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Research Article

Evaluating the Impact of Steroid Withdrawal on Outcomes in Kidney Transplant Recipients: A Systematic Review and Meta-Analysis

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Abstract

Background and Objective: Kidney transplantation is the preferred treatment for patients with End-Stage Kidney Disease (ESKD), offering better survival and quality of life compared to dialysis. While corticosteroids effectively prevent acute rejection, their long-term use is associated with significant adverse effects. This systematic review and meta-analysis aim to evaluate the risks and benefits of steroid withdrawal compared to continued steroid therapy in kidney transplant recipients. **Method:** A comprehensive literature search was conducted across PubMed, Scopus, Web of Science, and Embase to identify studies comparing Steroid Withdrawal (SW) to Steroid Continuation (SC) in kidney transplant recipients. Eligible studies included randomized controlled trials and observational studies reporting on outcomes such as survival, acute rejection, graft failure, new-onset diabetes, and infections. **Results:** Our search identified 2,946 articles, resulting in 62 studies included in the final analysis. For mortality, the Risk Ratio (RR) for the SW group was 0.833 (95% CI 0.743, 0.934; p=0.002), indicating a 16.7% lower risk of mortality compared to SC. The analysis of acute rejection from 23 studies showed an RR of 1.441 (95% CI 1.180, 1.759; p=0.001), indicating a 44.1% higher risk in the SW group. For death-censored graft failure, the RR was 0.980 (95% CI 0.939, 1.022; p=0.344), showing no significant difference between groups. New-onset diabetes showed an RR of 0.827 (95% CI 0.679, 1.006; p=0.058), suggesting a trend towards lower risk in the SW group. Infection rates showed no significant difference (RR 0.988, 95% CI 0.823, 1.185; p=0.8. **Conclusions:** This meta-analysis highlights the complex balance between minimizing steroid-related side effects and ensuring adequate immunosuppression in kidney transplant recipients. Standardized protocols for steroid withdrawal and further research into patient selection criteria are essential for optimizing long-term outcomes.

Keywords: kidney transplantation, steroid withdrawal, clinical outcomes, acute rejection, mortality, graft failure, immunosuppression.

Introduction

Individuals suffering from End-Stage Kidney Disease (ESKD) need renal replacement therapy, which can be delivered *via* dialysis or kidney transplantation [1,2]. Kidney transplantation is typically considered the best treatment option for suitable candidates, as it can restore a near-normal lifestyle and offers better survival rates and life quality compared to dialysis [3,4]. Despite significant progress in short-term outcomes of kidney transplantation since the 1980's long-term results have only marginally improved [5]. The primary reasons for graft failure are death with a functioning graft and chronic allograft nephropathy [6,7]. Consequently, improving patient survival and extending graft durability has become a crucial objective in kidney transplantation research and practice [6].

Corticosteroids have long been recognized for their ability to suppress inflammation and immune responses, and have been employed to prevent organ rejection since the early days of kidney transplantation. While effective in averting acute rejection, prolonged steroid use is associated with significant health risks and mortality [8,9]. The adverse effects of steroids are wide-ranging, including thinning of the skin, increased body weight, bone loss, and eye lens clouding [10-12]. These drugs can also worsen cardiovascular and metabolic health factors, such as elevated blood pressure, high blood sugar, and abnormal lipid levels, potentially heightening the risk of infections [12-15].

The medical community has shown growing attention to methods that decrease steroid usage, including Steroid Withdrawal (SW) protocols. These approaches seek to lessen the long-term negative impacts of steroids while maintaining adequate immunosuppression. Numerous studies have explored SW's efficacy in kidney transplant recipients, but outcomes have been mixed [16-18]. Certain investigations suggest increased risks of acute rejection and graft failure, while others indicate minimal impact on graft survival and better metabolic outcomes. The variability in these results, combined with the lack of standardized SW protocols, highlights the need for a more thorough understanding of the clinical implications of discontinuing steroids in this patient population. Throughout the years, multiple Randomized Controlled Trials (RCTs) and observational studies have attempted to compare steroid withdrawal with steroid continuation in renal transplant patients [18-20]. However, these studies vary in their design, patient cohorts, and follow-up periods, making it difficult to draw definitive conclusions about the safety and effectiveness of steroid withdrawal. Considering the clinical relevance of these findings, a comprehensive systematic review and meta-analysis is crucial to consolidate the existing evidence and offer clearer guidance for transplant specialists.

This systematic review and meta-analysis aim to contribute to the ongoing discussion regarding the advantages and disadvantages of discontinuing steroid use in kidney transplant patients. The study's primary objective is to assess the impact of steroid withdrawal versus continued steroid administration on crucial clinical outcomes, including patient survival, acute rejection episodes, graft failure, the development of new-onset diabetes, and infection rates. Through a comprehensive analysis of existing literature and statistical synthesis of data, this research endeavors to elucidate the balance between minimizing steroid-related side effects and maintaining sufficient immunosuppression. The ultimate goal is to furnish transplant physicians with evidence-supported guidelines for enhancing immunosuppressive regimens in individuals who have received kidney transplants.

Methods

Search Strategy

An extensive review of literature was performed using four key databases: PubMed, Scopus, Web of Science, and Embase. This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines. The focus was on identifying research that examined the outcomes of SW versus maintaining steroid treatment in kidney transplant patients. The search encompassed studies published up to September 15, 2024, without any restrictions on language. To locate relevant studies, the search strategy employed a mix of keywords and Medical Subject Headings (MeSH) terms associated with "steroid withdrawal," "kidney transplant," and "immunosuppression."

Eligibility Criteria

To be considered for inclusion, research had to meet the following requirements: (1) be either RCTs or observational studies that compared Steroid Withdrawal (SW) with Steroid Continuation (SC) in kidney transplant patients; (2) report on relevant clinical outcomes, including survival, acute rejection, graft failure, new-onset diabetes, or infections; (3) have full-text articles accessible; and (4) involve human subjects. The selection process excluded studies with inadequate data, literature reviews, conference abstracts, and case reports.

Study Selection

A pair of autonomous evaluators examined the headings and summaries of all collected publications to determine their suitability. Following the elimination of duplicate and unrelated entries, complete manuscripts were obtained for thorough assessment. Any disagreements between the evaluators were settled through dialogue or by seeking input from an additional reviewer.

Data extraction

Two independent reviewers extracted data using a standardized form. For each study, they documented the following: author, country, study design, setting, intervention (comparing steroid withdrawal to maintenance), average age, percentage of female participants, sample sizes for both groups, duration of follow-

up, and study endpoints. The reviewers also gathered outcome data, including measures of survival, acute rejection rates, death-censored graft failure, new-onset diabetes, and infection rates. Key findings for each outcome were summarized. To ensure accuracy and consistency, any disagreements between reviewers were resolved through discussion.

Risk of bias assessment

To evaluate potential bias in the selected studies, researchers employed two assessment tools: The cochrane risk of bias tool for randomized controlled trials and the Newcastle-Ottawa Scale for observational studies. Each study was categorized as having low, unclear, or high risk of bias. This classification was based on various factors, including the method of sequence generation, how allocation was concealed, the presence of blinding, the completeness of outcome data, and whether there was selective reporting of results.

Statistical analysis

Statistical analysis was performed using Comprehensive Meta-Analysis version 3.3. Risk Ratios (RR) and their 95% Confidence Intervals (CI) were computed using a random-effects model. The Higgins I^2 statistic was employed to evaluate heterogeneity among studies, with values exceeding 50% considered significant. To further investigate heterogeneity sources, a leave-one-out analysis was implemented. The presence of publication bias was examined through funnel plots, while Egger's test was applied to quantify any asymmetry in the data.

Results

Study selection

Our search of PubMed, Scopus, Web of Science, and Embase identified 2,946 articles. After the removal of duplicates and exclusion of irrelevant records, 1,488 studies remained for further screening. During the screening process, 1236 studies were excluded because they did not meet the predefined criteria, leaving 252 studies for the full-text assessment. Of these, 250 were evaluated for eligibility and further articles were excluded due to inappropriate outcomes or insufficient data. Ultimately, 62 studies were considered eligible and were included in the final meta-analysis [21-83] (Figure 1).

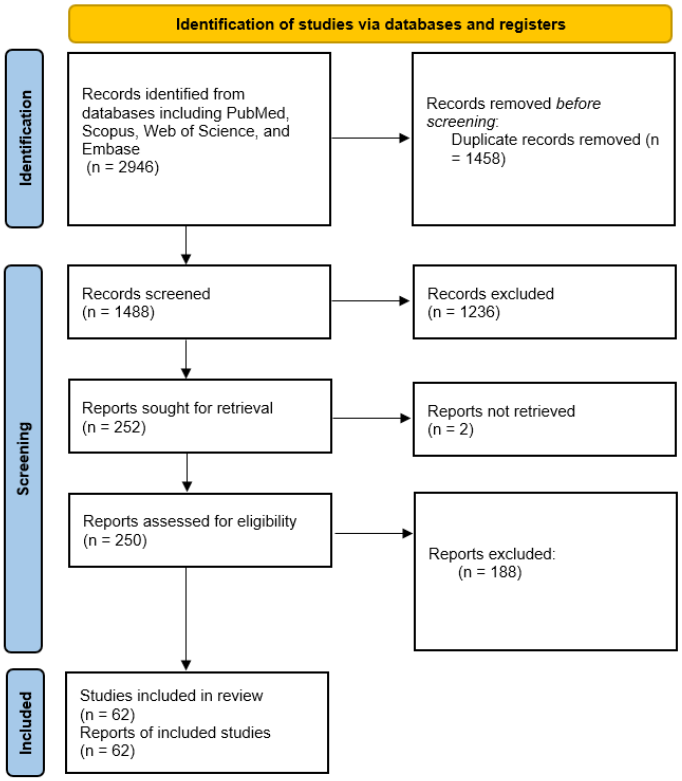


Figure 1: PRISMA flow chart of included studies.

Baseline characteristics and quality assessment

The baseline characteristics of the included studies demonstrate significant variability across multiple parameters. The study designs predominantly consisted of RCTs, with a smaller number of observational studies. These studies were conducted across a wide range of countries, including the USA, Germany, Italy, France, and others, and the sample sizes varied greatly, from as few as 10 to more than 160,000 participants. The follow-up periods also differed substantially, ranging from 6 months to several years. The average age of participants in most studies was in the mid-40s to mid-50s, although some studies included younger or older populations. Gender distribution was generally balanced, though

some studies had a higher proportion of either males or females. Most studies focused on critical clinical endpoints such as mortality, graft loss, acute rejection, and graft function, often measured through markers like Serum Creatinine (SCr) and Creatinine Clearance (CrCl). The timing of steroid withdrawal interventions varied, typically occurring between a few days to several months post-transplantation. This diversity in study design, sample size, and outcomes highlights the heterogeneity of the available data. The baseline characteristics of the included studies are presented in Table 1, and the assessment of the risk of bias is included in the supplementary file.

Author	Country	Design	Setting	Intervention	Age		Gender (Female)		Sample Size		Follow up	Study Endpoint
					Withdraw	Maintenance	Withdraw	Maintenance	Withdraw	Maintenance		
Ahsan et al, 1999[9]	USA	RCT	Multicentre	3 months after transplantation	50 (20-71)	50 (18-74)	34%	45%	134	132	1 year	acute rejection episode or treatment failure within 1-year post-transplant
Albert et al, 1985[10]	Germany	RCT	Single Centre	3 to 6 months after transplantation	30 (10-51)	38 (10 to 51)	44%	32%	25	25	13 months	NS
Aswad et al, 1998[11]	USA	RCT	Single Centre	6 months after transplantation	NR	NR	NR	NR	11	10	NR	
Kramer et al, 2012[4]	USA	RCT	Multicentre	day 1 after transplantation	44 ± 12	43 ± 13	35%	40%	152	151	3 years	Mortality, Graft loss, Biopsy-proven acute rejection, NODAT, Infection, CMV infection, Malignancy, Cardiovascular events, SCr (μM), CrCl (mL/min)
Benfield et al, 2010[12]	USA	RCT	Multicentre	6 to 12 months after transplantation	11 ± 5	12 ± 6	44%	37%	73	59	3 years	Mortality, Graft loss, Acute rejection
Boletis et al, 2001[13]	Greece	RCT	Single Centre	6 months after transplantation	43 ± 11	38 ± 11	41%	19%	34	32	1 year	Mortality, Graft loss, Acute rejection, SCr (mg/dL)
Boots et al, 2002[7]	Netherlands	RCT	Multicentre	6 months after transplantation	54 ±14	48 ± 13	61%	35%	28	34	2.7 year	Mortality, Graft loss, Acute rejection, Biopsy-proven acute rejection, SCr (mg/dL), CrCl (mL/min), NODAT, Infection
Bouma et al, 1996[14]	Netherlands	RCT	Multicentre	1 year after transplantation	48 ± 13	54 ± 12	31%	31%	42	42	1 year	Mortality, Graft loss, Acute rejection, Biopsy-proven acute rejection, NODAT, Infection, Malignancy, Cardiovascular event, CrCl (mL/min)
Burke et al, 2000[8]	USA	RCT	Single Centre	3 months after transplantation	46.5	47.1	NR	NR	26	25	3 years	SCr (mg/dL), mortality, acute rejection
De Vecchi et al, 1986[15]	Italy	RCT	Single Centre	day 1 after transplantation	36 ± 12	36 ± 10	48%	35%	25	26	2 years	Mortality, Graft loss, Acute rejection, SCr (mg/dL)
del Castillo et al, 2005[16]	Spain	RCT	Multicentre	6 months after transplantation	47 ± 11	47 ± 11	53%	26%	70	72	1 year	Mortality, Graft loss, Acute rejection, SCr
DOMINOS Study 2012[17]	France	RCT	Multicentre	4 to 6 months after transplantation	51 ± 12	51 ± 10	36%	32%	110	112	6 months	Mortality, Graft loss, SCr, CrCl, eGFR
EVIDENCE Study 2014[18]	Italy	RCT	Multicentre	3 months after transplantation	48 ± 12	49 ± 13	32%	28%	68	71	9 months	Mortality, Graft loss, Biopsy-proven acute rejection, CrCl, eGFR
Farmer et al, 2006[19]	UK	RCT	Single Centre	1 year after transplantation	44 ± 15	45 ± 13	32%	40%	44	48	1 year	Biopsy-proven acute cellular rejection, SCr
FRANCIA Study 2007[13]	France	RCT	Multicentre	day 1 after transplantation	48 (19-65)	48 (17-65)	28%	35%	98	99	1 year	Mortality, Graft loss, Acute rejection, SCr
FREEDOM Study 2008[18]	USA	RCT	multicentre	7 days after transplantation	43 ± 13	47 ± 13	48%	41%	116	109	1 year	Mortality, Graft loss, Biopsy-proven acute rejection, NODAT, Infection, CMV infection
Gulanikar et al, 1991[17]	Canada	RCT	Multicentre	3 months after transplantation	39 ± 1	40 ± 1	35%	41%	260	263	5 years	Mortality, Graft loss, Biopsy-proven acute rejection, CrCl, eGFR
Höcker et al, 2009[18]	Germany	RCT	Multicentre	12 to 24 months after transplantation	10 ± 1	11 ± 1	35%	32%	23	17	2 years	Mortality, Graft loss, Acute rejection, Biopsy-proven acute rejection, Infection, CrCl
INFINITY Study 2013[19]	France	RCT	Multicentre	NR	NR	NR	NR	NR	131	131	6 months	Mortality, Graft loss, Acute rejection, SCr
Isoniemi et al, 1990[20]	Finland	RCT	Single Centre	10 weeks after transplantation	49 ± 13	47 ± 11	53%	38%	32	29	4 years	Mortality, Graft loss, Acute rejection, SCr
Jankowska-Gan et al, 2009[21]	USA	RCT	Single Centre	1 year after transplantation	NR	NR	36%	10%	32	10	3 years	Mortality, Graft loss, Acute rejection, SCr
Johnson et al, 1989[22]	UK	RCT	Single Centre	1 day after transplantation	NR	NR	NR	NR	376	182	7 years	Mortality, Graft loss, CMV infection
Kacar et al, 2004[23]	Turkey	RCT	Single Centre	2 years after transplantation	NR	NR	NR	NR	31	30	NR	Mortality, Graft loss, Acute rejection, SCr
Kim et al, 2002[24]	USA	RCT	Multicentre	4 days after transplantation	48	48	NR	NR	12	11	2 years	Mortality, Graft loss, acute rejection, NODAT
Kumar et al, 2005[25]	USA	RCT	Single Centre	7 days after transplantation	50 ± 13	54 ± 13	28%	28%	45	32	1 year	Mortality, Graft loss, acute rejection, NODAT
Laftavi et al, 2005[26]	USA	RCT	Single Centre	7 days after transplantation	50 ± 13	51 ± 12	35%	36%	32	28	1 year	Mortality, Graft loss, Acute rejection, SCr
Lebranchu et al, 1999[27]	Europe	RCT	Multicentre	3 months after transplantation	45 (18-69)	46 (18-71)	43%	41%	252	248	1 year	Mortality, Graft loss, Acute rejection, Biopsy-proven acute rejection, Infection, CrCl
Maiorca et, 1988[28]	Italy	RCT	Single Centre	6 months after transplantation	33 ± 10	35 ± 9	30%	29%	31	35	27 months	Mortality, Graft loss, acute rejection, NODAT
Matl et al, 2000[29]	Czech Republic	RCT	Single Centre	1 year after transplantation	50 ± 9	47 ± 13	45%	26%	46	42	1 year	Mortality, Graft loss, Acute rejection, SCr
Mericq et al, 2013[30]	Chile	RCT	Multicentre	6 days after transplantation	6 ±3	6 ±4	50%	42%	14	16	1 year	Mortality, Graft loss, Acute rejection
Montagnino et al, 2005[31]	Italy	RCT	Multicentre	7 days after transplantation	44 ± 10	46 ± 12	31%	38%	65	68	3 years	Mortality, Graft loss, Acute rejection, Biopsy-proven acute rejection, Infection, CrCl
Nagib et al, 2015[32]	Egypt	RCT	Single Centre	4 days after transplantation	5-62 years		24%	26%	214	214	66 months	Mortality, Graft loss, Biopsy-proven acute rejection, CrCl
Nematalla et al, 2007[33]	Egypt	RCT	Single Centre	4 days after transplantation	30 ± 11	29 ± 10	20%	36%	50	50	1 year	Mortality, Graft loss, Acute rejection, Biopsy-proven acute rejection, Infection, CrCl
Nott et al, 1985[34]	UK	RCT	Single Centre	1 day after transplantation	NR	NR	NR	NR	59	58	1 year	Mortality, Graft loss, Biopsy-proven acute rejection, CrCl
Park et al,1994[35]	Korea	RCT	Multicentre	3 months after transplantation	NR	NR	NR	NR	141	153	1 year	Mortality, Graft loss, Acute rejection, Biopsy-proven acute rejection, Infection, CrCl
Pelletier et al, 2006[36]	USA	RCT	Single Centre	at different time points after transplantation but >14 days	45 ± 14	45 ± 14	22%	31%	60	60	3 year	Mortality, Graft loss, Acute rejection, SCr, NODAT
Pisani et al, 2001[37]	Italy	RCT	Single Centre	6 months after transplantation	41	45	33%	30%	15	15	NR	Mortality, Graft loss, Acute rejection, SCr, NODAT, CMV infection
Ponticelli et al, 1997[38]	Italy	RCT	Multicentre	5 days after transplantation	41 ± 11	41 ± 11	39%	32%	115	117	9 years	Mortality, Graft loss, Acute rejection, Biopsy-proven acute rejection, Infection, CrCl
Ratcliffe et al, 1993[39]	UK	RCT	Single Centre	1 year after transplantation	48 ± 14	48 ± 14	35%	31%	49	51	1 year	Mortality, Graft loss, Acute rejection, CrCl
Sandrini et al, 2009[40]	Italy	RCT	Single Centre	5 days after transplantation	50 ± 11	50 ± 11	NR	NR	49	47	4 years	Mortality, Graft loss, Acute rejection, CrCl
Schulak et al, 1989[41]	USA	RCT	Single Centre	at different time points after transplantation but >14 days	44 ± 13	43 ± 12	50%	34%	32	35	2 year	Mortality, Graft loss, Acute rejection, CrCl
Smak Gregoor et al, 1999[42]	Netharlands	RCT	Multicentre	6 months after transplantation	52 (19-68)	51 (19-70)	32%	37%	76	73	18 months	Mortality, Graft loss, Biopsy-proven acute rejection, Infection, CrCl
Sola et al, 2002[43]	Spain	RCT	Single Centre	3 months after transplantation	NR	NR	NR	NR	46	46	2 year	Mortality, Graft loss, Acute rejection, CrCl
Stiller et al, 1983[44]	Canada	RCT	Multicentre	No steroids at any time	NR	NR	33%	36%	33	36	NR	Mortality, Graft loss, Acute rejection
THOMAS Study 2002[45]	Europe	RCT	Multicentre	3 months after transplantation	46	47	33%	38%	281	277	6 months	Mortality, Graft loss, Acute rejection, Biopsy-proven acute rejection, Infection, CrCl
Vincenti et al, 2003[46]	NR	RCT	Multicentre	5 days after transplantation	49 ± 11	49 ± 12	55%	28%	40	43	1 year	Mortality, Graft loss, Biopsy-proven acute rejection, Infection, CrCl
Woodle et al, 2005[47]	USA	RCT	Multicentre	8 days after transplantation	47 ± 12	47 ± 13	31%	36%	197	200	5 years	Mortality, Graft loss, Biopsy-proven acute rejection, Infection, CrCl
Zhu et al, 2008[48]	China	RCT	Single Centre	6 months after transplantation	44 (26-65)		NR	NR	45		2 year	Mortality, Graft loss, Acute rejection, Biopsy-proven acute rejection, Infection, CrCl
Werbel et al, 2021[49]	USA	Observational	Multicentre	NR	50 (42-56)	49 (42-55)	22%	24%	250	975	1 year	Mortality, Acute rejection, graft failure
Matas et al, 2019[50]	USA	Observational	Single Centre	Variable time > 14 days	56.3	51.6	43.3	37.9	8987		5 years	Mortality, Acute rejection, graft failure
Vock et al, 2020[51]	USA	Observational	Single Centre	Variable time > 14 days	54.8	52.7	NR	NR	169479		5 years	Mortality, Acute rejection, graft failure
Haller et al, 2017[52]	USA	observational	single Centre	NR	48 (15)		36%		5170		NR	Mortality, Acute rejection, graft failure
Stumf et al, 2024[53]	Germany	Observational	Multicentre	NR	53.5 ± 15.3	53.5 ± 15.3	35%	34%	111	135	5 years	Mortality, Acute rejection, graft failure
Woodle et al, 2021[54]	Canada	RCT	Multicentre	7 days after transplantation	46.5 (12.1)	46.3 (12.6)	31%	37%	191	194	5 years	Mortality, Graft loss, Acute rejection, Biopsy-proven acute rejection, Infection, CrCl
Dehucchi et al, 2011[55]	Chile	RCT	multicentre	6 months after transplantation	8.0±4.6	5.4±2.6	39%	48%	55	41	5 years	Mortality, Graft loss, Acute rejection, Biopsy-proven acute rejection, Infection, CrCl
Taber et al, 2017[56]	USA	Observational	Registry	NR	49.8 ± 12.7	49.5 ± 12.6	38.70%	38.60%	5565	5565	NR	Acute Rejection, Graft survival, patient survival
Andrada-Sierra et al, 2016[57]	Mexico	RCT	Single Centre	5 days after transplantation	23 ± 6	27 ± 11	35%	26%	37	34	1 year	Acute rejection
Sandwijk et al, 2018[58]	Amsterdam	RCT	Multicentre	6 months after transplantation	54.8 ± 14.6	57.5 ± 12.6	31.60%	32.40%	98	199	NR	Acute rejection
Lopez-Soler et al, 2017[59]	USA	Observational	Single Centre	NR	48.14 ± 13.5	43.96 ± 12.7	61.50%	55.40%	563	65	NR	Mortality, Acute rejection, graft failure
Zahir et al, 2019[60]	Saudi Arabia	Observational	Single Centre	5 days after transplantation	42.14 ± 16	39.56 ± 16	36%	54%	105	144	1 year	Acute rejection, Graft survival
Iwamoto et al, 2012[61]	Japan	Observational	Single Centre	NR	47 ± 12	46 ± 11	36.90%	33.30%	84	18	1 year	Acute rejection
Ueda et al, 2014[62]	USA	Observational	Multicentre	NR	51.8 ± 13.7	51.2 ± 13.4	36.40%	35.40%	363	509	4 years	Acute Rejection, Graft survival, patient survival

Table 1: Baseline characteristics of included studies.

Outcomes

Mortality: In the analysis of 28 studies, the Risk Ratio (RR) for mortality was 0.833 (95% CI 0.743, 0.934; p=0.002), indicating that patients in the Steroid Withdrawal (SW) group had a statistically significant 16.7% lower risk of mortality compared to those in the Steroid Continuation (SC) group. The Confidence Interval (CI) suggests a consistent benefit across most studies, and the moderate heterogeneity (I^2=41%) implies that the results are reasonably consistent. This suggests that withdrawing steroids does not negatively impact survival and may, in fact, improve it (Figure 2).

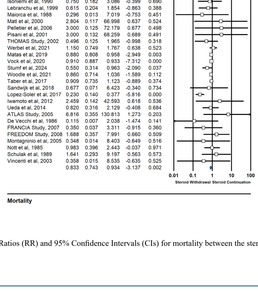
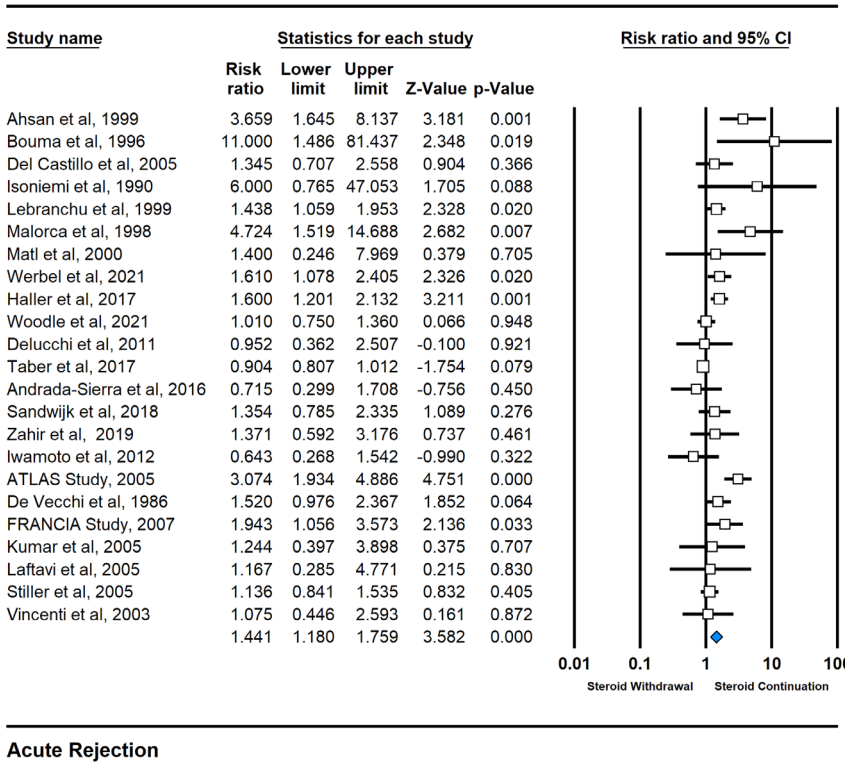


Figure 2: Forest plot of Mortality. Risk Ratios (RR) and 95% Confidence Intervals (CIs) for mortality between the steroid withdrawal and continuation groups.

Acute Rejection: In contrast, the analysis of 23 studies revealed that the RR for acute rejection was 1.441 (95% CI 1.180, 1.759; p=0.001), indicating that the SW group had a 44.1% higher risk of acute rejection than the SC group (Figure 3). The high heterogeneity (I^2=70%) suggests variability in the study outcomes, potentially influenced by differences in patient populations, follow-up durations, or immunosuppressive regimens. The increased risk of acute rejection with steroid withdrawal is a critical finding and suggests that, while steroid withdrawal may improve survival, it comes at the cost of a higher likelihood of acute rejection. A leave-one-out sensitivity analysis was performed to investigate heterogeneity, and the forest plot is included in the supplementary file.



Acute Rejection

Figure 3: Forest plot of acute rejection outcomes. Risk ratios (RR) and 95% confidence intervals (CIs) for acute rejection rates between groups.

Death-censored graft failure

For death-censored graft failure, the RR across the 20 studies was 0.980 (95% CI 0.939, 1.022; p=0.344), indicating no statistically significant difference between the SW and SC groups (Figure 4). The very low heterogeneity (I^2=0%) implies consistent findings across studies. This suggests that steroid withdrawal does not increase the risk of graft failure after accounting for patient deaths, indicating that the stability of the graft function is preserved regardless of whether steroids are continued or withdrawn.

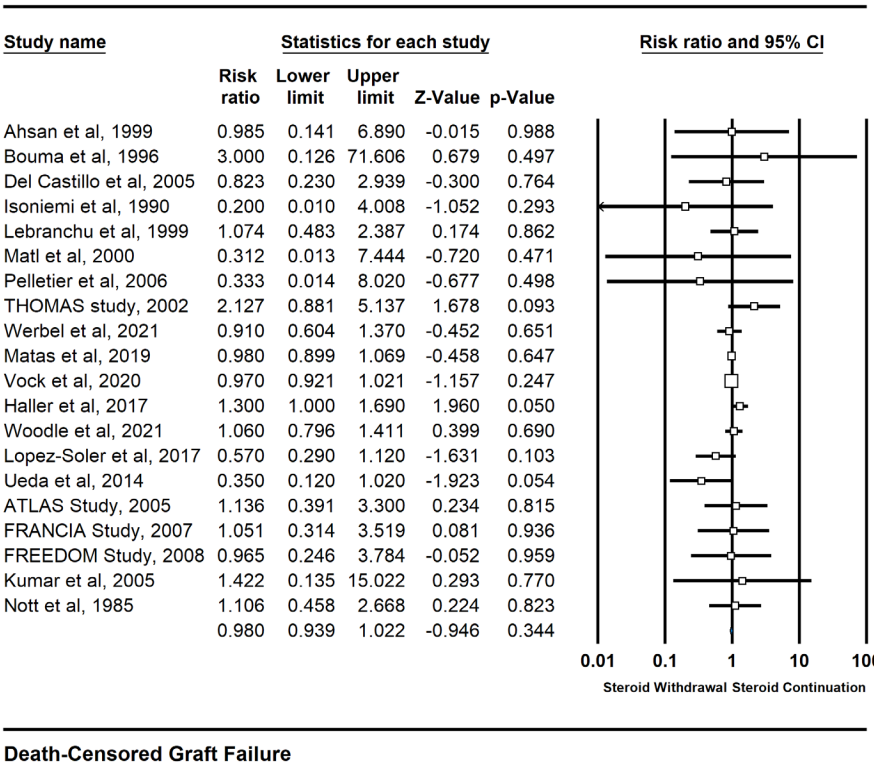


Figure 4: Forest plot of death-censored graft failure outcomes. Risk Ratios (RR) and 95% Confidence Intervals (CIs) for graft failure between groups.

New-onset diabetes:

Analysis of 16 studies showed an RR of 0.827 (95% CI 0.679, 1.006; p=0.058) for new-onset diabetes, suggesting a potential benefit of steroid withdrawal, with a 17.3% lower risk of diabetes in the SW group than in the SC group (Figure 5). Although this finding approached statistical significance, it did not reach the threshold ($p<0.05$). The low heterogeneity ($I^2=1.7\%$) supports the consistency of this outcome across the studies. The trend towards a reduced risk of diabetes highlights the possible benefit of avoiding the long-term metabolic side effects associated with steroid use.

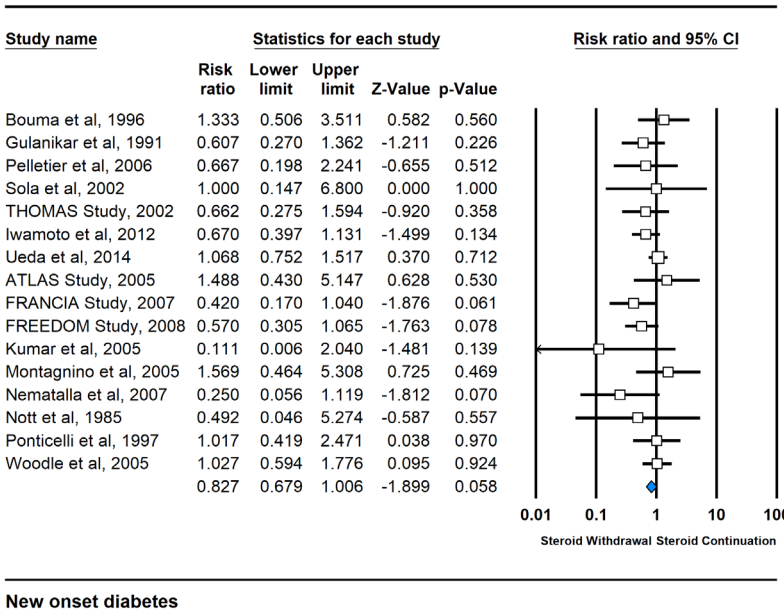


Figure 5: Forest plot of new-onset diabetes outcomes. Risk Ratios (RR) and 95% Confidence Intervals (CIs) for new-onset diabetes among the groups.

Infection:

Infection rates were assessed across 13 studies, with an RR of 0.988 (95% CI: 0.823, 1.185; p=0.895), showing no significant difference between the SW and SC groups. Negligible heterogeneity (I^2=0%) suggests highly consistent findings. This indicates that withdrawing steroids does not increase or decrease the risk of infection, which is a key concern for immunosuppression (Figure 6).

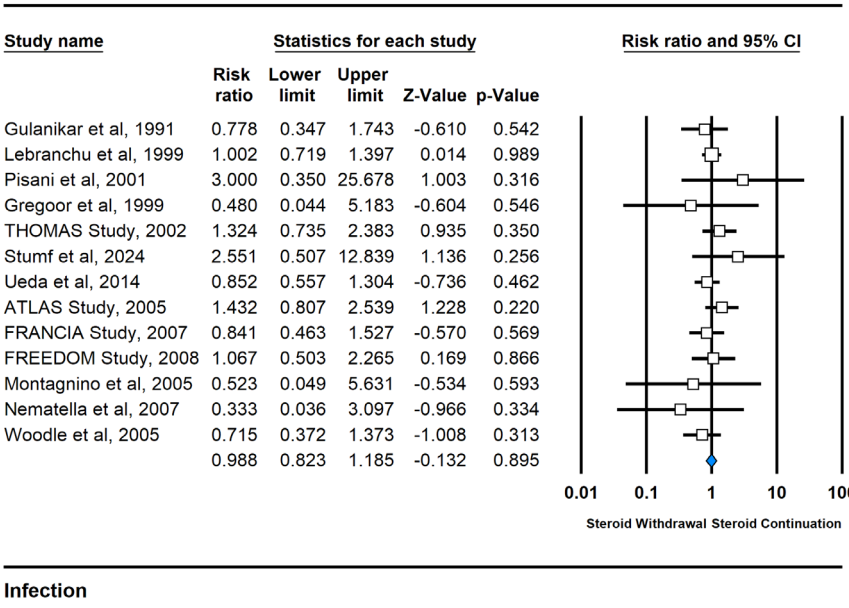


Figure 6: Forest plot of infection outcomes. Risk Ratios (RR) and 95% Confidence Intervals (CIs) for infection rates between groups.

Publication bias

Publication bias was assessed using funnel plots and Egger's test for all the outcomes. For survival (Figure 7a), the studies were fairly distributed, with an Egger intercept value of -0.305 (p=0.12), indicating no significant publication bias. In acute rejection (Figure 7b), a slight asymmetry was observed in the funnel plot, and the Egger intercept value was 1.56 (p=0.001), suggesting potential publication bias. For death-censored graft failure (Figure 7c), the studies were evenly distributed, with an Egger intercept of -0.04 (p=0.43), indicating no significant bias. New-onset diabetes (Figure 7d) showed no asymmetry, with an Egger intercept value of -0.73 (p=0.08). Similarly, for infection (Figure 7e), the studies were fairly distributed, and the Egger intercept value was -0.03 (p=0.46), indicating no evidence of publication bias.

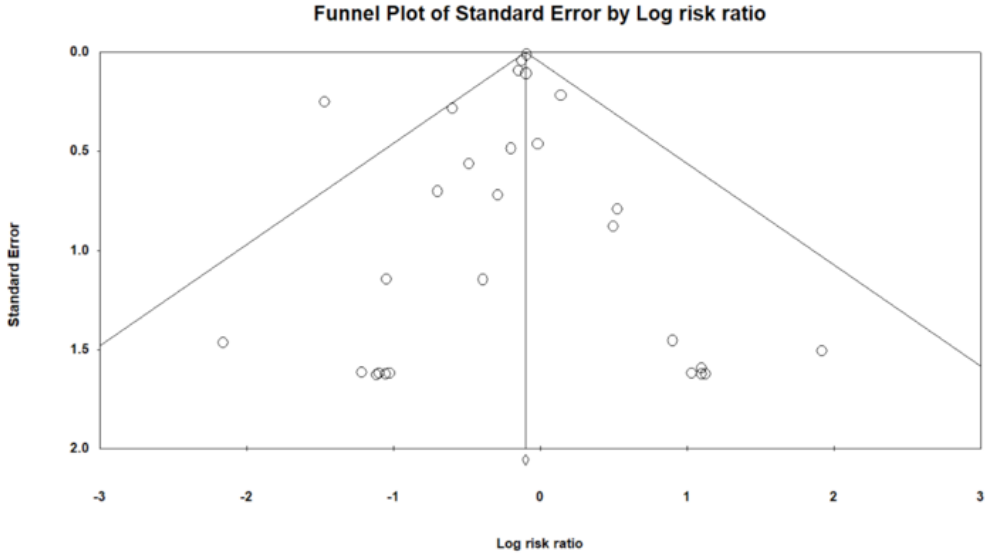


Figure 7a: Funnel plot for survival outcomes, showing no significant publication bias (Egger intercept: -0.305, p=0.12).

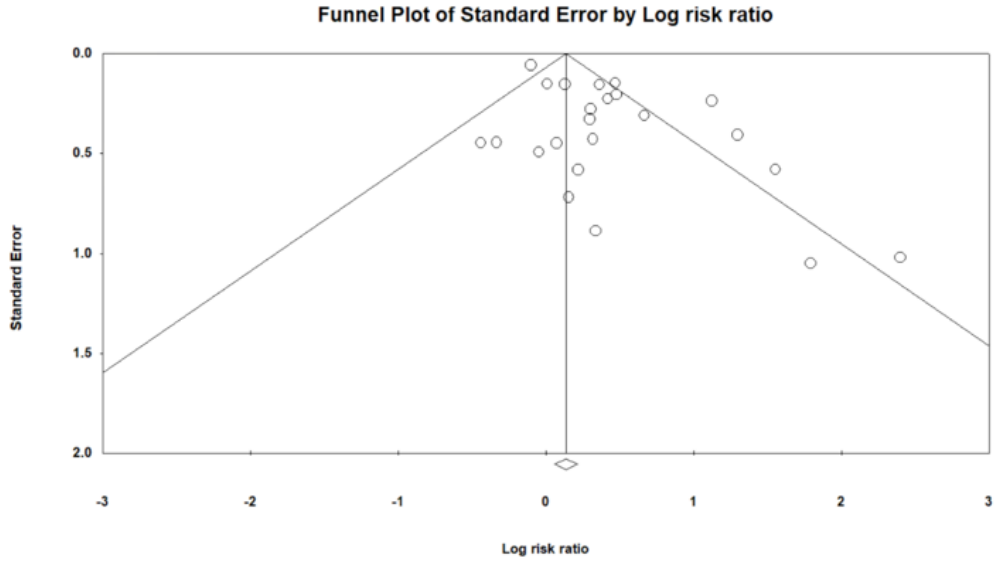


Figure 7b: Funnel plot for acute rejection outcomes, indicating potential publication bias (Egger intercept: 1.56, p=0.001).

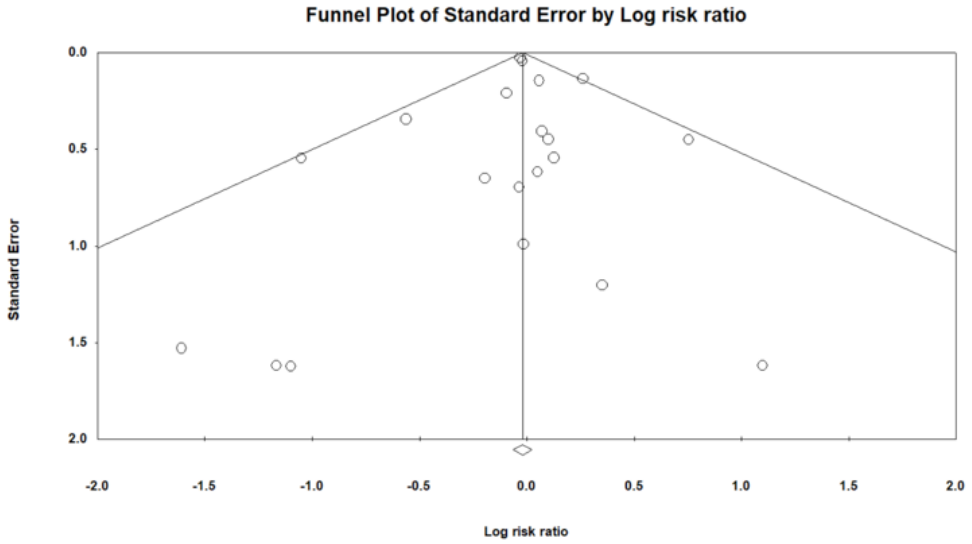


Figure 7c: Funnel plot for death-censored graft failure outcomes, showing no significant publication bias (Egger intercept: -0.04, p=0.43).

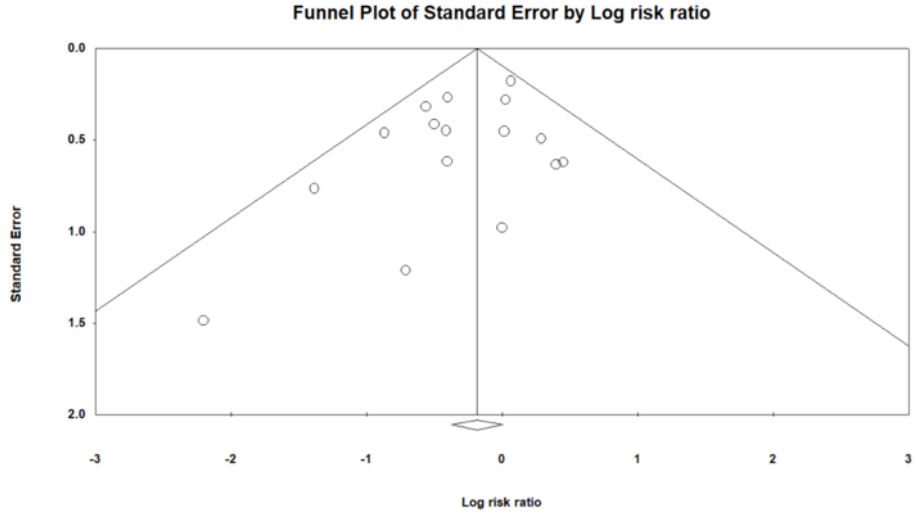


Figure 7d: Funnel plot for new-onset diabetes outcomes, showing no significant publication bias (Egger intercept: -0.73, p=0.08).

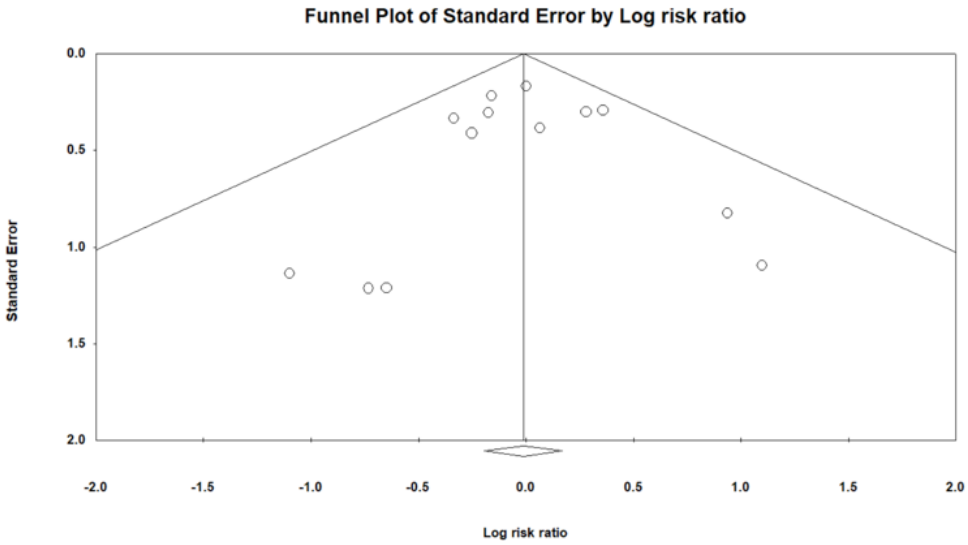


Figure 7e: Funnel plot for infection outcomes showing no significant publication bias (Egger intercept: -0.03, p=0.46).

Discussion

In kidney transplantation, steroid therapy plays a crucial role in immunosuppression, helping to decrease the likelihood of acute rejection and graft failure. Nevertheless, prolonged steroid use is linked to considerable negative effects, including metabolic issues such as diabetes, bone loss, and increased susceptibility to infections [84-87]. Consequently, there is growing attention to protocols for steroid withdrawal, which aim to reduce these adverse effects while preserving graft function and patient longevity. This meta-analysis seeks to compare the clinical outcomes of Steroid Withdrawal (SW) with Steroid Continuation (SC) in kidney transplant patients, emphasizing important endpoints like survival, acute rejection, graft failure, newly developed diabetes, and infection incidence.

This meta-analysis uncovers a nuanced balance between the benefits and risks of discontinuing steroids in kidney transplant patients. Those who stopped steroid use showed a decreased likelihood of developing diabetes, indicating that eliminating long-term steroid therapy may reduce metabolic complications often linked to extended immunosuppression. The consistency of this finding across studies, as evidenced by low heterogeneity, lends credibility to this potential advantage. However, the increased occurrence of acute rejection in patients who discontinued steroids is a significant concern. This higher rejection rate underscores the ongoing role of steroids in protecting the graft from immune-mediated harm, especially in the initial post-transplant period. Despite this risk, the rates of death-censored graft failure were statistically comparable between groups, suggesting that steroid withdrawal does not necessarily jeopardize long-term graft viability when patient deaths are not considered. Infection rates, a typical worry for immunosuppressed individuals, were not significantly different between groups, indicating that steroid withdrawal neither increased nor decreased infection risk. The low heterogeneity across studies reinforces the reliability of these observations.

After more than 20 years of implementing SW in kidney transplant procedures, identifying the most appropriate candidates for this approach remains problematic [88,89]. In the absence of standardized protocols, medical professionals continue to rely heavily on subjective assessments to evaluate individual risk factors and determine the necessity of ongoing steroid treatment [90,91]. While certain general risk indicators-such as heightened immune sensitization or the necessity for subsequent transplantation-suggest a need for more robust immunosuppressive therapy, these insights are primarily qualitative and hypothesis-based, lacking precise quantitative guidance. Furthermore, current research fails to address crucial clinical questions, such as establishing clear thresholds for these risk factors. This gap in knowledge is further emphasized by the inconsistent inclusion criteria used in the key trials that shaped current ESW practices, underscoring the necessity for more comprehensive, evidence-based guidelines [68,92,93].

Painter, et al. observed that prednisone is not directly responsible for the increase in body fat observed after transplantation [94]. However, it may play a role in hindering natural improvements in exercise capacity, potentially by restricting gains in muscle strength. The consistently low exercise capacity seen in all transplant recipients one year after surgery indicates that exercise training might be necessary to enhance physical function post-transplant. Research has also indicated that the responsiveness of

lymphocytes to cortisol could serve as an effective biomarker in identifying patients capable of maintaining steroid discontinuation [95-97].

Studies indicate that when given a 'no-risk' alternative, the majority of organ transplant recipients would prefer to stop taking steroids rather than other immunosuppressants [98,99]. Factors related to demographics could potentially predict prednisone-related side effects and guide decisions about steroid usage in this population. When developing protocols for future investigations on steroid discontinuation, researchers should consider the preferences of patients.

This comprehensive review and meta-analysis present several notable advantages. Primarily, it delivers an extensive evaluation of steroid discontinuation versus maintenance in kidney transplant patients, tackling a crucial clinical issue pertinent to long-term transplant results. Additionally, the incorporation of numerous studies from various populations and geographic areas enhances the applicability of the outcomes. The thorough search methodology, covering multiple major databases without language limitations, reduces the likelihood of overlooking relevant research and ensures a robust data collection. By concentrating on clinically meaningful endpoints such as survival, acute rejection, graft failure, new-onset diabetes, and infection, this study provides valuable, practical insights for medical professionals. The inclusion of both RCTs and observational studies improves the external validity of the results while upholding methodological quality through risk of bias evaluations. Lastly, sophisticated statistical methods, including random-effects modeling and sensitivity analysis, were utilized to address heterogeneity and confirm the stability of the findings, contributing to the overall credibility of the conclusions.

Several limitations exist in this systematic review and meta-analysis. Firstly, significant heterogeneity was noted in crucial outcomes, including acute rejection, potentially hindering the ability to draw consistent conclusions across diverse patient groups. Secondly, despite a thorough search strategy, the possibility of publication bias cannot be completely ruled out, especially for outcomes where funnel plots showed asymmetry. Thirdly, the lack of a standardized steroid withdrawal protocol presented a challenge, as studies varied in their approach, with some discontinuing steroids within months and others after a year. Fourthly, the diversity in immunosuppressive regimens, follow-up periods, and patient populations may have influenced the results, making direct study comparisons difficult. Lastly, the analysis relied on reported data, which could be subject to reporting bias or incompleteness, potentially impacting the accuracy of certain findings.

Future perspectives for this topic include the development of standardized protocols for steroid withdrawal in kidney transplant recipients, which would allow for more consistent comparisons across studies and provide clearer guidance for clinical practice. Further research should focus on identifying specific patient populations that may benefit most from steroid withdrawal, such as those with lower immunological risk, while balancing the risk of acute rejection. Additionally, long-term studies are needed to assess the impact of steroid withdrawal on graft survival and patient quality of life, especially concerning metabolic complications like diabetes. Incorporating patient preferences into study designs will also be essential, as personalizing immunosuppressive regimens based on both clinical and demographic factors may improve outcomes. Finally, the role of alternative immunosuppressive agents in mitigating the adverse effects of steroid withdrawal should be explored to create more comprehensive and patient-friendly treatment strategies.

Conclusion

This comprehensive systematic review and meta-analysis examines the effects of discontinuing steroids versus maintaining steroid therapy in kidney transplant patients. The findings reveal that while stopping steroids may decrease the likelihood of developing new-onset diabetes, it also increases the risk of acute rejection, emphasizing the importance of careful patient selection and vigilant monitoring. Although survival rates were better for those who do not continue steroid use, graft failure rates were comparable between both groups. These results highlight the challenge of weighing the advantages of reducing steroid-related side effects against the heightened risk of rejection, especially in immunologically high-risk patients. Additional studies should aim to establish standardized protocols for steroid withdrawal and identify specific patient groups that can safely stop steroid use while maintaining optimal long-term outcomes.

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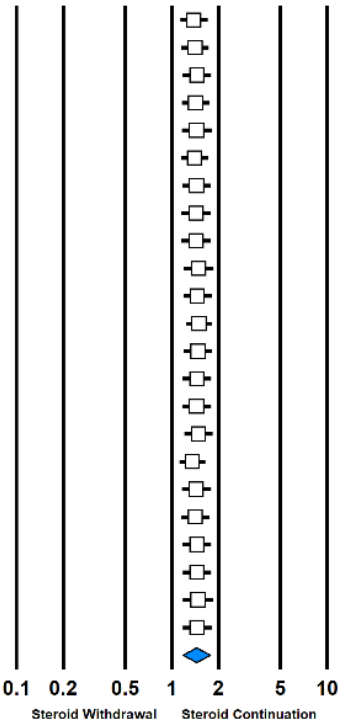
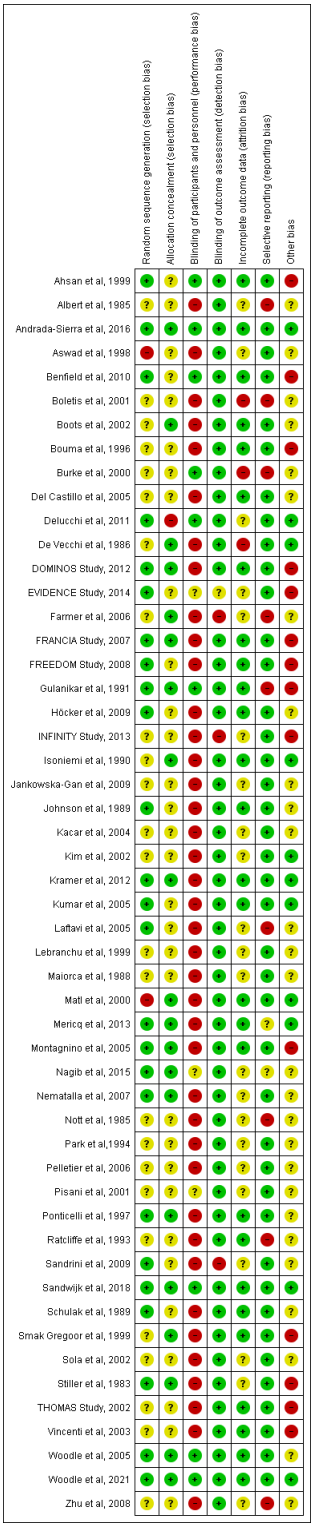
Supplemental Figure 1: leave one out analysis of acute rejection.

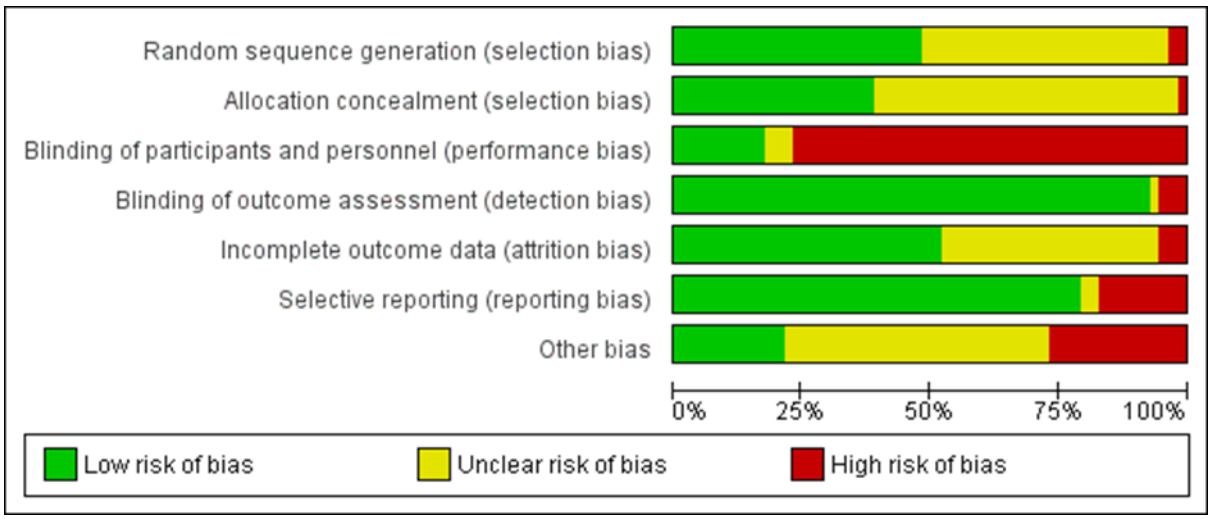
Study name	Statistics with study removed				
	Point	Lower limit	Upper limit	Z-Value	p-Value
Ahsan et al, 1999	1.387	1.141	1.686	3.280	0.001
Bouma et al, 1996	1.412	1.161	1.718	3.453	0.001
Del Castillo et al, 2005	1.447	1.176	1.781	3.497	0.000
Isoniemi et al, 1990	1.422	1.166	1.735	3.470	0.001
Lebranchu et al, 1999	1.445	1.167	1.789	3.379	0.001
Malorca et al, 1998	1.399	1.149	1.702	3.350	0.001
Matl et al, 2000	1.442	1.178	1.766	3.547	0.000
Werbel et al, 2021	1.431	1.162	1.763	3.367	0.001
Haller et al, 2017	1.431	1.159	1.766	3.337	0.001
Woodle et al, 2021	1.487	1.198	1.846	3.595	0.000
Delucchi et al, 2011	1.460	1.190	1.791	3.625	0.000
Taber et al, 2017	1.494	1.243	1.797	4.272	0.000
Andrada-Sierra et al, 2016	1.476	1.204	1.810	3.742	0.000
Sandwijk et al, 2018	1.448	1.175	1.784	3.479	0.001
Zahir et al, 2019	1.445	1.176	1.774	3.511	0.000
Iwamoto et al, 2012	1.481	1.208	1.814	3.785	0.000
ATLAS Study, 2005	1.357	1.127	1.635	3.225	0.001
De Vecchi et al, 1986	1.438	1.166	1.772	3.403	0.001
FRANCIA Study, 2007	1.419	1.157	1.740	3.356	0.001
Kumar et al, 2005	1.447	1.180	1.774	3.552	0.000
Laftavi et al, 2005	1.447	1.181	1.773	3.566	0.000
Stiller et al, 2005	1.474	1.186	1.831	3.503	0.000
Vincenti et al, 2003	1.457	1.186	1.788	3.591	0.000
	1.441	1.180	1.759	3.582	0.000



Acute Rejection

Supplemental Figure 2: Risk of bias summary and graph of randomized controlled trials.





Supplemental Table presenting the risk of bias assessment of observational studies using the Newcastle-Ottawa assessment Scale

Newcastle Ottawa Quality Assessment Scale									
Study Name	**Selection**				**Comparability**		**Outcome**		
	1	2	3	4	5	6	7	8	9
Werbel et al, 2021	*	*	*	*	*	*	*	*	*
Matas et al, 2019	*	*	*	*	*	-	*	*	*
Vock et al, 2020	*	*	*	*	*	*	*	-	*
Haller et al, 2017	*	*	*	*	*	-	*	-	*
Stumf et al, 2024	*	*	*	*	*	*	*	*	*
Taber et al, 2017	*	*	*	*	-	*	*	*	*
Lopez-Soler et al, 2017	*	*	*	*	*	-	*	*	*
Zahir et al, 2019	*	*	*	*	-	*	*	*	*
Iwamoto et al, 2012	*	*	*	-	*	-	*	*	*
Ueda et al, 2014	*	*	*	*	*	*	*	*	*

Newcastle-Ottawa Quality Assessment Scale			
Selection:	1	Representation of the intervention cohort	
	2	Selection of the non-intervention cohort	
	3	Has the correct intervention been utilized?	
	4	Outcome of Interest present at the start of study?	
Comparability:	5	Are the cohorts comparable based on the design or analysis: age, sex, and injury severity?	
	6	Are the cohorts comparable based on the design or analysis? Additional factors	
Outcome:	7	Was the outcome assessed?	
	8	Was the follow-up long enough for measured outcomes to occur?	
	9	Was the cohort follow-up long enough?	