Survey Report

Immunosuppression in Kidney Transplant

Version No.: 1.1

The study was conducted according to the approved protocol and in compliance with the protocol, Good Clinical Practice (GCP), and other applicable local regulatory requirements.

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1 INTRODUCTION

Kidney transplantation is the gold standard treatment for end-stage renal disease, offering improved quality of life and survival compared to dialysis [1]. The success of kidney transplantation largely depends on effective immunosuppression to prevent graft rejection while minimizing adverse effects. Over the past decades, significant advancements in immunosuppressive strategies have dramatically improved graft survival rates and patient outcomes [2]. The cornerstone of modern immunosuppression in kidney transplantation typically involves a combination of drugs, including calcineurin inhibitors (CNIs), antiproliferative agents, and corticosteroids [3]. Tacrolimus and Cyclosporine are the primary CNIs, while Mycophenolate and Azathioprine serve as the main antiproliferative agents. The introduction of novel agents like mammalian target of rapamycin (mTOR) inhibitors (e.g., Everolimus) has further expanded the immunosuppressive arsenal [4].

Despite these advances, the optimal immunosuppressive regimen remains a subject of debate, with variations in practice observed across different transplant centers and regions. Factors influencing the choice of immunosuppression include patient characteristics, immunological risk, comorbidities, and local experience. Moreover, the management of immunosuppression in special populations, such as elderly recipients, presents unique challenges and considerations [5]. The incidence of post-transplant complications, including infections like cytomegalovirus (CMV) disease, remains a significant concern and may be influenced by the choice of immunosuppressive agents [6]. Additionally, the long-term side effects of immunosuppression, such as nephrotoxicity, metabolic disorders, and increased cancer risk, necessitate a careful balance between efficacy and safety [7].

In India, where the burden of chronic kidney disease is high and access to transplantation is limited, optimizing immunosuppression strategies is crucial for maximizing the benefits of this scarce resource [8]. However, there is a paucity of data on current immunosuppressive practices among Indian transplant centers, particularly in light of recent advancements and evolving guidelines.

This study aimed to provide a comprehensive overview of immunosuppressive strategies employed across Indian transplant centers, focusing on the choice of agents, dosing regimens, and management of complications. By elucidating patterns of practice, areas of consensus, and variations in approach, this research seeks to inform evidence-based guidelines tailored to the Indian context.

2 RATIONALE OF THE STUDY

The need for this study stems from a critical knowledge gap in current immunosuppressive practices for kidney transplantation across Indian centers. Despite the growing prevalence of end-stage renal disease and increasing transplant rates in India, there is a lack of comprehensive data on how immunosuppression is managed nationwide. This gap hinders the development of standardized, evidence-based guidelines tailored to the Indian context. By surveying transplant specialists, this study aims to provide crucial insights into preferred agents, dosing strategies, and management approaches in various clinical scenarios. Understanding these practices is essential for several reasons: it will reveal the extent of variability in protocols among centers, assess the adoption of emerging therapies, identify population-specific considerations, and highlight areas for resource optimization. Moreover, the findings will inform clinical decision-making, guide future research priorities, and potentially influence health policies related to transplant care. In a resource-limited setting like India, optimizing immunosuppression protocols is vital to maximize transplant success while minimizing complications and healthcare costs. Ultimately, this study seeks to lay the groundwork for improving standardization of care, enhancing graft survival rates, and bettering overall outcomes for kidney transplant recipients across India.

3 STUDY OBJECTIVE

The primary objective of the study was to evaluate and characterize the current immunosuppression practices and preferences among kidney transplant specialists in India, with a focus on the choice of agents, dosing strategies, and management of complications in diverse patient populations.

4 METHODS

This study employed a cross-sectional, questionnaire-based design to evaluate and characterize the current immunosuppression practices and preferences among kidney transplant specialists in India, focusing on the choice of agents, dosing strategies, and management of complications in diverse patient populations. The target population comprised physicians practicing in India who manage patients with kidney transplants. Participants were recruited through professional networks and medical associations known to engage in kidney transplant care. Physicians were identified and invited to participate via professional network announcements and email invitations. Prior to participation, detailed information regarding the study's objectives, procedures, and confidentiality measures was provided to potential participants.

A structured questionnaire consisting of 15 questions was developed to gather data on physicians' clinical experience, prescribing practices, and perceptions regarding the use of immunosuppression in kidney transplant patients. The questionnaire was administered electronically to facilitate efficient data collection and ensure uniformity in responses. Responses to the survey were collected electronically using a secure platform to maintain participant anonymity and data confidentiality. Completed surveys were stored securely in compliance with applicable data protection regulations. A target sample size of 100 Indian physicians was selected to ensure the study's findings were based on a diverse and representative sample. This sample size was deemed adequate to support meaningful statistical analysis and draw reliable conclusions regarding immunosuppression practices in kidney transplant care.

Statistical analysis was conducted to summarize survey findings and identify key trends in prescribing patterns and preferences among participating physicians. Descriptive statistics were used to present frequencies and percentages of

responses. Study results were compiled into a comprehensive report detailing key findings and implications for clinical practice. Findings were intended for dissemination through scientific publication in peer-reviewed journals and presentation at relevant medical conferences, subject to suitability and acceptance by respective venues.

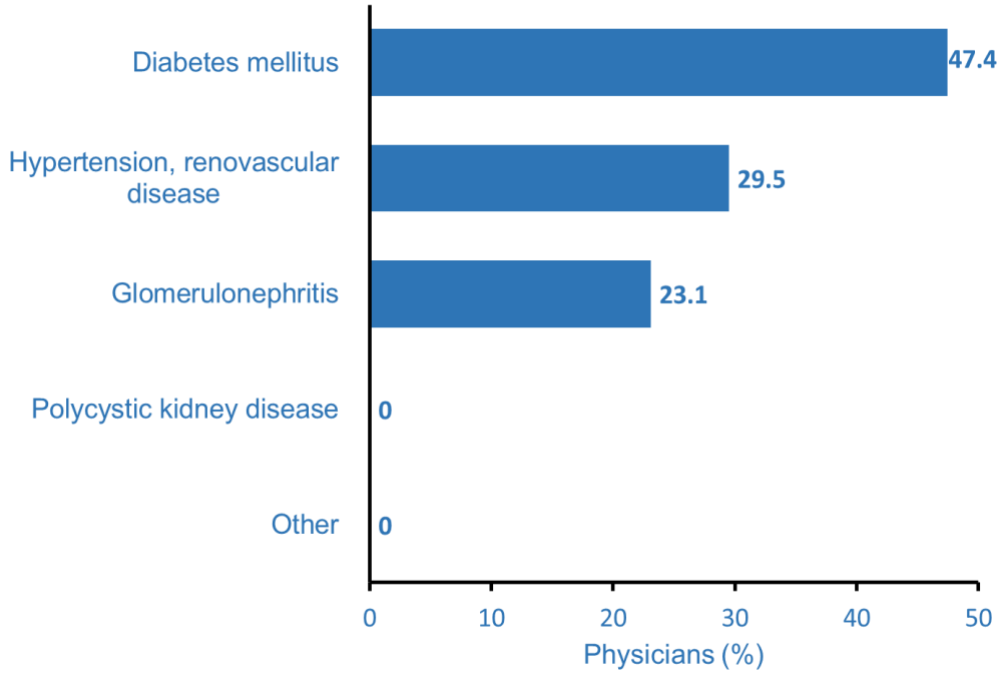
This study adhered to the ethical principles outlined in the Declaration of Helsinki. Ethical approval was sought from an Independent Ethics Committee. Participants were assured of their right to withdraw from the study at any time without any consequences. All responses were anonymized to ensure participant confidentiality.

5 RESULTS

A total of 78 HCPs participated in the survey. Below is the summary of the responses.

Question 1: Which of the following are common primary reasons of renal failure in your patients?

Options	Number of physicians (N=78)
Diabetes mellitus	37 (47.4)
Hypertension, renovascular disease	23 (29.5)
Glomerulonephritis	18 (23.1)
Polycystic kidney disease	0
Other	0
Data presented as n (%).	

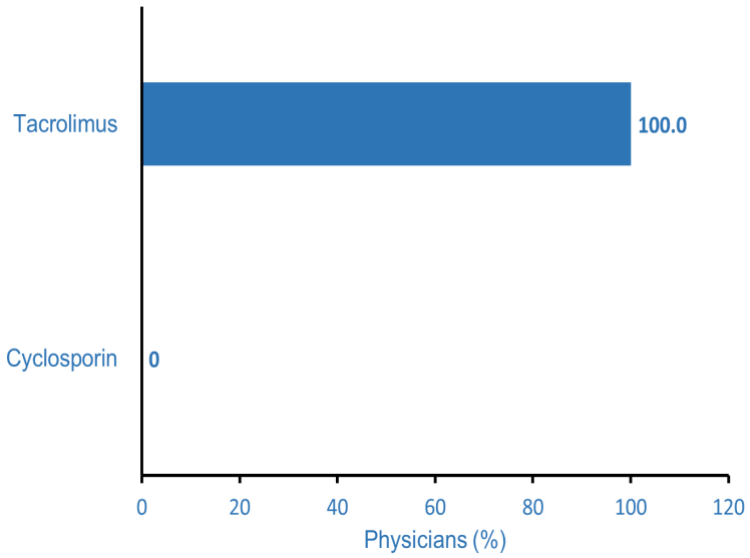


- Most common primary reason for renal failure in their patients was diabetes mellitus, reported by 37 physicians (47.4%).
- Hypertension and renovascular disease were the second most common causes, with 23 physicians (29.5%) which affects the renal failure in the patients.

- Glomerulonephritis was noted by 18 physicians, making up 23.1% of the responses, indicating that this condition is also a relevant but less prevalent cause of renal failure compared to diabetes and hypertension.
- Notably, no physicians reported polycystic kidney disease or other causes as primary reasons for renal failure.

Question 2: Which of the following is your preferred Calcineurin inhibitor (CNI) for immunosuppression in kidney transplant patients?

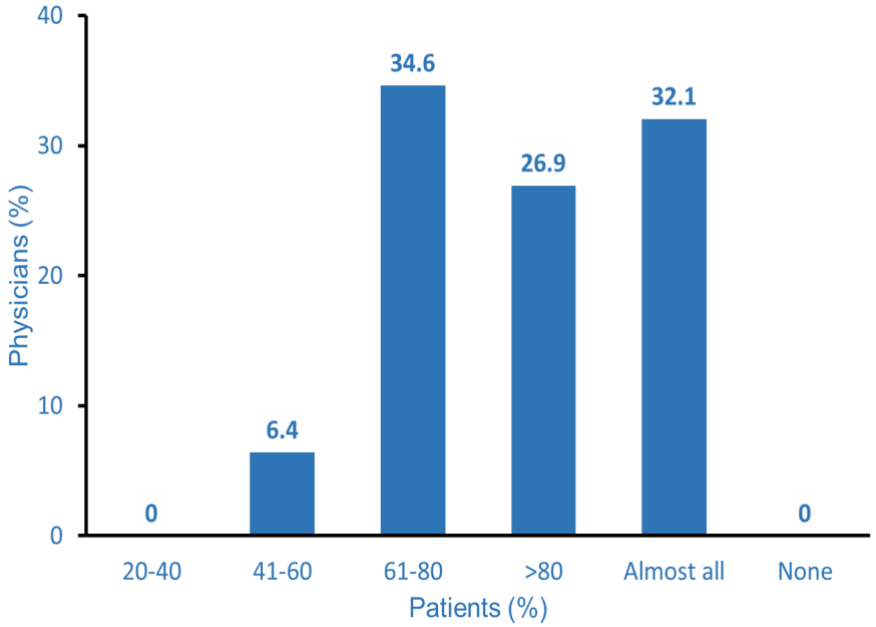
Options	Number of physicians (N=78)
Tacrolimus	78 (100.0)
Cyclosporine	0
Data presented as n (%).	



- In a survey of 78 physicians regarding their preferred calcineurin inhibitor (CNI) for immunosuppression in kidney transplant patients, all 78 physicians (100.0%) indicated a preference for Tacrolimus.
- None of the physicians preferred Cyclosporine for this kidney transplant.

Question 3: To what percentage of your transplant patient do you prescribe Tacrolimus?

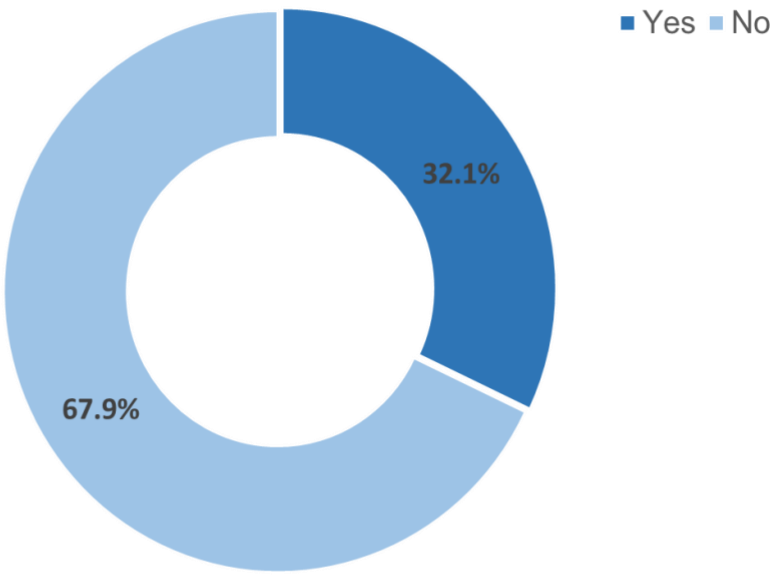
Options	Number of physicians (N=78)
20-40%	0
41-60%	5 (6.4)
61-80%	27 (34.6)
>80%	21 (26.9)
Almost all	25 (32.1)
None	0
Data presented as n (%).	



- A major proportion, 27 physicians (34.6%), prescribes Tacrolimus to 61-80% of their patients.
- The majority, 25 physicians (32.1%), prescribe Tacrolimus to almost all of their kidney transplant patients.
- Twenty-one physicians (26.9%) prescribe it to more than 80% of their patients.
- Five physicians (6.4%) prescribe it to 41-60% of their kidney transplant patients.
- No physicians reported prescribing Tacrolimus to less than 41% of patients or to none of their patients.

Question 4: In low-to-moderate immunological risk adult patients, Everolimus low dose steroid and reduced dose CNI can be considered first line preference?

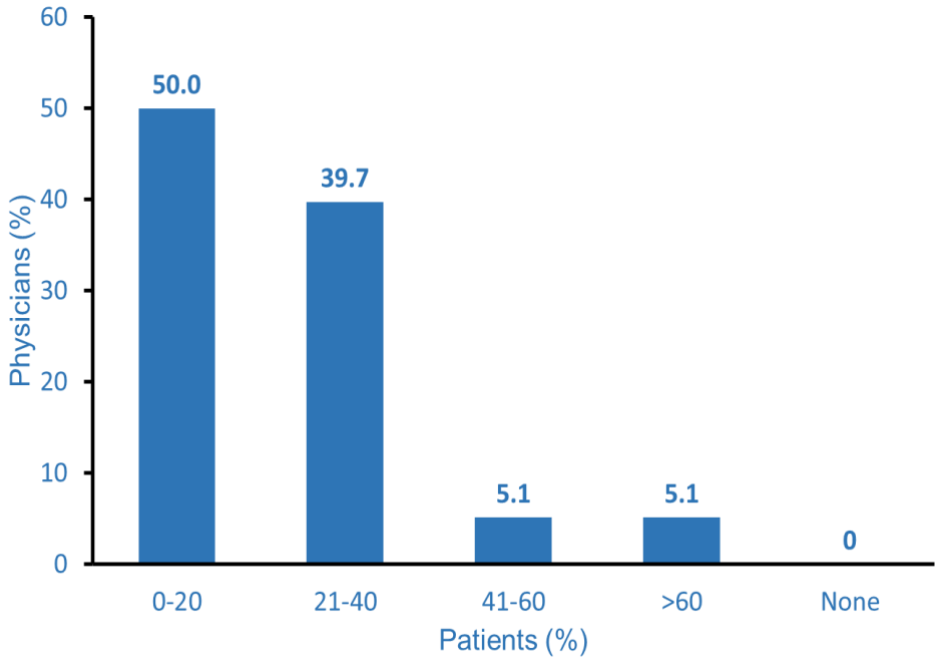
Options	Number of physicians (N=78)
Yes	25 (32.1)
No	53 (67.9)
Data presented as n (%).	



- In majority, 53 physicians (67.9%) did not consider Everolimus, low dose steroid and reduced dose CNI regimen as their first-line preference.
- Among the surveyed physicians, 25 (32.1%) supported the use of Everolimus, low-dose steroids, and reduced-dose CNI as a first-line preference in low-to-moderate immunological risk adult patients.

Question 5: What percentage of your patients receives Basiliximab?

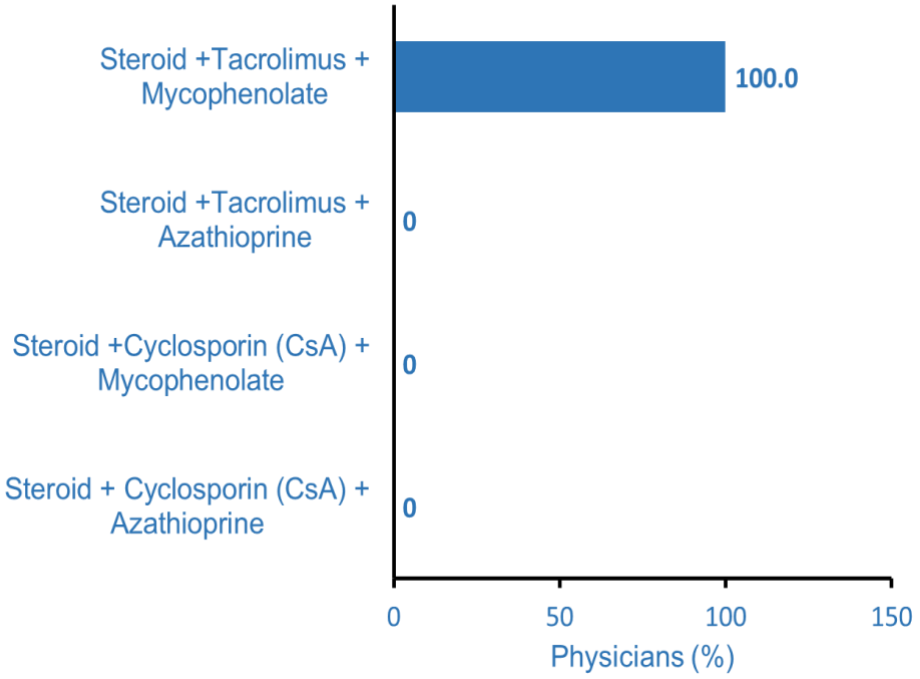
Options	Number of physicians (N=78)
0-20%	39 (50.0)
21-40%	31 (39.7)
41-60%	4 (5.1)
>60%	4 (5.1)
None	0
Data presented as n (%).	



- Half of the physicians (50.0%) reported that 0-20% of their patients receive Basiliximab.
- A notable group of physicians, 39.7%, reported that Basiliximab is given to 21-40% of their patients.
- Only a small fraction of physicians, 5.1%, prescribe Basiliximab to 41-60% of their patients, and the same percentage (5.1%) prescribe it to more than 60% of their patients.
- None of the physicians reported that they do not prescribe Basiliximab at all.

Question 6: Which of the following combinations (triple drug therapy) do you use in your clinical practice as an initial protocol for immunosuppression?

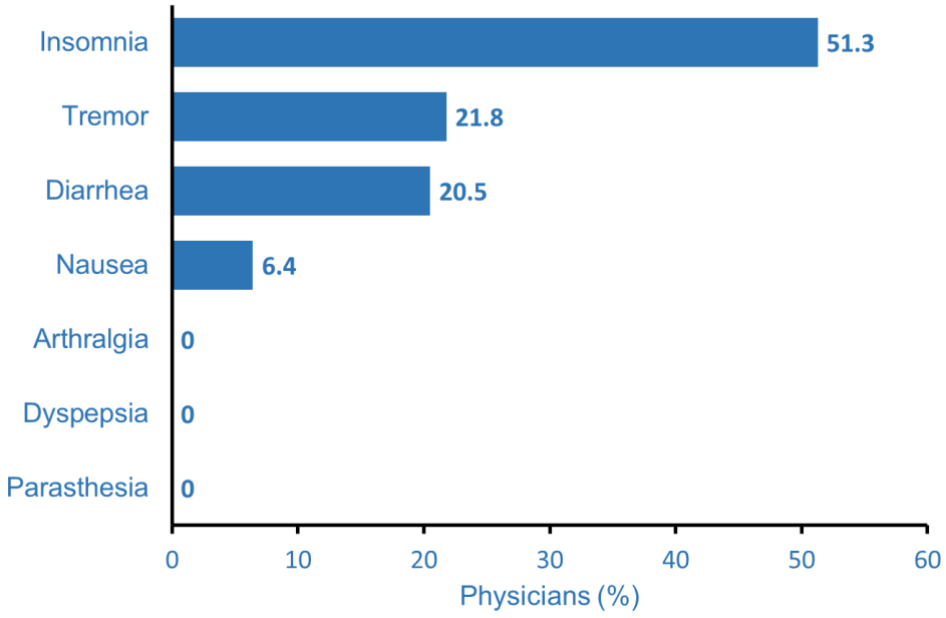
Options	Number of physicians (N=78)
Steroid +Tacrolimus + Mycophenolate	78 (100.0)
Steroid +Tacrolimus + Azathioprine	0
Steroid +Cyclosporine (CsA) + Mycophenolate	0
Steroid + Cyclosporine (CsA) + Azathioprine	0
Data presented as n (%).	



- In the clinical practice, all 78 physicians (100.0%) use the combination of Steroid, Tacrolimus, and Mycophenolate as an initial protocol for immunosuppression.
- None of the physicians reported the use of the combinations of Steroid + Tacrolimus + Azathioprine; steroid + Cyclosporine (CsA) + Mycophenolate; or steroid + Cyclosporine (CsA) + Azathioprine in their clinical practice.

Question 7: What are the common side effects that you observe in your patients taking Tacrolimus?

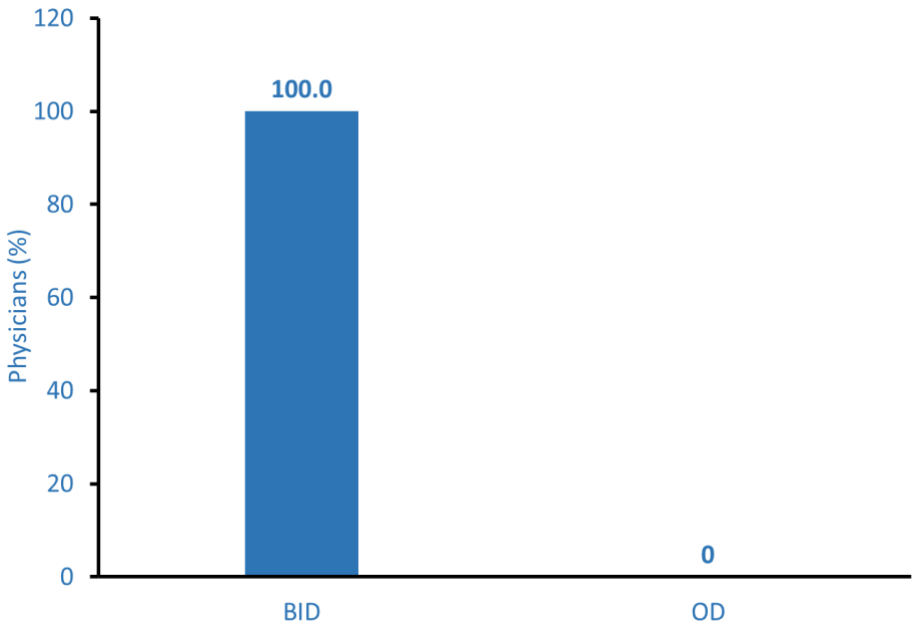
Options	Number of physicians (N=78)
Insomnia	40 (51.3)
Tremor	17 (21.8)
Diarrhea	16 (20.5)
Nausea	5 (6.4)
Arthralgia	0
Dyspepsia	0
Parasthesia	0
Data presented as n (%).	



- Insomnia was the most frequently reported side effect, noted by 40 physicians (51.3%).
- Tremor was the second most frequently reported side effect, noted by 17 physicians (21.8%).
- Diarrhea was observed by 16 physicians (20.5%), showing that it is a relatively common issue but less so than insomnia and tremor.
- Nausea was mentioned by 5 physicians (6.4%).
- No physicians reported arthralgia, dyspepsia, or paresthesia as side effects associated with Tacrolimus.

Question 8: Which dosing frequency do you prefer in your patients taking Tacrolimus?

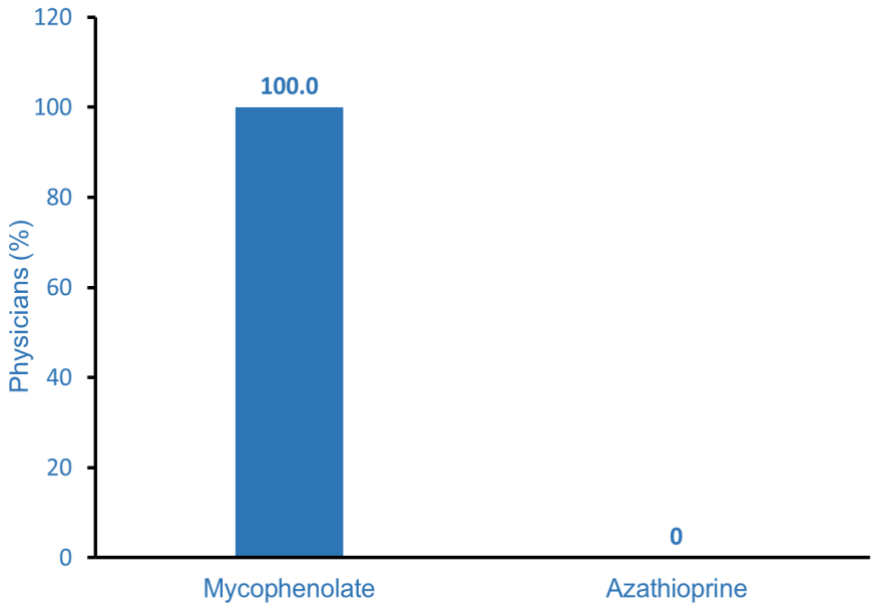
Options	Number of physicians (N=78)
BID	78 (100.0)
OD	0
Data presented as n (%).	



- All 78 physicians (100.0%) preferred administering Tacrolimus twice daily (BID) as their dosing frequency.
- None of the physicians prefer a once-daily (OD) dosing regimen for Tacrolimus.

Question 9: Which of the following is your preferred antiproliferative agent for immunosuppression in kidney transplant patients?

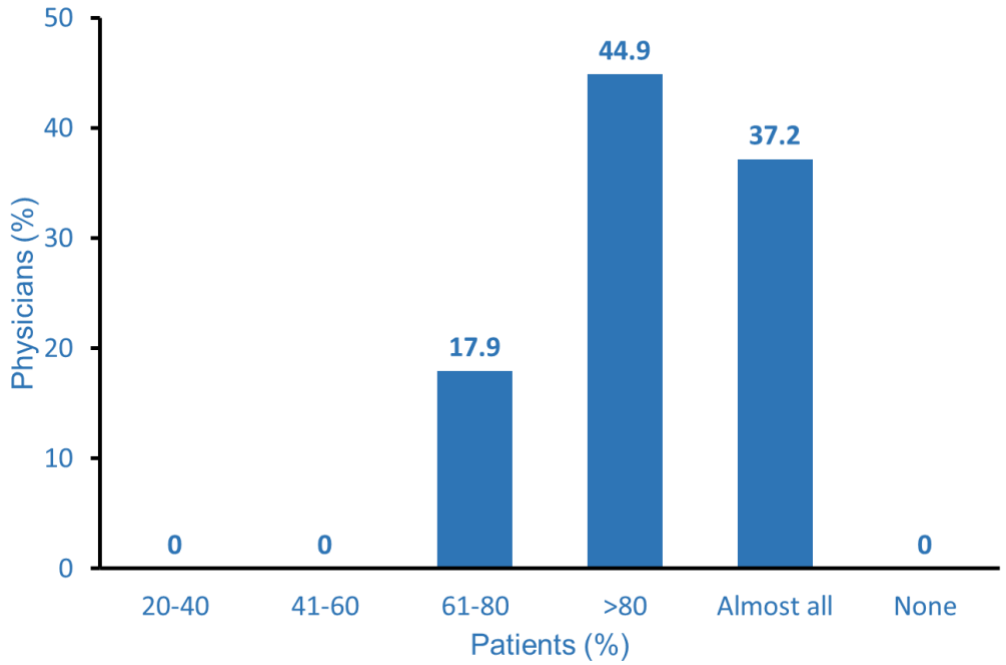
Options	Number of physicians (N=78)
Mycophenolate	78 (100.0)
Azathioprine	0
Data presented as n (%).	



- All 78 physicians (100.0%) preferred the Mycophenolate as antiproliferative agent for immunosuppression in the kidney transplant patients.
- None of the physicians preferred Azathioprine for kidney transplant patients.

Question 10: To what percentage of your transplant patient do you prescribe Mycophenolate?

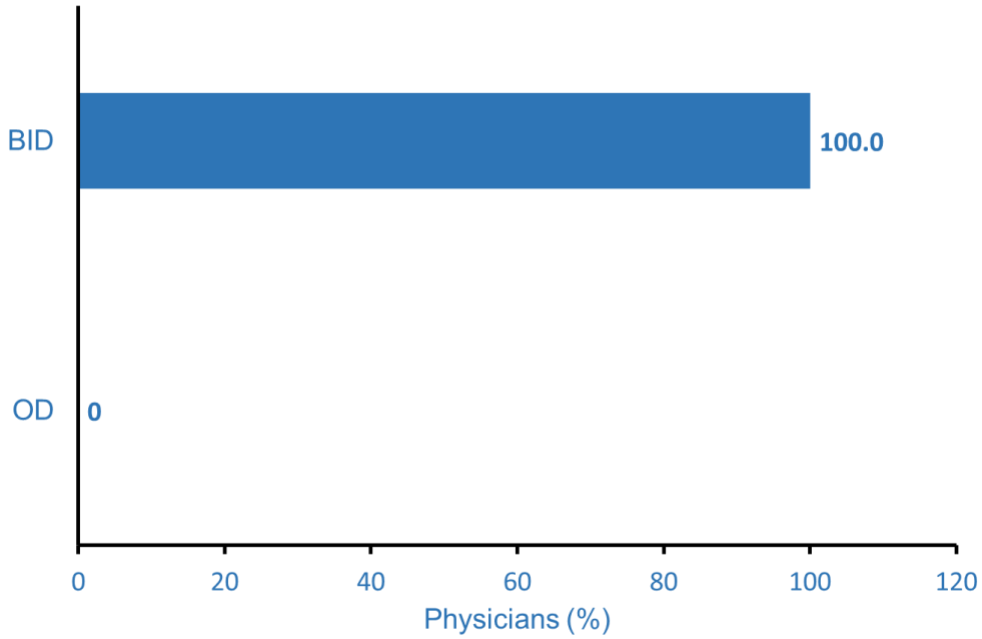
Options	Number of physicians (N=78)
20-40%	0
41-60%	0
61-80%	14 (17.9)
>80%	35 (44.9)
Almost all	29 (37.2)
None	0
Data presented as n (%).	



- A larger group of 35 physicians (44.9%) prescribe Mycophenolate to more than 80% of their patients.
- Additionally, 29 physicians (37.2%) prescribe it to almost all of their transplant patients.
- Fourteen physicians (17.9%) prescribe it to 61-80% of their patients.
- None of the physicians prescribe Mycophenolate to 20-40% or 41-60% of their patients.

Question 11: Which dosing frequency do you prefer in your patients taking Mycophenolate?

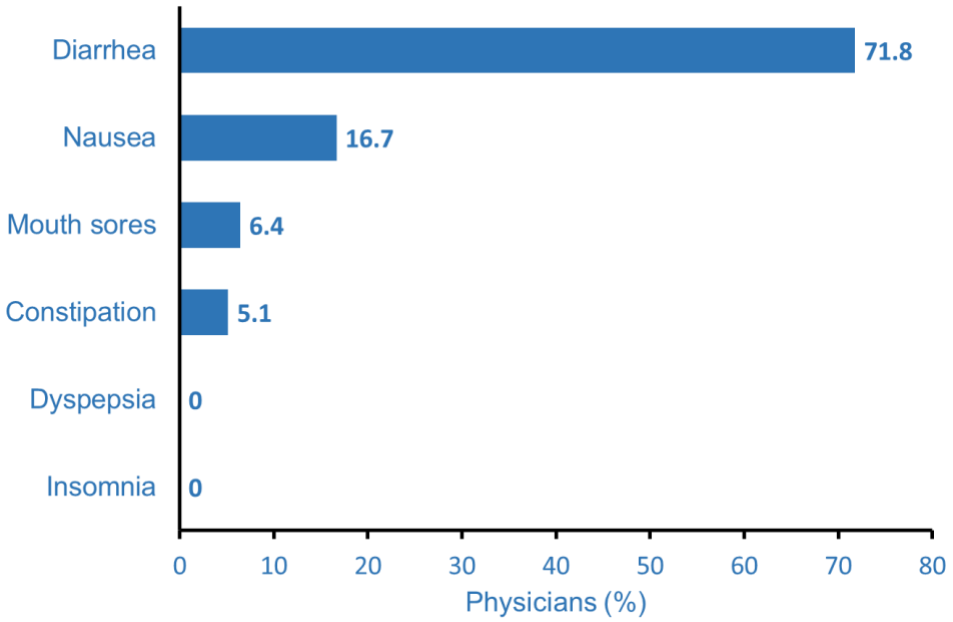
Options	Number of physicians (N=78)
BID	78 (100.0)
OD	0
Data presented as n (%).	



- All 78 physicians (100.0%) preferred administering Mycophenolate twice daily (BID) as their dosing frequency.
- None of the physicians prefer a once-daily (OD) dosing regimen for Mycophenolate.

Question 12: What are the common side effects that you observe in your patients taking Mycophenolate?

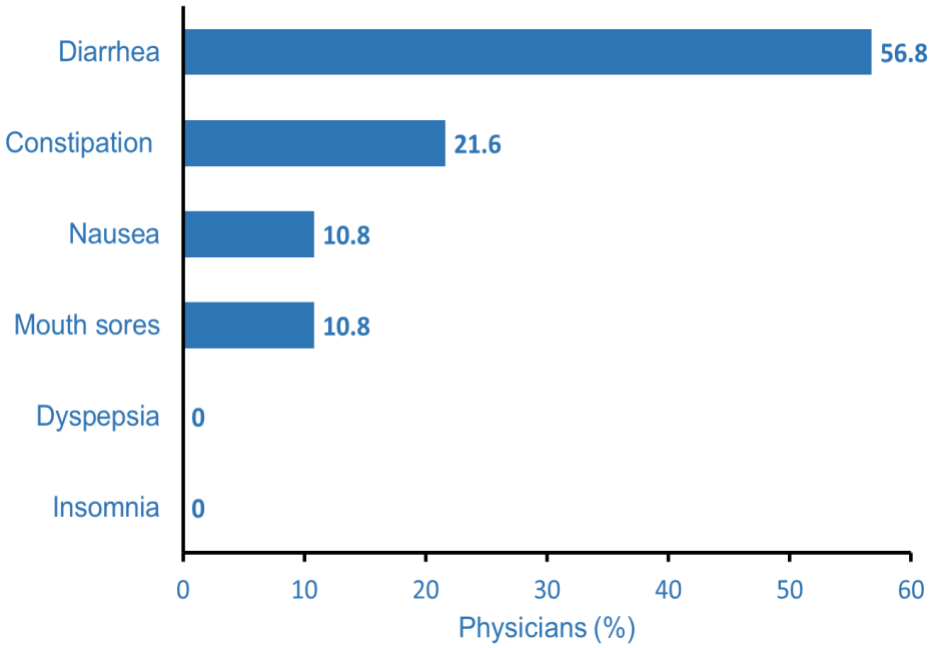
Options	Number of physicians (N=78)
Diarrhea	56 (71.8)
Nausea	13 (16.7)
Mouth sores	5 (6.4)
Constipation	4 (5.1)
Dyspepsia	0
Insomnia	0
Data presented as n (%).	



- Diarrhoea was the most frequently reported side effect, noted by 56 physicians (71.8%).
- Nausea was the second most frequently reported side effect, noted by 13 physicians (16.7%).
- Mouth sores was observed by 5 physicians (6.4%), by taking the Mycophenolate.
- Constipation was mentioned by 4 physicians (5.1%)
- No physicians reported dyspepsia, insomnia as side effects associated with Mycophenolate.

Question 13: Which Based on results of deceased donor kidney transplant recipients on low-dose CsA and no steroids, MMF had no significant benefits over AZA?

Options	Number of physicians (N=37)
Diarrhea	21 (56.8)
Constipation	8 (21.6)
Nausea	4 (10.8)
Mouth sores	4 (10.8)
Dyspepsia	0
Insomnia	0
Data presented as n (%).	

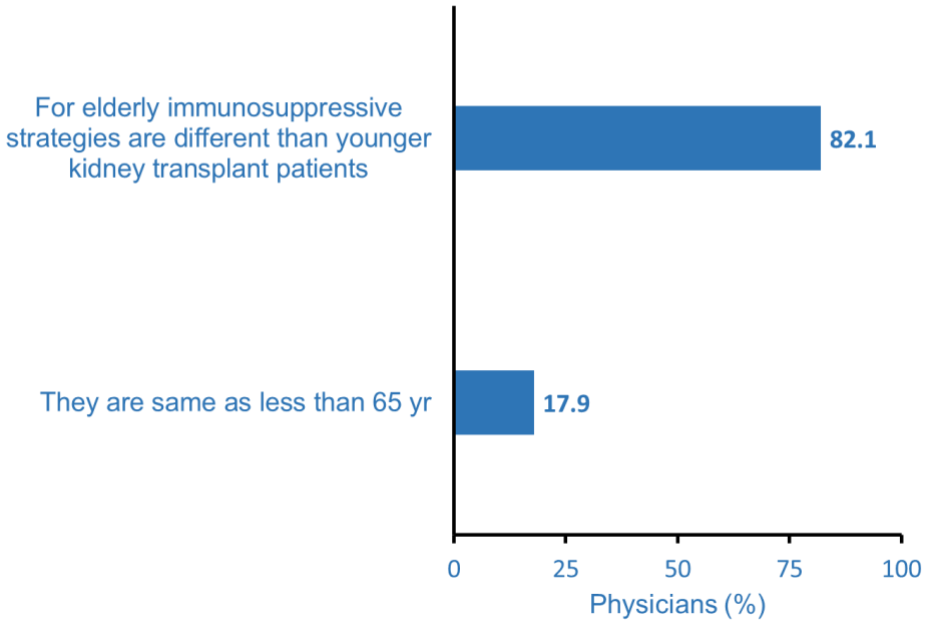


- Diarrhea was identified as the most prevalent side effect in deceased donor kidney transplant recipients on low-dose Cyclosporine (CsA) and no steroids, with 21 physicians (56.8%) reporting this observation.
- Constipation was noted as a significant side effect by 8 physicians (21.6%) in this patient population.
- Both nausea and mouth sores were reported as side effects by 4 physicians (10.8%) each, indicating their equal prevalence in these transplant recipients.

- Notably, none of the surveyed physicians reported dyspepsia or insomnia as side effects in deceased donor kidney transplant recipients on this specific immunosuppressive regimen.

Question 14: Immunosuppression strategies remain same or different with elderly more than 65 yr?

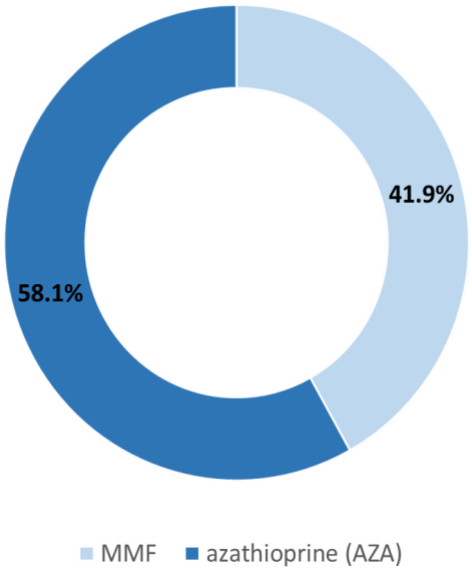
Options	Number of physicians (N=78)
They are same as less than 65 yr	14 (17.9)
For elderly immunosuppressive strategies are different than younger kidney transplant patients	64 (82.1)
Data presented as n (%).	



- A majority of physicians (82.1%) indicated that immunosuppression strategies for elderly patients (aged 65 years and older) differ from those for younger kidney transplant patients.
- Conversely, a smaller proportion of physicians (17.9%) reported that immunosuppression strategies remain the same for patients aged 65 years and older as they are for those younger than 65 years.

Question 15: CMV disease is more with?

Options	Number of physicians (N=74)
MMF	31 (41.9)
Azathioprine (AZA)	43 (58.1)
Data presented as n (%).	



- A majority of physicians (58.1%) reported that cytomegalovirus (CMV) disease is more commonly associated with Azathioprine (AZA).
- In contrast, 41.9% of physicians indicated that CMV disease is more common with Mycophenolate Mofetil (MMF).

6 SUMMARY

The survey revealed that diabetes mellitus was the most common primary cause of renal failure, reported by 47.4% of physicians, followed by hypertension and renovascular disease (29.5%), and glomerulonephritis (23.1%). Notably, no physicians cited polycystic kidney disease as a primary cause. All surveyed physicians preferred Tacrolimus over Cyclosporine for immunosuppression in kidney transplant patients. A significant portion of physicians (34.6%) prescribed Tacrolimus to 61-80% of their patients, while 32.1% prescribed it to nearly all patients. However, 67.9% of physicians did not consider Tacrolimus-based regimens as their first-line preference for low-to-moderate immunological risk patients.

Regarding Basiliximab use, 50% of physicians administered it to 0-20% of patients, while 39.7% used it in 21-40% of cases. All physicians reported using a combination of steroid, Tacrolimus, and Mycophenolate as their initial immunosuppressive protocol. Insomnia (51.3%) and tremor (21.8%) were the most common side effects of Tacrolimus. All physicians preferred twice-daily dosing for Tacrolimus and Mycophenolate. Mycophenolate was favored by all physicians over Azathioprine, with 44.9% prescribing it to more than 80% of patients.

Diarrhea (71.8%) and nausea (16.7%) were the most frequent side effects of Mycophenolate. For deceased donor kidney transplant recipients on low-dose Cyclosporine and no steroids, diarrhea (56.8%) and constipation (21.6%) were common side effects. A majority (82.1%) of physicians indicated that immunosuppressive strategies differ for elderly patients compared to younger ones. CMV disease was reported to be more common with Azathioprine by 58.1% of physicians and with Mycophenolate by 41.9%.

7 DISCUSSION

This survey-based study provides comprehensive insights into the current immunosuppression practices and preferences among kidney transplant specialists in India. The findings reveal that diabetes mellitus is the predominant cause of renal failure, followed by hypertension, renovascular disease, and glomerulonephritis. This aligns with global trends where metabolic diseases are leading causes of kidney failure. The universal preference for Tacrolimus over Cyclosporine among physicians underscores its perceived efficacy and safety profile. Notably, the majority of physicians prescribe Tacrolimus to a substantial portion of their patients, reflecting its central role in contemporary immunosuppressive regimens.

Despite the widespread use of Tacrolimus, a significant number of physicians do not consider it their first-line preference for low-to-moderate immunological risk patients, suggesting ongoing debate and consideration of individual patient profiles in treatment planning. The reported side effects, such as insomnia and tremor for Tacrolimus, and diarrhea for Mycophenolate, highlight the need for careful monitoring and management of adverse events to optimize patient outcomes.

The preference for twice-daily dosing of both Tacrolimus and Mycophenolate is indicative of efforts to balance efficacy and patient adherence. The complete lack of preference for Cyclosporine and Azathioprine emphasizes a shift towards more modern agents perceived as having better safety and efficacy profiles. The distinct immunosuppressive strategies for elderly patients, acknowledged by the majority of physicians, reflect an awareness of the unique challenges in this demographic, such as increased susceptibility to infections and drug toxicity.

The findings on CMV disease suggest a perceived higher risk with azathioprine compared to Mycophenolate, guiding physicians' choices towards the latter. The study's insights into side effect profiles and dosing preferences are crucial for informing clinical practice and improving patient care. Further research, including randomized controlled trials, could provide more definitive evidence to refine

these practices and address the identified gaps, ultimately enhancing the management of kidney transplant patients in diverse clinical settings.

8 CLINICAL RECOMMENDATIONS

- Screen and manage diabetes mellitus and hypertension early to prevent progression to renal failure.
- Prefer Tacrolimus as the primary calcineurin inhibitor for kidney transplant patients.
- Monitor and manage common side effects of Tacrolimus (insomnia, tremor) and Mycophenolate (diarrhea).
- Implement twice-daily dosing for Tacrolimus and Mycophenolate to enhance adherence.
- Develop specific immunosuppressive protocols for elderly patients.
- Consider Everolimus, low-dose steroids, and reduced-dose CNI for low-to-moderate immunological risk patients.
- Use Mycophenolate over Azathioprine to reduce CMV disease risk.
- Educate patients on the importance of adherence and prompt reporting of side effects.
- Assess the appropriate use of Basiliximab in transplant protocols.
- Promote continuous education and research for physicians on immunosuppressive therapy.
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9 CONSULTANT OPINION

To enhance the management of kidney transplant patients, it is recommended to conduct randomized controlled trials comparing the efficacy of Tacrolimus and Mycophenolate with other immunosuppressive regimens. These trials should investigate long-term outcomes, focusing on patient survival, graft function, and quality of life. Additionally, subgroup analyses are essential to identify optimal immunosuppressive protocols for specific patient populations, such as elderly patients and those with comorbidities like diabetes and hypertension.

Exploring the impact of side effect management on patient adherence and overall treatment success is crucial. Collecting real-world evidence will

supplement clinical trial data, offering valuable insights into the effectiveness and safety of immunosuppressive agents across diverse clinical settings. Furthermore, examining patient-reported outcomes can help understand the impact of immunosuppressive therapy on quality of life and treatment satisfaction, guiding more personalized treatment strategies.

Assessing the cost-effectiveness of various immunosuppressive protocols is also important to inform healthcare policy and reimbursement decisions. Continuous education and training for physicians on the latest advancements in immunosuppressive therapy for kidney transplant patients should be encouraged to ensure optimal patient care and outcomes.

10 MARKET OPPORTUNITIES

The preference for Tacrolimus (100%) and Mycophenolate (100%) among Indian physicians managing kidney transplant patients indicates significant market opportunities. There is a substantial demand for high-quality formulations, especially since many physicians prescribe these medications to over 60% of their patients. Addressing common side effects like diarrhea and nausea with supportive treatments can improve patient adherence and outcomes.

Innovative product formulations that reduce side effects or offer more convenient dosing schedules (e.g., once-daily) could capture a significant market share. Additionally, there is a niche market for tailored immunosuppressive strategies for elderly patients, providing opportunities for specialized therapies and protocols.

Overall, the widespread use of Tacrolimus and Mycophenolate, coupled with the need for improved side effect management and dosing convenience, presents considerable opportunities for pharmaceutical companies to expand their market presence in kidney transplant immunosuppression.

11 MARKET POSITIONING

Preferred Immunosuppression Regimen

Position Tacrolimus and Mycophenolate as the preferred immunosuppressive regimen for kidney transplant patients, emphasizing their unanimous endorsement by surveyed physicians. Highlight their efficacy and the high prescription rates to build trust among healthcare providers.

Targeted for High Compliance

Market these medications as ideal for patients requiring reliable and consistent immunosuppression. Emphasize the tailored benefits for elderly patients and those with specific side effect profiles, such as the management of common adverse effects like diarrhea and nausea.

Endorsed by Experts

Leverage the unanimous preference of Indian physicians for Tacrolimus and Mycophenolate to establish credibility and trust. Highlight the widespread adoption and positive feedback from the medical community to reassure patients and healthcare providers of their effectiveness and safety.

Focus on Patient-Centered Care

Promote the commitment to patient-centered care by addressing the most common side effects and offering supportive treatments. Emphasize the potential for improved patient adherence and outcomes through innovative product formulations and dosing schedules.

12 REFERENCES

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