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Progression to a severe form of COVID-19 among patients with chronic respiratory diseases

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**Abstract**

**Rationale:** Viral respiratory infections, including SARS-CoV-2 infection, can trigger respiratory symptoms among patients suffering from chronic respiratory diseases, leading to exacerbations and hospitalizations. Despite the tropism of SARS-CoV-2 into the respiratory tract, chronic respiratory diseases do not seem to be risk factors for severe forms of COVID-19.

**Objectives:** To assess whether hospitalized patients for COVID-19 with chronic respiratory diseases were at lower risk of developing a severe form than other patients.

**Methods:** This French study included patients admitted to hospital in COVID-19 ward, suffering from a SARS-CoV-2 infection, diagnosed on RT-PCR or chest computed tomography associated with clinical symptoms, from March 15 to June 30, 2020. Ambulatory patients who were tested in the emergency department and patients with severe hypoxaemia requiring intensive care were not included. All data were collected from electronic medical records up to discharge of the patient.

**Main Results:** 617 patients were included: 125 with a chronic respiratory disease, mainly chronic obstructive pulmonary disease (45%) and asthma (30%). The percentage of patients scoring 6 or higher on the WHO Clinical Progression Scale during hospital stay was lower in patients with chronic respiratory disease compared to those without chronic respiratory disease (21.6% versus 31.3%, respectively, p = 0.03). Among patients with chronic respiratory disease, temperature above 38 °C on admission (OR 16.88 (95% CI 4.01–71.00)), lymphopenia (OR 5.08 (1.25–20.72)), CPAP therapy (OR 4.46 (1.04–19.17)), and age (OR 1.09 (1.02–1.16)) were associated with an increased risk to reach a score of 6 or above.

**Conclusions:** Hospital admissions in COVID-19 ward of patients suffering from chronic respiratory diseases are at lower risk of developing a severe form of COVID-19, especially in patients with chronic obstructive pulmonary disease or asthma. Prospective studies would confirm our results and allow to better organize the follow-up of these patients in a pandemic period.

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**Introduction**

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has emerged in Wuhan Province, China, in December 2019 and rapidly spread around the world. France has been experiencing critical circumstances for public health, particularly in the Great East region, which includes the Nancy-Brabois University Hospital and the Metz-Thionville regional Hospital. From March 1st, 2020 to June 2, 2020, 14 416 patients were hospitalized in the Great East region for a Coronavirus Disease 2019 (COVID-19) [1]; the number of patients in intensive care units (ICU) reached a peak on April 3, with 971 hospitalizations, putting a strain on hospitals and health care workers [2].

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SARS-CoV-2 infection has a particular respiratory tropism and may lead to severe viral pneumonia and potentially acute respiratory distress syndrome (ARDS). Thus far, various epidemiological studies have suggested that underlying cardiovascular diseases are a risk factor for critical form of COVID-19 and in-hospital death [3,4]. The underlying pathophysiological mechanisms are currently not fully understood. However, data in the literature on the clinical and epidemiological characteristics of patients with chronic respiratory disease (CRD) affected by severe form of COVID-19 are scarce and controversial. In China, Guan et al., reports 6.1% of severe forms among 1099 hospitalized patients with only 12 patients (1.1%) who had chronic obstructive pulmonary disease (COPD) [5]. In New York, Petrelli et al. identified 453 patients with asthma or COPD hospitalized with COVID-19. Asthma or COPD did not appear as a risk factor for a critical illness [6]. Conversely, a recent meta-analysis of 3027 patients showed that smoking patients and patients suffering from respiratory diseases may be at a higher risk of progressing to a severe form of the disease [4]. Also, patients with interstitial lung diseases (ILD) seems to be at increased risk of death from COVID-19 [7].

Viral respiratory infection can trigger respiratory symptoms (dyspnea, cough, sputum) and lead to exacerbations of CRD [8,9]. We hypothesized that patients with chronic respiratory disease mainly consisting of asthma and COPD infected with SARS-CoV-2 do not or less frequently present with an inappropriate inflammatory response that can lead to critical forms of COVID-19 and potentially to death [10,11].

To our knowledge, no study has specifically evaluated the prevalence of critical forms of COVID-19 among patients with CRD (including COPD, asthma, bronchiectasis, ILD, pulmonary arterial hypertension (PAH), cystic fibrosis and obesity hypoventilation syndrome (OHS)) hospitalized for COVID-19. The main objective was to compare the risk of developing a severe form of the disease on COVID-19 ward admission of patients with CRD versus patients without CRD. Secondly, we sought to describe potential risk factors of severe forms of COVID-19 and clinical course of SARS-CoV-2 infection of these patients having CRD.

Material and methods

Study oversight

This multicentric retrospective study was conducted at the Nancy-Brabois university hospital (center 1) and the Metz-Thionville regional hospital (center 2) from March 15, 2020 to June 30, 2020. All patients were first admitted to the emergency department and tested for SARS-CoV-2 infection. In both centers, in case of major hypoxemia (requirement to FiO₂ > 50%), patients were admitted to ICU. Patients refused to ICU admission and patients with milder hypoxemia were admitted to dedicated COVID-19 wards and constitutes our study population. Ambulatory patients screened in the emergency department who did not present symptoms requiring hospitalization were not reported in our study.

All adult patients hospitalized in COVID-19 wards to both hospitals during this period with a confirmed diagnosis of SARS-CoV-2 infection with respiratory symptoms were included. Diagnosis of SARS-CoV-2 infection was made by a positive reverse transcriptase polymerase chain reaction (RT-PCR) on nasopharyngeal swab and/or chest computed tomography (CT) with typical abnormalities, as described by the Fleischner Society [12]. Clinical and biological outcomes were monitored up to the discharge of the patient. Patients received written information. All data were collected into an anonymous computerized database registered to the National Commission on Informatics and Liberty (n° 2020PI0081). The study design has been registered on ClinicalTrials (NCT04407169).

Data collection

Epidemiological, clinical, biological and radiological data were collected from electronic medical records. Background treatments with angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB II) were also identified.

Clinical data (body temperature, heart rate, pulse oxygen saturation, arterial blood pressure) were collected on admission to hospital. Time to hospitalization from symptom onset was recorded. In case of a transfer to an intensive care unit during hospitalization, time to invasive ventilation were collected.

Regarding chest computed tomography (CT), the severity of the parenchymal involvement was assessed by a radiologist, according to the percentage of ground-glass extension (less than 25%, 25 to 50%, 50 to 75% and more than 75%) in both centers. Specific treatments implemented during hospitalization were notified (remdesivir, hydroxychloroquine, lopinavir plus ritonavir, steroids, interferon). The in-hospital complications such as bacterial infection or venous thromboembolic disease were collected during the entire hospitalization. In-hospital death, in-ICU death, lengths of stay in ICU and in hospital were assessed at discharge. Specific data about patients with CRD were collected: lung function tests, respiratory treatment (systemic or inhaled corticosteroids, bronchodilators), long-term oxygen therapy, home mechanical ventilation and CPAP therapy. The severity of the disease was assessed by the GOLD classification for COPD and GINA for asthmatic patients. All the definitions used to characterize CRD are available in the online data supplement.

Study outcomes

The primary end point was a score on the World Health Organization Clinical Progression Scale equal or greater than six during hospitalization defining a severe form of COVID-19 [13]. The WHO Clinical Progression Scale provides a harmonized assessment of illness severity, clinical course and progression through the health-care system based on easily obtained data. This scale ranges from zero (uninfected) to ten (dead), a score of six or higher indicates acute respiratory failure requiring mechanical ventilation or high flow oxygen therapy.

Statistical analysis

Categorical variables were described by numbers and percentages, while continuous variables by median and interquartile range [first quartile Q1 - third quartile Q3]. Patients’ characteristics were compared between each group (those without any CRD and those with a CRD) using Chi-2 or Fisher’s exact test for qualitative variables and Wilcoxon Test for quantitative variables. The characteristics of the patients with CRD associated with severe form of COVID-19 were identified with a bivariate logistic regression model. Variables with a p-value < 0.2 in the bivariable model were eligible for the multivariable model. A stepwise selection procedure was applied to retain significant independent factors. The Kaplan–Meier estimates with 95% confidence intervals (CIs) were calculated to describe survival with the date of admission in the two cohort as the starting point. The significance threshold was set at 5%. Statistical analysis was performed using SAS 9.4 software.

Results

From March 15 to June 30, 2020, 1032 patients were hospitalized in both hospitals in dedicated COVID-19 wards. Finally, 636 patients met our inclusion criteria and 19 refused to participate to the study (Fig. 1). Among the 617 remaining patients, 547 had positive SARS-CoV-2 RT-PCR on nasopharyngeal swab (88.7%) and 70 were diagnosed on the basis of clinical presentation and radiological patterns.
We identified 125 patients with a chronic respiratory disease, of which the most frequent were COPD (n = 56; 44.8%) and asthma (n = 37; 29.6%). We also reported patients with interstitial lung disease (n = 15; 12%), bronchiectasis (n = 7; 5.6%), OHS (n = 3; 2.4%), PAH (n = 2; 1.6%), cystic fibrosis (n = 1; 0.8%) and other chronic respiratory diseases with restrictive ventilatory pattern (n = 4; 3.2%).

Clinical characteristics

Characteristics of the study population on admission are detailed in Table 1. The median age was 72 (interquartile range [IQR] [58–84] years) years, 330 (53.5%) were men and the median BMI was 26.3 kg/m² [23.5–30.9]. The most frequent comorbidities were systemic
hypertension (55.4%), diabetes mellitus (23.5%) and coronary heart disease (13.8%). Obstructive sleep apnea syndrome was reported in 58 (9.4%) patients. Patients with CRD were more frequently smokers or former smokers (63.1% versus 41.0%, p < 0.0001). There were no differences between patients with CRD and patients without CRD concerning age, sex and BMI. Vital signs (body temperature, heart rate, arterial blood pressure) were similar between the two groups (Table 2). Patients with CRD had a significantly reduced time period between the onset of symptoms and admission to hospital (median 5 days [3–8] versus 7 days [4–9], p = 0.013). Patients hospitalized in center two were slightly older (73 years old [60–85] versus 70.5 [55–83], p = 0.021) and there was a higher percentage of asthmatic patients, among patients with CRD, in center one (38.8% versus 19.0%, p = 0.015). Differences between the two centers are shown in Table S1.

Among COPD patients seen in both centers (n = 56), median age was 73.5 [63.5–83.5], with a majority of men (62.5%). Previous lung function tests were available in 32 patients (57%). Median forced expiratory volume in one second (FEV1) was 61.0 [45.5–71.5]% of predicted values. Median forced vital capacity (FVC) was 85 [73–91]%.

### Table 1

| Demographic data | Patients with CRD (n = 125) | Patients without CRD (n = 492) | p  |
|------------------|-----------------------------|---------------------------------|----|
| Age, years       | n = 125                     | n = 492                         | 0.711 |
| Male sex, n (%)  | n = 125                     | 72 [60–83]                      | 71 [58–84] |
| Male sex, n (%)  | n = 125                     | 65 [52]                        | 492 [265–519] |
| BMI, kg/m²       | n = 118                     | 26.4 [23.1–30.9]                | 418 [26.3–35.9] |
| Smoker or ex-smoker, n (%) | n = 103 | 65 [63.1]          | 310 [127–41] |
| Smoking history, pack-years | n = 45 | 30 [19–50]            | 87 [30–140] |
| Comorbidities    |                             |                                |     |
| Systemic arterial hypertension, n (%) | n = 125 | 75 [60]            | 267 [54.3] |
| Diabetes mellitus, n (%) | n = 125 | 34 [27.2]        | 111 [22.6] |
| Coronary heart disease, n (%) | n = 125 | 21 [16.8]       | 64 [13] |
| Neurovascular disease, n (%) | n = 125 | 15 [12]         | 43 [8.8] |
| Cancer, n (%)    | n = 125                     | 14.0 [11.2]                     | 46 [53] |
| Chronic renal failure, n (%) | n = 125 | 14 [11.2]       | 30 [6.1] |
| Obstructive sleep apnea, n (%) | n = 125 | 28 [22.4]     | <0.0001 |
| Immunodeficiency, n (%) | n = 125 | 15 [12]        | 47 [9.6] |
| Routine treatments |                             |                                |     |
| ACE inhibitor, n (%) | n = 125 | 22 [17.6]     | 81 [16.5] |
| ARB, n (%)       | n = 125                     | 24 [19.4]                      | 81 [16.5] |
| Immunosuppressant drug, n (%) | n = 125 | 12 [9.6]      | 44 [9] |

Values are expressed as median [IQR] or as number and frequency. n: available data. n: population size.

### Table 2

| Clinical features | Patients with CRD (n = 125) | Patients without CRD (n = 492) | p  |
|------------------|-----------------------------|---------------------------------|----|
| Mean arterial blood pressure, mmHg | n = 125 | 92 [82–100] | 489 [83–101] | 0.832 |
| Heart rate, beats.min⁻¹ | n = 125 | 85 [75–98] | 84 [73–95] | 0.337 |
| Pulse oxygen saturation, % | n = 125 | 95 [94–97] | 95 [93–97] | 0.598 |
| Body temperature, °C, n (%) | n = 125 | 31 [24.8] | 134 [27.4] | 0.558 |
| Time since onset of symptoms, days | n = 104 | 5 [3–8] | 429 [7–49] | 0.013 |
| Biological data |                             |                                |     |
| Leukocytes, G.L⁻¹ | n = 125 | 6.4 [5.1–10.2] | 6.5 [4.9–9] | 0.474 |
| Lymphocytes, G.L⁻¹ | n = 117 | 1.0 [0.6–1.4] | 0.9 [0.6–1.3] | 0.113 |
| CRP, ng.L⁻¹ | n = 122 | 63.5 [33–142] | 90 [42–146] | 0.008 |
| PCT, ng.mL⁻¹ | n = 80 | 0.1 [0.1–0.3] | 0.305 [0.1–0.4] | 0.106 |
| Troponin, pg.mL⁻¹ | n = 55 | 9 [3–30] | 215 [12–40] | 0.081 |
| CPK, IU.L⁻¹ | n = 24 | 121 [64.5–191.5] | 149 [54–502] | 0.323 |
| D-Dimers, μg.L⁻¹ | n = 35 | 1146 [628–2060] | 1363 [851–2644] | 0.233 |
| LDH, IU.L⁻¹ | n = 45 | 233 [194–302] | 310 [245–391.5] | 0.0003 |
| ASAT, IU.L⁻¹ | n = 115 | 30 [22–52] | 45 [29–63] | <0.0001 |
| ALAT, IU.L⁻¹ | n = 114 | 22.5 [15–38] | 28.5 [18–50] | 0.003 |
| Creatinine, mmol.L⁻¹ | n = 124 | 73.5 [59–97] | 79 [60–101.5] | 0.427 |
| SOFA score | n = 99 | 2 [1–3] | 3 [2–4] | 0.039 |
| PaO₂ on room air, mmHg | n = 45 | 63 [59–73] | 62 [57–69] | 0.244 |
| PaCO₂ on room air, mmHg | n = 45 | 36 [32–39] | 34 [31–36] | 0.012 |
| Radiologic data |                             |                                |     |
| CT scan on admission, n (%) | n = 125 | 96 [76.8] | 491 [382–77.8] | 0.811 |
| Ground-glass extension | n = 65 | 41 [63.1] | 128 [42.4] | 0.002 |
| 25–50%, n (%) | n = 25 | 17 [26.2] | 121 [40.2] | 0.034 |
| 50–75%, n (%) | n = 25 | 6 [9.2] | 46 [15] | 0.227 |
| >75%, n (%) | n = 25 | 1 [1.5] | 10 [3.3] | 0.445 |

Values are expressed as median [IQR] or as number and frequency. n: available data. n: population size.

CRP: C-Reactive protein, PCT: procalcitonin, CPK: creatine phosphokinase, LDH: lactate dehydrogenase, ALAT: alanine aminotransferase, ASAT: aspartate aminotransferase.
of predicted values with a median FEV1/FVC ratio of 60 [45.5–65.5]%.
Among them, 4 (12.5%) had mild COPD (FEV1 ≥ 80% predicted), 19
(59.4%) had moderate COPD (50% ≤ FEV1 < 80%) and 9 (28.1%) had
severe COPD (FEV1 < 50%). Three patients were treated with long-
term oxygen therapy and two were on non-invasive home ventila-
tion (NIV) for chronic respiratory failure. Concerning asthmatic
patients, seven patients (18.9%) had lung function data available.
Median FEV1 was 89 [88–108]% of predicted values with a median
FEV1/FVC ratio of 69.5 [58–84]%. None of them were GINA step 5 and
none were receiving maintenance systemic corticosteroids nor bio-
logics.

Radiological and laboratory test findings on admission

Overall, chest CT was carried out within the first 48 h of hospitali-
zation in 478 patients (77.6%) (Table 2). The majority (n = 366, 76.6%)
had typical bilateral multiple ground glass opacities or consolidations
with a standardized evaluation of extension. More patients with CRD
had ground-glass extension below 25% (63.1% versus 42.4%;
p = 0.002) compared to patients without CRD. Occurrence of pulmo-

nary embolism has not been systematically investigated.

Patients with CRD had a moderate inflammatory syndrome with
significantly lower CRP and LDH compared to patients without CRD
(CRP: 63.5 mg/L [23-142] versus 90 [42-146], p = 0.008; LDH: 233
UI/L [194–302] versus 311 [245–392], p = 0.0003). However, there was no difference concerning levels of troponin (p = 0.081) nor
D-dimers (p = 0.233).

On admission, arterial blood gas while breathing room air was
reported in 168 (34%) patients without CRD and 45 (36%) with CRD.
While there is no difference concerning hypoxaemia (PaO2:
63 mmHg [59–73] versus 62 mmHg [57–69], p = 0.244), we found a
lower pH (7.4 [7.4–7.5] versus 7.5 [7.4–7.5], p = 0.003) and higher
PaCO2 (36 mmHg [32–39] versus 34 mmHg [31–36], p = 0.013) in
patients with CRD.

Treatments and complications

Across all patients hospitalized for COVID-19, 115 patients
received treatments including lopinavir/ritonavir (n = 48; 7.8%), ste-
roid (n = 41; 6.7%), interferon (n = 11; 1.8%), hydroxychloroquine
(n = 9; 1.5%) or remdesivir (n = 6; 1%). Patients with CRD were treated,
during hospitalization, more frequently with inhaled corticosteroids
(3.2% vs 0.2%; p = 0.007), bronchodilators (40.8% vs 1.2%,
p = 0.081) nor
antibiotics (64.8% vs 52.4%, p<0.0001) and antibodies (64.8% vs 52.4%, p = 0.013).

The most frequent in-hospital complications were hepatic cytoly-
sis (ALAT or ASAT > 2 ULN) (60%), acute renal injury (Kidney Disease
Improving Global Outcomes stage 1 or higher) (25.8%), bacterial pul-
monary infection (8.3%) and venous thromboembolism (4.4%). The
only difference between the two groups was a more frequent hepatic
cytolysis among patients without CRD (55.6% versus 34.8%,
p<0.0001)(data not shown).

Outcomes

The percentage of patients scoring 6 or higher on the WHO Clinical
Progression Scale during hospital stay was lower in patients with
CRD compared to those without CRD with 27 patients (21.6%) com-
pared to 154 (31.3%), respectively (p = 0.03) (Table 3).

Results of the univariate analysis which determines the relation
between reaching a score of 6 or above and covariates among CRD
patients are shown in Table 4. Then, a multivariate logistic analysis
was performed including all covariates associated with a severe form
of COVID-19 among CRD patients in the bivariate analysis (Table 5).
Among CRD patients, age, temperature above 38 °C on admission,
lymphopenia below 1 G/L and CPAP therapy (i.e., before admission)
were independently associated with an increased risk of severe form
of COVID-19. The same analysis was performed among patients with-
out CRD, age and fever above 38 °C remained significantly associated
in the multivariate analysis. Conversely, in this latter group of
patients, lymphopenia on admission was not associated with a risk
of progression to a severe form of COVID-19 (data shown in Table S2).

Length of hospital stay was similar between the two groups:
8 days [5–12] in patients without CRD versus 8 days [5–13] in
patients with CRD, (p = 0.720). Overall, there were no significant dif-
ference between patients with and without CRD in mortality rates
(Fig. 2). In addition, there was also no differences in mortality rates
between patients with and without CRD among patients who de-
veloped a severe form of COVID-19 (p = 0.90).

Discussion

In this study, we report baseline characteristics, laboratory and
radiological data, and clinical course of adults diagnosed with COVID-
19 admitted to two hospitals in the Great East region outside ICU du-
ing the first pandemic wave, with a particular focus on patients with
CRD. Among hospitalized patients outside ICU, prevalence of severe
form of COVID-19 was significantly lower in patients with CRD.

The population in this cohort consisted mostly of men (53.5%),
overweight with multiples co-morbidities, especially cardiovascular,
in conjunction with previous studies. The age of our population
(median 72 years old and 62% of patients older than 65) is slightly
higher than that reported in previous studies but the comorbidities
identified are similar [5,6,14–16]. Also, the most common laboratory
test findings on admission were lymphopenia, hepatic cytolysis, and
a moderate inflammatory syndrome. The study of chest CT’s showed
that extent of ground glass opacification was moderate (below 50%) for
the majority of patients (83.3%), especially in patients with CRD.

Median time from symptom onset to hospitalization was sig-
ificantly lower among patients with CRD. Early hospitalization
during SARS-CoV-2 infection in patients with CRD could be
explained by faster onset of respiratory symptoms in these
patients. However, we cannot exclude that earlier hospitalization
in patients with CRD may be due to easier access to care in
patients with respiratory vulnerability.

Table 3

| Outcomes                                      | Patients with CRD (n = 125) | Patients without CRD (n = 492) | p     |
|-----------------------------------------------|-----------------------------|-------------------------------|-------|
| WHO scale ≥ 6, n (%)                          | n = 125                     | n = 492                       | 0.033 |
| Length of hospital stay, days                 | n = 125                     | n = 492                       | 0.720 |
| Length of ICU stay, days                      | n = 125                     | n = 492                       | 0.718 |
| In-hospital death, n (%)                      | n = 125                     | n = 492                       | 0.242 |
| In-ICU death, n (%)                           | n = 125                     | n = 492                       | 0.622 |

Values are expressed as median [IQR] or as number and frequency. n: available data. n: population size. ICU: intensive care unit; WHO scale: World health organization progression scale.
Among our study population, 125 patients (20.3%) admitted to COVID-19 ward were affected by a CRD. COPD was the most frequent condition identified with a prevalence of 9.1%, quite similar to the most recent estimated prevalence of COPD in France (8.4%) [17]. Our results are consistent with data from other cohorts of hospitalized patients with COVID-19. In China, the prevalence of COPD among hospitalized COVID-19 patients has ranged from 0% to 10%, in New York City from 2.4 to 14% and in Italy from 5.6 to 9.2% [18]. Asthma was the second most frequent condition reported in our population (5.9%). In previous studies, prevalence of asthma among hospitalized COVID-19 patients range from 0% [19] to 12.5% [20]. In line with our results, a recent French study found a 4.2% rate of asthma among COVID-19 ward hospitalized patients [21]. In 2018 in France, prevalence of asthma was 6.4% among adults [22].

It is then striking that CRD are not over-represented among these patients despite the well-established respiratory tropism of COVID-19, compared to the high prevalence of cardiovascular risk factors (diabetes mellitus, systemic arterial hypertension) [23]. Number of factors could explain this observation. First, due to person-to-person transmission of the virus, physical distancing is essential to avoid infection. Patients with CRD may be more accustomed to distancing measures suggesting that their behavior could have protected them against contamination with SARS-CoV-2. Second, the role of the renin-angiotensin-aldosterone system has been highlighted due to the ability of the virus to establish itself in the host through the use of ACE-2 receptor [24]. In asthmatics, reduced number of ACE-2 gene expression in airway cells may decrease susceptibility to infection [25]. Inhaled corticosteroids use is also associated with a decreased expression of ACE-2 gene in sputum cells [26]. By contrast, Leung et al. [27] demonstrated an up-regulation of ACE-2 in lower airways in COPD and current smokers. In our study, seven (12.5%) patients with COPD were current smokers: smoking status was not associated with a risk of developing a severe form of COVID-19. Third, inhaled corticosteroids could have a protective effect by modifying pulmonary immune response [28]. In vitro, Matsuyama et al. [29] demonstrated the suppression of coronavirus replication by ciclesonide, an inhaled corticosteroid. Budesonide combined with glycopyrronium and formoterol is able to inhibit the production of cytokines in cells exposed to HCoV-229E, another human coronavirus [30]. Whether use of inhaled corticosteroids protects against SARS-CoV-2 infection is still unknown and ongoing clinical trials are evaluating them as a therapeutic intervention [31,32].

Inappropriate inflammatory response seem to be the main cause of acute respiratory distress syndrome, leading to severe form of COVID-19 [33,34]. In our population, patients hospitalized for COVID-19 in dedicated ward with CRD have a significantly lower risk of developing a severe form of COVID-19 than patients without CRD. This observation could reflect that patients with CRD may be more frequently hospitalized than other patients for a pattern of viral pneumonia due to their greater respiratory vulnerability but developing an important inflammatory response less frequently than in other populations. Interestingly, we observed a significant lower inflammatory syndrome and lower lactate dehydrogenase level on admission in patients with CRD, possibly due to lower inflammatory systemic response to the infection or earlier hospitalization. Among them, fewer on admission and lymphopenia were associated with higher risk of severe form of COVID-19. However, there were no differences concerning troponin and d-dimers, two major prognostic factors [35,36]. The impact of airway epithelium and alveolar immune cells on the lack of inappropriate inflammatory response to SARS-CoV-2 infection, among patients with CRD remains to be clarified [37]. CPAP therapy was also associated with an increased risk of critical form, possibly due to the association of severe obstructive sleep apnea to metabolic dysfunction, cardiovascular diseases and systemic inflammation [38].

Due to a very heterogeneous study population in terms of CRD, we decided to perform subgroup analyses with a focus on patients with asthma or COPD (n = 93). Thus, 20 patients (21.5%) with asthma or COPD had a score greater than or equal to six versus 154 patients (31.3%) without CRD. The full results of this subgroup analysis are available in the supplement (tables S3-S6, figure S2). These results suggest that this group of patients with asthma or COPD follow the same trend as the general study population (i.e., prevalence of severe form of COVID-19 significantly lower in patients with CRD).

### Table 4

| Outcomes                                      | Severe form of COVID-19 (n = 27) | Non-severe form of COVID-19 (n = 98) | p       |
|-----------------------------------------------|----------------------------------|-------------------------------------|---------|
| Age, years                                    | n = 27                           | 75 [63–86]                          | 70 [54–82] | 0.049   |
| Diabetes mellitus, n (%)                      | n = 27                           | 13 (48.1)                           | 21 (21.4) | 0.006   |
| Coronary heart disease, n (%)                 | n = 27                           | 10 (37)                             | 11 (11.2) | 0.003   |
| Long-term oxygen therapy, n (%)               | n = 27                           | 4 (14.8)                            | 3 (3.1)   | 0.039   |
| CPAP, n (%)                                   | n = 26                           | 7 (26.9)                            | 9 (9.2)   | 0.046   |
| Body temperature > 38 °C, yes                 | n = 27                           | 16 (59.3)                           | 15 (15.3) | < 0.0001|
| Pulse oxygen saturation, %                   | n = 27                           | 94 (93–96)                          | 95 (94–97) | 0.008   |
| Leukocytes, G. L⁻¹                              | n = 27                           | 5.2 [4–8.8]                         | 6.8 [5.4–10.4] | 0.009   |
| Lymphocytes < 1 G. L⁻¹, yes                   | n = 25                           | 20 (80)                             | 40 (43.5) | 0.001   |
| Platelets, G. L⁻¹                              | n = 27                           | 174 [126–271]                      | 218 [174–299] | 0.017   |
| C-reactive protein, mg.L⁻¹                   | n = 25                           | 114 [60–142]                       | 44 [19–134] | 0.029   |
| Troponin, pg.mL⁻¹                              | n = 11                           | 16 [9.7–33]                        | 6.9 [3–23.5] | 0.042   |
| ASAT, IU/L⁻¹                                   | n = 25                           | 43 [27–67]                          | 27 [21–44] | 0.039   |
| Creatinine, μmol.L⁻¹                           | n = 27                           | 92 [78–142]                        | 67 [55–90] | 0.0005  |
| SOFA score                                    | n = 23                           | 3 [2–5]                            | 2 [1.5–3]   | 0.015   |

Values are expressed as median [IQR] or as number and frequency. n: available data. n: population size.
CPAP: continuous positive airway pressure. ASAT: aspartate aminotransferase. SOFA: Sepsis-related Organ Failure Assessment.

### Table 5

| Events | Available obs. | Odds ratio (95% CI) | p       |
|--------|----------------|---------------------|---------|
| Body temperature > 38 °C, yes                 | 13 / 25            | 16.88 (4.01–71)     | 0.0001  |
| Lymphocytes < 1 G/L, yes                      | 18 / 56            | 5.08 (1.25–20.72)   | 0.030   |
| Age (per 1 y. inc.)                           | 22 / 110           | 1.09 (1.02–1.16)    | 0.0071  |
| CPAP therapy, yes                             | 7 / 17             | 4.46 (1.04–19.17)   | 0.0443  |

Events: score of 6 or above on the WHO Clinical Progression Scale; available obs.: available observation. Inc: increment.
Despite the large cohort of patients included from two different centers and the standardized assessment of clinical course by WHO Clinical Progression Scale, our study has limitations. Severe forms of COVID-19 directly admitted to ICU could not be included. There is a possible higher prevalence of CRD patients in ICU but previous studies do not support this assumption [14,39]. Furthermore, our data are retrospective and concerns the first pandemic wave. Since then, management of COVID-19 has evolved with more frequent use of high-flow oxygen therapy, non-invasive ventilation or corticosteroid therapy, that may change the course of the disease [40,41]. It is important to note that most patients with CRD included had, prior to admission, mild to moderate chronic respiratory impairment. However, the most severe patients and in particular patients with severe COPD (FEV₁ <50%) did not develop severe form of COVID-19. Thus, there appears to be no relationship between the severity of the underlying CRD and the risk of developing a severe form of COVID-19. As our population is made up of a large majority of patients with chronic obstructive pulmonary disease and asthma (74.4%), results of our study are relevant to this population. Dedicated studies are needed to assess the risk of progression to severe form of COVID-19 among patients with other CRD.

In conclusion, our study is the first to demonstrate lower prevalence of severe form of COVID-19 among hospitalized patients in COVID-19 ward with CRD. Despite heterogeneous conditions (mainly patients with COPD and asthma), patients hospitalized in COVID-19 ward with CRD seem less likely to develop an inappropriate immune response leading to acute respiratory distress syndrome, directly affecting clinical practices. Age, fever on admission, lymphopenia and CPAP therapy should be systematically kept in mind in patients with CRD since this characteristic could help identify patients at risk of developing a severe form of COVID-19. Further in vitro and in vivo studies are needed to better understand the underlying pathophysiological mechanism of SARS-CoV-2 infection in patients with CRD.

Author’s contribution

SB: Conceptualization, Data curation, Formal analysis, Investigation, Methology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. MV: Conceptualization, Data curation, Formal analysis, Investigation, Methology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. AM: Conceptualization – Investigation, Methology, Project administration, Resources, Visualization, Writing – original draft, Writing – review & editing. MP: Conceptualization – Investigation, Methology, Project administration, Resources, Visualization, Writing – original draft, Writing – review & editing. BP: Conceptualization – Investigation, Methology, Project administration, Resources, Visualization, Writing – original draft, Writing – review & editing. AB: Conceptualization – Investigation, Methology, Project administration, Resources, Visualization, Writing – original draft, Writing – review & editing. CR: Conceptualization – Investigation, Methology, Project administration, Resources, Visualization, Writing – original draft, Writing – review & editing. CB: Conceptualization – Investigation, Methology, Project administration, Resources, Visualization, Writing – original draft, Writing – review & editing. AL: Conceptualization, Data curation, Formal analysis, Investigation, Methology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. CB: Conceptualization, Investigation, Methodology, Project administration, Resources, Visualization, Writing – original draft, Writing – review & editing. AC: Conceptualization, Data curation, Formal analysis, Investigation, Methology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Summary of the “take home” message

COVID-19 ward hospital admission for COVID-19 in patients with chronic respiratory disease (especially chronic obstructive pulmonary disease and asthma) seem to be at reduced risk to develop an acute respiratory distress syndrome than other populations. Support: none

Declaration of Competing interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.resmed.2021.100880.

References

[1] xxx Communiqué Coronavirus covid 19 – point de situation en Grand 2021 Est 03 04 20.pdf
[2] xxx 2021 CP_Coronavirus_GrandEst_120420.pdf
[3] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395(10229):1054-62.
[4] Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, et al. Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis. J Infect 2020;81(2):e16-25.
[5] Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382(18):1708-20.
[6] Petrilli CM, Jones SA, Yang Y, Rajagopalan H, D’Onofrio L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ 2020;369:m1966.
[7] Drake TM, Docherty AB, Harrison EM, Quint JK, Adamali H, Agnew S, et al. Outcomes of hospitalization for COVID-19 in patients with interstitial lung disease. An International Multicenter Study. Am J Respir Crit Care Med 2020;202 (12):1656-65.
[8] Castillo JR, Peters SP, Busse WW. Asthma exacerbations: pathogenesis, prevention, and treatment. J Allergy Clin Immunol Pract 2017;5(4):918-27.
[9] Wedzicha JA, Seemungal TAR. COPD exacerbations: defining their cause and prevention. Lancet 2007;370(9589):786-96.
[10] Blanco-Melo D, Nilsson-Payant BE, Liu W-C, Uhls H, Hoagland D, Mäller R, et al. Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19. Cell 2020;181(5):1036–1045.e9.
[11] Rabag D, Salah Eldin H, Taenmah M, Khattab R, Salem R. The COVID-19 cytokine storm; what we know so far. Front Immunol 2020;11:1446.
[12] Rubin GD, Ryerson CJ, Haraamati LB, Sverzellati N, Kanne JP, Raoof S, et al. The role of chest imaging in patient management during the COVID-19 pandemic: a multinational consensus statement from the Fleischner Society. Chest 2020;158 (1):6-16.
[13] WHO. Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis 2020;20(8):e192-7.
[14] Argenziano MG, Bruce SL, Slater CL, Tiao JR, Baldwin MR, Barg RC, et al. Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: retrospective case series. BMJ 2020;369:m1966.
[15] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan. China. Lancet. 2020;395(10223):497-506.
[16] Livingston E, Bucher K. Coronavirus Disease 2019 (COVID-19) in Italy. JAMA 2020;323(14):1335.
[17] Burgel P-R, Laurendeau C, Raherison C, Fuhrman C, Roche N. An attempt at modelling COPD epidemiological trends in France, Respir Ris 2018;18(1):130.
[18] Leung JM, Niioka M, Yang CWT, Sin DD. COVID-19 and COPD. Eur Respir J 2020;56(2):2002108.
[19] Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical characteristics of coronavirus disease 2019 in New York City. N Engl J Med 2020;382(24):2372-4.
