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Cytochrome P450 3A5 Polymorphisms and Infection Risk in Malaysian Kidney Transplant Recipients Receiving Tacrolimus: An Exploratory Multicentre Cohort Study

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Abstract: Background: Despite kidney transplantation being a life-saving intervention for end stage renal patients, it poses significant challenges due to the management of tacrolimus-based immunosuppressive therapy and the subsequent heightened infection risk. Genetic factors such as cytochrome P450 (CYP) 3A5 polymorphism, may alter tacrolimus drug exposure and consequently modulate susceptibility to infections. Such data is still lacking among kidney transplant recipients (KTRs) and hence the objective of this study was to explore the influence of CYP3A5 polymorphisms on infection occurrence in KTRs treated with tacrolimus. **Methods:** This multicentre, retrospective exploratory cohort study included adult patients who underwent kidney transplantation between 2020 and 2021, received anti-infective agents, and were maintained on tacrolimus-based treatment. Patients were followed-up for one-year post-transplant. DNA was extracted from blood samples and CYP3A5*1 and its variant CYP3A5*3 was determined by polymerase chain reaction. **Results:** Of the total KTRs (n=21), 38.1% (n=8) were wild type CYP3A5*1/*1, 47.6% (n=10) were heterozygous CYP3A5*1/*3, and 14.3% (n=3) were CYP3A5*3/*3. A high infection rate (85.71%, n=18) was observed, predominantly COVID-19 and cytomegalovirus, with peak incidence in the first three months and months 9–12 post-transplant. Infected patients were significantly older than non-infected patients, consistent with immunosenescence ($p<0.01$). Transaminitis was less likely in infected KTRs ($p=0.026$). CYP3A5 expresser status was not statistically associated with one-year infection risk. **Conclusions:** This exploratory study underscores the high number of CYP3A5*1 allele within the Malaysian KTR population. However, CYP3A5 polymorphism and infection risk was not observed to be associated within the one-year post-transplant. Our findings do highlight the potential value of pharmacogenetic variability in guiding individualised therapy in infected KTRs due to the possible protective role of CYP3A5*1 on tacrolimus-anti-infective transaminitis. Consequently, larger local studies are required to support the integration of genetic, clinical, and behavioural factors into personalised post-transplant care.

Keywords: CYP3A5; kidney transplant recipients; polymorphism; tacrolimus

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INTRODUCTION

Immunosuppressants are essential for preventing organ rejection after transplantation. Kidney transplant recipients (KTRs) are typically managed with a triple therapy comprising tacrolimus, mycophenolate, and corticosteroids, to maintain graft survival, particularly during the first critical year [1]. These agents suppress T- and B-cell activity, reducing rejection risk, but increasing infection susceptibility [2, 3]. Infections are most common within the first few months post-transplantation due to intense immunosuppression [3], with 30%–70% of infections occurring in the first year [4]. Common infections include bacterial urinary tract infections, viral infections such as cytomegalovirus (CMV), BK virus, and opportunistic fungal infections [5]. These infections remain a major cause of morbidity and contribute significantly to graft dysfunction and hospitalization in KTRs [6, 7]. The increased risk of infection during this period necessitates close monitoring and prophylaxis [1, 6, 7].

The cytochrome P450 (CYP) system, especially CYP3A4 and CYP3A5, is crucial for tacrolimus metabolism [8]. CYP3A5 polymorphisms also affect dosing; individuals with the *CYP3A5*1* allele or expressers require higher tacrolimus doses, while *CYP3A5*3* carriers or non-expressers are more prone to toxicity at standard doses than *CYP3A5*1* [9]. CYP3A5 non-expressers therefore tend to achieve higher tacrolimus trough concentrations, which has been linked to an increased risk of over-immunosuppression and infection, especially in the early post-transplant period [9]. On the other hand, CYP3A5 expressers may require higher tacrolimus doses and are more frequently associated with under-immunosuppression and rejection [9]. Consequently, the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines recommend a 1.5- to 2-fold higher initial dose for *CYP3A5*1* carriers, although close monitoring is required.

Despite this, CYP3A5 expressers have also been linked to a higher risk of infection among patients treated with tacrolimus [10, 11]. Among 134 KTRs, it was demonstrated that the *CYP3A5*1* allele had a higher incidence of viraemia than those with the *CYP3A5 *3/*3* genotype due to the higher doses required in these patients [10]. Similarly, tacrolimus-treated KTRs demonstrated that *CYP3A5*1* allele was independently associated with a higher occurrence of viral infections, including CMV, compared with *CYP3A5*3* carriers [11]. This association is interpreted as *CYP3A5*1* carriers metabolising tacrolimus more quickly, leading to the need for higher doses than their *CYP3A5*3* counterparts with limited monitoring. Therefore, the effects of CYP3A5 are not directly associated with infection but rather the need for higher doses that may have led to a deeper net immunosuppression, increasing the susceptibility of infection among the CYP3A5 expressers. However, other studies have failed to demonstrate a significant association between CYP3A5 genotype and clinical outcomes such as infection, when standard immunosuppressive management and monitoring are applied [12].

In Malaysia, CYP3A5 polymorphisms are prevalent in the population [13] and contribute to inter-individual variability in drug metabolism. CYP3A5 polymorphisms may significantly affect drug exposure and increase susceptibility to infection in KTRs receiving tacrolimus. However, current research on the impact of CYP3A5 polymorphisms in this population on risk of infection is limited and further investigations are warranted to determine the prevalence of CYP3A5 variants and their association with risk of infection to support precise dosing and reduce post-transplant complications. Therefore, this study aimed to explore the influence of CYP3A5 polymorphisms on infection risk in tacrolimus-treated KTRs.

Methods

Study design

This was an exploratory, multicentre, retrospective cohort study conducted across two kidney transplant facilities in the Ministry of Health hospitals in Malaysia. Adult patients aged > 18 years who received kidney transplants between January 2020 and December 2021, and maintained on a tacrolimus and mycophenolic acid-based immunosuppression regimen for a minimum of one year, with good adherence, were included. Individuals with incomplete medical records or those who underwent multiple organ transplants were excluded from the analysis.

Study sample

As this was a pilot investigation to characterize the frequency of CYP3A5 alleles in Malaysian KTRs and provide preliminary data to inform future larger studies, all eligible patients were included to ensure representation of both genotype groups. This approach aligns with current recommendations for pilot genetic studies in low-volume or rare populations and the STROBE guidelines [14].

Ethical approval

The study protocol was approved by the Universiti Kebangsaan Malaysia Research Ethics Committee

(UKM PPI/111/8/JEP-2022-431) and registered with the National Medical Research Register of the Ministry of Health, Malaysia (NMRR ID-22-00076-D3H (IIR)). This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the Malaysian Good Clinical Practice Guidelines. Written informed consent was obtained from all included patients following a face-to-face briefing on the study protocols.

Data collection

Patient data were retrieved from medical records and included demographic, clinical, medication and infection information at transplant and throughout the one-year post-transplant. The demographic data included age, sex, ethnicities. The clinical variables included blood pressure (BP), primary renal disease, co-morbidities, as well as dialysis modality, duration of dialysis, type of donor, induction treatment. Medication information included number of medications, tacrolimus doses and tacrolimus trough levels. Other information such as occurrence of transaminitis and infection variables which include types of infection, culture and sensitivity tests, type of antimicrobial agents used, time of infection occurrence (days) were collected.

DNA Extraction and SNP Genotyping

A 5 mL blood sample was collected from each participant. Genomic DNA was extracted from the blood samples using a Qiagen DNeasy Blood and Tissue Kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol. The purity of the extracted DNA was assessed. Polymerase chain reaction (PCR) was performed to amplify the purified copies of the CYP3A5 SNP (6986A>G) [15]. The PCR products were examined by gel electrophoresis, to ensure the quality of PCR product [16], followed by size separation and visualisation using a real-time transilluminator system (E-Gel® Safe Imager™, Life Technologies, Israel), with the *CYP3A5*3* allele identified by the presence of the 293 base pairs [15]. The identified products were purified using a commercially available PCR purification kit (Applied Biosystems). The purified DNA fragments were then sequenced using a Sanger sequencing performed by a BigDye® Terminator v3.1 Cycle Sequencing Kit and analysed on a 96-capillary 3730xl DNA Analyser at First BASE Laboratories Sdn. Bhd., Malaysia (Thermo Fisher Scientific, Waltham, MA, USA). Sequence Scanner (v2.0) was used to interpret the sequencing data, which were aligned against reference sequences using the BLAST program to confirm the presence of targeted polymorphisms. Sanger sequencing was performed on three randomly selected DNA samples from the study cohort to validate the accuracy of the genotyping method. The resulting sequencing data confirmed the genotype and validated the reliability of the results.

Statistical analysis

All statistical analyses were performed using the SPSS statistical software (version 23, IBM Corp., Armonk, NY, USA). Continuous variables are reported as means ± standard deviation (SD) or medians ± ranges, and categorical data are reported as counts and percentages. A t-test or analysis of variance (ANOVA), or its corresponding non-parametric test was used to compare means between two or more groups. Pearson's chi-squared test for independence was used to evaluate the association between categorical data, whereas Fisher's exact test was used if the assumptions of Pearson's chi-squared test for independence were not met. The association between allelic variants and survival was assessed using odds ratios (OR) with 95% confidence intervals (CIs), calculated using logistic regression. Statistical significance was set at $p < 0.05$. Adherence of the genotype groups to the Hardy–Weinberg equilibrium assumption was examined. The expected percentages for each genotype group were calculated based on the Hardy–Weinberg equation using allele frequencies ($p2 + 2pq + q2 = 1$) [15].

Results

Demographic data

A total of 21 patients were included in this study (Table 1). The average age at the time of transplant was 33.0 ± 7.7 years. Most recipients were men (n=13, 61.9%) and of Malay ethnicity (n=13, 61.9%). Hypertension was the most prevalent comorbidity (n = 16, 76.2 %) in the study population. Twenty (95.2%) patients were on dialysis prior to transplantation, with an average dialysis duration of 65.4 ± 65.0 months. Most transplants were from living-related donors (n=16, 76.2%), and basiliximab was the predominant induction treatment (90.5%).

Clinical and genetic characteristics one-year post transplant

A high infection rate of 85.7% (n=18) was observed within the first year after transplantation (Table 2). The highest number of infections occurred during the 1–3 and 10–12 months periods, with six episodes each. Conversely, fewer infections were reported in the <1 month (2 episodes), 4–6 month (1 episode), and 7–9 month (1 episode) intervals. This suggests that the early post-transplant period and end of the first year are high-risk periods for infection.

The most common infections were COVID-19 and CMV, occurring in 6 (33.3%) patients each, followed by urinary tract infections in 5 (27.8%) patients. Among the infections that underwent culture and sensitivity tests, *Enterococcus faecalis* was the most frequently identified pathogen (n=2, 25%), whereas two (25%) cultures showed no growth. A

wide range of antimicrobial agents were administered, with meropenem being the most frequently used antibacterial agent for the treatment of various infections (n=5, 41.7%). All patients received sulfamethoxazole/trimethoprim and nystatin as prophylaxis. The median time to infection varied significantly by type, with acute gastroenteritis appearing the earliest (median, 2 days), and COVID-19 appearing the latest (median, 319 days). The doses of tacrolimus reduced from months 1, 3, 6 to 12 within the one-year period, from 9.2 ± 6.1 mg/day to 6.9 ± 3.9 mg/day, 5.8 ± 3.4 mg/day and finally 5.3 ± 3.2 mg/day. Similarly, trough levels reduced from 8.5 ± 2.1 mg/mL to 7.3 ± 1.2 mg/mL, 6.7 ± 1.5 mg/mL to 6.4 ± 1.4 mg/mL, respectively, mirroring the reduction in doses.

Among the participants, 61.9% (n=26) carried the wild-type *CYP3A5*1* (wild-type) allele and 38.1% (n=16) carried the variant *CYP3A5*3* (variant) allele. Genotypically, 38.1% (n=8) were homozygous for the wild type (*1/*1), 47.6% (n=10) were heterozygous (*1/*3), and 14.3% (n=3) were homozygous for the variant (*3/*3). Thus, most individuals (n=18; 85.7%) carried at least one wild-type allele.

Table 3 presents a comparison of the baseline characteristics of KTRs who developed infections within one year (n=18) with those who did not (n=3). The comparison between patients receiving a kidney transplant revealed that those with infection were significantly older than those without ($p<0.01$). KTRs with infection had a significantly lower risk of transaminitis than those without infection ($p=0.03$). No other statistically significant differences were observed in the key demographic, clinical, and genetic characteristics between the infected and non-infected groups. Although patients with infection generally had lower diastolic blood pressure, these differences were not statistically significant. Similarly, the distribution of other demographics, clinical, medication, CYP3A5 allele and genotype was comparable between the two groups.

Factors associated with infection at one-year post transplant

No demographics, clinical, medication, CYP3A5 allele and genotype factors were significantly associated with the outcome at 1-year post-transplantation. Simple and multiple logistic regression models demonstrated that all variables, including demographic, clinical, medication and CYP3A5 characteristics had non-significant p-values (all $p > 0.05$) (Table 4). This indicated that none of the tested factors were predictive of infection within the one-year post-transplant.

DISCUSSION

In Malaysia, all KTRs were managed with the standard triple therapy of tacrolimus, mycophenolate and corticosteroid [1]. The predominance of male recipients is consistent with global trends that reflects a higher end-stage prevalence [17, 18]. In the cohort, Malays were the more predominant ethnics, in-line with the demographic composition of the Malaysian population [19]. Interestingly, pretransplant blood pressure values indicated a high prevalence of poorly controlled hypertension. Although this is expected in end-stage kidney disease, it is also a recognised contributor to cardiovascular and infectious complications following transplantation [18]. In the present cohort, the majority carried at least one *CYP3A5*1* allele. This finding is consistent with previous pharmacogenetic studies, which demonstrated a higher prevalence of the *CYP3A5*1* allele among Malays and Indians [19].

There was a high infection rate among KTRs, with COVID-19 and CMV being the most common infections. The time to infection was highest during the first three months and months 9-12, consistent with the vulnerability for opportunistic pathogens during immunosuppression [3]. CMV occurrence during the earlier phase post-transplant suggests the possible effects of early induction of immunosuppression. This period is critical as it often coincides with an increase in doses during induction immunosuppression. Furthermore, as the genetic profile of the cohort revealed a high prevalence of *CYP3A5*1* expressers, this may have led to earlier low trough levels, necessitating higher tacrolimus dosing, subsequently increasing the risk of infectious complications if not monitored frequently.

Infected patients were significantly older than non-infected patients, which is consistent with age-related immunosenescence that increases susceptibility to infection [3]. Previous studies have demonstrated that this increased vulnerability among older KTRs is largely attributable to age-related immune dysfunction, a higher burden of comorbidities, and reduced physiological reserve [20]. Importantly, even after adjustment for immunosuppressive regimens, graft function, and rejection episodes, age has been shown to remain an independent risk factor for infection [20]. Advancing age is associated with reduced naïve T-cell populations, impaired antigen presentation, and dysregulated inflammatory signalling, all of which compromise host defence against bacterial and viral pathogens [20, 21]. In addition, elderly KTR have been reported to carry a greater burden of comorbid conditions, such as diabetes and cardiovascular diseases, which further predisposes them to infectious complications [22]. As such, there is a need to ensure a more strategic

infection prevention strategy including closer surveillance of immunosuppressant doses, vaccinations, and optimised anti-infectives among older KTRs.

Interestingly, transaminitis was observed in a third of KTRs, although elevations in liver enzymes were less significant in patients with infection within the study population. Although transaminitis could be a result of viral infection such as the CMV virus, often resulting in elevations of liver enzymes due to hepatocellular injury or tissue-invasive disease [23], this was not observed in the current work. The interaction of hepatotoxic agents such as antivirals and tacrolimus, as well as broad spectrum anti-infectives have been reported to cause transaminitis via direct toxicity or CYP3A interactions [24, 25], albeit uncommon. Notably, the significantly less risk of transaminitis in those that were infected could have suggested a possible protective role of reduced enzyme activity among CYP3A5 expressers. This trend mirrors other findings on CYP-mediated hepatotoxicity [26, 27], demonstrating the role of CYP3A5 expressers in reducing risk of tacrolimus toxicity and transaminitis with the use of antivirals. In addition to this, although tacrolimus doses were maintained, the possible lowering of mycophenolate doses in some patients during infection episodes to reduce over-immunosuppression further contributes to this liver protective effect. Collectively, the need to closely monitor liver enzymes with the use of anti-infectives among KTRs is vital, with further work determining effects of CYP3A5 in a larger population. In this regard, no association was found between infection and CYP3A5 expressers and non-expressers. Despite this, the high number of expressers among KTRs in the Malaysia population does point towards the potential need for integrating CYP3A5 genotyping into routine care to enable individualised dosing and safer tacrolimus use [24, 25], especially during the early post-transplantation or infection episodes [3], and its possible drug interactions. Potentially, CYP3A5 likely plays a central role in tacrolimus toxicity, underscoring the need for close monitoring of tacrolimus levels and potential CYP3A-mediated interactions with antivirals, particularly in the evaluation of transaminitis.

These findings do have a few limitations. Notably, as an exploratory study, only 21 KTRs were recruited over the two-year study period, limiting the sample size. This reflects the lower number of kidney transplants performed in Malaysia. Additionally, the focus on CYP3A5 alone excludes other potentially relevant genes such as CYP3A4, ABCB1, SLCO1B1, warranting future pharmacogenetic exploration. Unmeasured confounders, such as use of herbal medications, common among the local population, as well as hygiene, may also impact the outcomes. Finally, retrospective data collection may have introduced bias owing to incomplete records, and the observational design may have limited causal inference.

CONCLUSION

CYP3A5 genotype into post-transplant care. This study highlights the prevalence of CYP3A5 polymorphisms among KTRs and their potential role in infection, especially during the high-risk early post-transplantation period, which is marked by intense immunosuppression and polypharmacy. Although the small sample size limits definitive conclusions, these findings support the relevance of pharmacogenetic variability in optimising post-transplant therapy. Given the multifactorial nature of complications, such as infection, transaminitis, and rejection, larger prospective studies are needed to assess genetic and non-genetic contributors. Additionally, incorporating pharmacogenetic testing into routine care may improve the precision of immunosuppressive and anti-infective therapies, reduce toxicity and enhance graft outcomes. The current study highlights the pressing need for local data to inform personalised management strategies in Malaysia, particularly during the critical first year after transplantation.

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