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Prognostic Efficacy of Pulse-Dose versus Standard Low-Dose Corticosteroids in Severe COVID-19 ARDS

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Research Article

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Abstract

Background

Low-dose corticosteroids reduce mortality in severe COVID-19, but clinicians frequently escalate to pulse-dose corticosteroid therapy in patients who continue to deteriorate, based on the assumption that stronger anti-inflammatory suppression improves outcome. Whether this dose escalation confers any real prognostic benefit remains unclear.

Methods

This retrospective, single-center cohort study included 188 adults with severe COVID-19-associated ARDS admitted to the ICU (April 2020–March 2022): 127 received standard low-dose corticosteroid and 61 received pulse-dose corticosteroid. The primary outcome was 28-day all-cause mortality; secondary outcomes were ICU/hospital length of stay, duration of mechanical ventilation, and the Day 0–10 trajectory of inflammatory and coagulation biomarkers. Because the proportional hazards assumption was violated and mortality was near-complete, the 28-day restricted mean survival time (RMST) was used as the primary survival summary, alongside Kaplan-Meier and Cox analyses. Biomarker trajectories were analyzed with linear mixed models and corrected for multiplicity (Benjamini-Hochberg), with pattern-mixture sensitivity analysis for missingness.

Results

28-day mortality was 99.2% (low-dose) vs 100% (pulse-dose; $p > 0.999$). Median survival was 8.0 vs 11.0 days (log-rank $p = 0.156$). The unadjusted RMST difference was 1.98 days (95% CI 0.00–3.95, $p = 0.050$), attenuating to 1.72 days (95% CI − 0.40 to 3.85, $p = 0.112$) after adjustment for age, SOFA score, and respiratory support level; pulse-dose therapy was not independently associated with survival (adjusted HR 0.78, 95% CI 0.56–1.10). ICU stay was shorter with low-dose therapy (8.0 vs 11.0 days, $p = 0.014$), likely reflecting baseline severity imbalance rather than treatment effect. After correction for multiple comparisons, no inflammatory or coagulation biomarker showed a significant between-group difference.

Conclusions

In this severe, late-phase ICU population, pulse-dose corticosteroid conferred no survival or mortality benefit over standard low-dose therapy, and apparent biomarker improvement did not translate into a genuine survival gain. Low-dose corticosteroid remains the evidence-based standard of care.

Introduction

Severe COVID-19 progresses to acute respiratory distress syndrome (ARDS) in a substantial proportion of patients, necessitating intensive care; mortality in this setting has been reported to range from 30–50% [1]. Clinical deterioration is driven not so much by direct viral injury as by an uncontrolled and excessive host inflammatory response. A distinguishing feature of this hyperinflammatory phenotype is that it is associated with higher mortality even in younger patients with fewer comorbidities; patients meeting hyperinflammation criteria at presentation have been shown to have a markedly increased risk of escalation of respiratory support or death [2]. Circulating inflammatory markers (interleukin-6, C-reactive protein, ferritin, procalcitonin, and the neutrophil-to-lymphocyte ratio) have prognostic value in distinguishing severe and fatal forms of the disease [3]. Controlling inflammation has therefore become central to the treatment of severe COVID-19.

Low-dose corticosteroids have been shown to reduce mortality in severe COVID-19[1]; this benefit appears to be greatest with low-dose regimens, and a dose of 6 mg/day dexamethasone has become the standard treatment[4]. Nevertheless, a subset of patients continues to deteriorate clinically despite standard treatment. Drawing on the hyperinflammation model, clinicians frequently switch these patients to pulse-dose corticosteroids (250–1000 mg/day methylprednisolone). The rationale is that a stronger and faster anti-inflammatory suppression will halt the progressing disease process and improve the patient's outcome [5]. Despite its widespread adoption, whether dose escalation actually provides any additional prognostic benefit remains uncertain.

This body of literature does not present a consistent picture. Meta-analyses comparing high- and low-dose regimens have found no significant difference in mortality, showing that low-dose therapy is as effective as high-dose therapy[6]; a meta-analysis focused on ARDS found that no regimen — early or late, high- or low-dose — reduced mortality, with any benefit confined to the methylprednisolone subgroup [7]. The study that tested this hypothesis most directly was a double-blind randomized trial comparing pulse methylprednisolone added to standard dexamethasone against placebo; no benefit was found in this trial[8]. In a propensity score–weighted cohort, high-dose corticosteroids were found to be associated with an increased probability of death[9]; the only small randomized trial directly comparing methylprednisolone with dexamethasone has been reported as underpowered to yield a reliable conclusion[4].

A common feature of the studies that appear to favor pulse or high-dose therapy is that they examined a different patient population or a different time window. The randomized trial linking pulse methylprednisolone to a survival benefit was conducted outside the ICU, in the early pulmonary phase, against a background in which no steroids at all were being given; thus, the benefit observed in that trial likely reflects the superiority of early steroid initiation over no steroid at all, rather than the superiority of pulse over low-dose therapy[10]. Similarly, the benefit of methylprednisolone has been found to be significant only in patients requiring respiratory support who have multiple elevated inflammatory markers and in whom treatment is started early, whereas it does not reach significance in the general

patient population [11]. The view that best explains these conflicting results is that any benefit may be related less to dose per se than to patient phenotype and treatment timing.

This body of literature leaves a gap in two respects. First, data directly comparing pulse-dose with standard low-dose therapy — particularly in severe, mechanically ventilated ICU patients in the late phase — are limited and conflicting; no consensus has emerged on the optimal dose, agent, or timing of administration. Second, and comparatively less studied, is whether the biochemical improvement observed under corticosteroid therapy actually corresponds to a true survival benefit. A causal mediation analysis has shown that high-dose corticosteroids do not reduce mortality in the late phase and may even be associated with increased mortality, and that any potential benefit emerges only when inflammatory markers genuinely decline [5]. Tissue-level data support this distinction: dexamethasone measurably suppresses circulating markers of tissue breakdown, yet in patients who die the fibroproliferative process continues, and this suppression is not reflected in survival [12]. These findings suggest that, under intensive corticosteroid therapy, improvement in biomarkers may reflect the drug's expected pharmacodynamic effect rather than genuine regression of the disease process. Together, these two gaps make it necessary to evaluate — within the same cohort — whether dose escalation has any real prognostic benefit in severe, late-phase ICU patients, and how the trajectory of biomarkers relates to survival.

This study aimed to retrospectively compare pulse-dose corticosteroid therapy with standard low-dose therapy, in terms of prognosis, survival, and resource utilization, in adult patients followed in the ICU for severe COVID-19 ARDS. The primary outcome was 28-day all-cause mortality; secondary outcomes were ICU and hospital length of stay, duration of invasive mechanical ventilation, and the trajectory of inflammatory and coagulation markers from Day 0 to Day 10. By examining, within the same cohort, whether any improvement in biomarkers translated into survival, we assessed whether the observed biochemical improvement corresponded to a genuine clinical benefit or a misleading laboratory improvement.

Materials and Methods

Study Design and Ethical Approval

This study was designed as a single-center, non-interventional, retrospective cohort study conducted in the Anesthesiology Intensive Care Unit of Aydın State Hospital between April 2020 and March 2022. Of 258 patients with severe COVID-19 pneumonia screened during this period, 70 were excluded (60 had not received corticosteroid therapy, 7 had an ICU stay of less than 24 hours, 2 were admitted primarily for a non-COVID-19 diagnosis, and 1 had a do-not-resuscitate order for terminal malignancy), leaving a final cohort of 188 patients with confirmed severe viral ARDS who were included in the analysis.

The study protocol was approved by the Aydın Adnan Menderes University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (Decision No. 13; Protocol No. 2026/13). All

procedures were carried out in accordance with the Declaration of Helsinki and Good Clinical Practice principles. Because of the retrospective design of the study, the requirement for informed consent was waived by the ethics committee, and patient data were de-identified. Reporting of the study followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist for observational research.

The overall study design, including patient selection, baseline assessment, corticosteroid treatment allocation, and outcome ascertainment, is summarized in Fig. 1.

Study Population

The target population of the study consisted of adult patients (≥ 18 years) admitted to the intensive care unit with a diagnosis of severe COVID-19 pneumonia during the study period. Severe COVID-19 pneumonia was defined as a positive SARS-CoV-2 RT-PCR test or typical bilateral involvement on thoracic computed tomography, together with severe hypoxemia requiring intensive care ($SpO_2 \leq 90\%$ or $PaO_2/FiO_2 < 300$). Exclusion criteria were the absence of both RT-PCR positivity and typical thoracic CT findings, age under 18 years, and pregnancy or lactation. Patients with a “do-not-resuscitate” order due to terminal-stage malignancy, as well as patients admitted to the ICU primarily for a diagnosis other than COVID-19, were also excluded. To reduce early mortality bias, patients with an ICU stay of less than 24 hours were excluded.

After ICU admission, patients were divided into two cohorts according to the corticosteroid regimen administered by the treating intensivist. The standard low-dose group received intravenous dexamethasone 6 mg/day or methylprednisolone 40–80 mg/day (0.5–1 mg/kg), while the pulse-dose group received intravenous methylprednisolone 250–1000 mg/day. All patients concurrently received the institution's standard-of-care treatment, including broad-spectrum antibiotics and, where clinically indicated, antiviral or immunomodulatory agents. Because of the retrospective design of the study, no a priori power analysis was performed to determine sample size.

Data Collection

Study data were collected retrospectively from patients' ICU follow-up charts and the hospital's electronic health records. Demographic characteristics, comorbidities, indicators of disease severity at ICU admission, the corticosteroid regimen administered, methods of respiratory support, laboratory parameters, and clinical outcomes were obtained using a predefined data extraction framework.

Laboratory values were recorded serially from tests performed as part of routine clinical monitoring during patients' ICU course; because these measurements were based on clinical routine rather than a standardized research protocol, the timing of sampling varied according to each patient's clinical course.

Variables and Outcomes

The primary outcome of the study was defined as 28-day all-cause mortality. Secondary outcomes, focusing on the use of ICU resources, included length of ICU stay, length of hospital stay, and total duration of invasive mechanical ventilation. In addition, to assess the physiological response to corticosteroid dose escalation, the trajectory of inflammatory and coagulation biomarkers — C-reactive protein, lactate dehydrogenase, fibrinogen, D-dimer, ferritin, and procalcitonin — from baseline (Day 0) to Day 10 was monitored as a secondary outcome.

The main independent variable was the corticosteroid regimen received by the patient (pulse-dose or standard low-dose). Demographic and clinical variables recorded at baseline included age, sex, comorbidities (hypertension, ischemic heart disease, diabetes mellitus), disease severity at ICU admission (Sequential Organ Failure Assessment [SOFA] and Acute Physiology and Chronic Health Evaluation II [APACHE II] scores), and respiratory support requirements (non-invasive ventilation and prone positioning).

Statistical Analysis

Normality of continuous variables was assessed with the Shapiro-Wilk test. Because group sizes were limited and unbalanced, nonparametric methods were preferred for all comparisons regardless of distribution. Continuous variables are presented as median (minimum–maximum), and categorical variables as frequency (percentage).

Between-group comparisons of continuous variables were performed using the Mann-Whitney U test; the Hodges-Lehmann median difference and 95% confidence interval (CI) were reported as the effect measure. Categorical variables were compared with Pearson's chi-square test, or Fisher's exact test when any expected cell count was below five; the risk difference was given as the effect measure. Secondary continuous outcomes — length of ICU and hospital stay and duration of invasive mechanical ventilation — were likewise compared with the Mann-Whitney U test and interpreted at a descriptive level, taking into account the competing risk of death. Twenty-eight-day all-cause mortality was assessed with Fisher's exact test.

Overall survival was estimated using the Kaplan-Meier method; median survival times and 95% CIs were derived from the survival functions, and the unadjusted between-group difference was tested with the log-rank test. Cox proportional hazards models were built both unadjusted and adjusted for age, Sequential Organ Failure Assessment (SOFA) score, and ordinal level of respiratory support (high-flow nasal cannula, noninvasive ventilation, and prone positioning; range 0–3). The proportional hazards assumption was examined using scaled Schoenfeld residuals. Because this assumption was not met and in-hospital mortality was near-complete — conditions under which the hazard ratio and the log-rank test poorly discriminate between groups — the 28-day restricted mean survival time (RMST) was adopted as the primary survival summary. The between-group RMST difference and 95% CI were

estimated at the 28-day horizon; the covariate-adjusted RMST difference was obtained via pseudo-observation regression using variance-robust standard errors.

The Day 0–Day 10 trajectory of inflammatory and coagulation biomarkers was analyzed on the natural logarithm scale using linear mixed-effects models with a group×time interaction and a patient-level random intercept; results are expressed as Day 0–Day 10 fold-change ratios. Because missingness at later time points increased in a manner related to mortality, multiplicity across the 16-marker panel was controlled using the Benjamini-Hochberg false discovery rate, treating the panel as a single test family. Since missingness was related to death and most likely not random, a sensitivity analysis based on pattern-mixture delta-adjustment (tipping-point analysis) was performed for both within-group trajectories and between-group effects; the magnitude of departure from a random-missingness mechanism at which each result's direction or significance changed was quantified. Within-group Day 0–Day 10 comparisons are susceptible to survivorship bias, and death is a competing event for longitudinal outcomes; these features were addressed not only through complete-case inference but also through the RMST framework and the missing-data sensitivity analysis.

Standard analyses were performed using jamovi (version 2.6.44; The Jamovi Project) and JASP (version 0.19.3). The restricted mean survival time, covariate-adjusted RMST, linear mixed-effects models, and missing-data sensitivity analyses were carried out in R (version 4.3.3; R Foundation for Statistical Computing, Vienna, Austria), with survival calculations performed using the survival and survRM2 packages. All tests were two-sided, and $p \leq 0.05$ was accepted as the threshold for statistical significance.

Results

A total of 188 patients who received corticosteroid therapy for severe COVID-19-associated acute respiratory distress syndrome were analyzed; 127 patients received standard low-dose therapy and 61 received pulse-dose therapy. At baseline, the pulse-dose group was younger than the low-dose group (Hodges-Lehmann median difference − 5.0 years, 95% CI − 10.0 to − 2.0, $p = 0.010$) and presented with a lower SOFA score (median difference − 1.0, 95% CI − 2.0 to 0.0, $p = 0.006$). Noninvasive ventilation (80% vs 56%, $p = 0.001$) and prone positioning (77% vs 35%, $p < 0.001$) were applied more frequently in the pulse-dose group; malignancy ($p = 0.039$), tocilizumab use ($p = 0.033$), and anakinra use ($p = 0.033$) also differed significantly between groups. The groups were similar in comorbidity burden and APACHE II score (Table 1).

Twenty-eight-day all-cause mortality occurred in 126 of 127 patients (99.2%) in the low-dose group and in all 61 patients (100%) in the pulse-dose group; there was no statistically significant difference between groups ($p > 0.999$) (Table 2).

Median survival time was 8.0 days (95% CI 7.0–10.0) in the low-dose group and 11.0 days (95% CI 9.0–11.0) in the pulse-dose group; no significant difference was observed on the log-rank test ($p = 0.156$) (Fig. 2). The proportional hazards assumption was violated (scaled Schoenfeld residuals, global p =

0.0178; Supplementary Figure S1), and the unadjusted Cox model yielded a hazard ratio of 0.81 for pulse-dose therapy (95% CI 0.60–1.10, p = 0.182). The 28-day restricted mean survival time reached 9.81 days (95% CI 8.61–11.01) in the low-dose group and 11.79 days (95% CI 10.22–13.35) in the pulse-dose group; the between-group difference corresponded to 1.98 days (95% CI 0.00–3.95, p = 0.050). After adjustment for age, SOFA score, and level of respiratory support, this difference decreased to 1.72 days (95% CI − 0.40 to 3.85, p = 0.112). In the adjusted Cox model, pulse-dose therapy was not independently associated with survival (HR 0.78, 95% CI 0.56–1.10, p = 0.161); in contrast, older age (HR 1.01 per year, 95% CI 1.00–1.03, p = 0.040) and a higher level of respiratory support (HR 1.18 per level, 95% CI 1.01–1.38, p = 0.035) were independently associated with mortality, whereas SOFA score showed no independent association (HR 1.06, 95% CI 0.99–1.12, p = 0.091) (Table 2).

Among secondary outcomes, ICU length of stay was shorter in the low-dose group (median 8.0 vs 11.0 days, p = 0.014); duration of invasive mechanical ventilation did not differ significantly between groups (median 5.0 vs 8.0 days, p = 0.073) (Table 2).

After correction for multiple comparisons across the 16-marker panel (Benjamini-Hochberg false discovery rate), none of the inflammatory or coagulation biomarkers showed a significant group×time difference between Day 0 and Day 10; the smallest corrected value was q = 0.067 for erythrocyte sedimentation rate. At the unadjusted level, group×time differences were detected for D-dimer (fold-change ratio 1.67, p = 0.014), erythrocyte sedimentation rate (0.64, p = 0.004), white blood cell count (1.25, p = 0.039), neutrophil count (1.25, p = 0.049), and neutrophil-to-lymphocyte ratio (1.34, p = 0.037). Between-group comparisons at Day 10 were nonsignificant for all biomarkers (Table 3, Supplementary Table S1).

In the pattern-mixture sensitivity analysis, the apparent within-group decreases in C-reactive protein, fibrinogen, and erythrocyte sedimentation rate observed in the low-dose group were sensitive to departures from a random-missingness mechanism. The decrease in C-reactive protein was reversed at a shift of 1.01 standard deviations in the unobserved values of patients who died — corresponding to values approximately 2.8-fold higher than those of survivors; the decreases in fibrinogen and sedimentation rate were reversed at shifts of 0.24 and 0.65 standard deviations (approximately 1.6-fold), respectively. Between-group results remained stable across the same range of assumptions; unadjusted group×time differences approached the null value under a symmetric shift (Supplementary Table S2).

Table 1
Baseline demographic and clinical characteristics of patients with severe COVID-19 ARDS by corticosteroid treatment group

Variables	Low dose (n = 127)	Pulse (n = 61)	Effect size (95% CI)	p
Age (years)	76.0 (30.0–98.0)	69.0 (28.0–91.0)	-5.0 (-10.0; -2.0)	**0.010**
Sex, male	79 (62.2)	37 (60.7)	-1.5 (-16.4; +12.7)	0.838
Number of comorbidities	1.0 (0.0–5.0)	1.0 (0.0–4.0)	+ 0.0 (+ 0.0; +0.0)	0.691
Diabetes mellitus	25 (19.7)	13 (21.3)	+ 1.6 (-9.8; +14.9)	0.795
Hypertension	47 (37.0)	22 (36.1)	-0.9 (-14.9; +13.9)	0.900
Chronic kidney disease	22 (17.3)	8 (13.1)	-4.2 (-14.0; +7.9)	0.461
COPD	14 (11.0)	12 (19.7)	+ 8.6 (-1.8; +21.1)	0.108
Atrial fibrillation	11 (8.7)	3 (4.9)	-3.7 (-10.7; +5.6)	0.554
Heart failure	5 (3.9)	0 (0.0)	-3.9 (-8.9; +2.4)	0.176
Malignancy	1 (0.8)	4 (6.6)	+ 5.8 (+ 0.4; +14.9)	**0.039**
SOFA	5.0 (2.0–13.0)	4.0 (2.0–11.0)	-1.0 (-2.0; +0.0)	**0.006**
APACHE II	20.0 (8.0–44.0)	21.0 (11.0–42.0)	+ 0.0 (-2.0; +2.0)	0.807
Mask oxygen	110 (86.6)	49 (80.3)	-6.3 (-18.9; +4.4)	0.264
High-flow oxygen (HFNC)	24 (18.9)	11 (18.0)	-0.9 (-11.7; +12.0)	0.887
Noninvasive ventilation (NIV)	71 (55.9)	49 (80.3)	+ 24.4 (+ 10.1; +36.3)	**0.001**
Prone positioning	44 (34.6)	47 (77.0)	+ 42.4 (+ 27.7; +54.1)	**< 0.001**
Mechanical ventilation	126 (99.2)	61 (100.0)	+ 0.8 (-5.2; +4.3)	1.000
Tocilizumab	7 (5.5)	9 (14.8)	+ 9.2 (+ 0.5; +20.6)	**0.033**
Anakinra	0 (0.0)	3 (4.9)	+ 4.9 (+ 0.6; +13.5)	**0.033**
Remdesivir	0 (0.0)	1 (1.6)	+ 1.6 (-1.6; +8.7)	0.324
Immune plasma	2 (1.6)	0 (0.0)	-1.6 (-5.6; +4.5)	1.000

Continuous variables are presented as median (min–max) owing to nonparametric distribution, and groups were compared using the Mann-Whitney U test. Categorical variables are presented as n (%); the chi-square test was used, with Fisher's exact test applied when the expected frequency was < 5. Effect size is the Hodges-Lehmann median difference for continuous variables and the risk difference

(percentage points) for categorical variables. **Significant p-values are shown in bold** ($p \leq 0.05$). Vaccination status was unknown in 96.8% of cases and was therefore not included in the table. CI, confidence interval; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II; HFNC, high-flow nasal cannula.

Table 2
Survival and ICU resource utilization by corticosteroid treatment group

Outcomes	Low dose (n = 127)	Pulse (n = 61)	Effect size (95% CI)	p
28-day all-cause mortality, n (%)	126 (99.2)	61 (100.0)	+ 0.8 (-5.2; +4.3)	> 0.999
Median survival time (days)	8.0 (7.0–10.0)	11.0 (9.0–11.0)	—	0.156
RMST @28 days (days) □	9.81 (8.61–11.01)	11.79 (10.22–13.35)	—	—
RMST difference, pulse − low dose (days) □	—	—	1.97 (0.00; 3.95)	**0.050**
Hazard ratio (Cox) □	Reference	0.81 (0.60; 1.10)	—	0.182
ICU length of stay (days), median (min–max)	8.0 (1.0–36.0)	11.0 (1.0–36.0)	+ 2.0 (+ 0.0; +4.0)	**0.014**
Mechanical ventilation duration (days), median (min–max)	5.0 (0.0–30.0)	8.0 (1.0–37.0)	+ 2.0 (+ 0.0; +4.0)	0.073

Survival was compared between groups using the Kaplan-Meier method and the log-rank test. □ Because the proportional hazards assumption was violated (global Schoenfeld p = 0.0178), the primary estimand is the restricted mean survival time (RMST). □ The Cox hazard ratio is provided for raw comparison purposes only; its discriminative ability is limited because mortality was near-saturated (187/188 events). ICU and mechanical ventilation durations were assessed with the Mann-Whitney U test, with effect size given as the Hodges-Lehmann difference. **Significant p-values are shown in bold** ($p \leq 0.05$). RMST, restricted mean survival time; CI, confidence interval; ICU, intensive care unit.

Table 3
Comparison of Day 0–10 inflammatory and coagulation biomarker trajectories by group

Biomarkers	Group	Day 0	Day 1	Day 5	Day 10	Group × time effect (95% CI)	p
CRP (mg/L)	Low dose	136.5 (79.3–179.9)	127.1 (70.3–199.6)	110.5 (58.4–176.1)	98.0 (48.0–156.6)	0.83 (0.57; 1.22)	0.342
	Pulse	123.0 (72.2–191.2)	113.5 (79.7–173.9)	83.2 (33.8–117.8)	82.1 (34.7–183.5)		
Ferritin (ng/mL)	Low dose	443.7 (204.9–915.8)	568.7 (245.1–1032.8)	655.0 (335.1–1497.0)	738.6 (334.6–1368.3)	0.92 (0.74; 1.14)	0.439
	Pulse	430.9 (285.6–1078.1)	589.0 (315.6–1302.4)	650.2 (306.4–1175.6)	871.1 (378.2–1650.0)		
D-dimer (ng/mL)	Low dose	1500.0 (780.0–4062.5)	1955.0 (1055.0–4365.0)	3120.0 (1700.0–9150.0)	3040.0 (1785.0–6365.0)	1.67 (1.11; 2.52)	0.014
	Pulse	1075.0 (690.0–2237.5)	1255.0 (695.0–3090.0)	1970.0 (1087.5–5420.0)	4040.0 (1480.0–7770.0)		
Fibrinogen (mg/dL)	Low dose	466.6 (275.4–655.2)	452.2 (264.1–594.5)	403.9 (222.0–580.1)	394.0 (210.0–611.7)	0.89 (0.72; 1.09)	0.264
	Pulse	557.1 (384.8–678.3)	502.9 (375.8–644.5)	501.0 (343.4–613.0)	414.0 (212.6–584.1)		
Procalcitonin (ng/mL)	Low dose	0.220 (0.090–1.250)	0.330 (0.110–2.260)	0.605 (0.150–2.843)	0.815 (0.253–3.900)	1.21 (0.61; 2.40)	0.585
	Pulse	0.120 (0.068–0.412)	0.140 (0.070–0.505)	0.190 (0.098–0.992)	0.575 (0.152–2.993)		

Cell values are given as median (Q1–Q3 interquartile range). The group × time effect is the between-group ratio of the Day 0–10 change (linear mixed model, patient random effect, natural logarithm scale; a ratio below 1 indicates a relatively more pronounced decrease in the pulse-dose group). A Benjamini-Hochberg false discovery rate correction for multiple biomarkers was applied; **after correction, no biomarker showed a significant between-group difference**. Raw p-values are given in the table. Because missingness was related to death, the findings were confirmed with pattern-mixture and tipping-point sensitivity analyses. CRP, C-reactive protein; LDH, lactate dehydrogenase; CI, confidence interval

Biomarkers	Group	Day 0	Day 1	Day 5	Day 10	Group × time effect (95% CI)	p
LDH (U/L)	Low dose	461.5 (327.2–637.8)	520.5 (397.5–692.8)	610.0 (441.0–792.5)	570.0 (435.0–802.0)	0.88 (0.74; 1.05)	0.151
	Pulse	513.5 (331.8–686.2)	594.5 (403.8–724.5)	534.0 (425.8–737.5)	516.5 (379.0–922.8)		
Lactate (mmol/L)	Low dose	1.8 (1.3–2.6)	1.7 (1.1–2.1)	1.9 (1.3–3.1)	2.0 (1.5–4.2)	0.84 (0.65; 1.09)	0.186
	Pulse	2.0 (1.4–2.6)	1.6 (1.3–2.1)	1.6 (1.2–2.1)	1.9 (1.5–3.0)		
Sedimentation rate (mm/h)	Low dose	59.0 (43.2–75.8)	53.0 (36.8–74.8)	55.0 (42.0–76.0)	56.0 (36.2–79.5)	0.64 (0.47; 0.87)	0.004
	Pulse	61.5 (45.8–79.0)	59.0 (39.2–77.2)	50.5 (30.8–69.8)	51.0 (14.0–69.2)		

Cell values are given as median (Q1–Q3 interquartile range). The group × time effect is the between-group ratio of the Day 0–10 change (linear mixed model, patient random effect, natural logarithm scale; a ratio below 1 indicates a relatively more pronounced decrease in the pulse-dose group). A Benjamini-Hochberg false discovery rate correction for multiple biomarkers was applied; **after correction, no biomarker showed a significant between-group difference**. Raw p-values are given in the table. Because missingness was related to death, the findings were confirmed with pattern-mixture and tipping-point sensitivity analyses. CRP, C-reactive protein; LDH, lactate dehydrogenase; CI, confidence interval

Discussion

In this cohort of patients followed in the intensive care unit for severe COVID-19-associated ARDS, pulse-dose corticosteroid therapy could not be shown to improve either mortality or time to death compared with standard low-dose therapy. The first point to note in interpreting this finding is that mortality occurred in nearly all patients in both arms. When the event is this saturated, the "survival rate" metric loses its capacity to carry information; the only dimension that can still be meaningfully interpreted is how long death could be delayed. Shifting the primary estimand to the 28-day restricted mean survival time (RMST) is therefore a methodological necessity, not a preference. Viewed through this lens, the pulse-dose arm showed a survival profile that was, on average, about two days earlier than the low-dose arm; after adjustment for baseline imbalances, this difference fell to roughly one-and-a-half to two days and lost statistical significance. It is clear that a difference of less than two days is not, on a clinical scale, a magnitude that would change practice in a disease where ICU stays are measured in weeks. A

methodologically critical detail here is that the unadjusted hazard ratio and the restricted mean survival time point in different directions; this apparent contradiction is not an inconsistency but an expected picture in data where the hazard functions do not behave proportionally over time. Indeed, Dormuth et al. have shown that in dozens of studies with crossing curves, the classical log-rank approach fails to detect the difference that alternative methods can detect[13]. Relying on a single summary measure in this dataset would therefore be misleading; taken as a whole, the evidence points to the absence of any signal that could be interpreted in favor of pulse therapy. The most extreme conclusion this study can support is that a superiority of pulse-dose therapy could not be demonstrated; this design cannot establish a verdict of either superiority or equivalence.

This result is consistent with the literature showing that escalating corticosteroid dose does not translate into an additional survival benefit in severe COVID-19; the real question here, however, is why it does not. The physiological assumption underlying dose escalation is that a stronger anti-inflammatory suppression will produce a better outcome. The study that tests this assumption most cleanly is the double-blind, randomized trial by Salvarani et al., which compared pulse methylprednisolone against placebo on a dexamethasone background: a tenfold dose added on top of standard therapy neither accelerated discharge nor reduced the risk of ICU admission or death[8]. Had benefit truly been a matter of dose, it would have been expected to appear in this design. The Cochrane review points to the same gap, showing that benefit is essentially concentrated at the low dose, that shifting the dose upward brings no additional superiority, and that the single small randomized trial directly comparing methylprednisolone with dexamethasone is not sufficient to yield a reliable conclusion[4]. The observational literature reinforces this picture: the meta-analyses by Tan et al. and Jiang et al. found high-dose therapy to be neutral with respect to mortality, and Jiang et al. could not detect benefit in any of the early/late or high/low dose subgroups[6,7]. Even more striking, Kumar et al., applying propensity-weighted adjustment, found high-dose methylprednisolone to be associated with increased mortality risk[9]; this suggests that dose escalation may be not merely ineffective but potentially harmful. The study by Joshi et al., titled "less is more," and the critical COVID-19 cohort of Odhiambo et al. likewise confirm that high dose does not confer a mortality advantage [14,15]. The two studies closest to our own suggest that the issue may concern molecule choice as well as dose alone: at equipotent high doses, Kovacevic et al. found dexamethasone superior to methylprednisolone, particularly in the most severely ill intubated patients, while Kellogg et al. associated dexamethasone with lower mortality after adjustment for age and disease severity[16,17]. The study by Yaqoob et al., which corresponds most directly to our comparison, completes the picture: pulse-dose therapy increased ICU-free days but had no effect whatsoever on mortality[18]. Taken together, these studies not only support our own negative finding but also provide it with an interpretive framework: the factor limiting outcome in severe ARDS appears to be processes other than the strength of inflammatory suppression.

The existence of results in the literature that appear to favor pulse or high-dose therapy does not weaken this interpretation; explaining these results actually strengthens our own framework. This is because the common denominator of the positive studies is that they examined a patient population or time window

systematically different from our cohort. The study by Edalatifard et al., which associated pulse methylprednisolone with a marked survival benefit, was conducted outside the ICU, in the early inflammatory phase before ARDS developed, and against a background entirely free of steroids; the benefit obtained means "early steroid is superior to no steroid at all," not "pulse is superior to low dose"[10]. Mastruzzo et al. similarly reported a favorable outcome in the early phase by making the need for non-invasive ventilation an exclusion criterion — that is, by excluding the most severely ill patients from the outset — and by combining treatment with remdesivir[19]. In the study by Pinzón et al., the protocol was never applied in the ICU; the apparent benefit emerged among ward patients and largely in the shadow of unbalanced concomitant treatments, and moreover the mortality difference did not cross the statistical threshold[20]. The study by Saeed et al., which reported unusually large effects in favor of methylprednisolone infusion in ventilated ARDS, can be weighed alongside the rigorous, double-blind Salvarani data only as fragile counter-evidence, given the weakness of its blinding and effect sizes that strain the limits of biological plausibility[8]. The explanation that most consistently reconciles this scattered picture is that benefit may be a matter of phenotype and timing rather than dose. Climente-Martí et al. detected a methylprednisolone benefit only in the subgroup with multiple elevated inflammatory markers, and in the analysis by Jiang et al. as well, benefit remained confined to the methylprednisolone subgroup[9,11]. Reinforcing this hypothesis at the mechanistic level, Daenen et al. showed that when high-dose corticosteroid was initiated late in the ICU course, it did not reduce mortality and may even have increased it[5]. Our cohort, by definition, sits at this "late and severe" end of the spectrum; extrapolating the positive results obtained from early, milder, or biomarker-selected populations to our setting would therefore be clinically misleading.

The conceptual axis of this study is the "healing illusion": the apparent improvement in inflammatory and coagulation biomarkers does not correspond to a genuine survival gain. Our own data illustrate this phenomenon concretely; over the day 0–10 follow-up, after correction for multiple comparisons, no biomarker — whether inflammatory or hematologic — shows a difference between groups that survives correction. The clinical danger that must be emphasized here is that the common bedside inference — "if the markers are falling, the patient must be improving" — is not reliable in this disease. The most direct external evidence for this interpretation comes from Pillay et al.: dexamethasone measurably lowered circulating markers of tissue breakdown and the principal inflammatory indicators, yet this decrease was not reflected in survival[12]. The causal mediation analysis by Daenen et al. clarifies why: the relationship between corticosteroid and outcome operates through suppression of inflammation, but only when the markers actually fall; when they do not, the harm remains[5]. In other words, a fall in biomarkers is a sign of the drug's expected pharmacodynamic effect, not evidence that the underlying process has reversed. The finding by Bello et al. sharpens this distinction: in survivors, inflammatory markers fall during the middle period of the illness, whereas in patients who die they either fail to fall or actually rise[21]. The fact that the fall in markers is not dose-dependent — that is, that a low dose is already sufficient to achieve suppression — is evident in both the Kumar and Climente-Martí data[9,11]; this explains why the additional suppression that might be achieved with pulse therapy has no clinical counterpart. Finally, Sayah et al.,

by showing that the principal inflammatory markers fall under corticosteroid independently of outcome, demonstrated the fallacy of reading these indicators as evidence of clinical improvement in a patient receiving steroids[3]. The pattern in our own data — the absence of a between-group difference in biomarkers and the failure of the observed change to translate into survival — fits exactly within this framework and confirms the illusion referenced in the study's title.

The pathophysiological meaning of this pattern is why suppressing inflammation alone is not sufficient in the late phase of severe COVID-19. The conditional relationship demonstrated by Daenen et al. implies that the problem is not inflammatory burden alone; even if markers fall, the trajectory does not change if underlying alveolar damage, fibroproliferation, or concomitant infectious processes continue to progress[5]. The tissue-remodeling data of Pillay et al. give concrete form to this interpretation: in patients who die, collagen turnover continues to rise throughout the ICU stay, meaning that the fibroproliferative process cannot be halted by steroid[12]. The fact that the hyperinflammatory phenotype described by Manson et al., despite occurring in younger and less comorbid patients, carries higher mortality is a reminder that inflammatory indicators must be interpreted together with clinical trajectory, not in isolation[2]. Taken together, this body of evidence offers a defensible explanation for why dose escalation fails to work in late-saturated ARDS: the available evidence suggests that the problem may stem not from an insufficient dose but from the process having already passed the window in which it could respond to the drug.

In a picture where survival benefit could not be demonstrated, the risks that dose escalation would bring tip the decision decisively in one direction. In the study by Yaqoob et al., which corresponds most directly to our own, pulse-dose therapy significantly increased the incidence of acute kidney injury requiring renal replacement[18]; this is a cost specific to the pulse strategy that cannot be disregarded. Xu et al. identified high daily methylprednisolone dose as an independent risk factor for COVID-19-associated invasive pulmonary aspergillosis and showed that this complication significantly increased long-term mortality[22]. Haque et al. and Kumar et al. associated cumulative steroid dose with secondary bacterial infection, and Odhiambo et al. observed more dysglycemia and superimposed pneumonia at high dose[9,15,23]. It should be noted that these signals are not absolute; the data of Salvarani et al. and Joshi et al. did not show a marked excess of adverse events with short courses[8,14]. Nevertheless, the interpretation is clear: in a context where no proven benefit exists, adding renal, infectious, and metabolic risks to the other side of the scale further tips the clinical decision in favor of low dose.

Although the secondary outcomes point in the same direction, they must be interpreted with caution. ICU length of stay was shorter in the low-dose group, and duration of invasive mechanical ventilation showed the same tendency. However, reading these differences directly as a treatment superiority would be misleading; the fact that the pulse group received markedly more intensive respiratory support at baseline — with rates of non-invasive ventilation and prone positioning nearly double — shows that these durations are intertwined with disease severity. In other words, the longer stay may not be a consequence of pulse therapy but a reflection of pulse therapy having been directed toward more

severely ill patients. Joshi et al. reported that length of stay was prolonged at high dose, whereas Tan et al. and Jiang et al. reported no significant difference in such outcomes[6,7,14]; our own observation is consistent with this framework and does not permit the secondary outcomes to be presented as independent evidence of benefit.

The methodological stance of this study supports the reliability of its findings. Choosing RMST as the primary estimand in data where the proportional hazards assumption is violated aligns with recommendations increasingly established in the field; Dormuth et al. emphasized that the classical test loses power under this condition, while An et al. stressed that measures such as RMST should be preferred when proportionality is violated[13,24]. As Gu et al. have shown, although RMST is robust, it is sensitive to the choice of truncation time, and a single summary measure can conceal time-dependent effects; the truncation time was therefore fixed at the clinically meaningful 28 days, and the finding is presented together with median survival[25]. Multivariable adjustment for baseline imbalances, handling of longitudinal biomarkers with an appropriate mixed model together with correction for multiple comparisons, and reporting of effect sizes with confidence intervals are elements that reduce the fragility of the results.

Alongside these strengths, the findings must be read in light of several important limitations. The retrospective, observational design leaves the study open to confounding by indication and selection bias; the fact that patients who received pulse therapy were a younger group but one receiving more intensive respiratory support shows that this bias is concretely present in this dataset. As Suissa has shown, the apparent treatment benefit in observational studies can be inflated by immortal time bias and confounding, and approaches the truth with appropriate adjustment; the loss of significance of the difference after adjustment in our data is consistent with this expectation, although the effect of unmeasured confounders cannot be entirely excluded[26]. The fact that mortality occurred in almost all patients made multivariable logistic regression infeasible; although this limitation was managed by shifting the analysis to the survival-time axis, it must be acknowledged that the saturation of the event limits the discriminative power of the methods. The fact that missingness in longitudinal biomarkers is related to death — that is, is not random in nature — gives rise to survivorship bias in paired within-group comparisons; as Pugh has suggested, this should be addressed with mixed models and sensitivity analyses, but it must be remembered that this assumption itself cannot be verified[27]. The possibility that circulating biomarkers may incompletely reflect the response occurring in lung tissue is a limitation also noted by Pillay et al.[12]. In addition, there are inconsistencies in sample and event counts between the current data version and the original article, and the analysis will be re-validated with the final data file. Finally, the single-center design and 28-day follow-up limit the generalizability of the results and the inferences that can be drawn about the late fibroproliferative phase.

At the clinical level, the practical implication of these findings is clear: the evidence-based standard for managing severe COVID-19 ARDS remains low-dose dexamethasone. Pirracchio et al. associated low-dose corticosteroid with a mortality benefit in severe pulmonary infections, the Cochrane review

demonstrated that benefit is concentrated at the low dose, and the data of Tan, Jiang, Kumar, Joshi, and Odhiambo et al. reinforce this framework[1,4,6,7,9,14,15]. Our own results provide no justification for recommending pulse-dose therapy in routine practice. That said, scientific integrity does not require entirely rejecting the pulse strategy either; the data of Jiang, Climente-Martí, and Manson et al. keep alive the hypothesis that a possible benefit may be confined to a hyperinflammatory phenotype and an early time window[2,7,11]. The correct reading is that this study shows dose escalation to confer no benefit in a late-stage, severely ill ICU population, but that this cannot be extended beyond this population or into a verdict of causality.

These limitations also define the direction for future research. Priority should be given to a randomized design that stratifies patients by inflammatory biomarker level and directly compares pulse with low dose; such a design would make it possible to test in which phenotype and time window a possible benefit emerges. Tracking not only mortality as the outcome but also the trajectory of biomarkers and its link to survival will directly illuminate the "healing illusion" phenomenon. In studies of this kind, where proportional hazards is violated, basing the power calculation and the primary estimand on RMST, supplementing this with milestone hazard ratios, and pursuing multicenter validation would substantially increase the evidentiary value of the findings.

Conclusion

In this retrospective cohort of patients followed in the intensive care unit for severe COVID-19 ARDS, pulse-dose corticosteroid demonstrated superiority over standard low-dose therapy in neither mortality nor time to death; the sub-two-day survival difference that emerged in the adjusted analysis was neither statistically significant nor clinically decisive. No between-group difference that survived correction was found in inflammatory or coagulation biomarkers, and the apparent improvement in biomarkers was not reflected in survival. Although these findings do not permit a verdict of causality or equivalence, they support the conclusion that escalating corticosteroid dose confers no additional benefit in a severe, late-stage ICU population, and that low dose remains the evidence-based standard.

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Figures

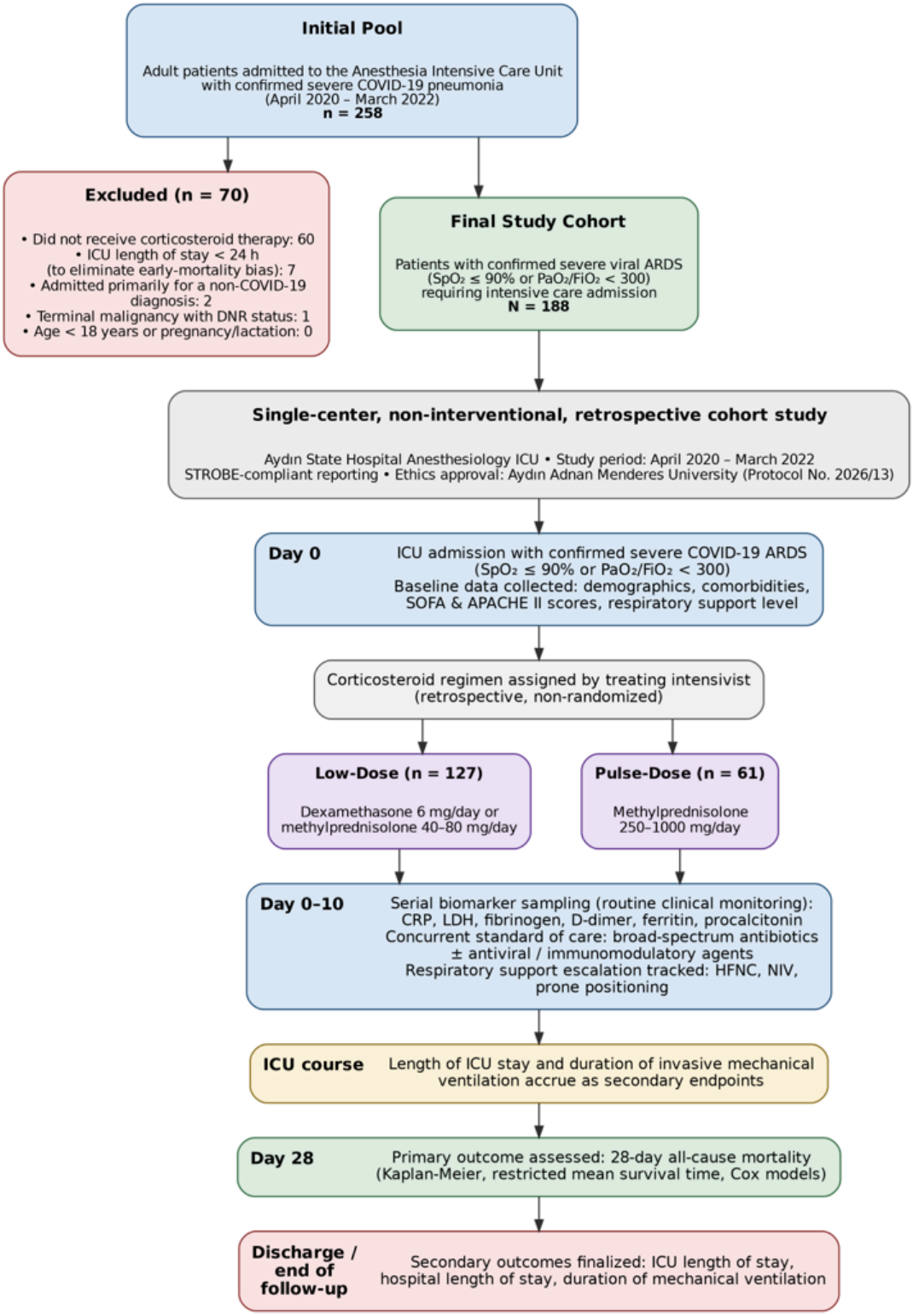


Figure 1

Study design overview. Patients screened for severe COVID-19 pneumonia were assessed for eligibility, and those meeting criteria for confirmed severe viral ARDS were included in the final cohort. Patients admitted to the intensive care unit (Day 0) underwent baseline assessment and were assigned a corticosteroid regimen (standard low-dose or pulse-dose therapy) by the treating intensivist. Clinical and

biomarker data were collected through Day 10, with the primary outcome (28-day all-cause mortality) and secondary outcomes ascertained at discharge or end of follow-up.

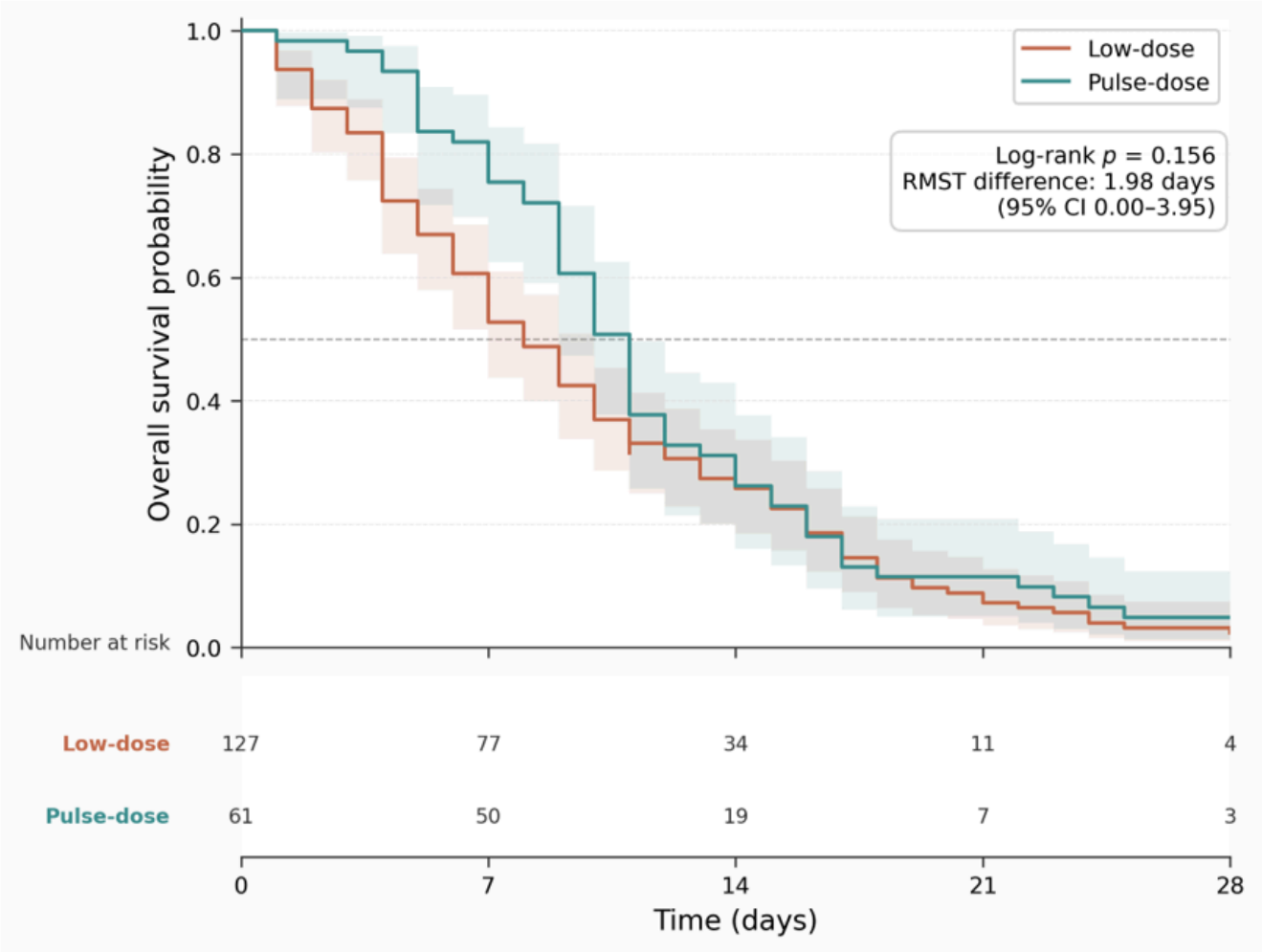


Figure 2

Kaplan-Meier survival analysis of pulse-dose versus standard low-dose corticosteroids. Twenty-eight-day overall survival curves; the orange line represents the standard low-dose group (median survival 8.0 days) and the teal line represents the pulse-dose group (median survival 11.0 days); shaded areas represent 95% confidence intervals, and the horizontal dashed line marks median survival. The log-rank test showed no significant difference in overall survival between groups (p=0.156). Because the proportional hazards assumption was violated (see Supplementary Figure S1), the primary summary measure is the 28-day restricted mean survival time; the between-group difference was 1.98 days (95% CI 0.00–3.95). Numbers of patients at risk are shown below the graph.

Supplementary Files

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- TableS1.docx