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Original article

# Clinical characteristics of and outcomes for patients with COVID-19 and comorbid lung diseases primarily hospitalized in a conventional pulmonology unit: A retrospective study

M. Riou [a,b,*], C. Marcot [a], M. Canuet [a], B. Renaud-Picard [a], E. Chatron [a], M. Porzio [a], T. Dégot [a], S. Hirschi [a], C. Metz-Favre [a], L. Kassegne [a], C. Ederle [a,b], N. Khayath [a,b], A. Labani [c], P. Leyendecker [c], F. De Blay [a,b], R. Kessler [a,d], COVID-19 pneumonia group [1]

[a] Chest diseases department, Strasbourg University Hospital, Strasbourg, France
[b] UR 3070 Federation of Translational Medicine, FHU Homicare, University of Strasbourg, Strasbourg, France
[c] Department of Radiology B, Strasbourg University Hospital, Strasbourg, France
[d] Inserm-UNISTRA, UMR 1260 "Regenerative NanoMedecine", University of Strasbourg, Strasbourg, France

**A R T I C L E   I N F O**

**A B S T R A C T**

*Background.* – Scant data are currently available about a potential link between comorbid chronic lung diseases (CLD) and the risk and severity of the coronavirus disease 2019 (COVID-19) infection.
*Methods.* – To describe the clinical characteristics of and outcomes for patients with COVID-19 infection, including patients with comorbid respiratory diseases, who have been primarily hospitalized in the pulmonology department of Strasbourg University Hospital, France. In this retrospective, single-center study, we included all confirmed cases of COVID-19 from March 3 to April 15, 2020. We then compared the symptoms, biological and radiological findings, and outcomes for patients with and without CLD.
*Results.* – Of the 124 patients that were enrolled, the median age was 62 years, and 75 patients (60%) were male. Overall, 40% of patients ($n = 50$) had preexisting CLD, including chronic obstructive pulmonary disease (COPD) ($n = 15$, 12%) and asthma ($n = 19$, 15%). Twenty-eight patients were transferred to the intensive care unit (ICU), and six patients died in our unit. CLD were not predictive of ICU hospitalization, but a significantly higher total mortality was observed (17.6% vs. 5.5%, $P < 0.05$) in these patients.
*Conclusions.* – Our results suggest the lack of an over-representation of CLD in COVID-19, representing 40% of patients in this cohort and even within a pulmonology department. CLD were not a risk factor for ICU management. However, a tendency to higher global mortality was observed in COVID-19 patients with CLD. Further studies are warranted to determine the risk of COVID-19 for patients with comorbid CLD.

## 1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread worldwide rapidly, with several million individuals infected and more than 900,000 deaths [1]. Despite a relative poor characterization of the mechanisms of COVID-19, known complications including pneumonia and acute respiratory failure led pulmonologists to prepare for the worst for their patients with comorbid chronic lung diseases (CLD) [2,3]. Indeed, many respiratory viruses cause more serious illness in patients with chronic airway diseases, such COPD or asthma [4–6]. Moreover, it has been demonstrated that SARS-CoV-2 gains entry into Type II pneumocytes through the membrane-bound angiotensin-converting enzyme 2 (ACE2) receptor. In view of these data, we can easily understand why rapidly

progressive severe diffuse alveolar damage is frequently observed in COVID-19.

Strasbourg is in a part of France that has had an extremely high number of cases of COVID-19 since the epidemic started in February 2020. We report our experiences of patients with COVID-19, including patients with CLD, who were primarily hospitalized in the pulmonology department at Strasbourg University Hospital, France. The aims of the present study were:

- to assess the frequency of comorbid CLD in these patients;
- to compare clinical, biological, and radiological findings and outcomes of patients with and without CLD.

## 2. Material and methods

### 2.1. Patients

This study retrospectively included all 124 consecutive COVID-19-infected patients that had been primarily hospitalized in the respiratory care department of Strasbourg University Hospital, France, between March 3 and April 15, 2020. Since the first outbreak of COVID-19, 60 of 86 beds in our department have been devoted to the treatment of SARS-CoV-2 pneumonia. Almost all COVID-19 patients with known CLD hospitalized at the emergency room at Strasbourg University Hospital were referred to our department. This study was submitted for approbation to the Institutional Review Board of the French Learned Society for Respiratory Medicine (CEPRO 2020-041).

### 2.2. Data collection

Demographic, clinical, laboratory, imaging examination, outpatient and in-hospital medications, and outcome data were obtained from medical records in the Strasbourg University Hospital database. Clinical data included any underlying CLD, such as COPD, asthma, interstitial lung disease, lung cancer, or other causes of chronic respiratory insufficiency. The observation period started on the date of hospitalization and ended when the patient left the pulmonology unit (discharge, transfer to the intensive care unit [ICU], or death).

### 2.3. Diagnosis of SARS-CoV-2 infection

Detecting the presence of SARS-CoV-2 RNA from a nasopharyngeal swab was performed for all patients on admission, in accordance with the protocol of our institution. A low-dose chest CT (Aquilon PRIME SP, Canon Medical Systems) without injection of iodine contrast was carried out for 120 patients on admission. The global percentage of abnormal lung parenchyma was visually estimated by a radiologist and classified into four categories: absent/minimal (< 10%), moderate (10–25%), extensive (26–50%), and severe/critical (> 50%) [7].

### 2.4. Statistical analysis

Descriptive analyses of quantitative data comprised the mean or median and dispersion parameters. Qualitative data were described according to population sizes and percentages. The Charlson Comorbidity Index Score was calculated for each patient. We compared COVID-19 patients with and without CLD. On a second time, patients that had died or been transferred into the ICU were compared to the others. Comparisons between groups were conducted using the chi-squared test for percentages and the Wilcoxon rank-sum test for continuous variables. To determine the association between potential predictors of either transfer to the ICU or death,

we used multivariate logistic regression analysis. $P < 0.05$ was considered statistically significant.

## 3. Results

### 3.1. Baseline characteristics of the total population

All patients had either positive Real-time reverse transcriptase-polymerase chain reaction (RT-PCR) results for SARS-CoV-2 detection and/or typical COVID-19 images on chest CT scan. Typical chest CT lesions consisted of diffuse bilateral ground-glass opacities in subpleural regions and pulmonary alveolar infiltrates as described in the literature [8]. Global percentages of abnormal lung parenchyma were > 50% in 20 patients, 26–50% in 36 patients, 10–25% in 40 patients, and < 10% of the total lung parenchyma in 24 patients.

The median age of the patients was 62 years old (interquartile range [IQR]: 54–72), and 60% were male. The median interval between the onset of COVID-19 symptoms and hospitalization was 7 days (IQR 4–10). The most common symptoms were fever (89%), cough (87%), dyspnea (80%), fatigue (76%), myalgia (41%), and diarrhea (41%). Two and 4 patients reported have taken non-steroidal anti-inflammatory drugs and oral corticosteroids before hospitalization, respectively.

The most common extra-respiratory comorbidities were hypertension (39%), diabetes mellitus (21%), sleep apnea syndrome (18%), and chronic heart failure (8%). Obesity was present in 36 patients (29%). Forty-five patients (36%) were either active ($n = 8$) or former ($n = 37$) smokers. These baseline characteristics are summarized in Table 1.

### 3.2. Patients with CLD

Fifty patients (40%) had a previously diagnosed underlying CLD. This included 19 asthmatic patients, 15 COPD (including 4 patients with asthma-COPD overlap syndrome [ACOS]), 9 lung cancer, 5 that had other causes of chronic lung disease (obesity hypoventilation syndrome [$n = 1$], Steinert myotonic dystrophy [$n = 1$], and pulmonary interstitial lung disease [$n = 3$]), and 2 lung transplanted. Sixty-two percent of these patients had a smoking history. In these patients, the interval between COVID-19 symptoms and hospitalization was shorter, compared to patients without underlying CLD (5 vs. 8 days, $P < 0.05$). With regards to the chest CT scans on admission, patients with CLD had less typical images of COVID-19 than other patients (64% vs. 98%, $P < 0.05$), with less extensive pulmonary damage (Table 1). With the exception of fever, symptoms were similar in patients without comorbid respiratory diseases, but patients with CLD had less crackles (58% vs. 84%) and also more sibilance (18% vs. 2.7%) than other patients ($P < 0.05$).

Nineteen patients were asthmatic, including 2 patients with severe asthma. Most of the patients (63.6%) presented with well-controlled asthma, according to the Global Initiative for Asthma's guidelines. Eighty percent had atopic asthma. Only one patient received biotherapy and oral corticosteroids.

Among the 15 patients with COPD, median forced expiratory volume in one second was 41% (IQR 28–57), according to the last spirometry that was performed before hospitalization. One and 5 patients were treated with noninvasive ventilation (NIV) and oxygen at home, respectively. One patient received long-term azithromycin three times a week.

Nine patients were previously followed-up for lung cancer, including six for adenocarcinoma. Five patients had undergone lung lobectomy a few years before the infection. Three patients received Osimertinib, Lorlatinib and Alectinib, respectively, and 2 patients were treated with chemotherapy.

**Table 1**
Demographics and clinical characteristics of patients with or without comorbid respiratory disease hospitalized with COVID-19.

| | Total (n = 124) | Patients with comorbid respiratory diseases (n = 50) | Others (n = 74) | P |
|---|---|---|---|---|
| Clinical characteristics | | | | |
| Male (N/%) | 75 (60%) | 26 (52%) | 49 (48%) | 0.11 |
| Age (years) | 62 (54–72) | 67 (56–72) | 62 (53–71) | 0.31 |
| BMI (kg/m$^2$) | 28.2 (24.3–31.1) | 28.6 (23.3–30.8) | 28.3 (25.5–33.3) | 0.79 |
| Arterial hypertension (N/%) | 53 (43%) | 18 (36%) | 35 (47%) | 0.21 |
| Diabetes (N/%) | 28 (22%) | 9 (18%) | 19 (25%) | 0.31 |
| Chronic heart failure (N/%) | 10 (8%) | 5 (10%) | 5 (6.7%) | 0.51 |
| Former or active smokers (N/%) | 51 (41%) | 31 (62%) | 20 (27%) | 0.0001 |
| Sleep apnea syndrome (N/%) | 22 (18%) | 9 (18%) | 13 (17.5%) | 0.95 |
| Charlson Comorbidity Index Score | 3 (2–5) | 4 (3–6) | 2 (1–4) | 0.0003 |
| Underlying comorbid respiratory disease | – | – | – | – |
| COPD (N/%) | – | 15 (30%) | – | – |
| Asthma (N/%) | – | 19 (38%) | – | – |
| Interstitial lung disease (N/%) | – | 3 (6%) | – | – |
| Lung cancer (N/%) | – | 9 (18%) | – | – |
| Lung transplantation (N/%) | – | 2 (4%) | – | – |
| Obesity hypoventilation syndrome (N/%) | – | 1 (2%) | – | – |
| Steinert myotonic dystrophy (N/%) | – | 1 (2%) | – | – |
| Interval between symptom onset and hospitalization (days) | 7 (4–10) | 5 (3–8) | 8 (5–11) | 0.00001 |
| Positive SARS-CoV-2  RT-PCR results (N/%) | 118 (95%) | 47 (94%) | 71 (96%) | 0.62 |
| Chest CT-scan | – | – | – | – |
| COVID-19 typical images | 105 (84.6%) | 32 (64%) | 73 (98.6%) | 0.000001 |
| Pulmonary damages < 10% lung parenchyma | 24 (19%) | 20 (40%) | 4 (5.4%) | 0.000001 |
| Pulmonary damages 10–25% lung parenchyma | 40 (32%) | 12 (24%) | 28 (38%) | 0.1 |
| Pulmonary damages 26–50% lung parenchyma | 36 (29%) | 8 (16%) | 28 (38%) | 0.008 |
| Pulmonary severe damages > 50% (N/%) | 20 (16%) | 6 (12%) | 14 (19%) | 0.30 |
| Symptoms | – | – | – | – |
| Fever | 110 (89%) | 39 (78%) | 71 (96%) | 0.002 |
| Fatigue | 95 (76%) | 37 (74%) | 58 (78%) | 0.57 |
| Myalgia/arthralgia | 51 (41%) | 20 (40%) | 31 (42%) | 0.83 |
| Pharyngodinia | 6 (5%) | 2 (4%) | 4 (5.4%) | 0.72 |
| Anosmia | 25 (20%) | 10 (20%) | 15 (20%) | 0.97 |
| Digestive disorders | 51 (41%) | 16 (32%) | 35 (47%) | 0.09 |
| Cough | 109 (88%) | 45 (90%) | 64 (86%) | 0.55 |
| Dyspnea | 100 (80%) | 43 (86%) | 57 (77%) | 0.21 |
| Thoracic pain | 15 (12%) | 8 (16%) | 7 (9.5%) | 0.27 |
| Confusion | 6 (5%) | 3 (6%) | 3 (4%) | 0.62 |
| Crackles | 91 (73%) | 29 (58%) | 62 (84%) | 0.001 |
| Wheezing | 11 (9%) | 9 (18%) | 2 (2.7%) | 0.003 |

BMI: body mass index (calculated as weight in kilograms divided by height in meters squared); COPD: chronic obstructive respiratory disease; COVID-19: coronavirus disease 2019. Quantitative variables are presented as median and interquartile range. N (%), where N is the total number patients with available data. Two groups of patients (with or without comorbid lung disease) were compared. Respectively, 3 and 2 patients were active smokers in the group of patients with chronic respiratory disease and the other group. The Charlson Comorbidity Index Score was calculated for each patient to compare all comorbid diseases.

The 2 lung transplanted patients were treated with immunosuppressants (tacrolimus, mycophenolate mofetil and corticosteroids).

### 3.3. Treatment and outcomes

A total of 28 patients (22%) required ICU management and mechanical ventilation (Table 2). Six cases died in our unit, and 11 patients underwent therapeutic limitation, including eight with CLD (the decision not to transfer the patient to the ICU was made in the event of clinical aggravation). Up to date, a total of 113 cases (91%) had been discharged alive.

All patients received antibiotics for pneumonia: 103 (83%) received cephalosporin, and 73 (59%) received a combination of cephalosporin and macrolide. Patients were also given antiviral treatment (lopinavir/ritonavir; n = 14), hydroxychloroquine (n = 50, 40%), and tocilizumab (n = 3, 2%). Patients who were treated with tocilizumab have participated to the clinical trial CORIMMUNO-TOCI (NCT04331808).

Ten patients were treated with curative anticoagulation before hospitalization: 2 with vitamin K antagonists and 8 with direct oral anticoagulants. Curative anticoagulation with low-molecular-weight heparin treatment was started in 9 patients; all required ICU and 4 had a proved pulmonary embolism by chest CT angiography. During hospitalization, 18 patients received intravenous or oral corticosteroids.

In terms of ventilatory support, 91 patients (73%) underwent nasal oxygen on admission, including 40 patients with CLD. The median maximal oxygen requirement during hospitalization was 4 L.min$^{-1}$. An arterial blood gas test was performed for each patient on admission, including 93 patients under oxygen. The median partial pressure of oxygen (pO$_2$) and partial pressure of arterial carbon dioxide (pCO$_2$) were 74 mmHg (IQR 66–82) and 34 mmHg (IQR 32–38), respectively. Patients with CLD had higher pCO$_2$ than other patients (P < 0.05; Table 2), but only five patients had hypercapnia over 45 mmHg at admission, including three patients with COPD.

During hospitalization, 12 patients, including eight patients with CLD, underwent NIV to treat either acute respiratory failure with acidosis or continuous airway pressure (CPAP). During this procedure, limitation of virus aerosolization was primordial, using NIV systems with a minimum air leak and functional expiratory filters. One patient used high flow nasal Oxygenotherapy (HFNO) during hospitalization with a favorable issue. No patient with sleep apnea syndrome underwent their usual CPAP treatment during hospitalization, so as to limit virus aerosolization.

**Table 2**
Outcomes of patients with COVID-19 with or without comorbid respiratory disease.

| | Total (n = 124) | Patients with comorbid respiratory diseases (n = 50) | Others (n = 74) | P |
|---|---|---|---|---|
| ICU hospitalization (N/%) | 28 (22.5%) | 7 (14%) | 21 (28%) | 0.06 |
| Died in pulmonology unit (N/%) | 6 (5%) | 4 (8%) | 2 (2.7%) | 0.08 |
| Died (in total) (N/%) | 11 (9%) | 7 (14%) | 4 (5%) | 0.09 |
| Discharged alive (N/%) | 113 (91%) | 43 (86%) | 70 (94%) | 0.45 |
| Therapeutic limitation (N/%) | 11 (9%) | 8 (16%) | 3 (4%) | 0.02 |
| Hospitalization duration (days) | 8 (5–13) | 10 (6–15) | 8 (5–12) | 0.12 |
| Oxygen on admission (L.min$^{-1}$) | 2 (0–3) | 2 (1–4) | 2 (0–3) | 0.16 |
| Maximal oxygen requirement (l.min$^{-1}$) | 4 (2–10) | 4 (2–15) | 4 (2–9) | 0.69 |
| Oxygen on admission (N/%) | 93 (75%) | 40 (80%) | 53 (71.6%) | 0.29 |
| Nebulization (N/%) | 11 (9%) | 8 (16%) | 3 (4%) | 0.02 |
| Noninvasive ventilatory support (N/%) | 12 (10%) | 8 (16%) | 4 (5.4%) | 0.05 |
| pO2 on admission (mmHg) | 74 (66–82) | 69 (63–79) | 76 (67–82) | 0.62 |
| pCO2 on admission (mmHg) | 34 (32–38) | 36 (33–43) | 34 (32–38) | 0.05 |
| pCO2 >45 mmHg at the admission (N/%) | 7 (5.6%) | 7 (14%) | 0 (0%) | 0.0009 |
| Respiratory rate on admission (/min) | 24 (20–26) | 24 (22–26) | 24 (20–26) | 0.53 |
| Maximal CRP (mg/L) | 126 (59–185) | 102 (49–158) | 142 (77–220) | 0.36 |
| Lymphopenia (N/%) | 88 (71%) | 35 (70%) | 53 (71%) | 0.84 |
| Neutropenia (N/%) | 3 (2.4%) | 2 (4%) | 1 (1.3%) | 0.33 |

CRP: C-reactive protein; ICU: intensive care unit; pO$_2$: partial pressure of oxygen; pCO$_2$: partial pressure of arterial carbon dioxide.

### 3.4. Patients transferred to the ICU or that died

Characteristics of patients transferred to the ICU or died are summarized in Table 3. Median time between admission in hospital and transfer in ICU was 3 days (IQR 1–5). The ICU criteria were severe hypoxemic respiratory failure defined by desaturation requiring supplemental oxygen at a high rate (a mean of $11 \pm 4$ L.min$^{-1}$) or worsening tachypnea with a high respiration rate (mean $33 \pm 6$/min). All patients were hypoxemic, despite oxygen administration (mean pO$_2$ $60 \pm 7$ mmHg) at the time of transfer to the ICU, and no patient was hypercapnic (mean pCO$_2$ $34 \pm 4.5$ mmHg). These patients had more severe pneumonia on the chest CT scans that were performed on admission (P = 0.05). Ten patients developed ventilator-associated pneumonia.

Having an underlying CLD was not a risk factor for admission into the ICU in the multivariate logistic regression analysis. A tendency of higher mortality in the pulmonology unit for these patients was observed (8% vs. 2.7%, P = 0.08). However, CLD were not considered a risk factor for death in the multivariate logistic regression analysis. Hypoxemia and the severity of the chest CT pulmonary damage on admission were independently associated with ICU admission or death (Nagelkerke R square = 0.27, P < 0.04). Moreover, the Charlson Comorbidity Index score was not predictor of mortality or ICU admission.

## 4. Discussion

In response to the COVID-19 pandemic, pulmonologists have been rapidly confronted with a massive influx of patients that were infected by SARS-CoV-2. Our data confirm that severe COVID-19 cases are due to pneumonia that is associated with hypoxemic respiratory failure [1]. The most common symptoms in our cohort were fever, tachypnea, cough and crackles. This agrees with prior literature data [9–12]. Hypoxemia on admission was a predictor of either admission into the ICU or of death. Furthermore, monitoring oxygen saturation with pulse oximetry and respiration rate helped identify patients at risk of severe respiratory failure, which subsequently prompted earlier transfer to the ICU. Moreover, our study confirmed that the severity of chest CT pulmonary damage on admission was a predictive factor for admission into the ICU, suggesting that these patients should be closely monitored during hospitalization [13].

Only one patient used HFNO during hospitalization. In March 2020, during the first outbreak of the pandemic, there was an important concern that HFNO may increase bio-aerosol dispersion in the environment, leading to a trend to avoid HFNO among COVID-19 patients and to prefer early intubation. To date, the scientific evidence of generation and dispersion of bio-aerosols via HFNO shows a similar risk to standard oxygen masks, and clinicians should consider HFNO in hypoxemic selected Covid-19 patients [14].

ACE2 receptors being abundant on the surface of type I and II pneumocytes, pulmonologists expected a more severe clinical presentation and massive hospitalization for COVID-19 in patients with CLD [15]. It was confirmed by 2 meta-analyses in patients with COPD [16,17]. In a large cohort of patients with COVID-19, concomitant CLD were associated with worse outcomes [9].

However, contrary to these expectations, patients in our cohort with CLD were not hospitalized more often than other patients. In our study, 40% of patients had preexisting CLD. Asthma was the main cause (19 patients, 15.3%) and COPD was the second-most common cause (15 patients, 12%), including four patients with ACOS. As the risk of COVID-19 infection in patients with underlying CLD in the general population remains unknown, and general data on COVID-19 in asthma or COPD patients appear discordant, it is difficult to conclude about the frequency of hospitalization of the patients with CLD [11,12,18–21]. A recent article has highlighted a low incidence of COVID-19 in COPD patients (24 cases in 1590) [22]. This aligns with a recent meta-analysis that included 10 studies involving 3402 patients hospitalized for COVID-19, which revealed a COPD rate of 0.95% [23]. As a pulmonology care unit, we expected even more patients with comorbid CLD, especially since these patients were primarily referred to us for hospitalization at Strasbourg University Hospital. The percentages of patients with CLD in our cohort are relatively similar to those reported in the general French population, which emphasizes the absence of over-representation of comorbid CLD in COVID-19, especially since these results are based on pulmonology hospitalizations [24,25]. Our results align with recent data from the American Centers for Disease Control (CDC) [26]. Moreover, these data must be interpreted with caution owing to asthma and COPD being heterogeneous diseases with a large number of subtypes and phenotypes.

Several hypotheses have been proposed to explain the absence of over-representation of comorbid respiratory diseases in COVID-19:

**Table 3**
Demographics and clinical characteristics of COVID-19 patients that were transferred into ICU or died compared to the others.

| | Covid-19 patients that were transferred into ICU or died (n = 34) | Other (n = 90) | P |
|---|---|---|---|
| **Clinical characteristics** | | | |
| Male (N/%) | 25 (73%) | 50 (55%) | 0.06 |
| Age (years) | 68 (55–76) | 60 (53–70) | 0.10 |
| BMI (kg/m$^2$) | 28.6 (24.3–31.1) | 27.4 (24.3–30.4) | 0.85 |
| Arterial hypertension (N/%) | 18 (53%) | 32 (35.5%) | 0.07 |
| Diabetes (N/%) | 7 (20%) | 20 (22%) | 0.84 |
| Heart failure (N/%) | 3 (9%) | 7 (8%) | 0.84 |
| Former or active smokers (N/%) | 17 (50%) | 34 (38%) | 0.21 |
| Sleep apnea syndrome (N/%) | 7 (20%) | 15 (16%) | 0.61 |
| Charlson Comorbidity Index Score | 3 (2–5) | 3 (1–4) | 0.38 |
| Comorbid respiratory disease (all causes, N/%) | 11 (32%) | 39 (43%) | 0.26 |
| COPD (N/%) | 4 (12%) | 11 (12%) | 0.94 |
| Asthma (N/%) | 2 (6%) | 17 (19%) | 0.07 |
| Interval between symptoms and hospitalization (days) | 7 (4–10) | 7 (4–10) | 0.71 |
| Positive SARS-CoV-2          RT-PCR results (N/%) | 32 (94%) | 86 (95%) | 0.74 |
| **Chest CT-scan on admission** | | | |
| Pulmonary damages < 10% lung parenchyma | 5 (15%) | 19 (21%) | 0.42 |
| Pulmonary damages 10–25% lung parenchyma | 6 (17%) | 34 (38%) | 0.03 |
| Pulmonary damages 25–50% lung parenchyma | 11 (32%) | 25 (28%) | 0.61 |
| Pulmonary severe damages > 50% (N/%) | 12 (35%) | 8 (9%) | 0.05 |
| Oxygen on admission (L.min$^{-1}$) | 3 (2–5) | 1 (0–3) | 0.004 |
| Maximal oxygen requirement (L.min$^{-1}$) | 13 (9–15) | 2.5 (1–4) | 0.0001 |
| Nebulization (N/%) | 3 (9%) | 8 (9%) | 0.99 |
| Noninvasive ventilatory support (N/%) | 3 (9%) | 9 (10%) | 0.84 |
| pO$_2$ on admission (mmHg) | 76 (66–85) | 73 (65–83) | 0.77 |
| pCO$_2$ on admission (mmHg) | 35 (33–39) | 34 (32–38) | 0.76 |
| pCO$_2$ > 45 mmHg on admission (N/%) | 1 (3%) | 6 (6.6%) | 0.42 |
| Respiratory rate on admission (/min) | 24 (22–30) | 22 (20–26) | 0.04 |
| Respiratory rate on transfer (/min) | 32 (28–40) | 18 (16–20) | 0.0002 |
| Therapeutic limitation | 6 (17.6%) | 5 (5.5%) | 0.03 |
| Maximal CRP (mg/L) | 218 (111–269) | 123 (51–158) | 0.000006 |
| Lymphopenia (N/%) | 30 (88%) | 61 (68%) | 0.02 |
| Neutropenia (N/%) | 0 | 3 (3.3%) | 0.28 |

BMI: body mass index (calculated as weight in kilograms divided by height in meters squared); COPD: chronic obstructive respiratory disease; COVID-19: coronavirus disease 2019; pO$_2$: partial pressure of oxygen; pCO$_2$: partial pressure of arterial carbon dioxide. For patient not transferred in ICU or died (other), the respiratory rate on transfer corresponds to the value at the time of hospital discharge.

- an underdiagnosis of comorbid CLD, which is also observed in the general population [27]: in a range of reported studies, as well as in our cohort, COPD was identified through known diagnosis, which may itself be underestimated. In addition, no spirometry was performed during hospitalization, due to a high-risk of virus aerosolization;
- the French COVID-19 containment strategy: early on, patients' associations and the media warned patients with CLD to self-isolate through preventive actions. Indeed, these patients may have begun respecting these containment rules prior to the general population. Preventive measures (i.e., social distancing, respiratory hygiene, handwashing, and wearing face coverings in public settings) are beneficial to protect the general public and persons with underlying medical conditions. Moreover, increased adherence to daily inhaler medication therapy has been reported for patients with asthma or COPD, during the first weeks of the COVID-19 pandemic [28];
- a protective role of CLD against COVID-19: reduced *ACE2* gene expression in airway cells from asthmatic allergic patients has been previously described [29], which could contribute to decreased susceptibility to COVID-19 in these patients. Importantly, non-atopic asthma was not associated with reduced *ACE2* expression. Conversely, it has recently been demonstrated that smokers and those with COPD have increased airway expression of ACE2 [30]. The relevance of these findings still must be confirmed in larger cohort studies. Moreover, specific autoimmune responses that are elicited by the chronic disease itself could also play a protective role [31,32];
- the potential protective role of therapies in CLD: Iwabuchi et al. reported three cases of COVID-19 pneumonia that were

successfully treated with ciclesonide inhalation [33]. Inhaled corticosteroids (ICS), either alone or in combination with bronchodilators (long-acting muscarinic antagonists and ß-2 agonists), which are employed in both asthma and COPD, have been shown to inhibit in-vitro coronavirus replication and cytokine production [34]. In view of these data, ICS might (at least partially) mitigate local inflammation in the lungs and inhibit proliferation of the virus by antiviral activity [35]. Peters et al. reported lower expression of ACE2 and transmembrane protease serine 2 (TMPRSS2) in the sputum cells of asthmatic patients taking ICS [36]. Conversely, ICS use in asthma and COPD has been associated with an increased risk of upper respiratory tract infections and change in the lung microbiome [37,38]. Macrolides, which are at times prescribed as long-term therapy in COPD, could represent another beneficial treatment in COVID-19, although the mechanisms of azithromycin against SARS-CoV-2 are still unclear [39]. Further controlled studies are warranted to confirm the ICS' potential benefits in COVID-19.

In our cohort, two lung transplant recipients were hospitalized for COVID-19. One of these patients did not exhibit severe infection, while the other displayed severe infection and required immediate transfer to the ICU for mechanical ventilation. Currently, data on COVID-19 in solid organ transplant recipients are limited [40]. No patients with pulmonary arterial hypertension (PAH) were hospitalized for COVID-19 in our pulmonology unit during the observation period. PAH-specific medication, such as phosphodiesterase-5 inhibitors and endothelin receptor antagonists, may exert protective effects in these patients, in terms of the paucity of hospitalized PAH-COVID-19 patients [41].

In our study, CLD were not a risk factor for ICU management. However, a tendency to higher global mortality was observed in patients CLD, though this was not considered a risk factor for death in the multivariate logistic regression analysis. Similar results have been described in a recent metanalysis [42], and data from two studies have revealed a higher mortality rate of 60% [43,44]. In our cohort, these results could be partially explained by more medical decisions about therapeutic limitations for patients with advanced lung disease. In our center, therapeutic limitation was a collegial decision that involved ICU staff, pulmonary department staff, and patient and family discussion.

There are several limitations to this study. First, it was a single-center retrospective study, and we only considered patients that were primarily hospitalized in the conventional pulmonology unit. Data on patients with CLD that were directly managed in the ICU were not taken into account. Furthermore, CLD include a lot of different diseases with various prognosis (COPD with long term oxygen therapy versus asthma for example). Lastly, COPD and asthma are underdiagnosed in the general population, and several patients that were hospitalized in our unit could have had no known COPD or asthma diagnosis. Our report only includes short-term data, and we are unaware of long-term outcomes in these patients, particularly in terms of respiratory consequences.

## 5. Conclusions

Our results suggest the lack of an over-representation of CLD in COVID-19, even within a pulmonology department. CLD were not a risk factor for ICU management. However, a tendency to higher global mortality was observed in COVID-19 patients with CLD. Further studies are needed to better describe and understand the mechanisms of COVID-19 in this patient subgroup.

## Statement of Ethics

Written consent was obtained from patients during hospitalization, which articulated that they had no objections to the use of their clinical or paraclinical data. This study was submitted for approbation to the Institutional Review Board of the French Learned Society for Respiratory Medicine.

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## Author contributions

MR collected and analyzed the data and wrote the manuscript. RK reviewed and edited the manuscript and contributed to the discussion. FDB reviewed and edited the manuscript. MR, CM, MC, BRP, EC, MP, TD, SH, CMF, LK, NK and CE contributed to the medical follow-up of the patients and reviewed the manuscript. AL and PL contributed to the chest CT-scans analyze and reviewed the manuscript. All authors are the guarantor of this work and, as such, have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

## Disclosure of interest

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The other authors declare that they have no competing interest.

## References

[1] Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270–3, http://dx.doi.org/10.1038/s41586-020-2012-7.

[2] Santa-Olalla Peralta P, Cortes-Garcia M, Vicente-Herrero M, Castrillo-Villamandos C, Arias-Bohigas P, Pachon-del Amo I, et al. Risk factors for disease severity among hospitalised patients with 2009 pandemic influenza A (H1N1) in Spain, April–December 2009. Euro Surveill 2010;15, http://dx.doi.org/10.2807/ese.15.38.19667-en.

[3] Deslée G, Zysman M, Burgel P-R, Perez T, Boyer L, Gonzalez J, et al. Chronic obstructive pulmonary disease and the COVID-19 pandemic: reciprocal challenges. Respir Med Res 2020;78:100764, http://dx.doi.org/10.1016/j.resmer.2020.100764.

[4] Nicholson KG, Kent J, Ireland DC. Respiratory viruses and exacerbations of asthma in adults. BMJ 1993;307:982–6, http://dx.doi.org/10.1136/bmj.307.6910.982.

[5] Papadopoulos NG, Christodoulou I, Rohde G, Agache I, Almqvist C, Bruno A, et al. Viruses and bacteria in acute asthma exacerbations – a GA² LEN-DARE systematic review. Allergy 2011;66:458–68, http://dx.doi.org/10.1111/j.1398-9995.2010.02505.x.

[6] van Rijn AL, van Boheemen S, Sidorov I, Carbo EC, Pappas N, Mei H, et al. The respiratory virome and exacerbations in patients with chronic obstructive pulmonary disease. PLoS One 2019;14:e0223952, http://dx.doi.org/10.1371/journal.pone.0223952.

[7] Revel M-P, Parkar AP, Prosch H, Silva M, Sverzellati N, Gleeson F, et al. COVID-19 patients and the radiology department – advice from the European Society of Radiology (ESR) and the European Society of Thoracic Imaging (ESTI). Eur Radiol 2020, http://dx.doi.org/10.1007/s00330-020-06865-y.

[8] Song F, Shi N, Shan F, Zhang Z, Shen J, Lu H, et al. Emerging 2019 novel coronavirus (2019-nCoV) pneumonia. Radiology 2020;295:210–7, http://dx.doi.org/10.1148/radiol.2020200274.

[9] Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis 2020;94:91–5, http://dx.doi.org/10.1016/j.ijid.2020.03.017.

[10] Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020;8:420–2, http://dx.doi.org/10.1016/S2213-2600(20)30076-X.

[11] Zhang J-J, Dong X, Cao Y-Y, Yuan Y-D, Yang Y-B, Yan Y-Q, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy 2020, http://dx.doi.org/10.1111/all.14238.

[12] 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, http://dx.doi.org/10.1056/NEJMoa2002032.

[13] Zhao W, Zhong Z, Xie X, Yu Q, Liu J. Relation between chest CT findings and clinical conditions of coronavirus disease (COVID-19) pneumonia: a multicenter study. AJR Am J Roentgenol 2020;214:1072–7, http://dx.doi.org/10.2214/AJR.20.22976.

[14] Li J, Fink JB, Ehrmann S. High-flow nasal cannula for COVID-19 patients: low risk of bio-aerosol dispersion. Eur Respir J 2020;55, http://dx.doi.org/10.1183/13993003.00892-2020.

[15] Halpin DMG, Faner R, Sibila O, Badia JR, Agusti A. Do chronic respiratory diseases or their treatment affect the risk of SARS-CoV-2 infection? Lancet Respir Med 2020, http://dx.doi.org/10.1016/S2213-2600(20)30167-3.

[16] Zhao Q, Meng M, Kumar R, Wu Y, Huang J, Lian N, et al. The impact of COPD and smoking history on the severity of COVID-19: a systemic review and meta-analysis. J Med Virol 2020, http://dx.doi.org/10.1002/jmv.25889.

[17] Lippi G, Henry BM. Chronic obstructive pulmonary disease is associated with severe coronavirus disease 2019 (COVID-19). Respir Med 2020;167:105941, http://dx.doi.org/10.1016/j.rmed.2020.105941.

[18] 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;395:497–506, http://dx.doi.org/10.1016/S0140-6736(20)30183-5.

[19] Zhang J-J, Cao Y-Y, Dong X, Wang B-C, Liao M-Y, Lin J, et al. Distinct characteristics of COVID-19 patients with initial rRT-PCR-positive and rRT-PCR-negative results for SARS-CoV-2. Allergy 2020, http://dx.doi.org/10.1111/all.14316.

[20] Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol 2020, http://dx.doi.org/10.1016/j.jaci.2020.04.006.

[21] Grandbastien M, Piotin A, Godet J, Abessolo-Amougou I, Ederlé C, Enache I, et al. SARS-CoV-2 pneumonia in hospitalized asthmatic patients did not induce severe exacerbation. J Allergy Clin Immunol Pract 2020;8:2600–7, http://dx.doi.org/10.1016/j.jaip.2020.06.032.

[22] Guan W-J, Liang W-H, Zhao Y, Liang H-R, Chen Z-S, Li Y-M, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J 2020, http://dx.doi.org/10.1183/13993003.00547-2020.

[23] Emami A, Javanmardi F, Pirbonyeh N, Akbari A. Prevalence of underlying diseases in hospitalized patients with COVID-19: a systematic review and meta-analysis. Arch Acad Emerg Med 2020;8:e35.

[24] Patout M, Zysman M, Raherison Semjen C, Perez T, Cuvelier A, Roche N. Epidemiology and COPD screening in France. Workshop from the Société de pneumologie de langue française (SPLF). Rev Mal Respir 2014;31:693–9, http://dx.doi.org/10.1016/j.rmr.2014.05.003.

[25] Riviere S, Delmas M-C, Iwatsubo Y. Asthma and socioeconomic characteristics in France in 2012. Rev Mal Respir 2018;35:287–94, http://dx.doi.org/10.1016/j.rmr.2017.12.002.

[26] Garg S, Kim L, Whitaker M, O'Halloran A, Cummings C, Holstein R, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019 – COVID-NET, 14 States, 2020. MMWR Morb Mortal Wkly Rep 2020;69:458–64, http://dx.doi.org/10.15585/mmwr.mm6915e3.

[27] van Schayck CP, Chavannes NH. Detection of asthma and chronic obstructive pulmonary disease in primary care. Eur Respir J Suppl 2003;39:16s–22s, http://dx.doi.org/10.1183/09031936.03.00040403.

[28] Kaye L, Theye B, Smeenk I, Gondalia R, Barrett MA, Stempel DA. Changes in medication adherence among patients with asthma and COPD during the. J Allergy Clin Immunol Pract 2020, http://dx.doi.org/10.1016/j.jaip.2020.04.053.

[29] Jackson DJ, Busse WW, Bacharier LB, Kattan M, O'Connor GT, Wood RA, et al. Association of respiratory allergy, asthma, and expression of the SARS-CoV-2 receptor ACE2. J Allergy Clin Immunol 2020, http://dx.doi.org/10.1016/j.jaci.2020.04.009.

[30] Leung JM, Yang CX, Tam A, Shaipanich T, Hackett T-L, Singhera GK, et al. ACE-2 expression in the small airway epithelia of smokers and COPD patients: implications for COVID-19. Eur Respir J 2020:55, http://dx.doi.org/10.1183/13993003.00688-2020.

[31] Mukherjee M, Nair P. Autoimmune responses in severe asthma. Allergy Asthma Immunol Res 2018;10:428–47, http://dx.doi.org/10.4168/aair.2018.10.5.428.

[32] Caramori G, Casolari P, Barczyk A, Durham AL, Di Stefano A, Adcock I. COPD immunopathology. Semin Immunopathol 2016;38:497–515, http://dx.doi.org/10.1007/s00281-016-0561-5.

[33] Iwabuchi K, Yoshie K, Kurakami Y, Takahashi K, Kato Y, Morishima T. Therapeutic potential of ciclesonide inahalation for COVID-19 pneumonia: report of three cases. J Infect Chemother 2020, http://dx.doi.org/10.1016/j.jiac.2020.04.007.

[34] Yamaya M, Nishimura H, Deng X, Sugawara M, Watanabe O, Nomura K, et al. Inhibitory effects of glycopyrronium, formoterol, and budesonide on coronavirus HCoV-229E replication and cytokine production by primary cultures of human nasal and tracheal epithelial cells. Respir Investig 2020;58:155–68, http://dx.doi.org/10.1016/j.resinv.2019.12.005.

[35] Halpin DMG, Singh D, Hadfield RM. Inhaled corticosteroids and COVID-19: a systematic review and clinical perspective. Eur Respir J 2020, http://dx.doi.org/10.1183/13993003.01009-2020.

[36] Peters MC, Sajuthi S, Deford P, Christenson S, Rios CL, Montgomery MT, et al. COVID-19 related genes in sputum cells in asthma: relationship to demographic features and corticosteroids. Am J Respir Crit Care Med 2020, http://dx.doi.org/10.1164/rccm.202003-0821OC.

[37] Yang M, Chen H, Zhang Y, Du Y, Xu Y, Jiang P, et al. Long-term use of inhaled corticosteroids and risk of upper respiratory tract infection in chronic obstructive pulmonary disease: a meta-analysis. Inhal Toxicol 2017;29:219–26, http://dx.doi.org/10.1080/08958378.2017.1346006.

[38] Yang M, Zhang Y, Chen H, Lin J, Zeng J, Xu Z. Inhaled corticosteroids and risk of upper respiratory tract infection in patients with asthma: a meta-analysis. Infection 2019;47:377–85, http://dx.doi.org/10.1007/s15010-018-1229-y.

[39] Ohe M, Shida H, Jodo S, Kusunoki Y, Seki M, Furuya K, et al. Macrolide treatment for COVID-19: will this be the way forward? Biosci Trends 2020;14:159–60, http://dx.doi.org/10.5582/bst.2020.03058.

[40] Pereira MR, Mohan S, Cohen DJ, Husain SA, Dube GK, Ratner LE, et al. COVID-19 in solid organ transplant recipients: initial report from the US epicenter. Am J Transplant 2020, http://dx.doi.org/10.1111/ajt.15941.

[41] Horn EM, Chakinala M, Oudiz R, Joseloff E, Rosenzweig EB. Could pulmonary arterial hypertension patients be at a lower risk from severe. Pulm Circ 2020;10, http://dx.doi.org/10.1177/2045894020922799 [2045894020922799].

[42] Alqahtani JS, Oyelade T, Aldhahir AM, Alghamdi SM, Almehmadi M, Alqahtani AS, et al. Prevalence, severity and mortality associated with COPD and smoking in patients with. PLoS One 2020;15:e0233147, http://dx.doi.org/10.1371/journal.pone.0233147.

[43] Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, 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 Respir Med 2020;8:475–81, http://dx.doi.org/10.1016/S2213-2600(20)30079-5.

[44] 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;395:1054–62, http://dx.doi.org/10.1016/S0140-6736(20)30566-3.