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ORIGINAL RESEARCH

High-Dose Corticosteroids in Critically Ill COVID-19 Patients: A Retrospective Cohort Study from Suriname

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Background: High-dose corticosteroids (HDS) are established treatment for non-COVID-19 acute respiratory distress syndrome (ARDS) because of their anti-inflammatory effects. In COVID-19 patients requiring oxygen therapy or invasive mechanical ventilation, 6mg dexamethasone daily reduces mortality. In severe COVID-19 pneumonia, higher corticosteroid doses are sometimes administered in an attempt to reduce mortality. This study evaluated the effect of HDS compared to standard-dose dexamethasone on IC mortality and superinfection rates in Suriname.

Methods: This retrospective cohort study included patients with PCR-confirmed severe COVID-19 pneumonia admitted to ICUs in Suriname, between June 2020 and October 2021. Data was analyzed from a random sample of patients extracted from a larger database originally collected for another ICU COVID-19 study. Patients received standard-dose corticosteroids (SDS) and/or HDS (dexamethasone >6 mg daily or equivalent). Treatment with HDS was analyzed as a time-dependent exposure. Predictors of mortality were identified through logistic regression and incorporated as covariates in a time-updated Cox survival model. Chi-square test compared bacterial superinfections between treatment groups.

Results: Of 103 included patients, 36 (35%) received HDS. Invasive mechanical ventilation, septic shock, bacterial superinfection, creatinine elevation, age, CXR score, and P/F ratios were associated with mortality in univariable analysis. In multivariable analysis, only age (OR 1.10 per year, p=0.022) and invasive mechanical ventilation (OR 8.28, p=0.046) remained significant. Time-updated survival analysis showed no significant harm or benefit with HDS (HR 1.99, 95% CI:0.78–5.09, p=0.15) and no increased superinfection rates (p=1.00).

Conclusion: This first Surinamese study of HDS in severe COVID-19 pneumonia found no improved outcomes compared to SDS, nor increased bacterial superinfections. Our findings do not support HDS escalation in this population. The identified mortality risk factors provide valuable guidance for recognizing high-risk patients.

Keywords: infectious diseases, virology, COVID-19, corticosteroid

Introduction

The emergence of SARS-CoV-2 caused a global COVID-19 pandemic, with high mortality and morbidity rates.[1] The primary reason for hospitalization of COVID-19 patients, is the need for supplemental oxygen therapy due to hypoxemia.[2–4] In cases of progressive respiratory failure intensive care unit (ICU) admission is often required, with the majority of patients meeting the Berlin criteria for acute respiratory distress syndrome (ARDS).[2,5,6] Severe

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inflammation, characterized by elevated levels of (pro)-inflammatory cytokines, has been strongly associated with increased mortality in these patients.[3,7–10]

In 2021, low-dose corticosteroids became the standard immunosuppressive therapy for hypoxic COVID-19 patients, based on evidence that demonstrated reduced disease progression and mortality risk.[11–13] Current COVID-19 guidelines recommend 6 mg of dexamethasone daily for up to 10 days. In contrast, for non-COVID-19 ARDS, guidelines advise significantly higher corticosteroid doses to mitigate severe inflammation.[14] Consequently, clinicians sometimes resort to high-dose corticosteroids (HDS) in severe COVID-19 pneumonia. However, the efficacy and safety of HDS in this context is not fully clear, with existing studies reporting conflicting outcomes and some reporting harm.[15–18]

A meta-analysis comparing high- and standard-dose corticosteroid regimens in hospitalized COVID-19 patients found no differences in mortality outcomes.[19] A rather recent randomized controlled trial in mechanically ventilated patients—comparable to the ICU cohort described in this thesis—demonstrated that high-dose corticosteroids neither reduced nor increased mortality. However, most data comes from high-income countries in Europe and North America and outcomes may vary substantially between countries, because of differences in healthcare infrastructure and access to supportive care.[20–22] Another observational study examined the effect of HDS when administered after standard-dose treatment, and found that HDS were associated with increased mortality.[23] Timing plays a critical role, as late administration of HDS, once irreversible fibro-proliferation is predominant, could be harmful.[24] Beyond this lack of demonstrated benefit, there are safety concerns, as the immunosuppressive effect of HDS could raise the risk of superinfections.[24–27] This risk could be particularly concerning in low- and middle-income countries, where the burden of infectious diseases is more substantial.[28]

This study aimed to examine the effect of HDS compared to the standard 6mg dexamethasone regimen on ICU mortality and the incidence of bacterial superinfections in patients with severe COVID-19 pneumonia in Suriname. Given the limited evidence on HDS treatment in COVID-19 ICU patients from South American low- and middle-income countries, our multicenter study provides relevant data to support the refinement of existing guidelines and advance evidence-based decision-making in this context.

Materials and Methods

Study Design

This study was a retrospective multicenter cohort study conducted in Suriname. We analyzed data from a random sample of 104 patients extracted from a larger database originally collected for a study investigating convalescent plasma (CCP) treatment effects in COVID-19 patients.[29] Patients were admitted to the intensive care units (ICUs) of the Academic Hospital Paramaribo or the Wanica Regional Hospital in Suriname from June 2020 to October 2021. The Academic Hospital Paramaribo is a tertiary referral center with a 15-bed closed-format ICU, 24/7 in-house intensivist coverage, and a nurse-to-patient ratio of approximately 1:2. The ICU follows a closed model, meaning that all care is coordinated and led by a dedicated team of intensivists, ensuring continuity and protocol-based decision-making. The estimated annual ICU admission capacity is between 850 and 1500 patients. The Wanica Regional Hospital is a secondary care facility with a 9-bed ICU that was opened specifically during the COVID-19 pandemic. During this period, in-house intensivist coverage was present on a temporary basis to support critical care delivery. The unit operated under an open ICU model with a nurse-to-patient ratio of approximately 1:3. Following the pandemic, the ICU was closed due to staffing shortages and is currently non-operational. The inclusion criteria were: (1) age ≥18 years, (2) PCR-confirmed SARS-CoV-2 infection, (3) admission to ICU with severe COVID-19 pneumonia characterized by P/F ratio <300 mmHg and room air oxygen saturation <93%,[30] and (4) treatment with either SDS and/or HDS during their ICU stay. An overview of the study inclusion process is shown in Figure 1.

Data Collection

Data was collected from the hospital's paper-based records using standardized data collection forms. Patient data, including demographics, body mass index (BMI), comorbidities and radiological and laboratory parameters were collected from the day of ICU admission until ICU discharge or death. Ventilation parameters FiO_2 and PaO_2 were

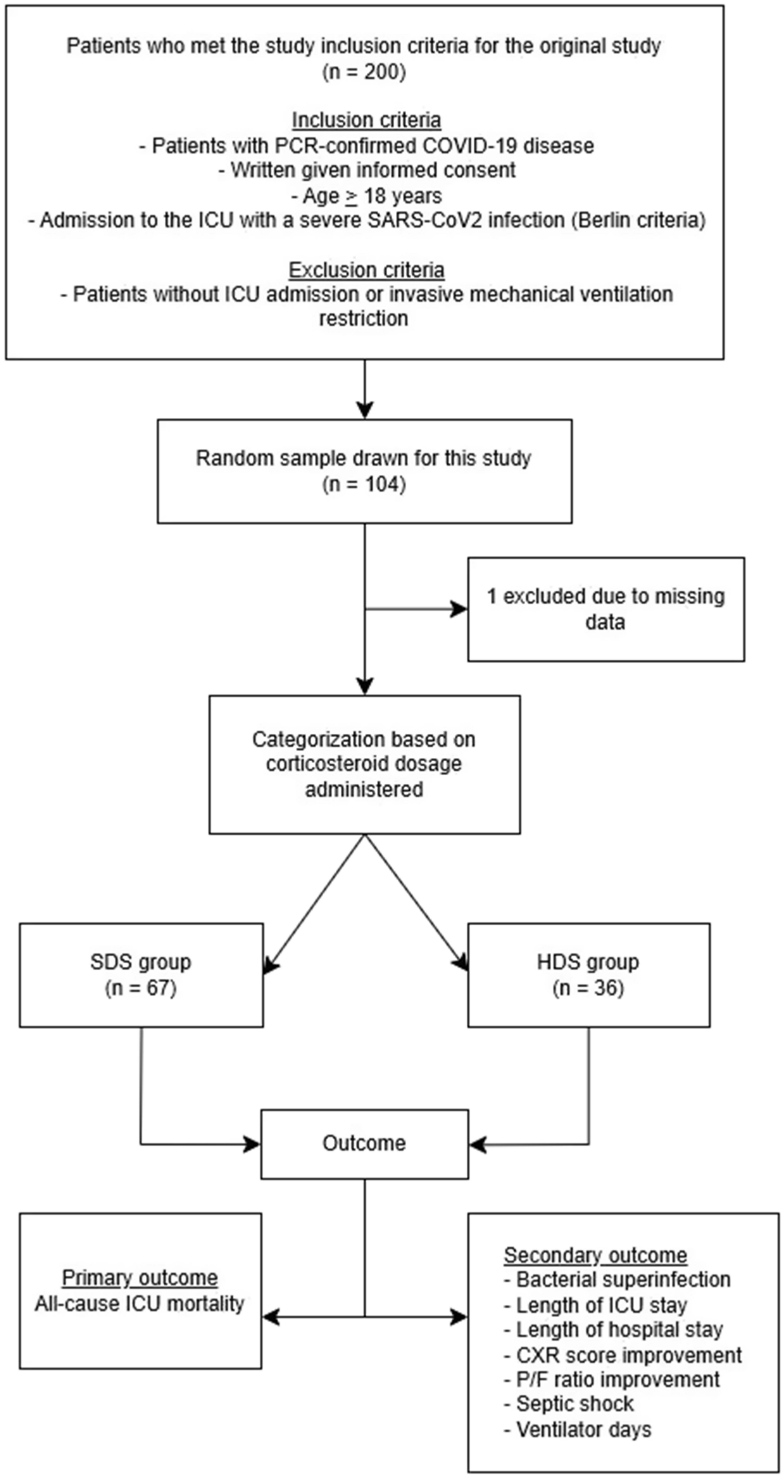

Figure 1 Flow diagram of patient selection and study inclusion process. Flow diagram showing patient selection with inclusion and exclusion criteria. Severe SARS-CoV-2 disease was defined as requiring ICU admission, P/F ratio < 300 mmHg, and room air oxygen saturation < 93%.[30] HDS was defined as treatment with >6 mg/kg of dexamethasone per day or equivalent. SDS was defined as treatment with 6 mg of dexamethasone per day. Patients with a documented invasive mechanical ventilation restriction (Do Not Intubate [DNI] status), due to prognosis, comorbidities, or patient wishes, were excluded. Flow diagram of the patient selection and study design, with 104 randomly sampled patients of 200 patients meeting the inclusion criteria (PCR-confirmed COVID-19, informed consent, age ≥18, ICU admission with severe infection). Patients were categorized by steroid treatment into standard dose corticosteroids (SDS, n=67) or high-dose corticosteroids (HDS, n=36). Both groups were analyzed for primary outcome (all-cause ICU mortality) and secondary outcomes (bacterial superinfection, ICU stay length, hospital stay length, CXR score improvement, P/F ratio improvement, septic shock, and ventilator days).

Abbreviations: HDS, High-dose corticosteroids; ICU, Intensive Care Unit; P/F ratio, PaO2/FiO2 ratio; PCR, polymerase chain reaction; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SDS, Standard-dose corticosteroids.

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assessed on the day of admission and day 2 to measure oxygen balance changes using the calculated PaO_2/FiO_2 (P/F) ratio. In patients receiving conventional oxygen therapy, estimated FiO_2 values were used (0.21 + (0.03 × oxygen flow rate in L/min)) to calculate P/F ratios.[31,32] Data on the development of septic shock were collected, defined as hemodynamic instability requiring inotropic support, body temperature >38.5°C or hypothermia, and increased serum levels of lactate (>4 mmol/L) and inflammatory markers (CRP). Chest x-rays were also performed upon ICU admission and after two days. These images were evaluated using the COVID-19 CXR scoring system, which divides each lung into three zones with severity scores ranging from 0 to 3 per zone, yielding a total score between 0 and 18.[33,34] Two investigators cross-checked the data to minimize data entry errors. Blood, urine and sputum cultures were obtained every 24–48 hours as part of routine monitoring for microbiological surveillance. In the event of fever or clinical deterioration, additional cultures from relevant sites (eg, tracheal aspirates) were collected.

Study Exposure

We evaluated the effect of high-dose corticosteroid treatment (HDS) compared to standard-dose corticosteroids (SDS) in patients with severe COVID-19 pneumonia admitted to the ICU. HDS was defined as dexamethasone > 6 mg per day or an equivalent corticosteroid, while SDS was defined as dexamethasone 6 mg per day (Table S1). SDS was initiated upon ICU admission, or continued if previously started during ward stay, and administered once-daily oral or intravenous dexamethasone for a maximum of 10 days. HDS varied in both corticosteroid type (ie, methylprednisolone and dexamethasone) and dosage during the study period. HDS could be initiated at any time from ICU admission until discharge and was thus considered as a time-updated exposure. Initially, the decision to start HDS was made by the attending physician following multidisciplinary discussion. From July 2021, this decision was based on protocols established at the Academic Hospital Paramaribo, extrapolated from general ARDS guidelines.[35] The protocol indicated to start HDS treatment for any patient that had at least 15 liters of oxygen suppletion. Multiple HDS regimens were administered, including: 5 days of 20mg dexamethasone followed by 5 days of 10mg dexamethasone; methylprednisolone 1000mg for 1–3 days; or dexamethasone 100mg for 1–3 days. A copy of the original protocol (in Dutch) is provided in the online supplement.

Study Outcome

The primary outcome in our analysis was all-cause ICU mortality. Patients were monitored from ICU admission until ICU discharge or death, with no follow-up monitoring after ICU discharge. Secondary outcomes included length of ICU stay, length of hospital stay, duration of invasive mechanical ventilation, changes in CXR score and P/F ratio between admission day and day 2, and occurrence of bacterial superinfection. Bacterial superinfections were defined as the identification of pathogens in sputum, urine, or blood cultures, subsequently interpreted by clinical microbiologists and/or intensivists, taking into account the clinical presentation of the patient, in order to exclude contamination. Diagnostic testing for *Aspergillus* and *Strongyloides* was not available.

Statistical Analysis

Follow-up began at baseline (ICU admission) and continued until ICU discharge or death, whichever occurred first. Baseline variables were summarized and compared between patients who received HDS and SDS using a Kruskal–Wallis test for continuous variables and Pearson's $\chi 2$ test for categorical variables. Missing data were imputed using multiple imputation (20 imputations, 5 iterations) using the MICE package for R statistical software.

The use of HDS and SDS was defined as a dichotomous variable (yes or no). Due to limited availability of ward-level data, corticosteroid treatment duration (SDS and HDS) was modeled starting from ICU admission, regardless of whether treatment had already been initiated on the ward. We used a sequential analytical approach to evaluate the association between corticosteroid treatment strategy and ICU mortality. First, we conducted univariable logistic regression analyses to identify potential predictors of ICU mortality. Variables with $P \leq 0.05$ in the univariable analysis were subsequently entered into a multivariable logistic regression model to determine which factors remained associated with mortality.

To evaluate the time-dependent association between corticosteroid dosing strategy and mortality while accounting for potential temporal changes in risk, we conducted a time-updated survival analysis using Cox proportional hazards modeling. The primary exposure variable was corticosteroid dosing strategy (HDS versus SDS), with ICU mortality as the outcome of interest. Specifically, patients could transition from SDS to HDS over time, and this transition was modeled using a time-dependent covariate indicating current dosing status (HDS vs SDS). This approach allows for an accurate reflection of treatment dynamics in clinical practice. We adjusted the model for significant covariates identified in our preliminary analyses and other clinically relevant factors, including age, invasive mechanical ventilation, day 2 P/F ratio, CXR score, C-reactive protein levels, and presence of septic shock. The majority of the covariates included in the model were treated as fixed at baseline (age, CRP level, chest X-ray score, and septic shock), with the exception of invasive mechanical ventilation and the P/F ratio on day 2, which were modeled time-dependent and included as proxies for respiratory distress progression. Hazard ratios with 95% confidence intervals were calculated, and a p-value ≤ 0.05 was considered statistically significant. Model fit was assessed using the likelihood ratio test and robust score test. The discriminative ability of the model was evaluated using the concordance statistic. The method was implemented following the approach described in Therneau's survival package documentation.To compare the incidence of bacterial superinfections between the corticosteroid treatment groups the Chi-square test was used. All analyses were performed on a convenience sample without a priori or post hoc sample size calculations.[36] Analyses were conducted using RStudio (version 4.4.1).[37]

Results

Description of the Study Population

Between June 2020 and October 2021 104 patients with severe COVID-19 pneumonia were included in our study from the Academic Hospital Paramaribo and the Regional Wanica Hospital. Patients with a documented invasive mechanical ventilation restriction (Do Not Intubate [DNI] status), due to prognosis, comorbidities, or patient wishes, were excluded from the study. One patient was excluded from data analysis due to missing of >50% of the data. In total, 103 patients were included in analysis of whom 36 (35%) received HDS at any point in time during their ICU stay, which was initiated at a median days of 3 days after ICU admission (Figure 2). Of the patients that received HDS treatment, one

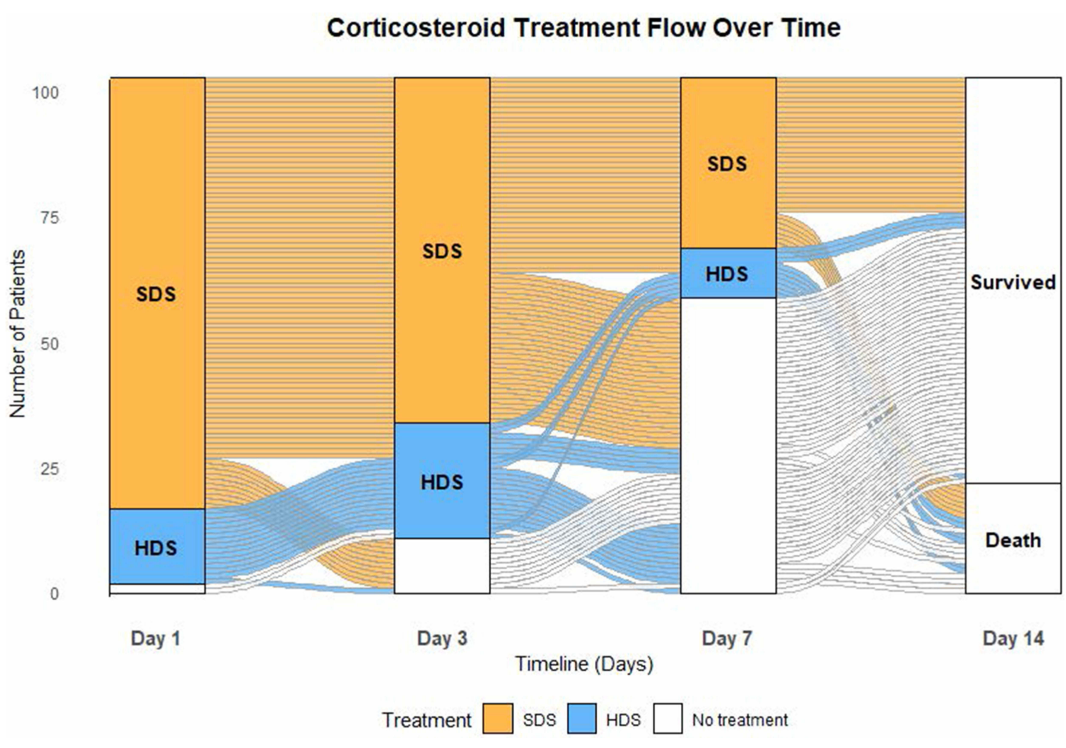

Figure 2 Corticosteroid treatment regimens flow over time. Each flow represents an individual patient and their corticosteroid treatment over time, shown at ICU days 1, 3, 7, and 14. HDS was defined as treatment with >6 mg/kg of dexamethasone per day or equivalent. LDS was defined as treatment with 6 mg of dexamethasone per day. "None" means no corticosteroids were administered at that point in time. At the end of follow-up outcome is presented as either "Survived" or "Death". Flow diagram showing corticosteroid treatment (SDS and HDS) regimens over time (days 1, 3, 7, and 14) for all 103 patients. Each horizontal flow line represents one patient's treatment course, with final outcomes indicated as "Survived" or "Death" at the end of follow-up.

Abbreviations: SDS, Standard-dose corticosteroids; HDS, High-dose corticosteroids.

patient (2.8%) was treated with 1000 mg methylprednisolone, 17 (47.2%) received the dexamethasone 20 mg/10 mg regime and 13 (36.1%) solely received the dexamethasone 120 mg course. The remainder of the HDS group, n= 5 (13,9%) received the dexamethasone 20 mg/ 10 mg regime as well as the dexamethasone 120 mg.

Patient Characteristics

In our cohort, the median time from symptom onset to ICU admission was 5 days (IQR: 3–7). Patients who received HDS had a significantly longer duration between symptom onset and ICU admission compared to those who did not receive HDS (7 days [IQR: 4.75–8] vs 4 days [IQR: 2–7], p = 0.005). Thirty percent of the patients received invasive mechanical ventilation, with the remaining 70% receiving non-invasive respiratory support through conventional oxygen therapy or high-flow nasal cannula (Optiflow). The median age of the study population at baseline was 53 years [IQR=44 – 61], median BMI was 29.8 kg/m2 [IQR= 26.2–34.9] and 59 (58%) of the patients were male (Table 1). The patients were predominantly of Javanese ethnicity (29.1%), followed by Maroons (20.4%). There were no significant differences between the HDS and SDS groups for the above mentioned variables. The most prevalent comorbidity was hypertension with a prevalence of 42% (HDS) and 52% (SDS), respectively. There was a significant difference (p=0.004) in diabetes mellitus prevalence and oral antidiabetics use between the HDS group (42%) and the

Table 1 Demographics and Clinical Characteristics

		All Patients (n=103)	SDS (n=71)	HDS (n= 36)	p-value
Age	Years, median [IQR]	53 [44–62]	54 [45–65]	50 [44–59]	0.34
Gender	Male, n (%)	59 (58%)	40 (57%)	21 (58%)	>0.99
BMI	Median (IQR)	29.8 [26.2–34.9]	29.7 [25.8–33.4]	31.5 [26.8–35.3]	0.07
Comorbidities					
Diabetes mellitus, n (%)		29 (28%)	24 (35%)	5 (14%)	0.04
Hypertension, n (%) ^		50 (48%)	35 (52%)	15 (42%)	0.53
Chronic lung disease, n (%)		6 (6%)	4 (6%)	2 (6%)	>0.99
Ischemic heart disease, n (%) ^		5 (5%)	5 (8%)	0 (0%)	0.16
Renal disease, n (%) ^		12 (12%)	12 (18%)	0 (0%)	0.007
Ethnicity					0.87
Javanese, n (%)		30 (29%)	18 (26.9)	12 (33.3)	
Maroon, n (%)		21 (20%)	16 (23.9)	5 (13.9)	
Hindustani, n (%)		19 (18%)	12 (17.9)	7 (19.4)	
Creole, n (%)		16 (15%)	11 (16.4)	5 (13.9)	
Amerindian, n (%)		7 (7%)	4 (6.0)	3 (8.3)	
Mix, n (%)		9 (9%)	5 (7.5)	4 (11.1)	
Other		1 (1%)	1 (1.5)	0 (0.0)	
Medication before admission					
Oral antidiabetics, n (%)		29 (29%)	24 (37%)	5 (14%)	0.021
Insulin, n (%)		7 (7%)	6 (9%)	1 (3%)	0.62
ACEi/ANGIIB, n (%)		20 (19%)	15 (24%)	5 (14%)	0.25

(*Continued*)

Table 1 (Continued).

	All Patients (n=103)	SDS (n=71)	HDS (n= 36)	p-value
Laboratory parameters				
C-reactive protein (mg/l), median [IQR] ~	151.0 [74.0–237.5]	155.0 [64.0–261.0]	143.0 [101.3–206.0]	0.86
Hemoglobin (mmol/l), median [IQR]	7.7 [6.7–8.3]	7.7 [7.0–8.4]	7.5 [6.4–8.1]	0.18
Leukocytes (x10^9/L)	10.5 [7.4–14.8]	10.8 [7.6–15.0]	10.2 [6.4–14.5]	0.45
Platelets (x10^9/L), median [IQR]	221 [166–307]	225 [172–309]	217 [165–280]	0.66
D-dimer (ng/mL), median [IQR] ~	364.0 [172.0–887.0]	296 [147.0–778]	381 [310.8–1120.3]	0.044
Creatinine (μmol/L), median	101 [77–143]	99 [71–132]	103 [80–200]	0.28
ALAT (IU/L), median [IQR]	42 [30–58]	42 [25–58]	43 [33–60]	0.60
ASAT (IU/L), median [IQR]	48 [36–70]	43 [30–71]	49 [41–69]	0.27
Respiratory and imaging parameters				
Invasive mechanical ventilation (%)	31 (30%)	19 (28%)	12 (33%)	0.76
CXR score at ICU admission (SD)	8.61 (4.04)	8.00 (4.43)	9.72 (2.93)	0.039
CXR score at day 2 of ICU stay (SD)	7.90 (4.08)	7.47 (4.53)	8.69 (2.99)	0.16
PaO_2 /FIO_2 ratio at ICU admission, median [IQR]	103 [78–143]	100 [79–135]	114 [76–145]	0.67
PaO_2 /FIO_2 ratio at day 2 of ICU stay, median [IQR]*	160 [101–236]	179.0 [98–238]	148 [108–220]	0.87

Notes: Data are n (%), or median [IQR]. High dose steroids was defined as treatment with >6 mg/kg of dexamethasone per day or equivalent. Standard-dose corticosteroids was defined as treatment with ≤6 mg/kg of dexamethasone per day or equivalent. ARDS score was based on the Berlin criteria. CRX score was defined as described by Borghesi et al[33] * Five patients have missing data for P/F ratio on day 2. ^ Three patients have missing data for hypertension, ischemic heart disease and renal disease. ~ Two patients have missing data for CRP and D-dimer. One patient has missing data for leukocytes, gender, diabetes mellitus and chronic lung disease. **Alt text**: Table showing demographics and clinical characteristics of 103 COVID-19 patients at ICU admission, comparing HDS and SDS groups. Significant differences (p<0.05) were found for renal disease, diabetes mellitus, oral antidiabetic use, d-dimer levels, and CXR score. Statistical testing used Kruskal–Wallis test for continuous variables and Pearson's $\chi 2$ test for categorical variables.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ANGIIB, angiotensin II receptor blockers; HDS, high dose corticosteroids; SDS, standard-dose corticosteroids; SD, standard deviation.

SDS group (35%). Of the collected laboratory parameters, D-dimer was the only significantly different parameter between the HDS and SDS groups, with D-dimer levels being higher in the HDS group (381 [310.8–1120.3] ng/mL) compared to the SDS group (296 [147.0–778] ng/mL) (p = 0.044). CCP was administered to 12 patients (33%) in the HDS group and 20 patients (30%) in the SDS group, with no significant difference between groups.

Predictors of ICU Mortality

In our patient population, 22 out of 103 patients (21%) died. In univariable logistic regression analysis, several factors were significantly associated with ICU mortality (Table S2). Invasive mechanical ventilation (OR 8.71, p<0.001), septic shock (OR 6.12, p<0.001), and bacterial superinfection (OR 5.44, p<0.001) were all associated with significantly increased mortality risk. Other significant predictors included serum creatinine levels (OR 1.003 per unit increase, p=0.009), chest X-ray score (OR 1.16 per point increase, p=0.026), age (OR 1.04 per year, p=0.029), and day 2 P/F ratio (OR 0.99 per unit increase, p=0.032), indicating a higher risk of mortality with higher creatinine levels, age and chest X-ray scores, and a lower risk of mortality with improved oxygenation. Neither diabetes mellitus (OR 0.52, 95% CI 0.16–1.69, p=0.277) nor ethnicity (OR 0.88, 95% CI 0.66–1.16, p=0.353) was significantly associated with mortality. Additionally, we explored associations between individual ethnic groups and mortality by comparing each group separately to the rest of the cohort using Fisher's exact tests. These analyses also did not reveal any significant

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differences. In the multivariable analysis age remained a significant independent predictor (adjusted OR 1.10 per year, 95% CI: 1.02–1.20), as did invasive mechanical ventilation (adjusted OR 8.39, 95% CI: 1.20–84.12) (Table 2).

Time-Updated Survival Analysis

To account for the time-dependent effects of steroid therapy, we conducted a time-updated survival analysis using Cox proportional hazards modeling. After adjusting for covariates age, invasive mechanical ventilation, day 2 P/F ratio, CXR score, C-reactive protein, and occurrence of septic shock, there was no significant difference between HDS and SDS on the risk of ICU mortality (Table 3). In this analysis, septic shock was the only variable significantly associated with ICU mortality. The overall model showed good discriminative ability with a concordance statistic of 0.801 (SE=0.042) and was statistically significant (likelihood ratio test p=0.02, robust score test p=0.05).

Table 2 Multivariable Analysis of Factors Associated with Mortality in Severe COVID-19 Pneumonia

Variables	Adjusted Odds Ratio (95% CI)	p-value
Invasive mechanical ventilation	8.28 (1.06–64.54)	0.05
Age (per year)	1.10 (1.01–1.19)	0.02
Septic shock	3.03 (0.51–18.08)	0.23
Bacterial superinfection	3.42 (0.65–17.88)	0.15
Creatinine (per unit)	1.00 (1.00–1.01)	0.46
CXR Score at ICU admission (per point)	1.04 (0.84–1.30)	0.71
P/F Ratio on day 2 (per unit)	1.00 (0.99–1.01)	0.44

Notes: In patients with severe COVID-19 pneumonia adjusted odds ratios for ICU mortality were calculated from a multivariable logistic regression model. Variables were selected based on clinical relevance and prior univariable analysis. P-values <0.05 were considered statistically significant. Multivariable analysis table showing factors associated with mortality in severe COVID-19 pneumonia, with invasive mechanical ventilation and age identified as significant predictors. Results presented as adjusted odds ratios with 95% confidence intervals and p-values.

Table 3 Results of Time-Updated Cox Proportional Hazards Model for Mortality

Variables	Hazard Ratio (95% CI)	p-value
High-dose corticosteroids	1.99 (0.78–5.09)	0.15
Invasive mechanical ventilation	2.10 (0.85–5.19)	0.11
P/F ratio on day 2	1.00 (0.99–1.01)	0.87
Age (per year)	1.04 (1.00–1.09)	0.073
CXR score*	1.07 (0.97–1.18)	0.20
CRP*	1.00 (0.99–1.00)	0.43
Septic shock	3.55 (1.51–8.36)	0.004

Notes: Time-updated survival analysis of corticosteroid treatment was conducted with a Cox proportional hazards model with covariates. Hazard ratios represent the effect of each variable on mortality risk after adjustment for all other variables in the model. * CXR score and CRP levels were collected on day of ICU admission. Time-updated Cox proportional hazards model results for mortality, with septic shock as the only variable significantly associated with mortality.

Abbreviations: CI, confidence interval; CRP, C-reactive protein; CXR, chest X-ray; P/F, PaO_2/FiO_2.

Bacterial Superinfections and Other Secondary Outcomes

Thirty-one patients (30.1%) of the 103 included patients were diagnosed with a bacterial superinfections during their ICU stay. These were diagnosed via urine culture (n=6), sputum culture (n=18), and blood culture (n=7). In the HDS group, 11 (31%) patients developed bacterial superinfections, with 9 (82%) of these diagnosed prior to HDS initiation. No significant difference in the incidence of bacterial superinfections was observed between the HDS and SDS groups (31% vs 30%, p=1.00) (Table 4). *Pseudomonas aeruginosa* was the most frequently isolated pathogen, followed by *Klebsiella pneumoniae* and *Staphylococcus aureus*. None of the secondary outcomes showed significant differences between the SDS and HDS groups in our study (Table 5).

Table 4 Bacterial Pathogens in Patients with Severe COVID-19 Pneumonia Stratified by Treatment

Bacteria	All Patients	HDS	SDS	p-value
Positive culture, n	31	11	20	1.00
Staphylococcus aureus, n	5	4	1	0.15
Escherichia coli, n	3	2	1	0.59
Klebsiella pneumoniae, n	5	3	2	0.64
Pseudomonas aeruginosa, n	6	3	3	1.00
Enterococcus faecalis, n	1	1	0	0.48
Other gram-positive bacteria, n	6	2	4	0.64
Othergram-negative bacteria, n	4	3	1	0.11

Notes: This table shows the number of patients with severe COVID-19 pneumonia with positive cultures for each bacterial pathogen. No statistically significant differences were observed between high-dose corticosteroids (HDS; >6mg dexamethasone daily or equivalent) and standard-dose corticosteroids (SDS; 6mg dexamethasone daily) treatment groups.
Abbreviations: E. coli, Escherichia coli; E. faecalis, Enterococcus faecalis; K. pneumoniae, Klebsiella pneumoniae; Other gram+, Other gram-positive bacteria; Other gram-, Other gram-negative bacteria; P. aeruginosa, Pseudomonas aeruginosa; S. aureus, Staphylococcus aureus.

Table 5 Secondary Outcomes in Patients Treated with SDS versus HDS

Secondary Outcome	Variable	SDS (n=67)	HDS (n=36)	P-value
	Bacterial superinfection, n (%)	20 (28.6)	11 (31.4)	0.82
	ICU days, median [IQR]	6 [3–11]	7 [5–11]	0.45
	Hospital days, median [IQR]	15 [8–22]	13 [8–16]	0.15
	Received invasive mechanical ventilation, n (%)	19 (28%)	12 (33%)	0.66
	Septic shock, n (%)	20 (29.9)	12 (33.3)	0.82
	Ventilator days, median [IQR]	5 [3–11]	5 [4–9]	0.92
	Delta CXR Score, median [IQR]	0.00 [−3.00, 2.00]	−2.00 [−3.00–0.50]	0.51
	Delta P/F ratio, median [IQR]	35 [10–112]	35 [1–100]	0.70

Notes: Data are n(%) or median [IQR]. Delta CXR score is the difference in CXR score between day zero and day two of ICU admission. Bacterial superinfections were defined as the identification of pathogens in sputum, urine or blood cultures, subsequently interpreted by clinical microbiologists and/or intensivists to exclude contamination. Delta PFR is the difference in P/F ratio measured on day 0 and day 2 of ICU admission. Missing variables were found in the SDS group for Delta P/F ratio (n=4) and Delta CXR score (n=3). In the HDS group missings were found for Delta P/F ratio (n=1) and Delta CXR score (n=1). **Alt text**: Comparison of secondary outcomes between SDS and HDS treatment groups, showing no significant differences between the groups.
Abbreviations: CXR, Chest X-Ray; HDS, high dose corticosteroids; ICU, Intensive Care Unit; IQR, interquartile range; PFR, P/F Ratio; SDS, standard-dose steroids.

Discussion

This study was the first in Suriname to investigate the effects of HDS in patients with severe COVID-19 pneumonia. Our time-updated survival analysis revealed no significant survival harm or benefit associated with HDS therapy compared to standard-dose corticosteroids. Furthermore, we found no significant difference in secondary bacterial infection rates between the two treatment groups, addressing an important safety concern often raised regarding HDS.

Our study contributes necessary data from a South American middle-income country to the ongoing global debate on HDS in severe COVID-19 pneumonia. The substantial heterogeneity in type, timing, and dosing of corticosteroid therapy across COVID-19 studies makes direct comparisons and robust conclusions difficult. While the emerging consensus suggests that HDS offer no survival benefit in severe COVID-19 pneumonia, evidence primarily comes from high-income countries in Europe and North America. Our findings from Suriname, addressing this important geographical and resource-setting gap, align with both the meta-analysis and the two published randomized clinical trials on this topic, demonstrating no survival benefit from HDS in this patient population.[16,18,19]

However, it is important to recognize that some observational studies do report potential harm. One key study found increased mortality associated with HDS in patients with non-resolving COVID-19-related ARDS, where HDS was initiated at a median of 16 days after ICU admission.[23] Evidence from non-COVID-19 ARDS studies has established that timing is highly important in this context, with benefits predominantly observed in early HDS administration.[24,38] In our study, HDS was initiated at a median of 3 days after ICU admission, which is generally considered early and within the optimal window.[14,23] Nevertheless, given the constrained ICU capacity in Suriname during the COVID-19 pandemic, delays in ICU admission have likely influenced how early treatment truly was in clinical terms. An inherent limitation of observational studies investigating HDS in severe COVID-19 pneumonia is indication bias, as patients with more severe illness are more likely to receive HDS. Despite statistical adjustments, residual indication bias persists in observational research and influences outcomes.

When administering immunosuppressive therapies like HDS in low and middle-income countries with higher endemic infectious disease prevalence and potentially limited antimicrobial stewardship, superinfections are an important safety concern. To monitor for this in our study, microbiological cultures were obtained every 24–48 hours. HDS was administered as a short-term treatment and we found no significant increase in bacterial superinfections among patients receiving HDS. This aligns with one of the few other COVID-19 studies from South America[17] studying HDS, which demonstrated that 250–500 mg of methylprednisolone for three subsequent days did not significantly increase bacterial superinfection rates. Prior literature has shown that safety concerns indeed primarily arise with prolonged corticosteroid regimens, rather than with pulse therapy.[27,39] Notably, the microbiological profile in our cohort from Suriname, with Gram-negative bacteria *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* being the most prevalent, shows remarkable similarities to large COVID-19 ICU studies from Europe.[40,41] This suggests that despite geographical and resource differences, microbiological patterns are consistent across healthcare settings. Clinically, minimal evidence of superinfections with fungal, parasitic, or yeast pathogens, although these may have been underdiagnosed due to the limitation of diagnostic capabilities and cost constraints in our setting. Although HDS did not increase the risk of superinfections, superinfections were associated with increased mortality in our study and caution therefore remains important.

In addition to this, invasive mechanical ventilation, higher age, septic shock, lower P/F ratios, creatinine elevation and higher CXR scores were also associated with increased mortality in our study. These results are in line with the majority of existing literature on mortality predictors in severe COVID-19 pneumonia.[6,42–45] Although this was not the aim of our study, it demonstrates which characteristics influence outcomes in this patient population and on which factors risk stratification could be based. Interestingly, the proportion of COVID-19 ICU patients in Suriname receiving invasive mechanical ventilation was lower than most other studies on severe COVID-19 pneumonia, suggesting differences in patient population or clinical practice.[46–48] Since all patients in our study had a P/F ratio <300 mmHg, we contemplate that this may be related to limited ICU capacity.The national ethnic distribution of Suriname includes Hindostani (37%), Creole (31%), Javanese (15%), Amerindian (4%), Chinese (2%), and others (9%). Our cohort showed overrepresentation of Javanese (29% vs 14%) and Amerindian (7% vs 4%) populations compared to national Surinamese demographics.[49] While mortality did not differ significantly among ethnic groups, this finding suggests potential ethnicity-related variations in COVID-19 severity requiring ICU care. Other studies from Suriname and Mexico similarly reported high fatal infection rates among indigenous populations, but not among Javanese patients.[50,51] Furthermore, the incidence of septic shock was substantial in our cohort, affecting 31% of the patients. As previous studies have shown benefits of HDS in septic shock, particularly through their mineralocorticoid effects, patients with concurrent septic shock may represent a distinct subpopulation who could respond differently to HDS.[14] While we adjusted for septic shock in our survival model, this could have influenced outcomes.

Our study has some limitations. HDS treatment was not randomly assigned but initially determined by physician discretion and later by protocols based on specific patient characteristics, introducing potential indication bias. Although we adjusted for confounders, the observational nature of our study precludes drawing robust recommendations regarding HDS in patients with severe COVID-19 pneumonia in Suriname. Another limitation of this study is the inability to capture and account for steroid administration prior to ICU admission due to limited ward-level data. This may have affected the precision of the estimated impact of steroid therapy, particularly in patients who had already been started on steroids prior to ICU admission. Additionally, HDS was administered in varying dosages and this heterogeneity makes subgroup analysis desirable; however, our limited sample size restricted statistical power for detecting smaller treatment effects. Despite these limitations, our study provides valuable data from an underrepresented setting in the global COVID-19 literature and our systematic assessment of secondary infections addresses an important safety concern particularly relevant in low- and middle-income countries. Furthermore, our time-updated analytical approach effectively captures the real-world management of corticosteroid treatment escalation in severe COVID-19 pneumonia.

In light of this evidence, our findings raise important questions regarding the routine use of high-dose corticosteroids (HDS) in patients with severe COVID-19 pneumonia, particularly in ICU protocols currently applied in Suriname and similar settings. While definitive conclusions cannot be drawn from our small observational cohort, the observed association between HDS and increased mortality warrants careful reflection on current practice. Future randomized controlled trials should investigate optimal dosing strategies by comparing the 6 mg dexamethasone regimen (established for COVID-19), the 20 mg regimen (commonly used in non-COVID ARDS), and intermediate doses (eg, 10–12 mg) to assess whether lower doses provide equivalent efficacy with improved safety. In addition, future studies should aim to identify subgroups of critically ill patients who may benefit from a more personalized corticosteroid approach, possibly informed by host-response phenotyping or disease trajectory. Exploring alternative immunomodulatory strategies also remains essential to improve clinical outcomes.

Our findings further underscore the heterogeneous nature of ARDS. Whereas studies in non-COVID-19 ARDS have generally reported benefits of HDS, such benefits have not been observed in COVID-19-related ARDS. This highlights the importance of distinguishing between ARDS etiologies when designing treatment strategies. In conclusion, our findings do not support the routine use of high-dose corticosteroids in patients with severe COVID-19 pneumonia in Suriname. Although we observed no significant increase in bacterial superinfections with HDS administration, the absence of a measurable survival benefit raises concerns about the clinical value of escalating corticosteroid doses beyond standard regimens in this patient population. These results highlight the need for cautious evaluation of existing ICU protocols and support further research into more tailored immunomodulatory strategies that align with the evolving understanding of COVID-19-related ARDS.

Abbreviations

ARDS, acute respiratory distress syndrome; BMI, body mass index; CCP, convalescent plasma; CI, confidence interval; COVID-19, coronavirus disease 2019; CRP, c-reactive protein; CXR, chest x-ray; FiO2, fraction of inspired oxygen; HDS, high-dose corticosteroids; HR, hazard ratio; ICU, intensive care unit; IQR, interquartile range; OR, odds ratio; P/F ratio, partial pressure of oxygen in arterial blood to fraction of inspired oxygen ratio; PaO2, partial pressure of oxygen in arterial blood; PCR, polymerase chain reaction; RECOVERY, randomized evaluation of COVID-19 therapy; SARS-CoV -2, severe acute respiratory syndrome coronavirus 2; SDS, standard-dose corticosteroids; SE standard error.

Data Sharing Statement

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

Ethical Approval

The study was approved by the Suriname Ministry of Health's Ethics Review Board (registration no. IGAP02-482020; ISRCTN18304314) and conducted according to the principles of the Declaration of Helsinki. The initial protocol was subsequently amended and re-approved to include the analysis of corticosteroid treatment in COVID-19 ICU patients. Written informed consent was given by the patient or a relative and patients who objected to participation were excluded from the study.

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Disclosure

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