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List of Abbreviations:

CI – Confidence interval

HFNC – Heated high-flow nasal cannula

HIV – Human Immunodeficiency Virus

HR – Hazard Ratio

ICU – Intensive Care Unit

IPTW – Inverse Probability of Treatment Weighting

MSM – Marginal Structural Model

MV – Mechanical Ventilation

NC - Nasal Cannula

NIV – Non-Invasive Ventilation

OR – Odds Ratio

Abstract

Background: Adjunctive corticosteroids improve outcomes in HIV-associated Pneumocystis jirovecii pneumonia (PCP), but their role in non-HIV patients is uncertain. Prior evidence has largely been limited to binary treatment groups and has rarely accounted for daily or cumulative dose effects.

Research Question: What is the dose–response relationship between adjunctive corticosteroids and outcomes in non-HIV immunocompromised adults with PCP requiring supplemental oxygen?

Methods: We conducted a multicenter retrospective cohort analysis of 375 non-HIV immunocompromised adults with proven or probable PCP hospitalized between 2019–2025. All patients were hypoxemic at treatment initiation. Corticosteroid exposure was modeled as a continuous, cumulative time-varying dose over 21 days using marginal structural models with inverse probability of treatment weighting to adjust for baseline covariates and time-varying illness severity.

Results: Of 375 patients, 351 (93.6%) received corticosteroids. The most common etiologies of immunosuppression were hematologic malignancy (30%), solid tumors on chemotherapy (30%), autoimmune disease (17%), and solid organ transplantation (14%); 56% required ICU admission and 44% died within 90 days. Greater cumulative steroid dose was associated with increased risk of 90-day mortality (weighted HR 1.01 per 100 mg prednisone-equivalent, 95% CI 1.00–1.02, p=0.006). Steroid exposure was not associated with risk of intubation (HR 0.99, 95% CI 0.97–1.02) or faster liberation from advanced respiratory support (HR 1.00, 95% CI 0.98–1.02).

Interpretation: In non-HIV PCP with hypoxemia, higher cumulative corticosteroid exposure was not associated with improved respiratory outcomes and was linked to increased mortality. Use of doses exceeding trial-tested regimens should be approached with caution.

Pneumocystis jirovecii Pneumonia (PCP) is an opportunistic fungal infection that rose to prominence during the Human Immunodeficiency Virus (HIV) epidemic.[1] With the advent of highly active antiretroviral therapy (HAART), the incidence of HIV-associated PCP has declined, and the epidemiologic burden has shifted toward non-HIV immunocompromised populations in high-income countries.[2-4] Despite this transition, treatment paradigms remain largely extrapolated from studies in HIV-positive cohorts, raising concern about their applicability to immunologically distinct populations. Non-HIV patients with PCP experience higher mortality despite a lower organism burden, a paradox thought to reflect an intensified and dysregulated host inflammatory response amid a less reversible underlying disease process.[5-7]

Modulation of the inflammatory response with adjunctive corticosteroids became the subject of extensive investigation in HIV-associated PCP in the 1990's, with multiple randomized trials demonstrating a mortality benefit in patients with moderate to severe hypoxemia.[8-12] More recently, corticosteroids have also shown promise in acute respiratory distress syndrome (ARDS), further reinforcing use in severe pulmonary inflammation.[13] As a result, adjunctive steroids are frequently administered in non-HIV PCP. Small retrospective studies and meta-analyses have yielded inconsistent findings: some suggest possible benefit in patients with respiratory failure while other demonstrate no improvement or even potential harm.[14-19] Importantly, dosing strategies in these studies have been highly heterogeneous—ranging from HIV-derived tapers to pulse methylprednisolone—and frequently reported as simple binary exposure without detail on daily or cumulative dose.

Most recently, a multicenter randomized trial provided the first high-quality evidence in non-HIV PCP.[20] While the study did not achieve its primary endpoint of reducing 28-day mortality, adjunctive corticosteroids were associated with lower rates of intubation and a reduced

90-day mortality. This much-needed trial offers critical insight into the binary use of adjunctive steroids but, by design, was unable to address the impact of variable dosing strategies.

A critical knowledge gap thus persists: the relationship between corticosteroid dose and outcomes in non-HIV PCP. Clarifying this dose–response is essential to guide rational prescribing—striking the balance between beneficial modulation of inflammation and avoidance of steroid-associated harms. To address this, we conducted a multicenter cohort study of hypoxemic, non-HIV immunocompromised adults with PCP, modeling corticosteroid exposure as a continuous, cumulative, time-varying dose and applying marginal structural models with inverse probability of treatment weighting to address time-dependent confounding.

Study Design and Methods

This study was approved by the Mayo Clinic institutional review board (ID: 67 24-005981) with a waiver of informed consent given its retrospective design. Adult patients (≥18 years) hospitalized between January 2019 and February 2025 at multiple sites within a single health system were screened for inclusion if they had either an ICD diagnostic code for Pneumocystis jirovecii pneumonia (PCP) or a positive *P. jirovecii* PCR from sputum or bronchoalveolar lavage (BAL). All candidate records underwent manual investigator chart review to confirm the clinical diagnosis. Eligible patients were required to have proven or probable PCP per the European Organization for Research and Treatment of Cancer/ Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) definitions and to be hypoxemic (requiring supplemental oxygen) at treatment initiation (e-Figure 1).[21]

Proven PCP was defined as microscopic identification of the organism in sputum, BAL, or lung biopsy. Probable PCP required an immunocompromising condition plus characteristic imaging findings with either β-D-glucan (BDG) >80 pg/mL or a positive PCR assay. Our health

system uses a PCR platform targeting a single-copy gene to improve specificity for infection over colonization.[22,23] If the treating team documented that a positive PCR reflected colonization rather than infection, the patient was excluded, and this adjudication was not overridden. Other exclusions included: patients with a treatment course started outside our system (incomplete data), repeat episodes (only the index episode analyzed), and two patients who underwent transplantation during PCP treatment (where corticosteroid use was protocol-driven for transplant rather than PCP).

After eligibility confirmation, data were abstracted by manual chart review into a Research Electronic Data Capture (REDCap) database.[24] Collected variables included demographics, comorbidities, etiology of immunosuppression, hospital/ICU course, respiratory support, and outcomes. Corticosteroid exposure prior to PCP therapy (agent, dose, duration) was recorded. "Chronic" use was defined as >14 consecutive days of systemic steroids before PCP therapy; administration within 5 days before treatment start was also captured. Time zero was defined as the initiation of anti-Pneumocystis therapy.

To capture dynamic illness severity, we documented the daily highest level of oxygen support (room air, nasal cannula, high-flow nasal cannula (HFNC), non-invasive ventilation (NIV), invasive mechanical ventilation (MV), extra corporeal membrane oxygenation (ECMO)) and the highest FiO_2 sustained for ≥2 hours each day. Patients discharged before day 21 were coded as room air (FiO_2 0.21) to preserve the continuity of time-varying covariates. This design allowed incorporation of evolving severity into time-updated models and reduced misclassification due to rapid clinical deterioration. Corticosteroid exposure was quantified as the cumulative absolute prednisone-equivalent dose (mg) administered during the 21-day follow-up period, truncated at the time of death or day 21, whichever occurred first, consistent with

prior HIV-associated and non-HIV PCP studies. The primary outcome was 90-day all-cause mortality from the initiation of anti-Pneumocystis therapy. Secondary outcomes included 30-day all-cause mortality, the need for new intubation among patients who were not intubated at treatment start, and liberation from advanced respiratory support, defined as transition from HFNC, NIV, MV, or ECMO to nasal cannula or room air with at least 72 hours of continuous stability without re-escalation in oxygen support. In addition, we prespecified subgroup analyses to further examine heterogeneity of effects. These included evaluation of 90-day mortality stratified by the underlying etiology of immunosuppression (solid organ transplant, hematologic malignancy, autoimmune disease, or solid tumor on chemotherapy), as well as analyses restricted to ICU patients who were intubated at baseline, in whom we modeled both 90-day mortality and time to successful extubation. An additional subgroup analysis was done on patients who were not receiving chronic steroids.

For visualization purposes, we also generated Kaplan–Meier survival curves and cause-specific cumulative incidence plots. These figures were produced for the entire cohort and for the ICU subgroup to illustrate unadjusted associations with mortality and liberation from mechanical ventilation. Because these plots are descriptive and not weighted, they should be interpreted as exploratory visual tools rather than as adjusted effect estimates.

We employed marginal structural models (MSMs) with stabilized inverse probability of treatment weighting (IPTW) to address confounding by indication and treatment–severity feedback (e-Figure 2). MSMs are designed to simulate treatment randomization at each time point by re-balancing the distribution of baseline and time-varying confounders across treatment levels. Probability density of corticosteroid dose was estimated using generalized boosted modeling and incorporated both baseline covariates (age, sex, ICU admission, comorbidities,

immunosuppression etiology, chronic steroid use, early steroid initiation, oxygen support at baseline) and time-varying severity (daily highest oxygen support modality and FiO_2). Weights were recalculated each day of follow-up using updated severity covariates, ensuring that both illness trajectory and cumulative steroid exposure were modeled dynamically over time. Because corticosteroid dose was modeled as a continuous, time-varying exposure with weights recalculated daily, Pearson correlations between dose and covariates at each time point were used to assess balance.. Stabilized weights were checked for outliers and winsorized as needed at the 95^{th} percentile..

Weighted time-varying Cox models were then used to estimate the association between absolute cumulative corticosteroid dose and each outcome. Covariates with residual imbalance after weighting (absolute value of correlation greater than 0.1-0.2) were included in models. For outcomes precluded by death (intubation, recovery), we estimated cause-specific hazards with death treated as a censoring event. Cumulative incidence functions (CIFs) and Gray's test were used solely for descriptive visualization and not for effect estimation. Potential nonlinearity of the dose–response relationship was assessed using restricted cubic splines.

Sensitivity analyses included 7-day landmark analyses of the association between 7-day cumulative dose and outcomes, restricting to patients alive and event-free at day 7, with IPTW recalculated within that at-risk population using baseline confounders. Proportional hazards assumptions were tested with Schoenfeld residuals.

Subgroup MSMs were performed for each immunosuppression etiology, for steroid-naive patients (those without ≥14 days of corticosteroid exposure prior to PCP diagnosis), and for ICU patients intubated at baseline. For the latter, weighted Cox models estimated associations with 90-day mortality and time to extubation.

Statistical analysis was conducted using R software version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria); the WeightIt package was used to conduct IPTW.

Results

A total of 375 non-HIV immunocompromised patients with PCP required supplemental oxygen and were eligible for inclusion during this study period (e-Figure 1). Of these patients, 351 (93.6%) received adjunctive corticosteroids (Table 1).[25] The median age of the cohort was 66 years (IQR 57–74), and 59% were male. The most common etiologies of immunosuppression were hematologic malignancy (113 patients, 30.1%), solid tumors on chemotherapy (112, 29.9%), autoimmune disease (64, 17.1%), and solid organ transplantation (52, 13.9%). Smaller proportions had chronic lung disease (28.3%) or chronic kidney disease (25.3%). Trimethoprim–sulfamethoxazole was the predominant treatment regimen (299 patients, 79.7%), with atovaquone, clindamycin/primaquine, or pentamidine used less commonly. More than half of patients were already receiving chronic corticosteroids before PCP diagnosis (207, 55.2%).

At the time of PCP treatment initiation, 206 patients (54.9%) required only nasal cannula oxygen, 83 (22.1%) were managed on HFNC, 27 (7.2%) on NIV, and 59 (15.7%) required invasive mechanical ventilation or ECMO. Overall, 211 patients (56.3%) were admitted to the ICU during their hospitalization. The overall 90-day mortality rate was high, with 165 patients (44.0%) dying within 90 days of PCP treatment initiation.

Corticosteroid exposure was consistently associated with increased risk of 90-day mortality (Table 2). In unweighted time-varying Cox models, each additional 100 mg in cumulative prednisone-equivalent dose was associated with a 2% higher hazard of death (HR 1.02; 95% CI 1.01–1.03; $p < 0.001$). After using IPTW to weight the cohort accounting for baseline and time-varying severity, this association persisted, though attenuated (HR 1.01; 95%

CI 1.00–1.02; p = 0.006). Restricted cubic spline analyses further supported this relationship, showing a monotonic, linear increase in mortality risk with escalating cumulative steroid dose and no evidence of a protective threshold (Figure 1; ANOVA p-value for non-linearity: 0.263). In sensitivity analyses limited to patients alive and event-free at day 7, cumulative steroid exposure again predicted higher 90-day mortality (unweighted HR 1.03; 95% CI 1.01–1.05; p = 0.002; weighted HR 1.03; 95% CI 1.00–1.06; p = 0.038). These results demonstrate that the association was not driven solely by patients who died very early in the course of therapy. In contrast, the association of cumulative steroid dose with 30-day mortality was less robust, with a non-significant HR in MSM analysis (HR 1.01; 95% CI 1.00–1.02; p = 0.11) and borderline significant HR in landmark analysis (HR 1.03; 95% CI: 1.00–1.07; p = 0.049) after weighting.

To assess sensitivity of these results to unmeasured confounding, we calculated an E-value for the MSM-weighted HR (1.01; 95% CI 1.00–1.02; p = 0.006) equal to 1.10, indicating that an unmeasured confounder with an association with higher steroid dose and mortality of at a risk ratio of at least 1.10 could explain the observed association.

Unadjusted visualizations (Figure 2) showed worse outcomes with higher corticosteroid exposure. In cumulative incidence plots, patients receiving above-median daily doses had significantly slower liberation to nasal cannula (Gray's test p < 0.001) and higher mortality (Gray's test p = 0.0019) than those receiving below-median daily doses. Similarly, Kaplan–Meier survival curves by quartile demonstrated progressively higher 90-day mortality for groups with higher average daily dose (log-rank p < 0.001). These findings illustrate the raw association between dose and outcomes but remain unadjusted and subject to time-varying confounding. In contrast, weighted MSM analyses attenuated these signals, confirming that higher steroid

exposure was not associated with respiratory benefit and instead tracked with modest, dose-dependent increases in mortality.

Among patients not intubated at baseline, cumulative steroid dose was not associated with risk of subsequent intubation in MSM weighted models as shown in Table 2 (HR 0.99; 95% CI 0.97–1.02; p = 0.6). Results were similar in landmark analyses. Similarly, in patients requiring advanced respiratory support (HFNC, NIV, MV, or ECMO) at baseline, corticosteroid exposure was not associated with faster liberation to nasal cannula or room air (weighted HR 1.00; 95% CI 0.98–1.02; p = 0.9). Restricted cubic spline analysis again showed no evidence of a nonlinear relationship for these endpoints (ANOVA p-value: 0.186). Thus, higher steroid doses were not linked to either avoidance of intubation or to more rapid recovery from advanced support.

In prespecified subgroup analyses (Table 3), no mortality benefit was observed in any immunosuppression category. Patients with hematologic malignancy showed a harmful signal in unweighted models (HR 1.03; 95% CI 1.01–1.06; p = 0.007), which attenuated to non-significance after weighting (HR 1.02; 95% CI 0.99–1.05; p = 0.2). Patients with solid tumors, autoimmune diseases, or solid organ transplants demonstrated no significant associations between steroid exposure and mortality. Results were consistent when restricted to steroid-naïve patients, with higher cumulative corticosteroid exposure again associated with increased 90-day mortality (weighted HR 1.01 per 100 mg prednisone-equivalent, 95% CI 1.00–1.02; p = 0.02) (Table 3).

Among ICU patients intubated at baseline, unadjusted Kaplan–Meier survival curves suggested worse survival with higher corticosteroid exposure, and cumulative incidence plots showed slower liberation from mechanical ventilation among patients receiving greater average daily doses (e-Figure 3). However, these unadjusted visual signals attenuated in weighted MSMs.

After using IPTW, cumulative steroid dose was not significantly associated with 90-day mortality (HR 1.00; 95% CI 0.96–1.05; p = 0.8) or time to extubation (HR 0.99; 95% CI 0.95–1.04; p = 0.8). Together, these findings highlight that while unadjusted curves suggest a harmful effect of higher doses in the ICU, more rigorous adjusted analyses do not support a statistically significant association, and no subgroup demonstrated clear evidence of benefit from higher dosing

Discussion

In this large, multicenter cohort of hypoxemic, non-HIV immunocompromised adults with PCP, we found that greater cumulative corticosteroid exposure was consistently associated with higher 90-day mortality, even after rigorous adjustment for time-varying confounding with MSM/IPTW and in 7-day landmark analyses. The effect size was modest per 100 mg increase in cumulative prednisone-equivalent dose (≈2% unweighted; ≈1% after weighting) but clinically meaningful when accumulated across full treatment courses. Given the sensitivity of these results to unmeasured confounding, however, further studies are needed to confirm these findings. Importantly, we observed no evidence of benefit for key respiratory outcomes: higher doses did not reduce the risk of subsequent intubation among patients not intubated at baseline, nor did it accelerate liberation from advanced support among those already on HFNC, NIV, MV, or ECMO. Subgroup analyses by immunosuppression etiology and in ICU patients intubated at treatment initiation were directionally similar and non-significant after weighting. Spline modeling suggested a monotonic, approximately linear relationship between cumulative dose and 90-day mortality without an identifiable “safe” high-dose threshold.

Because patients with more severe or prolonged illness are often treated with longer or higher-dose corticosteroid courses, apparent dose–response associations in unadjusted

observational studies may reflect underlying illness severity rather than a causal effect of therapy. To address this potential time-dependent confounding, we employed marginal structural models with daily inverse probability weighting, which reweight observations based on evolving oxygen support modality and FiO_2 each day. This approach balances patients with comparable illness trajectories and substantially mitigates the bias introduced by continued therapy in sicker patients. Consistent results in our 7-day landmark analysis—restricted to patients alive and event-free at day 7 and with cumulative dosing determined before day 7—further support that the observed association was not driven by immortal-time or treatment-continuation bias.

Our findings should be interpreted as complementary to the recent randomized trial, which tested a moderate steroid regimen with a taper [20]. While this trial did not meet the primary 28-day mortality endpoint, it reported lower intubation rates and reduced 90-day mortality. Our real-world dose–response analysis addresses a different question—whether escalating beyond moderate regimens confers additional benefit—and suggests it does not. Taken together, these data suggest that if steroids are used, adherence to moderate regimens is prudent, and dose escalation appears unlikely to provide benefit and may cause harm. Although the effect size per 100 mg increment may seem numerically small(HR 1.01), it reflects the cumulative nature of exposure. For example, each additional 500 mg corresponds to an approximately 5% higher risk of 90-day mortality and each 1,000 mg yields an approximately 10% higher risk. Thus, when interpreted across full treatment courses, the magnitude of effect is clinically meaningful. To illustrate this difference in risk, the predicted cumulative incidence of mortality for MV patients in the ICU by day 90 was 66.7% (95% CI: 54.6%, 78.4%) for the 25th percentile of cumulative steroid dose (380 mg) and 69.1% (95% CI: 57.1%, 80.5%), for the 75th percentile of cumulative steroid dose (940 mg).

Several features strengthen inference. We used manual case verification and required hypoxemia at treatment initiation, reducing diagnostic and indication heterogeneity. We captured daily exposure and severity (highest modality and FiO_2) and applied MSM/IPTW to address treatment–severity feedback—an issue conventional regression cannot fully solve. The mortality association persisted across analytic specifications (unweighted, weighted, and landmark), and the dose–response was smooth and monotonic on restricted cubic splines, arguing against reliance on a single threshold or artifact. Subgroup consistency—with no benefit in any immunosuppression category—supports generalizability across common clinical phenotypes in non-HIV PCP.

These results align with prior observational studies, which have largely failed to demonstrate benefit and in some cases suggested harm.[26-28] In a recent prospective multicenter ICU study, corticosteroid initiation after PCP confirmation was associated with earlier death, with median prednisone-equivalent doses of 80 mg/day (IQR 60–95)[19] Our cohort showed similar variability, with a median daily dose of 37.5 mg (IQR 15 – 60). Prior work highlighted both uncertainty in effect estimates and marked heterogeneity of steroid dosing, illustrating the limitations of treating exposure as a binary variable. By contrast, our analysis leverages granular daily dosing data and modern causal inference methods to provide a more refined estimate of the dose–response, clarifying that escalating cumulative steroid doses does not improve respiratory outcomes and instead tracks with increased mortality risk.

Notably, the apparent harmful signals observed in some subgroups, such as hematologic malignancy, attenuated after IPTW/MSM adjustment, and no subgroup demonstrated a statistically significant association except for steroid-naïve patients, in whom higher cumulative corticosteroid exposure remained associated with increased 90-day mortality (weighted HR: 1.01

per 100 mg, 95% CI: 1.00-1.02; p = 0.02). We interpret this persistence among steroid-naïve patients as consistent with the primary analysis rather than evidence of differential subgroup effects. Overall, the attenuation of estimates in subgroup analysis after weighting likely limited power rather than evidence that corticosteroid dose has no effect in these populations. This pattern underscores that while subgroup-specific estimates should be interpreted cautiously, the overall monotonic dose–response observed in the full cohort is consistent and robust.

Clinically, our findings argue against dose escalation as a rescue strategy for patients with worsening oxygenation. When adjunctive corticosteroids are used in non-HIV PCP—such as following the moderate regimen tested in the RCT performed by Lemiale, et al.[20]—further escalation in response to day-to-day uncertainty or deterioration appears unlikely to improve outcomes and may contribute to excess mortality. In these situations, clinicians should instead reassess for competing diagnoses and complications (e.g., co-pathogens, drug toxicity, GVHD, fluid status) before increasing steroid exposure and consider steroid-sparing strategies where appropriate.

Consistent with other contemporary non-HIV PCP cohorts, our proportion of proven infections was low (36 of 375 patients, 9.6%). The randomized trial by Lemiale, et al[20] reported a similar proven rate of 16.5%, and a large multicenter retrospective study by Bienvenu et al. found 18.9%.[29] This pattern likely reflects the increasing reliance on highly specific PCR-based diagnostics and the lower organism burden typically observed in non-HIV immunocompromised patients.[5]

Our study has several limitations. Owing to its retrospective design, causality cannot be inferred, and residual confounding remains possible despite advanced adjustment methods. Patients were heterogeneously complex immunocompromised hosts, and steroid administration

was non-random, potentially influenced by clinician preference or concurrent inflammatory conditions. The calculated E-value for the MSM-weighted mortality association was 1.10, which reflects the small per-100 mg effect size. This indicates that even a relatively weak unmeasured confounder could theoretically account for the observed association; however, we emphasize that daily severity adjustment, IPTW, and MSM methods substantially reduce the most plausible sources of bias. The E-value is therefore best interpreted as underscoring that the effect is modest on a per-100 mg basis, though clinically meaningful when accumulated across full treatment courses. We also expressed corticosteroid exposure as absolute prednisone-equivalent milligrams rather than weight-normalized dosing, consistent with prior PCP studies; however, this approach may not fully account for variability in patient body habitus. Subgroup analyses by etiology of immunosuppression may be underpowered given smaller sample sizes. Although delays in initiating anti-Pneumocystis therapy are known to adversely affect survival, we anchored analyses to the start of PCP treatment to preserve causal interpretation of adjunctive steroid exposure; as such, antibiotic delays could not be directly incorporated. Finally, although this was a multicenter study, all sites were within a single health system, which may limit generalizability.

Interpretation

In this large multicenter cohort of hypoxemic, non-HIV immunocompromised adults with PCP, greater corticosteroid exposure was consistently associated with higher 90-day mortality without measurable benefit for preventing intubation or accelerating recovery. These findings complement the recent randomized trial, which addressed the binary question of whether adjunctive steroids should be used at all. Our analysis, by contrast, defines the dose–response relationship across real-world practice, showing that escalation beyond trial tested dosing provides no additional respiratory benefit and may be harmful.

Together, the two studies deliver a coherent clinical message: if adjunctive corticosteroids are prescribed for non-HIV PCP, they should be given judiciously at moderate doses. Dose escalation in response to clinical deterioration should be avoided, as it appears unlikely to improve outcomes and may contribute to excess mortality. Future randomized work is needed to determine whether any subgroups of non-HIV patients derive net benefit, but until then, cautious restraint is warranted.

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Figure Legends

Figure 1. Dose–response relationship between cumulative corticosteroid exposure and outcomes in non-HIV PCP. Restricted cubic spline models from marginal structural models (MSMs) with daily inverse probability weighting demonstrate the association of cumulative steroid dose (x100 mg prednisone-equivalent) with (A) hazard of 90-day mortality and (B) hazard of liberation from advanced respiratory support (HFNC, NIV, MV, or ECMO). Shaded areas represent 95% confidence intervals. ANOVA p-values for nonlinearity are shown; no significant departure from linearity was observed.

Figure 2. Unadjusted cumulative incidence and Kaplan–Meier curves of outcomes by corticosteroid exposure. (Top) Cumulative incidence of liberation to nasal cannula (solid lines) and mortality (dashed lines) stratified by above- versus below-median average daily prednisone -equivalent mg dose. Patients receiving higher doses had significantly slower liberation (Gray's test $p < 0.001$) and higher mortality (Gray's test $p = 0.0019$).(Bottom) Kaplan–Meier survival curves of 90-day mortality stratified by quartiles of 21-day average daily corticosteroid dose. Increasing dose quartiles were associated with progressively higher mortality (log-rank $p < 0.001$). These analyses are descriptive and do not account for time-varying confounding. Weighted marginal structural models (presented in the main text) attenuated these unadjusted signals, confirming that higher cumulative steroid exposure was not associated with respiratory benefit and was linked to modest increases in mortality.

Study Question: What is the dose–response relationship between adjunctive corticosteroids and outcomes in non-HIV immunocompromised adults with PCP requiring supplemental oxygen?

Results: In a 375-patient multicenter cohort, greater cumulative corticosteroid exposure was consistently associated with increased 90-day mortality, without improvement in risk of intubation or liberation from advanced support.

Interpretation: In non-HIV PCP, escalation beyond moderate, trial-tested steroid regimens appears unlikely to improve respiratory outcomes and may contribute to harm.

Table 1. Demographics and Clinical Characteristics	
Variable	Total (N=375)
Age, Median (IQR)	66.0 (57.0, 74.0)
Biologic Sex, Male (n, %)	220 (58.7%)
BMI, Median (IQR)	26.8 (22.7, 30.2)
Diabetic, n (%)	90 (24.0%)
Hypertension, n (%)	186 (49.6%)
Chronic Kidney Disease, n (%)	95 (25.3%)
Chronic Lung Disease, n (%)	106 (28.3%)
Etiology of Immunosuppression	
Solid Organ Transplant, n (%)	52 (13.9%)
Hematologic Malignancy, n (%)	113 (30.1%)
Autoimmune Disease , n (%)	64 (17.1%)
Solid Tumor on Chemo, n (%)	112 (29.9%)
Steroids Only, n (%)	37 (9.9%)
Proven Infection, n (%)	36 (9.6%)
Probable Infection, n (%)	339 (90.4%)
Positive Beta-D-Glucan, n (%)	48 (12.8%)
PCR Positive, n (%)	138 (36.8%)
Positive Beta-D-Glucan and PCR Positive, n (%)	153 (40.8%)
Final Treatment Regimen, n (%)	
Atovaquone	55 (14.7%)
Clindamycin/Primaquine	17 (4.5%)
Pentamidine	4 (1.1%)
Trimethoprim/Sulfamethoxazole	299 (79.7%)
Chronic Steroids, n (%)	207 (55.2%)
Chronic Steroid Dose (mg), Median (IQR; all patients)	10.0 (5.0, 30.0)
Hematologic Malignancy	7.5 (12.0, 40.0)
Solid Tumor on Chemo	8.0 (4.0, 20.0)
Autoimmune Disease	17.5 (10.0, 37.5)
Solid Organ Transplant	5 (5, 10)
Oxygen Support at time of treatment start, n (%)	
Nasal Cannula	206 (54.9%)
HFNC	83 (22.1%)
NIV	27 (7.2%)
Mechanical Ventilation	57 (15.2%)

ECMO	2 (0.5%)
ICU Admit, n (%)	211 (56.3%)
Treated with Steroids, n (%)	351 (93.6%)
21-Day Mean Daily Steroid Dose Quartiles (mg), n (%)	
[0.0, 28.5)	94 (25.1%)
[28.5, 40.5)	99 (26.4%)
[40.5, 56.7)	89 (23.7%)
[56.7, 1,270.0]	93 (24.8%)
Steroids started within 48 hours of treatment start, n (%)	331 (88.3%)
Steroids started before PCP treatment, n (%)	214/365 (58.6%)
Liberation from HFNC or higher, n(%)	98/169 (58.0%)
Need for Intubation, n (%)	49/316 (15.5%)
Mortality (30-day), n(%)	132 (35.2%)
Mortality (90-day), n (%)	165 (44.0%)

Abbreviations: BMI: Body mass index, PCR: polymerase chain reaction, HFNC: high flow nasal cannula, NIV: non-invasive ventilation, ECMO: Extra-corporeal membrane oxygenation

Table 2. Primary and Secondary Outcomes: MSM and Landmark Analyses with IPTW
(HR per 100 mg cumulative prednisone-equivalent dose)

	Before Weighting		**After Weighting**	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Primary Outcome: 90-Day Mortality				
MSM (165 events/375 patients)	1.02 (1.01, 1.03)[c]	<0.001	1.01 (1.00, 1.02)[b]	0.006
7-Day Landmark (112 events/322 patients)	1.03 (1.01, 1.05)[b]	0.002	1.03 (1.00, 1.06)[a]	0.038
Secondary Outcome: 30-Day Mortality				
MSM (132 events/375 patients)	1.02 (1.01, 1.03)[c]	<0.001	1.01 (1.00, 1.02)	0.11
7-Day Landmark (79 events/322 patients)	1.03 (1.01, 1.06)[b]	0.002	1.03 (1.00, 1.07)[a]	0.049
Secondary Outcome: Liberation				
MSM (98 events/169 patients)	1.00 (0.97, 1.02)	0.7	1.00 (0.98, 1.02)	0.9
7-Day Landmark (30 events/64 patients)	0.99 (0.90, 1.10)	0.9	1.02 (0.99, 1.06)	0.2
Secondary Outcome: Intubation				
MSM (49 events/316 patients)	1.00 (0.99, 1.02)	0.7	0.99 (0.97, 1.02)	0.6
7-Day Landmark (9 events/119 patients)	0.96 (0.86, 1.09)	0.5	0.99 (0.95, 1.04)	0.7

Abbreviations: CI = Confidence Interval, HR = Hazard Ratio, MSM = Marginal Structural Model, IPTW = Inverse Probability of Treatment weighting

Footnotes: a. $p<0.05$; b. $p<0.01$; c. $p<0.001$

Table 3. Subgroup Analyses. (HR per 100 mg cumulative prednisone-equivalent dose)

90-Day Mortality versus Cumulative Steroid Dose, by Subgroup

	Before Weighting		After Weighting	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Hematologic Malignancy (37 events/113 patients)	1.03 (1.01, 1.06)[b]	0.007	1.02 (0.99, 1.05)	0.2
Solid Tumor on Chemo (63 events/112 patients)	1.01 (1.00, 1.02)	0.11	1.01 (1.00, 1.02)	0.2
Autoimmune Disease (25 events/64 patients)	1.05 (0.99, 1.12)	0.11	1.04 (0.99, 1.10)	0.11
Solid Organ Transplant (17 events/52 patients)	1.10 (0.92, 1.31)	0.3	1.08 (0.92, 1.27)	0.4
Steroid Naive (67 events/168 patients)	1.02 (1.01, 1.03)[c]	<0.001	1.01 (1.00, 1.02)[a]	0.02

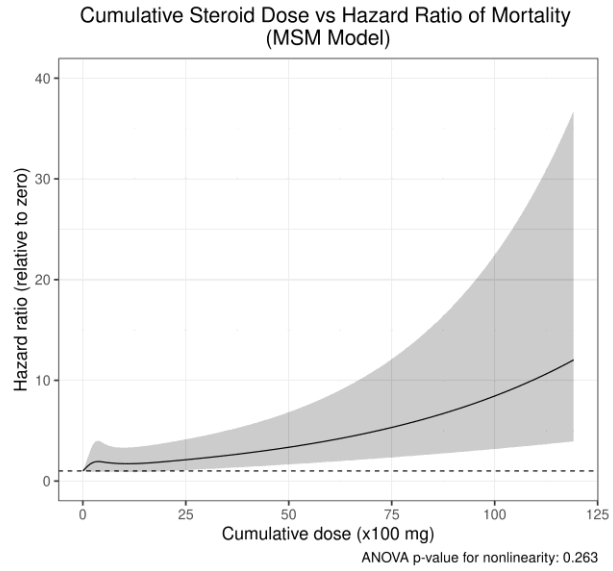
Mortality and Liberation versus Cumulative Steroid Dose in ICU Patients on MV

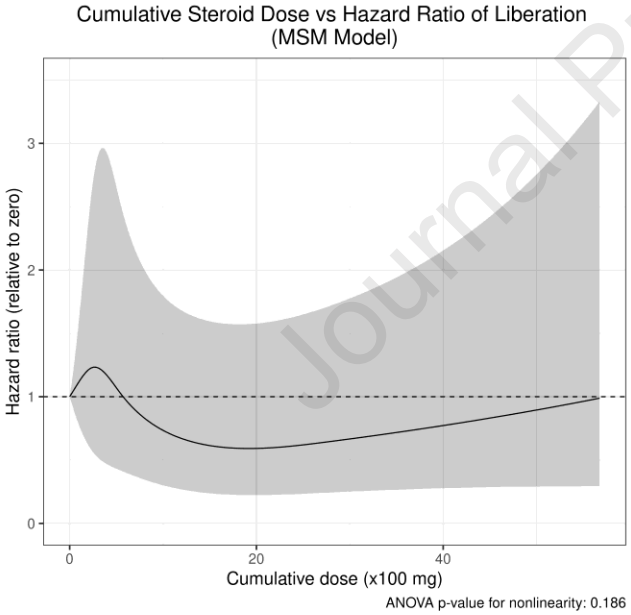
	Before Weighting		After Weighting	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
90-Day Mortality (38 events/57 patients)	1.01 (0.98, 1.05)	0.5	1.00 (0.96, 1.05)	0.8
Liberation (26 events/57 patients)	0.99 (0.94, 1.04)	0.6	0.99 (0.95, 1.04)	0.8

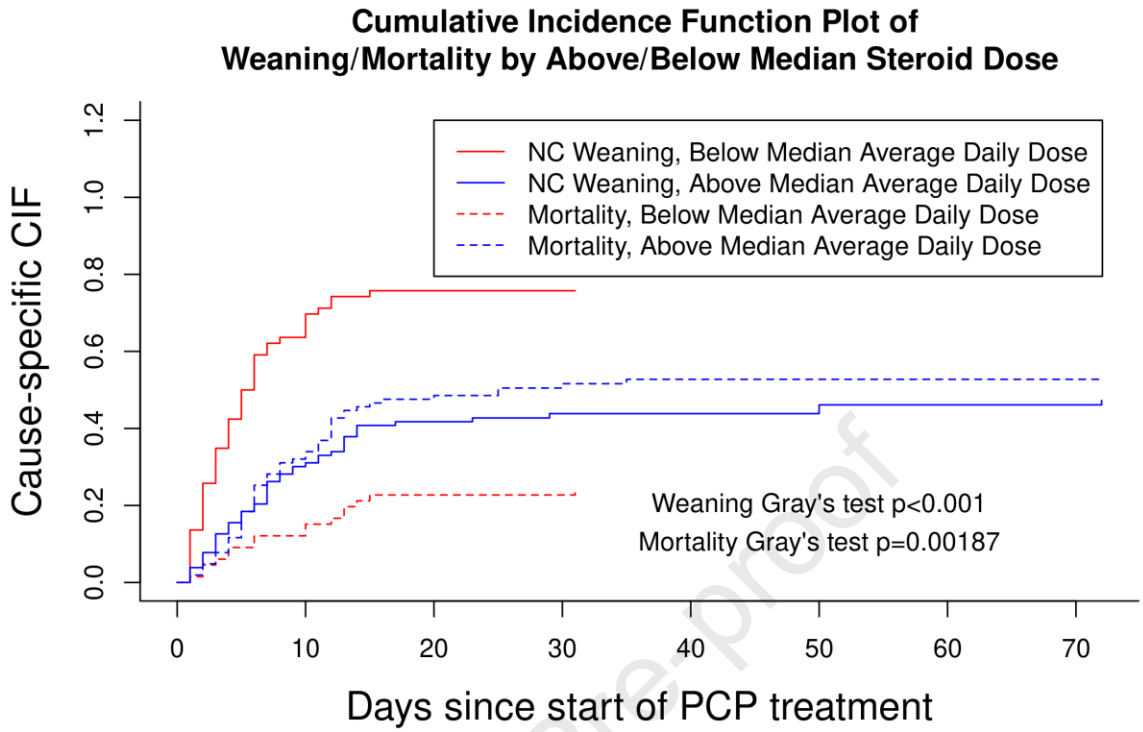
Footnotes: a. <0.05; b. p<0.01; c. p<0.001

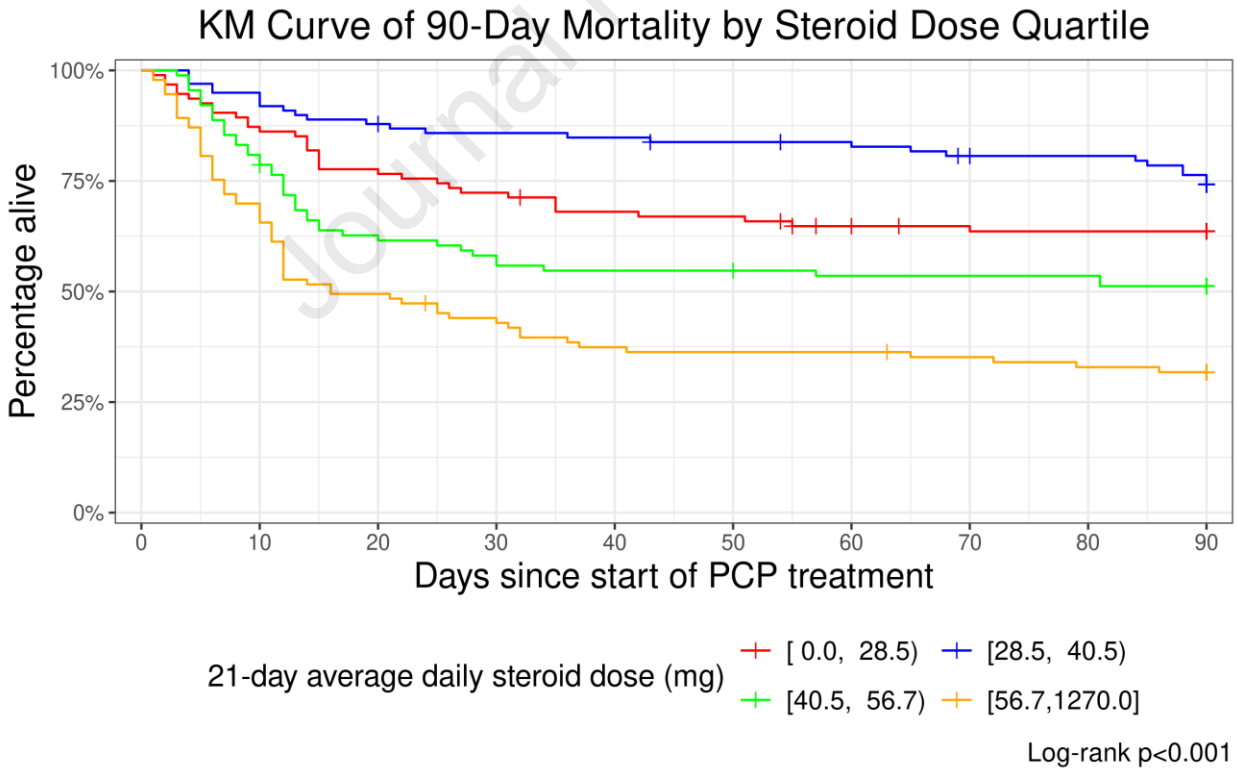
Abbreviations: CI = Confidence Interval, HR = Hazard Ratio

Figure 1

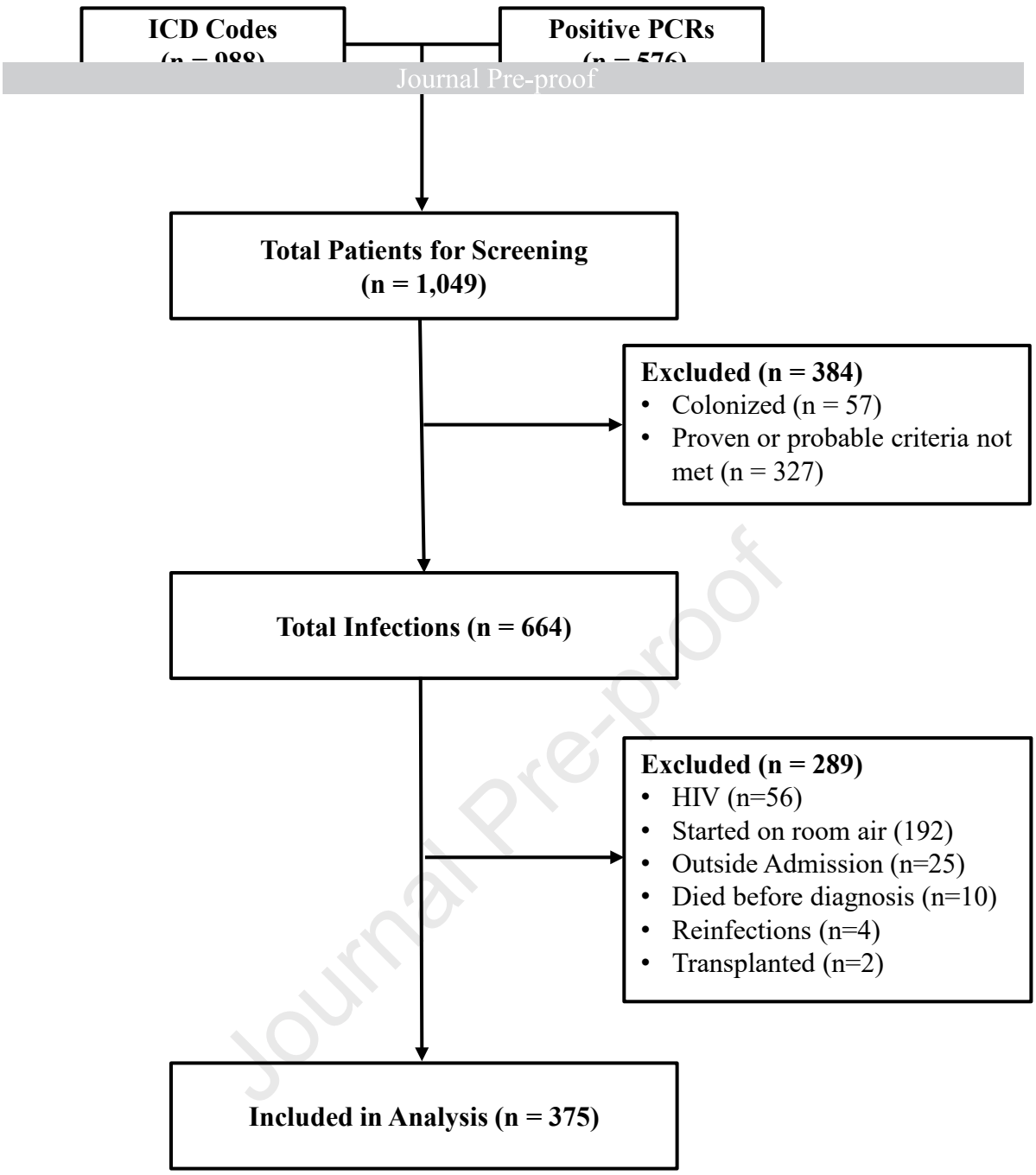








e-Figure 1



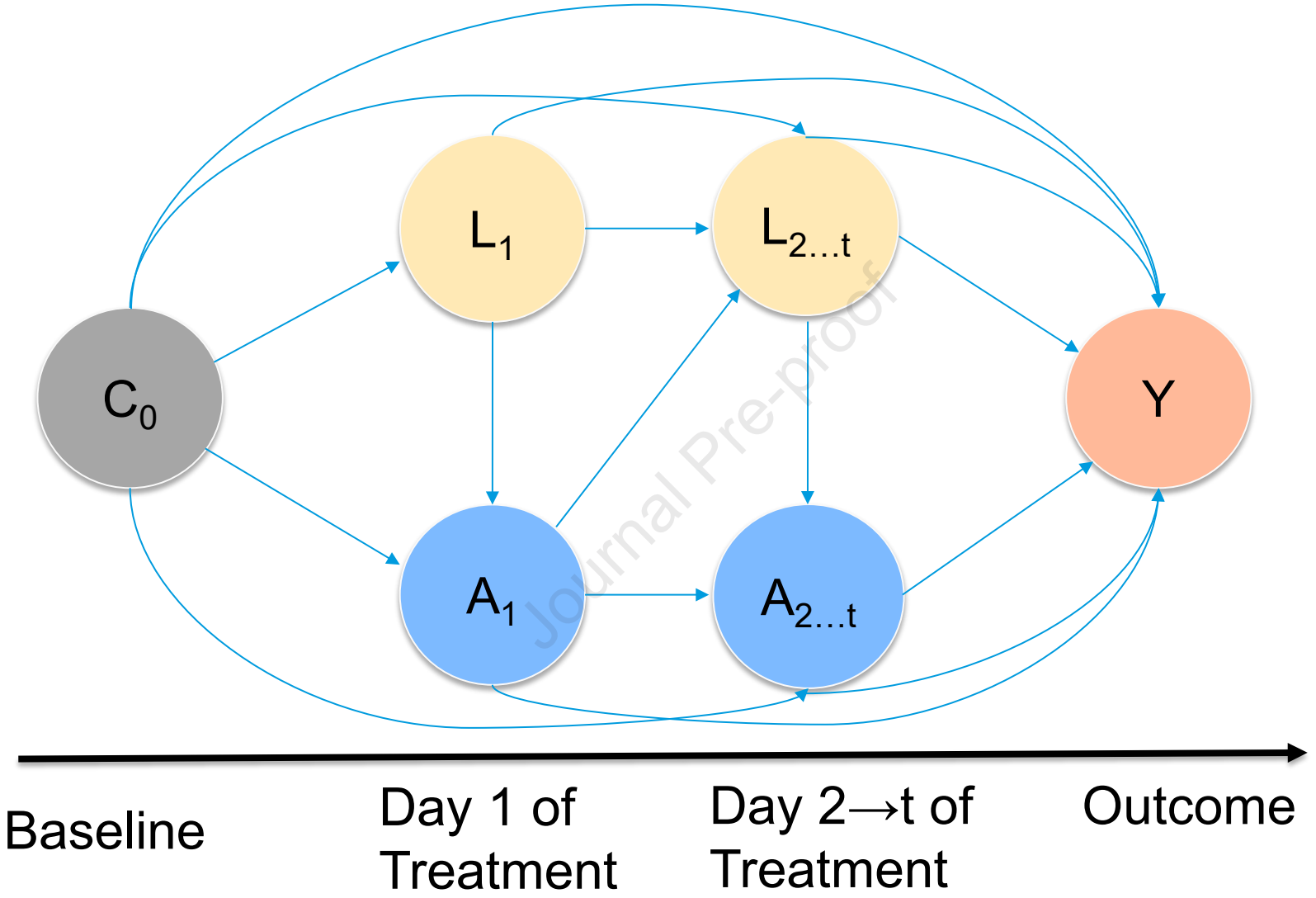
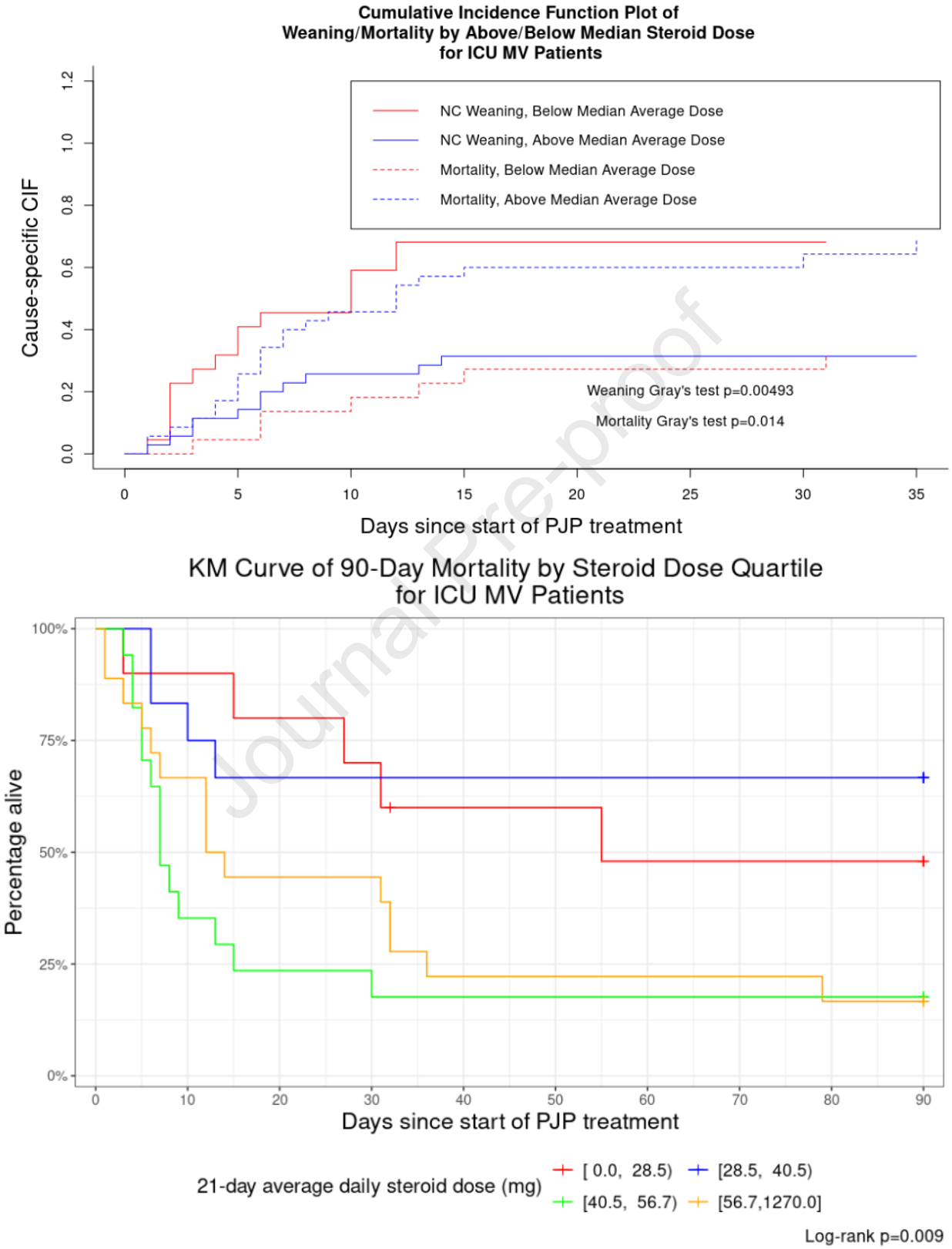


Figure Legend: C_0 = baseline covariates; L_t = time-varying severity (FiO_2, oxygen modality); A_t = daily corticosteroid exposure (prednisone-equivalent mg); Y = clinical outcomes (mortality, intubation)

e- Figure 3



e-Figure 1. Flow diagram illustrating case screening, exclusions, and final cohort inclusion. A total of 1,049 patients were screened by ICD or PCR code, with sequential exclusions for colonization, non-proven/probable infection, HIV positivity, room-air initiation, outside admissions, deaths prior to diagnosis, reinfections, and peri-transplant cases, yielding 375 non-HIV immunocompromised patients with hypoxemic PCP included in the final analysis.

e-Figure 2. Directed acyclic graph (DAG) illustrating the causal framework motivating the marginal structural model. Baseline covariates (C_0) influence both initial and subsequent illness severity (L_t) and corticosteroid dosing (A_t). Daily severity and corticosteroid exposure evolve jointly over time, each affecting the other and ultimately influencing clinical outcomes (Y). L_t represents time-varying illness severity (FiO_2, oxygen modality); A_t represents daily corticosteroid exposure (prednisone-equivalent mg); and Y represents outcomes (mortality, intubation).

e-Figure 3. Outcomes in ICU patients requiring invasive mechanical ventilation, stratified by corticosteroid dose. *(A)* Cumulative incidence functions for liberation from mechanical ventilation (solid lines) and 90-day mortality (dashed lines), comparing patients who received above- versus below-median average daily corticosteroid doses. Patients treated with higher doses had delayed weaning and higher mortality (Gray's test for weaning p=0.0049; Gray's test for mortality p=0.014). *(B)* Kaplan–Meier curves of 90-day mortality stratified by quartiles of 21-day average daily prednisone-equivalent dose. Mortality increased across quartiles, with the highest-dose group demonstrating the worst survival (log-rank p=0.009).