* genotypes were determined using Fluorescence Resonance Energy Transfer (TaqMan Assay Reagents for allelic discrimination, Applied Biosystems, Foster City, CA, USA). Determination of the TAC level in the blood samples was performed using a microparticle enzyme immunoassay (MEIA, IMx, Abbot Laboratories, Wiesbaden, Germany). In our previous study (unpublished data), we investigated other mutant alleles that have been reported in Asian populations such as *CYP3A5*9*, but it was not detected in the Thai population (samples from 400 healthy volunteers). In this study, we investigated only *CYP3A5*3*, which is the most common mutant allele in Asian populations.

Data collection

Chart reviews and computerized records provided the data on the attainment of the target therapeutic TAC level at day 3 after transplant, graft function, total doses of TAC and numbers of TDM during hospitalization. Graft function was divided into three categories based on the levels of serum creatinine (SCr) and/or requirement for dialysis during the first week after transplantation: (1) instant graft function (SCr < 1.5 mg/dL), (2) slow graft function (SCr > 1.5 mg/dL but did not require dialysis), and (3) delayed graft function (dialysis required in the first week after transplant). The unit cost of TDM was US $29.4, and the cost of genotyping was US $23.6. The total charges of hospitalization for transplantation were collected and adjusted by the cost-to-charge ratio to obtain the direct medical cost. All costs were valued in 2016 Thai Baht (THB), which were converted into United States dollars (US $1 = 34 THB).

Statistical analysis

Statistically significant differences in patient characteristics, therapeutic TAC level at day 3 after transplant, and delayed graft function status across the three *CYP3A5* genotypes were examined using the appropriate tests. The data distribution was assessed in all outcome variables for normality and equality of variance. Total doses of TAC, length of stay, TAC and TDM costs, and total hospitalization cost were not normally distributed so they were compared between genotypes using a generalized linear model (GLM) with gamma distribution family and log-link function. The number of TDM samples during hospitalization for transplantation was compared using an analysis of covariance (ANCOVA). A multivariable analysis was used to determine whether the attainment of the target therapeutic TAC level at day 3 after transplant (yes vs. no), conventional fixed versus genotype-guided initial doses during the first 3 days after transplant, and delayed graft function were independent predictors of

all study outcomes. The covariates to be adjusted included donor's and patient's demographics, patient's clinical conditions, modes and duration of renal dialysis. Two-sided *P* values of less than 0.05 were considered to be statistically significant. Stata version 14.0 was used as a statistical software package for data analysis.

Results

Table 1 summarizes the baseline characteristics of patients by *CYP3A5* genotype. Of 125 study patients, 16 (12.8%) had *CYP3A5*1/*1*, 59 (47.2%) had *CYP3A5*1/*3* and 50 (40%) had *CYP3A5*3/*3* genotypes. The baseline characteristics of the allograft recipients were similar across the three genotypes. The majority of the patients were male, with an average age ranging from 39 to 45 years. Before the transplantation, 88 patients (70.4%) received hemodialysis and 37 patients (29.6%) received peritoneal dialysis. The duration of the dialysis ranged from 54 to 61 months.

At day 3 after transplantation, the subtherapeutic level of TAC was found in the majority of patients (93.8% in *CYP3A5*1/*1*, 59.3% in *CYP3A5*1/*3*, and 24.0% in *CYP3A5*3/*3*). There was a significant difference in the percent of patients who achieved the target therapeutic level across the three genotypes. The *CYP3A5*3/*3* group had the highest percent of patients achieving the target therapeutic level (38.0%) compared with the *CYP3A5*1/*1* (6.3%), and *CYP3A5*1/*3* (33.9%) groups ($P < 0.001$). The difference in the proportion of patients who had delayed graft function did not reach statistical significance among the *CYP3A5*1/*1* (50.0%), *CYP3A5*1/*3* (27.1%) and *CYP3A5*3/*3* (32.0%) genotypes. For all genotypes, the patient characteristics between the conventional fixed dose and the genotype-guided dose groups were similar (data not shown).

During hospitalization, the total dose of TAC was highest in the *CYP3A5*1/*1* patients, followed by those in the *CYP3A5*1/*3* and in *CYP3A5*3/*3* patients, respectively. However, the number of samples for TDM and the length of hospital stay did not differ among genotypes (Table 2). The hospital stay in the *CYP3A5*1/*1* group was longest, and those in the *CYP3A5*1/*3* and *CYP3A5*3/*3* groups were similar to each other. Delayed graft functioning was associated with an additional stay of 17.2 days (95% confidence

Table 1 Baseline and medical characteristics and graft function of study patients undergoing a kidney transplant according to their *CYP3A5* genotype

	*CYP3A5*1/*1* (N = 16)	*CYP3A5*1/*3* (N = 59)	*CYP3A5*3/*3* (N = 50)	*P* value
Recipient age (years), mean (SD)	44.9 (9.8)	42.9 (10.1)	39.3 (10.2)	NS
Recipient body weight (kilograms), mean (SD)	57.9 (11.7)	57.4 (10.5)	58.5 (13.1)	NS
Recipient male, N (%)	9 (56.3)	37 (62.7)	34 (68.0)	NS
Dialysis, N (%)	16 (100.0)	59 (100.0)	50 (100.0)	NS
Hemodialysis, N (%)	10 (62.5)	42 (71.2)	36 (72.0)	NS
Duration of dialysis (months), mean (SD)	54.2 (34.6)	61.2 (36.1)	59.4 (40.3)	NS
Number of HLA mismatch, N (%)				
HLA-A mismatch ≥ 2	5 (31.3)	13 (22.0)	9 (18.0)	NS
HLA-B mismatch ≥ 2	1 (6.3)	7 (11.9)	10 (20.0)	NS
HLA-DR mismatch ≥ 2	0	2 (3.4)	0	NS
Donor age (years), mean (SD)	44.0 (10.4)	37.3 (13.6)	36.9 (14.4)	NS
Donor male, N (%)	14 (87.5)	45 (76.3)	39 (78.0)	NS
Panel reactive antibody > 20%, N (%)	6 (37.5)	12 (20.3)	9 (18.0)	NS
Number of marginal donor, N (%)	6 (37.5)	10 (17.0)	10 (20.0)	NS
Average ischemic time (h), mean (SD)	17.7 (4.4)	17.2 (4.5)	16.9 (5.0)	NS
TAC level at day 3 after transplant, N (%)				< 0.001
Within therapeutic range	1 (6.3)	20 (33.9)	19 (38.0)	
Subtherapeutic range	15 (93.8)	35 (59.3)	12 (24.0)	
Over therapeutic range	0	4 (6.8)	19 (38.0)	
Graft function status during the first week after transplant, N (%)				NS
Instant graft function	4 (25.0)	19 (32.2)	20 (40.0)	
Slow graft function	4 (25.0)	24 (40.7)	14 (28.0)	
Delayed graft function	8 (50.0)	16 (27.1)	16 (32.0)	

CYP3A5, cytochrome P450 3A5; SD, standard deviation; HD, hemodialysis; HLA-DR, human leukocyte antigen D related; h, hour; TDM, therapeutic drug monitoring; TAC, tacrolimus; NS, not statistically significant

Table 2 TAC dose, TDM, length of hospital stay and hospitalization cost of patients undergoing a kidney transplant according to their *CYP3A5* genotype

	*CYP3A5*1/*1* (N = 16)	*CYP3A5*1/*3* (N = 59)	*CYP3A5*3/*3* (N = 50)	*P* value
Total dose of TAC (mg)				
Mean (SD)	257.9 (167.0)	156.1 (80.5)	125.0 (74.8)	
Median (IQR)	177.0 (131.3–350.5)	131.5 (94.5–211.5)	105.8 (69.5–162.0)	$^{\$}P = 0.024$, $^{\#}P < 0.001$
Number samples of TDM drawn, mean (SD)	16.5 (4.5)	15.0 (3.0)	16.0 (4.5)	$^{\$}$NS, $^{\#}$NS
Length of hospital stay (day), median (IQR)	32.5 (17.5–38.5)	24.0 (17.0–29.0)	24.5 (17.0–32.0)	$^{\$}$NS, $^{\#}$NS
Instant or slow graft functioning	17.5 (16.5–25.0)	18.5 (15.0–29.0)	19.5 (15.0–25.0)	
Delayed graft functioning	38.0 (35.0–49.0)	28.0 (26.0–30.0)	38.5 (31.0–48.5)	
Cost of TAC and TDM during hospitalization ($), median (IQR)	1062 (838–1588)	859 (708–1139)	761 (580–1097)	$^{\$}$NS, $^{\#}P = 0.008$
Cost of hospitalization ($), median (IQR)	9097 (6667–11,602)	6467 (4950–7714)	5604 (3732–8115)	$^{\$}$NS, $^{\#}P = 0.041$

TAC, tacrolimus; TDM, therapeutic drug monitoring; *CYP3A5*, cytochrome P450 3A5; SD, standard deviation; IQR, interquartile range; NS, not significant; $, US dollar

$^{\$}$Comparing between *CYP3A5*1/*1* versus **1/*3*

$^{\#}$Comparing between *CYP3A5*1/*1* versus **3/*3*

interval, 9.3–25.2 days). The median costs of TAC and TDM and the total hospitalization costs were lowest in the *CYP3A5*3/*3* group ($761 and $5604) and highest in the *CYP3A5*1/*1* group ($1062 and $9097). The median costs of total hospitalization by subgroups are presented in Fig. 1a, b.

Table 3 shows the results of the multivariate analysis. Achieving the target therapeutic level by day 3 and having genotype-guided initial doses were not statistically associated with the costs of TAC and TDM or the total hospitalization cost, while the delayed graft functioning was a significant predictor of the costs. The *CYP3A5*1/*1* patients had a higher cost of TAC and TDM by $165 and a higher total hospitalization cost by $2787 compared to the *CYP3A5*1/*3* patients, despite marginal significance. Compared to the *CYP3A5*3/*3* patients, the *CYP3A5*1/*1* patients had a significantly higher cost of TAC and TDM (by $309, $P = 0.008$) and a higher total hospitalization cost (by $3275, $P = 0.041$). Both TAC and TDM costs and total hospitalization cost were significantly higher in patients who had delayed graft functioning than in patients who did not have delayed graft functioning ($528, $P < 0.001$ and $2872, $P = 0.033$, respectively).

Discussion

The primary finding of this study is that the *CYP3A5* genotype was a significant predictor of total hospitalization cost for kidney transplantation. The costs of TAC and TDM and total hospitalization cost in patients with the *CYP3A5*1/*1* genotype were significantly higher than those in patients with the *CYP3A5*3/*3* genotype. Genotyping appears to be a cost-conscious tool that can assist physicians to optimize the TAC doses in conjunction with TDM, even though genotype-guided initial doses and achieving the target therapeutic TAC level at day 3 after transplant did not decrease the costs associated with transplantation.

This study aimed to compare the hospitalization costs in patients with different *CYP3A5* genotypes, as this enzyme is associated with TAC metabolism. All of the study patients followed the same immunosuppressive therapy and usual medical activities according to a standard treatment protocol in Thailand. The only different intervention was the initial TAC doses in the patients with genotype-guided doses. TDM could be performed at any time at the physician's discretion after the second dose of TAC was administered after transplantation, except for during the specified times for monitoring the TAC level described in the trial protocol. Dose adjustment in the fixed-dose control and genotype-guided group could be made during the first 3 days if there was a clinical indication for patient safety. Therefore, the present study replicated the real world practice rather than the experimental conditions. Nonexpressers (*CYP3A5*1/*1* patients) required a higher TAC dose than expressers (*CYP3A5*1/*3* and **3/*3* patients), which partly translated to higher hospitalization costs. A higher proportion of patients with the *CYP3A5*1/*1* genotype required dialysis in the first week after transplant, which reflected the delayed graft functioning and resulted in a higher cost. This finding conforms with a majority of previous studies which have shown that patients with the *CYP3A5*1/*1* genotype have a higher incidence of acute rejection, leading to a higher hospitalization cost and a longer hospital stay [11–13].

The initial dose in the conventional fixed-dose group in our study protocol (0.1 mg/kg/day) was lower than that in other reports (0.2 mg/kg/day) [3, 4]. The proportion of patients in the present study who achieved a target

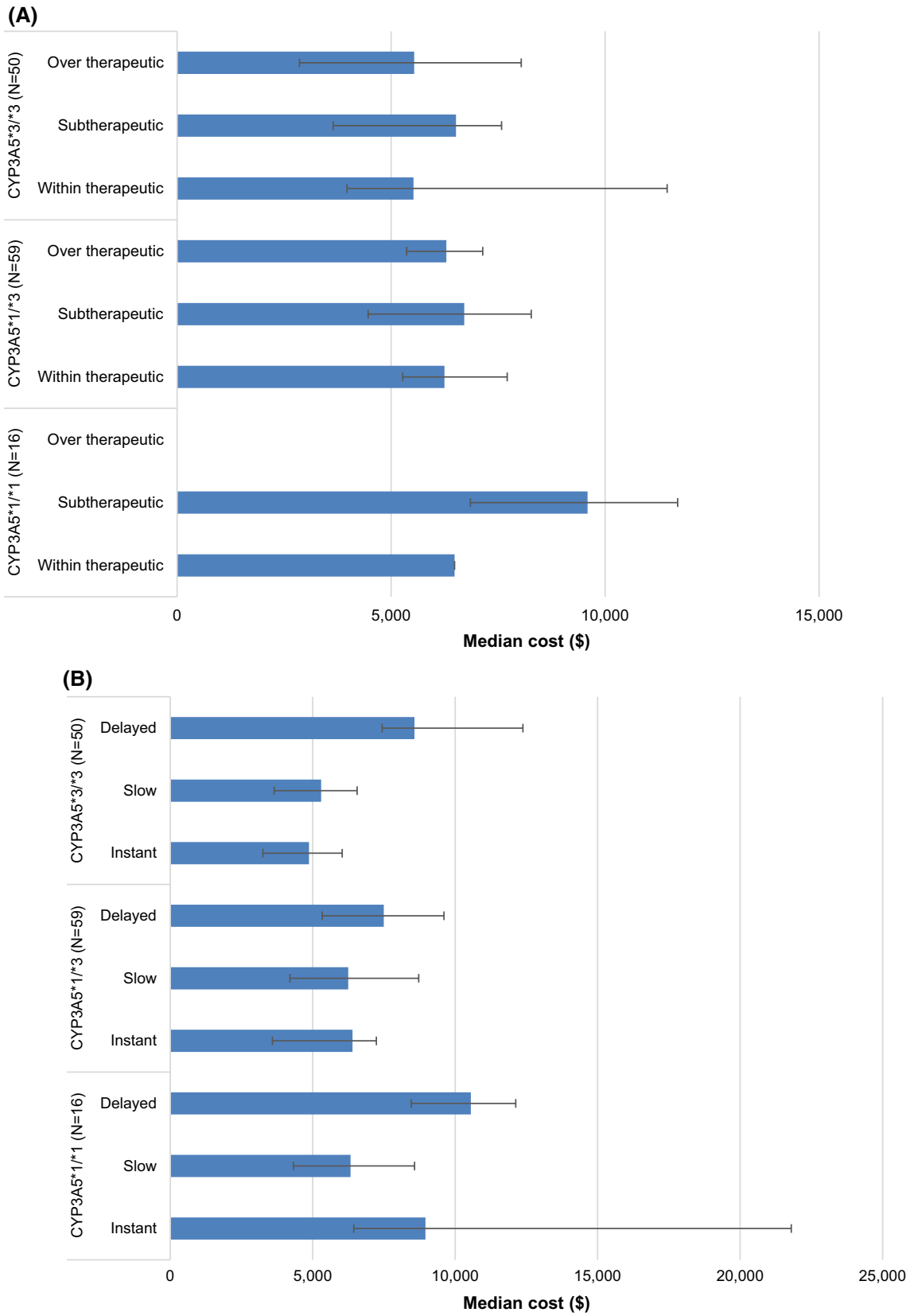

Fig. 1 Median costs of hospitalization ($) of patients undergoing a kidney transplant and interquartile ranges by subgroups. **a** Subgroups by TAC level at day 3 after transplant. **b** Subgroups by graft function status during the first week after transplant

Table 3 Factors associated with the cost of TAC and TDM and hospitalization cost in patients undergoing a kidney transplant

	Differences in cost of TAC and TDM ($)	*P* value	Differences in total hospitalization cost ($)	*P* value
*CYP3A5*1/*1* versus *CYP3A5*1/*3*	165 (51–382)	0.134	2787 (−217 to 5791)	0.069
*CYP3A5*1/*1* versus *CYP3A5*3/*3*	309 (81–538)	0.008	3275 (132–6417)	0.041
Within therapeutic range at day 3 after transplant (yes vs. no)	−22 (−158 to 113)	0.746	−543 (−2153 to 1067)	0.508
Conventional fixed dose versus genotype-guided dose[a]	−18 (−135 to 100)	0.770	−42 (−1530 to 1446)	0.956
Delayed graft function during the first week after transplant (yes vs. no)	528 (299–756)	<0.001	2872 (237–5507)	0.033

TAC, tacrolimus; TDM, therapeutic drug monitoring; *CYP3A5*, cytochrome P450 3A5; $, US dollar

[a]For initial doses during the first 3 days of kidney transplant

therapeutic TAC level at day 3 (23.8%) was slightly lower than that in other reports from western countries (range 29.1–35.6%) and a previous report in Thailand (42% in non-expressers and 47% in expressers) [2]. This discrepancy may help explain why the attainment of the target therapeutic level at day 3 did not affect the hospitalization cost in the present study.

Some study limitations should be addressed. Despite the small number of patients in each genotype, the different hospitalization costs among the *CYP3A5*1/*1* and **3/*3* patients were statistically significant. An additional analysis of hospitalization cost by a quantile regression (data not shown) resulted in a similar conclusion in that the cost for *CYP3A5*1/*1* was higher than that for *CYP3A5*3/*3* at the median and 75th percentile with a statistically marginal significance level ($P=0.079$ and 0.103, respectively) and at the 25th percentile with a statistically nonsignificant level ($P=0.475$). The detailed cost components were not fully examined since they were expected to have a modest contribution to the difference in total hospitalization costs among genotypes when the kidney transplant was paid for by the DRG system. The present study used data from an RCT. Therefore, the patients were monitored closely by specialist physicians and multiple dose adjustments of TAC were performed using TDM regardless of the initial dosing strategies. Some factors, such as hemoglobin, hematocrit, liver function, and serum albumin level, have been reported to modify TAC pharmacokinetics and clinical outcomes in previous studies [14–16] but were not considered in the present study.

To be acceptable and applicable in the clinical practice of kidney transplantation, genotyping information should help decrease delayed graft function, adverse drug events, time and number of dose modifications to achieve the target therapeutic TAC level, drug cost for induction therapy, length of hospital stay, and hospitalization cost. The present study recommended that an increase in the reimbursement rate for patients with the *CYP3A5*1/*1* genotype should be considered. A full economic evaluation of genotype-guided TAC dosing for patients with kidney transplants would require an estimation of both the short-term and long-term clinical outcomes. When the evidence on clinical outcomes of genotyping becomes available, the full economic evaluation can be conducted.

Conclusion

This study confirms that patients having the *CYP3A5*1/*1* genotype require a higher dose of TAC and have a higher additional hospitalization cost for kidney transplants than the *CYP3A5*3/*3* patients. The benefits of genotype detection in patients with *CYP3A5*1/*1* should be considered for a higher reimbursement rate because of the substantial differences in hospitalization cost for kidney transplants among patients with different *CYP3A5* genotypes.

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Conflicts of interest All authors declare that they have no conflicts of interest.

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