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Association of Extended Steroid Treatment With Bloodstream Infection in Critically Ill Patients With COVID-19: A National, Multicenter, Propensity Score-Matched Study

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ABSTRACT

Background: The impact of steroid treatment on mortality outcomes in patients with coronavirus disease 2019 (COVID-19) has been widely demonstrated, while its effect on secondary infections, such as bloodstream infections (BSIs), is controversial. Recent studies have reported the survival benefits of using steroids for a standard duration compared to extended use, though their impact on the risk of BSIs remains debated. This study investigated whether extended steroid use is associated with the risk of BSIs and mortality in critically ill patients with COVID-19.
Methods: This national multicenter retrospective study conducted at 22 university-affiliated hospitals evaluated the effect of steroid treatment duration in hospitalized patients with COVID-19 treated with more than high-flow nasal cannula therapy. Patients were divided into two groups according to the duration of corticosteroid treatment: extended (> 10 days) and standard (≤ 10 days). Propensity score matching was performed by adjusting for covariates. Baseline characteristics and clinical outcomes were compared between the two groups.
Results: Among 1,114 patients, 378 with a hospital length of stay (LOS) exceeding 10 days were included. Each group of the propensity score–matched cohort had 189 patients, with no significant differences in demographic characteristics between the two groups, except for the incidence of BSIs (extended group vs. standard group, 49.7% vs. 36.0%, $P = 0.043$). After

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Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Kim S, Lee J. Data curation: Ryoo J, Cho HJ, Kim SC, Park S, Lee SH, Park O, Kim T, Yeo HJ, Cho WH, Lee J. Writing - original draft: Kim S, Lee J. Writing - review & editing: Kim S, Lee J.

adjusting for confounding factors, extended use of steroids remained significantly associated with BSIs (odds ratio [OR], 2.25; 95% confidence interval [CI], 1.25–4.04; $P = 0.007$). The use of a mechanical ventilator, extracorporeal membrane oxygenation, continuous renal replacement therapy, and a longer hospital LOS were associated with BSIs. In-hospital mortality was associated with an older age, higher body mass index, higher sequential organ failure assessment score at admission, and the presence of a BSI (OR, 2.47; 95% CI, 1.50–4.05; $P < 0.001$). Kaplan-Meier survival analysis demonstrated no significant difference in in-hospital mortality between the extended and standard groups.

Conclusion: Extended steroid therapy was significantly associated with a higher incidence of BSIs in critically ill patients with COVID-19.

Keywords: Coronavirus; Adrenal Cortex Hormones; COVID-19; SARS-CoV-2; Steroids; Bloodstream Infections; Korea

INTRODUCTION

Most patients with coronavirus disease 2019 (COVID-19) experience a mild course of the disease; however, a minority may develop severe pneumonia, leading to life-threatening respiratory failure or acute respiratory distress syndrome. Currently, the standard treatment for COVID-19 is stratified based on the severity of the disease.[1]

Systemic steroids have been widely administered during the COVID-19 pandemic. In recent studies, such as the RECOVERY trial and several meta-analyses, reduced mortality was observed with steroid treatment in patients with COVID-19, especially in those who required oxygen support with or without a mechanical ventilator.[2-4] Based on these results, guidelines recommend the use of steroids in hospitalized patients with severe illness who require high-flow nasal cannula oxygen delivery, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).[1,4,5] The RECOVERY trial evaluated the administration of 6 mg of dexamethasone once daily for up to 10 days, which is the current recommended dose for hospitalized adults with COVID-19.[2] Although there is clear evidence that steroids can benefit some patients with COVID-19 who require oxygen therapy, many unresolved issues remain.

To date, there are no definitive answers regarding the optimal dose and type of steroids, timing of initiation, and duration of administration in patients with severe COVID-19. Furthermore, steroids can cause various adverse effects. Generally, steroid administration is associated with hyperglycemia, steroid-induced neuromyopathy, gastrointestinal bleeding, and secondary infections.[6-9] Critically ill patients are particularly susceptible to secondary infections. This increased vulnerability is due to the frequent performance of invasive procedures, such as mechanical ventilation, and the use of central venous catheters.[10,11] Several clinical trials have aimed to investigate secondary infection as an adverse event during steroid treatment in patients with COVID-19; however, most were discontinued after the release of the results of the RECOVERY trial or did not show sufficient statistical power.[12-14] Additionally, studies addressing the relationship between the duration of steroid use and the risk of bloodstream infection (BSI) in patients with severe COVID-19 are lacking.

In this study, using data from critically ill patients with COVID-19 treated at 22 university-affiliated hospitals across South Korea, we investigated the risk factors for BSI in these

patients who received steroid treatment, including the duration of steroid use, and examined the factors influencing their prognosis.

METHODS

Study population

This was a nationwide, multicenter, retrospective observational cohort study using data collected from patients admitted to 22 university-affiliated hospitals between January 2020 and August 2021. The eligible subjects were hospitalized patients with COVID-19 aged ≥ 19 years who had received high-flow nasal cannula oxygen, mechanical ventilation, or ECMO. Patient registration protocols dictated the exclusion of patients who were not hospitalized in the intensive care unit (ICU), did not undergo blood cultures, did not receive oxygen therapy, or received only low-flow oxygen therapy. Among the original cohort, patients with missing values in matching covariants or those with a hospital length of stay (LOS) and ICU LOS shorter than 10 days were excluded from the study.

Data collection and definitions

The following data were collected by trained coordinators at each center: 1) demographic data, including age, sex, body mass index (BMI), laboratory findings, comorbidities, the Clinical Frailty Scale, COVID-19 vaccination status, timing of COVID-19 diagnosis, and sequential organ failure assessment (SOFA) score at hospital admission; 2) initial dose of steroids and duration of steroid treatment; 3) ICU admission treatment and information regarding the use of rescue therapies, including remdesivir, tocilizumab, vasopressors, ECMO, and continuous renal replacement therapy (CRRT); 4) cultured pathogens during hospitalization; and 5) clinical outcomes, such as in-hospital mortality and hospital and ICU LOS.

Patients were divided into two groups according to the duration of steroid treatment: extended (> 10 days) and standard (≤ 10 days). BSI development was defined as a positive blood culture for one or more bacterial or fungal organisms occurring at least 48 hours after ICU admission, and multiple infections in one individual were counted as one BSI case. Polymicrobial infections were not separately specified. Data were reviewed by two separate investigators to determine whether the organism was clinically significant or a contaminant. Isolates from blood cultures were excluded if they were considered contaminants and not true causes of BSI, based on clinical and microbiological data, and in accordance with CDC criteria.[15,16] In cases of disagreement between the two investigators, the discordant cases were discussed with an infectious disease specialist, and a final decision was made. The initial steroid dose was defined as the dexamethasone-equivalent dose.

Propensity score matching

Propensity score matching was performed to mitigate the potential bias caused by confounding variables, acknowledging the likelihood of uneven baseline patient characteristics between the extended and standard groups. After excluding patients with missing values in the matching covariates, propensity score matching was performed using the nearest-neighbor method to produce balanced cohorts and evaluate the effects of steroid duration. Patients were matched 1:1 by propensity score using the covariates of age, sex, BMI, COVID-19 vaccination status, comorbidities such as diabetes mellitus, cardiovascular disease, chronic lung disease, chronic neurological disease, an immunocompromised state, connective tissue disease, hematologic malignancy and solid tumor, absolute neutrophil

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count, partial pressure of oxygen (PaO_2), fraction of inspired oxygen (FiO_2), SOFA score at admission, Clinical Frailty Scale score at admission, hospital LOS, use of mechanical ventilation, use of ECMO, use of CRRT, tocilizumab treatment, and initial dose of steroids as the confounding factors.

Statistical analysis

Continuous variables are expressed as medians and interquartile ranges and categorical variables as numbers and percentages. Baseline characteristics were compared using the χ^2 test or Fisher's exact test for categorical variables and the *t*-test or Mann-Whitney *U* test for continuous variables. Multivariate logistic regression analyses were performed to investigate the association between patient characteristics and in-hospital mortality or the presence of BSI. In addition to the duration of steroid use, the model included clinically meaningful variables (age, BMI, initial steroid dose, PaO_2/FiO_2 ratio, SOFA score, use of mechanical ventilation, ECMO use, CRRT use, and hospital LOS). Clinical parameters with a *P* value of 0.05 in the univariate logistic regression were included in the multivariate logistic regression. To evaluate the goodness-of-fit of the logistic regression model, we used the Hosmer-Lemeshow test.[17] The test results indicated an adequate fit between the model and the observed data. The goodness-of-fit was computed to assess the relevance of the logistic regression model. Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were calculated. The probabilities of in-hospital survival for each group were estimated using the Kaplan-Meier method and compared using the log-rank test. All tests were two-sided, and *P* values < 0.05 were considered statistically significant. All statistical analyses were performed using R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Ethics statement

This study was conducted in accordance with the relevant legislation and the protocol was approved by the Ethics Committee of Seoul St. Mary's Hospital (KC23RIDI0860). The study complies with the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines, and the requirement for informed consent was waived due to the retrospective design of the study.

RESULTS

Baseline characteristics

Among 1,114 patients with COVID-19, 166 were excluded. A total of 948 patients were included in the final study (**Fig. 1**). The baseline patient characteristics are presented in **Table 1**. All the patients included in this study were prescribed steroids. The median duration of steroid use was 13.0 days (10.0–22.0) and the initial dexamethasone-equivalent dose was 6 mg (6.0–10.0). BSI occurred in 192 cases, with ICU and in-hospital mortality observed in 205 (21.6%) and 236 cases (24.9%), respectively.

Clinical characteristics and outcomes before and after propensity score matching according to duration of steroid treatment

The clinical characteristics and outcomes of the short and extended steroid treatment groups are shown in **Table 2**. In this study, 608 patients (64.1%) were treated with steroids for more than 10 days. The proportion of patients with cardiovascular disease and hematological malignancy in the extended group was higher than that in the standard group (13.5% vs. 7.6%, $P = 0.009$ and 2.3% vs. 0.0%, $P = 0.011$, respectively). Additionally, the extended group

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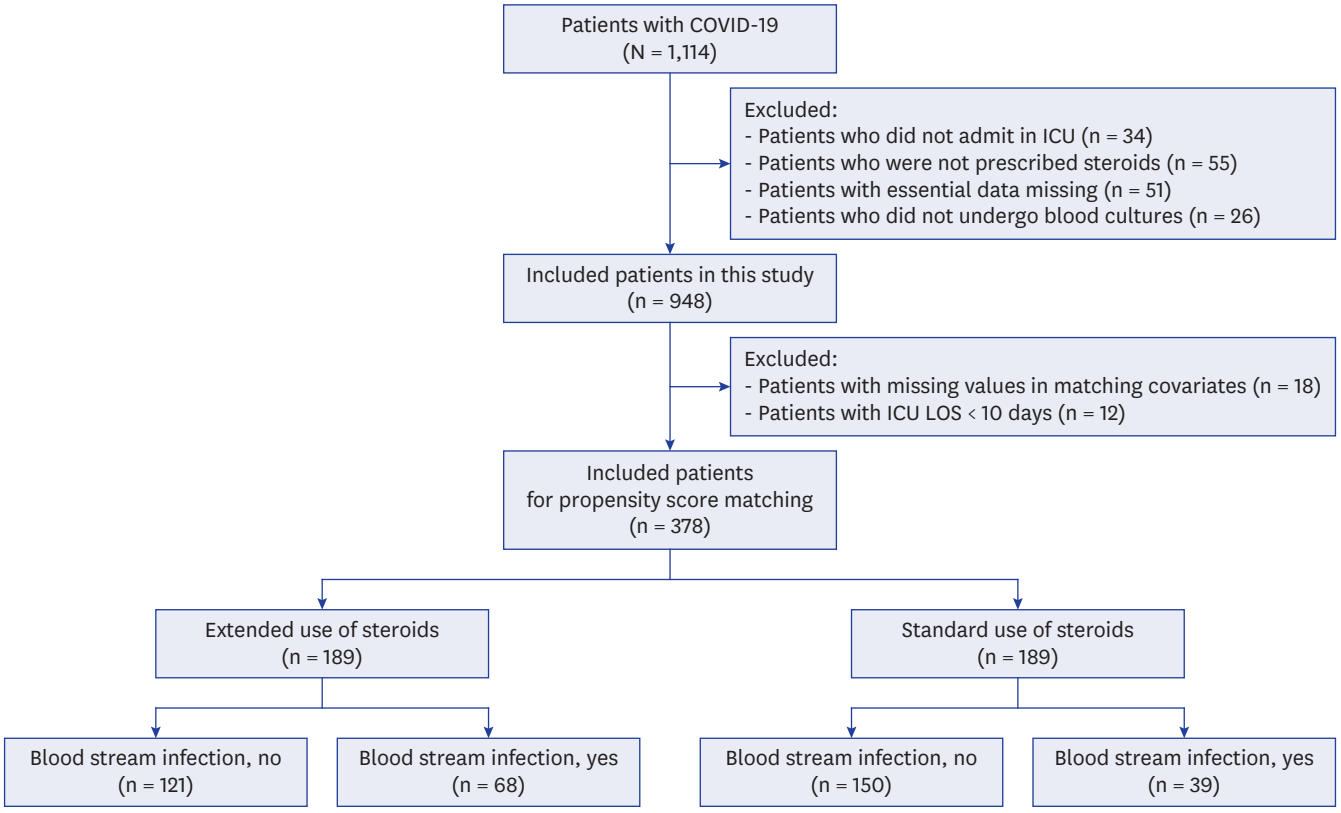

Fig. 1. Study flow diagram.
COVID-19 = coronavirus disease 2019, ICU = intensive care unit, LOS = length of stay.

exhibited a higher proportion of patients who received tocilizumab (10.7% vs. 5.9%, $P = 0.019$) and a higher initial steroid dosage (6.0 mg [6.0–11.7] vs. 6.0 mg [6.0–6.0], $P < 0.001$). The PaO_2/FiO_2 ratio was lower (131.2 [91.0–196.8] vs. 147.5 [101.3–241.1], $P = 0.004$) and the SOFA score was higher (4.0 [3.0–6.0] vs. 4.0 [3.0–5.0], $P = 0.007$) in the extended group. Moreover, a greater percentage of patients in the extended group required mechanical ventilation (66.6% vs. 50.3%, $P < 0.001$) and there was a higher incidence of BSI (23.2% vs. 15.0%, $P = 0.003$). Furthermore, both ICU LOS (17.0 days [11.0–34.0] vs. 14.0 [10.0–24.0], $P < 0.001$) and hospital LOS (25.0 days [17.0–46.0] vs. 20.0 [13.0–29.5], $P < 0.001$) were significantly longer in the extended group.

After 1:1 propensity score matching of 378 patients using the nearest-neighbor method (189 each in the extended and standard groups), the study groups were well-balanced in terms of baseline characteristics and disease severity (**Table 2**, **Fig. 2**). After matching, the median duration of steroid treatment in the extended group was significantly longer at 19.0 days (14.0–29.0) compared to 10.0 days (7.0–10.0) in the standard group ($P < 0.001$). There were no significant differences in demographic characteristics, comorbidities, or initial disease severity represented by vital signs, except for systolic blood pressure, laboratory data, SOFA score, PaO_2/FiO_2 ratio, and COVID-19 treatments such as remdesivir and tocilizumab (**Table 2**). Regarding clinical outcomes, there were no significant differences in ICU and hospital LOS, ICU mortality, or in-hospital mortality between the two groups. However, the rate of BSI development was higher in the extended group than in the standard group (36.0% vs. 20.6%, $P = 0.001$).

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Table 1. Baseline characteristics of the overall study population

Characteristics	Values (N = 948)
Age, yr	69.0 (60.0–77.0)
Sex, male	573 (60.4)
BMI, kg/m^2	24.6 (22.2–27.1)
COVID-19 variant surge	
Pre-delta dominant period (2020.1.20–2021.7.24)	786 (82.9)
Delta dominant period (2021.7.25–2022.1.15)	161 (17.0)
Omicron dominant period (2022.1.16–2022.9.3)	1 (0.1)
History of COVID-19 vaccination (n = 847)	45 (5.3)
Underlying diseases	
Hypertension	516 (54.4)
Diabetes	317 (33.4)
Cardiovascular disease	108 (11.4)
Chronic lung disease	75 (7.9)
Chronic neurological disease	121 (12.8)
Chronic kidney disease	68 (7.2)
Chronic liver disease	27 (2.8)
Immunocompromised	25 (2.6)
Connective tissue disease	13 (1.4)
Hematologic malignancies	14 (1.5)
Solid tumor	67 (7.1)
Clinical Frailty Scale score at admission	3.0 (2.0–4.0)
Treatment	
Remdesivir	713 (75.2)
Tocilizumab	85 (9.0)
Steroids	948 (100.0)
Duration of steroid use, days	13.0 (10.0–22.0)
Initial dose of steroids (dexamethasone-equivalent), mg	6.0 (6.0–10.0)
Vital signs	
Systolic blood pressure, mmHg	132.0 (119.0–146.0)
Diastolic blood pressure, mmHg	75.0 (67.0–85.0)
Heart rate, beats/min	80.0 (70.0–92.0)
Respiratory rate, breaths/min	22.0 (20.0–26.0)
Body temperature, ℃	36.8 (36.4–37.4)
Glasgow Coma Scale score	15.0 (15.0–15.0)
PaO_2/FiO_2 ratio	140.0 (92.9–201.7)
SOFA score	4.0 (3.0–5.0)
Life-supporting interventions	
High-flow nasal cannula therapy	772 (81.4)
Mechanical ventilation	576 (60.8)
Extracorporeal membrane oxygenation	116 (12.2)
Renal replacement therapy	110 (11.6)
Outcomes	
Blood stream infection	192 (20.3)
ICU length of stay, days	16.0 (10.0–29.0)
Hospital length of stay, days	23.0 (15.5–40.0)
ICU mortality	205 (21.6)
In-hospital mortality	236 (24.9)

Data are presented as number (percentage) or median (interquartile range).
BMI = body mass index, COVID-19 = coronavirus disease 2019, SOFA = sequential organ failure assessment, ICU = intensive care unit, PaO_2 = partial pressure of oxygen, FiO_2 = fraction of inspired oxygen.

BSI

The characteristics of the identified BSI pathogens are listed in **Table 3**. In the propensity score-matched cohort, bacteria constituted the largest portion of BSI in both the extended and standard groups (89.7% and 75.0%, respectively). Gram-positive cocci were the most frequently identified bacteria, followed by Gram-negative bacteria. Candida spp. accounted for the majority of the fungi. Although fungemia was more frequent in the extended group, it was not statistically significant (30.0% vs. 16.2%, $P = 0.231$).

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Table 2. Baseline characteristics and outcomes before and after propensity score matching

Characteristics	Unmatched (N = 948)			Matched (N = 378)		
	Extended (n = 608)	Standard (n = 340)	*P* value	Extended (n = 189)	Standard (n = 189)	*P* value
Age, yr	69.0 (60.0–77.0)	70.0 (60.0–78.0)	0.562	72.0 (64.0–79.0)	71.0 (63.0–79.0)	0.614
Sex, male, n (%)	363 (59.7)	210 (61.8)	0.580	81 (42.9)	75 (39.7)	0.601
Body mass index, kg/m^2	24.8 (27.2–27.3)	24.4 (22.3–26.8)	0.446	24.8 (22.0–27.4)	24.4 (22.2–26.5)	0.326
History of COVID-19 vaccination, n (%)	26 (5.0)	19 (5.8)	0.736	4 (2.1)	7 (3.7)	0.541
COVID-19 variant surge,[a] n (%)			0.594			0.601
Pre-delta dominant period	509 (83.7)	276 (81.4)		166 (87.8)	159 (84.1)	
Delta dominant period	98 (16.1)	63 (18.6)		23 (12.2)	30 (15.9)	
Omicron dominant period	1 (0.2)	0 (0.0)		0 (0.0)	0 (0.0)	
Underlying diseases, n (%)						
Hypertension	335 (54.8)	183 (53.8)	0.832	106 (56.1)	115 (60.8)	0.404
Diabetes	210 (34.5)	107 (31.5)	0.374	70 (37.0)	67 (35.4)	0.831
Cardiovascular disease	82 (13.5)	26 (7.6)	0.009	18 (9.5)	14 (7.4)	0.579
Chronic lung disease	49 (8.1)	26 (7.6)	0.920	9 (4.8)	12 (6.3)	0.653
Chronic neurological disease	81 (13.3)	40 (11.8)	0.557	26 (13.8)	23 (!2.2)	0.759
Chronic kidney disease	50 (8.2)	18 (5.3)	0.122	8 (4.2)	9 (4.8)	1.000
Chronic liver disease	20 (3.3)	7 (2.1)	0.374	4 (2.1)	3 (1.6)	1.000
Immunocompromised	21 (3.5)	4 (1.2)	0.059	4 (2.1)	3 (1.6)	1.000
Connective tissue disease	11 (1.8)	2 (0.6)	0.152	2 (1.1)	2 (1.1)	1.000
Hematologic malignancies	14 (2.3)	0 (0.0)	0.011	0 (0.0)	0 (0.0)	1.000
Solid tumor	45 (7.4)	22 (6.5)	0.686	12 (6.3)	12 (6.3)	1.000
Clinical Frailty Scale score at admission	3.0 (2.0–4.0)	3.0 (2.0–4.0)	0.432	3.0 (2.0–4.0)	3.0 (2.0–4.0)	0.238
Treatment, n (%)						
Remdesivir	445 (73.2)	268 (78.8)	0.065	144 (76.2)	146 (77.2)	0.903
Tocilizumab	65 (10.7)	20 (5.9)	0.019	9 (4.8)	8 (4.2)	1.000
Steroids						
Duration of steroid use, days	19.0 (14.0–29.5)	10.0 (7.0–10.0)	< 0.001	19.0 (14.0–29.0)	10.0 (7.0–10.0)	< 0.001
Initial dose of steroids, mg[b]	6.0 (6.0–11.7)	6.0 (6.0–6.0)	< 0.001	6.0 (6.0–6.0)	6.0 (6.0–6.0)	0.413
Vital signs						
Systolic blood pressure, mmHg	132 (120.0–146.0)	130.0 (116.0–145.0)	0.046	134 (122.0–147.0)	130.0 (112.0–144.0)	0.032
Diastolic blood pressure, mmHg	76.0 (67.0–85.0)	74.0 (65.0–83.5)	0.021	75.1 ± 13.7	74.0 ± 13.3	0.437
Heart rate, beats/min	81.0 (70.0–94.0)	78.0 (68.0–90.0)	0.013	79.0 (68.0–92.0)	80.0 (69.0–91.0)	0.931
Glasgow Coma Scale score	15.0 (14.0–15.0)	15.0 (15.0–15.0)	0.033	15.0 (14.0–15.0)	15.0 (14.0–15.0)	0.410
Laboratory findings						
White blood cell count, × 10^9 cells/L	7.5 (5.5–11.0)	7.5 (5.1–10.8)	0.501	7.7 (5.8–10.9)	7.9 (5.3–11.6)	0.944
ANC, × 10^9 cells/L	6.5 (4.4–9.9)	6.2 (3.7–9.1)	0.094	6.7 (4.7–10.1)	6.7 (4.0–10.2)	0.891
Platelet count, × 10^9 cells/L	187.5 (136.5–240.5)	189.0 (135.0–238.0)	0.889	181.0 (133.0–230.0)	180.0 (130.0–238.0)	0.646
ALC, × 10^9 cells/L	0.7 (0.5–1.0)	0.7 (0.5–1.0)	0.075	0.7 (0.5–0.9)	0.7 (0.5–0.9)	0.998
PaO_2/FiO_2 ratio	131.2 (91.0–196.8)	147.5 (101.3–214.1)	0.004	138.2 (94.0–205.0)	141.1 (97.8–197.5)	0.462
SOFA score	4.0 (3.0–6.0)	4.0 (3.0–5.0)	0.007	4.0 (3.0–5.0)	4.0 (3.0–6.0)	0.568
Life-supporting interventions, n (%)						
High-flow nasal cannula therapy	480 (78.9)	292 (85.9)	0.011	148 (78.3)	155 (82.0)	0.439
Mechanical ventilation	405 (66.6)	171 (50.3)	< 0.001	148 (78.3)	138 (73.0)	0.281
Extracorporeal membrane oxygenation	74 (12.2)	42 (12.4)	1.000	28 (14.8)	39 (20.6)	0.178
Renal replacement therapy	68 (11.2)	42 (12.4)	0.653	33 (17.5)	34 (18.0)	1.000
Outcomes, n (%)						
Blood stream infection	141 (23.2)	51 (15.0)	0.003	68 (36.0)	39 (20.6)	0.001
ICU length of stay, days	17.0 (11.0–34.0)	14.0 (10.0–24.0)	< 0.001	21.0 (16.0–37.0)	22.0 (15.0–31.0)	0.518
Hospital length of stay, days	25.0 (17.0–46.0)	20.0 (13.0–29.5)	< 0.001	28.0 (19.0–45.0)	26.0 (18.0–41.0)	0.221
ICU mortality	129 (21.2)	76 (22.4)	0.745	55 (29.1)	61 (32.3)	0.577
Hospital mortality	150 (24.7)	86 (25.3)	0.893	58 (30.7)	68 (36.0)	0.326

Matched covariates: age, sex, body mass index, COVID-19 vaccination, diabetes, cardiovascular disease, chronic lung disease, chronic neurological disease, immunocompromised status, connective tissue disease, hematological malignancy, solid tumor, treatment with tocilizumab, ANC, PaO_2, FiO_2, SOFA score, hospital length of stay, Clinical Frailty Scale score at admission, use of mechanical ventilation, use of extracorporeal membrane oxygenation, use of continuous renal replacement therapy, and initial dose of steroids.

COVID-19 = coronavirus disease 2019, ANC = absolute neutrophil count, ALC = absolute lymphocyte count, PaO_2 = partial pressure of oxygen, FiO_2 = fraction of inspired oxygen, SOFA = sequential organ failure assessment, ICU = intensive care unit.

[a]Pre-delta dominant period, 2020.1.20–2021.7.24; Delta dominant period, 2021.7.25–2022.1.15; Omicron dominant period, 2022.1.16–2022.9.3.

[b]Dexamethasone-equivalent.

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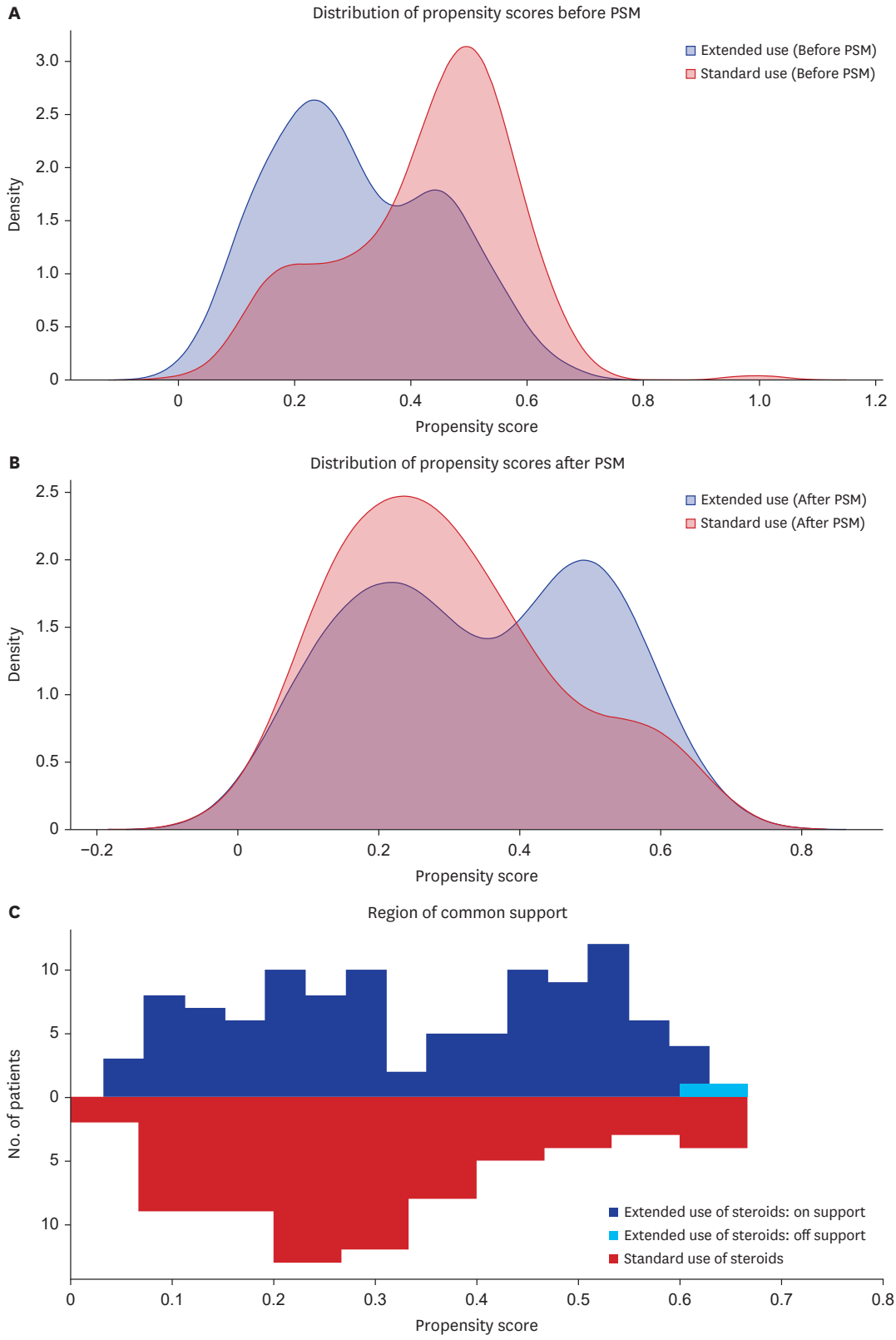

Fig. 2. Distribution before (**A**) and after (**B**) PSM between the standard and extended steroid treatment group. (**C**) Region of common support between the standard and extended steroid treatment group.
PSM = propensity score matching.

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Table 3. Identified pathogen of blood stream infection

Variables	Unmatched		Matched	
	Extended	Standard	Extended	Standard
Bacteria, n (%)	121 (85.8)	40 (76.9)	61 (89.7)	30 (75.0)
Gram-positive cocci	86	29	41	22
Staphylococcus aureus	7	2	1	1
Coagulase negative staphylococcus	61	21	31	15
Streptococci species	2	0	0	0
Enterococci species	21	8	11	8
Gram-negative bacteria	42	14	27	14
Klebsiella pneumoniae	16	4	13	4
Escherichia coli	6	1	4	1
Pseudomonas aeruginosa	4	0	2	0
Others[a]	17	9	9	9
Other gram-positive bacteria	10	5	4	2
Fungus, n (%)	20 (14.2)	12 (23.1)	11 (16.2)	12 (30.0)
Candida species	17	12	9	12
Other fungi	3	0	2	0

Data are presented as number (percentage). Percentages represent the proportion of patients in whom a specific pathogen was identified among those who developed bloodstream infections.
[a]Others: *Acinetobacter baumannii* (25), *Burkholderia cepacia* (2), *Clostridium perfringens* (2).

Fig. 3 shows the results of the multivariate analysis of the clinical factors associated with the occurrence of BSI, presented on a logarithmic scale to accommodate the asymmetric CIs. According to the analysis, the usage of steroids for more than 10 days was significantly associated with the occurrence of BSI (OR, 2.77; 95% CI, 1.59–4.80; $P < 0.001$). Other independent risk factors for the occurrence of BSI were the use of mechanical ventilation (OR, 2.81; 95% CI, 1.11–7.13; $P = 0.029$), use of ECMO (OR, 2.80; 95% CI, 1.44–5.45; $P = 0.002$), use of CRRT (OR, 4.04; 95% CI, 2.09–7.84; $P < 0.001$), and hospital LOS (OR, 1.02; 95% CI, 1.01–1.03; $P < 0.001$).

Risk factors for in-hospital mortality

Table 4 shows the clinical characteristics based on in-hospital mortality in the propensity score–matched cohort. Notably, the proportion of patients with BSI (41.3% vs. 21.8%, $P < 0.001$), median age (70.0 years [61.0–78.0] vs. 74.0 years [66.0–81.0], $P = 0.001$), prevalence of chronic kidney disease (2.8% vs. 7.9%, $P = 0.044$), white blood cell counts (7.4 [5.4–10.7] vs. 8.6 [6.3–13.9] × 10^9 cells/L, $P = 0.007$), absolute neutrophil counts (6.2 [4.1–9.1] vs. 7.5 [5.2–12.1] × 10^9 cells/L, $P = 0.004$), SOFA score (4.0 [3.0–5.0] vs. 5.0 [3.0–7.0], $P < 0.001$), use

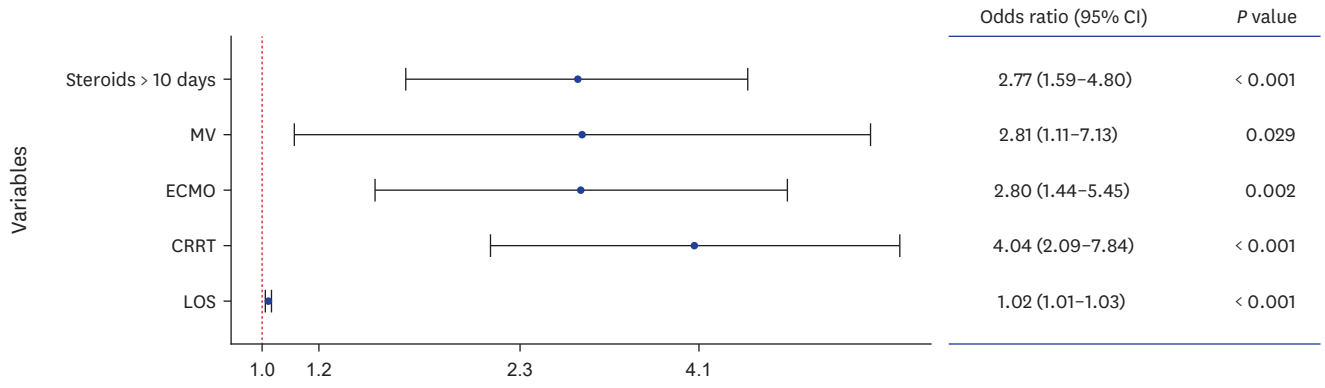

Fig. 3. Multivariable analysis of factors independently associated with blood stream infection among critically ill patients with coronavirus disease 2019.
MV = mechanical ventilation, ECMO = extracorporeal membrane oxygenation, CRRT = continuous renal replacement therapy, LOS = length of stay, CI = confidence interval.

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Table 4. Clinical characteristics according to in-hospital mortality in propensity score-matched cohort

Characteristics	Matched (N = 378)		
	Survived (n = 252)	Died (n = 126)	*P* value
Age, yr	70.0 (61.0–78.0)	74.0 (66.0–81.0)	0.001
Sex, male, n (%)	148 (58.7)	74 (58.7)	1.000
Body mass index, kg/m^2	24.6 (22.1–27.1)	24.5 (22.0–27.1)	0.866
History of COVID-19 vaccination, n (%)	10 (4.0)	1 (0.8)	0.160
Underlying diseases, n (%)			
Hypertension	140 (55.6)	81 (64.3)	0.130
Diabetes	94 (37.3)	43 (34.1)	0.623
Cardiovascular disease	18 (7.1)	14 (11.1)	0.267
Chronic lung disease	15 (6.0)	6 (4.8)	0.812
Chronic neurological disease	30 (11.9)	19 (15.1)	0.482
Chronic kidney disease	7 (2.8)	10 (7.9)	0.044
Chronic liver disease	5 (2.0)	2 (1.6)	1.000
Immunocompromised	5 (2.0)	2 (1.6)	1.000
Connective tissue disease	3 (1.2)	1 (0.8)	1.000
Hematologic malignancies	0 (0.0)	0 (0.0)	
Solid tumor	12 (4.8)	12 (9.5)	0.117
Clinical Frailty Scale score at admission	3.0 (2.0–4.0)	3.0 (2.0–4.0)	0.196
Treatment, n (%)			
Remdesivir	198 (78.6)	92 (73.0)	0.282
Tocilizumab	10 (4.0)	7 (5.6)	0.661
Steroids			
Duration of steroid use, days	11.0 (10.0–19.0)	10.0 (10.0–20.0)	0.518
Initial dose of steroids, mg[a]	6.0 (6.0–6.0)	6.0 (6.0–6.0)	0.670
Vital signs			
Systolic blood pressure, mmHg	131.5 (120.0–146.0)	132.5 (118.0–145.0)	0.705
Diastolic blood pressure, mmHg	75.2 ± 13.7	73.1 ± 13.1	0.139
Heart rate, beats/min	94.4 ± 14.9	92.6 ± 14.9	0.262
Glasgow Coma Scale score	15.0 (15.0–15.0)	15.0 (13.0–15.0)	0.002
Laboratory findings			
White blood cell count, × 10^9 cells/L	7.4 (5.4–10.7)	8.6 (6.3–13.9)	0.007
ANC, × 10^9 cells/L	6.2 (4.1–9.1)	7.5 (5.2–12.1)	0.004
Platelet, × 10^9 cells/L	187.0 (133.5–239.5)	177.5 (128.0–226.0)	0.132
ALC, × 10^9 cells/L	0.7 (0.5–0.9)	0.7 (0.4–0.9)	0.209
PaO_2/FiO_2 ratio	144.2 (101.8–208.2)	130.2 (79.0–171.3)	0.004
SOFA score	4.0 (3.0–5.0)	5.0 (3.0–7.0)	< 0.001
Life-supporting interventions, n (%)			
High-flow nasal cannula therapy	213 (84.5)	90 (71.4)	0.004
Mechanical ventilation	164 (65.1)	122 (96.8)	< 0.001
Extracorporeal membrane oxygenation	19 (7.5)	48 (38.1)	< 0.001
Renal replacement therapy	12 (4.8)	55 (43.7)	< 0.001
Blood stream infection, n (%)	55 (21.8)	52 (41.3)	< 0.001
ICU length of stay, days	20.0 (15.0–29.0)	26.0 (18.0–42.0)	< 0.001
Hospital length of stay, days	26.0 (18.5–45.0)	27.0 (19.0–44.0)	0.732

COVID-19 = coronavirus disease 2019, ANC = absolute neutrophil count, ALC = absolute lymphocyte count, PaO_2 = partial pressure of oxygen, FiO_2 = fraction of inspired oxygen, SOFA = sequential organ failure assessment, ICU = intensive care unit.
[a]Dexamethasone-equivalent.

of mechanical ventilation (96.8% vs. 65.1%, $P < 0.001$), use of ECMO (38.1% vs. 7.5%, $P < 0.001$), use of CRRT (43.7% vs. 4.8%, $P < 0.001$), and ICU LOS (26.0 days [18.0–42.0] vs. 20.0 days [15.0–29.0], $P < 0.001$) were significantly higher among the deceased patients. In contrast, the Glasgow Coma Scale score (15.0 [15.0–15.0] vs. 15.0 [13.0–15.0], $P = 0.002$) and PaO_2/FiO_2 ratio (144.2 [101.8–208.2] vs. 130.2 [79.0–171.3], $P = 0.004$) were notably lower in patients who did not survive.

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The occurrence of BSI was independently associated with in-hospital mortality (adjusted OR, 2.47; 95% CI, 1.50–4.05; $P < 0.001$) in the multivariate logistic regression analysis after adjusting for potential confounding factors (**Table 5**). Other independent risk factors for in-hospital mortality included an older age (adjusted OR, 1.04; 95% CI, 1.01–1.06; $P < 0.001$), higher BMI (adjusted OR, 1.06; 95% CI, 1.00–1.12, $P = 0.044$), and higher SOFA score (adjusted OR, 1.18; 95% CI, 1.08–1.29; $P < 0.001$).

Finally, Kaplan-Meier survival analysis demonstrated no significant difference in the in-hospital mortality rate between the extended and standard groups (log-rank test, $P = 0.121$) (**Fig. 4**).

Table 5. Multivariable logistic regression analysis of risk factors for in-hospital mortality

Risk factors	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.03 (1.01–1.05)	< 0.001	1.04 (1.01–1.06)	< 0.001
Body mass index	1.02 (0.97–1.08)	0.425	1.06 (1.00–1.12)	0.044
Chronic kidney disease	3.02 (1.12–8.13)	0.029		
Clinical Frailty Scale score at admission	1.07 (0.95–1.21)	0.268		
White blood cell count	1.04 (1.01–1.09)	0.023		
Absolute neutrophil count	1.03 (1.00–1.06)	0.035	1.02 (1.00–1.05)	0.076
PaO_2/FiO_2 ratio	1.00 (0.99–1.00)	0.007		
SOFA score	1.23 (1.13–1.33)	< 0.001	1.18 (1.08–1.29)	< 0.001
Occurrence of blood stream infection	2.52 (1.58–4.00)	< 0.001	2.47 (1.50–4.05)	< 0.001

OR = odds ratio, CI = confidence interval, PaO_2 = partial pressure of oxygen, FiO_2 = fraction of inspired oxygen, SOFA = sequential organ failure assessment.

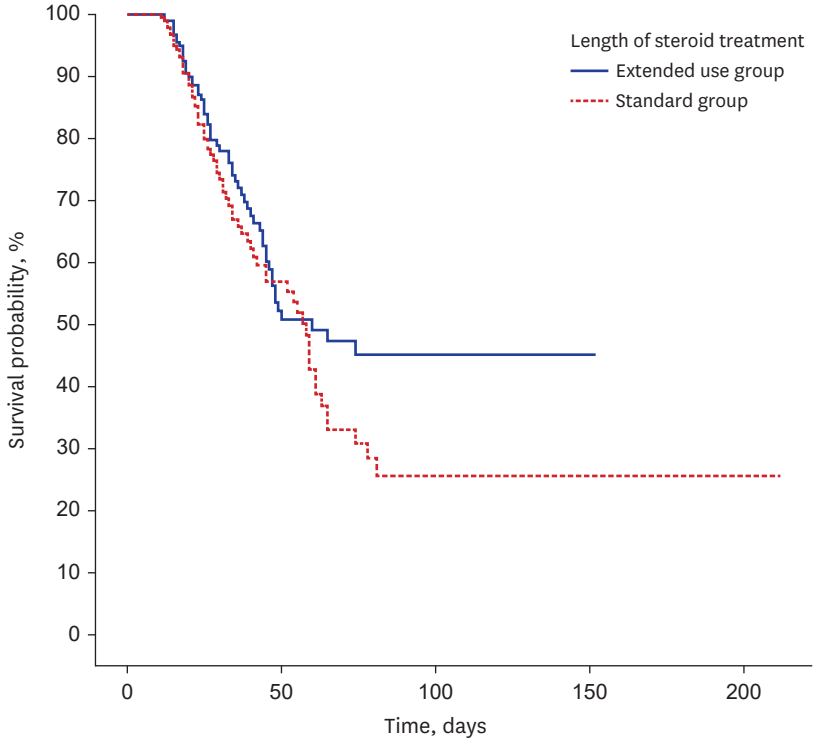

Fig. 4. Kaplan-Meier survival analysis plot for in-hospital mortality between the standard and extended steroid treatment group.

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DISCUSSION

In this nationwide multicenter propensity score–matched study, we evaluated the effects of prolonged steroid therapy on the outcomes of critically ill patients with COVID-19. Our results indicate that extended steroid use, which is commonly prescribed but does not enhance in-hospital survival, is associated with the occurrence of BSI. Furthermore, BSI occurrence was significantly correlated with increased in-hospital mortality among these patients, even after adjusting for various clinical and laboratory parameters. To the best of our knowledge, this is the first multicenter investigation focusing on the adverse effects of extended steroid treatment in this patient group.

In this study, the occurrence of BSI was associated with extended steroid use. Furthermore, it was also significantly correlated with increased in-hospital mortality. Secondary infections commonly occur as complications in patients with acute respiratory failure or acute respiratory distress syndrome caused by viral infections.[18,19] Critically ill patients are susceptible to secondary infections due to immunosuppression associated with severe illness, the use of invasive life support devices, and prolonged hospitalization.[20-22] Secondary infections occur in approximately 5–40% of critically ill patients with COVID-19.[13,23,24] Recent studies have shown that the overall rate of BSI in patients with COVID-19 varies from 5.3% to 43.6%.[25-27] In some patients with COVID-19, however, there has been no clear evidence on steroid-causing BSI. Buetti et al.[28] have reported that while the use of agents such as tocilizumab and anakinra in patients with COVID-19 was associated with the occurrence of BSI, steroid use did not influence the occurrence of BSI. However, another multicenter retrospective study has reported an association between the occurrence of BSI and a combination of steroid and tocilizumab therapy.[25] Additionally, the use of steroids increases the odds of any secondary infection in critically ill patients with COVID-19,[29,30] and another single-center retrospective study has reported findings consistent with our research, indicating that the extended use of steroids is associated with the occurrence of BSI.[31] BSIs induce a critical complication of sepsis and septic shock. Previous studies have also reported the significant impact of BSI on morbidity and mortality in critically ill patients with COVID-19.[10,25] Our study supports these findings and expands upon the aforementioned results.

In this study, extended steroid use did not reduce in-hospital mortality. The use of steroids has shown benefits in the treatment of critically ill patients with COVID-19 and has been widely adopted, with current guidelines recommending use for up to 10 days.[1,4] However, real-world applications often involve longer treatment,[32] as seen in the present study. Despite this, there is limited systematic research on the consequences of prolonged steroid use that might increase the risk of adverse events, such as delayed viral clearance, particularly in critically ill patients with COVID-19.[33] Although the study did not exclusively focus on critically ill patients, a recent meta-analysis indicated that using steroids for > 7 days did not offer a survival benefit in hospitalized patients with COVID-19.[34] Given these findings, it is crucial to consider the potential risks of extended steroid use, necessitating further targeted research to optimize the therapies for critically ill patients.

The present study has some limitations. First, it was a secondary analysis of a retrospective cohort study. Therefore, the reasons for the prolonged use of steroids have not been properly determined. Some patients may have been deliberately treated with extended steroids, whereas others may have received extended steroids for therapeutic immunomodulation under different conditions. These differences may have influenced the patient outcomes.

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Secondly, we did not consider the cumulative dose of steroids administered. However, in patients with COVID-19, where immunosuppression over a certain period is necessary to prevent immune-mediated inflammation, the duration of steroid treatment can affect outcomes independently of the cumulative dosage. Third, this study focused only on BSIs. Our findings did not include other secondary infections, such as ventilator-associated pneumonia or urinary tract infections. Fourth, there might be a potential bias for patients who, owing to their severe condition and subsequent rapid deterioration after admission, either did not have the opportunity to be treated with steroids or were administered steroids for an insufficient duration. However, we endeavored to address this by only including patients who were hospitalized in the ICU for 10 days or more in our study.

In this study, the extended use of steroids was associated with an increased risk of BSI in critically ill patients with COVID-19. In addition, the presence of BSIs was associated with a higher mortality risk. However, no correlation was observed between extended steroid use and in-hospital mortality. These findings have important clinical implications, as they suggest that clinicians should be cautious about prolonged steroid use in critically ill COVID-19 patients and closely monitor for signs of BSI. Further prospective studies are required to clarify the effect of prolonged steroid use in critically ill patients with COVID-19.

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