



High-dose corticosteroids are associated with higher mortality in patients with COVID-19 ARDS: Results from a nationwide observational study

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ABSTRACT

Background: Optimal corticosteroid dosing strategies remain unclear for severe coronavirus disease 2019 (COVID-19) patients admitted to the intensive care unit (ICU). This study compared mortality among patients treated with high-dose versus standard-dose corticosteroids.

Methods: This prospective cohort study included adult patients with COVID-19 ARDS, defined according to Berlin criteria for ARDS, across 22 centers in the Netherlands between March 2020 and January 2021. Mortality hazards were compared between patients receiving high-dose (>6 mg dexamethasone or equivalent) and standard-dose (6 mg dexamethasone or equivalent) corticosteroids using marginal structural models to adjust for time-varying confounding related to initiation of high-dose therapy. Models were constructed using pooled logistic regression with stabilized inverse probability of treatment weights to emulate a per-protocol analysis.

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, Acute Respiratory Distress Syndrome; ATS, American Thoracic Society; BMI, Body Mass Index; CI, Confidence Interval; COVID-19, Coronavirus Disease 2019; CRP, C-Reactive Protein; FiO₂, Fraction of Inspired Oxygen; HDS, High-Dose Steroids; HR, Hazard Ratio; ICU, Intensive Care Unit; IL-6, Interleukin-6; IPW, Inverse Probability Weighting; IQR, Interquartile Range; IR, Incidence Rate; JAK, Janus Kinase; PaO₂, Partial Pressure of Arterial Oxygen; PRoACT, Protective Ventilation in Acute Respiratory Distress syndrome with COVID-19; PRoVENT, Protective Ventilation Network; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SELECT, Steroids in Hospitalized Patients with COVID-19 in The Netherlands; SOFA, Sequential Organ Failure Assessment; WHO, World Health Organization.

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Results: Data from 848 patients were analyzed: 378(44.6%) received high-dose and 470 (55.4%) standard-dose corticosteroids. Among those treated with high-dose corticosteroids, 63 (16.7%) started therapy within the first day after ICU admission, and 315(83.3%) started at a median of 9 days(IQR = 4–14) after admission. During a median 28 days of follow-up, 183 patients in the high-dose and 154 in the standard-dose group died [incident rate = 2.12 per 100 person-days, 95% confidence interval (CI) = 1.81–2.43 and 1.41 per 100 person-days, 95% CI = 1.13–1.63, respectively]. In the marginal structural model, high-dose corticosteroids were associated with increased mortality (hazard ratio = 2.45, 95%CI = 1.97–3.05). Risk was higher in male patients or those with late initiation (>1 day) of therapy.

Conclusion: In patients with COVID-19 ARDS, high-dose corticosteroids were associated with higher mortality during the first 28 days after ICU admission.

Trial registration: [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/NCT05403359) NCT05403359; <https://clinicaltrials.gov/ct2/show/NCT05403359>

1. Introduction

Acute Respiratory Distress Syndrome (ARDS) is a life-threatening condition, with mortality rates that persist around 40% despite extensive research and improved understanding of its pathophysiology [1,2]. In late 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged, which caused Coronavirus disease 2019 (COVID-19). By 2020, SARS-CoV-2 became pandemic and resulted in increasing numbers of patients with ARDS requiring mechanical ventilation in the Intensive Care Unit (ICU) [3,4].

Severe inflammation, characterized by elevated levels of pro-inflammatory cytokines, has been strongly associated with increased mortality in patients with COVID-19 ARDS patients [5–8]. Recognizing inflammation as a key pathophysiological mechanism, corticosteroids were one of the first effective and affordable therapeutics identified to improve patient outcomes in hospitalized COVID-19 patients on oxygen support [9,10]. The highest benefit on 28-day mortality was observed in patients receiving invasive mechanical ventilation. International guidelines have since then included recommendations to commence a standard regimen of dexamethasone 6 mg for 10 days in all COVID-19 patients on oxygen or ventilatory support [11].

However, this standard dosing contrasts with non-COVID-19 ARDS management, where the American Thoracic Society (ATS) guidelines recommend much higher corticosteroid doses, such as 20 mg dexamethasone daily for five days or a loading dose of 1 mg/kg/day methylprednisolone followed by a tapering schedule [12–15]. Consequently, for COVID-19 patients directly presenting with ARDS or experiencing progressive pulmonary deterioration despite this standard corticosteroid therapy, escalation to high-dose corticosteroids is often considered. Whether increasing the dose of corticosteroids compared with maintaining the standard regimen is more effective to suppress harmful immune responses and improve clinical outcomes remains unclear. Furthermore, these findings may have implications for non-COVID-19 ARDS management, given that optimal corticosteroid dosing remains a matter of ongoing debate.

In addition to variation in dosing, the timing of high-dose corticosteroid administration has also differed considerably in both clinical practice and research. In non-COVID-19 ARDS studies, the optimal window appears to be early in the disease course, specifically within 72 h after ARDS diagnosis, and late administration has proved to be detrimental [13,15]. Conversely, the practice for COVID-19 ARDS patients during the pandemic was administering high-dose corticosteroids during late-stage disease as a rescue therapy, potentially missing the optimal therapeutic window [16].

Previous clinical trials and observational studies on high-dose corticosteroid regimens in COVID-19 ARDS patients have led to conflicting results and often lacked generalizability [9,16–21]. The Steroids in Hospitalized Patients with COVID-19 in the Netherlands (SELECT) study includes individual patient data of intensive care unit (ICU) care from 22 participating ICUs in the Netherlands [22]. In this study, we aimed to compare the hazards of mortality between COVID-19 ARDS patients treated with high-dose corticosteroids and COVID-19 ARDS

patients receiving standard-dose corticosteroids. We hypothesized that early administration of high-dose corticosteroids would be beneficial in this patient population.

2. Methods

2.1. Study design

The SELECT study was designed as a secondary analysis of data collected within the PRoVact-COVID database, an observational, longitudinal, prospective cohort study [23]. This database integrates data from the PRoVENT-COVID study and PRoAcT-COVID study (clinicaltrials.gov study identifiers NCT04346342 and NCT04719182, respectively). In brief, the PRoVact-COVID study included patients who had either high clinical suspicion of COVID-19 or confirmed SARS-CoV-2 infection and who were being mechanically ventilated. Between 7 March 2020 and 29 January 2021, patients were recruited from 22 participating ICUs in the Netherlands. Data were collected throughout the entire ICU stay, including patient characteristics, vital parameters, (ventilator) machine settings, medication, laboratory values, and outcomes.

The study was approved by the local Medical Ethics Review Committee under protocol number MEC-2017-417 and conducted according to the principles of the Declaration of Helsinki. Due to the urgency of conducting research in patients with COVID-19, an exemption for consent was approved by the Medical Research Ethics Committee at the Erasmus Medical Center.

2.2. Data collection

Local physicians and data collectors obtained baseline and demographic variables, including available disease severity scores [e.g., Acute Physiology and Chronic Health Evaluation (APACHE) II or IV, the Simplified Acute Physiology Score II, or the Sequential Organ Failure Assessment (SOFA) score]. Ventilation parameters FiO₂ and PaO₂ were assessed daily to measure oxygen balance changes using the calculated PaO₂/FiO₂ (P/F) ratio. ARDS severity was classified according to the current Berlin definition for ARDS [24].

Data collection began on the first calendar day that a patient received invasive ventilation at a participating ICU, irrespective of hospital or ICU admission date (i.e., day 0). For each day until day 28, hospital discharge, or death, an assessment was made to determine whether the patient was invasively ventilated. Any calendar day during which a patient received invasive ventilation was considered a ‘ventilation day’, regardless of the duration of ventilation on that day or whether it was performed through an orotracheal tube or a tracheostomy.

Local physicians and data collectors recorded detailed daily information up to day 28, including the dates of ICU discharge, hospital discharge, death, and whether the patient experienced thromboembolic events, such as deep vein thrombosis or pulmonary embolism. Dates of ICU discharge, hospital discharge and death were also registered.

All data were entered into a password-secured, internet-based,

electronic case report form (Castor EDC). Before analysis, the study coordinators screened all data for potentially erroneous or incomplete recordings and verified and corrected information, where appropriate, with the help of local physicians and data collectors. After cleaning, the database was closed for analysis. We used the dataset closed on 24 April 2024.

2.3. Study population

We included patients in the SELECT study who were aged ≥ 18 years, diagnosed with COVID-19, had the Berlin criteria for ARDS [24], and received either standard-dose or high-dose corticosteroids. We excluded all patients who were transferred to another clinical center (due to data unavailability), pregnant, or did not have sufficient data to allow significant calculation of weights for inverse probability weightings.

2.4. Definition of treatment

High-dose corticosteroids were defined as >6 mg/day dexamethasone or an equivalent dose of another corticosteroid: >200 mg cortisone, >160 mg hydrocortisone, >40 mg prednis(ol)one, >32 mg methylprednisolone, or >6 mg betamethasone. Standard-dose corticosteroids were defined as 6 mg/day dexamethasone or equivalent: 200 mg cortisone, 160 mg hydrocortisone, 40 mg prednis(ol)one, 32 mg methylprednisolone, or 6 mg betamethasone (Supplementary Table 1). Patients were classified as receiving either treatment if the respective corticosteroid dose was administered for one day or more. We assigned patients to their exposure at the time of laboratory measurement, which was updated every day during ICU stay and hence time-varying. Data on the type of corticosteroid treatment, dose of corticosteroid, and date of commencement and discontinuation were recorded.

2.5. Definition of outcome

All-cause mortality was the primary outcome of the analysis. Patients were monitored from the time of admission to the ICU until hospital discharge. Follow-up monitoring of the study outcome did not occur after hospital discharge, and thus all reported deaths were in-hospital.

2.6. Statistical analysis

Baseline was defined as the first study visit at which the patient was admitted to the ICU and had complete data on all covariates. Follow-up continued until day 28 after ICU admission, ICU discharge, or death, whichever occurred first.

Two patient groups were defined based on corticosteroid exposure during follow-up: those who received only standard-dose corticosteroids (6 mg dexamethasone daily) and never a higher dose (hereafter referred to as “standard-dose”), and those who received high-dose therapy, with or without prior standard dosing (hereafter referred to as “high-dose”).

Baseline characteristics of the study population were summarized using counts and percentages for categorical variables, and medians with interquartile ranges (IQR) for continuous variables. For patients who received high-dose corticosteroids, characteristics at the visit prior to initiation were also summarized. Distributions were compared using Pearson's χ^2 test or Fisher's exact test for categorical variables, and the Kruskal–Wallis test for continuous variables.

To account for the time-varying confounding of commencing high-dose corticosteroids, we used marginal structural models to estimate the effect of high-dose versus standard-dose corticosteroids on mortality. Under the assumptions of unmeasured confounding, correct model specification and positivity, the effect estimate can be interpreted as a causal effect [25]. Baseline confounders were age, sex at birth, and body-mass index (BMI). Time-varying confounders were PaO₂/FiO₂ ratio and C-reactive protein (CRP) levels. For time-varying confounders, the last observations were carried forward until a new measurement

became available. We computed time-varying stabilized weights defined as the inverse of the probability of belonging to the high-dose corticosteroid dosing strategy using the ‘ipw’ package in R. The stabilized weight typically includes an inverse probability of censoring weight, yet due to the lack of determinants associated with censoring (i.e., non-informative), this weight was not included. We fitted a pooled logistic regression model that included the final weights to estimate the hazard ratio (HR) of mortality for high-dose versus standard-dose corticosteroid therapy. To account for repeated measurements per patient, we calculated 95% confidence intervals (95%CI) from robust standard error estimates. The result from this model emulates a per protocol analysis.

In *post-hoc* analysis, we ran each model within subgroups of patients to determine whether effects differed across strata of clinically-relevant factors. These factors included sex (female and male), body-mass index (BMI, >30 kg/m² and ≤ 30 kg/m²), SOFA score (>7 and ≤ 7), and CRP (>200 mg/L and ≤ 200 mg/L). We chose CRP among all other inflammatory markers as CRP had the fewest missing data and is used more often in routine clinical care, while the cutoff of 200 mg/L was chosen as it indicates increased survival benefits for standard corticosteroid therapy during community-acquired pneumonia [26]. For factors that were also included in the weights, they were excluded in the logistic regression model estimating the probability of treatment. We also ran models in which the high-dose corticosteroid group was stratified on timing of commencing their high-dose regimen [i.e., <1 versus ≥ 1 day (or 24 h), <3 versus ≥ 3 days, and <7 versus ≥ 7 days].

In sensitivity analyses, we excluded all patients who were recruited prior to the second epidemic wave (i.e., before 1 October 2020) as there was substantial variability in administering corticosteroid treatments and extensive heterogeneity of COVID-19-related treatment protocols during the first epidemic wave of SARS-CoV-2 (Supplementary Fig. 1). We also ran sensitivity analysis by (1) excluding those with prior use of corticosteroids and (2) those with other immunomodulatory agents (i.e., baricitinib, JAK inhibitors, and IL-6 receptor antagonists (tocilizumab/sarilumab), as the use of these therapies could be an indication of poorer clinical improvement and could influence results. Finally, we performed an *E*-value analysis to assess the minimum strength of association that a potential unmeasured confounder (e.g., compliance of the lungs, failure to reduce sedation, etc.) would need to have with both high-dose corticosteroids and mortality to explain away the main association [27,28]. This analysis was conducted on the HR and the lower limit of its 95%CI.

Statistical analyses were carried out using R (v4.4.3, R Core Team 2023, Vienna, Austria). These analyses pertain to work packages 2 and 3 of the original protocol [22], with final analysis using time until death as the primary outcome and employing a marginal structural model.

3. Results

3.1. Description of the study population

We retrieved data from 1870 patients included in the PRoVAcT-COVID cohort. Of them, we excluded 1022 patients (flowchart of exclusions in Fig. 1). In total, we analyzed data from 848 patients, of whom 378 (44.6%) were in the high-dose and 470 (55.4%) in the standard-dose corticosteroid therapy groups.

In Table 1, the characteristics of the study population at inclusion are summarized and compared between high-dose and standard-dose corticosteroid therapy groups. Compared to patients in the standard-dose corticosteroid group, patients in the high-dose group had a lower percentage with prior use of corticosteroids ($p < 0.001$), lower percentage with heart failure ($p = 0.018$), higher percentage of controlled ventilation (overall $p < 0.001$), higher need of vasoactive medication ($p = 0.0027$), and higher levels of C-reactive protein ($p = 0.0008$). Of note, there were no differences in median age, BMI, and distribution of sex between groups at inclusion (Table 1).

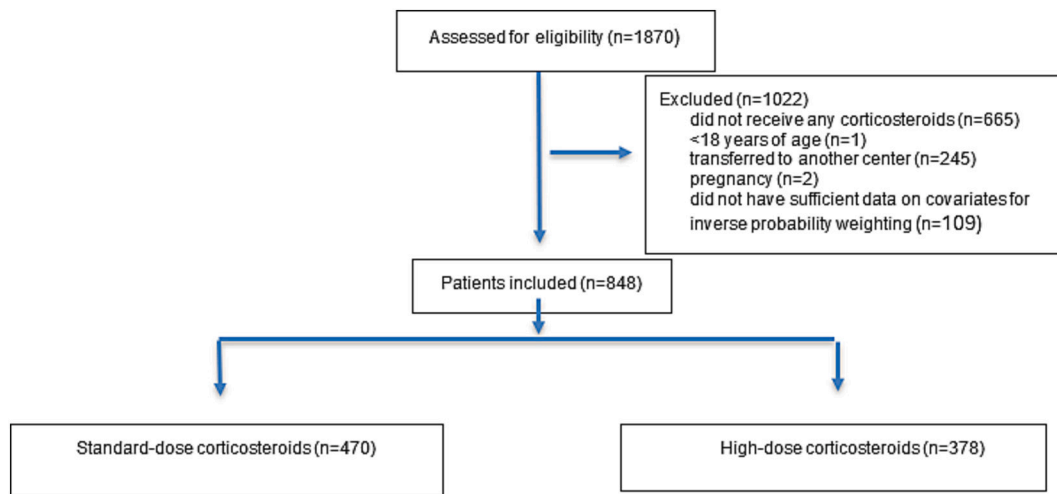


Fig. 1. Flowchart of patient selection.

Table 1
Characteristics of the study population.

	Corticosteroid treatment group			$p^{1,2}$	$p^{2,3}$
	Standard-dose (n = 470)	High-dose (n = 378)			
	Inclusion	Inclusion	Visit prior to begin high-dose		
Age, years	65 (58–72)	66 (59–72)	–	0.13	
Male sex	345 (73.4)	283 (74.9)	–	0.69	
Body mass index, kg/m ²	28.5 (25.6–32.3)	28.2 (25.5–31.8)	–	0.33	
Prior use of corticosteroids	256 (55.1)	136 (36.9)	–	<0.001	
Any comorbidity	277 (58.9)	218 (57.7)	–	0.76	
Hypertension	173 (36.8)	134 (35.4)	–	0.74	
Diabetes	144 (30.6)	106 (28.0)	–	0.45	
COPD	46 (9.8)	36 (9.5)	–	0.99	
Chronic kidney disease	50 (10.6)	25 (6.6)	–	0.054	
Heart failure	28 (6.0)	9 (2.4)	–	0.018	
Hematological malignancy	5 (1.1)	5 (1.3)	–	0.98	
SOFA score	7 (6–10)	8 (6–10)	8 (6–11)	0.19	0.99
Ventilator mode ⁴			–	<0.001	
Controlled ventilation ⁵	273 (60.9)	249 (67.3)	–		
Pressure-support ventilation	140 (31.3)	58 (15.7)	–		
Intellivent-ASV	24 (5.4)	9 (2.4)	–		
Other	11 (2.5)	37 (10.0)	–		
Missing	22 (4.7)	17 (4.6)	–		
Ventilator settings			–		
Tidal volume, mL	447 (397–500)	437 (381–490)	449 (393–523)	0.26	0.32
PaO ₂ /FiO ₂ ratio	120 (95–160)	117 (84–161)	131 (93.2–179)	0.11	0.86
P _{peak} or P _{max} , cmH ₂ O	26 (23–30)	27 (24–31)	26 (21–31)	0.72	0.61
ARDS severity ⁶				0.11	0.20
Mild	62 (13.2)	45 (11.9)	61 (16.1)		
Moderate	267 (56.8)	194 (51.3)	222 (58.7)		
Severe	141 (30.0)	139 (36.8)	95 (25.1)		
Heart rate, b/min	82 (69–101)	88 (69–102)	86 (72–148)		0.69
Need of vasopressors/inotropics	404 (86.5)	352 (93.1)	–	0.0027	
Mean arterial blood pressure, mmHg	82 (72–94)	80 (71–92)	79 (71–90)	0.12	0.0022
C-reactive protein, mg/L	110 (53–194)	133 (67–242)	134 (63–242)	0.0008	0.65
D-dimer, mg/L	1.00 (0.15–3.92)	1.00 (0–2.84)	1.32 (0.15–3.23)	0.087	<0.001

Abbreviations: ARDS, acute respiratory distress syndrome; ASV, adaptive support ventilation; COPD, Chronic Obstructive Pulmonary Disease; SOFA, Sequential Organ Failure Assessment.

All data are n (%) for categorical variables and median (interquartile range) for continuous variables.

¹ Participants receiving standard-dose and high-dose corticosteroid therapy were compared using Pearson's χ^2 test for categorical variables and Kruskal-Wallis test for continuous variables.

² Comparison is between visits at inclusion.

³ Comparison is between visits at inclusion (for those in the standard-dose groups) and at first visit prior to commencing high-dose corticosteroids (for those in the high-dose group).

⁴ First day of intubation.

⁵ Controlled ventilation refers to the combined categories of volume-controlled and pressure-controlled ventilation.

⁶ Determined from the P/F-ratio: mild, 200–300; moderate, 100–200; severe, <100. [24].

3.2. Follow-up of the study population

Median follow-up was 28 days (IQR = 19–28), with a slightly shorter follow-up period in the high-dose corticosteroid group ($p = 0.017$) (Table 2). For those commencing high-dose corticosteroids, 63 (16.7%) patients received treatment within the first day after admission at the ICU. The remaining 315 (83.3%) patients commenced high-dose corticosteroids at median of 9 days (IQR = 4–14) after ICU admission. At the time of initiating high-dose corticosteroids, mean arterial blood pressure remained numerically comparable and median lymphocyte and D-dimer levels showed numerical increases compared to baseline. Nevertheless, all three variables remained significantly different compared to those of

Table 2

Treatment and clinical outcomes during follow-up, stratified on those who received high-dose versus standard dose corticosteroid therapy.

	Corticosteroid treatment group		p^1
	Standard-dose ($n = 470$)	High-dose ($n = 378$)	
Study follow-up time, days	28 (20–28)	28 (19–28)	0.017
Type of corticosteroids used ²			
Dexamethasone (n)	392 (83.4)	90 (23.8)	
Dose administrated (mg)	–	12 (8–20)	
Cumulative days of use	7 (4–10)	7 (3–10)	
Hydrocortisone (n)	17 (3.6)	46 (12.2)	
Dose administrated (mg)	–	270 (200–300)	
Cumulative days of use	2 (1–3)	3 (1–4)	
Prednis(o)lone (n)	80 (17.0)	175 (46.3)	
Dose administrated (mg)	–	75 (60–89)	
Cumulative days of use	6 (3–11)	10 (4–16)	
Methylprednisolone (n)	10 (2.1)	143 (37.8)	
Dose administrated (mg)	–	280 (170–1000)	
Cumulative days of use	3 (2–10)	4 (3–7)	
Other anti-inflammatory drugs used			
Any anti-inflammatory drug (n)	57 (12.1)	114 (30.2)	<0.001
Hydroxychloroquine	28 (6.0)	76 (20.1)	<0.001
Colchicine	3 (0.6)	2 (0.5)	0.99
Tocilizumab	11 (2.3)	18 (4.8)	0.082
Other	16 (3.4)	22 (5.8)	0.13
Care-related			
Interventions during ICU stay (n)			
Tracheostomy	54 (11.8)	76 (20.3)	0.0012
Complications (n)			
Hyperglycaemia ³	227 (49.5)	235 (62.3)	0.0003
Any thromboembolic event (n)	62 (13.2)	93 (24.6)	<0.0001
Deep venous thrombosis ⁴	51 (10.9)	82 (21.7)	<0.0001
Pulmonary embolism ⁴	11 (2.3)	11 (2.9)	0.76
In hospital mortality	154 (32.8)	183 (48.4)	<0.0001
Clinical follow-up ⁵			
Ventilation duration, days	9 (5–18)	19 (11–31)	<0.0001
ICU length of stay, days	12 (7–21)	20 (13–35)	<0.0001
Hospital length of stay, days	21 (14–31)	28 (19–46)	<0.0001

All data are n (%) for categorical variables and median (interquartile range) for continuous variables.

Missing values: tracheostomy (standard-dose, $n = 1$).

Abbreviations: ICU, Intensive Care Unit.

¹ Patients receiving standard-dose and high-dose corticosteroid therapy were compared using Pearson's χ^2 test for categorical variables and Kruskal-Wallis test for continuous variables.

² For each corticosteroid treatment, data are provided on any use during follow-up and what was the maximal dose given during high-dose therapy (i.e., “dose administrated”). Information is also provided on the cumulative duration of use in days, regardless of dose. Patients could have received more than one corticosteroid treatment during follow-up.

³ Hyperglycaemia was defined by the use of insulin as either a bolus given more than 2 times or continuously during ICU stay.

⁴ Identified on radiographic imaging.

⁵ The time in these data includes follow-up that was not part of study follow-up (i.e., all follow-up time 28 days from ICU admission).

patients receiving standard-dose corticosteroids at inclusion ($p = 0.0022$, $p < 0.001$, $p < 0.001$, respectively) (Table 1).

Clinical outcomes are summarized in Table 2. While including time at the ICU beyond the study follow-up time, median ICU, hospitalization, and ventilation duration were all significantly higher in those with high-dose versus standard-dose corticosteroids (all $p < 0.0001$). During follow-up, hyperglycemia occurred more commonly in the high-dose versus standard-dose groups ($p = 0.0003$).

3.3. Effect of high-dose corticosteroids on overall mortality

During follow-up, 337 (39.7%) patients died (IR = 1.72 per 100 person-days, 95%CI = 1.54–1.90), of whom 183 (42%) were in the high-dose corticosteroids group (IR = 2.12 per 100 person-days, 95%CI = 1.31–1.68) and 154 (54.3%) in the standard-dose corticosteroid group (IR = 1.41 per 100 person-days, 95%CI = 1.97–3.05). In-hospital death occurred at a median of 18 days (IQR = 13–24) in the high-dose and of 13 days (IQR = 8–19) in the standard-dose corticosteroid groups. Deaths in the group receiving high-dose corticosteroids occurred at a median of 8 days (IQR = 4–15) after commencing treatment.

As shown in Fig. 2, the predicted survival probability curves illustrate the difference between exposure groups in terms of mortality during follow-up. High-dose corticosteroid therapy was associated with a 2.43-times higher risk of mortality compared to patients in the standard-dose group. This association was similar in sensitivity analyses in which only patients in the second epidemic wave (HR = 2.42, 95%CI = 1.90–3.13) were included (Supplementary Fig. S2A). The association between high dose corticosteroids and mortality was also similar in the analysis in patients without prior corticosteroid use (HR = 2.37, 95%CI = 1.73–3.25) and in the analysis in which only patients without any other immunomodulatory agents (HR = 2.43, 95%CI = 1.90–3.12) were included. From the E -value analysis, the minimum HR that an unmeasured confounder would need to have with both high-dose corticosteroids and mortality to explain away this association was 3.11 (lower limit = 2.57). The median IPW used in the marginal structural model run on the overall study population was 0.99 (IQR = 0.91–1.05; minimum = 0.42, maximum = 4.30).

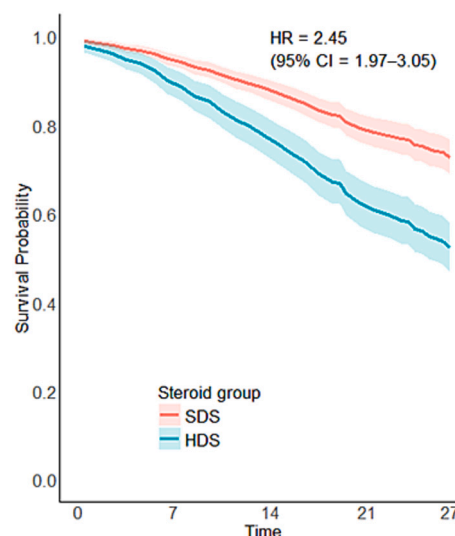


Fig. 2. Predicted survival curves of patients receiving high-dose versus standard dose corticosteroid therapy.

Predicted survival curves from the marginal structural model run on the overall population are presented in solid lines with bootstrapped 95% confidence intervals. These curves were stratified on high-dose (labeled as “HDS”) versus standard dose (labeled as “SDS”) corticosteroid therapy. Abbreviation: CI, confidence interval; HR, hazards ratio.

3.4. Post hoc analyses of effect of high-dose corticosteroids on overall mortality

In subgroup analyses (Table 3), male patients had a higher hazard of mortality when treated with high-dose corticosteroids compared to the standard-dose. Those with a BMI $> 30 \text{ kg/m}^2$, CRP levels $\leq 200 \text{ mg/L}$ or a SOFA score ≤ 7 also had a slightly higher risk of mortality when exposed to high-dose corticosteroids compared to the standard-dose; however, the 95%CI of these HR were mostly overlapping with those who had a $\leq 30 \text{ kg/m}^2$, CRP levels > 200 and SOFA score > 7 , respectively (Table 3).

The results from stratifying patients based on the timing of high-dose corticosteroid initiation are shown in Fig. 3. When comparing patients who received high-dose corticosteroids within the first day (< 1 day) of ICU admission to those who started treatment later (≥ 1 day), only the latter group showed a significantly increased hazard of death. However, when comparing patients who received high-dose corticosteroids within the first three days (< 3 days) to those who started at or after day 3 (≥ 3 days), both groups had a significantly increased risk of mortality, with a stronger association in the latter. The differences in associations were less pronounced when comparing < 7 versus ≥ 7 day delay in receiving high-dose corticosteroids.

4. Discussion

In this study among patients with COVID-19 ARDS, treatment with high-dose corticosteroids was associated with increased mortality when compared to patients treated with standard-dose steroids. The association between high-dose corticosteroids and increased mortality was more pronounced in patients who were male and notably, in those who received high-dose corticosteroids more than 24 h after ICU admission.

Our findings demonstrate a clear negative effect of high-dose corticosteroids on mortality when compared to the standard-doses recommended in current COVID-19 guidelines. Previous studies investigating high-dose corticosteroids in patients with severe COVID-19 have yielded conflicting results, with some suggesting benefits on mortality [17,18] and others showing no effect [9,19] or even harmful effects [16,20]. Many of these studies included heterogeneous patient populations with varying levels of respiratory support—ranging from oxygen therapy to invasive ventilation or extracorporeal membrane oxygenation. Since the effectiveness of high-dose corticosteroids depends on the severity of hypoxemia [29], our study addressed this limitation by focusing exclusively on the most severely affected patients—those requiring

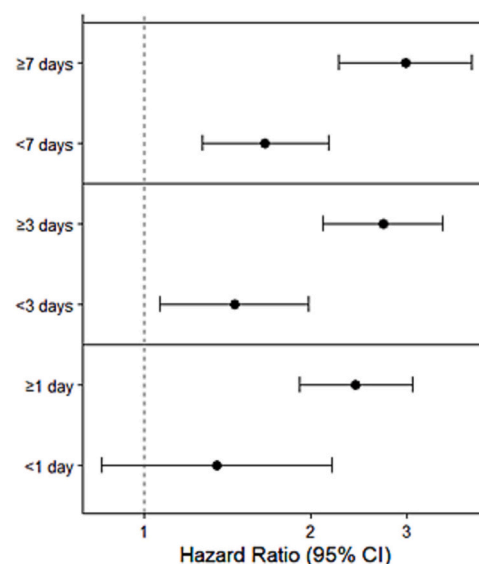


Fig. 3. Differences in effect of high-dose corticosteroids on mortality depending on timing of commencement.

Hazards ratios and 95% confidence intervals (CI) were calculated from a pooled logistic-regression model with robust confidence intervals. Separate models were run by stratifying those with high-dose corticosteroid therapy on day of commencing therapy (< 1 or ≥ 1 day or 24 h, < 3 or ≥ 3 days, and < 7 or ≥ 7 days) compared to standard dose therapy.

mechanical ventilation and fulfilling the Berlin criteria for ARDS.

In contrast to our results, the randomized control trial, RECOVERY, found no significant benefit or harm on mortality with high-dose corticosteroids in mechanically ventilated COVID-19 patients [30]. Nevertheless, patients were randomized to receive high-dose corticosteroids shortly after hospital admission in this trial, whereas high-dose corticosteroids were commenced a median of 9 days after start of mechanical ventilation in our cohort. Increased mortality has also been observed in another study where high-dose corticosteroids were administered a median of 15 days after start of mechanical ventilation in COVID-19 patients [16]. When high-dose corticosteroids were administered within 24 h of the start of mechanical ventilation in our study, there was no effect of high-dose therapy on mortality—this lack of effect was also observed in the RECOVERY trial. However, the increased risk of mortality appeared when high-dose corticosteroid therapy was given after 24 h, suggesting that timing is a critical determinant of the worsening effects of corticosteroids. The current ATS and SCCM-ARDS guidelines recommend initiating high-dose corticosteroid treatment early after ARDS diagnosis (< 72 h) [15,31]. Given the clear lack of benefit for initiation of high-dose corticosteroids, these recommendations should not be extended to COVID-19 ARDS patients.

In addition to timing and dosing, we identified males to have a particularly increased risk of mortality from receiving high-dose corticosteroid treatment in our study. One possible explanation for this finding could be the stronger biological immune responses observed in females compared to males, as evidenced by higher T cell activation during SARS-CoV-2 infection [32,33].

Several factors may underlie the observed increased risk of mortality with high-dose corticosteroids. One potential explanation relates to patient selection. Two inflammatory phenotypes have been described in patients with ARDS, described as hyperinflammatory and non-hyperinflammatory. The former is associated with improved outcomes during ARDS interventions, including immunomodulation with simvastatin [34]. In COVID-19 ARDS, similar phenotypes exist, with the hyperinflammatory phenotype showing improved survival during standard-dose dexamethasone [35]. In this context, it is possible that patients in the high-dose corticosteroid arm were more frequently

Table 3
Effect of high-dose corticosteroids on mortality stratified by subgroups.

Subgroups	n of deaths	N ¹	HR (95%CI)
Sex at birth			
Female	70	220	1.66 (1.01–2.75)
Male	267	628	2.16 (1.66–2.82)
BMI			
$\leq 30 \text{ kg/m}^2$	204	522	1.95 (1.44–2.63)
$> 30 \text{ kg/m}^2$	128	320	2.10 (1.44–3.08)
SOFA score during follow-up			
≤ 7	61	216	1.91 (1.18–3.07)
> 7	177	414	1.78 (1.28–2.50)
CRP levels during follow-up			
$\leq 200 \text{ mg/L}$	228	608	2.15 (1.64–2.81)
$> 200 \text{ mg/L}$	109	240	1.91 (1.21–3.02)

Hazards ratios (HR) and 95% confidence intervals (CI) were calculated from a pooled logistic-regression model with robust confidence intervals.

¹For variables considered during follow-up, the total number within a subgroup (N) is given for the baseline visit. Missing at baseline: BMI (n = 6), SOFA (n = 218).

Abbreviations: BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; N, number of patients; SOFA, sequential organ failure assessment.

exhibiting the hypo-inflammatory subphenotype and therefore could not benefit from this treatment dosing. These phenotypes could not be assessed in our database and this hypothesis remains thus speculative. Furthermore, some patients may have been critically ill due to complications such as ventilator-associated pneumonia or catheter-related bloodstream infections, in which high-dose corticosteroids were more likely given and were unable to provide clinical benefit. We did not collect data on causes of death—a limitation shared with the vast majority of epidemiological studies worldwide [36]—making it impossible to determine the true mechanisms explaining these results.

This study has other limitations. One limitation is its observational design, which inherently introduces bias from non-randomized interventions and thus increases the potential for indication bias and differential loss to follow-up. Although we used marginal structural models to account for time-varying confounding, unmeasured confounders—particularly subjective clinical decision-making factors—may still have influenced our results. We performed an *E*-value analysis to understand the extent of confounding that needs occur to explain away this association and observed that the unmeasured confounder would have to have a relatively strong association with both high-dose corticosteroids and mortality, making residual confounding an unlikely explanation for these findings. A major strength of our study lies in a large cohort from 22 participating ICUs across the Netherlands, which encompasses the heterogeneity of ICU management across diverse centers. Moreover, while most previous clinical trials used standardized protocols for administering high-dose corticosteroids early after ICU admission, clinical practice often involves later administration, particularly in cases of non-resolving ARDS. Therefore, we believe that the results of this study provide a closer estimate of the effectiveness of high-dose corticosteroids, generalizable to many settings.

5. Conclusions

High-dose compared to standard-dose corticosteroids was associated with increased mortality in patients with COVID-19 ARDS. This harmful effect was most pronounced in male patients. When initiated within 72 h after the start of mechanical ventilation, the harmful effect was attenuated but no clear benefit emerges. These findings suggest that high-dose corticosteroids should not be used in COVID-19 ARDS.

CRedit authorship contribution statement

Anders Boyd: Writing – original draft, Visualization, Validation, Supervision, Methodology, Formal analysis, Conceptualization. **Katrijn Daenen:** Writing – original draft, Visualization, Project administration, Formal analysis, Data curation. **Sarah Stoof:** Writing – review & editing. **Hugo D.G. van Willigen:** Writing – review & editing. **Diederik Gommers:** Writing – review & editing. **Hazra S. Moeniralam:** Writing – review & editing, Data curation. **Corstiaan A. den Uil:** Writing – review & editing, Data curation. **Nicole P. Juffermans:** Writing – review & editing. **Merijn Kant:** Writing – review & editing, Data curation. **Abraham J. Valkenburg:** Writing – review & editing, Data curation. **Janesh Pillay:** Writing – review & editing, Data curation. **Eric van Gorp:** Writing – review & editing, Supervision. **Janke Schinkel:** Writing – review & editing, Funding acquisition, Conceptualization. **David M.P. van Meenen:** Writing – review & editing, Data curation. **Robin Goossen:** Writing – review & editing, Data curation. **Frederique Paulus:** Writing – review & editing, Supervision, Data curation. **Virgil Dalm:** Writing – review & editing, Supervision. **Lieuwe D.J. Bos:** Writing – review & editing, Funding acquisition, Conceptualization. **Henrik Endeman:** Writing – original draft, Supervision, Funding acquisition, Conceptualization. **Jilske A. Huijben:** Visualization, Supervision, Project administration, Methodology, Formal analysis.

Consent for publication

Not applicable. This manuscript does not contain any individual person's data in any form (including individual details, images, or videos).

Ethics approval and consent to participate

The study was approved by the local Medical Ethics Review Committee of the Erasmus University Medical Center under protocol number MEC-2017-417 and conducted according to the principles of the Declaration of Helsinki. Due to the urgency of conducting research in patients with COVID-19, an exemption for consent was approved by the Medical Research Ethics Committee at the Erasmus University Medical Center. An opt-out informed consent procedure (MEC-2022-0297) was used and patients who expressed objections to participation were excluded from the study.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: (Henrik Endeman reports financial support was provided by ZonMw. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.)

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jcrc.2026.155670>.

Data availability

The data sets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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