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RESEARCH ARTICLE

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Factors associated with dexamethasone efficacy in COVID-19. A retrospective investigative cohort study

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Abstract

Dexamethasone has demonstrated efficacy in reducing mortality in COVID-19. However, its practical use is badly defined. We aimed to investigate factors associated with dexamethasone efficacy in real life. Our retrospective study was conducted in two university hospitals between September and November 2020 and included all the consecutive hospitalized patients with a laboratory-confirmed SARS-CoV-2 infection assessed by RT-PCR, treated with intravenous dexamethasone (6 mg/day). Among 111 patients, 10.6% necessitated a transfer into the intensive care unit (ICU) and the 28-day mortality rate was 17.1%. The 28-day mortality rate was significantly lower in patients who demonstrated improvement at 48 h (hazard ratio [HR]: 0.17, 95% confidence interval [CI]: 0.04–0.78, $p = 0.02$) and 96 h (HR: 0.07, 95% CI: 0.02–0.31, $p = 0.0005$) after dexamethasone initiation. Apart from well-known risk factors (age, hypertension, active cancer, severe lesions on chest computed tomography [CT] scan), we found that a high viral load in nasopharyngeal swab (Cycle threshold <30) at dexamethasone initiation was associated with higher 28-day mortality (66.6% vs. 36.7%, $p = 0.03$). Patients who did not receive antibiotics at dexamethasone initiation had a higher rate of transfer into the ICU (55.6% vs. 23.5%, $p = 0.045$) with a trend towards higher mortality in case of severe or critical lesions on CT scan (75.0% vs. 25.0%, $p = 0.053$). Patients who did not improve within 2–4 days after steroid initiation have a bad prognosis and should receive additional anti-inflammatory drugs. Our data suggest better efficacy of dexamethasone in patients with a low or negative viral load, receiving broad-spectrum antibiotics.

KEYWORDS

antibiotics, COVID-19, dexamethasone, intensive care unit, mortality

1 | INTRODUCTION

Since December 2019, COVID-19, the disease due to the new coronavirus,[1] SARS-CoV-2, has induced more than 5 million deaths around the world.[2] The course of COVID-19 is characterized by the succession of several phases.[3] The early infection presents with constitutional symptoms (fever, dry cough) and a high viral load. Then occurs pneumonia characterized by dyspnea with or without hypoxia and blood inflammation of various severity. The last stage is characterized by the occurrence of an acute respiratory syndrome

(ARDS), systemic inflammation, and disseminated coagulation, usually with a low viral load. Several drugs aiming at decreasing inflammation have been tried to treat moderate to severe COVID-19 pneumonia with conflicting results[4] and to date, only corticosteroids, especially dexamethasone, demonstrated a significant reduction of mortality in patients receiving oxygen in a large randomized controlled trial.[5] In France, dexamethasone is now the standard of care in patients hospitalized with moderate to severe COVID-19 pneumonia associated with excessive systemic inflammation.[6] However, corticosteroids in this context may be associated with delayed viral clearance such as observed in other coronavirus-induced severe pneumonia,[7–9] increased opportunistic infection,[9,10] hyperglycemia [11] and other side effects. Data are still lacking on the precise timing of initiation and practical use of dexamethasone in COVID-19. In this retrospective study, we aimed to investigate factors associated with dexamethasone efficacy in real life.

2 | METHODS

2.1 | Patients

We retrospectively included all consecutive adult patients (aged ≥18 years) admitted with a laboratory-confirmed SARS-CoV-2 infection assessed by RT-PCR on nasopharyngeal swabs and treated with intravenous dexamethasone (6 mg/day) between September and November 2020 in two internal medicine departments (La Conception and La Timone, University Hospital of Marseille, France). Patients were not included if they have been previously hospitalized in the intensive care unit (ICU) or if they had an ongoing hematological malignancy. Clinical, biological, radiological, and follow-up data of these patients were collected from electronic medical records. We assessed the clinical status of patients using the National Early Warning Score (NEWS 2).[12,13] We considered that the patients had a good clinical response to the treatment if they reached at least 2 of the following items: (1) decrease of the fraction of inspired oxygen (F_iO_2) requirement ≥8%, (2) decrease of C-reactive protein (CRP) >20%, (3) decrease of NEWS 2 ≥1. We registered day 1 of dexamethasone therapy as D1 dexamethasone. Viral load was analyzed by repeated semi-quantitative RT-PCR from nasopharyngeal swabs. Negative results for viral RNA detection were defined as a cycle threshold (Ct) value ≥35. Patients were considered to have a low viral load when the Ct value was ≥30 and <35 in nasopharyngeal swabs. The F_iO_2 was indicated by the mechanical ventilator or by the high-flow nasal cannula and was calculated in patients receiving oxygen by low-flow nasal cannula according to the formula: $F_iO_2 = 21 + [4 \times (\text{oxygen flow in liter/min})]$. Patients underwent a low-dose chest computed tomography (CT) and were classified into five different grades based on the extent of lung parenchymal lesions (minimal <10%, moderate: 10%–25%, intermediate: 25%–50%, severe: 50%–75% and critical >75%). Soluble urokinase Plasminogen Activator Receptor (suPAR) level was assessed by immunoturbidimetry.

2.2 | Laboratory tests

Viral RNA was extracted from 200 µl of naso- and oro-pharyngeal swab fluid and/or sputum, using the EZ1 Virus Mini Kit v2.0 (Qiagen®). For the detection of SARS-CoV-2 RNA we used two different RT-PCR systems with a hydrolysis probe and the Light-Cycler Multiplex RNA Virus Master kit (Roche Diagnostics®). The first system targets the envelope protein (E)-encoding gene and uses a synthetic RNA positive control (supplied by the Charité virology institute—Universitätsmedizin Berlin, Berlin, Germany[14]). The second system was designed in-house, targets the spike protein-encoding gene (forward primer: 5′-AAACTTGTGCCCTTTTGGTG-3'; reverse primer: 5′-TGCTGATTCTCTTCCTGTTCC-3'; probe: 5′-CGCCACC AGATTTGCATCTG-3′), and uses a synthetic RNA positive control ordered from Eurogentec®.

2.3 | Ethical

This study was approved by the Institutional Review Board of Assistance Publique—Hôpitaux de Marseille (GDPR number PADS21-4). The study was conducted according to the Declaration of Helsinki.

2.4 | Statistical analysis

Quantitative variables were described using medians and interquartile range (IQR); categorical variables were described using numbers and percentages. Quantitative data were compared using the Student *t* or Mann–Whitney *U* test, while qualitative data were compared with the Chi-square or Fisher's exact test when appropriate. Survival and cumulative "survival or transfer into ICU" were estimated by means of the reverse Kaplan–Meier method and they were compared between groups using stratified log-rank tests. The tests were two-sided. All p values <0.05 were considered significant. All analyses were performed with R software (R Foundation for Statistical Computing).

3 | RESULTS

3.1 | Characteristics of the population

One hundred and eleven patients were included. The main characteristics of the population are presented in Table 1. The median age was 73 years (IQR: 61–82, range: 42–98), with 63 male patients (56.8%). The main comorbidities were obesity (55.4%), hypertension (52.3%), type 2 diabetes (32.4%) and cardiovascular diseases (22.5%).

Twenty-six patients (23.4%) had a "do-not-resuscitate" status. Lung CT showed typical lesions of COVID-19 in 105 out of 109 patients, consisting in minimal, moderate, intermediate, severe, and critical lesions in 11%, 33.9%, 29.4%, 20.2%, and 1.8%, respectively.

TABLE 1 Main characteristics of the studied population

Characteristics	Patients (n = 111)
Age (years)[a]	73 [61–82]
Male gender[b]	63 (56.8)
Body mass index[a]	27.7 [24.7–32.3]
Comorbidities[b]	
- Obesity	31/56 (55.4)
- Hypertension	58 (52.3)
- Diabetes	36 (32.4)
- Cardiovascular disease	25 (22.5)
- Dyslipidemia	22 (19.8)
- Chronic lung disease	19 (17.1)
- Chronic kidney failure	11 (9.9)
- Currently smoking	7/97 (7.2)
- Dementia	8 (7.2)
- Immunosuppression	5 (4.5)
- Cancer	5 (4.5)
Duration of hospital stay[a]	10 [8–14]
Grade of lung involvement[b]	
- No lesion	4/109 (3.7)
- Minimal	12/109 (11.0)
- Moderate	37/109 (33.9)
- Intermediate	32/109 (29.4)
- Severe	22/109 (20.2)
- Critical	2/109 (1.8)
COVID-19 management[b]	
- Heparins	111 (100)
- Antibiotics	97 (87.4)
- Anakinra	2 (1.8)
- Ruxolitinib	6 (5.4)
- Hydroxychloroquine	21 (18.9)
Oxygen Duration[a]	8.5 [5–13.8]
Mechanical ventilation[b]	4/85 (4.7)
Intensive care unit transfer[b]	9/85 (10.6)
28-day mortality[b]	19 (17.1)

[a]Median [range].
[b]n (%).

The median suPAR level was 6.8 ng/ml (IQR: 5.4–10.3) and 11/30 patients (36.7%) had a suPAR level >6 ng/ml. Ninety-seven patients (87.4%) received large-spectrum antibiotics such as azithromycin in 81 patients (73%), ceftriaxone in 64 patients (57.7%), ertapenem in 26 patients (23.4%) and piperacillin-tazobactam in 14 patients (12.6%). All patients were treated with heparin and had a monitored anti-Xa activity.

3.2 | Evolution of patients receiving dexamethasone

Nine patients of the 85 eligible patients (10.6%) necessitated a transfer into the ICU, four of them (4.7%) requiring invasive mechanical ventilation. The 28-day mortality rate was 17.1%. The main characteristics of dexamethasone management and adverse events are presented in Table 2.

The patients received dexamethasone for a median of 7 days (IQR: 6–9, range: 2–15). On dexamethasone, patients' oxygen flow requirement decreased after a median of 3 days (IQR: 1–6) following the initiation of the treatment. At D1 dexamethasone, the median F_iO_2 was 37% (IQR: 33–51), increased to 40.5% (IQR: 33–49, $p = 0.88$) after 48 h and remained at 37% (IQR: 25–50, $p = 0.23$) after 96 h. F_iO_2 requirement significantly dropped in patients 144 h after the initiation of dexamethasone (37% vs. 29%, $p = 0.005$). The oxygen supplementation was stopped after a median of 7 days (IQR: 4–12) following dexamethasone initiation. Fever rapidly disappeared (median: 1 day, IQR: 0–3) after the initiation of dexamethasone. NEWS 2 significantly decreased in patients 48 h (5 vs. 4, $p = 0.011$) and 96 h (5 vs. 3, $p < 0.0001$) after the initiation of dexamethasone, whereas CRP level decreased in 2 days in median (IQR: 1–3): 117.5 mg/L (IQR: 69–177) at D1 dexamethasone versus 56.5 mg/L (IQR: 29–97) after 48 h. Fifty-eight patients (52.3%) developed one or more adverse events under dexamethasone: 35 patients (31.5%) needed insulin for glucose control, 29 patients (26.1%) had hypokalemia, 19 patients (17.1%) had hypertension or cardiac failure and 12 patients (10.8%) developed infections. On D1 dexamethasone, 82 patients (73.9%) were receiving antibiotics and 63 of 108 patients (58.3%) had an RT-PCR Ct value ≥30.

3.3 | Early predictive response to dexamethasone

After adjustment for risk factors such as age and hypertension, the 28-day mortality rate was significantly lower in patients who had a good response (as defined in the method section) at 48 h (hazard ratio [HR]: 0.17, 95% confidence interval [CI]: 0.04–0.78, $p = 0.02$) and 96 h (HR: 0.07, 95% CI: 0.02–0.31, $p = 0.0005$) after dexamethasone initiation (Figure 1).

Similarly, the composite score consisting in 28-day mortality rate and/or transfer into the ICU was lower in patients with a good response at 48 h (HR: 0.17, 95% CI: 0.06–0.51, $p = 0.002$) and 96 h (HR: 0.02, 95% CI: 0.01–0.1, $p < 0.0001$) after dexamethasone initiation (Figure 2).

3.4 | Factors associated with an early good response after dexamethasone

The factors associated with a good response (as defined in the method section) at 48 h after dexamethasone initiation were a younger age (68 vs. 76 years, $p = 0.025$) and a low viral load in nasopharyngeal swab (Ct >30) at D1 dexamethasone (58.9% vs. 38.4%, $p = 0.049$). The factors associated with a good response at

TABLE 2 Management of dexamethasone, evolution under treatment, and adverse events

	Patients (n = 111)
Duration of dexamethasone therapy[a]	7 [6–9]
Viral load at dexamethasone introduction[a]	31 [21–36]
Viral load ≥30 Ct at dexamethasone introduction[b]	63/108 (58.3)
Antibiotics at dexamethasone introduction[b]	82 (73.9)
Delay before oxygen decrease following dexamethasone introduction[a]	3 [1–6]
Delay before fever disappearance following dexamethasone introduction[a]	1 [0–3]
Delay before CRP decrease following dexamethasone introduction[a]	2 [1–3]
Oxygen duration after Dexamethasone[a]	7 [4–12]
FiO_2 at dexamethasone introduction[a]	37 [33–51]
FiO_2 48 h after dexamethasone introduction[a]	41 [33–49]
FiO_2 96 h after dexamethasone introduction[a]	37 [25–50]
FiO_2 144 h after dexamethasone introduction[a]	29 [0–45]
NEWS 2 at dexamethasone introduction[a]	5 [4–6.5]
NEWS 2 48 h after dexamethasone introduction[a]	4 [3–6]
NEWS 2 96 h after dexamethasone introduction[a]	3 [2–5]
Adverse events under dexamethasone[b]:	58 (52.3)
- Hyperglycemia	35 (31.5)
- Hypokaliemia	29 (26.1)
- Hypertension or cardiac failure	19 (17.1)
- Infectious disease	12 (10.8)

Abbreviations: CRP, C-reactive protein; Ct, cycle threshold; FiO_2, fraction of inspired oxygen; NEWS, National Early Warning Score.

[a]Median [range].

[b]n (%).

96 h after dexamethasone initiation were a low viral load in nasopharyngeal swab (Ct >30) at D1 dexamethasone (82.1% vs. 42.9%, $p < 0.001$), the presence of antibiotics at D1 dexamethasone (72.4% vs. 48.0%, $p = 0.025$) and a higher blood eosinophilic count at D1 dexamethasone (39/mm^3 vs. 8.1/mm^3, $p = 0.014$). Circulating suPAR or suPAR >6 ng/ml were not associated with the good response at 48 h or 96 h after dexamethasone initiation.

3.5 | Factors associated with mortality and ICU requirement after dexamethasone

The risk factors associated with mortality on dexamethasone treatment were: age (83 years [range: 73–98] vs. 68.5 years [range: 42–96], $p < 0.0001$), hypertension (73.7% vs. 47.8%, $p = 0.04$), active cancer (15.8% vs. 2.2%, $p = 0.03$), severe lesions on low-dose chest CT scan (43.8% vs. 19.1%, $p = 0.0002$), secondary infection following dexamethasone therapy (26.3% vs. 8.7%, $p = 0.04$) and a high viral load in nasopharyngeal swab (Ct <30) at D1 dexamethasone (66.6% vs. 36.7%, $p = 0.03$, Figure 3). The absence of antibiotics at the time of dexamethasone initiation seemed to be associated with a higher mortality in patients with severe or critical lesions on CT scan (75.0% vs. 25.0% death on antibiotics, $p = 0.053$).

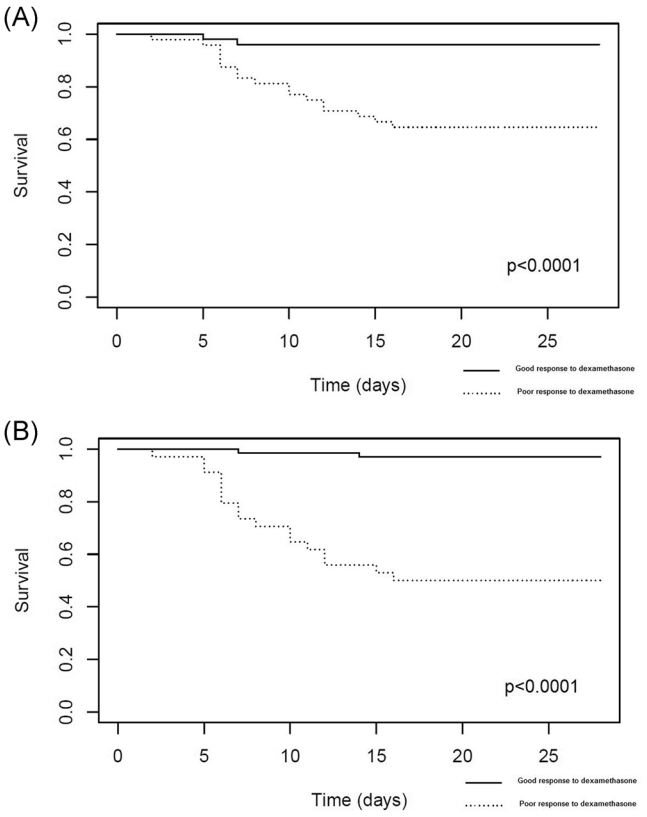

FIGURE 1 Kaplan–Meier survival curve for 28-day cumulative survival rates. Comparison (using stratified log-rank tests) between patients with a good and a poor response 48 h (A) and 96 h (B) after dexamethasone initiation

The risk factors associated with ICU requirement on dexamethasone were underlying immunosuppression (22.2% vs. 2.9%, $p = 0.045$) and the absence of antibiotics at D1 dexamethasone (55.6% vs. 23.5%, $p = 0.045$, Figure 4). In patients transferred to the ICU, 3 (33%) were diagnosed with a bacterial infection shortly after ICU admission (Pseudomonas Aeruginosa: 1, Enterococcus Faecium: 1, Enterobacter Cloacae: 1) and 7 patients (78%) received at least one new line of antibiotics after ICU admission.

4 | DISCUSSION

In our cohort, the 28-day mortality rate was 17.1%, whereas transfer into the ICU was necessary for 10.6%, and 4.7% of patients required invasive mechanical ventilation. These results are comparable to those reported in the RECOVERY trial in which the incidence of

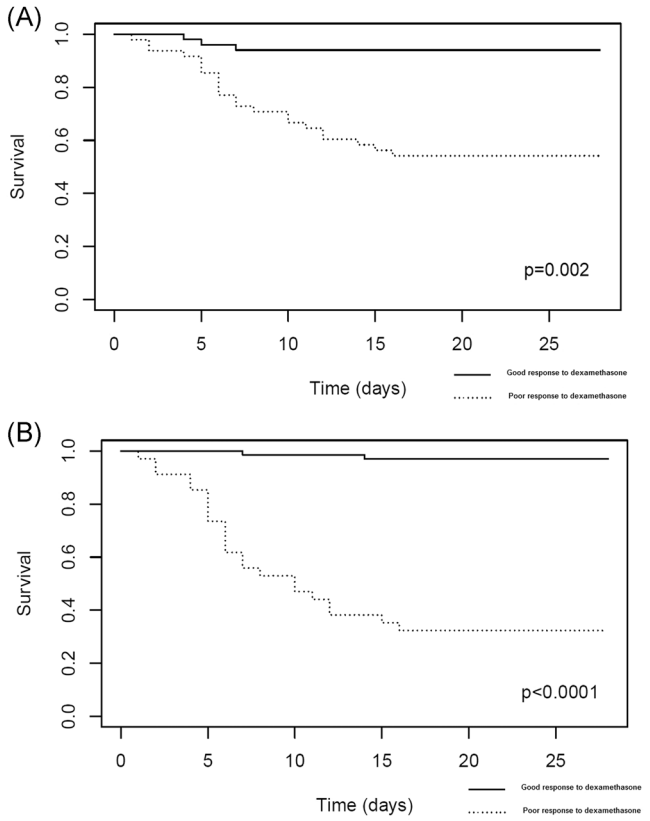

FIGURE 2 Kaplan–Meier survival curve for 28-day cumulative survival or transfer into ICU. Comparison (using stratified log-rank tests) between patients with a good and a poor response 48 h (A) and 96 h (B) after dexamethasone initiation. ICU, intensive care unit

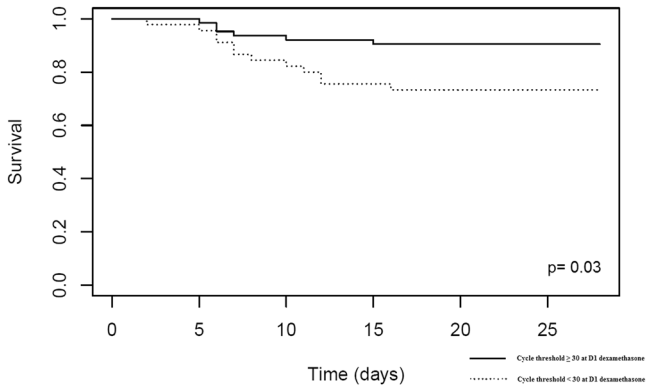

FIGURE 3 Viral load at dexamethasone initiation as a predictor of 28-day mortality. Kaplan–Meier survival curve for 28-day cumulative survival rates. Comparison (using stratified log-rank tests) between patients with a cycle threshold ≥ or <30 on nasopharyngeal SARS-CoV2 RT-PCR at dexamethasone initiation

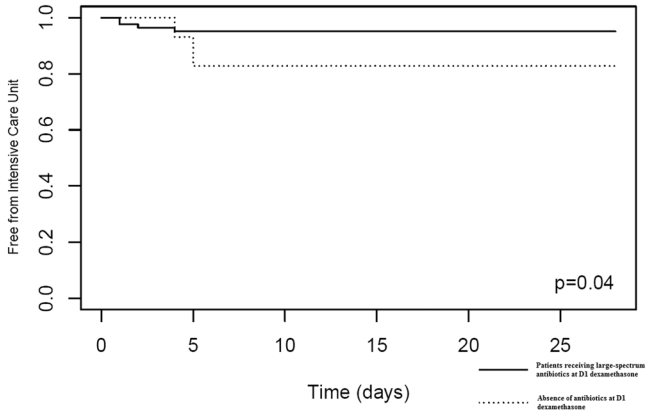

FIGURE 4 Large-spectrum antibiotic treatment at the time of dexamethasone initiation as a predictor of transfer into the ICU. Kaplan-Meier survival curve for 28-day transfer into the ICU rates. Comparison (using stratified log-rank tests) between patients receiving large-spectrum antibiotics or not at dexamethasone initiation. ICU, intensive care unit

death was 23.3% and the rate of patients who progressed to mechanical ventilation was 5.7% in patients receiving oxygen without invasive mechanical ventilation and confirm that steroid treatment is effective compared to historical standard-of-care in patients with moderate to severe pneumonia requiring oxygen supplementation associated with systemic biological inflammation.[5]

In this study, we observed that the viral load, at the time of dexamethasone initiation, was associated with mortality. The higher the viral load, the higher the mortality, in accordance with previous reports.[15]

We observed, however, that dexamethasone was associated with significant side effects that were not reported in the RECOVERY trial but were expectable and should be considered in patients with other comorbidities such as type 2 diabetes, hypertension, or cardiovascular diseases.

Steroid treatment during COVID-19 has been controversial and in several hundred patients treated in China, no benefit was reported, initially leading the WHO to recommend against corticosteroid treatment.[16–19] This may be due to heterogeneity in the doses and timing of the treatment. In the RECOVERY study, for example, no benefit and possibly detrimental effects were observed in patients who did not require oxygen treatment.[5] Conversely, the patients who mostly benefited from steroid treatment were those admitted into the ICU requiring invasive mechanical ventilation.[5] This may be expectable when considering that the severity of pneumonia parallels the severity of lung and systemic inflammation.[20] Patients not requiring oxygen may, firstly, be not severe enough to require immunomodulation or secondly, too early in their disease, possibly still in the course of the viral phase. In favor of this hypothesis, we observed in our cohort, that the 28-day mortality rate was significantly lower when dexamethasone was initiated in patients with a low or negative viral load (Ct ≥30). Natural control of viral replication usually occurs after 7–10 days of infection, but in real life, the beginning of the disease may be difficult to precisely ascertain and carriage may be prolonged in older or immunocompromised patients, suggesting that longitudinal checking of the viral load may be useful before considering dexamethasone initiation. In addition, we observed that transfer into the ICU was less frequent in patients

who received large-spectrum antibiotics at D1 dexamethasone, notably in those with severe CT-scan lung lesions, suggesting that a part of hospitalized patients with COVID-19 may have underlying bacterial coinfections as recently reported by others[21–25] and supported by the fact that 3/9 of our patients who needed transfer into the ICU had a concomitant proven bacterial infection. These data should be interpreted with caution, and we are concerned by the risk of inducing antibio-resistance through the large prescription of broad-spectrum antibiotics, but our observations, as well as recent reports, suggest that the use of empirical antibiotics may be considered prior or concomitantly to dexamethasone initiation, especially in previously immunocompromised patients or in those with extended pulmonary lesions.

At the time of severe COVID-19 pneumonia, patients have a low viral load but develop an excessive inflammatory response, especially in the lungs and demonstrate increased concentrations of circulating proinflammatory cytokines such as interleukin (IL)-1, IL-6, tumour necrosis factor-α, IL-18, chemokines, interferons.[3,20,26,27] This "cytokine storm" contributes to lung injury and the development of ARDS.[20,28] To fight the cytokine storm, anticytokine treatments targeting one cytokine have been used in severe COVID-19 with controversial results.[4] Contrary to targeted anticytokine strategies, corticosteroids have a broad spectrum of anti-inflammatory action through inhibition of nuclear factor-kappa B.[29,30] Depending on the disease timing, various inflammatory pathways may be involved in COVID-19, explaining that dexamethasone may be more efficient than treatments targeting only one cytokine. However, as reported by several studies, including the RECOVERY trial, dexamethasone does not appear to control all the patients and a significant percentage of them will undergo invasive mechanical ventilation, prolonged disease, and death.[5,31] One of the most important findings of this study is the fact that patients who did not have a good response to treatment 48 and 96 h after the initiation of dexamethasone (consisting in decreased oxygen requirement, CRP, or NEWS 2) had higher mortality and ICU transfer rates. Thus, a poor response to treatment appeared to be predictable very early, 2–4 days, after the initiation of dexamethasone. Patients may then necessitate the addition of other treatments, such as tocilizumab, baricitinib or anakinra, or completely different drug associations to control their disease.[32-35]

We acknowledge limitations to this study. First, it is retrospective, based on a limited number of patients which did not allow us to perform multivariate analysis. Second, the RT-PCR analysis was not quantitative as in another previous report,[15] however, this semi-quantitative technique is routinely used in patient care and is easy to compare along time for each individual patient.

In conclusion, our data suggest a better efficacy of dexamethasone in patients with a low or negative viral load, under antibiotics therapy. If the clinical condition does not improve within the 4 first days of treatment, additional therapy should be considered.

AUTHOR CONTRIBUTIONS

Conceptualization: Robin Arcani, Raphaël Cauchois, Rodolphe Jean, Marie Koubi, Gilles Kaplanski. *Methodology*: Robin Arcani, Raphaël Cauchois, Quentin Gomes De Pinho, Jean-Baptiste Dalmas, Estelle Jean, Baptiste Andre, Véronique Veit, Gilles Kaplanski. Validation: Robin Arcani, Raphaël Cauchois, Pierre Suchon, Estelle Jean, Baptiste Andre, Véronique Veit, Marie Koubi, Gilles Kaplanski. *Formal analysis*: Robin Arcani, Pierre Suchon, Gilles Kaplanski. *Investigation*: Robin Arcani, Rodolphe Jean, Pierre-André Jarrot, Quentin Gomes De Pinho, Jean-Baptiste Dalmas, Estelle Jean, Baptiste Andre, Véronique Veit, Marie Koubi. *Writing—Original draft preparation*: Robin Arcani, Raphaël Cauchois, Pierre Suchon, Marie Koubi, Gilles Kaplanski. *Writing—Reviews and editing*: all the authors. All authors contributed to the study's conception and design. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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