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## ORIGINAL ARTICLE

# A Retro-Prospective Study on Utilization of Tacrolimus in Renal Transplant Patients in a Tertiary Care Center

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**ABSTRACT**
*Tacrolimus is an essential component of immunosuppressive medication and has dramatically improved outcomes for kidney transplant patients. Despite improvements in treatment, maintaining graft survival in kidney transplantation remains a difficulty. Enhancing kidney transplant outcomes requires reducing risk factors for kidney graft rejection and survival. It also requires altering tacrolimus regimens in the early and maintenance stages post-transplantation. Tacrolimus has a constrained therapeutic window, which results in a narrow optimal drug exposure range. Underimmunosuppression has a significant chance of deteriorating kidney function and leading to graft failure, as well as long-term hazards such as production of donor-specific antibodies and antibody mediated rejection. On the other hand, persistent over- immunosuppression raises the possibility of negative drug-related side effects. To study the utilization and to evaluate Tac dosing in relation to the protocol, we aimed to achieve the target Tac trough concentration (C0) and assess the prevalence of Tac side effects. This involved an ongoing review of healthcare professional prescribing, pharmacist interventions, and patient's use of the medication. The process included a comprehensive review of patient's prescriptions, dosing patterns, and medication data before, during, and after dispensing. The goal was to ensure appropriate medication decision-making and positive patient outcomes. A total of 100 subjects, ≥ 18 years of age and the patients who had undergone renal transplant in the year 2021-2022 were considered for the study. The study concludes that for the third month the tac levels should be usually between 10-15 ng/ml, whereas Tac levels between 5-10ng/ml are deemed to be causing graft rejections. In the sixth month and ninth month tac levels more than 10ng/ml seem to be leading cause for post-transplant comorbidities. The most common post-transplant comorbidities being UTI's (urinary tract infections) about 28%, DM (diabetes mellitus) about 12%, infections (viral-CMV, BKV; bacterial-klebsiella; fungal- sinusitis, candidiasis) about 15% and graft rejections about 6%. As part of the evaluation, we assessed both the therapeutic efficacy and safety profile of the drug. Our study revealed minimal occurrences of acute graft rejections in the subjects, indicating the therapeutic effectiveness of tacrolimus. Decreased incidence of post- transplant comorbidities ensures the safety of tacrolimus.*
***Keywords:*** *Tacrolimus, Kidney transplant, safety, Effectiveness, Immunosuppression*

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## INTRODUCTION

Tacrolimus is an immunosuppressive drug used for prophylaxis of organ rejection following organ transplantation. It is a macrolide that was discovered in the fungus *Streptomyces tsukubaensis*, which was discovered in Japanese soil [1-3]. It gained FDA approval for liver transplantation in 1994, later approved for preventing acute rejection in kidney transplantation. Over the past decade, it has become the preferred calcineurin inhibitor for preventing rejection in renal transplantation. It functions by reducing immune system activity to protect the transplanted organ. It is primarily metabolized in the liver, over 98% of the dose undergoes metabolism via the CYP450-3A4 system. Half-life of it is about 4 to 41 hours

(on average about 12 hours). It is excreted approximately 95% through biliary route and approximately 2.4% as unchanged drug through urinary excretion [4-7]. It binds to the immunophilin FK506-binding protein in the cytoplasm. The formed complex then binds to the calcineurin enzyme, inhibiting the dephosphorylation of the nuclear factor of activated T cells (NFAT). Consequently, this prevents NFATc from translocating into the nucleus and attaching to the nuclear promoter of the interleukin-2 (IL-2) gene. The outcome is the inhibition of IL-2 production, crucial for complete T-cell activation. It interacts with various drugs; CYP3A4 inhibitors like Ketoconazole, Fluconazole, and Erythromycin increase its concentration, while CYP3A4 inducers like Rifampicin, Phenytoin, and Carbamazepine decrease its concentration [8,9]. It possesses a narrow therapeutic index, requiring routine therapeutic drug monitoring and dose adjustment to maintain desired levels for optimal therapeutic effects. Higher peripheral blood concentrations may lead to nonspecific consequences, while lower concentrations can result in sub-therapeutic effects. It is available in capsule form in doses of 5mg, 1mg, and 0.5mg. It, as a cornerstone of immunosuppressive medication, has significantly enhanced the outcomes for kidney transplant patients [10,11]. The general therapeutic range is 5-20ng/ml. It is most frequently prescribed as part of a dual- or triple-drug regimen along with corticosteroids and mycophenolate mofetil (MMF). Most patients are given two doses of immediate-release tacrolimus capsules twice daily, spaced every 12 hours [12].

**Contraindications:** Hypersensitivity, Polyoxyl 60 hydrogenated castor oil (HCO- 60) or other components of the formulation.

**Adverse Drug Reactions:**

**Cardiovascular**: hypertension, cardiac arrhythmias, and angina pectoris, **Central nervous system**: tremors, headaches, and strange dreams, **Dermatologic**: alopecia, rash, pruritis, and acne vulgaris, **Metabolic and endocrine**: Reduced serum bicarbonate, reduced serum iron, new-onset diabetes after transplant (NODAT), hyperkalemia, hyperphosphatemia, hyperlipidemia, hyperuricemia, hypervolemia, hypokalaemia, hyponatremia, hypophosphatemia, metabolic acidosis, and weight gain are all associated with this condition, **Gastrointestinal**: Diarrhoea, vomiting, nausea, and discomfort in the abdomen, **Genitourinary**: Urinary tract infections, **Hepatic**: Tests indicate abnormal hepatic function, **Infection**: herpes zoster infection, BK virus, Bacterial infection, candidiasis, cytomegalovirus, Epstein-Barr infection, herpes simplex infection, other opportunistic infection, **Neuromuscular and skeletal**: muscle cramps, Arthralgia, **Ophthalmology**: Blurred vision and other visual disturbances, **Otis**: Tinnitus, otitis media, and otalgia, **Renal**: Renal failure syndrome, renal tubular necrosis, decreased GFR, nephrotoxicity, acute renal failure, increased blood urea nitrogen (BUN), and increased serum creatinine (SCr).

Monitoring tacrolimus levels in transplant patients is crucial for optimizing drug dosages. The gradual reduction of target levels over time helps minimize nephrotoxicity and adverse effects associated with long-term use, especially when combined with other immunosuppressants. Tacrolimus trough concentrations must be routinely monitored to taper the dose for each patient and ensure the best possible medication exposure. Utilize whole blood concentrations, preferably drawn around 30 minutes before the subsequent dose, for effective monitoring [13-15]. Tacrolimus monitoring often occurs daily to weekly throughout the first three months of treatment. Monitoring frequency usually declines in individuals who are deemed stable and are further along in the post- transplant process. Monitoring of tacrolimus levels is beneficial, and the target level should be kept less than 20 ng/ml and preferably less than 10 ng/ml to reduce the risk of side effects (SEs).

**Tacrolimus Dosage Regimen**

Preoperative: 0.15 mg/kg orally; Postoperative: Initially 0.025–0.05 mg/kg intravenously via continuous infusion until the patient can tolerate oral intake, then 0.15 mg/kg orally twice a day.

**Target Tacrolimus Levels (ng/ml whole blood):** First 2 weeks: 20–25; 1 month: 15–20; 3 months: 10–15; Chronically: 5–12.

**Renal Transplant:** A kidney transplant is often the treatment of choice for kidney failure, compared with a lifetime on dialysis. A kidney transplant can treat chronic kidney disease or end-stage renal disease to help patients feel better and live longer. Compared with dialysis, kidney transplants are associated with better quality of life [16,17].

**Post Transplant Treatment:** It includes immunosuppressants therapy. To help the prevention of allograft rejections induction therapy and maintenance therapy are used.

**Induction**: Involves the use of immunosuppressive agents during the immediate post- transplant timeframe until the maintenance levels are achieved. Agents involved in induction therapy are Basiliximab, Alemtuzumab, Rituximab, and Anti-Thymocyte Globulin (ATG).

**Maintenance**: Involves the use of immunosuppressive agents in the early and extended post- transplant period and is typically maintained for life. Agents involved in maintenance therapy are Tacrolimus

(Prograf, Envarsus, Astagraf), Cyclosporine (Neoral, Gengraf, Sandimmune), Mycophenolic Acid (CellCept, Myfortic), and Azathioprine.
The following are maintenance treatments that are now offered.
**a. Corticosteroids**: Corticosteroids have been utilized in kidney transplantation. Long-term steroid use, however, is linked to several negative side effects, including hypertension, newly developed diabetes following transplantation, osteoporosis, fractures, hyperlipidemia, and growth retardation. Steroid-sparing techniques are being used more frequently because of the emergence of powerful maintenance and induction medications.
**b. Calcineurin Inhibitors**: The cornerstone of maintenance immunosuppression in all solid organ transplants has been calcineurin inhibitors (CNIs): CNI-based regimens using cyclosporine A (CyA) or tacrolimus. For tacrolimus, the beginning dose is 0.15-0.30 mg/kg, while for cyclosporine, it is 6-10 mg/kg.12-hour tacrolimus trough in the 8–12 ng/mL range can be desired during the first three months following transplantation, followed by a level of 6–10 ng/mL during the following four to twelve months. For the first several months on cyclosporine, a 12-hour trough of 250–350 ng/mLp is maintained, followed by a slowing down of target levels.
**c. Mycophenolate Mofetil and Mycophenolic Acid**: MMF is a prodrug that esterase hydrolyses to become MPA in the gut. Inosine monophosphate dehydrogenase, a significant enzyme involved in purine synthesis through the salvage pathway in T-cells and B-cells, is inhibited by MPA. A pooled analysis of studies including 1493 recipients showed that MMF significantly reduced acute rejection events and increased graft and patient survival over the course of one year.
**Triple Drug Therapy**: Tacrolimus, steroids, and mycophenolate mofetil have superior graft survival rates and a lower incidence of rejection than tacrolimus and steroids alone.

## MATERIAL AND METHODS

**Methodology**: In our investigation into the utilization of tacrolimus in renal transplant patients, we pursued both retrospective and prospective study methodologies to gain comprehensive insights. The retrospective study spanned a period of two years, specifically 2021 and 2022, during which data was meticulously extracted from the Medical Records Department (MRD). This data, essential for our analysis, was compiled using a tailored data collection form crafted for the study's objectives. Over a duration of three months, we meticulously reviewed and documented appropriate information, capturing the intricacies of tacrolimus utilization within the renal transplant patient population. Concurrently, a prospective study was undertaken to further enrich our understanding of tacrolimus utilization in these patients. This study, conducted over a parallel three-month timeframe, focused on gathering real-time data from patients routine checkup files sourced from the outpatient department [18-20]. Utilizing a similar data collection form as in the retrospective study, we diligently recorded relevant details related to tacrolimus usage and patient outcomes. This prospective approach enabled us to capture current trends and practices surrounding tacrolimus administration and monitoring within the renal transplant patient cohort [21-23]. By pooling insights from both retrospective and prospective studies, we aimed to generate a holistic perspective on tacrolimus utilization, thereby facilitating informed decision-making and potentially enhancing patient care within this specialized clinical domain.
**Study Criteria**: Inclusion criteria encompassed individuals aged over 18 years who were undergoing treatment with tacrolimus following renal transplant. This selection ensured a targeted focus on the population of interest - renal transplant patients managed with tacrolimus therapy. Conversely, exclusion criteria were implemented to refine the study population further. Patients below 18 years were excluded, as were pregnant and lactating women, due to potential complications and differing medical needs.
Additionally, individuals in the immediate post-renal transplant phase within the initial month of therapy were omitted to minimize confounding variables associated with early transplant recovery. Through these criteria, we aimed to establish a cohesive cohort for evaluating prescribing patterns, dosing strategies, tacrolimus blood concentrations (tac levels), serum creatinine levels, and therapeutic outcomes. This approach allowed for a refined exploration of the factors influencing treatment efficacy and patient outcomes within this specific context.

## RESULTS

Our study titled Utilization of tacrolimus in renal transplant patients in a tertiary care Center - A Retro-Prospective study was conducted at APOLLO Hospitals, to study the utilization of tacrolimus in renal transplant patients. Our study included a total of 100 subjects. Subjects ≥18 years of age and the patients who had undergone renal transplant in the year 2021-2022 are considered. Out of which 36 were prospective cases as in the patients who come for regular follow ups in the outpatient department and the

rest 64 were retrospective cases which were collected from the medical record department. The percentage of patients who underwent transplantation in the year 2021 was 49% whereas in the year 2022 were seemed to be 51%. Our study indicates notable gender disparities, showing a higher prevalence of kidney failure among males requiring transplantation compared to females (75% vs. 25%) as presented in. As the study population was stratified by age group, the utilization of tacrolimus for immunosuppression therapy showed an increase from 6% in the 18-25 years age group to 22% in the 55-65 years age group, which notably had the highest number of patients in our study. This trend might be attributed to the increasing occurrence of comorbidities associated with advancing age, eventually leading to kidney failure. Most of the population in our study are under healthy weight BMI whereas around 21% are overweight and 6% are at risk of obesity. When mean of individual risk factors was calculated between the population of study it was found that hypertension has an upper hand in kidney failure followed by diabetes mellitus, hypothyroidism. (Table 1).

**TABLE 1: Distribution of patients based on comorbidities**

| Comorbidities | No. Of Patients |
|---|---|
| HTN | 47 |
| DM | 04 |
| HTN DM | 24 |
| HTN HTH DM | 07 |
| HTH | 03 |
| HTN HTH | 06 |
| NON | 09 |
| TOTAL | 100 |

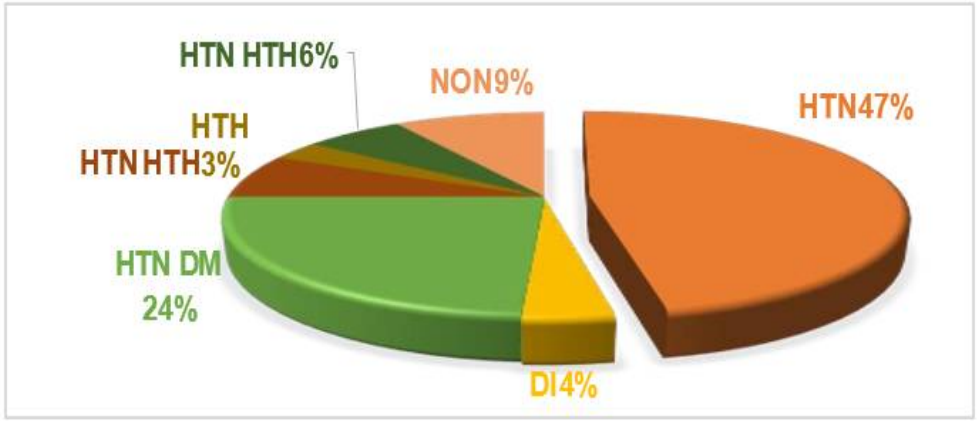


**Figure 1: Distribution of patients based on comorbidities**

Another anticipated outcome of the study was to analyze the dosing regimen of tacrolimus. The dosage of tacrolimus was progressively reduced from 3MG/BD in the third month to 0.5MG/BD by the twelfth month, aiming to keep the tacrolimus levels within the desired range as tacrolimus is a narrow therapeutic index drug and can lead to toxicity if the dose is not tapered. (Table 2, Figure 2).

**TABLE 2: Dose Tapering Pattern of Tacrolimus**

| Dose | 3-3mg | 2.5-2.5mg | 2-2.5mg | 2-2mg | 2-1.5mg | 1.5-1.5mg | 1-1.5mg | 1-1mg | 1-0.5mg | 0.5-0.5mg |
|---|---|---|---|---|---|---|---|---|---|---|
| Months | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |

 


**Figure 2: Dose Tapering Pattern of Tacrolimus**

To monitor the effectiveness of tacrolimus, Tac levels at the third, sixth, and ninth months were assessed. In the third month, 65% of the population exhibited Tac levels between 10- 15 ng/ml (Table 3, Figure 3), while in the sixth month 37% had Tac levels between 5-10 ng/ml (Table 4, Figure 4).

TABLE 3: DISTRIBUTION OF PATIENTS BASED ON THIRD MONTH TAC LEVELS

| TAC levels range | No. of patients |
|---|---|
| 05-10 | 11 |
| 10-15 | 65 |
| >15 | 09 |
| Not Found | 15 |

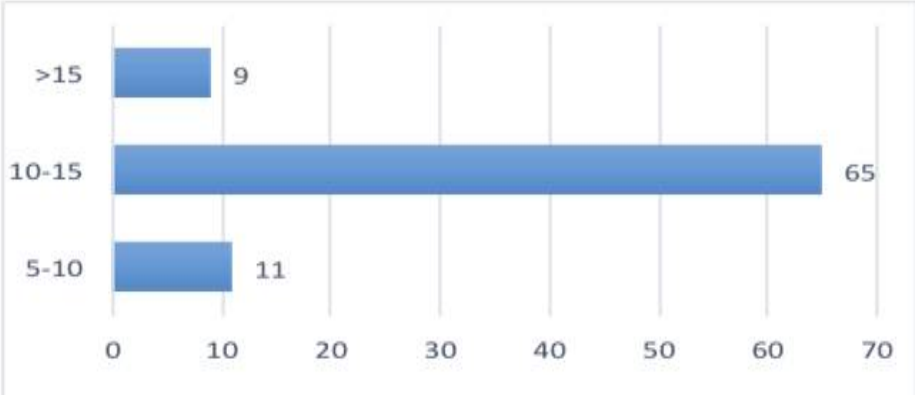


**Figure 3: Distribution of patients based on third month TAC levels**

**TABLE 4: Distribution of patients based on sixth month TAC levels**

| TAC levels range | No. of patients |
|---|---|
| 05-10 | 37 |
| 10-15 | 27 |
| >15 | 03 |
| Not Found | 25 |

 

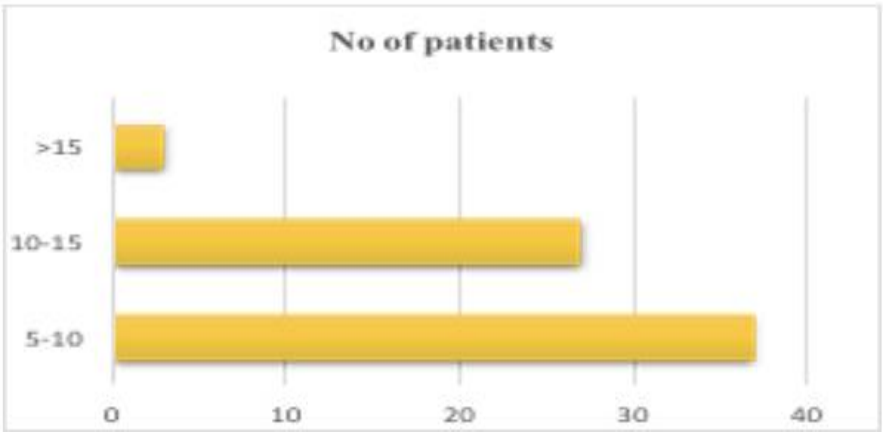


**Figure 4: Distribution of patients based on sixth month TAC levels**

By the ninth month, around 29% of the population showed Tac levels below 5-10 ng/ml (Table 5, Figure 5). The commonest post-transplant comorbidity was urinary tract infections of about 28%. The incidence of post-transplant diabetes mellitus was about 12%.

TABLE 5: DISTRIBUTION OF PATIENTS BASED ON NINTH MONTH TAC LEVELS

| TAC levelsrange | No. of patients |
|---|---|
| 05-10 | 29 |
| 10-15 | 15 |
| >15 | 00 |
| Not Found | 56 |

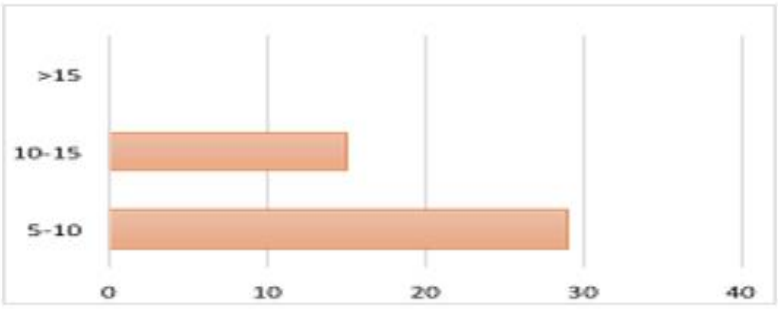


Figure 5: Distribution of patients based on ninth month TAC levels

It is common when drug therapy includes tacrolimus and corticosteroids. As the patients were on immunosuppressive therapy they had seemed to be exposed to various viral infections (CMV, BKV), bacterial infections (klebsiella), fungal infections (sinusitis, candidiasis) and the percentage of exposure was found to be 15% (Table 6, Figure 6).

**TABLE 6: Distribution of patients based on post-transplant comorbidities**

| Post TX Comorbidities | No of patients | % |
|---|---|---|
| **UTI** | 28 | **28%** |
| **DM** | 12 | **12%** |
| **Infections** | 15 | **15%** |
| **Graft Rejections** | 06 | **06%** |
| **TAC Toxicity** | **02** | **02%** |

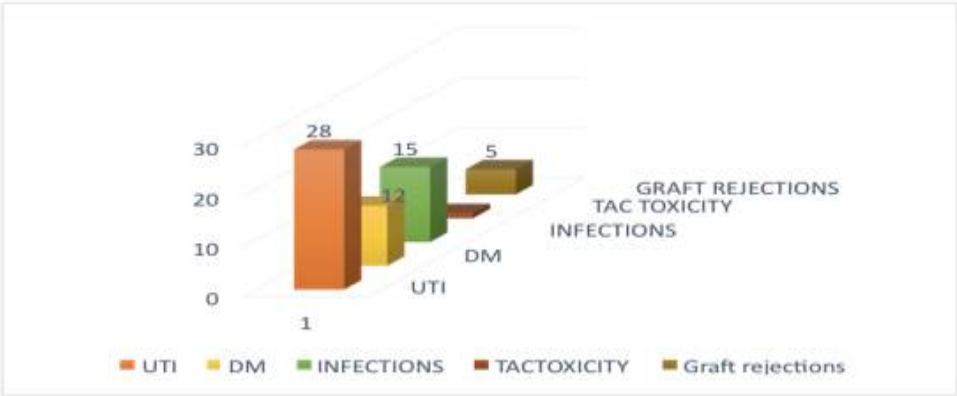


**Figure 6: Distribution of patients based on post-transplant comorbidities**

A case was observed with elevated tacrolimus levels reaching about 18ng/ml, indicative of tacrolimus toxicity, accompanied by an increase in serum creatinine - a sign of acute kidney injury. Recognizing the sensitivity of the situation, two doses of tacrolimus were withheld, and subsequent treatment was administered, resulting in a decrease in tacrolimus levels. Concurrent drug therapy for diabetes (linagliptin, insulin), for hypothyroidism (levothyroxine), for hypertension (nifedipine, cilnidipine, metoprolol, bisoprolol, clonidine, moxonidine, prazosin, furosemide) these drugs tend to show NO drug-drug interactions with tacrolimus.

**DISCUSSION**

The findings of our study shed light on various aspects of tacrolimus utilization in renal transplant patients at a tertiary care center, offering valuable insights into treatment patterns, patient demographics, comorbidities, dosage regimen, monitoring, and post-transplant complications. Firstly, the distribution of renal transplantations across the years 2021 and 2022 indicates a relatively balanced trend, with a slight increase noted in 2022. This may reflect ongoing advancements in transplant procedures, increased awareness, and possibly an uptick in the prevalence of end-stage renal disease necessitating transplantation. Our study shows a notable gender disparity in renal transplant cases, with a higher prevalence among males compared to females. This observation aligns with existing literature suggesting a higher incidence of renal failure among men, possibly attributed to factors such as lifestyle, genetics, and occupational exposures. Analysis of comorbidities reveals hypertension as a predominant risk factor for kidney failure, followed by diabetes mellitus and hypothyroidism. The age-stratified distribution of comorbidities highlights an alarming trend of increasing comorbidities with advancing age, emphasizing the need for targeted preventive interventions and regular screenings in elderly renal transplant recipients. The dosage regimen of tacrolimus, a cornerstone immunosuppressive agent in transplant management, demonstrates a gradual tapering strategy aimed at maintaining therapeutic efficacy while mitigating the risk of toxicity. The observed decline in tacrolimus levels over time underscores the importance of vigilant monitoring and dose adjustments to achieve optimal therapeutic outcomes and minimize adverse events. Post-transplant complications, notably urinary tract infections and post-transplant diabetes mellitus, underscore the multifaceted challenges faced by renal transplant recipients. The susceptibility to various infections necessitates a comprehensive approach to infection prevention, including prophylactic measures and early detection strategies. A noteworthy case of tacrolimus toxicity highlights the critical role of prompt recognition and management of adverse drug reactions in transplant care. The successful resolution of elevated tacrolimus levels enhances the importance of timely intervention and close monitoring in mitigating potential complications. Lastly, the absence of significant drug-drug interactions between tacrolimus and commonly prescribed medications for concurrent comorbidities provides reassurance regarding the safety and feasibility of combination therapy in renal transplant recipients. In conclusion, our study contributes to the growing body of evidence on tacrolimus utilization in renal transplant patients, offering valuable insights into treatment practices, patient demographics, comorbidities, dosage optimization, monitoring strategies, and post- transplant complications. These findings strengthen the importance of personalized, multidisciplinary care approaches tailored to the individual needs of transplant recipients to optimize outcomes and enhance long-term graft survival. Further research is warranted to explore novel therapeutic strategies and address emerging challenges in transplant medicine.

## CONCLUSION

The study concludes that utilization of tacrolimus was an efficient process in which the prescription and dosing pattern of tacrolimus were found to be rational as there were no major drug interactions. Being narrow therapeutic range drug, maintenance of drug levels within the therapeutic range is important hence close observation on tac levels is required and eventually dose tapering should be done to ensure safety, effectiveness, and well-balanced therapeutic management with other immunosuppressive drugs. As part of the evaluation, we assessed both the therapeutic effect and safety profile of the drug. Our study revealed minimal occurrences of acute graft rejections in the subjects, indicating the therapeutic effectiveness of tacrolimus. Decreased incidence of post- transplant comorbidities ensures the safety of tacrolimus. For the third month the tac levels should be present between 10-15 ng/ml whereas between 5- 10ng/ml is deemed to be causing graft rejections. In the sixth month and ninth month tac levels more than 10ng/ml seem to be leading cause for post-transplant comorbidity. We observed intra-patient variability in tacrolimus levels despite administering the same doses. This variability could be attributed to patient-related factors such as non-adherence to the medication regimen, delayed laboratory visits, or blood sample collection occurring after the patient had taken the tacrolimus dose.

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