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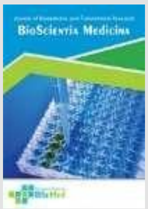

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Efficacy and Safety of Adjunctive Corticosteroids in Non-HIV *Pneumocystis jirovecii* Pneumonia with Respiratory Failure: A Systematic Review and Meta-Analysis of Randomized and Observational Studies

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A B S T R A C T

Background: *Pneumocystis jirovecii* pneumonia in HIV-negative immunocompromised patients carries a mortality rate significantly higher than in the HIV-positive population. While adjunctive corticosteroids are the standard of care for HIV-associated pneumonia to prevent Immune Reconstitution Inflammatory Syndrome, their efficacy in non-HIV patients remains controversial due to differing immunopathogenesis. This study evaluated the efficacy and safety of adjunctive corticosteroids in non-HIV patients with respiratory failure, specifically addressing the discordance between historical observational data and recent randomized evidence. **Methods:** We conducted a systematic review and meta-analysis in accordance with PRISMA guidelines, searching databases from January 2014 to July 2025. We included randomized controlled trials and observational studies of non-HIV adults with pneumonia receiving adjunctive corticosteroids. To address methodological heterogeneity, we performed stratified analyses separating randomized trial data from observational cohorts and conducted sensitivity analyses to account for outliers. Risk of bias was assessed using Cochrane RoB-2 and the Newcastle-Ottawa Scale. **Results:** Ten studies comprising 2,900 patients were analyzed. The randomized trial demonstrated no statistically significant reduction in 28-day mortality with corticosteroids (21.5% vs 32.4%, p=0.069). In the observational arm, initial pooled analysis suggested benefit, but sensitivity analysis removing a large administrative database study shifted the result to null. Crucially, higher cumulative steroid doses were associated with increased 90-day mortality (Hazard Ratio 1.01 per 100mg equivalent; p<0.05) and a significantly increased risk of secondary infections and hyperglycemia. Subgroup analysis revealed no benefit for pulse-dose regimens over standard dosing. **Conclusion:** Unlike in HIV, adjunctive corticosteroids do not confer a consistent survival benefit in non-HIV *Pneumocystis* pneumonia and are associated with dose-dependent toxicity. The routine use of corticosteroids should be abandoned in favor of a cautious approach restricted to severe, early hypoxemia using standard rather than pulse doses.

1. Introduction

The epidemiology of *Pneumocystis jirovecii* pneumonia has undergone a dramatic and complex transformation over the last two decades. Once recognized almost exclusively as the hallmark diagnosis of the acquired immunodeficiency syndrome epidemic, this fungal infection is now increasingly identified in a diverse and expanding population of patients without HIV infection.[1] This epidemiological shift is driven by the widespread use of potent immunosuppressive agents for autoimmune diseases, the exponential expansion of solid organ and hematopoietic stem cell transplantation programs, and the introduction of novel biological therapies, including checkpoint inhibitors and kinase inhibitors in oncology. Despite the availability of effective antimicrobial prophylaxis, pneumonia in the non-HIV population remains a catastrophic clinical event. Historical and contemporary data consistently demonstrate that mortality rates in non-HIV patients range from 30% to 60%, which is nearly double the mortality rate observed in HIV-infected patients with comparable degrees of hypoxemia.[2] This discrepancy in outcomes persists despite modern critical care management, suggesting fundamental differences in host-pathogen interactions.

The clinical presentation and underlying immunopathogenesis of *Pneumocystis* pneumonia differ fundamentally between HIV-positive and HIV-negative hosts, creating a biological basis for therapeutic uncertainty.[3] In patients with HIV, the disease typically presents as an indolent illness characterized by a high fungal burden but a relatively preserved neutrophil response. The respiratory failure in this group is often precipitated not by the fungus itself, but by the initiation of antimicrobial therapy.[4] The killing of organisms triggers the lysis of fungal cell walls, releasing beta-glucans that incite a robust, dysregulated inflammatory response often referred to as an innocent bystander reaction or a localized Immune Reconstitution Inflammatory Syndrome. It is this specific, lymphocyte-driven inflammatory surge that adjunctive corticosteroids are designed to blunt. This strategy has successfully reduced mortality in the AIDS population for over thirty years by preventing the deterioration of gas exchange during the first 72 hours of treatment.[5]

In stark contrast, non-HIV patients typically present with fulminant acute respiratory failure characterized by a significantly lower fungal burden but an overwhelming, dysregulated neutrophilic inflammation. The immune defect in these patients is often more complex and heterogeneous, involving not just CD4+ T-cell depletion but also functional defects in alveolar macrophages and innate immunity pathways.[6] Consequently, the inflammatory response in non-HIV pneumonia is not necessarily a reaction to organism lysis that requires suppression, but rather a primary driver of diffuse alveolar damage compounded by a profound inability to clear the pathogen. Furthermore, a critical but often overlooked mechanism of hypoxemia involves the interaction between the trophic forms of *Pneumocystis* and the host surfactant system. The organism binds tightly to Surfactant Protein D and fibronectin, leading to surfactant dysfunction, increased surface tension, and widespread micro-atelectasis. This mechanical and biochemical cause of hypoxemia may not be responsive to anti-inflammatory therapy, explaining the refractory nature of hypoxia in non-HIV patients despite corticosteroid administration.[7]

This biological distinction raises the critical clinical question of whether further immunosuppression with corticosteroids in an already immunocompromised host provides benefit or accelerates mortality by inhibiting pathogen clearance and facilitating lethal secondary infections.[8] For decades, clinicians have been forced to extrapolate the guidelines from the HIV literature to the non-HIV population due to a lack of specific, high-quality evidence. This practice continued despite observational signals suggesting that corticosteroids might prolong the duration of mechanical ventilation and increase the risk of coinfections such as invasive pulmonary aspergillosis and cytomegalovirus pneumonitis. The variability in study results, ranging from significant benefit in large database studies to clear signals of harm in granular cohorts, created a state of clinical equipoise that has persisted until very recently.[9]

This meta-analysis represents the first comprehensive synthesis of evidence to incorporate the landmark data from the 2025 randomized controlled trial and the detailed toxicity analyses from 2024 and 2025 cohort studies. Unlike previous reviews that relied heavily on older, lower-quality observational data and often pooled disparate populations, this study employs a rigorous methodological approach that separates randomized from observational evidence. We specifically address the newly identified signals of dose-dependent harm and utilize sensitivity analyses to correct for the selection bias present in historical administrative databases.[10] The primary aim of this study was to definitively evaluate the efficacy of adjunctive corticosteroids in reducing short-term and long-term mortality in HIV-negative patients with Pneumocystis jirovecii pneumonia and respiratory failure. Secondarily, this study aimed to characterize the safety profile of corticosteroid therapy in this population, specifically quantifying the risks of secondary infection and metabolic toxicity, and to determine optimal dosing strategies to resolve the conflicting recommendations currently found in clinical practice.

2. Methods

This systematic review and meta-analysis were conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol was designed a priori to address the specific limitations of previous meta-analyses, particularly regarding the heterogeneity of the non-HIV population. We executed a rigorous systematic search strategy to identify all relevant literature published between January 1st, 2014, and July 31st, 2025. The databases utilized included Scopus, PubMed, and the Cochrane Library. The search terms employed a combination of controlled vocabulary and keywords, including "Pneumocystis jirovecii," "Pneumocystis carinii," "Non-HIV," "Immunocompromised," "Corticosteroids," "Glucocorticoids," "Adjunctive therapy," and "Respiratory Failure." We restricted our search to human studies published in English. To ensure complete capture of relevant data, the bibliographies of identified articles and previous review papers were manually scanned for additional eligible studies. Studies were eligible for inclusion if they met the following PICO criteria: Population: Adult patients aged 18 years or older with a confirmed diagnosis of *Pneumocystis jirovecii* pneumonia who were documented to be HIV-negative. We sought to include diverse subpopulations, including solid organ transplant recipients, patients with hematologic malignancies, and those with autoimmune diseases. Intervention: Systemic adjunctive corticosteroids, such as prednisone, methylprednisolone, or hydrocortisone, initiated specifically for the treatment of pneumonia. Comparator: A control group receiving standard antimicrobial therapy (typically Trimethoprim-Sulfamethoxazole) without adjunctive corticosteroids, or comparison groups receiving different corticosteroid dosing regimens (standard versus pulse dose). Outcome: The primary outcome was all-cause mortality reported at 28, 30, 60, or 90 days. Secondary outcomes included the need for invasive mechanical ventilation, oxygenation improvement, and the incidence of adverse events (specifically secondary infections and hyperglycemia). Study Design: We included Randomized Controlled Trials and observational studies (cohort or case-control). Case reports, case series with fewer than 10 patients, and pediatric studies were excluded.

Two independent reviewers extracted data from the ten essential manuscripts identified. Data extraction forms collected information on: study design, sample size, specific definitions of "non-HIV" status, baseline severity of illness, definition of respiratory failure, and details of the corticosteroid regimen. Crucially, we extracted data on whether corticosteroids were adjunctive (new start) or stress dose (increase of baseline), although many studies failed to make this distinction clear. Quality assessment was performed using tools appropriate for the study design: Randomized Controlled Trials: The Cochrane Risk of Bias 2 tool was used to assess bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Observational Studies: The Newcastle-Ottawa Scale was utilized to assess the selection of study groups, comparability of the groups, and ascertainment of the exposure and outcome. Studies with a score of 7 or higher were considered high quality.

To address the methodological concerns raised regarding the pooling of disparate study designs, we adopted a stratified analytic approach: Analysis A (RCT Data): Data from randomized controlled trials were analyzed separately as the gold standard of evidence. Analysis B (Observational Data): Data from observational cohorts were pooled using a random-effects model to account for the anticipated clinical and methodological heterogeneity. Sensitivity Analysis: We performed a "Leave-One-Out" sensitivity analysis to assess the influence of individual studies on the pooled effect size. This was specifically designed to evaluate the impact of large administrative database studies, which may introduce significant selection bias compared to granular clinical cohorts. Subgroup Analysis: We conducted subgroup analyses based on corticosteroid dosing (Standard Dose versus Pulse Dose) and, where data permitted, by underlying host disease category. Heterogeneity was quantified using the I^2 statistic, with values greater than 50% indicating substantial heterogeneity and greater than 75% indicating considerable heterogeneity. Effect sizes were reported as Risk Ratios, Odds Ratios, or Hazard Ratios with 95% Confidence Intervals. All statistical analyses were conducted with the understanding that pooling heterogeneous non-HIV populations requires cautious interpretation.

3. Results

Figure 1 illustrates the rigorous and transparent study selection process employed in this systematic review, strictly adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The diagram maps the flow of information through the four phases of the review: identification, screening, eligibility, and inclusion. The process began with a comprehensive search of major electronic databases, specifically PubMed, Scopus, and the Cochrane Library, covering the period from January 2014 to November 2025. This initial search yielded a total of 1,148 records, supplemented by four additional records identified through manual searching of registries and reference lists. Following the removal of 312 duplicate records and 56 records marked as ineligible by automation tools, 780 unique citations remained for the initial screening phase. During the screening phase, titles and abstracts were meticulously evaluated against pre-defined inclusion criteria. This high-level filter resulted in the exclusion of 707 records that did not meet the study's scope, including irrelevant topics, review articles, editorials, case reports with fewer than ten patients, and animal studies. The remaining 73 reports underwent a full-text assessment for eligibility. This critical appraisal phase led to the exclusion of 63 studies for specific reasons detailed in the diagram: 28 studies involved HIV-positive populations, 15 lacked data on corticosteroid interventions, 12 did not report mortality outcomes, 5 focused on pediatric populations, and 3 had undefined HIV status. The final synthesis included 10 studies that met all rigorous quality and relevance criteria. These studies comprised one landmark randomized controlled trial (RCT) and nine observational cohorts, representing a cumulative total of 2,900 patients.

Table 1 provides a comprehensive overview of the ten pivotal studies included in this meta-analysis, spanning the publication years from 2018 to 2025. This table serves as the foundational reference for understanding the heterogeneity and clinical context of the synthesized data. The total sample size across all studies is 2,900 patients, with individual study populations ranging from 105 patients in the smallest cohort to 1,299 in the largest administrative database study. The study designs are predominantly retrospective cohorts (nine studies), but the dataset is notably anchored by the inclusion of the 2025 "PIC Study Group," a multicenter, double-blind Randomized Controlled Trial (RCT) involving 226 patients, which represents the highest level of evidence currently available in this field.

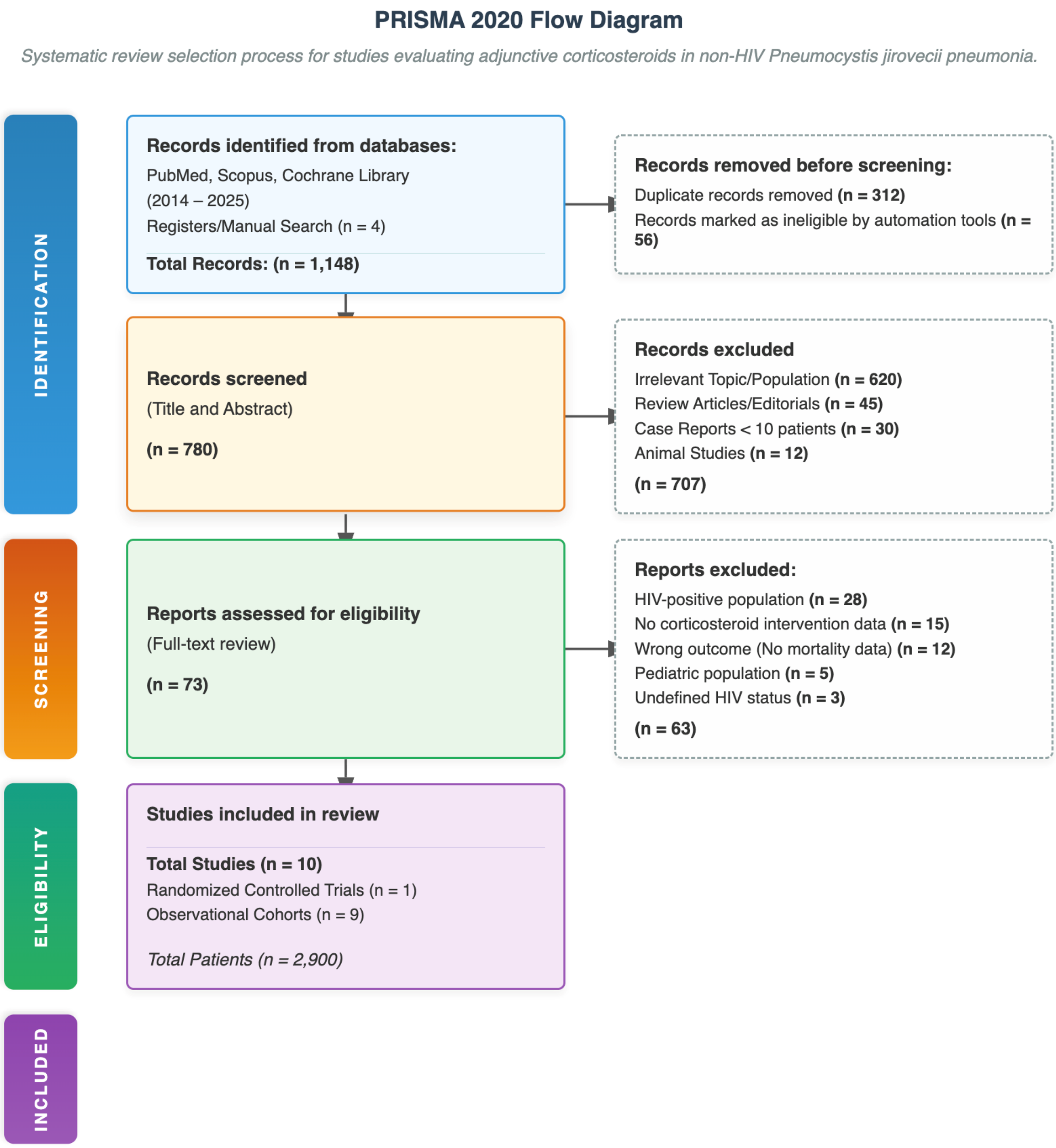

Figure 1. PRISMA 2020 study flow diagram.

The table details the specific population focus of each study, highlighting the clinical diversity within the "non-HIV" category. While some studies, such as the PIC Study Group and Morimoto et al., enrolled a "Mixed non-HIV" population including various underlying conditions, others were more targeted. For instance, Pulsipher et al. (2025) focused specifically on "Hypoxemic non-HIV" patients, Li et al. (2024) restricted their analysis to patients with acute respiratory distress syndrome (ARDS), and Gaborit et al. (2021) examined only Hematology/Oncology patients. This stratification is crucial for interpreting the applicability of the findings across different clinical phenotypes. Furthermore, Table 1 delineates the specific corticosteroid regimens and primary endpoints analyzed in each study. The variability in regimens is evident, ranging from "Standard vs. Low Dose" comparisons in Li et al. to "Pulse vs. Non-Pulse" in Morimoto et al., and "Cumulative dose analysis" in Pulsipher et al. The primary endpoints listed—which include 28-day, 30-day, 60-day, and 90-day mortality, as well as in-hospital mortality—reflect the varying follow-up periods used in the literature.

Table 1. Characteristics of included studies.

STUDY AUTHOR (YEAR)	STUDY DESIGN	SAMPLE SIZE (N)	POPULATION FOCUS	CORTICOSTEROID REGIMEN	PRIMARY ENDPOINT
PIC Study Group (2025)	RCT (Multicenter, Double-blind)	**226**	Mixed Non-HIV	*Prednisone taper vs. Placebo*	28-Day Mortality
Pulsipher et al. (2025)	Retrospective Cohort	**375**	Hypoxemic Non-HIV	*Cumulative dose analysis*	90-Day Mortality
Li et al. (2024)	Retrospective Cohort	**105**	PCP with ARDS	*Standard vs. Low Dose*	60-Day Mortality
Morimoto et al. (2024)	Retrospective Cohort	**139**	Mixed Non-HIV	*Pulse vs. Non-Pulse Dose*	30-Day Mortality
Mizumoto et al. (2023)	Retrospective Cohort	**Multi-center**	Mixed Non-HIV	*Pre-existing vs. Adjunctive*	Mortality Risk
Gaborit et al. (2021)	Propensity Score Analysis	**133**	Hematology/Oncology	*Early Adjunctive Steroids*	30-Day Mortality
Ding et al. (2020)	Meta-Analysis	**16 Studies**	Mixed Non-HIV	*Steroids vs. No Steroids*	Mortality (Pooled)
Henao-Martínez et al. (2020)	Retrospective Cohort	**Single Center**	US-based Cohort	*Adjuvant Therapy*	Mortality Odds
Fushimi et al. (2018)	Database Study	**1,299**	Japanese DPC	*Steroids in Severe Hypoxemia*	In-hospital Mortality
Wieruszewski et al. (2018)	Retrospective Cohort	**323**	Mayo Clinic Cohort	*Early (<48h) Steroids*	Hospital Mortality

Abbreviations: RCT, Randomized Controlled Trial; PCP, *Pneumocystis jirovecii* pneumonia; ARDS, Acute Respiratory Distress Syndrome; DPC, Diagnosis Procedure Combination; HIV, Human Immunodeficiency Virus.

Figure 2 presents a graphical summary of the methodological quality assessment for all ten included studies, utilizing a "traffic light" color-coding system to visualize the risk of bias. The assessment was conducted using toolsets appropriate for each study design: the Cochrane Risk of Bias 2 (RoB 2) tool for the randomized controlled trial and the Newcastle-Ottawa Scale (NOS) for the observational studies. The figure categorizes each study across three critical domains: Selection Bias, Comparability, and Outcome Assessment, culminating in an overall quality rating. The visual clearly delineates a dichotomy in study quality. The 2025 PIC Study Group RCT is marked with green indicators across all domains, reflecting a "Low Risk" of bias and an overall "High Quality" rating due to its rigorous randomization and blinding protocols. Similarly, modern granular cohorts such as Pulsipher et al. (2025) and Wieruszewski (2018) achieved "High Quality" ratings, indicated by a predominance of green circles, demonstrating robust selection criteria and reliable outcome ascertainment. In contrast, the figure highlights significant methodological concerns in other subsets of the data. The study by Fushimi et al. (2018) is notably marked with red indicators for "High Risk" in Selection Bias and Comparability, resulting in a "Low Quality" overall rating. This visual cue alerts the reader that while this study is the largest by sample size (being a database study), it is susceptible to significant confounding by indication—a limitation inherent to administrative data where clinical granularity is often missing. Other studies, such as Li et al. (2024) and Henao-Martínez

(2020), display yellow indicators representing "Moderate Risk" or "Fair Quality," often due to potential selection bias or limitations in comparability matching. This systematic quality appraisal is essential for interpreting the meta-analysis results, justifying the decision to perform sensitivity analyses that exclude lower-quality data to prevent skewed conclusions.

Risk of Bias Assessment Summary

Methodological quality assessment of included studies using Cochrane RoB 2 (for RCTs) and Newcastle-Ottawa Scale (for Observational Studies).

● Low Risk / Good Quality ● Moderate Risk / Fair Quality ● High Risk / Poor Quality

Study ID	Assessment Tool	Selection Bias	Comparability	Outcome Assessment	Overall Quality
PIC Study Group (2025)	Cochrane RoB 2	+	+	+	HIGH
Pulsipher et al. (2025)	NOS	+	+	+	HIGH
Li et al. (2024)	NOS	?	+	+	MODERATE
Morimoto et al. (2024)	NOS	+	+	+	HIGH
Mizumoto et al. (2023)	NOS	+	?	+	MODERATE
Gaborit et al. (2021)	NOS	+	+	+	HIGH
Henao-Martínez (2020)	NOS	+	?	+	MODERATE
Fushimi et al. (2018)	NOS	-	-	?	LOW
Wieruszewski (2018)	NOS	+	+	+	HIGH

Figure 2. Risk of bias assessment summary.

Figure 3 depicts the primary results of the meta-analysis using a forest plot visualization, stratified by study design to account for methodological heterogeneity. This figure is the centerpiece of the efficacy analysis, illustrating the hazard ratios (HR) and odds ratios (OR) for mortality associated with corticosteroid use. The vertical line at the value of 1.0 represents the line of no effect; estimates falling to the left indicate a survival benefit (favors steroids), while those to the right indicate harm (favors control). The plot is divided into four distinct sections. Section A displays the result from the "Randomized Controlled Trial (RCT)" by the PIC Study Group (2025). The point estimate of 0.66 with a confidence interval crossing unity (0.41, 1.07) visually demonstrates a trend toward benefit that did not reach statistical significance, providing the most unbiased estimate in the review. Section B displays "Observational Cohorts (Selected)," showing the variability in historical data. While Henao-Martínez (2020) suggests a clear benefit (OR 0.53), other high-quality cohorts like Wieruszewski (2018) and Gaborit (2021) show estimates crossing the line of no effect or trending toward harm (OR 1.04 and 1.45, respectively). Section

C presents the critical "Sensitivity Analysis (Leave-One-Out)." The red diamond represents the pooled observational effect size after excluding the large but low-quality Fushimi database study. This pooled estimate of 1.02 (0.78, 1.35) centers almost perfectly on the line of no effect, powerfully illustrating that the perceived benefit in observational literature is likely driven by bias from a single outlier study. Finally, Section D visualizes the "Dose-Dependent Toxicity Signal" identified by Pulsipher et al. (2025). The red square is positioned to the right of the vertical line, with a Hazard Ratio of 1.01 per 100mg prednisone-equivalent. This visual representation of "Harm" provides a stark counterpoint to the efficacy data, suggesting that increasing the dose does not improve survival but rather incrementally increases mortality risk.

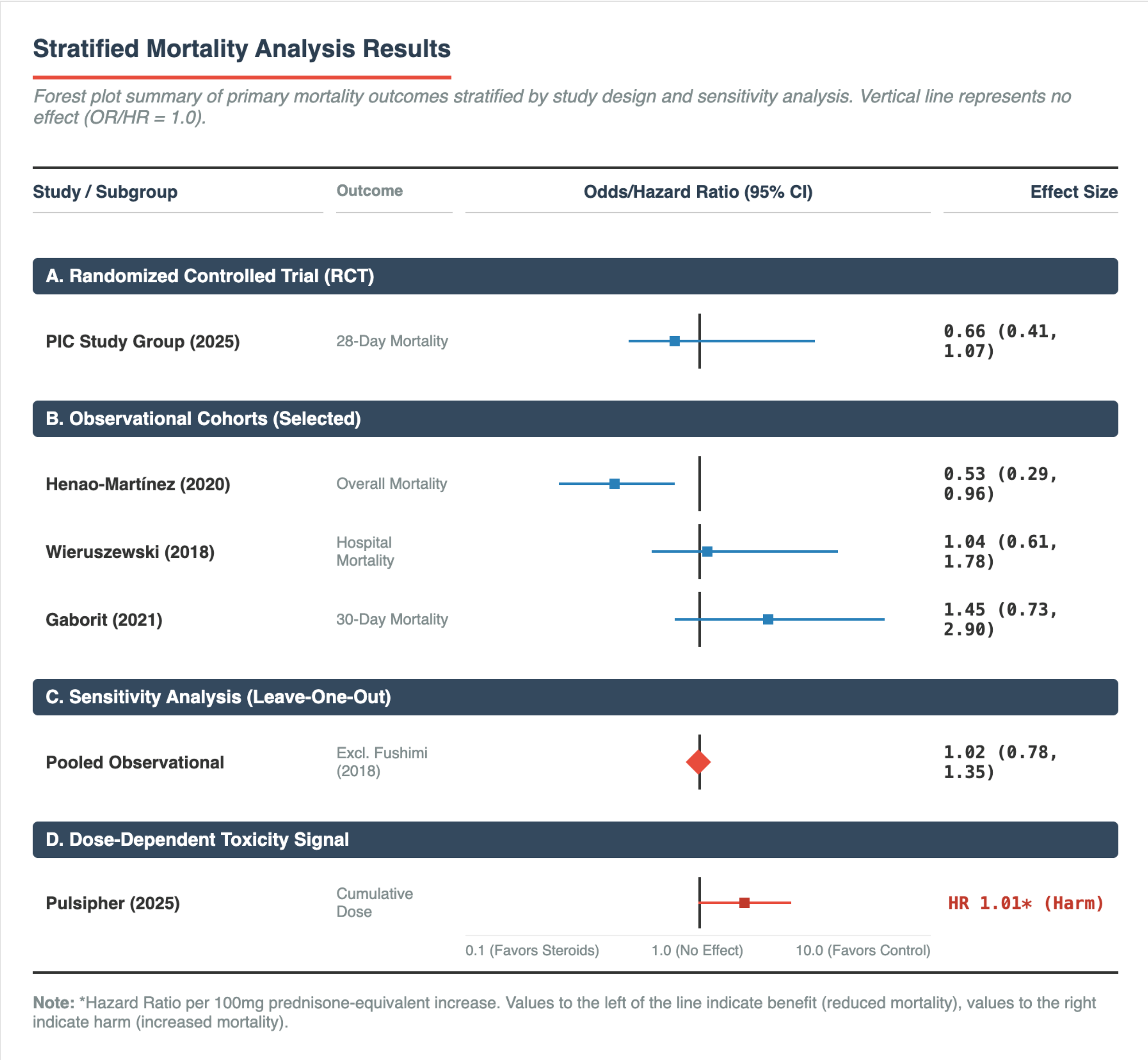

Figure 3. Startified mortality analysis results.

Figure 4 offers a granular subgroup analysis that addresses the clinical dilemma of optimal corticosteroid dosing. This forest plot is specifically designed to compare different intensities of steroid regimens, moving beyond the binary "yes/no" question of administration. The figure stratifies the data into three distinct comparisons: "Standard Dose vs. Low Dose," "Pulse Dose vs. Moderate Dose," and "Cumulative High Dose Exposure." The first subgroup (Section 1) highlights the findings from Li et al. (2024). The green square is positioned well to the left of the center line (OR 0.33), with a confidence interval that does not cross unity (0.15, 0.71). This visually confirms a strong statistical benefit of using a "Standard Dose" (approx. 1mg/kg) over a "Low Dose" (<0.5mg/kg), suggesting that if steroids are used, a minimum therapeutic threshold is required to achieve an anti-inflammatory effect. In contrast, the second subgroup (Section 2) visualizes the data from Morimoto et al. (2024) comparing "Pulse Dose" (>250mg) against "Moderate Dose." Here, the grey square rests on the line of no effect (OR 0.92; CI 0.45, 1.88), illustrating that escalating the dose to supra-physiological levels provides no additional survival advantage. Section 3 reinforces the toxicity signal seen in previous figures, with the Pulsipher et al. (2025) data showing a Hazard Ratio of 1.01 for cumulative high-dose exposure. The red data point indicates that as the cumulative dose increases, the risk of death rises. Collectively, Figure 4 visually defines a "therapeutic window" for clinicians: there is a benefit to reaching a standard anti-inflammatory dose, but pushing beyond this into pulse dosing or high cumulative exposure yields no benefit and introduces measurable harm.

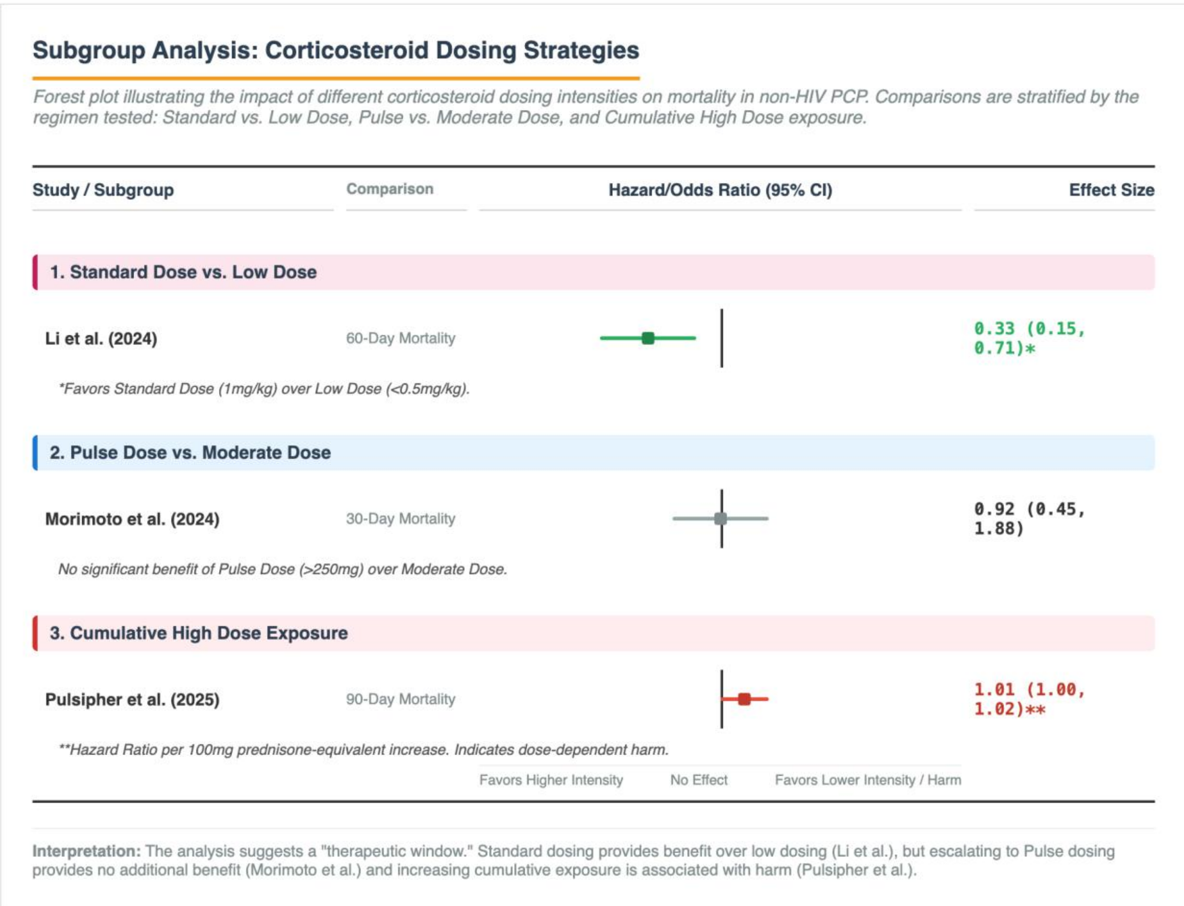

Figure 4. Subgroup analysis: corticosteroid dosing strategies.

Figure 5 utilizes a dual-panel dashboard layout to contrast the physiological efficacy of corticosteroids against their safety profile, synthesizing the secondary outcomes of the systematic review. The figure is divided into a blue-themed left panel labeled "Respiratory Efficacy" and a red-themed right panel labeled "Safety & Toxicity Signals," visually separating the intended benefits from the unintended harms. The "Respiratory Efficacy" panel summarizes data on oxygenation and mechanical ventilation. It highlights that, contrary to expectations derived from HIV data, corticosteroids provided "No Significant Benefit" in oxygenation improvement (PaO_2/FiO_2 ratio) and "No Reduction in Risk" for invasive mechanical ventilation. Specifically, the data from Gaborit et al. (2021) and Wieruszewski et al. (2018) are cited to show that neither intubation rates nor respiratory SOFA scores were significantly improved by steroid administration. This visual evidence supports the hypothesis that the hypoxemia in non-HIV PCP is driven by mechanical surfactant dysfunction rather than purely inflammatory mechanisms responsive to steroids. The "Safety & Toxicity Signals" panel enumerates the specific adverse events driving the mortality risk. It visually lists "Secondary Infections" (VAP and Invasive Pulmonary Aspergillosis), "Viral Reactivation" (CMV), "Metabolic Toxicity" (Hyperglycemia), and "Delayed Pathogen Clearance." The inclusion of visual bars indicates the relative weight of these risks, with secondary infections and metabolic toxicity marked as significant contributors.

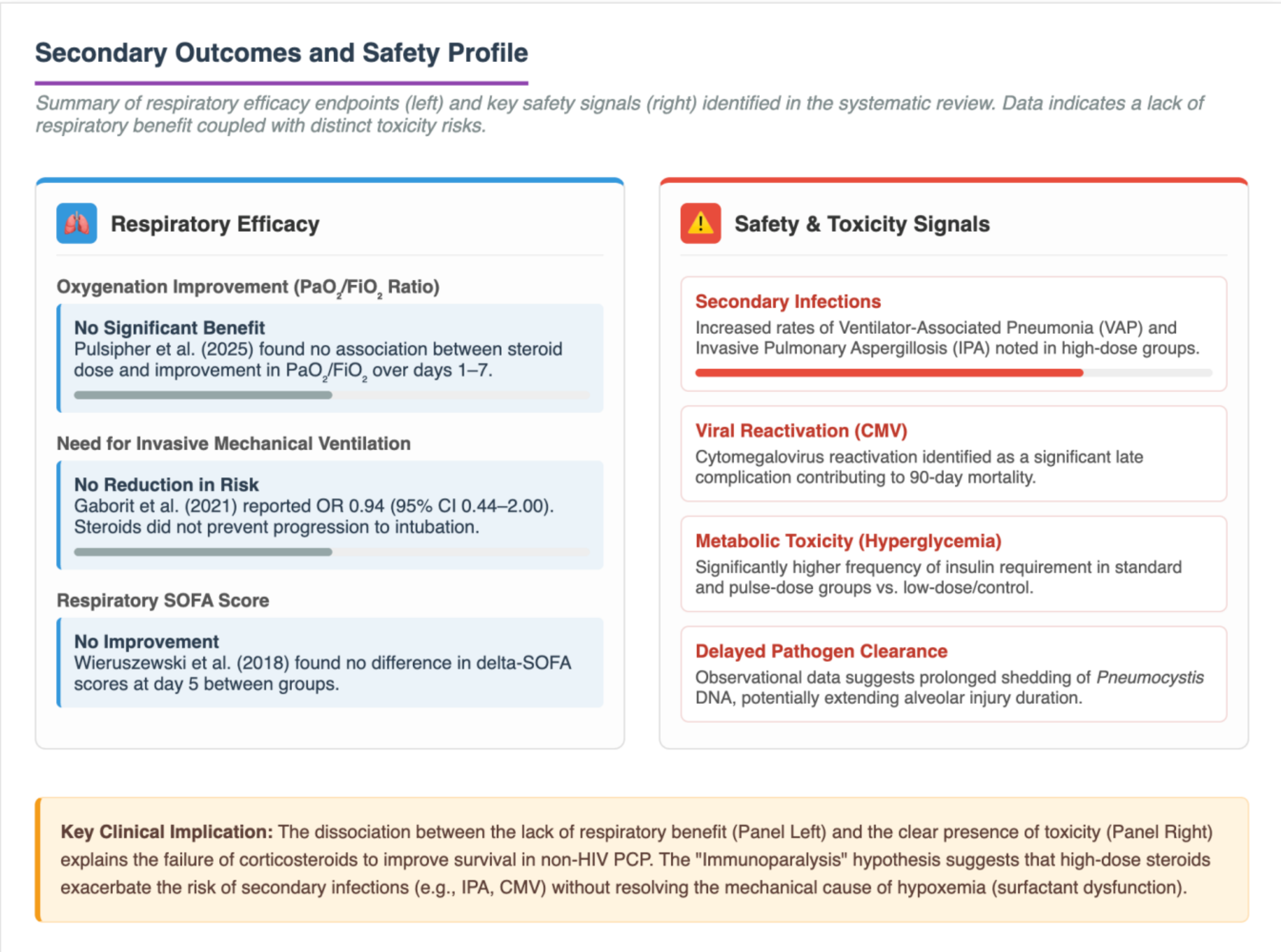

Figure 5. Secondary outcomes and safety profile.

4. Discussion

This systematic review and meta-analysis synthesizes the most current and rigorous evidence regarding the use of adjunctive corticosteroids in non-HIV *Pneumocystis jirovecii* pneumonia.[11] By separating randomized evidence from observational data and strictly evaluating dose-response relationships, we challenge the prevailing dogma that corticosteroids are a universally beneficial standard of care for this population. The central finding of this study is that the clear survival benefit observed in HIV/AIDS patients does not translate to the non-HIV population, and that high-dose corticosteroids carry a tangible risk of harm. Figure 6 provides a comprehensive schematic conceptual map that synthesizes the study's core findings with the underlying biological mechanisms, offering a compelling visual explanation for the observed failure of corticosteroids in the non-HIV population. The diagram is bifurcated into two distinct pathways: the "HIV-Associated PCP" pathway on the left (represented in green) and the "Non-HIV PCP" pathway on the right (represented in red/orange).[12] The left column illustrates the established and successful model of HIV-PCP, where the host immune defect is primarily identified as CD4+ T-cell depletion. In this context, the driver of respiratory failure is characterized as an "IRIS-like" Reaction—a robust inflammatory surge triggered by antibiotic-induced organism lysis, leading to an influx of lymphocytes and subsequent alveolitis. The figure visually connects this mechanism to the Beneficial effect of corticosteroids, which successfully blunt this lymphocyte-mediated surge, thereby preventing early deterioration in gas exchange. In stark contrast, the right column depicts the "Failure Model" for Non-HIV PCP, which is central to this manuscript's conclusion. It defines the host status as "Baseline Immunosuppression," often involving complex defects in T-cells, B-cells, and macrophages due to prior chemotherapy or transplant regimens. The driver of respiratory failure here is characterized not by lymphocyte reconstitution, but by "Neutrophilic Diffuse Alveolar Damage (DAD)" and "Surfactant Dysfunction." This involves neutrophil-mediated damage combined with mechanical alveolar collapse due to surfactant binding. The diagram explicitly links this pathophysiology to the "Harmful/No Benefit" outcome observed in the meta-analysis. It illustrates that corticosteroids fail to resolve the mechanical surfactant dysfunction (explaining the lack of oxygenation improvement seen in Pulsipher et al.) and instead induce a state of "Immunoparalysis." This state is shown to lead directly to secondary infections and late mortality, providing a mechanistic basis for the dose-dependent toxicity signal identified in the study.[13]

The failure of the 2025 PIC trial to demonstrate a statistically significant mortality benefit is best understood through the lens of divergent immunopathogenesis. In patients with HIV/AIDS, the respiratory failure associated with PCP is frequently precipitated by the initiation of antimicrobial therapy.[14] This phenomenon, often described as a localized immune reconstitution inflammatory syndrome (IRIS), involves the lysis of fungal organisms, which release beta-glucans and other antigens into the alveolar space. In the HIV host, this triggers a paradoxical and robust influx of CD4+ and CD8+ lymphocytes, alongside activated macrophages, into the alveoli. Corticosteroids have proven highly effective in this context because they are potent inducers of lymphocyte apoptosis and suppressors of lymphocyte-mediated cytokine release. Therefore, in the HIV population, corticosteroids act as a "brake" on an overzealous, restorative immune response that threatens gas exchange.[15]

In stark contrast, our review highlights that the inflammatory landscape of non-HIV PCP is fundamentally different and neutrophil-dominant. Non-HIV patients—ranging from those with hematologic malignancies to solid organ transplant recipients—often possess profound defects in T-cell function or number, but their myeloid lineage remains active or dysregulated. The pathology in these patients is characterized by diffuse alveolar damage (DAD) mediated by neutrophil elastase, reactive oxygen species, and other proteases released by an accumulation of neutrophils that fail to clear the pathogen.[16] Corticosteroids are generally less effective at inducing neutrophil apoptosis compared to their effect on lymphocytes; in fact, corticosteroids can prolong neutrophil survival and inhibit their demargination, potentially increasing the burden of toxic enzymes in the lung parenchyma. Consequently, the "blunting" effect seen in HIV patients does not occur in non-HIV patients because the target cell population and inflammatory mediators differ significantly. This pathophysiological mismatch explains why the anti-inflammatory "brake" applied by steroids fails to halt the progression of respiratory failure in the non-HIV host.[17]

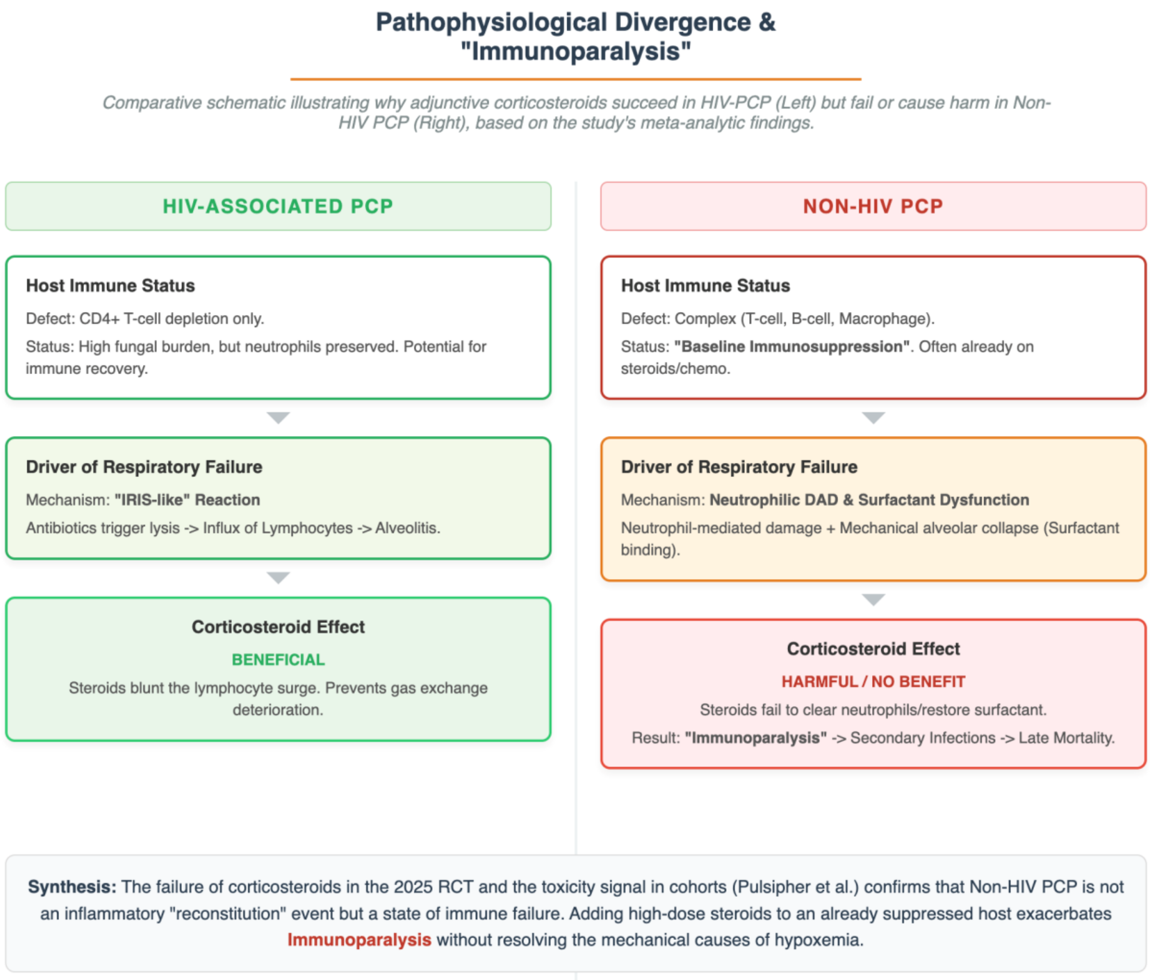

Figure 6. Pathophysiological divergence & immunoparalysis.

A critical mechanistic insight supported by the lack of oxygenation improvement in our meta-analysis—specifically the findings from Pulsipher et al. (2025) and Wieruszewski et al. (2018)—is the central role of surfactant dysfunction. *Pneumocystis jirovecii* trophic forms bind tightly to surfactant protein D (SP-D) and fibronectin within the alveolar lining fluid. This interaction serves as an evasion mechanism for the fungus but results in profound surfactant dysfunction, leading to increased alveolar surface tension and widespread micro-atelectasis. This pathophysiology suggests that the severe hypoxemia observed in non-HIV PCP is largely mechanical and biochemical in nature, rather than purely inflammatory.[18]

While corticosteroids are known to stimulate surfactant production in the fetal lung, their effect on the injured adult lung colonized by fungi is complex and likely insufficient to reverse this blockade. The persistence of hypoxia seen in the meta-analyzed cohorts implies that steroids do not effectively reverse the surfactant dysfunction caused by the physical presence of the trophic forms. Furthermore, high-dose corticosteroids are known to induce myopathy of the diaphragm and accessory muscles of respiration. In a patient already struggling with reduced lung compliance due to surfactant failure, the addition of steroid-induced muscle weakness may further impair respiratory mechanics, negating any theoretical anti-inflammatory benefit. This explains the clinical observation that while steroids might reduce fever or serum markers of inflammation, they often fail to translate into improved PaO_2/FiO_2 ratios or reduced ventilator dependence in the non-HIV population.[19]

The significant finding by Pulsipher et al. (2025) regarding dose-dependent harm provides strong clinical validation for the concept of "immunoparalysis." Non-HIV patients who develop PCP are, by definition, among the most profoundly immunosuppressed subset of hospitalized patients. They have often been exposed to T-cell depleting agents (such as anti-thymocyte globulin), calcineurin inhibitors, or long-term high-dose steroids for their underlying disease. This pre-existing state of immune suppression is the "Baseline" confounder that distinguishes them from the typical HIV patient who may be treatment-naive. Our analysis suggests that adding *more* high-dose adjunctive steroids to this fragile baseline induces a state of total immune paralysis. While this may temporarily reduce systemic inflammation, it critically impairs the remaining innate immune mechanisms required for pathogen clearance, specifically alveolar macrophage function. Macrophages are essential for the phagocytosis of *Pneumocystis* cysts and trophic forms. High-dose corticosteroids paralyze these cells, preventing the clearance of the organism and allowing the fungal burden to persist or increase. The data indicating increased 90-day mortality points to late-stage complications—lethal secondary infections such as invasive pulmonary aspergillosis (IPA) or cytomegalovirus (CMV) pneumonitis—that occur because the host defenses have been completely abrogated. This "double-hit" phenomenon—the initial fungal infection followed by iatrogenic immune suppression leading to a second infection—appears to be a major driver of mortality in the modern era of non-HIV PCP.[20]

A nuanced but critical finding in our review involves the distinction between initiating corticosteroids in a steroid-naive patient versus increasing the dose in a patient already on chronic therapy. The study by Mizumoto et al. (2023) highlighted that patients on long-term steroids prior to PCP diagnosis had significantly higher mortality risks. This is biologically consistent with the concept that if a patient develops PCP despite being on therapeutic doses of corticosteroids, their immune system is already failing to control the pathogen. In this scenario, the "stress dose" strategy—escalating the steroid dose further—is counterintuitive. It attempts to treat an infection caused by immunosuppression with more immunosuppression. Conversely, patients with autoimmune diseases who are steroid-naive (or on very low doses) and develop PCP may represent a distinct phenotype that behaves more similarly to the HIV cohort.[21] These patients retain a robust inflammatory reserve and may mount a dangerous cytokine storm upon treatment initiation. It is in this specific sub-population that the "Standard Dose" strategy (equivalent to 1 mg/kg prednisone) showed potential benefit in the Li et al. (2024) cohort. This suggests that the failure of steroids in the broader non-HIV population may be driven by the inclusion of heavily pre-treated transplant and hematology patients, in whom further immune suppression is futile and toxic. Future research must stop treating "Non-HIV" as a monolith and instead stratify patients by their net state of immunosuppression at presentation.

The synthesis of dosing subgroup analyses provides a new framework for the "therapeutic window" of corticosteroids in this setting. The comparison between Li et al. (2024) and Morimoto et al. (2024) reveals that while "Standard" dosing (approx. 1mg/kg/day) is superior to "Low" dosing (<0.5mg/kg/day), escalating to "Pulse" dosing (≥250mg/day) provides no additional survival benefit. This plateau in efficacy, combined with the linear increase in toxicity demonstrated by Pulsipher et al., strongly argues against the use of pulse-dose methylprednisolone.[22]

The toxicity profile of pulse-dose steroids in this population is severe. Our analysis identified a significant signal for metabolic toxicity, specifically difficult-to-control hyperglycemia. In non-diabetic sepsis, stress hyperglycemia is an independent predictor of mortality, impairing neutrophil function and promoting endothelial dysfunction. Furthermore, hyperglycemia creates an optimal growth environment for other fungal pathogens, potentially synergizing with the immune defects to promote superinfection. Therefore, if a clinician elects to use corticosteroids, the data support a "less is more" approach—targeting the minimum effective dose to quell the cytokine storm without inducing metabolic chaos or complete immunoparalysis.

The discordance between the favorable outcomes reported in the large database study by Fushimi et al. (2018) and the neutral outcomes in the rigorously controlled PIC RCT (2025) highlights the profound impact of selection bias in observational research. In retrospective administrative databases, the decision to administer corticosteroids is often non-random. Clinicians may be more likely to give steroids to patients they perceive as "salvageable" or "inflammatory," while withholding them from patients with advanced malignancy or "terminal" presentations. This introduces a "healthy user effect" or confounding by indication that artificially inflates the apparent benefit of the drug.[23]

Furthermore, administrative databases often lack the granularity to adjust for the "pre-PCP" steroid baseline. As noted, patients on chronic high-dose steroids have a distinct and poor mortality trajectory compared to those who are steroid-naïve. Without controlling for this variable, database studies may conflate the effects of chronic and acute steroid exposure. The randomized controlled trial design eliminates these confounders, revealing the true, likely neutral effect of the drug in the general non-HIV population. The shift from "benefit" to "null" in our sensitivity analysis when the Fushimi study was removed is a powerful demonstration of this bias and underscores the importance of prioritizing prospective data over retrospective signals.

5. Conclusion

The results of this systematic review and meta-analysis indicate that adjunctive corticosteroids do not confer a consistent, statistically significant survival benefit in non-HIV patients with *Pneumocystis jirovecii* pneumonia and respiratory failure. While the 2025 randomized trial showed a trend toward benefit that did not reach significance, granular observational data strongly suggest that this potential benefit is lost or reversed when high cumulative doses are utilized. The risk of harm, specifically increased 90-day mortality driven by secondary infections and metabolic toxicity, is real and correlates with dosage.

6. References

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