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Tacrolimus outcomes in adult kidney transplants: a decade review

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ABSTRACT

Tacrolimus remains a principal immunosuppressive agent in kidney transplantation, yet its reported efficacy and safety vary due to differences in study design, treatment regimens, and patient characteristics. Objectives: To summarize recent evidence on the clinical performance of tacrolimus in adult kidney transplant recipients and identify factors contributing to variability in outcomes. A narrative review was conducted using PubMed as the primary database because of its comprehensive indexing of clinical and pharmacological studies relevant to transplant immunosuppression. Additional databases were screened to ensure completeness. Studies published between 2015 and 2025 were searched using predefined keywords. Of 91 open-access articles identified, 19 met the inclusion criteria and were analyzed. Results: Reported clinical outcomes demonstrated wide variability across studies. Acute rejection ranged from 0–18.8%, while biopsy-proven acute rejection varied substantially (0–85%). Graft loss occurred in 0–15% of recipients and mortality in 0–8%. Major adverse events were also heterogeneous, including cytomegalovirus (CMV) infection (0–16.9%), new-onset diabetes after transplantation (NODAT) (0–22.8%), and tremor (3–28.6%). Variability in findings was largely influenced by differences in study methodology, concomitant immunosuppressive protocols, monitoring practices, population characteristics, and limited ethnic diversity, as most participants were Caucasian. Tacrolimus maintains a strong efficacy–safety profile in adult kidney transplantation. Future studies with more diverse populations, standardized therapeutic drug monitoring, and longer follow-up durations are required to enhance generalizability and support individualized immunosuppressive management.

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1. INTRODUCTION

Globally, the number of kidney transplant procedures continues increases in more than 110 countries, with 12 new kidney recipients per 100.000 population [1]. Despite this growth, access remains uneven across regions and outcomes vary considerably due to demographic, clinical, and system-level factors [2]. In Indonesia, the number of kidney transplant recipients has also risen steadily over the past decade,

supported by the expansion of transplant centers and improvement in national referral systems [3]. This growing population underscores the need for optimized and evidence-based immunosuppressive strategies.

In Indonesia, 629 kidney transplantations have been successfully performed in 12 transplant centers [3]. The benefits of kidney transplantation not only reduce the risk of complications but also improve the recipient's quality of life [4]-[6]. The first-year graft survival rate after kidney transplantation in two meta-analysis studies was 92.83% and 92.48%, respectively [7], [8]. The survival rate of grafts in the first year in countries such as the United States, South Korea, China, Iran, and Africa was 97.8%, 97.1%, 97.8%, 90.8%, and 89.4%, respectively [9]-[12].

Kidney transplantation (KT) is the primary treatment for patients with end-stage chronic kidney disease, providing superior long-term survival, improved quality of life compared with dialysis [13]. Despite these advantages, the durability of transplant success depends heavily on maintaining effective and balanced immunosuppression to prevent acute and chronic rejection. This need for precise control of the immune response has shaped modern post-transplant management and underscores the central role of calcineurin inhibitors in current practice. Among these agents, tacrolimus has long been established as a first-line of maintenance immunosuppressive therapy. Tacrolimus is commonly administered in combination with mycophenolate mofetil and corticosteroids, forming the backbone of standard post-transplant regimens. Despite this established efficacy, important concerns remain regarding long-term safety, including risks of metabolic complications, infections, and neurotoxicity, as well as substantial variability in clinical outcomes across different patient populations and treatment settings [14]-[16]. These persistent uncertainties highlight the need for a more comprehensive and updated synthesis of recent evidence.

However, tacrolimus clinical performance is influenced by multiple factors, including pharmacogenomic variability, ethnic differences, concomitant immunosuppressive regimens, and therapeutic drug monitoring (TDM) practices [17]. Its narrow therapeutic index necessitates precise therapeutic drug monitoring to achieve optimal blood concentration. Subtherapeutic levels increase the risk of graft rejection, whereas supratherapeutic levels may cause significant toxicity [15], [18], [19]. Recent studies have reported heterogeneous results regarding safety outcomes such as infection risk, metabolic complications, nephrotoxicity, neurotoxicity, and hepatotoxicity, due to immunosuppression [20]-[26]. These adverse effects underscore the importance of balancing efficacy and safety through individualized dosing strategies, suggesting that tacrolimus therapy requires ongoing reevaluation as new evidence emerges.

Despite extensive clinical experience with tacrolimus, few reviews have synthesized recent evidence on both its efficacy and long-term safety, particularly across diverse populations and evolving immunosuppressive practices [27]. Existing reviews have also not fully addressed the safety concerns related to long-term complications, such as metabolic, infectious, and neurotoxic effects, that have become more evident in contemporary studies [28]-[30]. Moreover, many prior summaries focus on restricted outcomes, older datasets, or single patient groups, leaving clinicians without a comprehensive picture of how benefits and risks vary across clinical settings. This lack of updated and integrated evidence complicates clinical decision-making, especially when clinicians must balance rejection prevention with the risks of overt immunosuppression.

Several systematic and narrative reviews have examined tacrolimus therapy over the past decade. However, these syntheses typically address specific aspects-such as de novo immunosuppressive regimens, formulation comparisons, or long-term outcomes-rather than providing a unified evaluation of contemporary evidence across efficacy, safety, pharmacologic variability, and real-world clinical data [21], [27], [31], [32]. Consequently, no review has yet consolidated findings from the most recent decade (2015-2025), a period marked by major advances in transplant care and the availability of increasingly diverse global patient data. This gap underscores the need for a broad and contemporary synthesis to guide individualized, evidence-based decision-making in current transplant practice.

Therefore, this narrative review aims to summarize recent evidence on the efficacy and safety of tacrolimus in adult kidney transplant recipients, identify key factors contributing to clinical variability, and highlight persistent gaps that require further investigation. This work contributes several advances that distinguish it from prior syntheses. First, it presents an updated and comprehensive evaluation of evidence from 2015–2025, capturing the most recent decade during which significant advances have occurred in transplant management. Second, this review offers a quantitative consolidation of key efficacy and safety outcomes, including acute rejection, biopsy-proven rejection, graft loss, mortality, cytomegalovirus (CMV) infection, new-onset diabetes after transplantation (NODAT), and tremor, allowing readers to directly compare numerical ranges across studies rather than rely on descriptive summaries alone. Third, by integrating findings across diverse tacrolimus formulations and immunosuppressive regimens, the review highlights regimen-specific patterns that have not been thoroughly examined in earlier work. By applying a thematic narrative synthesis and highlighting variability across study designs, monitoring strategies, and population characteristics, this review provides a more integrated understanding of tacrolimus performance in

contemporary transplant practice. The significance of this work lies in its potential to support individualized immunosuppressive management, inform clinical decision-making, and guide future research toward improving transplant outcomes across diverse patient populations.

2. METHOD

2.1. Search strategy and data sources

This narrative review was conducted to synthesize recent evidence on the efficacy and safety of tacrolimus in adult kidney transplant recipients. PubMed was selected as the primary database due to its comprehensive and authoritative indexing of biomedical, clinical, pharmacological, and transplant-related studies, which aligns directly with the scope of this review [33]. Additional databases with overlapping coverage were screened to ensure completeness. PubMed includes MEDLINE-indexed clinical trials, observational studies, transplant registries, and pharmacotherapy research that are essential for evaluating tacrolimus outcomes.

To ensure completeness and avoid potential database bias, we also screened additional databases with overlapping coverage (such as Google Scholar and Semantic Scholar) to confirm that no major studies were missed. However, PubMed remained the central source due to its methodological consistency, high-quality peer-reviewed content, and standardized indexing, which support more reliable screening within the timeframe. The search covered studies published between 2015 to 2025 using the following Medical Subject Headings (MeSH) keywords and Boolean combinations: ("kidney transplantation" [MeSH Terms] OR "renal transplantation" [MeSH Terms]) AND "Tacrolimus" [MeSH Terms] AND ("treatment" [MeSH Terms]).

A narrative review approach was selected for this study due to the substantial heterogeneity among the included articles. The studies varied widely in design (randomized trials, prospective cohorts, retrospective analyses), population characteristics, tacrolimus formulations, concomitant immunosuppressive regimens, outcome definitions, reporting of trough concentrations, and follow-up durations. These differences made it methodologically inappropriate to pool data quantitatively or apply a meta-analytic model, as statistical aggregation would risk generating misleading or noninterpretable summary estimates. Although structured frameworks such as PRISMA offer standardized procedures for systematic reviews, the objective of this work was to integrate diverse evidence, highlight clinical patterns, and link findings with pharmacological mechanisms, aims that are better suited to thematic narrative synthesis. This rationale has now been clearly articulated to enhance transparency regarding the chosen methodological approach.

2.2. Eligibility criteria and study selection

Studies were included if they: i) involved adult kidney transplant recipients, ii) evaluated tacrolimus efficacy and safety, either with or without a comparison group, iii) were original research articles, and iv) were available as open-access full texts. Exclusion criteria were: pediatric populations, case reports, editorials, non-English publications, and studies without tacrolimus-specific outcomes. Additional relevant studies were identified through manual reference screening of selected full-text articles. Following the examination of references from the selected full-text articles, additional studies were incorporated using identical inclusion criteria. This review also considered phase II, III, or IV clinical trials that evaluate the effectiveness and safety of tacrolimus as an immunosuppressive treatment in kidney transplant patients. Phase II trials were analyzed mainly for preliminary efficacy signals, dose–response patterns, and early safety observations. Phase III trials were compared thematically to evaluate confirmed efficacy, rejection outcomes, and standardized safety endpoints. Phase IV and real-world studies were synthesized to assess long-term tolerability, adverse-event variability, and effectiveness in routine clinical practice. These findings were then integrated narratively, rather than numerically, to identify consistent patterns across phases (e.g., rejection control, metabolic complications) while respecting the methodological differences of each trial type.

2.3. Data extraction

As this was a narrative review, no formal protocol registration or systematic PRISMA-based screening was undertaken. Instead, relevant studies were selected based on their scientific relevance and methodological quality to provide a comprehensive overview of the current evidence. The selection process involved reviewing titles, abstracts, and full texts to ensure suitability for the inclusion criteria. The data were then extracted descriptively, focusing on the: i) study characteristics: design, setting, and sample size; ii) intervention details: tacrolimus regimen, duration, and comparator drugs (if applicable); iii) clinical outcomes: efficacy and safety endpoints; iv) key findings and clinical implications.

For each study included, data were extracted on study design, population characteristics, tacrolimus regimen, efficacy, and safety outcomes. Extracted data were recorded in standardized tables to support comparison across studies. The gathered data were summarized and organized according to major outcome domains, including graft function, rejection rates, patient survival, and adverse effects.

2.4. Analytical and synthesis approach

A thematic narrative synthesis was applied to integrate findings across the selected studies. The synthesis proceeded in three stages: i) thematic categorization, in which studies were grouped into key domains include efficacy outcomes, safety, and factor influencing clinical variability; ii) narrative comparison, where results were compared across studies within each thematic domain to identify convergent evidence, divergent findings, and potential explanatory factors; and iii) quantitative summary, in which numerical indicators, such as rates of acute rejection, incidence of adverse events, were summarized descriptively to support interpretation of patterns identified in the thematic analysis [34], [35]. The results were interpreted to highlight the patterns, consistencies, and gaps in the existing literature regarding the clinical performance of tacrolimus in kidney transplant recipients.

2.5. Narrative quality appraisal

A brief domain-based quality appraisal was conducted to enhance the interpretability of the findings. Each included study was evaluated across several methodological criteria: clarity of study design and population, adequacy of sample size, transparency in reporting tacrolimus dosing, completeness of efficacy and safety outcome reporting, and potential sources of bias such as confounding or selection bias [36].

Overall, randomized controlled trials and well-designed prospective cohorts demonstrated stronger methodological clarity, with explicit descriptions of patient populations, standardized tacrolimus regimens, and comprehensive reporting of both efficacy and adverse events. These studies generally exhibited lower risk of bias and provided more robust evidence regarding the effects of tacrolimus on rejection rates, graft outcomes, and safety profiles [37].

In contrast, several retrospectives, single-center, or real-world observational studies showed methodological limitations, including smaller sample sizes, inconsistent reporting of trough concentrations or dosing adjustments, and incomplete documentation of safety outcomes. These gaps increase the potential for bias and may contribute to the heterogeneity observed across studies [38]. The purpose of this assessment is not to generate a formal score or hierarchy of evidence but to highlight the variability in methodological rigor among the included studies. Recognizing these differences is essential for contextualizing the review findings and understanding how variations in study design may influence reported clinical outcomes.

3. RESULTS AND DISCUSSION

3.1. Review of the results of the articles included

A literature search of the PubMed database, covering the last 10 years (2015–2025), was performed and accessed on May 27, 2025. A total of 91 relevant, open-access articles were initially identified using the following MeSH Terms: (kidney transplantation [MeSH Terms] OR renal transplantation [MeSH Terms]) AND Tacrolimus [MeSH Terms] AND (treatment [MeSH Terms]).

Articles were screened according to predefined inclusion criteria. Seventy-one publications were excluded for the following reasons: lack of a specific focus on tacrolimus (n = 34), absence of efficacy or safety evaluation (n = 28), unrelated to kidney transplantation (n = 5), study duration <6 months (n = 2), population <18 years (n = 2), and incomplete data (n = 1). Consequently, 20 studies fulfilled all the eligibility criteria and were included in the present narrative review (Figure 1).

Based on a review of the 19 studies summarized in Table 1, most trials employed an open-label design (n = 19), which facilitates implementation but may introduce perception bias. Only one study by Rostaing *et al*. incorporated a blinded design [39]-[58]. Large multicenter investigations, including those by [42] (Europe, n = 1,198) and [45] (multi-country, n = 861), have demonstrated the global utilization of tacrolimus. The majority of studies compared two treatment arms, whereas [42] and [44] included up to four comparative groups. Extensive multicenter trials, such as those by [46] encompassing 72 international centers, provide robust generalizability. However, the predominance of open-label designs highlights the need for future trials with stronger blinding to reduce the potential bias. Although the efficacy of tacrolimus is well established globally, further research emphasizing long-term safety outcomes and rigorous trial methodology remains essential to support evidence-based clinical decisions (Table 1).

3.2. Patient demographics and characteristics

Table 2 presents the demographic and clinical characteristics of the 19 studies that evaluated the tacrolimus-based immunosuppressive regimens. The study population showed considerable variation, with a mean age ranging from 29.97 to 59.6 years and a male predominance exceeding 60% across most cohorts. The mean body mass index (BMI) ranged from 25 to 29 kg/m². The majority of participants were Caucasian (>70%), while only a small proportion originated from Asian populations (1–14%). Large multicenter trials, such as those by [42] and [45] enrolled thousands of patients across multiple countries, reflecting the global scope of tacrolimus use, whereas smaller single- or dual-center studies, such as [40] and [58] involved

limited patient numbers. The therapeutic regimens varied substantially, including standard tacrolimus (STD Tac), combinations with mycophenolate mofetil (MMF), prednisone, immediate-release tacrolimus (IR-Tac), extended-release tacrolimus (ER-Tac), and adjunctive agents, such as basiliximab and corticosteroids. These regimen variations reflect ongoing efforts to optimize the efficacy while minimizing adverse effects. Nevertheless, the predominance of male and Caucasian participants in many studies warrants caution when extrapolating the results to female and Asian populations. Variations in the demographic composition and treatment protocols remain critical for interpreting the differences in the efficacy and safety outcomes of tacrolimus therapy (Table 2).

Differences between immediate-release and prolonged-release tacrolimus formulations provide important context for understanding the variability observed in the reported outcomes. Immediate-release tacrolimus, given twice daily, is associated with greater peak–trough fluctuations, which may contribute to neurotoxic events such as tremor and increase the risk of subtherapeutic exposure leading to rejection. In contrast, once-daily prolonged-release formulations offer smoother pharmacokinetic profiles with reduced peak concentrations, potentially improving tolerability and adherence [59], [60]. Several studies included in this review showed that prolonged-release tacrolimus demonstrated comparable rejection rates to immediate-release formulations but with lower rates of neurotoxicity and more stable trough levels [45], [60]. These patterns are consistent with established pharmacokinetic theory, which predicts that reduced variability in exposure leads to improved safety and more predictable immunosuppressive effects. The integration of these formulation-specific findings adds important depth to the interpretation of the tabled results.

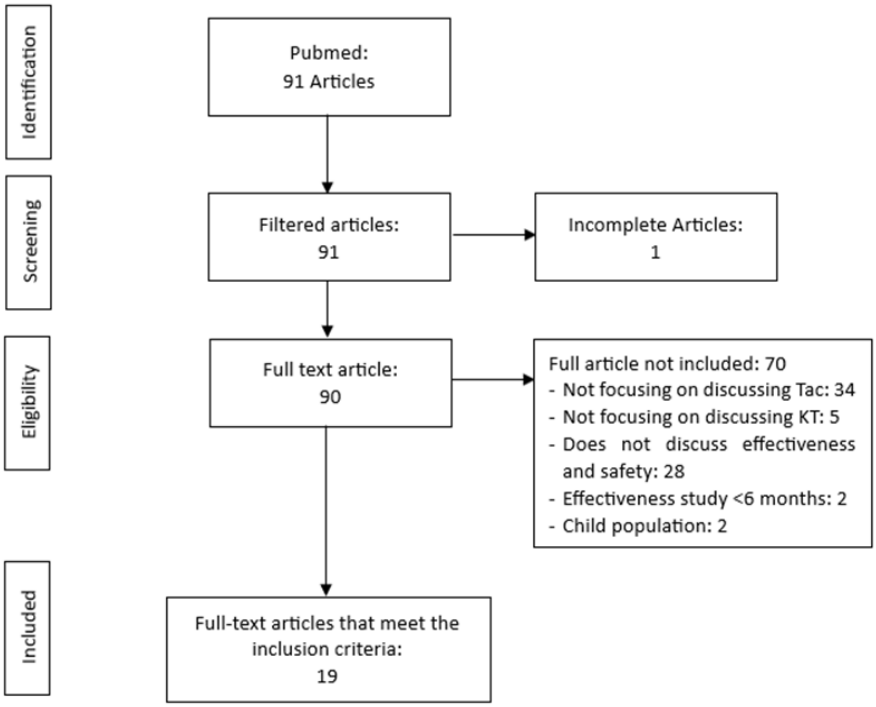

Figure 1. Flowchart of article search and identification

3.3. Effectiveness of tacrolimus

3.3.1. Acute rejection and biopsy-proven acute rejection

Table 3 (see Appendix) summarizes the incidence of acute rejection (AR) and biopsy-proven acute rejection (BPAR) across 19 studies that evaluated various tacrolimus-based immunosuppressive regimens. Most trials adopted an intention-to-treat (ITT) approach and reported a full-analysis-set (FAS) population. The incidence of BPAR varies widely, ranging from 0% to 23.5% [42], [47], [50].

In a multicenter trial by Albano *et al.* [42], the BPAR rate reached 19.6% in the extended-criteria donor (ECD) group receiving a prolonged-release (PR) tacrolimus 0.3 mg/kg + mycophenolate mofetil + corticosteroid regimen. This higher rate was attributed to the greater histologic injury commonly observed in ECD kidneys compared to standard criteria donor (SCD) grafts, which contributes to poorer post-transplant renal function. Moreover, recipients of ECD kidneys are typically older and have additional comorbidities that predispose them to unfavorable outcomes. The highest BPAR incidence (23.5%) occurred in the low-

dose tacrolimus + other antihypertensive therapy (OAHT) group compared to the non-ACEi/ARB-based antihypertensive regimens. Greater interstitial inflammation and fibrosis in the OAHT group were thought to underlie this finding, as renin–angiotensin system inhibition in the ACEi/ARB group mitigated T cell-mediated rejection [44].

BPAR-free outcomes (0%) were reported in two studies utilizing immediate-release tacrolimus (IR-Tac) and low-dose tacrolimus + mycophenolate mofetil + prednisone (Low Tac + MMF + Pred) regimens [47], [50]. The favorable outcomes in the IR-Tac group were attributed to its lower bioavailability, which is associated with reduced post-transplant adverse effects and improved graft function [47]. In general, these findings underscore that tacrolimus remains an effective standard immunosuppressive therapy; however, the risk of acute rejection continues to warrant careful monitoring, particularly among recipients with high-risk profiles or multiple comorbidities.

3.3.2. Graft loss

Table 3 (see Appendix) summarizes the graft loss outcomes of studies evaluating various immunosuppressive mens incorporating tacrolimus in kidney transplant recipients. The graft loss rate reported by [40] was 0% in patients receiving tacrolimus + mycophenolate mofetil (MMF) + prednisone, whereas [44] observed a higher rate (10.3%) in the low-dose tacrolimus + other antihypertensive therapy (LOW Tac + OAHT) group. The same regimen also demonstrated the highest BPAR incidence (23.5%), attributed to greater fibrosis and interstitial inflammation in the OAHT group, whereas ACEi/ARB-based regimens were associated with lower rates due to renin–angiotensin system inhibition, which mitigates T-cell–mediated rejection [47]. A 0% graft loss rate was similarly observed in a study by [49] using a standard extended-release tacrolimus (TacER) + MMF + corticosteroid regimen, suggesting that optimized dosing reduces inflammation and acute rejection, thereby improving graft survival. Collectively, these findings indicate that tacrolimus exposure levels and accompanying immunosuppressive combinations play a pivotal role in influencing graft loss outcomes.

3.3.3. Mortality

Table 3 (see Appendix) summarizes the number and percentage of patient deaths reported across studies evaluating tacrolimus-based immunosuppressive regimens in kidney transplant recipients. Mortality rates varied considerably between studies, ranging from 0% in trials such as [41], which evaluated standard tacrolimus and low-dose tacrolimus plus everolimus regimens, to 8% in the study by [55]. In the study by [41], tacrolimus concentrations remained within the therapeutic range throughout the 12-month follow-up period, contributing to a reduced risk of rejection and improved graft survival. Conversely, Rostaing *et al*. [55] reported higher mortality (8%) with both LCPT + MMF + corticosteroids and IR-Tac + MPA + corticosteroid regimens, with deaths primarily attributed to cardiopulmonary complications and sepsis. These findings highlight the variability in patient survival outcomes among tacrolimus-based regimens and suggest that differences in immunosuppressive strategies, observation periods, and baseline patient characteristics may influence mortality rates. Nonetheless, direct inter-study comparisons should be interpreted with caution because of the heterogeneity in population profiles and study designs.

Table 1. List of studies

Author	Clinical trial phase	Blinding	Number of centers	Region	Total samples	Outcome effectiveness	Safety outcome	Group
[40]	-	Open-label	1 centers	Netherlands	40	Y	N	2
[41]	4	Open-label	7 centers	Korea	345	Y	N	2
[42]	3b	Open-label	Multicenter	Europe	1198	Y	Y	4
[43]	-	Open-label	4 centers	Korea	77	Y	Y	2
[44]	3b	Open-label	13 centers	Canada	281	Y	N	4
[45]	3	Open-label	Multicenter	International	861	Y	N	2
[46]	-	Open-label	72 centers	International	715	Y	Y	2
[47]	3	Open-label	47 centers	United States of America	55	Y	N	2
[48]	-	Open-label	1 centers	United States of America	528	Y	N	2
[49]	4	Open-label	16 centers	France	186	Y	Y	2
[50]	-	-	1 centers	China	32.	Y	Y	2.
[51]	-	Open -label	1 centers	Austria	141	Y	N	2
[52]	-.	Open-label	1 centers	United States of America	178	Y	Y	2
[53]	-	Open-label	1 centers	Austria	87	Y.	Y	2
[54]	-	Open-label	52 centers	Canada, United States of America	613	Y	Y	2
[55]	3	Blinded	68 centers	United States of America, Europe, Asia Pasific	543	Y	Y	2
[56]	4	Open-label	58 centers	Europe. Asia Pasific	730	Y	Y	2
[57]	-	Open-label	1 centers	Belanda	79	Y	Y	2
[58]	-	Open-label	1 centers	Czech Republic	20	Y	N	2

Table 2. Main characteristics of publications

Author	Regimen	Population (N)	Median age (Year)	Male (%)	Female (%)	BMI (kg/m²)	Asian (%)	White (%)	Black/ African American (%)	Others (%)
[40]	Belatacept+MMF+Pred	20	57	701	30	-	51	85	10	-
	Tac+MMF+Pred	20	55	801	20	-	10	80	10	-
[41]	Low Tac + EC-MPS + Corticosteroid	164	43.4	57.9	42.1	-	-	-	-	-
	STac + L EC-MPS + Corticosteroid	171	44.7	54.4	45.6	-	-	-	-	-
[42]	IR Tac 0.2 + MMF + Corticosteroid (ECD)	154	56.5	71.43	28.6	25.3	1.3	97.4	1.3	-
	IR Tac 0.2 + MMF + Corticosteroid (SCD)	155	45.2	65.23	34.8	25.5	3.2	94.2	2.6	-
	PR Tac 0.2 + MMF + Corticosteroid (ECD)	155	56.3	68.43	31.6	25.7	1.3	94.8	3.9	-
	PR Tac 0.2 + MMF + Corticosteroid (SCD)	147	44.7	68.03	32.0	25.9	1.4	93.2	5.4	-
	PR Tac 0.3 + MMF + Corticosteroid (ECD)	153	55.6	68.03	32.0	26.2	0.7	96.7	2.6	-
	PR Tac 0.3 + MMF + Corticosteroid (SCD)	151	44.7	66.23	33.8	24.8	3.3	94.7	2.0	-
	PR Tac 0.2 + MMF + Basiliximab + Corticosteroid (ECD)	158	54.4	69.03	31.0	25.3	1.3	95.6	3.2	-
	PR Tac 0.2 + MMF + Basiliximab + Corticosteroid (SCD)	125	42.8	60.8	39.2	25.2	4.0	91.2	4.8	-
[43]	Everolimus + Low Tac	38	44.71	50.0	50.0	-	-	-	-	-
	STD Tac	39	46.49	51.28	48.7	-	-	-	-	-
[44]	LOW Tac+ACEi/ARB3	71	-	-	-	-	-	-	-	-
	LOW Tac+OAHT3	69	-	-	-	-	-	-	-	-
	STD Tac+ACEi/ARB3	71	-	-	-	-	-	-	-	-
	STD Tac+OAHT3	70	-	-	-	-	-	-	-	-
[45]	LCPT	4281	46.9	67.8	32.2	26.9	3.02	75.2	10.3	-
	Tac BID	4331	48.1	64.4	35.6	27.4	3.02	75.3	11.3	-
[46]	Everolimus	359	45.9	68.2	31.8	-	-	70.2	1.1	-
	CNI Total	356	46.7	70.8	29.2	-	-	75.8	1.4	-
	Tacrolimus	231	47.3	69.3	30.7	-	-	74.9	2.2	-
	CsA	125	45.4	73.6	26.4	-	-	77.6	05	-
[47]	LCPT	26	44.1	77	23	29.2	-	-	-	-
	IR-Tac	29	48.1	76	24	27.8	-	-	-	-
[48]	Tacrolimus + Inhibitor IMPDH	528	49.3	69.7	30.3	-	-	30.1	27.5	42.4
[49]	LTacER+MMF/EC-MPS+Steroid	87	51.1	69	31	24.7	-	87	-	-
	STacER+MMF/EC-MPS+Steroid	99	52.5	60	40	24.6	-	90	-	-
[50]	Low Tac + MMF+Pred	16	29.97	93.8	6.2	-	-	-	-	-
	Tac STD + MMF+Pred	16	30.63	68.87	31.2					-
[51]	TAC+MMF/EC-MPA+Steroid	96	53	65	35	-	2	97	1	-
	CSA+MMF/EC-MPA+Steroid	45	4	-	-	-	-	-	-	-
[52]	Low Tac + Sirolimus	88	46.5	67	33	28.2	13	-	-	-
	MMF+Sirolimus	90	47.9	69	31	28.9	11	-	-	-
[53]	CSA to TAC MR4+ MMF + Prednison	28	64	90	10	-	-	97	3	-
	TAC to TAC MR4 +MMF+Pred	59	55.8	76	24	-	-	98	2	-
[54]	EVR+Low Tac	306	50.0	67.0	33.0*	-	5.6	64.1	22.9	-
	MMF+STD Tac	304	48.4	66.4	33.6*	-	3.6	66.1	24.3	-
[55]	LCPT	268	44.8	64.9	35.1	-	3.7	75.7	3.7	-
	IR-Tac	275	46.9	65.8	34.2	-	3.6	77.8	5.5	-
[56]	Tac prolonged release + MMF	287	49.6	62.4	37.6*	25.3	6.5	92.4	-	1.1
	Tac prolonged release + Sirolimus	282	49.2	66.0	34.0*	25.4	5.9	91.9	-	2.2
[57]	Tac mono	38	59.6	76.0	24.0*	-	-	-	-	-
	Tac+MMF	41	59.0	71.0	29.0*	-	-	-	-	-
[58]	TAC Mono	13	55	-	-	-	-	-	-	-

3.4. Safety of tacrolimus

3.4.1. Cytomegalovirus (CMV) infection incidents

Table 4 (see Appendix) summarizes the incidence of cytomegalovirus (CMV) infection across studies evaluating various tacrolimus-based immunosuppressive regimens. The reported incidence varied markedly, ranging from 0% in the tacrolimus monotherapy (TAC mono) group in the study by [58] to 16.9% in the low-dose extended-release tacrolimus (low TacER) + MMF/EC-MPS + corticosteroid group reported by [49]. In a study by [58] all recipients were CMV-seropositive but received prophylactic antiviral therapy, effectively preventing CMV infection. Conversely, the higher incidence observed by [49] may be related to differences in prophylaxis duration, tacrolimus exposure, and serostatus of donors and recipients. These variations indicate that CMV infection risk is influenced by multiple factors, including the choice of immunosuppressive regimen, immunological status of the transplant population, and preventive antiviral strategies employed.

3.4.2. Incidence of new-onset diabetes after transplant (NODAT)

Table 4 (see Appendix) summarizes the incidence of new-onset diabetes after transplantation (NODAT) reported in eight studies evaluating tacrolimus-based regimens. The incidence ranges from 0% to 22.8% across studies [42], [49]. Large multicenter trials, such as Albano *et al.* [42], demonstrated significant variability in NODAT occurrence, with a higher incidence observed in the immediate-release tacrolimus 0.2 mg/kg + MMF + corticosteroid (ECD) regimen, likely related to tacrolimus-induced insulin resistance [42], [43], [50]. These findings suggest that the immunosuppressive regimen type, tacrolimus dosage, and patient-specific metabolic profiles play critical roles in determining the risk of NODAT.

3.4.3. Tremor

Table 4 (see Appendix) presents the data on the incidence of tremors reported in several studies evaluating tacrolimus-based regimens. In the 6-month trial by [42], tremor occurred in 7.2%–13.5% of patients across groups receiving immediate-release tacrolimus (IR-Tac 0.2/0.3 mg/kg) and prolonged-release tacrolimus (PR-Tac 0.2 mg/kg) in combination with MMF and corticosteroids. Qazi *et al*. [54] reported a higher incidence (28.6%) with the MMF + standard tacrolimus regimen over 12 months, whereas [55] observed tremor rates of 18.5% and 22% with the IR-Tac and LCPT regimens, respectively, during a 24-month follow-up. The highest incidence (28.6%) was observed in the MMF + standard tacrolimus group [54]. Tremor in these studies was attributed to tacrolimus-related neurotoxicity affecting the central nervous system [61]-[63]. Although not all studies reported tremor data, the available evidence indicates that neurologic adverse effects, such as tremor, can occur in a clinically significant proportion of patients receiving tacrolimus, with variable frequency across regimens.

The variability observed in acute rejection and biopsy-proven acute rejection reflects fundamental differences in immunological risk profiles, center-specific protocols, and therapeutic drug monitoring (TDM) practices [64]. From a mechanistic perspective, tacrolimus acts by inhibiting calcineurin and suppressing IL-2–mediated T-cell activation; therefore, inadequate trough levels or fluctuating drug exposure can lead to breakthrough rejection [65]. This aligns with previous pharmacokinetic studies demonstrating that tacrolimus exhibits a narrow therapeutic index and high interindividual variability influenced by CYP3A5 genotype, drug–drug interactions, and adherence patterns [66]. These mechanistic factors help explain why centers with rigorous TDM and genotype-informed dosing report lower rejection rates.

The wide range of graft loss and mortality parallels findings from long-term transplant registries, which report that outcomes depend not only on immunosuppressive potency but also on cardiovascular comorbidities, infection control, and early post-transplant complications [67]. The relatively low mortality rates across the reviewed studies are consistent with global improvements in post-transplant care, yet differences in follow-up duration and patient risk profiles may still influence outcomes.

Safety events also demonstrated substantial heterogeneity. CMV infection is biologically plausible given that calcineurin inhibitors alter cellular immunity and may increase susceptibility to viral reactivation [68]. Similarly, the incidence of NODAT supports existing evidence that tacrolimus impairs pancreatic β-cell function and reduces insulin secretion, particularly at higher trough concentrations [69]. The variability in tremor reflects the neurotoxic potential of tacrolimus, which is known to correlate with peak levels and central nervous system penetration [70]. These findings align with prior comparative studies showing that tacrolimus has a higher neurotoxic and diabetogenic risk than cyclosporine [71].

The heterogeneity across efficacy and safety outcomes can be interpreted through a combination of pharmacological theory, genetic variability, differences in concomitant immunosuppressive regimens, and center-level practices. Integrating these elements provides a more coherent understanding of how tacrolimus performs across diverse clinical settings and highlights the need for individualized dosing strategies, genotype-guided therapy, and standardized monitoring protocols [72].

When compared with alternative immunosuppressants, tacrolimus continues to demonstrate superior rejection prevention compared with cyclosporine, consistent with findings from major trials and meta-analyses. However, tacrolimus is associated with a higher risk of neurotoxicity and NODAT, while cyclosporine exhibits more pronounced cosmetic adverse effects and less favorable graft-survival trends [73]. Meanwhile, belatacept offers improved renal function and metabolic profiles but carries a higher early rejection risk and requires intravenous administration, limiting its global applicability [74]. Including these comparisons situates tacrolimus within the broader therapeutic landscape and clarifies why it remains the primary agent in contemporary transplant practice despite recognized safety challenges.

Overall, while tacrolimus remains a primary therapy for improving graft and patient survival in kidney transplantation, adverse effects, including infection, post-transplant diabetes, and tremors, remain major clinical challenges. The findings of this review should be interpreted cautiously due to the considerable heterogeneity across the included studies. While reductions in acute rejection were generally consistent, the wide variability in biopsy-proven rejection, graft loss, and adverse event rates reflects differences in study design, population characteristics, monitoring strategies, and outcome definitions. These inconsistencies indicate that the results represent overall trends rather than definitive comparative estimates.

Long-term safety outcomes also varied substantially, particularly regarding chronic nephrotoxicity, CMV infection, and NODAT, which were influenced by differences in follow-up duration, prophylaxis protocols, and trough-level stability [22]. Additionally, tacrolimus exposure is highly affected by drug–drug interactions involving CYP3A4/5 modulators and by pharmacogenomic factors such as CYP3A5 and ABCB1 polymorphisms [75]. These elements contribute to interpatient variability in efficacy and toxicity, underscoring the need for individualized dosing and standardized monitoring frameworks [76]. Future research should move beyond descriptive observational work and incorporate more rigorous study designs that can clarify causality and reduce bias. Multicenter randomized controlled trials with blinding are needed to evaluate tacrolimus regimens across diverse populations and healthcare systems, enabling more reliable comparisons of efficacy and safety. Pharmacogenomic investigations, particularly involving CYP3A5 and ABCB1 polymorphisms, should be expanded to support individualized dosing algorithms and explain interpatient variability [17]. Additionally, comparative effectiveness trials that include emerging immunosuppressants such as belatacept or next-generation calcineurin inhibitors—may clarify whether alternative agents provide advantages in long-term graft survival or metabolic safety. Real-world registry-based studies could help monitor long-term adverse events and identify practice differences across transplant centers. Finally, implementation research is needed to evaluate how standardized therapeutic drug monitoring and genotype-guided dosing can be feasibly integrated into clinical workflows, especially in resource-limited settings.

4. CONCLUSION

Tacrolimus continues to demonstrate a favorable efficacy-safety balance in adult kidney transplantation, yet its clinical performance remains heterogenous across population and treatment settings. These findings highlight the need for more individualized immunosuppressive strategies, including optimized therapeutic drug monitoring, early identification of patients at risk for metabolic or infectious complications, and careful adjustment of concomitant immunosuppressive regimens. For clinical practice, consistent implementation of standardized tacrolimus target levels and integration of pharmacogenomic considerations may improve patient outcomes and reduce variability in therapy response.

From a policy and system perspective, strengthening national and regional transplant registries, improving access to high-quality laboratory monitoring, and harmonizing clinical practice guidelines will help support more equitable and data-driven transplant care. Expanding transplant data from Asian and other underrepresented populations is particularly important to enhance global generabizability and ensure that dosing recommendations reflect diverse genetic and clinical profiles. This review also acknowledges several limitations within the available literature. Many studies varied in design, had relatively short follow-up durations, lacked standardized reporting of trough concentrations, or involved homogenous populations, predominantly Caucasian cohorts. These limitations restrict the ectent to which findings can be extrapolated to broader clinical settings. Future research should focus on large, multicenter studies with diverse populations, standardized monitoring protocols, and longer-term outcome assessment to refine tacrolimus optimization and support precision-based immunosuppressive management.

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AUTHOR CONTRIBUTIONS STATEMENT

This journal uses the Contributor Roles Taxonomy (CRediT) to recognize individual author contributions, reduce authorship disputes, and facilitate collaboration.

Name of Author	C	M	So	Va	Fo	I	R	D	O	E	Vi	Su	P	Fu
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C : **C**onceptualization
M : **M**ethodology
So : **So**ftware
Va : **Va**lidation
Fo : **Fo**rmal analysis
I : **I**nvestigation
R : **R**esources
D : **D**ata Curation
O : Writing - **O**riginal Draft
E : Writing - Review & **E**diting
Vi : **Vi**sualization
Su : **Su**pervision
P : **P**roject administration
Fu : **Fu**nding acquisition

CONFLICT OF INTEREST STATEMENT

Authors state no conflict of interest.

ETHICAL APPROVAL

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was not required because the study used anonymized, publicly available data and did not involve direct interaction with human participants.

DATA AVAILABILITY

The data supporting the findings of this study are available from the corresponding author, [L], upon reasonable request.

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APPENDIX

Table 3. Outcome effectiveness: acute rejection and biopsy-proven acute rejection, graft loss, and mortality

Author	Population	Time point	Regimen	Sample (N)	Outcome effectiveness			
					Type of rejection	Rejection (%)	Graft loss (%)	Mortality (%)
[40]	ITT	12 months	Belatacept+MMF+Pred	20	BPAR	55	15	0
	ITT	12 months	Tac+MMF+Pred	20	BPAR	10	0	5
[41]	FAS	12 months	Low Tac+ EC-MPS+ Corticosteroid	164	BPAR	1.8	0	0
	FAS	12 months	STac+Low EC-MPS+Corticosteroid	171	BPAR	1.2	0	0
[42]	FAS	6 months	IR Tac 0.2 + MMF + Corticosteroid (ECD)	154	BCAR	15.6	8.4	1.3
	FAS	6 months	IR Tac 0.2 + MMF + Corticosteroid (SCD)	155	BCAR	11.6	3.2	0
	FAS	6 months	PR Tac 0.2 + MMF + Corticosteroid (ECD)	155	BCAR	12.3	10.3	1.9
	FAS	6 months	PR Tac 0.2 + MMF + Corticosteroid (SCD)	147	BCAR	8.2	8.8	1.4
	FAS	6 months	PR Tac 0.3 + MMF + Corticosteroid (ECD)	153	BCAR	19.6	9.8	2.6
	FAS	6 months	PR Tac 0.3 + MMF + Corticosteroid (SCD)	151	BCAR	12.6	3.3	0
	FAS	6 months	PR Tac 0.2 + MMF + Basiliximab + Corticosteroid (ECD)	158	BCAR	13.3	9.5	1.3
	FAS	6 months	PR Tac 0.2 + MMF + Basiliximab + Corticosteroid (SCD)	125	BCAR	12.0	6.4	0
[43]	ITT	12 months	Everolimus + Low Tac	38	BPAR	2.63	0	0
	ITT	12 months	STD Tac	39	BPAR	0	0	0
[44]	ITT	60 months	LOW Tac+ACEi/ARB	71	BPAR	15.5	5.6	2.8
	ITT	60 months	LOW Tac+OAHT	69	BPAR	23.5	10.3	4.4
	ITT	60 months	STD Tac+ACEi/ARB	71	BPAR	12.7	4.2	4.2
	ITT	60 months	STD Tac+OAHT	70	BPAR	10.1	2.9	5.8
[45]	ITT	12 months	LCPT	428	BPAR	8.2	1.9	2.1
	ITT	12 months	Tac BID	433	BPAR	9.5	2.3	1.8
[46]	ITT	12 months	Everolimus	359	BPAR	4.8	0.6	0.83
	ITT	12 months	CNI Total	356	BPAR	2.0	1.1	0.84
	ITT	12 months	Tacrolimus	231	BPAR	0.9	1	0.43
	ITT	12 months	CsA	125	BPAR	4.1	1.6	1.6
[47]	ITT	12 months	LCPT	26	BPAR	4	0	0
	ITT	12 months	IR-Tac	29	BPAR	0	0	0
[48]	ITT	12 months	Tac + Inhibitor IMPDH	528	BPAR	10	5.9	3
[49]	ITT	12 months	LTacER+MMF+Steroid	87	BPAR	11	1	1
	ITT	12 months	STacER+MMF +Steroid	99	BPAR	3	0	0
[49]	ITT	12 months	LTacER+MMF+Steroid	87	BPAR	11	1	1
	ITT	12 months	STacER+MMF +Steroid	99	BPAR	3	0	0
[50]	ITT	24 months	Low Tac + MMF+Pred	16	AR	0	0	0
	ITT	24 months	Tac STD + MMF+Pred	16	AR	18.8	0	0
[51]	ITT	24 months	TAC+MMF/EC-MPA+Steroid	96	-	-	1	1
	ITT	24 months	CSA +MMF/EC-MPA+Steroid	45	-	-	0	1

Table 3. Outcome effectiveness: acute rejection and biopsy-proven acute rejection, graft loss, and mortality (continued)

Author	Population	Time point	Regimen	Sample (N)	Outcome effectiveness			
					Type of rejection	Rejection (%)	Graft loss (%)	Mortality (%)
[52]	ITT	6 months	Low Tac + Sirolimus	88	BPAR	9	4	5
	ITT	6 months	MMF+Sirolimus	90	BPAR	13	3	3
[53]	ITT	12 months	CSA to TAC MR4+MMF+ Pred	28	BPAR	7	3	0
	ITT	12 months	TAC to TAC MR4 +MMF+Pred	59	BPAR	7	1	2
[54]	FAS	12 months	EVR+Low Tac	306	BPAR	19.1	4	6
	FAS	12 months	MMF+STD Tac	304	BPAR	11.2	12	5
[55]	ITT	24 months	LCPT + MMF + Corticosteroid	268	BPAR	17.2	4.1	8
	ITT	24 months	IR-Tac + MMF + Corticosteroid	275	BPAR	18.2	5.5	8
[56]	ITT	12 months	Tac prolonged release + MMF	287	AR	7.3	10	4
	ITT	12 months	Tac prolonged release + Sirolimus	282	AR	8.3	8	1
[57]	ITT	6 months	Tac mono	38	BPAR	7.9	2	6
	ITT	6 months	Tac+MMF	41	BPAR	9.8	2	8
[58]	ITT	60 months	TAC Mono	13	BPAR	15	1	1
	ITT	60 months	SIR Mono	7	BPAR	85	2	1

Table 4. Incidence of cytomegalovirus infection, new-onset diabetes after transplant (NODAT), and tremor in studies

Author	Population	Time point	Regimen	Sample (N)	Safety outcome		
					CMV Infection (%)	NODAT (%)	Tremor (%)
[40]	ITT	12 months	Belatacept+MMF+Pred	20	-	-	-
	ITT	12 months	Tac+MMF+Pred	20	-	-	-
[41]	FAS	12 months	Low Tac+ EC-MPS+ Corticosteroid	164	-	-	-
	FAS	12 months	STac + L EC-MPS + Corticosteroid	171	-	-	-
[42]	FAS	6 months	IR Tac 0.2 + MMF + Corticosteroid (ECD)	154	10.4	22.8	12.3
	FAS	6 months	IR Tac 0.2 + MMF + Corticosteroid (SCD)	155	6.5	16.0	11.6
	FAS	6 months	PR Tac 0.2 + MMF + Corticosteroid (ECD)	155	15.5	15.1	13.5
	FAS	6 months	PR Tac 0.2 + MMF + Corticosteroid (SCD)	147	2.7	8.1	10.9
	FAS	6 months	PR Tac 0.3 + MMF + Corticosteroid (ECD)	153	16.3	17.2	9.2
	FAS	6 months	PR Tac 0.3 + MMF + Corticosteroid (SCD)	151	6.0	15.9	11.9
	FAS	6 months	PR Tac 0.2 + MMF+ Basiliximab+Corticosteroid (ECD)	158	10.8	14.4	12.0
	FAS	6 months	PR Tac 0.2+MMF+Basiliximab+ Corticosteroid (SCD)	125	4.0	10.1	7.2
[43]	ITT	36 months	Everolimus + Low Tac	38	-	13.16	-
	ITT	36 months	STD Tac	39	-	2.56	-
[44]	ITT	60 months	LOW Tac+ACEi/ARB3	71	-	-	-
	ITT	60 months	LOW Tac+OAHT3	69	-	-	-
	ITT	60 months	STD Tac+ACEi/ARB3	71	-	-	-
	ITT	60 months	STD Tac+OAHT3	70	-	-	-
[45]	ITT	12 months	LCPT	428	-	-	-
	ITT	12 months	Tac BID	433	-	-	-
[46]	ITT	12 months	Everolimus	359	9.4	10.7	-
	ITT	12 months	CNI Total	356	12.3	10.1	-
	ITT	12 months	Tacrolimus	231	-	13.3	-
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[47]	ITT	12 months	LCPT	26	-	-	-
	ITT	12 months	IR-Tac	29	-	-	-
[48]	ITT	12 months	Tacrolimus + Inhibitor IMPDH	528	-	-	-
[49]	ITT	12 months	LTacER+MMF/EC-MPS+Steroid	87	16.9	2.3	5.6
	ITT	12 months	STacER+MMF/EC-MPS+Steroid	99	14.1	2.2	3
[50]	ITT	24 months	Low Tac + MMF+Pred	16	-	6.3	-
	ITT	24 months	Tac STD + MMF+Pred	16	-	0	-
[51]	ITT	24 months	TAC+MMF/EC-MPA+Steroid	96	-	-	-
	ITT	24 months	CSA +MMF/EC-MPA+Steroid	45	-	-	-

Table 4. Incidence of cytomegalovirus infection, new-onset diabetes after transplant (NODAT), and tremor in studies (continued)

Author	Population	Time point	Regimen	Sample (N)	Safety outcome		
					CMV Infection (%)	NODAT (%)	Tremor (%)
[52]	ITT	6 months	Low Tac + Sirolimus	88	3.4	-	-
	ITT	6 months	MMF+Sirolimus	90	6.7	-	-
[53]	ITT	12 months	CSA to TAC MR4+MMF+ Pred	28	-	-	-
	ITT	12 months	TAC to TAC MR4 +MMF+Pred	59	-	-	-
[54]	FAS	12 months	EVR+Low Tac	306	4.2	8.2	16.67
	FAS	12 months	MMF+STD Tac	304	8.2	7.2	28.6
[55]	ITT	24 months	LCPT	268	11.16	20.5	22
	ITT	24 months	IR-Tac	275	9.1	15.3	18.5
[56]	ITT	12 months	Tac prolonged release + MMF	287	11.9	3.9	7.7
	ITT	12 months	Tac prolonged release + Sirolimus	282	3.8	6.8	7.1
[57]	ITT	6 months	Tac mono	38	5	-	-
	ITT	6 months	Tac+MMF	41	10	-	-
[58]	ITT	60 months	TAC Mono	13	0	-	-
	ITT	60 months	SIR Mono	7	0	-	-

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