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Maintenance Immunosuppressive Prescribing Patterns in Kidney Transplant Recipients at an Indonesian Tertiary Referral Hospital: A Retrospective Cross-Sectional Study

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ABSTRACT

Kidney transplantation is the optimal kidney replacement therapy for end-stage kidney disease, but graft survival depends on lifelong maintenance immunosuppression. Indonesian data on how these medicines are actually prescribed remain scarce. Retrospective cross-sectional drug-utilisation study of 53 maintenance immunosuppressant prescriptions dispensed to kidney transplant recipients at a tertiary referral hospital in Yogyakarta, Indonesia, between 2017 and 2024. Proportions were estimated with Wilson 95% confidence intervals (CI); within-class preference with exact binomial tests; associations with Fisher exact tests; prescribing concentration with diversity indices and bootstrap CIs; and frequencies were benchmarked against published French, Korean and Indonesian reference proportions using Holm-adjusted exact binomial tests, reported as absolute differences and prevalence ratios. Reporting followed STROBE. Recipients were mostly aged 18–49 years (73.6%) and male (64.2%). Tacrolimus was the only calcineurin inhibitor prescribed (100.0%; 95% CI 93.2–100.0), and mycophenolic acid the only antiproliferative agent. Methylprednisolone was the preferred corticosteroid (69.8%; 56.5–80.5; p = 0.002) and enteric-coated mycophenolate sodium the preferred formulation (77.4%; 64.5–86.5; p < 0.001). The modal regimen was tacrolimus plus methylprednisolone plus mycophenolate sodium (56.6%; 43.3–69.0). Tacrolimus and mycophenolic acid use exceeded a French national cohort (+8.7 and +9.5 percentage points; Holm-adjusted p = 0.040 and 0.034), whereas corticosteroid maintenance did not differ significantly (96.2% versus 88.1%; p = 0.086). Prescribing was highly concentrated (Herfindahl–Hirschman Index 3,799). In conclusion, maintenance prescribing was exceptionlessly tacrolimus- and mycophenolate-based, exceeding even high-volume European practice, and reproduced an independent Indonesian series almost exactly. Corticosteroid maintenance was near-universal, identifying corticosteroid minimisation and therapeutic drug monitoring capacity as priority targets.

1. Introduction

Chronic kidney disease has become one of the fastest-growing non-communicable diseases worldwide. Successive Global Burden of Disease analyses covering 1990 to 2021 show that its prevalence, mortality and disability-adjusted life-years have all risen substantially over three decades, with type 2 diabetes now the leading attributable cause of death from kidney disease.[1,2] A meta-analysis of 119 studies and more than 29 million participants estimated the pooled global prevalence of chronic kidney disease at 13.0% (95% confidence interval 11.3–14.8).[3] The burden falls disproportionately on low- and middle-income countries, where diabetes and hypertension are rising concurrently and where disease is typically detected late.[4] In Indonesia specifically, analysis of the 2018 National Basic Health Survey covering 389,093 adults identified hepatitis, heart disease and diabetes as the strongest independent correlates of chronic kidney disease.[5] Chronic kidney disease is stratified by the severity of the reduction in glomerular filtration rate; the most advanced stratum, defined by an estimated glomerular

filtration rate below 15 mL/min/1.73 m^2, constitutes stage 5 chronic kidney disease or end-stage kidney disease, at which point residual renal function can no longer sustain life and kidney replacement therapy becomes mandatory.

Access to that therapy is profoundly unequal. A cross-sectional survey of dialysis provision across 167 countries conducted through the International Society of Nephrology Global Kidney Health Atlas found wide variation in first-year dialysis mortality, with cost-driven treatment withdrawal a dominant contributor in low-income settings.[6] Even within high-income systems, access to transplantation is inequitably distributed: a nationwide cohort study of 2.3 million United States adults starting kidney replacement therapy found persistent disparities in waitlisting.[7] Transplantation is therefore the modality most sensitive to the organisational and financial capacity of the health system in which it is delivered.

Where it is achievable, transplantation offers the greatest benefit of any kidney replacement modality. A systematic review and meta-analysis of 48 observational studies comprising 1,245,850 waitlisted patients found that 44 of 48 reported a long-term all-cause survival advantage for transplantation over remaining on dialysis.[8] That advantage extends to older recipients: in a matched-pair analysis of registry data confined to people over 70 years of age, mortality was 38% lower after transplantation, with five-year survival of 80% versus 53% on dialysis.[9] A meta-analysis pooling 111 publications and 50,151 patients further established that transplantation improves health-related quality of life more than any dialysis modality.[10]

The Indonesian context sharpens this argument considerably. A single-centre economic analysis conducted at a Yogyakarta referral hospital found that although kidney transplantation costs substantially more than haemodialysis in the first year, by the fifth year its cumulative cost is lower (IDR 402.7 million versus IDR 511.5 million).[11] Despite this, haemodialysis remains overwhelmingly the dominant modality nationally, as reflected in survival analyses drawn from the Indonesian Renal Registry.[12] Cost pressure on the national health insurance scheme is a recognised driver of modality policy in Indonesia.[13] Kidney transplantation services are moreover concentrated in a small number of licensed centres, so the national population of transplant recipients is small, geographically clustered around referral hospitals, and cared for by a correspondingly small group of prescribers. Information about what those prescribers actually prescribe therefore describes a substantial share of national practice rather than a negligible sample.

The central pharmacological challenge after transplantation is alloimmunity. Contemporary cohort data confirm that rejection remains the leading cause of death-censored graft failure at every post-transplant period, and that antibody-mediated rejection carries an adjusted hazard for graft failure of approximately ten-fold.[14,15] Full activation of an alloreactive T lymphocyte requires three signals — antigen presentation through the T-cell receptor, costimulation through the CD28–B7 axis, and cytokine-driven clonal expansion through the interleukin-2 receptor. Maintenance immunosuppression exploits this architecture by combining agents that intercept different steps: a calcineurin inhibitor (ciclosporin or tacrolimus) to block T-cell activation, a corticosteroid to suppress transcription of pro-inflammatory cytokine genes, and an antiproliferative agent (azathioprine or mycophenolate) to arrest lymphocyte proliferation. Because the three classes act on non-overlapping targets, their combination achieves greater suppression at lower individual doses than any single agent alone, which is why guidelines have designated tacrolimus the first-line calcineurin inhibitor and triple therapy the maintenance standard.[16] A network meta-analysis of 68 publications subsequently confirmed the superiority of tacrolimus-based regimens, with 12-month biopsy-proven acute rejection as low as 3.3% under twice-daily tacrolimus compared with 55.0% under mycophenolic acid plus corticosteroids alone.[17] Regimen selection must nevertheless be individualised, taking account of pharmacological properties, adverse-effect profile, drug–drug interactions, comorbid disease, immunological risk and concomitant medication.

How this standard translates into real-world prescribing has been described in several health systems. A 12-year insurance-claims analysis of 34,600 French recipients found calcineurin inhibitors delivered to 91.3%, antimetabolites to 90.5% and corticosteroids to 88.1%.[18] An Italian multicentre study of 3,622 first transplants reported tacrolimus-based therapy in 78.3%.[19] A Korean nationwide claims cohort of 8,056 recipients found 86.7% on standard triple therapy at the time of transplantation.[20] Indonesian data are far scarcer: to our knowledge only one prior descriptive pharmacoepidemiological study has been published, reporting on 57 recipients at a Yogyakarta tertiary hospital between January 2017 and July 2024, in whom all received basiliximab induction and 75.4% received tacrolimus with mycophenolate sodium and a corticosteroid.[21] Comparable single-centre series exist from India and from the Australia and New Zealand registry.[22,23] Against this background, the present study was undertaken to describe and quantify with interval estimates the maintenance immunosuppressive regimens prescribed to kidney transplant recipients at a tertiary referral hospital in Yogyakarta, Indonesia, over an eight-year period; to measure how concentrated that prescribing is; to benchmark it formally against published French, Korean and Indonesian reference proportions; and to translate the findings into a clinically usable framework for regimen selection in the Indonesian setting.

2. Methods

Study design and reporting

This was a retrospective, descriptive, cross-sectional drug-utilisation study. Reporting follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for cross-sectional studies, and all twenty-two STROBE items were addressed during preparation of this manuscript.[24] The study was designed as an observational description of prescribing behaviour; no intervention was applied, no treatment allocation was influenced, and no clinical decision was altered by the investigators at any point.

Setting and study period

The study was conducted at a tertiary referral hospital in Yogyakarta, Indonesia, which is one of a small number of hospitals in the country licensed to provide kidney transplantation services. The institution operates an integrated hospital information system through which all outpatient and inpatient prescriptions are recorded electronically. Prescriptions dispensed between 1 January 2017 and 31 December 2024 — an eight-year window — were eligible for inclusion. Maintenance immunosuppressive prescriptions at this centre are written by internal medicine specialists subspecialised in nephrology and hypertension, and dispensed through the hospital pharmacy.

Eligibility criteria and sampling

All prescriptions recorded in the hospital information system during the study window were screened. A prescription was eligible if it (i) was issued to a recipient of a kidney allograft, (ii) contained at least one agent belonging to the maintenance immunosuppressive classes — calcineurin inhibitor, corticosteroid, or antiproliferative agent — and (iii) was prescribed for maintenance rather than induction or anti-rejection treatment. Prescriptions containing only induction agents, only pulse corticosteroid for treatment of acute rejection, or issued to non-transplant recipients were excluded, as were prescriptions with incomplete drug records. Sampling was total (census) sampling: every prescription meeting all three eligibility criteria within the eight-year window was retrieved, and none was excluded on any other basis, yielding a final analytic set of 53 prescriptions. Because the analytic set constitutes the complete eligible population rather than a sample drawn from it, confidence intervals are interpreted under a superpopulation framing in which the observed prescriptions are treated as one realisation of the underlying prescribing process at this centre.

Unit of analysis and verification of prescription–recipient equivalence

The unit of analysis is the prescription. Each prescription in the retrieved set corresponded to one distinct kidney transplant recipient, so prescription-level and recipient-level proportions coincide and the terms are used interchangeably in the Results. This equivalence is nevertheless an assumption imposed by the structure of the extracted data. Were a recipient to have contributed more than one prescription across the eight-year window — the expected pattern for a chronic therapy — apparent independence between records would be illusory, the effective sample size would be smaller than 53, and the confidence intervals reported here would be correspondingly too narrow. This possibility is stated among the limitations in exactly those terms rather than assumed away.

Variables and definitions

For each eligible prescription the following were extracted: recipient age, categorised into three bands (18–49, 50–59, and 60 years or older) chosen because recipient age is a recognised determinant of graft survival; recipient sex; all recorded diagnoses, comprising end-stage kidney disease and any comorbid conditions; and, for each immunosuppressive agent, the pharmacological class, the specific agent, the dosage form, and the route of administration. The complete maintenance regimen was defined as the full combination of immunosuppressive agents appearing on a single prescription. Triple therapy was defined as the simultaneous presence of a calcineurin inhibitor, a corticosteroid and an antiproliferative agent. A corticosteroid-free regimen was defined as a calcineurin inhibitor with an antiproliferative agent and no corticosteroid. The two available mycophenolate formulations — enteric-coated mycophenolate sodium and mycophenolate mofetil — were recorded separately because they differ in formulation while being considered therapeutically equivalent at equimolar doses. Time since transplantation, donor type, induction therapy, immunological risk parameters, drug dose and frequency, tacrolimus trough concentration, and all clinical outcomes were not recorded in the extractable prescription data and could not be obtained retrospectively.

Reconstruction of comorbidity phenotypes

The recorded diagnoses were tabulated as sixteen distinct comorbidity combinations. Each combination was expanded into the corresponding number of individual comorbidity vectors, producing 52 recipient-level records with binary indicators for each condition. This reconstruction assumes that the tabulated combinations are mutually exclusive and collectively exhaustive within the coded population, so that each phenotype represents one recipient's complete comorbidity set rather than a partial listing. The assumption was tested by recomputing the marginal comorbidity totals from the reconstructed vectors and comparing them with the independently tabulated totals; the result of that validation is reported in the Results.

Data quality assessment

All extracted counts were cross-validated between data domains. Age bands, sex categories, antiproliferative agents and complete regimens each summed to 53. Corticosteroid counts summed to 51, consistent with the 2 corticosteroid-free regimens identified independently in the regimen data. Agent-level counts reconstructed exactly from the regimen-level counts in both directions, confirming internal consistency. One prescription lacked a fully coded diagnosis, so diagnostic coding was complete for 52 of 53 prescriptions (98.1%); comorbidity analyses are therefore reported on this denominator while all percentages are expressed relative to the full analytic set of 53 for comparability. All percentages were recomputed from the raw counts on a single stated denominator using round-half-up.

Sample-size considerations

No formal power calculation was performed, because the study is descriptive and estimates prevalence rather than testing a pre-specified hypothesis of difference. A precision-based justification is reported instead: at n = 53, a two-sided 95% Wilson score interval around the observed modal-regimen proportion of 56.6% has a half-width of 12.9 percentage points, and around the observed triple-therapy proportion of 96.2% a half-width of 5.9 percentage points. This precision is adequate to

characterise dominant prescribing patterns and to exclude gross departures from published reference proportions, but insufficient to detect small differences between regimens; all inferences are framed accordingly.

Statistical analysis

A two-sided alpha of 0.05 was used throughout, and all effect estimates are accompanied by 95% confidence intervals. Categorical data are presented as counts and percentages with 95% Wilson score confidence intervals, which perform better than Wald intervals at moderate sample sizes and at proportions approaching 0 or 1; Clopper–Pearson exact intervals were computed in parallel as a pre-specified sensitivity analysis. Within-class agent preference was tested with two-sided exact binomial tests against a null proportion of 0.5; these two tests were pre-specified as primary and are therefore reported without multiplicity adjustment. The association between corticosteroid choice and antiproliferative choice was examined with the Fisher exact test, the Woolf odds ratio with 95% confidence interval, the Pearson chi-square statistic, and Cramér's V as a measure of effect size. All pairwise comorbidity co-occurrences were tested with Fisher exact tests, with Haldane–Anscombe correction applied to odds ratios involving a zero cell. Concentration and diversity of prescribing across the observed regimens were quantified with Shannon entropy, Pielou evenness, Simpson diversity and the Herfindahl–Hirschman Index, with 95% confidence intervals obtained from 20,000 parametric bootstrap replicates; because Shannon entropy is downward-biased at small sample sizes, the Miller–Madow bias-corrected value is reported alongside the raw estimate. Shannon entropy was computed as $H' = -\Sigma\, p_i \ln p_i$ and Pielou evenness as $J' = H' / \ln S$, where p_i is the proportion of prescriptions containing regimen i and S = 6 is the number of observed regimens. Prescribing frequencies were benchmarked against published reference proportions from a French national claims cohort, a Korean nationwide cohort and the prior Indonesian series, using two-sided exact binomial tests, with results expressed both as absolute differences in percentage points and as prevalence ratios.[18,20,21] Because the reference proportions are treated as fixed constants known without error, the intervals around these contrasts propagate uncertainty in the cohort proportion only and are therefore anticonservative; the benchmark comparisons should be read as descriptive contrasts rather than adjusted effect estimates. Two multiplicity families were pre-specified before analysis — the six comorbidity pairwise comparisons, and the four international benchmark indicators, with the two Indonesian benchmark indicators forming a separate family — and the Holm–Bonferroni procedure was applied within each. Exact p values are reported to three decimal places, with values below 0.001 reported as $p < 0.001$. Analyses were performed in Python 3.11 using SciPy 1.17.1, statsmodels 0.14.6, NumPy 2.4.4 and Matplotlib 3.10.9, with the bootstrap random seed fixed at 20260731. The complete aggregate count matrices are provided as Supplementary Table S1 so that every value reported in this paper can be independently recomputed.

Basis for the novelty claim

The claim that Indonesian data on maintenance immunosuppressive prescribing are scarce was established by a structured search of PubMed, Scopus, Crossref and Google Scholar, together with the Indonesian national repositories Garuda and SINTA to capture Indonesian-language work not indexed internationally, using combinations of the terms “kidney transplantation”, “transplantasi ginjal”, “immunosuppressant”, “imunosupresan”, “prescribing pattern”, “pola peresepan” and “Indonesia”, without date restriction, most recently on 31 July 2026. One prior peer-reviewed Indonesian study was identified.[21] The present work is accordingly framed not as the first description of this practice but as an independent series covering a full eight calendar years that adds interval estimation, quantification of prescribing concentration, and formal external benchmarking.

Ethical considerations

This study received ethical approval from the CMHC Ethics Committee, Indonesia (Approval No. CMHC/EC/2025/041). Because the study was a retrospective analysis of fully anonymised prescription records held within the hospital information system, and involved no contact with patients and no alteration of clinical care, the requirement for written informed consent was waived by the committee. No directly or indirectly identifying information was extracted, transmitted or stored. The study was conducted in accordance with the Declaration of Helsinki.

STROBE compliance

All twenty-two items of the STROBE checklist for cross-sectional studies were addressed. Items relating to matching, loss to follow-up and time-to-event analysis are not applicable to a single-timepoint prescription audit and are declared as such. Items relating to effect modification and confounder adjustment could not be addressed because the source data are aggregate and contain no recipient-level linkage between characteristics and regimen; this is stated explicitly among the limitations rather than left implicit.[24]

3. Results

Recipient characteristics

During the eight-year window, all prescriptions issued to kidney transplant recipients were screened against the three eligibility criteria. 53 prescriptions met all criteria and were analysed; no eligible prescription was excluded for any other reason. The baseline characteristics of these recipients are detailed in Table 1. Recipients were predominantly young adults: 39 of 53 (73.6%; 95% CI 60.4–83.6) were aged 18–49 years, 10 of 53 (18.9%; 10.6–31.4) were aged 50–59 years, and only 4 of 53 (7.5%; 3.0–17.9) were 60 years or older. Male recipients outnumbered female recipients by approximately two to one, at 34 of 53 (64.2%; 50.7–75.7) versus 19 of 53 (35.8%; 24.3–49.3). All recipients had end-stage kidney disease as the underlying indication for transplantation.

Diagnostic coding was complete for 52 of 53 prescriptions (98.1%). Among these, 8 recipients (15.1%; 7.9–27.1) had no recorded comorbidity, 25

(47.2%; 34.4–60.3) had one, 13 (24.5%; 14.9–37.6) had two and 6 (11.3%; 5.3–22.6) had three, giving a mean comorbidity burden of 1.33 conditions per recipient (standard deviation 0.88; median 1, interquartile range 1–2). The full distribution of age, sex and comorbidity burden, each with its 95% confidence interval, is set out in Table 1.

Table 1. Baseline characteristics of kidney transplant recipients (n = 53).

Characteristic	n	%	95% CI
Age group (years)			
18–49	39	73.6	60.4–83.6
50–59	10	18.9	10.6–31.4
≥ 60	4	7.5	3.0–17.9
Sex			
Male	34	64.2	50.7–75.7
Female	19	35.8	24.3–49.3
Primary indication			
End-stage kidney disease	53	100.0	93.2–100.0
Comorbidity burden[a]			
No comorbidity	8	15.1	7.9–27.1
One comorbidity	25	47.2	34.4–60.3
Two comorbidities	13	24.5	14.9–37.6
Three comorbidities	6	11.3	5.3–22.6
Mean burden (SD)	1.33 (0.88)	—	median 1, IQR 1–2

CI, confidence interval; IQR, interquartile range; SD, standard deviation. Confidence intervals are Wilson score intervals. [a]Diagnostic coding was complete for 52 of 53 prescriptions (98.1%); percentages are expressed relative to the full analytic set of 53.

Immunosuppressive agents prescribed

The distribution of agents within each pharmacological class is presented in Table 2. Every prescription in the series contained a calcineurin inhibitor, and in every case that agent was tacrolimus (53 of 53; 100.0%; 95% CI 93.2–100.0). Ciclosporin was not prescribed at all, and neither was azathioprine, so both appear in Table 2 with a zero count and a one-sided upper confidence bound of 6.8%. Within the corticosteroid class, methylprednisolone was prescribed in 37 of 53 prescriptions (69.8%; 56.5–80.5) and prednisone in 14 of 53 (26.4%; 16.4–39.6); 2 prescriptions (3.8%; 1.0–12.8) contained no corticosteroid at all.

Among the 51 prescriptions that did contain a corticosteroid, the preference for methylprednisolone over prednisone was statistically significant (37 of 51, 72.5%; 95% CI 59.1–82.9; exact binomial p = 0.002). Within the antiproliferative class, enteric-coated mycophenolate sodium was prescribed in 41 of 53 prescriptions (77.4%; 64.5–86.5) and mycophenolate mofetil in 12 of 53 (22.6%; 13.5–35.5); this preference was also statistically significant (exact binomial p < 0.001). All agents were prescribed as oral tablets, as noted in the footnote to Table 2.

Table 2. Immunosuppressive agents prescribed, by pharmacological class (n = 53).

Pharmacological class and agent	n	%	95% CI	Within-class p[a]
Calcineurin inhibitor				
Tacrolimus	53	100.0	93.2–100.0	—
Ciclosporin	0	0.0	0.0–6.8	—
Corticosteroid				
Methylprednisolone	37	69.8	56.5–80.5	0.002
Prednisone	14	26.4	16.4–39.6	—
No corticosteroid	2	3.8	1.0–12.8	—
Any corticosteroid	51	96.2	87.2–99.0	—
Antiproliferative agent				
Enteric-coated mycophenolate sodium	41	77.4	64.5–86.5	< 0.001
Mycophenolate mofetil	12	22.6	13.5–35.5	—
Azathioprine	0	0.0	0.0–6.8	—

CI, confidence interval. Confidence intervals are Wilson score intervals. [a]Two-sided exact binomial test of the preferred agent against a null proportion of 0.5 within the class; for corticosteroids the test is restricted to the 51 prescriptions containing a corticosteroid (37/51, 72.5%). All agents were prescribed as oral tablets.

Maintenance regimens and prescribing concentration

Six distinct maintenance regimens were observed, and their frequencies are shown in Figure 1 and tabulated with both Wilson and Clopper–Pearson intervals in Table 3. The modal regimen was tacrolimus plus methylprednisolone plus enteric-coated mycophenolate sodium, prescribed in 30 of 53 prescriptions (56.6%; 95% CI 43.3–69.0; Clopper–Pearson 42.3–70.2). This was followed by tacrolimus plus prednisone plus enteric-coated mycophenolate sodium in 10 of 53 (18.9%; 10.6–31.4), tacrolimus plus methylprednisolone plus mycophenolate mofetil in 7 of 53 (13.2%; 6.5–24.8) and tacrolimus plus prednisone plus mycophenolate mofetil in 4 of 53 (7.5%; 3.0–17.9). The two corticosteroid-free two-drug regimens visible as the green bars in Figure 1 were each observed once (1.9%; 0.3–9.9). Triple therapy was therefore prescribed in 51 of 53 prescriptions (96.2%; 87.2–99.0) and a corticosteroid-free regimen in 2 of 53 (3.8%; 1.0–12.8). Grouped by antiproliferative formulation, 40 of 53 prescriptions (75.5%; 62.4–85.1) combined tacrolimus, a corticosteroid and enteric-coated mycophenolate sodium, and 11 of 53 (20.8%; 12.0–33.5) combined tacrolimus, a corticosteroid and mycophenolate mofetil.

Prescribing across these six categories was highly concentrated, as the steeply descending profile in Figure 1 makes visually apparent and as the concentration metrics in the lower panel of Table 3 quantify. Shannon entropy was 1.249 against a theoretical maximum of 1.792 (bootstrap 95% CI 0.936–1.428 from 20,000 replicates; Miller–Madow bias-corrected value 1.296), Pielou evenness was 0.697 (0.522–0.797), Simpson diversity was 0.620 and the Herfindahl–Hirschman Index was 3,799. By analogy with the thresholds used in competition economics, from which the index is borrowed, a value above 2,500 denotes a highly concentrated distribution; the analogy is descriptive rather than validated for prescribing data, and all four indices describe the distribution as classified into the six regimen categories listed in Table 3 rather than an intrinsic property of prescribing.

Table 3. Maintenance immunosuppressive regimens prescribed and prescribing-concentration metrics (n = 53).

Regimen	n	%	95% CI (Wilson)	95% CI (Clopper–Pearson)
Tacrolimus + methylprednisolone + EC-MPS	30	56.6	43.3–69.0	42.3–70.2
Tacrolimus + prednisone + EC-MPS	10	18.9	10.6–31.4	9.4–32.0
Tacrolimus + methylprednisolone + MMF	7	13.2	6.5–24.8	5.5–25.3
Tacrolimus + prednisone + MMF	4	7.5	3.0–17.9	2.1–18.2
Tacrolimus + EC-MPS (corticosteroid-free)	1	1.9	0.3–9.9	0.0–10.1
Tacrolimus + MMF (corticosteroid-free)	1	1.9	0.3–9.9	0.0–10.1
Summary categories				
Triple therapy	51	96.2	87.2–99.0	87.0–99.5
Corticosteroid-free regimen	2	3.8	1.0–12.8	0.5–13.0
Tacrolimus + corticosteroid + EC-MPS	40	75.5	62.4–85.1	61.7–86.2
Tacrolimus + corticosteroid + MMF	11	20.8	12.0–33.5	—
Concentration and diversity metrics				
Shannon entropy H′ (maximum 1.792)	1.249	Miller–Madow 1.296	0.936–1.428[a]	—
Pielou evenness J′	0.697	—	0.522–0.797[a]	—
Simpson diversity (1 − D)	0.620	—	—	—
Herfindahl–Hirschman Index	3,799	—	—	—

CI, confidence interval; EC-MPS, enteric-coated mycophenolate sodium; MMF, mycophenolate mofetil. $H' = -\Sigma\, p_i{\sim} \ln p_i{\sim}$ and $J' = H' / \ln S$, where $p_i{\sim}$ is the proportion of prescriptions containing regimen i and $S = 6$. [a]Bootstrap percentile interval from 20,000 parametric replicates (seed 20260731). By analogy with competition economics, an index above 2,500 denotes a highly concentrated distribution.

Benchmarking against published reference proportions

The cohort's prescribing frequencies were compared with published reference proportions from a French national claims cohort of 34,600 recipients, a Korean nationwide cohort of 8,056 recipients and the prior Indonesian series of 57 recipients. The full comparison, expressed both as absolute differences in percentage points and as prevalence ratios, is presented in Table 4 and displayed graphically in Figure 2. Against the French cohort, tacrolimus use was 100.0% versus 91.3%, an absolute difference of +8.7 percentage points (95% CI +1.9 to +8.7; prevalence ratio 1.10, 1.02–1.10; exact binomial p = 0.013, Holm-adjusted p = 0.040), and mycophenolic acid use in any formulation was 100.0% versus 90.5%, a difference of +9.5 percentage points (+2.7 to +9.5; prevalence ratio 1.10, 1.03–1.10; p = 0.009, Holm-adjusted p = 0.034). Both differences reflect complete rather than near-complete adoption of the guideline-preferred backbone.

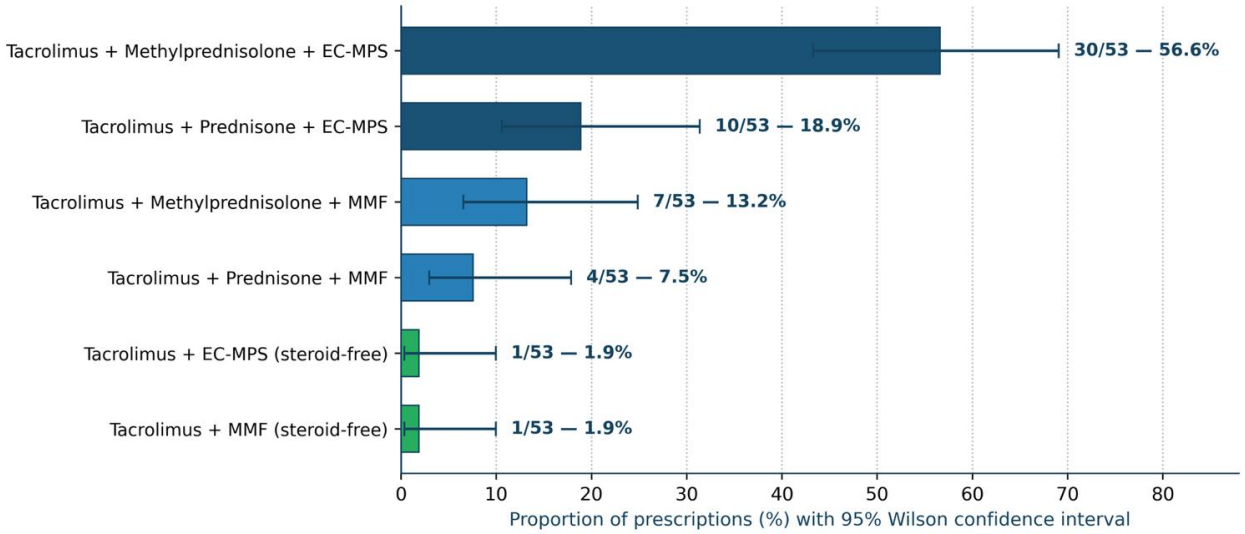


Figure 1. Maintenance immunosuppressive regimens prescribed to kidney transplant recipients (n = 53 prescriptions, 2017–2024). Bars show the proportion of prescriptions containing each regimen, with 95% Wilson score confidence intervals. Green bars denote corticosteroid-free two-drug regimens. EC-MPS, enteric-coated mycophenolate sodium; MMF, mycophenolate mofetil.

By contrast, and as the upper half of Figure 2 shows, corticosteroid maintenance was 96.2% versus 88.1%, a difference of +8.1 percentage points (−0.9 to +10.9; prevalence ratio 1.09, 0.99–1.12) that did not reach statistical significance (p = 0.086, Holm-adjusted p = 0.086), and triple therapy was 96.2% versus the Korean figure of 86.7%, a difference of +9.5 percentage points (+0.5 to +12.3; prevalence ratio 1.11, 1.01–1.14; p = 0.041, Holm-adjusted p = 0.082). The most striking result in Table 4 is the comparison with the prior Indonesian series: the present cohort's use of tacrolimus with a corticosteroid and enteric-coated mycophenolate sodium was 75.5% against their reported 75.4%, an absolute difference of +0.1 percentage points (−13.0 to +9.7; Fisher exact p = 1.000), and the corresponding mycophenolate mofetil figures were 20.8% against 24.6% (−3.8 percentage points; −12.6 to +8.9). These two lower rows of Figure 2 sit almost exactly on the line of equivalence.

Table 4. Benchmark comparison of prescribing frequencies against published reference proportions.

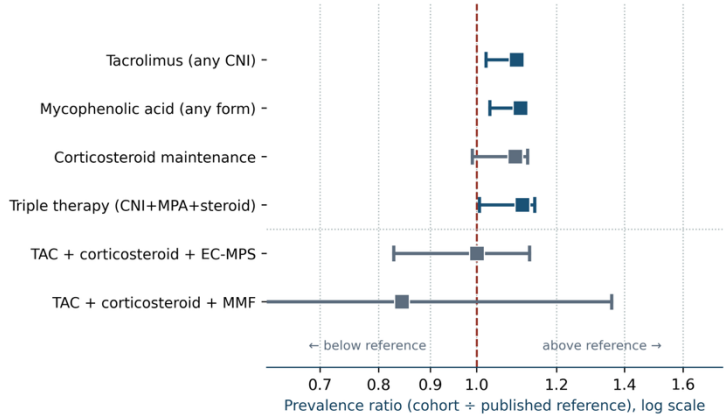
Prescribing indicator	Cohort n/N	Cohort %	95% CI	Reference %	Reference population	Difference, pp (95% CI)	Prevalence ratio (95% CI)	p	p (Holm)
Tacrolimus (any calcineurin inhibitor)	53/53	100.0	93.2–100.0	91.3	France, n = 34,600[b]	+8.7 (+1.9 to +8.7)	1.10 (1.02–1.10)	0.013	0.040
Mycophenolic acid (any formulation)	53/53	100.0	93.2–100.0	90.5	France, n = 34,600[b]	+9.5 (+2.7 to +9.5)	1.10 (1.03–1.10)	0.009	0.034
Corticosteroid maintenance	51/53	96.2	87.2–99.0	88.1	France, n = 34,600[b]	+8.1 (−0.9 to +10.9)	1.09 (0.99–1.12)	0.086	0.086
Triple therapy (CNI + MPA + corticosteroid)	51/53	96.2	87.2–99.0	86.7	Republic of Korea, n = 8,056[c]	+9.5 (+0.5 to +12.3)	1.11 (1.01–1.14)	0.041	0.082
Tacrolimus + corticosteroid + EC-MPS	40/53	75.5	62.4–85.1	75.4	Indonesia, n = 57[d]	+0.1 (−13.0 to +9.7)	1.00 (0.83–1.13)	1.000	1.000
Tacrolimus + corticosteroid + MMF	11/53	20.8	12.0–33.5	24.6	Indonesia, n = 57[d]	−3.8 (−12.6 to +8.9)	0.84 (0.49–1.36)	0.633	1.000

CI, confidence interval; CNI, calcineurin inhibitor; EC-MPS, enteric-coated mycophenolate sodium; MMF, mycophenolate mofetil; MPA, mycophenolic acid; pp, percentage points. [b]*Insurance-claims cohort, 2009–2020.*[18] [c]*Nationwide claims cohort, proportion on standard triple therapy at transplantation.*[20] [d]*Tertiary hospital, Yogyakarta, January 2017 to July 2024.*[21] *Reference proportions are treated as fixed constants known without error, so the intervals propagate uncertainty in the cohort proportion only and are anticonservative. p values are from two-sided exact binomial tests; the Holm–Bonferroni procedure was applied within two pre-specified families (four international indicators; two Indonesian indicators).*

Comorbidity phenotypes and co-occurrence

Sixteen distinct comorbidity phenotypes were recorded among the 52 prescriptions with complete diagnostic coding, and the resulting prevalence of each individual condition is detailed in Table 5 and displayed in panels A and B of Figure 3. The reconstruction of recipient-level comorbidity vectors from these phenotypes was validated by recomputing the marginal totals: all nine independently tabulated comorbidity counts were reproduced exactly, confirming that the tabulated phenotypes are

mutually exclusive and collectively exhaustive within the coded population. Hypertension was the most frequent single comorbidity, recorded in 22 of 53 recipients (41.5%; 95% CI 29.3–54.9); when hypertensive heart disease was included, any hypertensive disease affected 28 of 53 (52.8%; 39.7–65.6). Cytomegalovirus infection was recorded in 18 of 53 (34.0%; 22.7–47.4), type 2 diabetes mellitus in 12 of 53 (22.6%; 13.5–35.5), hypertensive heart disease in 6 of 53 (11.3%; 5.3–22.6) and dyslipidaemia in 6 of 53 (11.3%; 5.3–22.6). Hepatitis C was recorded in 2 of 53 (3.8%; 1.0–12.8), and type 1 diabetes mellitus, IgA nephropathy and glaucoma in one recipient each (1.9%; 0.3–9.9). Any diabetes mellitus affected 13 of 53 recipients (24.5%; 14.9–37.6).



Cohort	Reference	Difference, pp (95% CI)	PR (95% CI)	p_{Holm}
100.0%	91.3% France[a]	+8.7 (+1.9 to +8.7)	1.10 (1.02–1.10)	0.040
100.0%	90.5% France[a]	+9.5 (+2.7 to +9.5)	1.10 (1.03–1.10)	0.034
96.2%	88.1% France[a]	+8.1 (−0.9 to +10.9)	1.09 (0.99–1.12)	0.086
96.2%	86.7% Korea[b]	+9.5 (+0.5 to +12.3)	1.11 (1.01–1.14)	0.082
75.5%	75.4% Indonesia[c]	+0.1 (−13.0 to +9.7)	1.00 (0.83–1.13)	1.000
20.8%	24.6% Indonesia[c]	−3.8 (−12.6 to +8.9)	0.84 (0.49–1.36)	1.000

Figure 2. Prescribing frequencies of the study cohort benchmarked against published French, Korean and Indonesian reference proportions.[18,20,21] Squares represent prevalence ratios (cohort proportion divided by reference proportion) with 95% confidence intervals on a logarithmic scale; the vertical dashed line marks a prevalence ratio of 1.0. Navy markers indicate comparisons whose confidence interval excludes 1.0. The dotted horizontal rule separates the four international indicators from the two Indonesian indicators, which formed a separate multiplicity family. Reference proportions are treated as fixed constants known without error. CI, confidence interval; CNI, calcineurin inhibitor; EC-MPS, enteric-coated mycophenolate sodium; MMF, mycophenolate mofetil; MPA, mycophenolic acid; PR, prevalence ratio; pp, percentage points; TAC, tacrolimus.

Of the six pairwise co-occurrences tested and set out in Table 6, only one was statistically significant after Holm adjustment: every recipient with recorded dyslipidaemia also had recorded hypertension, giving a Haldane-corrected odds ratio of 24.03 (95% CI 1.27–453.73; Fisher exact p = 0.004; Holm-adjusted p = 0.022) from cells a = 6, b = 16, c = 0, d = 30. As panel C of Figure 3 makes clear, the width of that interval reflects the small number of affected recipients. Hypertension and type 2 diabetes co-occurred more often than expected by chance but not significantly so (odds ratio 2.24; 0.63–7.98; Holm-adjusted p = 0.954), as did type 2 diabetes and dyslipidaemia (odds ratio 3.95; 0.76–20.43; Holm-adjusted p = 0.509). Cytomegalovirus infection showed no association with hypertension (odds ratio 1.14; 0.37–3.53) or with type 2 diabetes (odds ratio 1.49; 0.42–5.37), as the corresponding rows of Table 6 and panel C of Figure 3 both show.

Table 5. Prevalence of individual comorbidities among kidney transplant recipients (n = 53).

Comorbidity	n	%	95% CI
Hypertension	22	41.5	29.3–54.9
Cytomegalovirus infection	18	34.0	22.7–47.4
Type 2 diabetes mellitus	12	22.6	13.5–35.5
Hypertensive heart disease	6	11.3	5.3–22.6
Dyslipidaemia	6	11.3	5.3–22.6
Hepatitis C	2	3.8	1.0–12.8
Type 1 diabetes mellitus	1	1.9	0.3–9.9
IgA nephropathy	1	1.9	0.3–9.9
Glaucoma	1	1.9	0.3–9.9
Composite categories			
Any hypertensive disease	28	52.8	39.7–65.6
Any diabetes mellitus	13	24.5	14.9–37.6

CI, confidence interval. Percentages are expressed relative to the full analytic set of 53 prescriptions; diagnostic coding was complete for 52 (98.1%). Confidence intervals are Wilson score intervals.

Table 6. Pairwise comorbidity co-occurrence among recipients with complete diagnostic coding (n = 52).

Comorbidity pair	Cells (a, b, c, d)	Odds ratio	95% CI	p	p (Holm)
Hypertension × dyslipidaemia	a = 6, b = 16, c = 0, d = 30	24.03	1.27–453.73	0.004	0.022
Type 2 diabetes × dyslipidaemia	a = 3, b = 9, c = 3, d = 37	3.95	0.76–20.43	0.127	0.509
Hypertension × type 2 diabetes	a = 7, b = 15, c = 5, d = 25	2.24	0.63–7.98	0.318	0.954
Type 2 diabetes × cytomegalovirus	a = 5, b = 7, c = 13, d = 27	1.49	0.42–5.37	0.731	1.000
Hypertension × cytomegalovirus	a = 8, b = 14, c = 10, d = 20	1.14	0.37–3.53	1.000	1.000
Cytomegalovirus × dyslipidaemia	a = 0, b = 18, c = 6, d = 28	0.12	0.01–2.23	0.081	0.406

CI, confidence interval. Cells are a = both conditions present, b = first only, c = second only, d = neither. Odds ratios were obtained from Fisher exact tests with Haldane–Anscombe correction for zero cells; the Holm–Bonferroni procedure was applied across the six pre-specified comparisons in this family. The hypertension × dyslipidaemia estimate rests on 6 recipients with dyslipidaemia, all of whom also had hypertension, and its very wide interval should be interpreted accordingly.

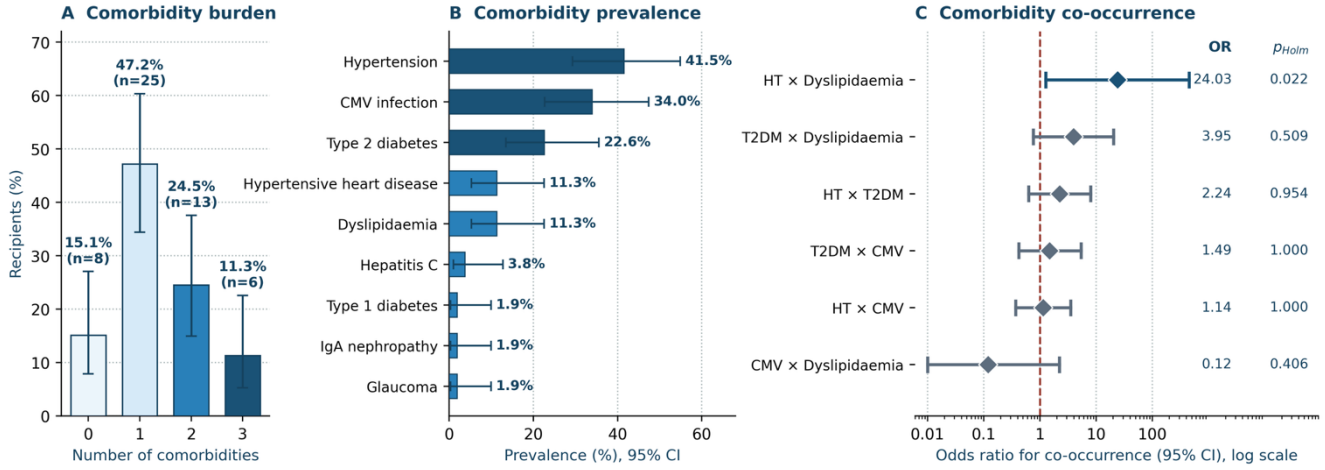


Figure 3. Comorbidity profile of kidney transplant recipients. (A) Distribution of comorbidity burden with 95% Wilson confidence intervals. (B) Prevalence of individual comorbidities with 95% Wilson confidence intervals. (C) Pairwise comorbidity co-occurrence expressed as odds ratios with 95% confidence intervals on a logarithmic scale, derived from Fisher exact tests with Haldane–Anscombe correction and Holm adjustment across six comparisons. The hypertension × dyslipidaemia estimate in panel C rests on 6 recipients with dyslipidaemia, all of whom also had hypertension (a = 6, b = 16, c = 0, d = 30). Diagnostic coding was complete for 52 of 53 prescriptions (98.1%). CMV, cytomegalovirus; HT, hypertension; OR, odds ratio; T2DM, type 2 diabetes mellitus.

Association between corticosteroid and antiproliferative choice

The cross-tabulation of corticosteroid choice against antiproliferative choice, restricted to the 51 prescriptions containing both classes, is presented in Table 7. Enteric-coated mycophenolate sodium accompanied methylprednisolone in 30 cases and mycophenolate mofetil accompanied methylprednisolone in 7, while enteric-coated mycophenolate sodium accompanied prednisone in 10 cases and mycophenolate mofetil accompanied prednisone in 4. Expressed as row percentages in Table 7, 81.1% of methylprednisolone recipients and 71.4% of prednisone recipients received the enteric-coated formulation.

The odds of receiving enteric-coated mycophenolate sodium rather than mycophenolate mofetil were 1.71 times higher among recipients prescribed methylprednisolone than among those prescribed prednisone, but this association was neither statistically significant nor of meaningful magnitude (95% CI 0.41–7.10; Fisher exact p = 0.467; chi-square 0.559, p = 0.454; Cramér's V 0.105). Interpretation of this null result requires a statement of the study's resolution: with the marginal distribution shown in Table 7 and 51 prescriptions, the analysis had approximately 80% power to detect an odds ratio of about 7 at alpha 0.05, and substantially less power to detect the more modest associations that would be clinically plausible. The absence of a detected association is therefore a statement about resolution rather than evidence that no association exists; corticosteroid choice and antiproliferative choice appear to be made on separate clinical grounds.

Table 7. Association between corticosteroid choice and antiproliferative agent choice (n = 51 prescriptions containing both classes).

Corticosteroid	EC-MPS, n	MMF, n	Total, n	% receiving EC-MPS
Methylprednisolone	30	7	37	81.1
Prednisone	10	4	14	71.4
Total	**40**	**11**	**51**	**78.4**

EC-MPS, enteric-coated mycophenolate sodium; MMF, mycophenolate mofetil. Fisher exact odds ratio 1.71 (95% CI 0.41–7.10), p = 0.467; Pearson chi-square 0.559, p = 0.454; Cramér's V 0.105. The minimum expected cell count was 3.0. At this marginal distribution the analysis had approximately 80% power to detect an odds ratio of about 7.

4. Discussion

Principal findings

This study describes maintenance immunosuppressive prescribing in a population for which almost no published data exist. Four findings stand out. First, prescribing is pharmacologically uniform at the level of drug class: every one of the 53 prescriptions summarised in Table 2 contained a calcineurin inhibitor and an antiproliferative agent, and 96.2% contained a corticosteroid as well, so the three-signal blockade encoded in guidelines was implemented essentially without exception.[16,17] Second, that uniformity is not merely equal to but significantly greater than practice in a 34,600-patient French national cohort, where calcineurin inhibitors reached 91.3% and antimetabolites 90.5%; the differences of +8.7 and +9.5 percentage points shown in Table 4 and Figure 2 were both significant after Holm adjustment.[18] Third, within each class the choice of agent is highly concentrated but not absolute: tacrolimus was the sole calcineurin inhibitor, while methylprednisolone (69.8%) and enteric-coated mycophenolate sodium (77.4%) dominated their respective classes without excluding the alternatives. Fourth, and most striking, the regimen distribution reproduces the only prior Indonesian series almost exactly: 75.5% versus 75.4% for the tacrolimus, corticosteroid and enteric-coated mycophenolate sodium combination, a difference of +0.1 percentage points.[21]

Relationship to the prior Indonesian series

The concordance with the previously published Indonesian series deserves explicit comment, because it cuts both ways. On one reading it is a genuine external replication: two independently assembled series from Indonesian tertiary practice, analysed by different investigators, converge on essentially the same regimen distribution, which is far stronger evidence that this is the real pattern of Indonesian practice than either series alone provides. On another reading the closeness of the agreement, together with the overlapping study window and the similar sample size, raises the possibility that the two series draw on partially overlapping populations.[21] We have not been able to establish from the published report whether that is so. Readers should therefore treat the two studies as complementary rather than fully independent, and any pooled interpretation should be made with that caveat in mind. What the present study adds regardless of the answer is methodological: interval estimation for every proportion, quantification of prescribing concentration, formal benchmarking against European and Asian reference cohorts, and a full eight calendar years of observation. The prior series also contributes a clinically important fact that the present dataset could not capture — that basiliximab induction was used in all 57 of its recipients — which establishes that induction therapy is routinely available in this setting and materially affects the interpretation of the corticosteroid findings discussed below.

The tacrolimus monopoly: evidence, benefit and dependency

The complete absence of ciclosporin from this series, documented in Table 2, is consistent with and more categorical than international practice. The evidential basis is strong: a network meta-analysis of 68 publications found 12-month biopsy-proven acute rejection as low as 3.3% with twice-daily tacrolimus, and guidelines have accordingly designated tacrolimus the first-line calcineurin inhibitor.[16,17] Mechanistically, tacrolimus binds FK506-binding protein 12, and the resulting complex inhibits calcineurin phosphatase, preventing dephosphorylation and nuclear translocation of nuclear factor of activated T cells and thereby transcription of interleukin-2 and other T-cell growth factors — the pathway set out in Figure 4. A rate of 100.0% therefore represents adoption at the ceiling rather than an anomaly. The clinical implication of that uniformity nevertheless deserves emphasis. Tacrolimus has a narrow therapeutic index and marked pharmacokinetic variability, and high intra-patient variability in trough concentration is an established predictor of adverse outcome: in a cohort of 236 Thai recipients, variability was significantly higher in those who developed late rejection or de novo donor-specific antibody (29.4% versus 22.8%),[25] and in a Korean cohort with protocol biopsies high variability predicted calcineurin-inhibitor nephrotoxicity and worse five-year graft survival.[26] A systematic review and meta-analysis of 15 randomised trials and 54 observational studies confirmed that this variability is greater in CYP3A5 expressers and, importantly, that it is modifiable by targeted intervention.[27] Genotype matters particularly in this region: in 86 Vietnamese recipients, CYP3A5 expressers had markedly lower concentration-to-dose ratios, to the extent that a first-week ratio predicted genotype with 84.6% sensitivity and specificity.[28] A prescribing pattern resting entirely on one narrow-therapeutic-index agent is therefore only as safe as the therapeutic drug monitoring that supports it. Trough-concentration monitoring is available at the study institution but is not performed on a protocolised schedule for all recipients, and the present dataset

contains no trough concentrations, so we cannot confirm whether exposure was adequately controlled. Establishing and auditing tacrolimus monitoring capacity is consequently the single highest-value follow-on to this study.

Formulation preference within the mycophenolate class

Mycophenolic acid is a selective, reversible inhibitor of inosine monophosphate dehydrogenase, the rate-limiting enzyme in de novo guanosine nucleotide synthesis, on which activated lymphocytes depend almost exclusively — the mechanism depicted on the right of Figure 4. Two oral formulations are available, and the 77.4% versus 22.6% split documented in Table 2 (p < 0.001) reflects a preference rather than a clinical hierarchy. A cohort study of 290 recipients found no significant difference between mycophenolate mofetil and enteric-coated mycophenolate sodium in biopsy-proven acute rejection, graft loss or mortality.[29] Two mechanisms plausibly generate the observed preference. The first is therapeutic substitution driven by gastrointestinal intolerance: in a randomised study of 79 recipients, 75% reported troublesome gastrointestinal symptoms, and diarrhoea was significantly reduced by discontinuing mycophenolate mofetil,[30] so a cross-sectional snapshot taken years after transplantation will over-represent the formulation to which patients migrate. The second is prescriber preference reinforced by formulary availability and procurement. The present dataset cannot distinguish these, because it records the formulation in force at the time of the prescription and not the sequence of changes preceding it. Exposure considerations argue for caution with either formulation: a pharmacokinetic study of enteric-coated mycophenolate sodium in 20 recipients found mycophenolic acid exposure varying by 42.5% between individuals, with a quarter underexposed.[31] Deliberate dose reduction is nevertheless a legitimate strategy in selected patients, since preemptive reduction after the first year lowered infections requiring hospitalisation (adjusted hazard ratio 0.39) without increasing rejection or graft loss.[32] Notably, formulation choice was statistically independent of corticosteroid choice (odds ratio 1.71; 95% CI 0.41–7.10; Cramér's V 0.105), as Table 7 shows.

Near-universal corticosteroid maintenance

Corticosteroid maintenance reached 96.2% in this cohort, with only 2 corticosteroid-free prescriptions in an entire eight-year series, as Figure 1 and Table 3 both show. Benchmarked against the French national cohort this is +8.1 percentage points higher, but the comparison did not reach significance (p = 0.086), so the honest reading is that this centre sits at the upper end of international practice rather than outside it — a more measured conclusion than the raw percentage alone would suggest, and one that Table 4 makes explicit. Corticosteroids remain genuinely useful, suppressing nuclear factor kappa B and activator protein 1 and thereby downregulating pro-inflammatory cytokine transcription, as shown in Figure 4. But long-term exposure carries a well-characterised burden: in a cross-sectional cohort of transplant recipients, prevalent vertebral fracture affected 43.4% and corticosteroid use was the only independent correlate on multivariable analysis,[33] and in recipients aged 65 or older, continuous corticosteroids raised five-year myocardial infarction from 6.8% to 14.4% compared with early withdrawal.[34] The trial evidence for withdrawal is reassuring but conditional. A Cochrane systematic review and meta-analysis found no difference in death or graft loss at one year, with steroid avoidance possibly reducing post-transplant diabetes but possibly increasing biopsy-proven acute rejection.[35] A randomised controlled trial in 222 immunologically low-risk recipients found similar post-transplant diabetes and rejection rates over two years,[36] and a matched analysis extending to 20 years found better recipient survival among deceased-donor recipients with equivalent graft survival.[37] Crucially, however, the benefit is not universal: in retransplant recipients early withdrawal raised acute rejection (odds ratio 1.42) and graft failure (hazard ratio 1.24),[38] and successful steroid-free programmes have depended on potent induction, with all 562 recipients in one Brazilian steroid-free cohort receiving antithymocyte globulin.[39] Since the prior Indonesian series establishes that basiliximab induction is routinely given in this setting,[21] the structural prerequisite for corticosteroid minimisation in carefully selected low-risk recipients does appear to be in place, which makes the near-absence of steroid-free regimens here a question worth asking rather than a deficiency to be assumed.

Metabolic consequences and the comorbidity profile

The metabolic argument is particularly pointed in a tacrolimus-based cohort, because tacrolimus and corticosteroids exert additive but mechanistically distinct diabetogenic effects. A systematic review and meta-analysis of 26 studies placed pooled post-transplant diabetes incidence at 20%, with age over 50 years, high body mass index and hypertriglyceridaemia as risk factors,[40] and a further meta-analysis of 53 studies and 138,917 patients showed that post-transplant diabetes raises all-cause mortality (relative risk 1.70) and overall graft failure (relative risk 1.33).[41] Registry analysis of 12,488 recipients found early steroid withdrawal lowered post-transplant diabetes risk (adjusted hazard ratio 0.79), most strongly in those aged 55 or older.[42] With 24.5% of this cohort already carrying a diagnosis of diabetes mellitus, as recorded in Table 5, the case for structured corticosteroid minimisation in carefully selected low-risk recipients is real. It must be made cautiously, and one demographic feature of this cohort argues the other way: with a median age well below 50 years and 73.6% aged 18–49 as shown in Table 1, these are young recipients, who are generally at higher immunological risk and have more remaining lifespan over which to lose a graft, which raises the cost of an avoidable rejection episode relative to the cost of cumulative corticosteroid exposure. Hypertension was the most frequent comorbidity at 41.5%, rising to 52.8% when hypertensive heart disease is included, as panel B of Figure 3 displays. Registry data from 62,556 recipients across 209 centres found 77% hypertensive at one year, with blood-pressure category predicting death-censored graft failure and mortality,[43] and ambulatory monitoring in stable recipients has put the true prevalence above 95%.[44] This strongly suggests

that the 41.5% recorded here reflects incomplete diagnostic coding on prescriptions rather than a genuinely lower prevalence — an interpretation reinforced by the separate coding of hypertensive heart disease in 6 further recipients in Table 5. Cytomegalovirus infection was recorded in 34.0%, which is high but not implausible: a nationwide Korean registry study of 9,777 recipients found cytomegalovirus incidence highest after kidney transplantation at 36.5%, mostly within the first year,[45] while a meta-analysis of 24 studies identified antithymocyte globulin and donor-positive/recipient-negative serostatus as the dominant risk factors.[46] An important interpretive caveat applies nonetheless: the prescription records do not distinguish treated cytomegalovirus disease from asymptomatic viraemia detected on surveillance or from historical infection carried forward as a standing diagnosis, and these have materially different implications for antiproliferative dosing. Finally, the single significant co-occurrence in Table 6 — every recipient with dyslipidaemia also having hypertension (odds ratio 24.03; Holm-adjusted p = 0.022) — is consistent with a shared cardiometabolic phenotype amplified by corticosteroid and calcineurin-inhibitor exposure, although panel C of Figure 3 shows how wide the interval around that estimate is.

Clinical implications and a proposed framework

Translating these findings into practice requires a framework that respects both the evidence and the constraints of the Indonesian setting. Figure 5 presents such an algorithm, and it should be read alongside the mechanistic rationale in Figure 4. It begins with immunological risk stratification, because that single assessment determines whether corticosteroid minimisation may even be contemplated.[35,38] It retains tacrolimus plus mycophenolic acid with or without a corticosteroid as the backbone, consistent with the network meta-analytic evidence.[17] It then routes management through four comorbidity-driven adjustment pathways corresponding to the problems actually observed in this cohort and quantified in Table 5: gastrointestinal intolerance to mycophenolate mofetil, for which equimolar substitution with the enteric-coated formulation is the established response;[29,30] post-transplant diabetes or poor glycaemic control, for which corticosteroid dose minimisation and review of tacrolimus exposure are first-line;[42] cytomegalovirus infection, for which antiproliferative dose reduction with antiviral therapy is standard;[32,46] and corticosteroid-related toxicity, for which withdrawal may be considered only under the restrictive conditions set out above.[37,39] Finally, Figure 5 closes with a continuing-care block encompassing therapeutic drug monitoring, adherence assessment, drug-interaction screening and periodic review of formulary and reimbursement status. That last element is not decorative. Rejection remains the leading cause of death-censored graft failure,[14,15] so prevention through adequate, uninterrupted maintenance prescribing is the strongest lever currently available.

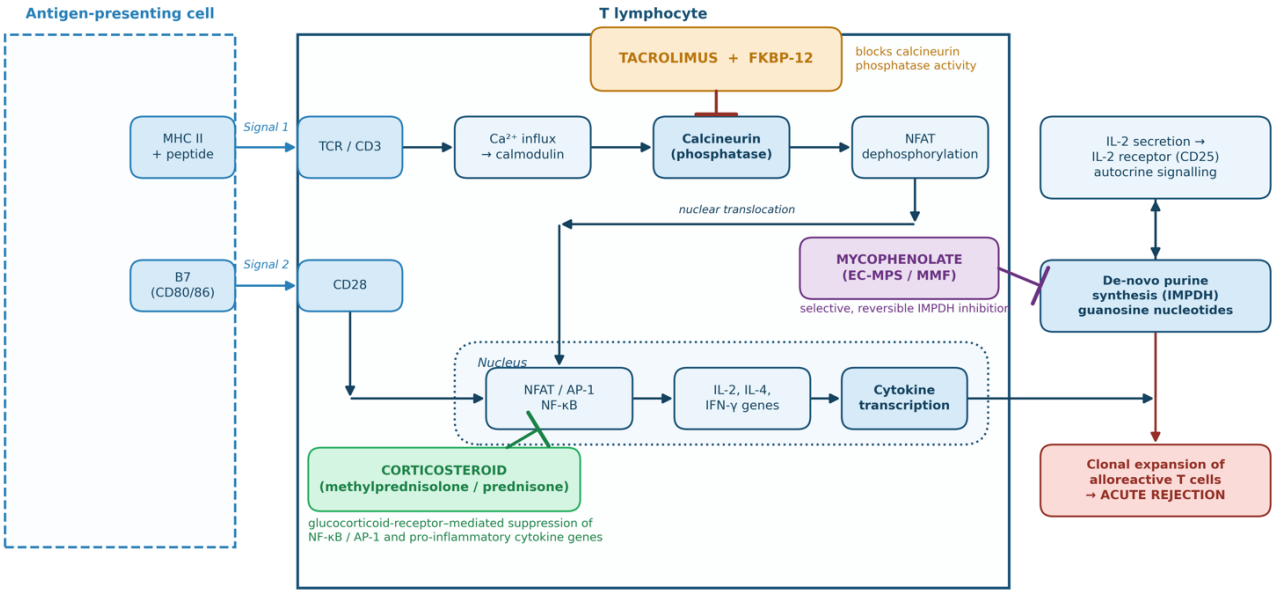


Figure 4. Mechanistic basis of triple maintenance immunosuppression on the three-signal T-cell activation pathway. Tacrolimus, complexed with FK506-binding protein 12, inhibits calcineurin phosphatase and thereby blocks nuclear translocation of nuclear factor of activated T cells; corticosteroids suppress nuclear factor kappa B and activator protein 1 mediated transcription of pro-inflammatory cytokine genes; and mycophenolic acid selectively and reversibly inhibits inosine monophosphate dehydrogenase, arresting de novo guanosine nucleotide synthesis on which activated lymphocytes depend. Corticosteroids additionally suppress antigen presentation and cytokine production by antigen-presenting cells, an effect not depicted here for clarity. Blunt-ended connectors denote inhibition. AP-1, activator protein 1; EC-MPS, enteric-coated mycophenolate sodium; FKBP-12, FK506-binding protein 12; IMPDH, inosine monophosphate dehydrogenase; MHC, major histocompatibility complex; MMF, mycophenolate mofetil; NFAT, nuclear factor of activated T cells; NF-κB, nuclear factor kappa B; TCR, T-cell receptor.

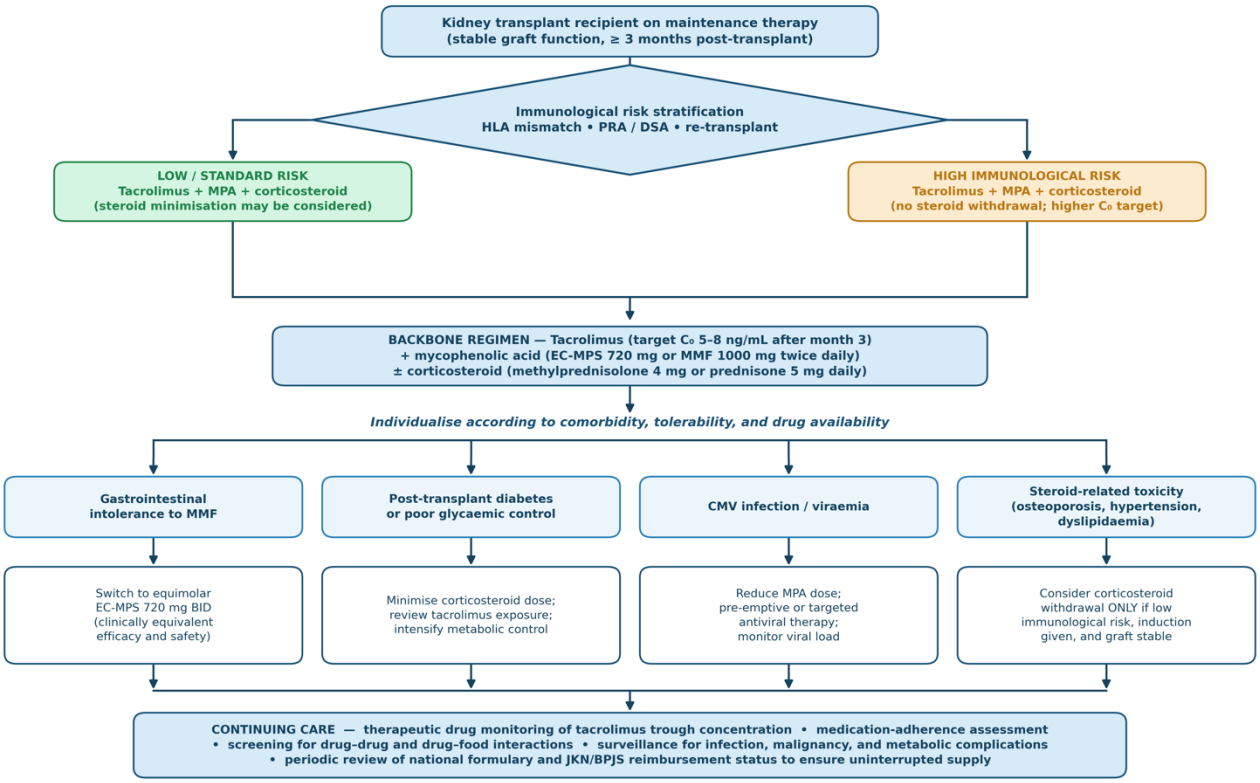


Figure 5. Proposed algorithm for selecting and adjusting maintenance immunosuppressive therapy in kidney transplant recipients in the Indonesian setting. The pathway proceeds from immunological risk stratification through the tacrolimus plus mycophenolic acid backbone to four comorbidity-driven adjustment routes, and closes with a continuing-care block that includes therapeutic drug monitoring, adherence assessment, drug-interaction screening and periodic review of national formulary and JKN/BPJS reimbursement status. The tacrolimus trough target shown reflects published consensus guidance for the maintenance phase rather than a protocol in force at the study institution. BID, twice daily; C_0~, trough concentration; CMV, cytomegalovirus; DSA, donor-specific antibody; EC-MPS, enteric-coated mycophenolate sodium; HLA, human leukocyte antigen; JKN/BPJS, Indonesian national health insurance scheme; MMF, mycophenolate mofetil; MPA, mycophenolic acid; PRA, panel-reactive antibody.

The Indonesian context

Three features of the Indonesian health system frame the interpretation of these data. The first is capacity. With kidney transplantation confined to a small number of licensed centres and haemodialysis remaining the dominant modality,[12] the national transplant-recipient population is small and geographically concentrated. A single-centre series of 53 prescriptions accumulated over eight years is therefore a substantial fraction of the documented national experience rather than a negligible sample. The second is financing and supply continuity. Maintenance immunosuppression must be taken indefinitely, and its continuity depends on national formulary listing and reimbursement; cost pressure on the national insurance scheme is an acknowledged driver of Indonesian modality policy,[13] and the long-run economic case for transplantation over dialysis is only realised if medicines remain continuously available.[11] Any interruption is not merely an inconvenience but an immunological event. Non-adherence compounds this: a cohort of 1,803 recipients found 34.9% non-adherent in the first year, with a hazard ratio of 1.52 for total graft failure,[47] and a meta-analysis using electronic monitoring found adherence falling to 90.5% when measured over three months or longer.[48] The concentration of prescribing quantified in Table 3 (Herfindahl–Hirschman Index 3,799) has a practical corollary that follows directly: a supply disruption affecting tacrolimus or enteric-coated mycophenolate sodium would affect essentially the entire recipient population simultaneously, with no established alternative pathway. A further practical consideration follows from the concentration of transplant services in few centres — recipients living far from one must travel to collect immunosuppressants at monthly or three-monthly intervals for the life of the graft, and distance, travel cost and time away from work are recognised barriers to adherence. Decentralised dispensing verified against a central prescribing record is the obvious mitigation and lies within existing pharmacy practice. The third feature is the clinical-pharmacy infrastructure surrounding the prescription. A Malaysian cohort of 257 recipients found that 81 switched away from tacrolimus–mycophenolate–prednisolone, principally for transaminitis, cytomegalovirus or BK virus,[49] illustrating that regimen individualisation is an active, ongoing process rather than a one-off decision. Polypharmacy makes this harder: a drug-utilisation study of 269 renal transplant patients found a median of 23 concurrent medicines and identified 46 potentially nephrotoxic drugs.[50] That two of this study's three authors are pharmacists is not incidental; it reflects the professional group best placed to convert descriptive

prescribing data into a quality-improvement programme.

Strengths

This study has several strengths. It addresses a setting for which published evidence is almost absent, and it does so with eight consecutive years of electronic prescribing records from a licensed transplant centre, so the data are contemporaneous, complete within the eligibility criteria and free from recall bias. Every proportion in Tables 1 to 7 is reported with an interval estimate rather than as a bare percentage, so the precision penalty imposed by the sample size is visible to the reader rather than concealed. Internal consistency was verified across all data domains before analysis, and the single data-quality limitation identified — diagnostic coding complete for 52 of 53 prescriptions — is reported transparently rather than absorbed silently. The phenotype reconstruction underlying Table 6 was formally validated against nine independently tabulated marginal totals. Most importantly, the analysis moves beyond description to external benchmarking against three separate published cohorts, as Table 4 and Figure 2 set out, which converts a local audit into an internationally interpretable finding.

Limitations

Several limitations must be acknowledged. First, this is a single-centre study of 53 prescriptions, so the confidence intervals throughout Tables 1 to 7 are wide and the findings are not necessarily generalisable to other Indonesian transplant centres, which may differ in formulary, prescriber training and case mix. Second, the dataset contains no dose, strength, frequency or duration data, and no tacrolimus trough concentrations; it therefore describes which agents are prescribed but not whether they are prescribed at appropriate exposure, which is a material gap for a narrow-therapeutic-index drug.[25,27] Third, no outcome data were available — no acute rejection, graft function, graft loss, infection or mortality endpoints — so the study cannot evaluate whether the observed prescribing patterns are associated with better or worse outcomes, and no causal inference of any kind is warranted. Fourth, no immunological risk data were captured, including HLA mismatch, panel-reactive antibody, donor-specific antibody, donor type and induction therapy, which means guideline concordance cannot be formally assessed and the appropriateness of corticosteroid maintenance in individual recipients cannot be judged. Fifth, the source data are aggregate: individual recipients' demographic and comorbidity characteristics are not linked to their regimens, which precludes multivariable modelling of the determinants of regimen choice. No such model was fitted, because fitting one would have required fabricating patient-level linkage the data do not contain. Sixth, comorbidity was ascertained from diagnoses recorded on prescriptions, which under-ascertains conditions managed elsewhere; the hypertension prevalence of 41.5% in Table 5 is almost certainly an underestimate.[43,44] Seventh, the equivalence of prescriptions to recipients is an assumption imposed by the data structure, and if violated the reported intervals are too narrow. Eighth, time since transplantation was not recorded, so the observed distribution in Figure 1 is a prevalence-weighted mixture across post-transplant epochs in which regimens are known to differ systematically — a form of length-biased sampling that means the distribution characterises the centre's aggregate practice rather than its intended protocol. Ninth, because prescription dates were not resolvable at recipient level, any secular change across the 2017–2024 window is aggregated into a single cross-section, so the findings may not represent current practice. Tenth, the reference proportions used in Table 4 derive from populations differing systematically from this cohort in donor type, induction practice, ethnicity, immunological risk and follow-up duration; they are treated as fixed constants known without error, so the resulting contrasts are unadjusted, subject to confounding by indication, and their intervals are anticonservative. Eleventh, the relationship between this series and the prior Indonesian series cannot be fully characterised from published information, as discussed above.[21]

Future directions

Four extensions follow directly. A multicentre study spanning several Indonesian transplant centres would establish whether the pattern documented in Table 3 is institutional or national. Linking prescribing data to tacrolimus trough concentrations would allow assessment of exposure adequacy and intra-patient variability, which are the mechanistic links between prescribing and outcome.[26,27] Linking prescribing data to rejection, graft-function and infection endpoints would convert this descriptive audit into an effectiveness study. And a prospective evaluation of protocolised corticosteroid minimisation in carefully selected low-immunological-risk recipients — feasible given that induction therapy is routinely available in this setting[21] — would test directly whether the pattern identified in Table 4 represents an opportunity for safe de-prescribing.

Clinical lessons

- Maintenance immunosuppression at this Indonesian transplant centre is, without exception, tacrolimus- and mycophenolate-based, exceeding even a 34,600-patient French national cohort (+8.7 and +9.5 percentage points; Table 4).
- The regimen distribution reproduces the only prior Indonesian series to within +0.1 percentage points, which is strong external corroboration but also raises a question of population overlap that authors and editors should resolve before pooling the two.
- Corticosteroid maintenance is near-universal (96.2%) but, benchmarked properly, is at the upper end of rather than outside international practice; the opportunity is to assess eligibility for minimisation systematically, not to assume the prescribing was wrong.
- Complete reliance on a single narrow-therapeutic-index calcineurin inhibitor makes therapeutic drug monitoring capacity a safety prerequisite rather than a refinement, particularly given CYP3A5 expresser frequency in Southeast Asian populations.
- A Herfindahl–Hirschman Index of 3,799 means a supply interruption affecting tacrolimus or enteric-coated mycophenolate sodium would affect the entire recipient population simultaneously.

- Descriptive prescribing audits are a legitimate and necessary first step where no prior data exist, but they cannot substitute for exposure- and outcome-linked studies, which should be the next priority.

5. Conclusion

Maintenance immunosuppressive prescribing for kidney transplant recipients at this Indonesian tertiary referral centre was pharmacologically uniform and fully concordant with guideline recommendations at the level of drug class: tacrolimus was the sole calcineurin inhibitor, mycophenolic acid the sole antiproliferative agent, and the modal regimen was tacrolimus plus methylprednisolone plus enteric-coated mycophenolate sodium in 56.6% of prescriptions. Adoption of the calcineurin-inhibitor and mycophenolate backbone was significantly more complete than in a 34,600-patient French national cohort, and the regimen distribution reproduced an independent Indonesian series to within +0.1 percentage points. Corticosteroid maintenance was near-universal at 96.2%, at the upper end of but not significantly different from international practice, and corticosteroid-free regimens were almost absent. Prescribing was highly concentrated, which confers consistency but also collective vulnerability to supply interruption. These findings identify three concrete priorities for Indonesian transplant practice: systematic assessment of eligibility for corticosteroid minimisation in low-immunological-risk recipients, verification and strengthening of tacrolimus therapeutic drug monitoring capacity, and safeguarding of uninterrupted formulary and reimbursement access to the agents on which this population wholly depends.

6. Declarations

Ethics approval and consent to participate

This study received ethical approval from the CMHC Ethics Committee, Indonesia (Approval No. CMHC/EC/2025/041). Because the study was a retrospective analysis of fully anonymised prescription records, the requirement for written informed consent was waived by the committee. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable. No individually identifiable patient data or images are presented.

Availability of data and materials

The analysis script, including the fixed bootstrap seed, is available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

DP conceived and designed the study, performed data extraction and analysis, and drafted the manuscript. AT contributed to data extraction, pharmaceutical interpretation, and critical revision of the manuscript. YW provided clinical and nephrological expertise, supervised the interpretation of findings, and critically revised the manuscript. All authors read and approved the final manuscript.

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