Impact of previous exposure to systemic corticosteroids on unfavorable outcome in patients hospitalized for COVID-19

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Abstract

Background: The impact of prior exposure to systemic corticosteroids on COVID-19 severity in patients hospitalized for a SARS-CoV-2 pneumonia is not known. The present study was designed to answer to this question.

Methods: The population study was the Covid-Clinic-Toul cohort which records data about all hospitalized patients with a positive reverse transcriptase polymerase chain reaction for a SARS-CoV-2 infection at Toulouse University hospital, France. Exposure to systemic corticosteroids was assessed at hospital admission. A propensity score (PS) according to corticosteroid exposure was calculated including comorbidities, clinical, radiological and biological variables that impact COVID-19 severity. The primary outcome was composite, including admission to intensive care unit, need of mechanical ventilation and death occurring during the 14 days after hospital admission. Logistic regression models adjusted for the PS (overlap weighting) provided odds ratios (ORs) and their 95% confidence intervals (95% CIs).

Results: Overall, 253 patients were included in the study. Median age was 64 years, 140 patients (59.6%) were men and 218 (86.2%) had at least one comorbidity. Seventeen patients (6.7%) were exposed to corticosteroids before hospital admission. Chronic inflammatory disease (n = 8) was the most frequent indication. One hundred and twenty patients (47.4%) met the composite outcome. In the crude model, the OR of previous exposure to systemic corticosteroids was 1.64; 95% CI: 0.60–4.44. In the adjusted model, it was 1.09 (95% CI: 0.65–1.83).

Conclusion: Overall, this study provide some evidences for an absence of an increased risk of unfavorable outcome with previous exposure to corticosteroids in the general setting of patients hospitalized for COVID-19.

Keywords: SARS-COV-2, COVID-19, Systemic corticosteroids, Mortality, Intensive care unit, Pharmacoepidemiology

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Background
Corticosteroid-based therapy is used to treat patients with severe coronavirus disease 2019 (COVID-19) to reduce inflammatory lung injury, notably when a major cytokine reaction is responsible for clinical worsening [1–4]. A recent prospective meta-analysis of clinical trials conducted by the World Health Organization (WHO) Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group showed that administration of systemic corticosteroids in critically ill patients with COVID-19, compared with usual care or placebo, was associated with lower 28-day all-cause mortality [5]. Moreover, exposure to systemic corticosteroids before COVID-19, responsible for immunosuppression, has been hypothesized to be associated with severe forms of COVID-19. Systemic exposure to corticosteroids has been associated with an increased risk of hospitalization in patients with rheumatic diseases (≥10 mg/day in prednisone-equivalent dosage, OR: 2.05; 95% CI: 1.06–3.96) [6]. A major increased risk of severe COVID-19 (defined by admission in intensive care unit – ICU, need of mechanical ventilation or death) was found in patients with chronic inflammatory bowel disease (OR: 6.9; 95% CI: 2.3–20.5) [7]. These studies were focused on patients with some autoimmune diseases and were not adjusted for clinical, biological and radiological markers of COVID-19 severity. The impact of previous exposure to corticosteroids in the general setting of patients hospitalized for COVID-19 is unknown.

We aimed to assess the impact of prior exposure to systemic corticosteroids on COVID-19 severity in patients hospitalized for reverse transcriptase polymerase chain reaction (RT-PCR)-proven SARS-CoV-2 infection.

Methods
Study population
The study was conducted within the Covid-Clinic-Toulcohort which records data about all hospitalized patients with a positive RT-PCR for a SARS-CoV-2 infection at Toulouse University hospital, France [8, 9]. This cohort has been approved by institutional review board (n°RnIPH 2020–31), in accordance with French law. All patients, or their representatives, were informed by a letter given at admission to hospital and/or sent to their place of residency. Exclusion criterion was opposition to data collection. We selected the patients included up to April 20, 2020 and with a chest computed tomography (CT) scan at admission. Patients from April 1st were prospectively included.

Exposure
Exposure to systemic corticosteroid at hospital admission was assessed by physicians and then extracted from electronic medical records. Drug, dosage, duration of use (categorized as short-term exposure for <7 days vs ≥7 days) and indication were described.

Outcome
The primary outcome was composite, including admission to ICU, need of mechanical ventilation and death occurring during the 14 days after hospital admission.

Covariables
The following variables were assessed at hospital admission: age (≥65 years vs. <65 years), sex, presence of hypertension, cardiovascular disease, cerebrovascular disease, chronic pulmonary disease, chronic liver disease, chronic kidney disease, diabetes, cancer, overweight, immunosuppression (excluding exposure to corticosteroids), oxygen saturation ≤92% or need of oxygen therapy, lymphopenia (<1.5×109/L), thrombocytopenia (<150×109/L), C-reactive protein (≥50 mg/L vs. <50 mg/L), extension of ground glass opacities at chest CT-scan categorized by absence or mild involvement (<25% of lung parenchyma) vs. moderate to critical involvement (≥25%).

Statistical analyses
For descriptive analyses, continuous variables were expressed by mean and standard deviation or median and interquartile range (IQR) depending on their distribution, and categorical variables by percentages. For comparatives analyses, multiple imputation (n = 5) was used to handle missing values [10]. A propensity score (PS) was calculated based on the covariables listed above [11]. Analyses were conducted using logistic regression models and were adjusted with overlap weighting (OW) on the PS, providing odds ratios (ORs) and their 95% confidence intervals (95% CIs) [12]. OW allows adjustment in population with large differences in covariables, by emphasizing the target population with the most overlap in observed characteristics between exposed and unexposed patients, and down-weighting the tails units. Exposed patients were weighted by the probability of not receiving corticosteroids (1–PS) and unexposed patients were weighted by the probability of receiving corticosteroids (PS) [13]. Statistical analyses were performed using SAS V9.4™ (SAS institute, Cary, NC, USA).

Results
Study population
Overall, 253 patients were included in the study. Characteristics of the patients are presented in Table 1. Median age was 64 years (IQR: 54–76), 140 patients (59.6%) were men, and 218 (86.2%) presented at least one comorbidity. The median duration of symptoms at the time of admission to hospital was 7 days (IQR: 4–10).
Exposure to corticosteroids

Seventeen patients (6.7%) were exposed to corticosteroids before hospital admission. Their characteristics are presented in Table 2. The most frequent corticosteroid was prednisone (n = 9). Fifteen patients (83.3%) had an exposure to corticosteroids ≥ 7 days; indications were chronic inflammatory disease (n = 8), solid organ transplantation (n = 4) and malignancies (n = 4). As compared

Table 1 Characteristics of the patients hospitalized for COVID-19 included in the study (n = 253)

| Age (years) | Total (n = 253) | Exposure to corticosteroids | Admission to ICU, mechanical ventilation, or death during the first 14 days |
|-------------|-----------------|-----------------------------|--------------------------------------------------------------------------------------------------|
| Median (IQR) | 65 (54–76) | 64 (54–76) | 73 (62–82) | 62 (50–75) | 68 (58–78) |
| ≥ 65 years, n (%) | 128 (50.6) | 117 (49.6) | 11 (46.7) | 59 (44.4) | 69 (57.5) |
| Sex | | | | | |
| Male, n (%) | 150 (59.3) | 141 (59.7) | 9 (52.9) | 69 (51.9) | 81 (67.5) |
| Female, n (%) | 103 (40.7) | 95 (40.3) | 8 (47.1) | 64 (48.1) | 39 (32.5) |
| Comorbidities | | | | | |
| ≥ 1 comorbidity, n (%) | 218 (86.2) | 201 (85.2) | 17 (100) | 111 (83.5) | 107 (89.2) |
| Overweight, (BMI: 25–30 kg/m²), n (%) | 85 (36.2) | 79 (35.6) | 6 (46.2) | 43 (36.1) | 41 (36.2) |
| Obesity, (BMI ≥ 30 kg/m²), n (%) | 68 (28.9) | 65 (29.3) | 3 (23.1) | 28 (23.5) | 40 (34.5) |
| Hypertension, n (%) | 102 (40.3) | 92 (39.0) | 10 (88.8) | 46 (34.6) | 56 (46.7) |
| Heart failure, n (%) | 10 (4.0) | 9 (3.8) | 1 (5.9) | 5 (3.8) | 5 (4.2) |
| History of coronary disease, n (%) | 24 (9.5) | 20 (8.5) | 4 (23.5) | 9 (6.8) | 15 (12.5) |
| History of cardiac surgery, n (%) | 3 (1.2) | 2 (0.9) | 1 (5.9) | 2 (1.5) | 1 (0.8) |
| History of cerebrovascular disease, n (%) | 16 (6.3) | 14 (6.0) | 2 (11.8) | 8 (6.0) | 8 (6.7) |
| Diabetes, n (%) | 49 (19.4) | 43 (18.2) | 6 (35.3) | 20 (15.0) | 29 (24.2) |
| Chronic lung disease, n (%) | 54 (21.3) | 45 (19.7) | 9 (52.9) | 24 (18.1) | 30 (25.0) |
| Chronic kidney disease, n (%) | 23 (9.1) | 19 (8.1) | 4 (23.5) | 11 (8.3) | 12 (10.0) |
| Chronic liver disease, n (%) | 2 (0.8) | 1 (0.4) | 1 (5.9) | 0 (0) | 2 (1.7) |
| Malignancy, n (%) | 27 (10.7) | 22 (9.3) | 5 (29.4) | 12 (9.0) | 15 (12.5) |
| Immunosuppression, n (%) | 20 (7.9) | 10 (4.2) | 10 (58.8) | 8 (6.0) | 12 (10.0) |

Time between first symptoms and hospital admission, median (IQR)^a

| | Total (n = 253) | Exposure to corticosteroids | Admission to ICU, mechanical ventilation, or death during the first 14 days |
| | | No (n = 133) | Yes (n = 120) |
| Age (years) | | 7 (4–10) | 7 (5–10) | 4 (2–4) | 7 (4–10) | 7 (4–9) |
| Sex | | | | | |
| Male, n (%) | | | | | |
| Female, n (%) | | | | | |
| Comorbidities | | | | | |
| ≥ 1 comorbidity, n (%) | | | | | |
| Overweight, (BMI: 25–30 kg/m²), n (%) | | | | | |
| Obesity, (BMI ≥ 30 kg/m²), n (%) | | | | | |
| Hypertension, n (%) | | | | | |
| Heart failure, n (%) | | | | | |
| History of coronary disease, n (%) | | | | | |
| History of cardiac surgery, n (%) | | | | | |
| History of cerebrovascular disease, n (%) | | | | | |
| Diabetes, n (%) | | | | | |
| Chronic lung disease, n (%) | | | | | |
| Chronic kidney disease, n (%) | | | | | |
| Chronic liver disease, n (%) | | | | | |
| Malignancy, n (%) | | | | | |
| Immunosuppression, n (%) | | | | | |

At hospital admission

| | Total (n = 253) | Exposure to corticosteroids | Admission to ICU, mechanical ventilation, or death during the first 14 days |
| | | No (n = 133) | Yes (n = 120) |
| Oxygen saturation ≤ 92% or need of oxygen therapy, n (%) | | | | |
| C-reactive protein level, > 50 mg/L, n (%) | | | | |
| Platelets count, < 150 × 10^9/L, n (%) | | | | |
| Lymphocytes, < 1.5 × 10^9/L, n (%) | | | | |

Chest CT-scan severity score

| | Total (n = 253) | Exposure to corticosteroids | Admission to ICU, mechanical ventilation, or death during the first 14 days |
| | | No (n = 133) | Yes (n = 120) |
| Absence or mild, n (%) | | | | |
| Moderate, severe, or critical, n (%) | | | | |

Exposure to corticosteroids, n (%) | | | | |

Composite outcome, n (%) | | | | |

| | Total (n = 253) | Exposure to corticosteroids | Admission to ICU, mechanical ventilation, or death during the first 14 days |
| | | No (n = 133) | Yes (n = 120) |
| Admission to ICU, n (%) | | | | |
| Mechanical ventilation, n (%) | | | | |
| Death, n (%) | | | | |

Abbreviations: BMI body mass index, CT computed tomography, ICU intensive care unit, IQR interquartile range

^aMissing data: body mass index, n = 18; time between first symptoms and hospital admission, n = 2; oxygen saturation, n = 2; C-reactive protein, n = 2, platelets count, n = 4; lymphocytes, n = 30

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| Patient | Age range (years) | Indication | Drug | Daily dose, mg | Duration | Comorbidities | Clinical finding | Biological findings | Chest CT-scan severity score | Outcome |
|---------|------------------|------------|------|---------------|----------|---------------|-----------------|-------------------|------------------------|---------|
| #1     | 31–40            | Multiple myeloma | Dexamethasone | 40 | 3 months | Overweight, cancer, multiple myeloma | – | – | Moderate | No |
| #2     | 61–70            | Crohn disease | Prednisolone | NA | Long-term | Overweight, chronic lung disease, Crohn disease | Need of oxygen | Lymphopenia, C-reactive protein ≥50 mg/L | Severe | ICU, mechanical ventilation, death |
| #3     | 81–90            | Horton disease | Prednisolone | 2.5 | Long-term | Hypertension, coronaropathy, diabetes | SaO2 ≤ 92% | Lymphopenia, thrombocytopenia, C-reactive protein ≥50 mg/L | Severe | Death |
| #4     | 71–80            | Glioblastoma | Prednisone | 20 | 1 year | Malignancy | – | Lymphopenia | Moderate | Death |
| #5     | 51–60            | Bronchitis | Prednisolone | 60 | 4 days | Overweight, hypertension | – | – | Moderate | No |
| #6     | 81–90            | Sarcoidosis | Prednisolone | 20 | 4 days | Overweight, hypertension, sarcoidosis, sleep apnea | SaO2 ≤ 92% | C-reactive protein ≥50 mg/L | Moderate | No |
| #7     | 61–70            | Renal transplant | Prednisone | 5 | 7 years | Overweight, hypertension, sleep apnea, diabetes, chronic kidney disease, renal transplant | – | Lymphopenia, thrombocytopenia | Moderate | ICU |
| #8     | 41–50            | Cardiac transplant | Prednisone | 5 | 11 years | Cardiac surgery, cardiac transplant | – | – | Absence | No |
| #9     | 81–90            | Giant cell arteritis | Prednisone | 3 | 4 years | Obesity, hypertension, heart failure, coronaropathy, sleep apnea, chronic kidney disease, diabetes, giant cell arteritis | SaO2 ≤ 92% | Lymphopenia, C-reactive protein ≥50 mg/L | Moderate | ICU, Death |
| #10    | 91–100           | Lymphoma | Prednisolone | 60 | 8 months | Chronic lung disease, diabetes, lymphoma | – | Lymphopenia | Moderate | No |
| #11    | 21–30            | Crohn disease | Prednisolone | 25 | 5 months | Immunosuppression | – | C-reactive protein ≥50 mg/L | Moderate | No |
| #12    | 71–80            | Oesophageal adenocarcinoma | Betametasone | 0.4 (30 drops) | 3 months | Overweight, coronaropathy, sleep apnea, malignancy | – | Lymphopenia, thrombocytopenia | Moderate | ICU |
| #13    | 71–80            | Renal transplant | Prednisone | 5 | 5 months | Hypertension, chronic kidney disease, chronic liver disease, diabetes, renal transplant | – | Lymphopenia, C-reactive protein ≥50 mg/L | Moderate | ICU, mechanical ventilation |
| #14    | 61–70            | Renal transplant | Prednisone | 5 | 2 years | Hypertension, cerebrovascular disease, sleep apnea, chronic kidney disease, renal transplant | – | Lymphopenia, thrombocytopenia | Moderate | ICU, mechanical ventilation |
| #15    | 71–80            | Rheumatoid arthritis | NA | NA | 6 weeks | Hypertension, rheumatoid arthritis | – | Lymphopenia | Moderate | No |
| #16    | 61–70            | Sarcoidosis | Prednisone | 6.5 | 1 year | Obesity, hypertension, COPD, sarcoidosis | – | Lymphopenia | Mild | ICU, death |
| #17    | 81–90            | Dermatomyositis | Prednisone | 70 | 1 month | Hypertension, lung fibrosis, malignancy dermatomyositis | Need of oxygen | Lymphopenia, thrombocytopenia, C-reactive protein ≥50 mg/L | Severe | Death |

Abbreviation: COPD chronic obstructive pulmonary disease, NA Not available
with non-exposed patients, those exposed to corticosteroids were older (≥65 years: 64.7% vs 49.6%), with a cause of immunosuppression (58.8% vs 4.2%), chronic lung disease (52.9% vs 19.7%) and hypertension (58.8% vs 39.0%). However, clinical, radiological, and biological markers of COVID-19 severity at hospital admission were comparable between the two groups (Table 1).

Outcome
One hundred and twenty patients (47.4%) met the composite outcome during the first 14 days of hospitalization; 61 (24.1%) required mechanical ventilation and 19 (7.5%) died (Table 1). The median time between admission and outcome occurrence was 1 day (IQR: 0–3 days). Ten patients exposed to corticosteroids (58.8%), all with an exposure ≥7 days, met the composite outcome (Table 2).

Comparative analyses
In the crude model, the OR of exposure to systemic corticosteroid at the time of admission to hospital with outcome occurrence was 1.64; 95% CI: 0.60–4.44. The PS distribution is presented in Supplementary Fig. S1. The PS was efficient in establishing balance for each covariable (data not shown). In the adjusted model with OW on the PS, the OR was 1.09 (95% CI: 0.65–1.83).

Discussion
In this study, we found a trend for an increased risk of poor outcome in COVID-19 hospitalized patients in case of previous exposure to corticosteroid before hospital admission. However, after adjustment for potential confounders, we found no evidence for an increased risk. This result differs from the two previously quoted studies in patients with rheumatoid disease or chronic inflammatory bowel disease [6, 7]. However, these were other settings, with no adjustment for other COVID-19 severity markers at the time of admission. Moreover, in the study conducted in patients with chronic inflammatory bowel disease, comorbidities were included quantitatively [7]. However, some comorbidities are expected to be more related with both exposure to corticosteroids and disease severity. That’s why we included each comorbidity in the PS calculation. Of note, patients exposed to corticosteroids in our cohort had more frequently chronic lung disease, hypertension, and cause of immunosuppression only.

This study conducted in the Covid-Clinic-Toul cohort presented strengths. The cohort is a clinical cohort with most of the data prospectively collected. Exposure to systemic corticosteroids was exhaustively assessed for each patient. Missing values were very rare and handled by multiple imputation. Adjustment using OW on the PS provided risk estimation by minimizing confusion bias due to important differences in the characteristics between exposed and unexposed patients.

Our study had several limitations. Data were restricted to a single hospital center. Only 6.7% (n = 17) of the patients were exposed to corticosteroids before hospital admission. This low sample size limited the interpretation of the results. Therefore, we could have only detected a major effect of corticosteroids on unfavorable outcome. Subgroup analyses by corticosteroids dosage, duration of exposure, and indications cannot be conducted due to this low number of exposed patients. Of note, 8 of the exposed patients (47%) in our cohort had a daily prednisone equivalent dosage < 10 mg, which was not associated with an increased rate of hospitalization in the study in patients with rheumatic disease [6]. Because previous exposure to systemic corticosteroids is strongly associated with their indication and because subgroups analyses were not possible, results need to be interpreted cautiously. Finally, we cannot exclude the presence of unmeasured confounding factors like smoking. However, these factors are certainly related to comorbidities included in the PS and it is not clear whether they impact COVID-19 severity.

Conclusion
Overall, this study provide some evidences for an absence of an increased risk of unfavorable outcome with previous exposure to corticosteroids in the general setting of patients hospitalized for COVID-19.

Abbreviations
CT: Computed tomography; ICU: Intensive care unit; OW: Overlap weighting; PS: Propensity score; RT-PCR: reverse transcriptase polymerase chain reaction

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s40386-021-00480-3.

Additional file 1: Figure S1. Propensity score distribution according to exposure to systemic corticosteroids prior to hospitalization by each imputation of missing data (5 imputations, panels A to E) in the study population (n=253). Blue bars: patients unexposed to systemic corticosteroids. Red bars: patients exposed to systemic corticosteroids.

Acknowledgments
The authors deeply thank Christophe Morin, Gaëlle Barencourt, Caroline Hurault-Delarue, Charlotte Vert and Julien Jacquot for their help in data acquisition and Isabelle Olivier for reglementary aspects.

Authors’ contributions
ML, A.S. and G.M. designed the study. ML carried out the data management, conducted the statistical analysis and wrote the manuscript. ML, G.M.B., P.D., N.K., S.C., A.S., G.M. and the collaborators included in the “Covid-clinic-Toul investigators group” included the patients and participated to data collection. ML., G.M.B., P.D., N.K., S.C., A.S., G.M. interpreted the results, critically reviewed the manuscript and gave final approval for submission. ML, G.M.B., P.D., N.K., S.C., A.S., G.M. also had full access to all of the data (including statistical reports) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.
Funding
The Covid-Clinic-Toul cohort is funded by Toulouse University hospital.

Availability of data and materials
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 and ethical restrictions. The data management and statistical analysis code is available on request from the corresponding author.

Declarations

Ethics approval and consent to participate
The observational Covid-Clinic-Toul cohort has been approved by the INSERM institutional committee. The study was also registered on the IND5 (Institut National des Données de Santé) registry, reference MR051510420. According to French law and to the European General Data Protection Regulation, because of the pure real-life observational design, patients, or if not possible their representatives, had to receive an information form explaining the study and their rights notably as regards possibility of opposition to data collection. According to the same regulations, signed consent is not mandatory. All patients included in the observational Covid-Clinic-Toul cohort, or their representatives, were informed by a letter given at hospital admission and/or sent to their residency. Information of all patients is indicated in their medical files. Exclusion criterion was opposition to data collection.

Consent for publication
Not applicable.

Competing interests
None declared.

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Received: 25 September 2020 Accepted: 24 February 2021
Published online: 11 March 2021

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