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Personalized corticosteroid treatment of patients with severe new coronavirus infection complicated by pneumonia: a prospective comparative study

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Персонифицированное лечение кортикостероидами пациентов с тяжелым течением новой коронавирусной инфекции, осложненной пневмонией: проспективное сравнительное исследование

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Abstract

INTRODUCTION: A new coronavirus infection caused by the SARS-CoV-2 coronavirus and the associated disease COVID-19 is accompanied by a high incidence of acute respiratory distress syndrome (ARDS) and pneumonia with respiratory failure. Corticosteroids are a therapeutic treatment option. **OBJECTIVE:** To determine the advantage of personalized corticosteroid dosing to reduce inflammation in pneumonia in patients with comorbid diseases. **MATERIALS AND METHODS:** A prospective comparative study was conducted among adult patients in the Republican Clinical Infectious Hospital and the Clinical Emergency Hospital (Ufa, Republic of Bashkortostan) from May 2020 to May 2021. Patients were divided into two groups: personalized corticosteroid administration in accordance with the level of the inflammation biomarker C-reactive protein (CRP) (n = 30) compared with conventional therapy (n = 28). Measurements of CRP levels in blood samples were carried out at the time of hospitalization and during the first 5 days of treatment. **RESULTS:** The intervention group had fewer days of respiratory support (9.4 [6.2–15.6] vs. 14.3 [7.1–21.4]; p = 0.003] and no differences in cumulative outcome (persistent respiratory support and/or death) and the incidence of nosocomial infection compared with the control group. Daily distribution of the inflammation biomarker CRP showed significantly lower levels on 2–4 days of treatment in the intervention group compared with the control group. **CONCLUSIONS:** In critically ill patients with COVID-19 associated pneumonia and comorbid diseases, a personalized approach to the corticosteroids prescribing slightly reduced the frequency of treatment ineffectiveness and significantly reduced the duration of respiratory support.

Реферат

АКТУАЛЬНОСТЬ: Новая коронавирусная инфекция (НКИ), вызванная коронавирусом SARS-CoV-2, и ассоциированное заболевание НКИ COVID-19 сопровождаются высокой частотой развития острого респираторного дистресс-синдрома (ОРДС) и пневмонии с дыхательной недостаточностью. Кортикостероиды являются терапевтическим вариантом лечения. **ЦЕЛЬ ИССЛЕДОВАНИЯ:** Определить преимущество персонифицированного дозирования кортикостероидов для уменьшения воспаления при пневмонии у пациентов с коморбидными заболеваниями. **МАТЕРИАЛЫ И МЕТОДЫ:** Проспективное сравнительное исследование было проведено среди взрослых пациентов с мая 2020 г. по май 2021 г. Пациенты были разделены на две группы: персонифицированное назначение кортикостероидов в соответствии с уровнем биомаркера воспаления С-реактивного белка (СРБ) (n = 30) в сравнении с обычной терапией (n = 28). Измерения уровней СРБ в образцах крови проводили на момент госпитализации и далее ежедневно в течение первых 5 сут лечения. **РЕЗУЛЬТАТЫ:** В группе вмешательства было меньше дней респираторной поддержки (9,4 [6,2–15,6] *vs* 14,3 [7,1–21,4]; p = 0,003) и отсутствие различий в кумулятивном исходе (стойкая зависимость от респираторной поддержки или смерть) и частоте развития нозокомиальной инфекции в сравнении с группой обычной терапии. Суточное распределение биомаркера СРБ показало статистически значимо более низкие уровни на 2–4-е сут лечения в группе вмешательства в сравнении с контрольной группой. **ВЫВОДЫ:** У критически больных пациентов с пневмонией, вызванной НКИ COVID-19,

и коморбидными заболеваниями персонифицированный подход к назначению кортикостероидов незначительно уменьшил частоту неэффективности лечения и статистически значимо уменьшил длительность респираторной поддержки.

KEYWORDS: COVID-19, ARDS, pneumonia, comorbid diseases, corticosteroids, personalized approach, C-reactive protein

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Introduction

The novel SARS-CoV-2 infection and associated COVID-19 disease is accompanied by a high incidence of acute respiratory distress syndrome (ARDS) and pneumonia with hypoxemic respiratory failure that need for respiratory support in the setting of the intensive care unit (ICU) [1–3].

Although the pathophysiology of COVID-19 remains not fully understood, organ damage, especially diffuse lung injury, is the result of both direct virus cytotoxicity and immune response dysregulation [4]. Theoretically, immunomodulatory drugs, including corticosteroids, may have the effect of reducing lung inflammation in COVID-19 and are being investigated as therapeutic approaches for the treatment of pneumonia [5, 6]. Corticosteroids suppress pulmonary and systemic inflammation, accelerate clinical resolution, reduce the incidence of systemic inflammation-related complications such as ARDS and septic shock, reduce the production of tumor necrosis factor and interleukins, and subsequent recruitment of inflammatory cells into the alveolar space [7, 8]. The efficacy and safety of corticosteroids among critically ill adult patients with viral pneumonia remains largely uncertain due to a lack of evidence from randomized clinical trials and uncertain results from observational studies [9]. The pros and cons of corticosteroids in the treatment of COVID-19 remain controversial [10–15]. At the beginning of the pandemic, there was opposition to the use of corticosteroids for severe pneumonia [16], because they could impair immune defenses and inhibit viral clearance, as was the case in patients with severe influenza [17]. Observational study reported that treatment with methylprednisolone was associated with reduced mortality among patients with ARDS associated with COVID-19 pneumonia [18]. More recent RECOVERY Collaborative Group trial have shown that the use of dexamethasone resulted in lower 28-day mortality among patients hospitalized with COVID-19 who were receiving either invasive mechanical ventilation

(MV) or oxygen alone, but not among those no receiving respiratory support [15]. Finally, recent meta-analyses have demonstrated the therapeutic efficacy of corticosteroids in COVID-19 [19–21]. According to the expert consensus statement, the following basic principles should be followed when using corticosteroids: (1) the benefits and harms should be carefully weighed before using corticosteroids; (2) corticosteroids should be used prudently in critically ill patients with 2019-nCoV pneumonia; (3) for patients with hypoxemia due to underlying diseases or who regularly use corticosteroids for chronic diseases, further use of corticosteroids should be cautious; and (4) the dosage should be low-to-moderate (≤0·5–1 mg/kg per day methylprednisolone or equivalent) and the duration should be short (≤7 days) [20]. The challenge now is to harness the benefits of corticosteroids and reduce side effects, thereby minimizing mortality and reducing ICU hospitalization time [22, 23].

Thus, recent studies have shown the benefit effects of corticosteroids in the treatment of pneumonia in reducing mortality, especially in a subgroup of critically ill patients requiring respiratory support [24]. Although the use of corticosteroids was associated with improved outcomes in pneumonia, their ideal dosage, initiation and duration of use remain uncertain when used regardless of the individual inflammatory response [25, 27].

Objective

The aim of this study was to assess the feasibility and safety of a personalized approach to the prescription of corticosteroids, considering the profile of the inflammation biomarker CRP, in reducing the need for respiratory support and the duration of treatment in the ICU in patients with COVID-19 associated pneumonia and comorbid diseases.

Materials and methods

This prospective, non-randomized, controlled clinical trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013) in the Republican Clinical Infectious Diseases Hospital and the Clinical Emergency Hospital (Ufa, Republic of Bashkortostan). The protocol was designed in accordance with the Recommendations for Interventional Trials 2013 statement. Due to the mixed study design, no written informed consent was obtained. An institutional ethics review board of Bashkir State Medical University (Ufa, Republic of Bashkortostan, Russia) approved this study (approval number: № 10 / 15.12.2021). The flow diagram of the study is shown in the Figure 1.

Corticosteroid administration

Patients with COVID-19 pneumonia and the respiratory support received corticosteroids at the dosage and duration of administration according to the daily level of the inflammation biomarker CRP compared to standard intensive care. In the conventional therapy group the use and dosage of corticosteroids were determined by the attending physician on the basis of the interim guidelines of the Ministry of Health of the Russian Federation [28]. In the intervention group the algorithm for dosing, titration and duration of corticosteroids use was selected on the basis of individual CRP levels based on retrospective data by Torres A., 2015 [29]. CRP levels in blood samples were measured at the time of ICU admission and then daily during the first 5 days of treatment:

- If the CRP level was greater than 200 mg/L, then the patient received 0.3 mg/kg dexamethasone or an equivalent dose of oral prednisolone;
- If the CRP level was between 151 and 200 mg/L, the patient received 0.15 mg/kg dexamethasone or an equivalent dose of prednisolone;
- If the CRP level was between 101 and 150 mg/L, then the patient received 0.1 mg/kg dexamethasone or an equivalent dose of prednisolone;
- If the CRP level was between 50 and 100 mg/L, then the patient received 0.05 mg of dexamethasone or an equivalent dose of prednisolone;
- If the CRP level was less than 50 mg/L, or if the patient's respiratory and general condition improved sufficiently within 4 days of treatment to consider transfer from the ICU, corticosteroids were discontinued. To do this, the following criteria should be presented: spontaneous respiration or low-flow oxygen therapy; PaO_2/FiO_2 ratio greater than 200 mmHg; regression of organ failure.

Outcomes

The primary cumulative outcome included persistent respiratory support and/or death. Preliminarily defined secondary outcomes included (1) the length of respiratory support measured over a daily basis; (2) episodes of nosocomial infection reported during treatment in the ICU; (3) levels of the inflammation biomarker CRP.

Statistical analysis

Statistical data processing was performed using the MedCalc software package (v 11.3.1.0, Belgium). Continuous variables are presented as median and 25 %–75 % interquartile range, the categorized variables are represented as absolute values (n) and relative frequency (percentage). Cross-sectional comparisons were made using the Mann-Whitney U-test for nonparametric variables and Pearson's χ^2-test or Fisher's exact test for the corresponding categorized variables. P values less than 0.05 were accepted statistically significant.

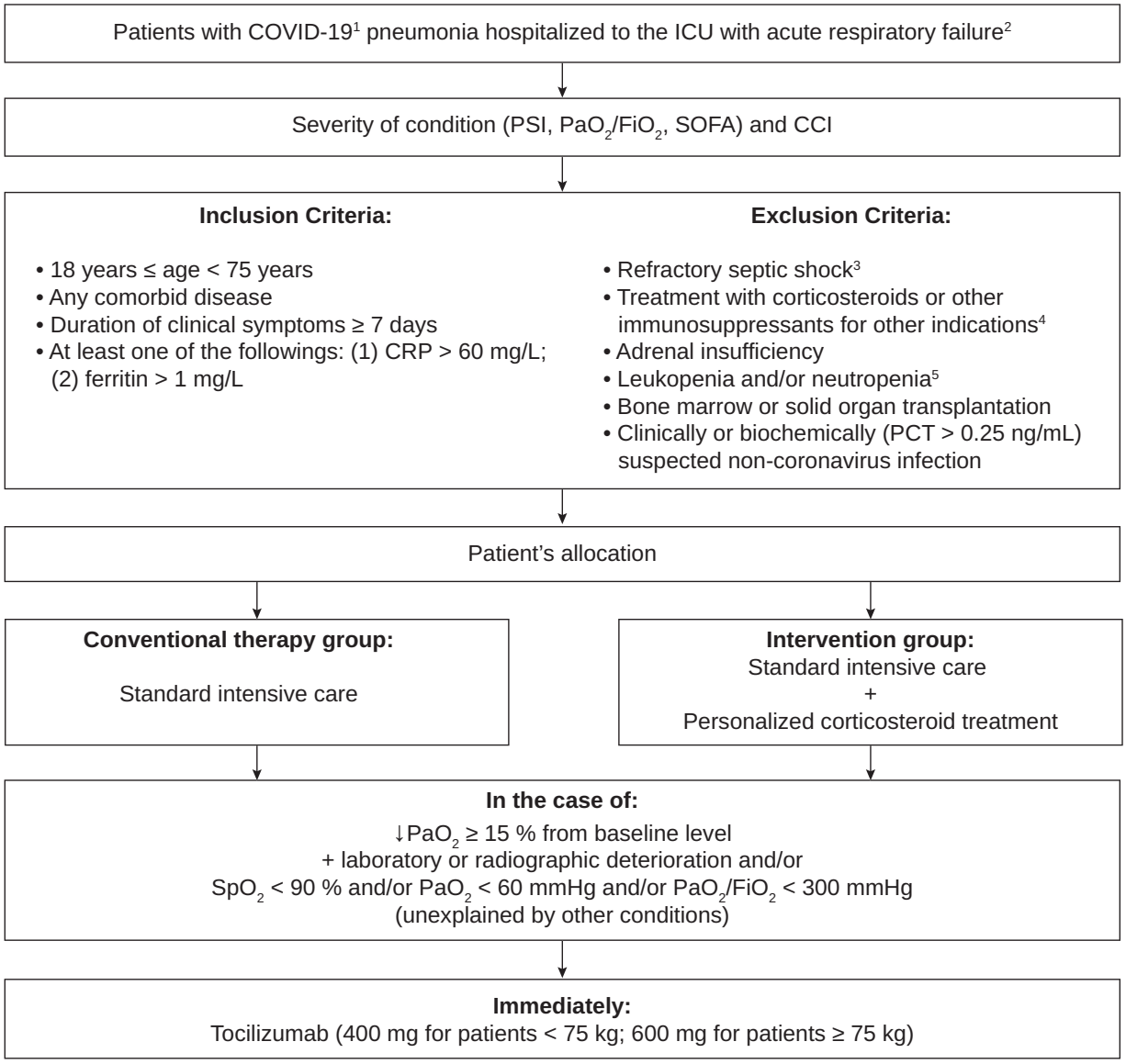

Fig. 1. Flowchart of the study

[1] High suspicion (clinical and radiographic [focal opacity or infiltrate on chest radiograph or CT scan] features, epidemiological history, absence of other infection) or confirmed by a positive polymerase chain reaction (PCR) test in nasal and pharyngeal swabs, or lower respiratory tract aspirate.

[2] PaO_2/FiO_2 < 200 mmHg (SpO_2 < 90 % when breathing room air or < 95 % by inhalation of 2 L of oxygen through nasal cannulas).

[3] Need for norepinephrine treatment at doses greater than 0.1 μg/kg/min and/or the use of vasopressor(s) at equivalent doses. The patients with no evidence of circulatory insufficiency at the time of admission whose condition required vasopressor medication after initiation of respiratory support were included provided that: (1) circulatory failure due to exposure of MV and sedatives; (2) blood lactate levels below 4 mmol/L; (3) norepinephrine doses below 0.25 μg/kg/min.

[4] Pre-hospitalization use of more than 15 mg/day of prednisolone (or equivalent) for more than 30 days or other immunosuppressive medications.

[5] Leukopenia <1 × 10^9/L and/or neutropenia <0,5 × 10^9/L.

Note. CCI, Charlson Comorbidity Index; CRP, C-reactive protein; FiO_2, inspired oxygen fraction; ICU, Intensive Care Unit; PaO_2, arterial oxygen pressure; PCR, polymerase chain reaction; PCT, procalcitonin; PSI, Pulmonary Severity Index; SOFA, Sequential Organ Failure Assessment; SpO_2, oxygen blood saturation.

Patients and settings

From May 2020 to May 2021, a total of 65 adult patients with laboratory-confirmed COVID-19 and/or diagnosed with International Classification of Diseases U07.1, version 10, admitted to the ICU for respiratory support, were consecutively included in this study. Patients who were transferred to another hospital (n = 2) or died (n = 5) in the first 24 hours of hospitalization, were excluded from the study, so 28 patients were included in the conventional therapy group and 30 patients in the intervention group. Thirty (51.7 %) patients were men, the mean age of the patients was 64 years and the mean body mass index was 29 kg/m^2; arterial hypertension, heart disease, and obesity were the most common comorbid diseases (Table 1). PCR test results were positive in 52 (89.6 %) patients. There were no significant differences in age, sex, body mass index, and comorbidities between the patient groups.

Results

The majority of patients (54; 93.1 %) had bilateral pneumonia at the time of admission. Some patients had the PaO_2/FiO_2 index of more than 300 mmHg at the time of hospitalization, but subsequently the index decreased to less than 200 up to 100 mmHg (Table 2).

All patients with acute respiratory failure received respiratory support and all critically ill patients received non-invasive or invasive MV (Table 3). There were no significant differences in the need for respiratory support between the patient groups. Vasopressor treatments were given equally to patients in the intervention or conventional therapy groups. Primary cumulative outcome was observed in 12 (40.0 %) patients in the intervention group compared to 17 (60.7 %) in the conventional therapy group. The duration of respiratory support was significantly longer in the conventional therapy group. During the ICU treatment, 9 (15.5 %) patients had episodes of nosocomial infection, half as long in the intervention group.

Daily distribution of the CRP levels showed a significantly lower level on days 2–4 of treatment in the intervention group compared with the conventional therapy group (Table 4).

Discussion

During the pandemic, we have witnessed changes in the standards of care. The proportion of patients with hyperinflammation decreased from 65 % in 2020 to 27 % in 2022, while the proportion of patients treated with corticosteroids increased from 25 % in 2020 up to 70 % in 2022. Dexamethasone has previously been shown to exacerbate the body's hyperinflammatory response [30–32]. Low-dose hydrocortisone did not significantly reduce treatment failure, defined as 21-day mortality or persistent respiratory support with high-flow oxygen therapy (HFO) or MV, among critically ill patients with acute respiratory failure associated with COVID-19 [11]. In another study, early use of short-duration, low-to-moderate dosage methylprednisolone was the more accurate immunomodulatory treatment and brought more benefits to severe patients

Table 1. Demographic variables of patients

Variables	All patients	Conventional therapy group	Intervention group	p value
Age, years	63.9 (52.7–70.0)	62.9 (51.9–67.1)	65.0 (53.5–72.7)	0.395
Sex, male/female	30/28	15/13	15/15	0.824
BMI, kg/m^2	29.2 (26.1–30.8)	28.6 (25.2–29.6)	29.7 (27.0–31.9)	0.081
Hypertension	29 (50.0)	15 (53.6)	14 (46.7)	0.603
Diabetes	11 (18.9)	5 (17.9)	6 (20.0)	0.840
Obesity	21 (36.2)	10 (35.7)	11 (36.7)	0.937
Heart Diseases	23 (39.6)	10 (35.7)	13 (43.3)	0.578
Lung Diseases	5 (8.6)	3 (10.7)	2 (6.7)	0.665
Kidney Diseases	3 (5.2)	2 (7.1)	1 (3.3)	0.605
Liver Diseases	2 (3.4)	1 (3.6)	1 (3.3)	1.000
Oncology	4 (6.9)	2 (7.1)	2 (6.7)	1.000
CCI >3	19 (32.8)	10 (35.7)	9 (30.0)	0.647

Note. Values are presented as number (percentage) or median (25 %–75 % interquartile range).
BMI — Body Mass Index; CCI — Charlson Comorbidity Index.

Table 2. Clinical and laboratory variables of patients

Variables	All patients	Conventional therapy group	Intervention group	*p* value
MBP, mmHg	84.5 (73.0–92.4)	82.1 (70.1–91.0)	86.7 (75.7–93.7)	0.078
HR, beat/min	85.4 (71.0–107.4)	84.9 (70.0–110.0)	85.9 (71.9–105.0)	0.834
RR, breath/min	26.4 (22.6–30.9)	27.0 (23.9–30.9)	25.9 (21.5–31.0)	0.339
Body temperature, °C	37.7 (36.7–38.9)	37.7 (36.6–39.0)	37.7 (36.9–38.9)	1.000
PaO_2/FiO_2, mmHg	135.8 (88.6–216.6)	132.3 (87.0–230.2)	139.1 (90.1–203.9)	0.688
Leukocytes, $\times 10^9$/L	8.6 (6.7–10.6)	8.6 (6.9–10.5)	8.6 (6.6–10.8)	1.000
Lymphocytes, $\times 10^9$/L	0.8 (0.6–1.4)	0.9 (0.4–1.3)	0.7 (0.7–1.4)	0.063
Platelets, $\times 10^9$/L	214.2 (160.6–271.8)	208.3 (161.4–269.7)	219.7 (159.8–273.8)	0.440
PCT, ng/mL	0.6 (0.4–0.9)	0.5 (0.3–0.8)	0.6 (0.4–1.0)	0.175
Glucose, mmol/L	7.9 (6.6–10.5)	7.7 (6.7–10.2)	8.1 (6.6–10.8)	0.431
Lactate, mmol/L	2.0 (1.8–2.6)	2.1 (1.9–2.4)	1.9 (1.7–2.7)	0.062
D-dimer, mg/L	2024 (1005–3884)	1570 (903–3260)	2449 (1101–4468)	0.005
SOFA, score	5.8 (3.0–8.8)	6.1 (3.0–9.3)	5.5 (3.1–8.3)	0.428

Note. Values are presented as median (25 %–75 % interquartile range).
FiO_2 — inspired oxygen fraction; HR — heart rate; MBP — mean blood pressure; PaO_2 — arterial oxygen pressure; PCT — procalcitonin; RR — respiration rate; SOFA — Sequential Organ Failure Assessment.

Table 3. Treatment modalities and outcomes

Variables	All patients	Conventional therapy group	Intervention group	*p* value
HFO	7 (12.1)	3 (10.7)	4 (13.3)	0.070
NIV	22 (37.9)	12 (42.9)	10 (33.4)	0.325
MV	29 (50.0)	13 (46.4)	16 (53.3)	0.304
Persistent respiratory support and/or death	29 (50.0)	17 (60.7)	12 (40.0)	0.118
Duration of respiratory support, days	11.8 (6.6–18.4)	14.3 (7.1–21.4)	9.4 (6.2–15.6)	0.003
Nosocomial infection	9 (15.5)	3 (10.7)	6 (20.0)	0.473

Note. Values are presented as number (percentage) or as median (25 %–75 % interquartile range).
HFO — high flow oxygen; MV — mechanical ventilation; NIV — non-invasive ventilation.

Table 4. C-reactive protein levels (mg/L)

Variables	All patients	Conventional therapy group	Intervention group	*p* value
1st day	151.4 (110.9–217.3)	155.2 (107.8–230.0)	147.8 (104.6–205.4)	0.597
2nd day	156.4 (105.8–198.4)	207.6 (118.3–229.9)	118.0 (94.2–168.9)	0.001
3rd day	103.9 (73.9–145.7)	134.9 (79.4–189.6)	75.0 (68.9–114.7)	0.001
4th day	72.2 (58.1–111.0)	86.4 (62.9–141.1)	58.9 (53.7–82.9)	0.001
5th day	86.9 (57.5–114.2)	86.9 (60.7–138.9)	87.0 (54.5–90.7)	0.989

Note. Values are presented as median (25 %–75 % interquartile range).

with COVID-19 [24]. Also, the results of COVIDICUS randomized clinical trial showed that high-dose dexamethasone did not significantly improve 60-day survival among ICU patients with COVID-19-related acute hypoxemic respiratory failure [33]. These findings support current interim clinical guidelines for the treatment of patients with COVID-19 pneumonia with low-dose dexamethasone (6 mg daily for 10 days). Recently published data from the RECOVERY and REACT working groups have confirmed the benefits of using corticosteroids in the treatment of severe forms of COVID-19, although they contribute to the development of hyperglycemia [15, 19]. The first controlled, open-label trial compared high-dose oral or intravenous dexamethasone (20 mg daily for 5 days, followed by 10 mg daily for another 5 days) with standard doses in 1272 hospitalized patients who were hypoxic but did not require HFO or invasive MV. The 28-day mortality rate was higher in the high-dose group than in the standard-dose group: 19 % vs 12 %. In the second prospective meta-analysis of clinical trials of critically ill 1703 patients with COVID-19, administration of systemic corticosteroids, compared with usual care or placebo, was associated with lower 28-day all-cause mortality. In the international multicenter COVID STEROID 2 trial among adult patients with COVID-19 and severe hypoxemia, 12 mg/d of intravenous dexamethasone compared with 6 mg/d did not result in statistically significant more days alive without life support at 28 days (invasive MV, circulatory support, or kidney replacement therapy). However, the trial may not have been powerful enough to identify a significant difference [34].

In the Bayesian analysis of COVID STEROID 2, a clinically-important difference for days alive without life support was at least 1 day. There was a 64 % chance that this was true for those who received 12 mg of dexamethasone. Further, there was a 94 % chance that there was any benefit for being alive and without life support at 28 days for those who received 12 mg of dexamethasone. A clinically important difference in 28-day mortality was defined as at least 2 % absolute difference (number needed to treat of, 50). There was an 81 % probability that those who received 12 mg of dexamethasone met this threshold [35]. Therefore, the absolute, short-term mortality benefit for 12 mg of dexamethasone relative to 6 mg was almost identical (4.5 %), but this was not significantly different based on a frequentist model. Note, that the probability of significant harm was no different than those who received 6 mg of dexamethasone. Thus, the evidence indicates that standard doses of dexamethasone should be used in hospitalized patients with COVID-19 who require HFO or MV.

The body's response to COVID-19 can be pro- or anti-inflammatory [36, 37]. In the absence of a standard definition of hyperinflammation, some biomarkers have shown abnormalities consistent with this state [38–41]. In particular, patients with hyperinflammation had the highest levels of CRP, a standard biomarker of inflammation associated with COVID-19. The hyperinflammatory pattern of ARDS was confirmed by elevated interleukin-6 levels [42].

In our study we hypothesized that increased corticosteroid use was associated with a decrease in the prevalence of hyperinflammation, and we assessed this association in 30 patients who personified dexamethasone use in the first 5 days of treatment and compared with 28 control patients who received conventional therapy. In our study, we confirmed the presence of a hyperinflammatory pattern in pneumonia. Using CRP levels, we found that hyperinflammation had an increased incidence of respiratory failure, requiring HFO up to MV.

The empirical use of corticosteroids in severe ARDS remains controversial, and the results of clinical trials vary considerably. In one study, methylprednisolone-induced down-regulation of systemic inflammation was associated with significant improvement in pulmonary and extrapulmonary organ dysfunction and reduction in duration of MV and ICU length of stay [43]. However, a larger study conducted in 2006 by the ARDS Network showed no clinical benefit in patients treated with methylprednisolone within 7 days of the onset of ARDS and increased mortality among patients treated more than two weeks after the onset of ARDS [44]. A recent DEXA-ARDS studied patients with established moderate-to-severe ARDS and found that patients treated early with dexamethasone had more ventilator-free days and lower overall mortality [45]. Different subphenotypes within ARDS showed different responses to corticosteroid treatment. Analysis of the latent classes of the ARMA and ALVEOLI studies identified a hyperinflammatory subphenotype that was characterised by more severe inflammation, shock, and metabolic acidosis and by worse clinical outcomes [46]. The hyperinflammatory phenotype showed a higher mortality rate, and a retrospective analysis of ARDS in COVID-19 observed the heterogeneity of treatment effect to corticosteroids, with improved mortality in the hyperinflammatory phenotype and worse mortality in the hypoinflammatory phenotype [16]. Although the empirical use of corticosteroids remains controversial in all patients with severe ARDS, there are likely distinct subgroups of ARDS in whom it is clinically effective.

In severe community-acquired pneumonia, a meta-analysis of previous randomized trials showed the reduction in all-cause mortality by approximately 3 %, need for MV by approximately 5 %, and hospital stay by approximately 1 day in patients treated with adjunctive corticosteroids [47]. During previous epidemics of coronavirus pneumonia, the lack of high-quality studies ruled out the rationale for the use of corticosteroids in severe ARDS [48]. In influenza pneumonia, despite the lack of randomized clinical trials and conflicting results from observational studies, it has been suggested that corticosteroids may increase the risk of death [16].

The results of our clinical trial suggest that the personalized approach to the prescribing, dosing, and duration

of corticosteroids under the control of the inflammation biomarker CRP is effective and safe in the treatment of severe COVID-19 associated pneumonia requiring ICU hospitalization and respiratory support in terms of reducing the incidence of cumulative outcome, defined as persistent respiratory support and/or death among critically ill patients with comorbid diseases. The personalized approach provided a more precise strategy for drug therapy in comparison with universal temporary guidelines.

A limitation of the study was the difficulty to assess the effect of other treatments administered concomitantly with corticosteroids. However, there was the evidence that comparable patients who were enrolled in other treatment modalities but did not receive a short course of dexamethasone ended up with longer hospital stays [12]. Given the hard period of pandemic in which the study was conducted, some data were incomplete or missing.

Conclusion

In our cohort of critical ill patients with COVID-19 associated pneumonia and comorbid diseases, the personalized approach to corticosteroid administration was associated with not significant reducing of the incidence of treatment failure (defined as persistent respiratory support and/or death) from 60.7 % to 40.0 %. Using the commonly available inflammation biomarker C-reactive protein, we found that hyperinflammation was associated with a high risk of respiratory failure, required significantly longer duration of respiratory support (14.3 days versus 9.4 days).

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References

[1] *Grasselli G., Zangrillo A., Zanella A., and COVID-19 Lombardy ICU Network.* Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy JAMA. 2020; 323(16): 1574–81. DOI: 10.1001/jama.2020.5394

[2] *Wu Z., McGoogan J.M.* Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020; 323(13): 1239–42. DOI: 10.1001/jama.2020.2648

[3] *Yang X., Yu Y., Xu J., et al.* Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respiratory Medicine. 2020; 8(5): 475–81. DOI: 10.1016/S2213-2600(20)30079-5

[4] *Квасников А.М., Боровкова Н.В., Петриков С.С. и др.* Регуляция апоптоза лимфоцитов у реанимационных больных с COVID-19. Анестезиология и реаниматология. 2023; 1: 49–55. DOI: 10.17116/anaesthesiology202301149 [*Kvasnikov A.M., Borovkova N.V., Petrikov S.S., et al.* Regulation of lymphocyte apoptosis in intensive care patients with COVID-19. Russian Journal of Anesthesiology and Reanimatology. 2023; 1: 49–55. DOI: 10.17116/anaesthesiology202301149 (In Russ)]

[5] *Лебедев Д.А., Доля Ю.Х., Савков Г.Е. и др.* Влияние тоцилизумаба и антиковидной плазмы на функцию легких при тяжелом течении COVID-19. Анестезиология и реаниматология. 2023; 4: 72–80. [*Lebedev D.A., Dolya Yu.Kh., Savkov G.E., et al.* Impact of Tocilizumab and convalescent plasma on lung function in severe COVID-19. Russian Journal of Anesthesiology and Reanimatology. 2023; 4: 72–80. (In Russ)] DOI: 10.17116/anaesthesiology202304172

[6] *Sanders J.M., Monogue M.L., Jodlowski T.Z., et al.* Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. JAMA. 2020; 323(18): 1824–36. DOI: 10.1001/jama.2020.6019

[7] *De Pascale G., Bello G., Antonelli M.* Steroids in severe pneumonia: a literature review. Minerva Anestesiologica. 2011; 77(9): 902–10.

[8] *Annane D., Sébille V., Troché G., et al.* A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. JAMA. 2000; 283(8): 1038–45. DOI: 10.1001/jama.283.8.1038

[9] *Arabi Y.M., Fowler R., Hayden F.G.* Critical care management of adults with community-acquired severe respiratory viral infection. Intens Care Med. 2020; 46(2): 315–28. DOI: 10.1007/s00134-020-05943-5

[10] *Angus D.C., Derde L., Al-Beidh F., et al.* Effect of Hydrocortisone on Mortality and Organ Support in Patients with Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. JAMA. 2020; 324(13): 1317–29. DOI: 10.1001/jama.2020.17022

[11] *Dequin P.F., Heming N., Meziani F., and CAPE COVID Trial Group and the CRICS-TriGGERSep Network.* Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19: A Randomized Clinical Trial. JAMA. 2020; 324(13): 1298–1306. DOI: 10.1001/jama.2020

[12] *Fadel R., Morrison A.R., Vahia A., and Henry Ford COVID-19 Management Task Force.* Early Short-Course Corticosteroids in Hospitalized Patients With COVID-19. Clin Infect Dis. 2020; 71(16): 2114–20. DOI: 10.1093/cid/ciaa601

[13] *Jeronimo C.M.P., Farias M.E.L., Val F.F.A., and Metcovid Team.* Methylprednisolone as Adjunctive Therapy for Patients Hospitalized with Coronavirus Disease 2019 (COVID-19; Metcovid): A Randomized, Double-blind, Phase IIb, Placebo-controlled Trial. Clin Infect Dis. 2021; 72(9): e373–e81. DOI: 10.1093/cid/ciaa1177

[14] *Lu X., Chen T., Wang Y., et al.* Adjuvant corticosteroid therapy for critically ill patients with COVID-19. Crit Care. 2020; 24(1): 241. DOI: 10.1186/s13054-020-02964-w

[15] *RECOVERY Collaborative Group, Horby P., Lim W.S., Emberson J.R., et al.* Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med. 2021; 384(8): 693–704. DOI: 10.1056/NEJMoa2021436

[16] *Russell C.D., Millar J.E., Baillie J.K.* Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet. 2020; 395(10223): 473–5. DOI: 10.1016/S0140-6736(20)30317-2

[17] *Moreno G., Rodríguez A., Reyes L.F., and GETGAG Study Group.* Corticosteroid treatment in critically ill patients with severe influenza pneumonia: a propensity score matching study. Intens Care Med. 2018; 44(9): 1470–82. DOI: 10.1007/s00134-018-5332-4

[18] *Wu C., Chen X., Cai Y., et al.* Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020; 180(7): 934–43. DOI: 10.1001/jamainternmed.2020.0994

[19] *WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne J.A.C., Murthy S., Diaz J.V., et al.* Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. JAMA. 2020; 324(13): 1330–41. DOI: 10.1001/jama.2020.17023

[20] *van Paassen J., Vos J.S., Hoekstra E.M., et al.* Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes. Crit Care. 2020; 24(1): 696. DOI: 10.1186/s13054-020-03400-9

[21] *Zayed Y., Barbarawi M., Ismail E., et al.* Use of glucocorticoids in patients with acute respiratory distress syndrome: a meta-analysis and trial sequential analysis. J Intens Care. 2020; 8: 43. DOI: 10.1186/s40560-020-00464-1

[22] *Shang L., Zhao J., Hu Y., et al.* On the use of corticosteroids for 2019-nCoV pneumonia. Lancet. 2020; 395(10225): 683–4. DOI: 10.1016/S0140-6736(20)30361-5

[23] *Vecchié A., Batticciotto A., Tangianu F., et al.* High-dose dexamethasone treatment for COVID-19 severe acute respiratory distress syndrome: a retrospective study. Intern Emerg Med. 2021; 16(7): 1913–9. DOI: 10.1007/s11739-021-02800-1

[24] *Yang L., Peng L., Wu W., et al.* Low-to-Moderate Dosage and Short-Term Use of Corticosteroids Benefit Patients with Severe COVID-19 Infections. Front Microbiol. 2022; 13: 953328. DOI: 10.3389/fmicb.2022.953328

[25] *Аврамов А.А., Иванов Е.В., Мелехов А.В., и др.* Факторы риска неблагоприятного исхода COVID-19 в ОРИТ перепрофилированных стационаров разного типа. Общая реаниматология. 2023;19(3):20-27. [*Avramov A.A., Ivanov E.V., Melekhov A.V., et al.* Risk Factors for COVID-19 Adverse Outcomes in ICU Settings of Various Types Repurposed Hospitals. General Reanimatology. 2023;19(3):20-27. (In Russ)] DOI:10.15360/1813-9779-2023-3-20-27

[26] *Сологорский С.В., Овечкин А.М., Хапов И.В., и др.* Факторы риска и методы прогнозирования клинического исхода COVID-19 (обзор). Общая реаниматология. 2022;18(1):31-38. [*Sokologorskiy S.V., Ovechkin A.M., Khapov I.V., et al.* Risk Factors of Severe Disease and Methods for Clinical Outcome Prediction in Patients with COVID-19 (Review). General Reanimatology. 2022;18(1):31-38. (In Russ)] DOI:10.15360/1813-9779-2022-1-31-38

[27] *Толочко М.В., Лейдерман И.Н., Хохунов О.А., и др.* Анализ клинической эффективности дексаметазона у пациентов со среднетяжелым течением COVID-19. Общая реаниматология. 2022;18(1):11-16. [*Tolochko M.V., Leyderman I.N., Khokhunov O.A., et al.* Assessment of Clinical Efficacy of Dexamethasone in Patients with Moderate COVID-19. General Reanimatology. 2022;18(1):11-16. (In Russ)] DOI:10.15360/1813-9779-2022-1-11-16

[28] *Временные методические рекомендации "Профилактика, диагностика и лечение новой коронавирусной инфекции (COVID-19)".* Версия 3 (03.03.2020) (утв. Министерством здравоохранения РФ). https://fmba.gov.ru/upload/medialibrary/69d/Vremennye_MR_COVID_19_03.03.2020_versiya_3_6_6.pdf [*Temporary guidelines "Prevention, diagnosis and treatment of new coronavirus infection (COVID-19)".* Version 3 (03.03.2020) (approved by the Ministry of Health of the Russian Federation) https://fmba.gov.ru/upload/medialibrary/69d/Vremennye_MR_COVID_19_03.03.2020_versiya_3_6_6.pdf (In Russ)]

[29] *Torres A., Sibila O., Ferrer M., et al.* Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. JAMA. 2015; 313(7): 677–86. DOI: 10.1001/jama.2015.88

[30] *Longobardo A., Snow T.A.C., Montanari C., et al.* COVID-19 and non-COVID ARDS patients demonstrate a distinct response to low dose steroids- A retrospective observational study. J Crit Care. 2021; 62: 46–8. DOI: 10.1016/j.jcrc.2020.11.012

[31] *Chen H., Xie J., Su N., et al.* Corticosteroid Therapy Is Associated with Improved Outcome in Critically Ill Patients With COVID-19 With Hyperinflammatory Phenotype. Chest. 2021; 159(5): 1793–802. DOI: 10.1016/j.chest.2020.11.050

[32] *Ho K.S., Narasimhan B., Difabrizio L., et al.* Impact of corticosteroids in hospitalised COVID-19 patients. BMJ Open Respir Res. 2021; 8(1): e000766. DOI: 10.1136/bmjresp-2020-000766

[33] *Bouadma L., Mekontso-Dessap A., Burdet C., and COVIDICUS Study Group.* High-Dose Dexamethasone and Oxygen Support Strategies in Intensive Care Unit Patients with Severe COVID-19 Acute Hypoxemic Respiratory Failure: The COVIDICUS Randomized Clinical Trial. JAMA Intern Med. 2022; 182(9): 906–16. DOI: 10.1001/jamainternmed.2022.2168

[34] *Munch M.W., Myatra S.N., Vijayaraghavan B.K.T., and COVID STEROID 2 Trial Group*. Effect of 12 mg vs 6 mg of Dexamethasone on the Number of Days Alive Without Life Support in Adults With COVID-19 and Severe Hypoxemia: The COVID STEROID 2 Randomized Trial. JAMA. 2021; 326(18): 1807–17. DOI: 10.1001/jama.2021.18295

[35] *Granholm A., Munch M.W., Myatra S.N., et al.* Dexamethasone 12 mg versus 6 mg for patients with COVID-19 and severe hypoxaemia: a pre-planned, secondary Bayesian analysis of the COVID STEROID 2 trial. Intensive Care Med. 2022; 48(1): 45–55. DOI: 10.1007/s00134-021-06573-1

[36] *Remy K.E., Brakenridge S.C., Francois B., et al.* Immunotherapies for COVID-19: lessons learned from sepsis. Lancet Respiratory Medicine. 2020; 8(10): 946–9. DOI: 10.1016/S2213-2600(20)30217-4

[37] *Notz Q., Schmalzing M., Wedekink F., et al.* Pro- and Anti-Inflammatory Responses in Severe COVID-19-Induced Acute Respiratory Distress Syndrome-An Observational Pilot Study. Front Immunol. 2020; 11: 581338. DOI: 10.3389/fimmu.2020.581338

[38] *Caricchio R., Gallucci M., Dass C., and Temple University COVID-19 Research Group.* Preliminary predictive criteria for COVID-19 cytokine storm. Ann Rheum Dis. 2021; 80(1): 88–95. DOI: 10.1136/annrheumdis-2020-218323

[39] *Manson J.J., Crooks C., Naja M., et al.* COVID-19-associated hyperinflammation and escalation of patient care: a retrospective longitudinal cohort study. Lancet Rheumatol. 2020; 2(10): e594–e602. DOI: 10.1016/S2665-9913(20)30275-7

[40] *Reddy K., Rogers A.J., McAuley D.F.* Delving beneath the surface of hyperinflammation in COVID-19. Lancet Rheumatology. 2020; 2(10): e578–e579. DOI: 10.1016/S2665-9913(20)30304-0

[41] *Zeng F., Huang Y., Guo Y., et al.* Association of inflammatory markers with the severity of COVID-19: A meta-analysis. International Journal of Infectious Diseases. 2020; 96: 467–74. DOI: 10.1016/j.ijid.2020.05.055

[42] *Sinha P., Furfaro D., Cummings M.J., et al.* Latent Class Analysis Reveals COVID-19-related Acute Respiratory Distress Syndrome Subgroups with Differential Responses to Corticosteroids. Am J Respir Crit Care Med. 2021; 204(11): 1274–85. DOI: 10.1164/rccm.202105-1302OC

[43] *Meduri G.U., Golden E., Freire A.X., et al.* Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. Chest. 2007; 131(4): 954–63. DOI: 10.1378/chest.06-2100

[44] *Steinberg K.P., Hudson L.D., Goodman R.B., et al.;* National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med. 2006; 354(16): 1671–84. DOI: 10.1056/NEJMoa051693

[45] *Villar J., Ferrando C., Martínez D., et al.*; dexamethasone in ARDS network. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet Respir Med. 2020; 8(3): 267–76. DOI: 10.1016/S2213-2600(19)30417-5

[46] *Calfee C.S., Delucchi K., Parsons P.E., et al.*; NHLBI ARDS Network. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. Lancet Respir Med. 2014; 2(8): 611–20. DOI: 10.1016/S2213-2600(14)70097-9

[47] *Siemieniuk R.A., Meade M.O., Alonso-Coello P., et al.* Corticosteroid Therapy for Patients Hospitalized with Community-Acquired Pneumonia: A Systematic Review and Meta-analysis. Ann Intern Med. 2015; 163(7): 519–28. DOI: 10.7326/M15-0715

[48] *Arabi Y.M., Mandourah Y., Al-Hameed F., and Saudi Critical Care Trial Group.* Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome. Am J Respir Crit Care Med. 2018; 197(6): 757–67. DOI: 10.1164/rccm.201706-1172OC